

CORDYCEPS

Cordyceps spp. · immunity and other effects

What the review by Das et al. in *Frontiers in Pharmacology* (2021) showed, and at what level of evidence

An insect-parasitizing fungus from Tibetan and traditional Chinese medicine. For patients and physicians: which effects are described, where they were observed (in a test tube, in animals or in humans), and what the review does not show.

SECTIONS

01 ABOUT THE REVIEW

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04 IMMUNITY

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06 METABOLISM AND ENDURANCE

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09 SUMMARY

700+

species in
the genus

2

controlled
trials in
humans

0

numbers on
the effect in
humans

HOW THIS DOCUMENT WORKS

IN PLAIN WORDS

The document moves from the question “what is this paper” to the question “what follows from it.” If you only need the bottom line, read section 09.

Boxes with an orange bar on the left, like this one, translate scientific language into everyday language. They can be read separately from the main text.

- **Cream boxes** contain the conclusions of the author of this guide, as well as highlighted quotes and the position of the review authors; the box heading says which.
- **A bracketed label** after a statement, for example [animals], tells you in whom or in what the result was obtained. The labels are explained on the next page.
- **“As cited in Das et al.”**: the review measured nothing itself; it retells other studies. We present them as the review describes them, with the author’s name and year from its reference list.
- Numbers and names are given as in the review. Abbreviations are spelled out at first mention or in the glossary at the end; the names of signaling-pathway molecules are collected in the glossary.

LABELS: PRECLINICAL

- [traditional use] how the fungus is used in folk medicine. This is experience of use, not testing.
- [chemical analysis] what was found in the fungus. It says nothing about the effect on the body.
- [in vitro] an experiment on cells in a test tube or dish.
- [in vitro · human cells] the cells were taken from humans, but the experiment is still in a test tube.
- [animals] an experiment in mice, rats and other animals.
- [preclinical] cells and/or animals; the review does not specify which.

IN PLAIN WORDS

A label follows every statement about an effect on the body. These are all the levels below “humans”: so-called preclinical research.

BEFORE YOU READ

LABELS: HUMANS AND OPINIONS

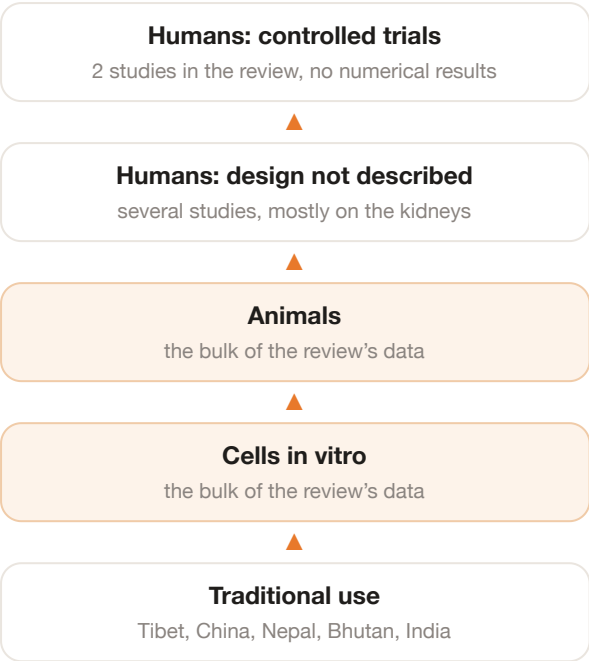
- [humans · design not described] people took part, but the review does not report how the study was designed.
- [humans · RCT] [humans · placebo-controlled] controlled trials. An RCT is a randomized controlled trial: groups are assigned at random; in a placebo-controlled trial the comparison is with a dummy pill.
- [review authors' opinion] an assumption of the authors, not the result of an experiment.
- [level not stated] the claim is given without saying in whom it was obtained.

IN PLAIN WORDS

The closer a label is to the word “humans,” the closer the result is to the question “will this help me.” Most labels in this document are “in vitro” and “animals.”

BEFORE YOU READ

EVIDENCE LADDER



Humans: controlled trials

2 studies in the review, no numerical results



Humans: design not described

several studies, mostly on the kidneys



Animals

the bulk of the review's data



Cells in vitro

the bulk of the review's data



Traditional use

Tibet, China, Nepal, Bhutan, India

IN PLAIN WORDS

Each step up is closer to an answer for humans. In the abstract the authors themselves write that the pharmacological activities of cordyceps have been “reported in pre-clinical studies,” that is, in cells and animals.

01

SECTION

ABOUT THE REVIEW

WHAT THIS SECTION COVERS

What this paper is, who wrote it and how the authors searched the literature.

The review measured nothing itself. It collects and retells other studies, so its reliability depends on how those studies were selected and appraised.

IN THIS SECTION

- **ARTICLE PROFILE**
- **HOW THE LITERATURE WAS SEARCHED**
- **WHAT THE METHODS LEAVE OUT**

ARTICLE PROFILE

Journal	Frontiers in Pharmacology, Ethnopharmacology section
Type	Literature review
Authors	17; first author Gitishree Das, corresponding author Jayanta Kumar Patra
Countries	South Korea, Mexico, India, Chile, Portugal
Dates	submitted 03 Sep 2020, accepted 02 Dec 2020, published 08 Feb 2021
Citation	volume 11, article 602364; doi:10.3389/fphar.2020.602364
Funding	National Research Foundation of Korea (NRF), Dongguk University
Conflict of interest	none declared

IN PLAIN WORDS

A **review** is a paper in which the authors gather studies already published on a topic. It contains no new experiments. A **DOI** is the article's permanent address: you can find it by that number at doi.org.

HOW THE LITERATURE WAS SEARCHED

- **Databases:** PubMed, SpringerLink, Elsevier journals, ScienceDirect, Scopus, Google search.
- **Keywords:** Cordyceps, cordycepin, immune system, immunostimulation, immunomodulatory, pharmacology, anti-cancer, anti-viral, clinical trials, ethnomedicine, phytochemical analysis, species names.
- The search covered article titles, abstracts and keywords.
- Reviews were generally excluded, but “in some instances” important reviews were considered.
- Only articles in English.
- Ethnobotanical reports “which lack substantial proof of the claim” were excluded.

IN PLAIN WORDS

The authors looked for papers on cordyceps in several scientific databases and in Google.

Ethnobotany studies how peoples use plants and fungi. Descriptions of such use without verification were not included in the review.

WHAT THE METHODS LEAVE OUT

The “Methodology” section does not state:

- how many studies were found and how many were included;
- which years the search covered;
- how studies were selected by design (cells, animals, humans);
- how study quality and risk of bias were assessed;
- whether results were pooled into a single estimate (meta-analysis).

CONCLUSION

This is a narrative review: studies are collected and retold but not weighted by quality. It is useful as a map of research directions, but not as proof of an effect.

IN PLAIN WORDS

A **meta-analysis** is a way to combine the results of many studies mathematically. **Bias** is a skew that makes a result look better or worse than it really is.

02

SECTION

THE FUNGUS

WHAT THIS SECTION COVERS

What cordyceps is: how many species there are, where it grows, how it lives off insects, how the wild fungus differs from the cultivated one, and what it has been used for in folk medicine for centuries.

The biology of the fungus is not a medical claim, so evidence labels here appear only on statements about its use.

IN THIS SECTION

- **GENUS AND SPECIES**
- **LIFE CYCLE**
- **WILD AND CULTIVATED**
- **TRADITIONAL USE**

GENUS AND SPECIES

700+

species in the genus
Cordyceps

≈20

parasitize
Elaphomyces fungi

- The remaining species parasitize insects and arachnids: beetles, butterflies and moths, termites, hymenopterans and others.
- Found in North America, Europe and Asia, mostly in China, Japan, Nepal, Bhutan, Vietnam, Korea, Thailand and the Indian Himalayas; grows in the mountains at 3,600–4,000 m. The species *C. gunnii* has been found in Australia.
- The best-studied species: **C. sinensis** (current name *Ophiocordyceps sinensis*) and **C. militaris**.

