

CORDYCEPS · HEART RHYTHM

CORDYCEPS AND ARRHYTHMIAS

A review of Wang et al. · Frontiers in Pharmacology
· 2022

Meta-analysis of 19 Chinese RCTs and a
computational search for mechanisms

What the article shows, at what level of evidence, and
what it does not show. For patients and physicians.

SECTIONS

01 ARTICLE

02 METHODS

03 EFFICACY

04 SAFETY

05 IN SILICO MECHANISMS

06 AUTHORS' EXPLANATIONS

07 SUMMARY

19

RCTs, all
from China

1,805

patients

7

candidate
genes,
computation
only

HOW THIS DOCUMENT WORKS

IN PLAIN WORDS

The document moves from the article itself to its methods, results, mechanisms, and bottom line. If you only need the conclusion, go to section 07.

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

- **Cream boxes** — the reviewer's assessment, not the text of the article.
- **A label in square brackets** after a statement shows the level of evidence. The key is on the next two pages.
- **Green** — favorable; **red** — a risk, limitation, or contradiction.
- Numbers, drug names, and results are given as in the article; decimals are written with a point.
- The only source is the Wang et al., 2022 article and the works it cites. Abbreviations are spelled out at first mention and in the glossary.

LABELS · HUMANS

LABEL	MEANING
[meta-analysis of RCTs]	several randomized trials in humans pooled together
[N RCTs]	the conclusion rests on N trials in humans (one to three)
[RCTs, no numbers]	trials in humans, but the result is given in words, without figures; “partly” — figures are not available for all
[traditional use]	used in practice; not proven in the article

IN PLAIN WORDS

These labels refer to data in humans. The higher the label in the list, the more reliable the data. “Traditional use” only means that the remedy is used; the article does not prove that it works.

LABELS · NON-HUMAN

LABEL	MEANING
[animals]	experiments in rats, mice, and other animals
[experiment]	an experiment whose model is not specified in the article
[tissue], [in vitro]	tissue samples, cells outside the body
[in silico]	computer calculation based on databases, without living cells
[hypothesis]	the authors' assumption, not tested in the article
[not cordyceps]	data on another substance or on the pathway in general
[label; label]	data of two levels in one study

IN PLAIN WORDS

These labels refer to data that do not come from trials in humans. Calculations and animal experiments suggest where to look, but do not answer whether the remedy will help a person.

01

SECTION

ARTICLE

WHAT THIS SECTION COVERS

Who published the work and where, what question it answers, and which product was studied.

The article has two independent parts: a review of clinical trials and a computational search for mechanisms. Their conclusions must be judged differently.

IN THIS SECTION

- **ARTICLE PROFILE**
- **FUNDING**
- **THE AUTHORS' QUESTION**
- **STARTING POINT**
- **NINGXINBAO CAPSULES**
- **TWO TYPES OF ARRHYTHMIA**
- **STUDY DESIGN**

ARTICLE PROFILE

Title Bidirectional regulatory effects of Cordyceps on arrhythmia: Clinical evaluations and network pharmacology

Journal Frontiers in Pharmacology, vol. 13, article 948173

Authors Lijuan Wang, Helin Sun, Meina Yang, Yulin Xu, Linlin Hou, Haomiao Yu, Xueyin Wang, Zhongwen Zhang, Jinxiang Han

Dates received May 19, 2022 · accepted July 18, 2022 · published August 19, 2022

DOI 10.3389/fphar.2022.948173

IN PLAIN WORDS

The authors work at universities and hospitals in Shandong Province (China). The article is open access under a CC BY license: anyone can read it.

DOI — the article's permanent digital address, which can be used to find it.

FUNDING

- Natural Science Foundation of China (82000788, 82004212).
- Chinese Postdoctoral Science Foundation (2021M702040).
- Key Research & Development Plan of Shandong Province (2018GSF118176, 2019GSF108168) and the Natural Science Foundation of Shandong Province (ZR2016HQ26).
- Guangdong Basic and Applied Basic Research Foundation (2019A1515110023).
- Bethune-Merck's Diabetes Research Foundation (B-0307-H-20200302, G2016014).
- Conflict of interest: the authors declared no commercial or financial relationships.