IN PLAIN WORDS

The name combines the Greek “kordyle” (club) and the Latin “ceps” (head): the fruiting body looks like a club. “Cordyceps” is not one fungus but hundreds of species with different compositions. This matters for everything that follows.

LIFE CYCLE

1 · Infection

spores carried by wind, rain or insects infect a larva; sometimes it eats food contaminated with mycelium



2 · Parasitism

over the winter the fungus consumes the larva's internal organs, leaving the exoskeleton



3 · Fruiting body

in spring it sprouts through the larva's mouth, matures in summer and releases spores



Harvest

in summer the fungus is collected by villagers while grazing yaks

IN PLAIN WORDS

Cordyceps does not grow out of the ground like an ordinary mushroom. It develops inside a living larva, completely replaces its tissues and emerges as a thin stalk. What is collected is a larva filled with fungus, with a stalk-like fruiting body.

WILD AND CULTIVATED

- Because of its popularity and over-harvesting, the wild fungus has become scarce. Since the 1970s scientists have been looking for ways to ferment and cultivate it.
- **C. militaris** is the second best-selling species in China, Japan and Korea. It is considered a cheaper substitute for *C. sinensis*.
- Large-scale trade in cordyceps began in the early 2000s. In many countries it is sold as a dietary supplement.
- The review describes *C. sinensis* as a dietary supplement that complies with FDA requirements (as cited in Das et al.: Wu et al., 2015).

IN PLAIN WORDS

Mycelium is the network of fungal threads; it can be grown in a fermenter. The **fruiting body** is the above-ground part, the “stalk.” Fungus from a mountain meadow and mycelium from a fermenter are different products; section 03 shows that their composition differs several-fold. The **FDA** is the US Food and Drug Administration. The review refers to compliance with dietary supplement requirements, not to a proven therapeutic effect.

TRADITIONAL MEDICINE

- In traditional Chinese medicine (TCM), a tonic for diseases of the respiratory tract, liver and kidneys, for high blood sugar and for tumors. [traditional use]
- For energy, endurance, aerobic capacity and “cellular immunity.” [traditional use]
- Local healers choose the dose and route “by trial and error” (as cited in Das et al.: Maity, 2013). The fungus is dissolved in milk, alcohol or hot water. [traditional use]

1964

Officially listed as a drug in the Chinese Pharmacopoeia

C. sinensis and *C. militaris* are used most often

IN PLAIN WORDS

A pharmacopoeia is an official national compendium of medicines. The review does not say what data the 1964 listing was based on. Tradition has no single dose.

FROM ALTITUDE TO COUGH

- For fatigue and weakness, and to ease the symptoms of altitude sickness.
[traditional use]
- TCM practitioners recommend regular intake of *C. sinensis* “to avoid infections, colds, and flues,” and for cough, phlegm, asthma and bronchial diseases. [traditional use]
- For lung fibrosis, including in patients with SARS (severe acute respiratory syndrome).
[traditional use]
- Benefits “have also been observed in athletes”: the review attributes them to a rise in cellular ATP but cites no study for this.
[review authors’ opinion]
- Some folk healers mix the fungus with yew leaf and ginseng root “as a cancer treatment.” [traditional use]

IN PLAIN WORDS

This is a list of what the fungus is used for, not of what has been proven. In TCM logic all these properties are explained by the fungus’s ability to “enrich the lung yin and yang.” **ATP** is the energy-storage molecule of the cell.

OTHER SPECIES

All rows of the table [traditional use]

SPECIES	FOLK USE
C. militaris	energy, aphrodisiac, respiratory diseases
C. pruinosa	stomach diseases, inflammation
C. bassiana	dermatitis, eczema; also a biological insecticide against pests
C. cicadae	convulsions in children, fever, tremor
C. guangdongensis	fatigue, avian influenza, inflammation, kidney failure
C. ophioglossoides	food; products with “antitumor, estrogenic, and anti-aging” properties; against excessive bleeding in childbirth

IN PLAIN WORDS

Each species has its own folk “specialty.” That is why the word “cordyceps” on a package without the species name tells you little.

03

SECTION

COMPOSITION

WHAT THIS SECTION COVERS

Which substances chemists have found in cordyceps. This is the foundation: what ends up in a product depends on the species, the part of the fungus, the way it is grown and the extraction method.

Not all of the substances found are “beneficial”: they include immunosuppressants (section 08).

IN THIS SECTION

- **CLASSES OF COMPOUNDS**
- **CORDYCEPIN AND ITS ACID**
- **POLYSACCHARIDES**
- **COMPOSITION BY PART OF THE FUNGUS**
- **EXTRACTION METHODS**

CLASSES OF COMPOUNDS

Nucleosides

Sterols

Flavonoids

Cyclic peptides

Phenolics

Bioxanthracenes

Polyketides

Alkaloids

Polysaccharides

a separate large class

- Cyclic peptides are the most abundant in most species; according to the abstract, they are the most studied class.
[chemical analysis]
- Table 1 of the review includes only compounds tested in a laboratory and is adapted from the review by Olatunji et al., 2018. Some compounds in it are marked as inactive.

IN PLAIN WORDS

The fungus contains dozens of groups of substances. In many cases it is unknown which of them is responsible for which effect.

CORDYCEPIN

HOW IT DIFFERS FROM ADENOSINE

Adenosine

without the oxygen atom at the 3' carbon
of ribose

= **cordycepin**

3'-deoxyadenosine

- It is notably abundant in *C. militaris*.
[chemical analysis]
- Because of its resemblance to adenosine, it is linked to intracellular targets, nucleic acids, apoptosis and the cell cycle (as cited in Das et al.: Tuli et al., 2013b). [preclinical]

IN PLAIN WORDS

Adenosine is a natural cell molecule involved in energy metabolism and signaling.

Cordycepin is an almost exact copy of it, missing one atom. The cell may “mistake” it for adenosine, and this changes how the cell works. **Apoptosis** is programmed cell death.

CORDYCEPIC ACID

- It was first thought to be an isomer of quinic acid; later it turned out to be crystalline **D-mannitol**. [chemical analysis]
- *C. sinensis* contains 7–29% of it, depending on the growth stage of the fungus.
[chemical analysis]
- It is credited with effects in liver fibrosis, a diuretic effect, an effect on plasma osmotic pressure and free-radical-scavenging properties. [level not stated]

NOTE

Judging by their titles in its reference list, the two papers the review cites here are a general review of liver fibrosis (Guo & Friedman, 2007) and a review of kidney injury from mannitol (Nomani et al., 2014). Neither studied cordyceps.

IN PLAIN WORDS

“Cordycepic acid” is in fact mannitol, a substance from the sugar alcohol group. The list of its “properties” in the review does not rest on experiments with cordyceps.

POLYSACCHARIDES

3–8%

polysaccharides in the
fruiting body

>16,000

molecular weight
associated with
antitumor activity

- The main ones: glucan, mannan, heteroglycan, glycoprotein.
[chemical analysis]
- Only β -(1→3)-glucan, galactosaminoglycan and proteopolysaccharide showed antitumor activity. [level not stated]
- With chemotherapy drugs, “synergism and increased body resistance” (as cited in Das et al.: Yang et al., 2005; Chen et al., 2006).
[animals]

IN PLAIN WORDS

Polysaccharides are long chains of sugars. In fungi they include **beta-glucans**.

Synergism is an enhanced effect when agents act together. Here it was described in mice with tumors, not in humans.

IMMUNE FRACTIONS

- **EPSF** is an exopolysaccharide fraction precipitated with 95% ethanol from the culture liquid of *C. sinensis*. Immunomodulatory and antitumor effects and free-radical scavenging have been described (as cited in Das et al.: Sheng et al., 2011). [preclinical]
- **PSF** is a polysaccharide fraction of *C. sinensis* mycelium. It switches macrophages from the M2 to the M1 type via the NF-κB signaling pathway (as cited in Das et al.: Chen W et al., 2010; 2012). [in vitro]

IN PLAIN WORDS

A **macrophage** is an immune cell that engulfs microbes and cell debris. **M1** macrophages are geared for attack, **M2** for healing and calming inflammation. **NF-κB** is a protein “switch” that turns on inflammation genes.

The M2→M1 switch was shown in cells in a test tube.

COMPOSITION BY PART OF THE FUNGUS

Ergosterol, mg/g



Protein, %



- Ergosterol: as cited in Das et al.: Li et al., 2011. Protein: Hsu et al., 2002.

[chemical analysis]

- Nucleoside content also differs between natural and cultured *C. sinensis*.

[chemical analysis]

IN PLAIN WORDS

The fruiting body contains about 7 times more ergosterol than the mycelium, and twice as much protein as fermenter-grown mycelium. Products made from different parts of the fungus cannot be considered equivalent.

NUCLEOSIDES AND MORE

- Adenine, adenosine, inosine, cytidine, cytosine, guanine, uridine, thymidine, uracil, hypoxanthine and guanosine have been isolated from *C. sinensis*; guanosine is the most abundant. [chemical analysis]
- Nucleosides are named as the main component linked to the medicinal use of *C. sinensis* (as cited in Das et al.: Li et al., 2001b). [level not stated]
- Sterols: ergosterol, its peroxide, sitosterol, campesterol and others. [chemical analysis]
- Unsaturated fatty acids: up to 57.84%. [chemical analysis]
- All essential amino acids, rare cyclic dipeptides, polyamines (spermidine, spermine, putrescine and others). [chemical analysis]

IN PLAIN WORDS

Nucleosides are the building blocks of DNA and RNA and related molecules. **Sterols** are relatives of cholesterol; fungal ergosterol is a precursor of vitamin D2.

EXTRACTION METHODS

METHOD	WHAT IT EXTRACTS · WHAT WAS NOTED
Water	polar compounds: nucleosides, polysaccharides; hot-water yield 25–30%
Alcohols	more nucleosides, polysaccharides, proteins; methanol extract is toxic to cancer cells
Ethyl acetate	low yield; sugars, adenosine, ergosterol, cordycepin; apoptosis of HL60 leukemia cells
Supercritical CO₂	nonpolar compounds, no toxic solvents; inhibition of colon and liver cancer cell growth

All rows [chemical analysis · in vitro]

IN PLAIN WORDS

Each solvent “pulls out” its own set of substances. So a “cordyceps extract” in one study and in another are different mixtures, and the result of one cannot be transferred to the other.

04

SECTION

IMMUNITY

WHAT THIS SECTION COVERS

The main topic of the review. What exactly is claimed, in which models it was obtained, and why the same fungus enhances the immune response in some studies and suppresses it in others.

At the end of the section: everything the review reports about immunity in humans.

IN THIS SECTION

- **WHAT IS CLAIMED**
- **WHERE THE DATA COME FROM**
- **MECHANISM: RECEPTORS**
- **ENHANCEMENT AND SUPPRESSION**
- **HUMAN CELLS**
- **HUMANS**

WHAT IS CLAIMED

Cordyceps, its extracts and compounds have been linked to:

- production of the cytokines IL-1 β , IL-2, IL-6, IL-8, IL-10, IL-12 and TNF- α ; [preclinical]
- enhanced phagocytosis by macrophages and mononuclear cells; [preclinical]
- production of nitric oxide (NO) via the enzyme iNOS; [preclinical]
- triggering of the inflammatory response via the MAPK signaling pathway; [preclinical]
- synergism with interferon- γ in cytokine production. [preclinical]

IN PLAIN WORDS

Cytokines are signaling proteins that immune cells use to communicate. **IL** stands for interleukins, **TNF- α** for tumor necrosis factor, and **interferon- γ** is an alarm signal in infection. **Phagocytosis** is the engulfing of microbes by cells. **NO** is a gas that macrophages use to damage microbes; **iNOS** is the enzyme that produces it. **MAPK** is a chain of proteins that relays a signal into the cell.

WHERE THE DATA COME FROM

QUOTE FROM THE REVIEW

“Most of the information on the effect of Cordyceps on the immune system derives from studies in cancer.”

TABLE 2 OF THE REVIEW

It is titled “Immunostimulatory and related bioactivities of Cordyceps spp.: in vitro and in vivo.” It contains not a single study in humans; human cells appear only in test-tube experiments.

IN PLAIN WORDS

In vivo means an experiment in a living organism, here animals. The immune response to a tumor in a mouse is not the same as the immunity of a healthy person who wants to get sick less often. Transferring one to the other requires separate testing.

MECHANISM: RECEPTORS

Simplified from Figure 2 of the review
[review authors' diagram]

Cordyceps components

polysaccharides, cordycepin and others



TLR

TLR2, 3, 4, 6

CLR

DC-SIGN, MR, MGL,
Dectin

receptors of antigen-presenting cells

MyD88 · TRIF · MAPK · ERK1/2 · NF-κB

signal inside the cell



Th1

inflammation; NLRP3, IL-
1β

Treg / Th2

restraint

IN PLAIN WORDS

Compounds from the fungus are “recognized” by sensors on immune cells. From there the signal can push the immune system either toward inflammation or toward restraining it. The diagram summarizes data from experiments in cells and animals.

THE DIAGRAM EXPLAINED

IN PLAIN WORDS

Antigen-presenting cells are the “scouts” of the immune system: they find foreign material and show it to other cells.

TLRs (Toll-like receptors) and **CLRs** (C-type lectin receptors) are their sensors that recognize molecules of microbes and fungi.

NF-κB is the main intracellular “switch” for inflammation genes.

Th1 is the branch of the immune response that leads to inflammation. **Treg** and **Th2** are branches that restrain it.

- As described in the review, cordyceps components can suppress NF-κB through the brake proteins SOCS and PI3K and degrade some TLRs, supporting the Treg/Th2 response. [preclinical]

TWO SIDES

ENHANCES

Cytokines ↑

IL-1 β , IL-6, TNF- α

Phagocytosis ↑

NK cells ↑

natural killers

RESTRAINS

NO, TNF- α , IL-12 ↓

T-cell proliferation ↓

Immunosuppression

after kidney transplant

QUOTE FROM THE REVIEW

Cordyceps “contains different compounds with the ability to strengthen the response of the immune system and also to control its exacerbated response.”

IN PLAIN WORDS

It is more accurate to call cordyceps not a “stimulant” but an **immunomodulator**: under different conditions and in different extracts the effect goes in different directions.

ENHANCEMENT: ANIMALS

- *C. militaris* polysaccharides (CMP) in mice with cyclophosphamide-suppressed immunity: lymphocyte proliferation and the phagocytic index increased (Wang M et al., 2012). [animals]
- CMP in mice: thymus and spleen indices, IgG levels, white blood cell count, and IFN- γ , TNF- α and IL-1 β mRNA increased (Liu et al., 2016). [animals]
- *C. gunnii* polysaccharides in normal mice, immunocompromised mice and mice bearing H22 tumors “probably” boost the immune response (Zhu et al., 2012b). [animals]
- Oral decoction of *C. sinensis* mycelium in mice: macrophage activation, increased GM-CSF (granulocyte-macrophage colony-stimulating factor) and IL-6 in intestinal Peyer’s patches (Koh et al., 2002). [animals]

IN PLAIN WORDS

Cyclophosphamide is a drug that suppresses immunity; it is used to create a model of immunodeficiency in mice. The **thymus and spleen** are immune organs. **IgG** is the main class of antibodies.