IN PLAIN WORDS

The work was funded by Chinese government science foundations and the Bethune-Merck Diabetes Research Foundation. The capsule manufacturer is not listed among the sponsors.

THE AUTHORS' QUESTION

- **Aim:** to assess the efficacy and safety of cordyceps in arrhythmias and to identify possible mechanisms.
- **Rationale:** according to the authors, antiarrhythmic drugs have not been proven to reduce mortality and cause digestive and cardiovascular side effects (cited from Hao et al., 2015).

IN PLAIN WORDS

The point about antiarrhythmic drugs is the authors' rationale, with a reference to a review on Chinese medicine. It is no reason to stop prescribed drugs: in all trials, the capsules were added to them.

STARTING POINT

- **Starting point:** the authors themselves write that there is no credible scientific evidence supporting the use of cordyceps to treat and prevent arrhythmias. The available RCTs are small and give inconsistent results, so, according to the authors, it is difficult to draw reliable conclusions about either the benefits or the possible side effects.

IN PLAIN WORDS

RCT — randomized controlled trial: participants are assigned to groups by lot so that the comparison is fair.

The work begins by admitting that there is no evidence base and tries to assemble one from existing small trials.

WHAT WAS STUDIED

Ningxinbao

Capsules, a standardized traditional Chinese medicine product

- Composition per the article: dry mycelium powder of cordyceps grown by liquid submerged fermentation.
- Widely used for arrhythmias, including atrioventricular block, refractory bradycardia, and conduction block. [traditional use]
- Dose in the RCTs: 0.5 g 3 times a day; in one RCT, 0.25 g 3 times a day.

IN PLAIN WORDS

What was studied was not the wild fungus or any supplement “with cordyceps,” but specific capsules made from fungal threads (mycelium) grown in a liquid medium. The fungal species and strain are not named in the article.

TWO TYPES OF ARRHYTHMIA

SLOW RHYTHM

Bradyarrhythmias

HR below 60 per minute



**Sinus bradycardia,
sinoatrial and AV
block, SSS**

FAST RHYTHM

Tachyarrhythmias

HR above 100 per minute



**Premature beats,
atrial flutter and
fibrillation**

IN PLAIN WORDS

HR — heart rate. **AV block** — a delay of the signal between the atria and the ventricles (AV — atrioventricular). **SSS** — sick sinus syndrome, a weak sinus node, the heart's “pacemaker.” **Premature beat** (extrasystole) — an extra, out-of-turn contraction.

“Bidirectional regulatory effects” in the title is the claim that one remedy helps with both slow and fast rhythms.

STUDY DESIGN

PART 1 · HUMANS

Meta-analysis

19 RCTs, 1,805 patients



Efficacy

share of “responders,”
HR



Safety

adverse events

PART 2 · CALCULATION

Network pharmacology

compound and gene
databases



Molecular docking

10 “compound —
protein” pairs



Mechanism scheme

hypothesis

IN PLAIN WORDS

The first part answers the question “what happened to the patients,” the second — “where the remedy could theoretically act.” The second does not confirm the first: a mechanism on a computer $\neq$ a clinical effect.

02

SECTION

METHODS

WHAT THIS SECTION COVERS

How the authors searched for and selected trials and how they pooled their numbers.

Also here: how to read RR, SMD, the confidence interval, and I^2 . These notations appear in all of the following sections.

IN THIS SECTION

- **SEARCH**
- **SELECTION CRITERIA**
- **COMPARISON DESIGN**
- **STATISTICS**
- **HOW TO READ THE NUMBERS**

TRIAL SEARCH

- **Databases:** PubMed and four Chinese ones — CNKI, Wanfang, VIP, SinoMed.
- In addition: reviews, editorials, clinicaltrials.gov, clinicaltrialresults.org, theheart.org, and reference lists of the retrieved studies.
- **Period:** from the earliest publications to December 30, 2021.
- **Query:** “Ningxinbao” or “Cordyceps” + arrhythmia terms + “randomized” + “blind.”
- Search and selection — by two authors, independently and in duplicate; the same two authors extracted the data and assessed quality (independence is not stated for this step).

IN PLAIN WORDS

Four of the five databases are Chinese; all 19 included trials were published in Chinese. The word “blind” in the query is an attempt to select trials in which participants or physicians did not know who was receiving what.

WHO WAS INCLUDED

INCLUSION CRITERIA

- Arrhythmia diagnosed according to the relevant guidelines.
- Randomization: Ningxinbao + routine therapy vs. routine therapy alone.
- At least 10 people in each group.
- Follow-up of at least 2 weeks.
- Quantitative data available: surrogate endpoints, cardiovascular events, or adverse events.

IN PLAIN WORDS

A surrogate endpoint is a measure that changes before the outcome (pulse, a lab test, an “efficacy rating”). It is easier to measure but is not the same as what matters to the patient: survival, stroke, hospitalization.

WHO WAS EXCLUDED

EXCLUSION CRITERIA

- Non-randomized or non-blinded trials.
- No definite diagnosis.
- Different traditional Chinese medicine (TCM) remedies compared with each other.
- Only symptom changes, without objective laboratory measurements.
- Low methodological quality: Jadad score below 2.

IN PLAIN WORDS

The Jadad scale is a short rating of RCT quality: how randomization was done, whether there was “blinding,” and whether dropouts were described. The higher the score, the more rigorous the trial. The included trials scored 3 or 4.

COMPARISON DESIGN

Patients with arrhythmia



Randomization



**Ningxinbao +
routine therapy**

918 people

**Routine therapy
only**

887 people

IN PLAIN WORDS

This is an “add-on” design: both groups received the same treatment, and one also got the capsules. It answers the question “is there a benefit from adding them to treatment,” but not “can cordyceps replace medications.”

The introduction mentions comparison with placebo, but under the inclusion criteria the control is routine therapy only. Whether the control group received a placebo is not described in the article.

STATISTICS

- RevMan 5.3.5 software (Cochrane Collaboration).
- **Yes/no outcomes:** RR in the abstract and tables, OR in the methods section.
- **Continuous outcomes:** SMD in the abstract and tables, MD in the methods section.
- **Heterogeneity:** chi-square test and I^2 .
- **Publication bias:** the fail-safe number method is stated; its result is not reported in the article.

IN PLAIN WORDS

RR — relative risk, **OR** — odds ratio, **SMD** — standardized mean difference, **MD** — simple mean difference. The methods and the results are described with different measures — the article's first internal inconsistency.

Chi-square — a test of whether differences between trials are due to chance.

Publication bias — unsuccessful trials are published less often. **Fail-safe number** — how many unpublished “null” trials would be needed for the result to stop being significant.

HOW TO READ RR

RELATIVE RISK

$$\text{RR} = \frac{\text{share of "responders" on Ningxinbao}}{\text{share of "responders" in control}}$$

RR 1 – no difference

IN PLAIN WORDS

RR = 1.24 means that the share of “responders” in the Ningxinbao group is 24% higher than in the control group, in relative terms.

95% CI (confidence interval) — the range in which the true value most likely lies. If it does not include 1, the difference is considered statistically significant.

A hypothetical example, not from the article: with 50% “responders” in the control group, RR 1.24 gives 62%. The article does not report absolute proportions by group.

HOW TO READ SMD AND I²

STANDARDIZED DIFFERENCE

$$\text{SMD} = (\text{mean}_1 - \text{mean}_2) \div \text{standard deviation}$$

SMD 0 — no difference

IN PLAIN WORDS

SMD expresses the difference between groups not in beats per minute but in units of the measure's spread. This allows pooling trials that measured in different ways. If the CI includes 0, the difference is not significant.