ENHANCEMENT: CELLS

- The polysaccharide CP2-S from *C. militaris*: macrophages show increased phagocytosis, NO production, “respiratory burst” and secretion of IL-1 β and IL-2. [preclinical]
- A low-molecular-weight polysaccharide from *C. militaris* activates splenic lymphocytes and NK cells via MAPK, NF- κ B and TLR2 (Bi et al., 2018). [preclinical]
- *C. sinensis* in U937 cells infected with group A streptococcus: IFN- γ , IL-12 and TNF- α rise, phagocytosis is enhanced (Kuo et al., 2007).
[in vitro]
- *C. sinensis* DNA activates bone marrow dendritic cells via TLR9 (Xiao et al., 2010).
[in vitro]

IN PLAIN WORDS

A **respiratory burst** is a sharp release of reactive oxygen species that a macrophage uses to kill a microbe. **NK cells** are “natural killers” of infected and tumor cells. All these data are responses of cells outside the human body.

INFLUENZA IN MICE

Acidic polysaccharide of *C. militaris*

fungus grown on germinated soybeans; given intranasally



Mice with influenza A

less virus in the lungs and bronchial lavage; higher survival

- The same polysaccharide increased TNF- α , IFN- γ , NO and iNOS expression in macrophages (Ohta et al., 2007).
[animals · in vitro]
- Aqueous extract of *C. guangdongensis* in H9N2 influenza: lung index lower by 22.1% (Yan et al., 2010). [animals]

IN PLAIN WORDS

The **lung index** is a measure of lung damage in animals. The compound was given to mice through the nose. The review provides no data on oral use for influenza in humans.

SUPPRESSION

- Methanol fractions of *C. sinensis* suppressed lymphocyte proliferation, NK cell activity and IL-2 and TNF- α production by human mononuclear cells (Kuo et al., 1996).
[in vitro · human cells]
- Ergosterol peroxide from *C. cicadae* reduced human T-cell proliferation and production of IL-2, IL-4, IL-10 and IFN- γ (Kuo et al., 2003).
[in vitro · human cells]
- A *C. gunnii* polysaccharide suppressed cellular and humoral immunity (Xiao et al., 2004a). [animals · in vitro]
- Aqueous extract of *C. militaris* suppressed NO, TNF- α and IL-6 production by activated macrophages (Jo et al., 2010). [in vitro]

IN PLAIN WORDS

The same fungi in other extracts slow down immune cells. **Humoral** immunity means antibodies; **cellular** immunity means the work of T cells and macrophages.

HUMAN CELLS

Cordycepin and *C. sinensis* (Zhou et al., 2008)

[in vitro · human cells]

RESTING CELLS

↑ **IL-1 β , IL-6, IL-8,
IL-10, TNF- α**

PHA-ACTIVATED

↓ **IL-2, IL-4, IL-5, IL-
12, IFN- γ , TNF- α**

- *C. sinensis* increased the activity of human blood NK cells in a test tube (Xu et al., 1992).

[in vitro · human cells]

- The review sees in this study a “hint” of immunopotentiality in immunodeficient patients. This was not tested in patients.

[review authors' opinion]

IN PLAIN WORDS

PHA (phytohemagglutinin) is a substance used in the laboratory to activate lymphocytes. At rest, the fungal compounds push cells on; when activated, they slow them down. A test-tube experiment does not show whether the compound reaches the cells after oral intake, or at what concentration.

A CONTRADICTION IN THE TABLE

TABLE 2, FIRST ROW

Activity: “**Immunostimulant.**” *C. militaris* polysaccharides, RAW264.7 macrophages.

Results: ↓ **NO**, ↓ **TNF-α**, ↓ IL-1β; in one of the studies in the same row, “↓ NO, TNF-α **and activates** macrophages.”

CONCLUSION

In the section on inflammation, the same review calls a decrease in NO and TNF-α an anti-inflammatory effect. The experimental conditions in this row are not explained, and the label “immunostimulant” does not follow from the results given.

IN PLAIN WORDS

RAW264.7 is a line of mouse macrophages for test-tube experiments. The table calls the effect stimulation, although its numbers show a decrease.

HUMANS: WHAT THERE IS

STUDY WHAT THE REVIEW SAYS

-
- | | |
|-------------------|---|
| Guan, 1992 | patients with chronic renal failure: polysaccharides improved cellular immunity and monocyte-macrophage function
[humans · design not described] |
|-------------------|---|
-
- | | |
|-----------------|---|
| Li, 2009 | after kidney transplantation: a “cost-effective immunosuppressive agent ... without obvious adverse effects”
[humans · design not described] |
|-----------------|---|
-
- | | |
|----------------------|---|
| Lin, Li, 2011 | use of <i>C. sinensis</i> for respiratory infections “by activating the immune response via innate immunity promotion”; the source is a book, and who observed this and how is not stated
[level not stated] |
|----------------------|---|
-

IN PLAIN WORDS

These are studies with patients, but for none of them does the review describe the study design: no comparison groups, no number of participants, no doses.

HUMANS: THE ONLY RCT

JUNG ET AL., 2019

Healthy adults, Korea; CBG-CS-2 mycelium (*Paecilomyces hepiali*). Randomized and double-blind, according to its title in the reference list. [humans · RCT]

- No numerical results are given.
- The review reports that the trial assessed efficacy and safety, but gives no data on adverse effects.

IN PLAIN WORDS

An **RCT** is a randomized controlled trial: participants are assigned to groups at random. The only RCT on immunity in the review is mentioned without a single number.

HUMANS: WHAT IT MEANS

CONCLUSION

The same *C. sinensis* is described in one study as improving immunity in kidney patients and in another as an immunosuppressant after kidney transplantation.

CONCLUSION

The review gives not a single number on the immune effect in humans: no group sizes, doses, duration or effect size.

- About Jung, 2019, the review writes that CBG-CS-2 components enhance NK cell activity and phagocytosis, but does not say whether this was obtained in the human trial.
[level not stated]

IN PLAIN WORDS

The claim that “cordyceps strengthens human immunity” is not supported by this review.

05

SECTION

INFLAMMATION AND TUMORS

WHAT THIS SECTION COVERS

Anti-inflammatory, antioxidant and antitumor effects, plus a short list of “exotic” effects: against microbes, parasites and viruses.

Almost everything here was obtained in cells and animals.

IN THIS SECTION

- **INFLAMMATION: ANIMALS**
- **INFLAMMATION: CELLS**
- **ANTIOXIDANT**
- **TUMORS**
- **OTHER**

INFLAMMATION: ANIMALS

- Ethanol extract of *C. militaris* mycelium reduced carrageenan-induced edema and iNOS expression in macrophages (Won & Park, 2005). [animals · in vitro]
- The peptide cordymin from *C. sinensis* lowered IL-1 β and TNF- α in carrageenan-induced inflammation and reduced the pain response (Qian et al., 2012). [animals]
- Aqueous extract of *C. militaris* in dextran sulfate-induced colitis: less weight loss, diarrhea, bleeding and mucosal damage (Han et al., 2011). [animals]
- Aqueous extract of *C. guangdongensis* in chronic bronchitis caused by cigarette smoke: less bronchial damage (Yan et al., 2014). [animals]

IN PLAIN WORDS

Carrageenan and **dextran sulfate** are substances used to induce inflammation artificially in animals: swelling and inflammation of the bowel. These are models of disease, not the human disease itself.

INFLAMMATION: CELLS

- Cordycepin in LPS-activated macrophages: blocks Akt, I κ B α and p38; reduces TNF- α , COX-2, iNOS and NF- κ B translocation to the nucleus (Kim et al., 2006). [in vitro]
- Cordycepin in BV2 microglial cells dose-dependently reduced NO, prostaglandin E2 and proinflammatory cytokines (Jeong et al., 2010). [in vitro]
- A butanol fraction of *C. bassiana* inhibits the I κ B/NF- κ B pathway, p38 and JNK (Kim T W et al., 2014). [in vitro]
- The CBG-CS-2 strain (*Paecilomyces hepiali*) reduces NO, iNOS and cytokines via NF- κ B and AP-1 (Park et al., 2014). [in vitro]

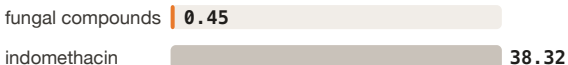
IN PLAIN WORDS

LPS (lipopolysaccharide) is a component of the bacterial wall; it is used to “switch on” inflammation in cells. **COX-2** (cyclooxygenase-2) is an enzyme of inflammation. **Microglia** are the immune cells of the brain. From these data the authors speak of “high potential” in neurodegenerative diseases; this has not been tested in humans.