I² — the share of differences between trials that cannot be explained by chance. 0% — the trials agree; the closer to 100%, the more they contradict each other.

p — the probability of getting such a result by chance if there is no effect. The threshold in the article is 0.05.

03

SECTION

EFFICACY

WHAT THIS SECTION COVERS

What happened to the patients: which trials were included, how much the share of treatment “responders” increased, and what happened to the heart rate.

Separately — results that rest on a single trial, and a contradiction between the article's text and its table.

IN THIS SECTION

- **WHAT WAS INCLUDED**
- **WHO THE PATIENTS WERE**
- **TOTAL EFFECTIVENESS**
- **HEART RATE**
- **SINGLE RCTS**

WHAT WAS INCLUDED

6

RCTs in
bradyarrhythmias ·
641 people

13

RCTs in
tachyarrhythmias ·
1,164 people

- Trial size — from 20 to 180 participants.
- Treatment duration — from 2 weeks to 1.5 years.
- All 19 were published in Chinese, all were conducted in China.
- All had parallel groups; Jadad score 4 in two, 3 in the rest.
- 16 trials used the “total effectiveness rate” as the primary outcome.

IN PLAIN WORDS

The trials are small and vary in duration — from two weeks to a year and a half. Not one was conducted outside China.

WHO THE PATIENTS WERE

Based on the trial titles in the article's reference list

GROUP	PATIENTS AND BACKGROUND THERAPY
Brady-arrhythmias	elderly patients with “slow-onset” arrhythmias; inferior myocardial infarction. Background therapy in 4 of 6 — trimetazidine
Tachy-arrhythmias	premature ventricular contractions (in CHD, viral myocarditis), ventricular arrhythmias in unstable angina, paroxysmal atrial fibrillation. Background therapy — amiodarone (6), propafenone (2), verapamil (1), metoprolol (1), Kordalong (1), “cardioplegia” (1) — neither name is explained in the article; in one trial (Xu, Zheng, 1992) the background therapy is not named

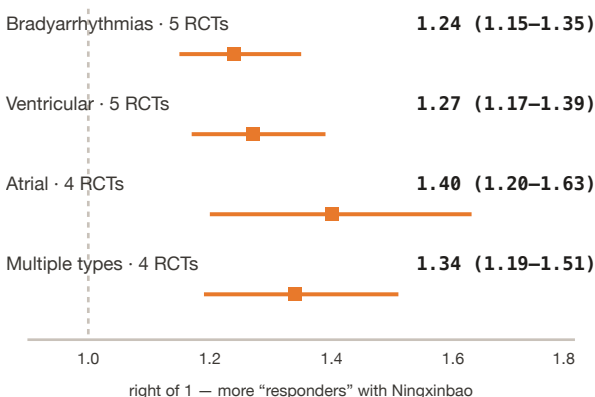
IN PLAIN WORDS

CHD — coronary heart disease. Amiodarone, propafenone, verapamil, and metoprolol are antiarrhythmic drugs; trimetazidine is a drug that affects metabolism in the heart muscle.

The patients differed widely. Pooling them into a single number is the authors' assumption.

TOTAL EFFECTIVENESS

RR and 95% CI, Ningxinbao + routine vs. routine



IN PLAIN WORDS

In all four groups, the share of “responders” is higher when the capsules are added, and no interval touches 1. This is a statistically significant result. [meta-analysis of RCTs]

THE SAME NUMBERS

GROUP	PARTICIPANTS	I ²
Bradyarrhythmias	236 / 225	37%
Ventricular	259 / 257	51%
Atrial	145 / 145	7%
Multiple types	182 / 176	88%

Participants: Ningxinbao group / control. In all groups $p < 0.0001$.

IN PLAIN WORDS

For bradyarrhythmias, 5 trials with 461 people were pooled. For tachyarrhythmias, the authors cite 11 trials with this outcome and divide them into three subgroups.