HUMAN NEUTROPHILS

C. sinensis compounds vs indomethacin, IC₅₀,
μg/mL [in vitro · human cells]

Superoxide anion



Elastase



- C. sinensis extracts suppressed the release of superoxide anion and elastase by neutrophils; five compounds, cordysinins A–E, were responsible. “Most of the compounds” outperformed indomethacin; the chart shows the values given in the review (Yang et al., 2011).

[in vitro · human cells]

IN PLAIN WORDS

IC₅₀ is the concentration at which the effect is inhibited by half: the smaller the number, the stronger the compound in a test tube. It says nothing about potency in the body.

Indomethacin is an anti-inflammatory drug, here the control.

ANTIOXIDANT

- Alcohol and aqueous extracts of cultured *C. sinensis*: minimal effect on superoxide, moderate inhibition of MDA formation (Yamaguchi et al., 2000a). [in vitro]
- Adenosine content is not associated with antioxidant activity; the polysaccharides are active (Li et al., 2001b). [preclinical]
- A *C. sinensis* polysaccharide in tumor-bearing mice increased SOD in the brain, liver and serum and GPx in the liver and brain, and lowered MDA (Chen et al., 2006). [animals]
- *C. militaris* polysaccharides (CMP-1 to CMP-4 and others) scavenged free radicals. [in vitro]

IN PLAIN WORDS

Free radicals are aggressive molecules that damage cells. **SOD** and **GPx** (superoxide dismutase, glutathione peroxidase) are enzymes that neutralize them. **MDA** (malondialdehyde) is a marker of radical damage to fats.

“ANTI-AGING”

- In old mice, *C. sinensis* improved learning and memory, increased SOD, catalase and GPx, and lowered brain monoamine oxidase and MDA in the brain and liver (Wang et al., 2004). [animals]
- In mice with D-galactose–induced “aging,” *C. sinensis* extract improved brain function and antioxidant enzymes (Ji et al., 2009). [animals]
- *C. guangdongensis* extended the mean lifespan of fruit flies (Yan et al., 2011).
[animals]

IN PLAIN WORDS

Aging in mice here means either the animal’s age or a model in which aging is accelerated with the substance D-galactose. Human lifespan was not studied in the review.

TUMORS: CELLS

- Cordycepin inhibits cancer cell proliferation via A3 adenosine receptors, the Wnt pathway, GSK3 β activation and cyclin D1 suppression (Yoshikawa et al., 2004–2008).
[in vitro · animals]
- Via the mTOR and AMPK signaling pathways; via caspases, apoptosis. [in vitro]
- At low concentration it increased the sensitivity of gallbladder cancer cells to gemcitabine and 5-fluorouracil (Wu et al., 2014). [in vitro]
- With 2'-deoxycoformycin, the effect against B16 melanoma cells increased 300-fold (Nakamura et al., 2015). [in vitro]

IN PLAIN WORDS

These are experiments in cancer cell lines. The review stresses that cordycepin acts through pathways “depending upon the cell type.” Gemcitabine and 5-fluorouracil are chemotherapy drugs.

TUMORS: ANIMALS

- C. militaris inhibited the growth of T-cell lymphoma transplanted into mice (Park et al., 2017). [animals]
- Oral aqueous extract of C. sinensis activated Kupffer cells of the liver in rats (Nakamura et al., 1999). [animals]
- Fermented C. sinensis with selenium in cervical cancer reduced oxidative stress (Ji et al., 2014); in whom the study was done is not stated. [level not stated]
- The cultivated fungus was more potent than the natural one against MCF-7, B16, HL-60 and HepG2 cells (Zhang Q et al., 2005).
[in vitro]

POSITION OF THE REVIEW AUTHORS

The anticancer effect “may be more difficult to be elucidated in clinical studies”; more preclinical studies are needed.

[review authors' opinion]

IN PLAIN WORDS

Kupffer cells are the macrophages of the liver. The review cites no studies in people with cancer that describe design and outcome. Section 08 covers a study in which C. sinensis, on the contrary, accelerated prostate cancer growth in mice.

OTHER

Individual compounds from different species

- Cicadapeptins I and II: zones of inhibition of *E. coli* growth of 16 mm. [in vitro]
- Against the malaria parasite *Plasmodium*: IC₅₀ 18 μM; against trypanosomes: IC₅₀ 8.63 μg/mL. [in vitro]
- Cordycommunin against *Mycobacterium tuberculosis*: MIC 15 μM. [in vitro]
- Cordysobin inhibits HIV-1 reverse transcriptase: IC₅₀ 8.2×10^{-3} μM. [in vitro]
- Annulatins are agonists of the cannabinoid receptors CB1 and CB2. [in vitro]
- Cordycepin kills diamondback moth larvae, acting through the digestive tract.

[animals · insect larvae]

IN PLAIN WORDS

MIC is the minimum concentration that inhibits the growth of a microbe. These are compounds isolated from individual species, not effects of taking cordyceps.

06

SECTION

METABOLISM AND ENDURANCE

WHAT THIS SECTION COVERS

Blood sugar, cholesterol, blood pressure, endurance and mood. This is where the review's only placebo-controlled trial with a described result is found: endurance in older adults.

IN THIS SECTION

- **BLOOD SUGAR: ROUTE OF ADMINISTRATION**
- **BLOOD SUGAR: ANIMALS**
- **LIPIDS AND BLOOD VESSELS**
- **ENDURANCE: HUMANS**
- **ENDURANCE: ANIMALS**
- **MOOD**

BLOOD SUGAR: ROUTE OF ADMINISTRATION

Polysaccharide of *C. sinensis* mycelium, mice (Kiho et al., 1993) [animals]

INTRAPERITONEAL

Plasma glucose ↓

in healthy mice and mice with STZ-induced diabetes

ORAL

“Slight” lowering

same conditions

- The polysaccharide CS-F30 increased the activity of glucokinase, hexokinase and glucose-6-phosphate dehydrogenase, accelerating glucose metabolism (Kiho et al., 1996). [animals]

IN PLAIN WORDS

STZ (streptozotocin) is a substance that destroys pancreatic cells; it is used to create diabetes in animals. An injection into the abdominal cavity had a clear effect, while oral intake had a weak one. People take cordyceps by mouth.

BLOOD SUGAR: ANIMALS

- CordyMax Cs-4 (a mycelial fermentation product of *C. sinensis*): in rats, lower basal glucose and insulin, higher insulin sensitivity (Balon et al., 2002; Zhao et al., 2002).
[animals]
- Rats with nicotinamide- and STZ-induced diabetes: less thirst, hyperglycemia and weight loss (Lo et al., 2004). [animals]
- *C. sinensis* extract supported β -cell survival in mice with type 2 diabetes (Kan et al., 2012). [animals]
- Aqueous extract of *C. militaris* enhanced HNF-1 α and GLUT2 protein and glucose uptake by liver cells. [in vitro]
- *C. militaris* cerebrosides inhibited the enzyme PTP1B (Sun et al., 2019). [in vitro]

IN PLAIN WORDS

β cells produce insulin. **GLUT2** is the “door” for glucose in liver cells. **PTP1B** is an enzyme that weakens the insulin signal. The review cites no trials in people with diabetes.

LIPIDS AND BLOOD VESSELS

- A protein component of *C. sinensis* lowered mean arterial pressure in rats and relaxed blood vessels via NO (Chiou et al., 2000).
[animals]
- Aqueous extract of the cultivated fungus in mice with atherosclerosis: less cholesterol deposition in the aorta (Yamaguchi et al., 2000b). [animals]
- Cordycepin increased lipoprotein lipase and hepatic lipase activity “with no toxicity” (Gao et al., 2011). [animals]
- A *C. militaris* polysaccharide lowered blood and liver lipids (Wang L et al., 2015). [animals]

POSITION OF THE REVIEW AUTHORS

As a first step, clinical pilot studies with small numbers of participants are needed to test the hypoglycemic, hypocholesterolemic and hypotensive effects.

[review authors' opinion]

IN PLAIN WORDS

Lipases are enzymes that break down fats. The authors themselves admit that this has yet to be tested in humans.

ENDURANCE: HUMANS

Cs-4 (C. sinensis) · 12 weeks

healthy older adults; double-blind, placebo-controlled
(Chen S et al., 2010)



Higher metabolic and ventilatory thresholds

[humans · placebo-controlled] the number of participants, dose and effect size are not given in the review

- Xiao et al., 1999: according to its title in the reference list, increased aerobic capacity in healthy older adults on Cs-4 (an abstract in a supplement to Med Sci Sports Exerc); in the text of the review the study is mentioned only in connection with the “anaerobic threshold.” [humans · design not described]
- The fungus’s reputation in sports: in 1993 world athletics champions spoke of a diet that included cordyceps (Kashyap et al., 2016). This is a story, not a study.
[level not stated]

IN PLAIN WORDS

According to the review, higher thresholds indicate better aerobic performance without fatigue in older people. This is the review’s strongest result by design among those with a described outcome.

ENDURANCE: ANIMALS

- CordyMax Cs-4 increased ATP levels in mouse liver (Dai et al., 2001). [animals]
- *C. sinensis* mycelium polysaccharides: mice swam longer to exhaustion, had more glycogen in the liver and muscles, and less lactate and urea in the blood (Li & Li, 2009; Yan et al., 2012). [animals]
- In rats, activation of metabolic regulators in muscle: AMPK, PGC-1, PPAR, the NRF-2 pathway (Kumar et al., 2011). [animals]
- *C. militaris* acts via the AMPK and AKT/mTOR pathways (Song et al., 2015). [animals]

IN PLAIN WORDS

Glycogen is the store of glucose in the liver and muscles. **Lactate** builds up in muscles with fatigue. **AMPK** is the cell's energy sensor. Swimming to exhaustion is a model of fatigue in mice.

MOOD

- A supercritical extract of *C. sinensis* in the mouse tail suspension test produced an antidepressant-like effect via the adrenergic and dopaminergic systems, but not the serotonergic system (Nishizawa et al., 2007).

[animals]

- Natural and cultured *C. sinensis* mycelium improved motor coordination in mice and showed “antidepressant-like activity” (Singh et al., 2014).

[animals]

- Vanadium-enriched *C. sinensis* in diabetic rats: lower glucose, higher insulin, less immobility in water (Guo et al., 2011).

[animals]

IN PLAIN WORDS

Tail suspension and immobility in water are behavioral tests in rodents. These are models, not a diagnosis of depression; mood in humans was not studied in the review. The review justifies the topic by saying that fatigue is “closely related” to depression.

07

SECTION

HORMONES AND KIDNEYS

WHAT THIS SECTION COVERS

Sex hormones and sperm: where the nickname “Himalayan Viagra” comes from and what lies behind it. Then the kidneys: the only topic on which the review cites several studies involving patients.

IN THIS SECTION

- **“HIMALAYAN VIAGRA”**
- **STEROIDOGENESIS**
- **OTHER HORMONES**
- **CONFLICTING DATA**
- **KIDNEYS: HUMANS**
- **KIDNEYS: ANIMALS**

“HIMALAYAN VIAGRA”

- That is what cordyceps is called in popular literature (as cited in Das et al.: Kashyap et al., 2016). [traditional use]
- Long-term cordycepin counteracted the decline of testicular function in middle-aged rats (Sohn et al., 2012). [animals]
- *C. militaris* mycelium improved sperm motility and morphology in subfertile boars and in rats (Lin et al., 2007; Chang et al., 2008). [animals]
- *C. militaris* protected the testes from bisphenol A and eased the drop in blood testosterone and LH (Wang et al., 2016). [animals]
- Cordycepin increases epididymal weight, sperm motility and the number of mature sperm (Kashyap et al., 2016). [level not stated]

IN PLAIN WORDS

LH (luteinizing hormone) is a pituitary hormone that triggers testosterone production. **Bisphenol A** is a plasticizer. The review gives no data on potency or fertility in humans.

STEROIDOGENESIS

Cordycepin, mouse Leydig cells (Leu et al., 2011)
[in vitro · animals]

Cordycepin



Adenosine receptors



cAMP → protein kinase A → StAR protein



Testosterone ↑

in cells and in mouse plasma

- In human granulosa cells, *C. sinensis* increased estradiol production via StAR and aromatase (Huang B M et al., 2004).

[in vitro · human cells]

- Hence the conclusion that it is “a brilliant candidate for increasing the fecundity of women.” Not tested in women.

[review authors' opinion]

IN PLAIN WORDS

Steroidogenesis is the synthesis of steroid hormones from cholesterol. **Leydig cells** produce testosterone in the testis, **granulosa cells** produce estradiol in the ovary. **StAR** is the protein that starts this synthesis.

OTHER HORMONES

- C. sinensis and its fractions increased plasma corticosterone in immature and mature mice (Leu et al., 2005). [animals]
- According to the review, cordyceps modulates the release of sex hormones: testosterone, estrogen and progesterone (Sohn et al., 2012). [level not stated]
- The species C. ophioglossoides is credited with “estrogenic” properties (section 02). [traditional use]

CONCLUSION

The signals concern both stress hormones and sex hormones. The review gives no measurements of these hormones in humans.

IN PLAIN WORDS

Corticosterone is the main stress hormone in rodents, the counterpart of human cortisol. If you have a hormone-dependent condition, discuss taking cordyceps with your physician.

CONFLICTING DATA

C. sinensis, mouse Leydig cells [in vitro]

TUMOR CELLS

Steroidogenesis ↑

Huang 2000; Chen 2005

NORMAL CELLS

Testosterone ↑

Huang 2001

but

Response to hCG ↓

all fractions; Wong 2007,
Hsu 2003b

CONCLUSION

Even in normal cells of a single species the results diverge. The review explains the difference between normal and tumor cells by different receptor subtypes, citing studies on corticotropin-releasing hormone rather than on cordyceps (Huang et al., 1995; 1997).

IN PLAIN WORDS

hCG (human chorionic gonadotropin) is the hormone used in these experiments to stimulate testosterone production. In some experiments the fungus raised testosterone; in others it lowered testosterone production in response to hCG.

KIDNEYS: HUMANS

- Kidney transplant patients (per the study title), long-term C. sinensis: less blood and protein in the urine, tissue restoration on histological analysis (Ding et al., 2011).
[humans · design not described]
- Combination with cyclosporin A in kidney transplantation; the benefit is that high doses of cyclosporin damage the kidneys (Ding et al., 2009). [level not stated]
- Older patients (per the study title): kidney protection from aminoglycoside antibiotics (Bao et al., 1994).
[humans · design not described]
- Chronic renal failure: improved kidney function (Guan et al., 1992).
[humans · design not described]

IN PLAIN WORDS

This is the most “human” topic in the review, but for none of the studies is it stated whether there was a control group, how many patients there were or what doses were used. The second reference on aminoglycosides (Heggors et al., 1996), judging by its title, is about the effect of aloe on wound healing.

KIDNEYS: ANIMALS

- *C. sinensis* protected podocytes in rats with diabetic nephropathy; per the study title, in combination with *Tripterygium wilfordii* polyglycosides (Hao et al., 2014). [animals]
- CmNo1 (fruiting body and mycelium of *C. militaris*) preserved kidney function in mice with type 2 diabetes (Yu et al., 2016).
[animals]
- *C. sobolifera* mycelium glycoproteins in cyclosporine-induced tubular injury in rats: less apoptosis, more magnesium reabsorption channels (Chyau et al., 2014).
[animals]
- Ergosterol peroxide from *C. cicadae* blocked TGF- β 1-induced activation of kidney fibroblasts (Zhu R et al., 2014). [in vitro]

IN PLAIN WORDS

Podocytes are the cells of the kidney filter. **Fibroblasts**, when activated, form scar tissue. The review links kidney protection to an increase in 17-hydroxycorticosteroids, 17-ketosteroids, SOD and free-radical scavenging, without saying in whom this was shown.