In the “multiple types” group $I^2 = 88\%$: the trials differ greatly from one another, and the pooled number is least reliable for them.

[meta-analysis of RCTs]

WHAT “EFFECTIVENESS” MEANS

ASSESSMENT

The criteria for the “total effectiveness rate” are not disclosed in the article: it is unknown what exactly counted as a response to treatment and whether it was defined the same way in all 16 trials.

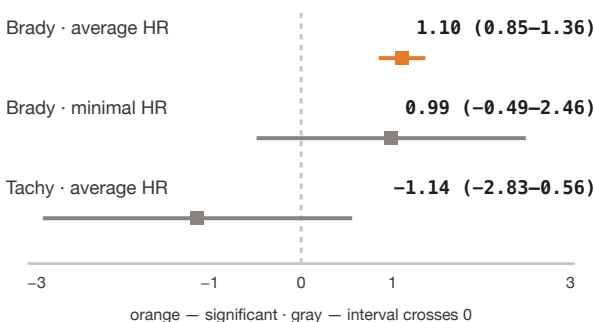
- RR is a relative measure; the table gives no proportions of “responders” by group, so the absolute benefit cannot be estimated.
- The outcome is a surrogate: the article has no data on mortality, strokes, or hospitalizations.

IN PLAIN WORDS

We know that “responders” increased by roughly 24–40% in relative terms. But we do not know what “responded” means, or how many people that is in actual numbers.

HEART RATE

SMD and 95% CI, 2 RCTs per row



IN PLAIN WORDS

Only one result is significant: in bradyarrhythmias, average HR increased with the capsules (2 RCTs, 272 people, I^2 0%).

[2 RCTs]

Minimal HR in bradyarrhythmias and average HR in tachyarrhythmias did not change significantly ($p = 0.19$, I^2 97%). [2 RCTs]

TEXT VS. TABLE

ARTICLE TEXT

“Significant increase” in average HR in tachyarrhythmias

$I^2 = 0\%$

TABLE 2

SMD -1.14 (-2.83 to 0.56)

$p = 0.19 \cdot I^2 = 97\%$

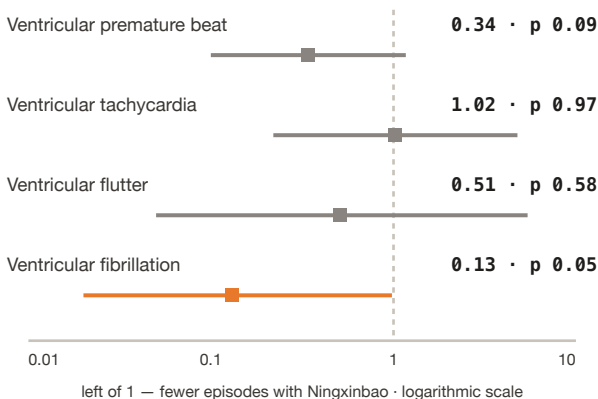
- A negative SMD means a decrease, not an increase; the interval crosses 0 — the difference is not significant.
- The text also describes minimal HR in bradyarrhythmias as significantly increased, although $p = 0.19$.
- In the same paragraph on bradyarrhythmias, one sentence earlier, the text states that HR after treatment did not differ between the groups.

IN PLAIN WORDS

In these places, the article's text is stronger than its own numbers. Trust the table.

VENTRICULAR ARRHYTHMIAS

One RCT (Tao et al., 2014): 40 / 41 people. RR and 95% CI



IN PLAIN WORDS

The article's text speaks of a “greater reduction” in all four disorders. By the numbers, three intervals widely cross 1, and for ventricular fibrillation the upper limit is 0.98 and $p = 0.05$ — right at the threshold of significance. [1 RCT]

SYMPTOMS

XU AND ZHENG, 1992

According to its title, a double-blind trial in 64 patients with arrhythmias. According to the article's authors, the capsules had a “mild effect”: they relieved palpitations and chest distress caused by premature ventricular contractions. [1 RCT]

IN PLAIN WORDS

Premature ventricular contractions (PVC in the article) — extra, out-of-turn contractions of the ventricles; a person feels them as “skipped beats” or “thumps.”