08

SECTION

SAFETY

WHAT THIS SECTION COVERS

What the review says about harm and about toxicity to cells, about immunosuppressant compounds in the fungi, about combination with drugs, and about a study in which cordyceps accelerated tumor growth in mice.

IN THIS SECTION

- **WHAT IS SAID ABOUT HARM**
- **CYTOTOXICITY**
- **THE “TOXIC EFFECTS” SECTION**
- **IMMUNOSUPPRESSANTS IN THE FUNGI**
- **COMBINATION WITH DRUGS**
- **BLOOD, SUGAR, PRESSURE**
- **PROSTATE CANCER IN MICE**
- **PROSTATE: CELL DATA**

WHAT IS SAID ABOUT HARM

- “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.” [review authors’ opinion]
- After kidney transplantation, “without obvious adverse effects” (Li et al., 2009).
[humans · design not described]
- The only RCT (Jung et al., 2019) also assessed safety, but the review gives no data on adverse effects. [humans · RCT]
- “New toxicological studies are needed to ensure their safety.” [review authors’ opinion]

CONCLUSION

“Not reported” does not mean “safe.” The review contains no frequencies of adverse effects, doses or durations of use in humans.

IN PLAIN WORDS

If harm is not mentioned, that does not mean it was looked for and not found. The review does not say how adverse effects were monitored in any of the human studies.

CYTOTOXICITY

Table 2 of the review, “Cytotoxicity” category

- Methanol extract of *C. bifusispora* killed CHO cells: cell death ratio 4.14 ± 0.25 at 4,000 $\mu\text{g/mL}$ [in vitro]; LD50 > 8.0 g/kg (Lu et al., 2013) [level not stated]
- Rugulosin and skyrin from *C. formosana* in CHO cells: LD50 18.3 ± 0.2 and 103.7 ± 5.9 $\mu\text{g/mL}$ (Lu et al., 2014). [in vitro]
- Cytochalasin from *C. taii* in 95-D, A-549 and HL-7702 cells: IC50 3.67–4.04 μM (Li et al., 2015). [in vitro]
- In Table 1, cordyheptapeptide A is also toxic to Vero cells (Isaka et al., 2007b). [in vitro]

IN PLAIN WORDS

Cytotoxicity is the ability to kill cells. **CHO**, **Vero**, **HL-7702** are cell lines of non-tumor origin: from Chinese hamster ovary, monkey kidney and human liver. **LD50** is the dose that kills half of the test subjects; LD50 in g/kg characterizes only acute poisoning in animals.

THE “TOXIC EFFECTS” SECTION

C. sinensis in a polypropylene bag



**Polycyclic aromatic hydrocarbons of the
fungus react with the plastic**



By-products harm the fungus itself

it must be grown in glass or metal

- These compounds are volatile and are lost on drying; strains have been bred that produce considerably less of them (Holliday et al., 2004). [chemical analysis]

CONCLUSION

The only section of the review devoted to toxicity (“Toxic effects of *Cordyceps* spp.”) describes harm to the fungal culture, not to humans.

IN PLAIN WORDS

This section does not answer the question “is cordyceps harmful to humans.”

Polypropylene is the plastic used to make growing bags.

IMMUNOSUPPRESSANTS

- Cyclosporin has been found in the species *Cordyceps subsessilis* (Segelken, 1996).
[chemical analysis]
- Immunosuppressants have also been isolated from the closely related species *Isaria sinclairii* (Mizuno, 1999).
[chemical analysis]
- A *C. gunnii* polysaccharide and methanol fractions of *C. sinensis* suppress the immune response (section 04). [preclinical]
- *C. sinensis* has been used as a “cost-effective immunosuppressive agent” after kidney transplantation (Li et al., 2009).
[humans • design not described]

IN PLAIN WORDS

Cyclosporin is a drug that suppresses immunity; it is prescribed after organ transplantation. If you take immunosuppressants or have a transplanted organ, discuss taking cordyceps with your treating physician: the review describes its effect on immunosuppression.

COMBINATION WITH DRUGS

- *C. sinensis* together with cyclosporin A in kidney transplantation (Ding et al., 2009).
[level not stated]
- Cordycepin increased the sensitivity of cancer cells to gemcitabine and 5-fluorouracil. [in vitro]
- With 2'-deoxycytosine, the effect of cordycepin increased 300-fold. [in vitro]
- Polysaccharides with chemotherapy drugs: “synergism.” [animals]

CONCLUSION

The review gives no data on drug interactions in humans. But everything listed is a signal that the fungus's components may alter how drugs work.

IN PLAIN WORDS

If you are receiving chemotherapy or immunosuppressants, discuss taking cordyceps with your treating physician in advance.

BLOOD, SUGAR, PRESSURE

- Among the proposed applications of cordyceps, the review lists anti-thrombotic and anticoagulant effects (as cited in Das et al.: Qian et al., 2012; Liu Y et al., 2015).
[level not stated]
- Lowering of blood sugar in mice and rats (section 06). [animals]
- Lowering of mean arterial pressure in rats (section 06). [animals]

CONCLUSION

If such effects exist in humans, they may add to the action of drugs with the same purpose. The review gives no data on this in humans.

IN PLAIN WORDS

If you take blood thinners, glucose-lowering or blood pressure-lowering drugs, discuss taking cordyceps with your physician: such combinations in humans were not studied in the review.

PROSTATE CANCER IN MICE

Ma et al., 2018 [animals]

C. sinensis



Testosterone ↑ · androgen receptor ↑



Growth of prostate cancer cells in mice ↑

IN PLAIN WORDS

Men with prostate cancer, or with suspected prostate cancer, should discuss taking cordyceps with their physician.

PROSTATE: CELL DATA

- In mouse Leydig tumor cells, cordycepin increased progesterone production, “activate[d] AR” and at the same time induced apoptosis (Pan et al., 2011). The review does not spell out AR, and a paragraph earlier it discusses adenosine receptors. [in vitro]
- In LNCaP human prostate cancer cells, apoptosis and autophagy have been described (Lee et al., 2014).

[in vitro · human cells]

CONCLUSION

The data contradict each other: in mice *C. sinensis* accelerated prostate cancer growth, while in cells the death of tumor cells is described. The review itself notes that cordycepin’s pathways of action depend on the cell type.

IN PLAIN WORDS

Apoptosis is programmed cell death; **autophagy** is the cell’s recycling of its own parts. Cell experiments do not show what will happen when a person takes the fungus.

09

SECTION

SUMMARY

WHAT THIS SECTION COVERS

An overview: the level of evidence for each effect, what the review shows and does not show, its weak points, and what follows from it in practice.

IN THIS SECTION

- EVIDENCE MAP
- WHAT IS KNOWN
- WHAT THE REVIEW DOES NOT SHOW
- WEAK POINTS OF THE REVIEW
- WHAT THE AUTHORS PROPOSE
- WHAT FOLLOWS FROM THIS

EVIDENCE MAP

	cells	ani- mals	humans, design?	RCT, placebo
Immunity	●	●	●	●
Endurance	○	●	●	●
Kidneys	●	●	●	○
Blood sugar	●	●	○	○
Lipids, blood pressure	●	●	○	○
Inflammation	●	●	○	○
Antioxidant	●	●	○	○
Tumors	●	●	○	○
Sex hormones	●	●	○	○
Influenza	●	●	○	○
Mood	○	●	○	○

● — the review includes at least one study at this level; ○ — none. “Humans, design?” — studies with patients that do not describe the study design. Human cells are counted under “cells.”

IN PLAIN WORDS

The right-hand columns are almost empty. The two orange dots in the “RCT, placebo” column are one study on immunity with no numbers and one on endurance with no effect size.

WHAT IS KNOWN

- Cordyceps comprises hundreds of species; composition depends on the species, the part of the fungus, the way it is grown and the extraction method. [chemical analysis]
- In cells and animals, fungal components alter cytokine production, phagocytosis and nitric oxide, both toward enhancement and toward suppression. [preclinical]
- In animals, effects on blood sugar, lipids, blood pressure, endurance, the kidneys and sex hormones have been described. [animals]
- In humans: one placebo-controlled trial (endurance in older adults), one RCT (immunity, no numbers), several kidney studies without a described design.
[humans · mixed designs]

IN PLAIN WORDS

The review shows well that the fungus contains many biologically active compounds and that they act in the laboratory. It shows almost nothing about how this works in humans.

WHAT THE REVIEW DOES NOT SHOW

- that oral intake strengthens the immunity of a healthy person or reduces the number of infections;
- what dose and duration of intake work in humans;
- how large the effect is in humans: not a single number;
- which species, which part of the fungus and which extract produce the described effects;
- how safe long-term use is;
- whether cordyceps treats cancer, diabetes or kidney disease in humans.

IMPORTANT

“Not shown” does not mean “does not work.” It means this review does not answer the question.

IN PLAIN WORDS

The review gives no grounds either for prescribing cordyceps or for claiming that it is useless.

WEAK POINTS OF THE REVIEW

- The methods do not describe how studies were selected and how their quality was assessed (section 01).
- Table 2 labels as “Immunostimulant” a row in which NO and TNF- α decrease (section 04).
- References do not always match the claim. The paper cited for a cordyceps polysaccharide (Gu et al., 2003) is, in the reference list, about withanolides from the plant *Physalis*; the one cited for kidney protection (Hegggers et al., 1996) is about aloe and wound healing.
- Conflicting results (immunity, testosterone) are listed but not analyzed.
- The “Toxic effects” section is about the fungal culture, not about humans.
- Only articles in English.

IN PLAIN WORDS

The review is useful as a catalog of research directions, but its claims need to be checked against the original sources.

WHAT THE AUTHORS PROPOSE

“Conclusions and Prospects” section
[review authors’ opinion]

Chemistry

identify still-unknown molecules



Preclinical

which compounds are more active and how they enhance
each other



New formulations

nano drugs with cordycepin



Toxicology

confirm safety



Clinical pilot studies

small groups: sugar, cholesterol, blood pressure

IN PLAIN WORDS

The authors call clinical pilot studies “the first step” of testing in humans: such data are still almost nonexistent. The anticancer effect, in their words, is even harder to test in humans.

WHAT FOLLOWS FROM THIS

CONCLUSION

The review is a map of hypotheses, not proof of benefit. It cannot be used to choose a species, form or dose of cordyceps for humans.

- “Strengthens immunity” is a preclinical claim in the review; in humans it is not supported by numbers.
- Cordyceps can both enhance and suppress the immune response.
- Discuss with your physician before taking it: after organ transplantation and when taking immunosuppressants, during chemotherapy, with prostate cancer, and when taking blood thinners, glucose-lowering or blood pressure-lowering drugs.

IN PLAIN WORDS

If you already take cordyceps or are considering it, tell your treating physician, especially if you have any of the conditions listed.

GLOSSARY: RESEARCH

In vitro: an experiment outside the body, on cells in a test tube or dish.

In vivo: an experiment in a living organism; in the review, animals.

Preclinical: studies in cells and animals before trials in humans.

RCT: randomized controlled trial; participants are assigned to groups at random.

Double-blind: neither the participant nor the investigator knows who receives the drug and who the placebo.

Placebo: a dummy pill that looks like the drug.

Meta-analysis: mathematical pooling of the results of several studies.

IC50, EC50, ED50: the concentration or dose that produces half of the maximum effect.

LD50: the dose that kills half of the test animals.

MIC: minimum inhibitory concentration, the lowest concentration that inhibits microbial growth.

GLOSSARY: IMMUNITY

Cytokines: signaling proteins of immune cells; **IL**, interleukins; **TNF- α** , tumor necrosis factor; **IFN- γ** , interferon gamma; **GM-CSF**, granulocyte-macrophage colony-stimulating factor.

Macrophage: a cell that engulfs microbes; **M1** is geared for attack, **M2** for healing.

Phagocytosis: engulfing of microbes and particles by a cell.

NK cells: “natural killers” of infected and tumor cells.

Th1: the branch of the response that leads to inflammation; **Th2**, **Treg:** restraining branches.

TLR, CLR: sensor receptors that recognize molecules of microbes and fungi.

NF- κ B, MAPK, ERK, JNK, p38, Akt: proteins that relay signals inside the cell.

NO, iNOS: nitric oxide and the enzyme that produces it.

LPS, PHA: substances used in experiments to activate immune cells.

IgG: the main class of antibodies.

Immunosuppressant: an agent that suppresses immunity.

GLOSSARY: CELL SIGNALS

MyD88, TRIF: adaptor proteins that relay the signal from TLRs into the cell.

DC-SIGN, MR, MGL, Dectin: receptors of the CLR group; **MR**, mannose receptor; **MGL**, macrophage galactose-type lectin.

NLRP3: a protein of the inflammasome, a complex that together with caspase-1 triggers inflammation.

AP-1: a factor that switches on inflammation genes; **IκBα:** a protein that keeps NF-κB outside the nucleus.

mTOR, Wnt, GSK3β: signaling pathways and enzymes that control cell growth and division.

HNF-1α: hepatocyte nuclear factor 1α. **PGC-1, PPAR:** regulators of energy metabolism; **NRF-2** switches on antioxidant defense.

cAMP: cyclic adenosine monophosphate, a messenger of hormonal signals inside the cell. **TGF-β1:** transforming growth factor β1, a signal for scarring.

mRNA: messenger RNA, a copy of a gene from which a protein is built. **U937:** a line of human monocyte-like cells.

GLOSSARY: FUNGUS AND METABOLISM

Mycelium: the network of fungal threads; **fruiting body:** the above-ground part of the fungus.

Cordycepin: 3'-deoxyadenosine; **cordycepic acid:** D-mannitol.

Polysaccharides, β -glucans: long chains of sugars.

Ergosterol: a fungal sterol, precursor of vitamin D2.

Free radicals: aggressive molecules; **SOD, GPx, catalase:** enzymes that neutralize them; **MDA:** a marker of damage to fats.

STZ, alloxan: substances used to induce diabetes in animals.

ATP: the energy-storage molecule; **glycogen:** the store of glucose; **AMPK:** the cell's energy sensor.

Steroidogenesis: synthesis of steroid hormones; **StAR:** the protein that starts it; **LH, hCG:** hormones that stimulate testosterone production.

TCM: traditional Chinese medicine. **FDA:** US Food and Drug Administration.

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SOURCE

Das G, Shin H-S, Leyva-Gómez G, Prado-Audelo MLD, Cortes H, Singh YD, Panda MK, Mishra AP, Nigam M, Saklani S, Chaturi PK, Martorell M, Cruz-Martins N, Sharma V, Garg N, Sharma R, Patra JK. Cordyceps spp.: A Review on Its Immune-Stimulatory and Other Biological Potentials. **Front Pharmacol**. 2021;11:602364. doi:10.3389/fphar.2020.602364

HOW TO READ THE REFERENCES

This guide is based on this review alone. Other studies are named as they appear in its reference list: “as cited in Das et al.” We have not read those studies ourselves and present their content as the review describes it. A **doi** is the article’s permanent address at doi.org. Open access, CC BY license.

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IN PLAIN WORDS

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IN PLAIN WORDS

Judging by their titles, these papers are not about what the review uses them to support. This may be a citation formatting error.

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board-certified endocrinologist (highest category)



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