The article gives no figures for this trial, only a verbal assessment. The trial is more than 30 years old.

INFLAMMATION MARKERS

One RCT (Cao et al., 2021): 66 / 66 people, 2 months, SMD

MARKER	SMD (95% CI)
hs-CRP	2.86 (2.37–3.35)
IL6	2.29 (1.84–2.73)
TNF	2.13 (1.70–2.56)

- The authors write that levels in the Ningxinbao group were “better” than in the control group. Why the difference is positive and in which direction the markers changed is not explained in the article. [1 RCT]

IN PLAIN WORDS

hs-CRP — high-sensitivity C-reactive protein, **IL6** — interleukin-6, **TNF** — tumor necrosis factor. All three are signals of inflammation in the blood. One trial in patients with ventricular arrhythmias on propafenone.

04

SECTION

SAFETY

WHAT THIS SECTION COVERS

Which adverse events are described, where there are numbers, and where there is only a verbal assessment.

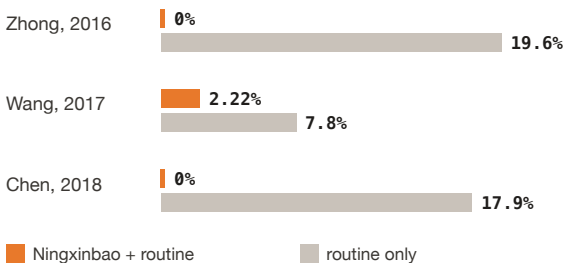
AE — adverse event: any unfavorable event during treatment, whether or not it is related to the treatment.

IN THIS SECTION

- **BRADYARRHYTHMIAS: NUMBERS**
- **TACHYARRHYTHMIAS AND OVERALL**
- **QUESTIONS ABOUT THE DATA**

AES IN BRADYARRHYTHMIAS

AE incidence in the three RCTs that report it as a number



- All 6 bradyarrhythmia trials mentioned AEs; three gave numbers. Digestive AEs were significantly less frequent in the Ningxinbao group. [3 RCTs]

IN PLAIN WORDS

In the three trials with numbers, there were fewer adverse events with the capsules than without them.

TACHYARRHYTHMIAS AND OVERALL

- 14 of 19 trials reported AEs: skin allergy, nausea, vomiting, abdominal discomfort, and others.
- In tachyarrhythmias, 8 trials described AEs quantitatively. The authors write of a “distinct difference” — fewer cardiovascular and digestive AEs in the Ningxinbao group. No numbers are given. [RCTs, no numbers]
- The abstract states that no serious AEs occurred with cordyceps.

IN PLAIN WORDS

The AEs described are skin allergy, stomach complaints, and others; the article does not say in which group they occurred. If such symptoms appear while taking the capsules, discuss with your physician whether to continue.

QUESTIONS ABOUT THE DATA

ASSESSMENT

Both groups received the same routine therapy. The article does not explain why adding the capsules lowered the incidence of AEs rather than raising it.

- The trials were small (20–180 people) and lasted from 2 weeks to 1.5 years; rare AEs may not show up in such samples.
- The meta-analysis did not separately analyze interactions between the capsules and antiarrhythmic drugs; only one trial (Liu, Chen, 2018), judging by its title, assessed the safety of the combination.
- There is no pooled estimate of AEs across all trials.

IN PLAIN WORDS

“No serious AEs” in small, short trials does not equal “safe for long-term use.” All participants were also being treated by physicians with routine drugs.

05

SECTION

IN SILICO MECHANISMS

WHAT THIS SECTION COVERS

The second half of the article is a computational search: which genes and signaling pathways might link cordyceps compounds to arrhythmias.

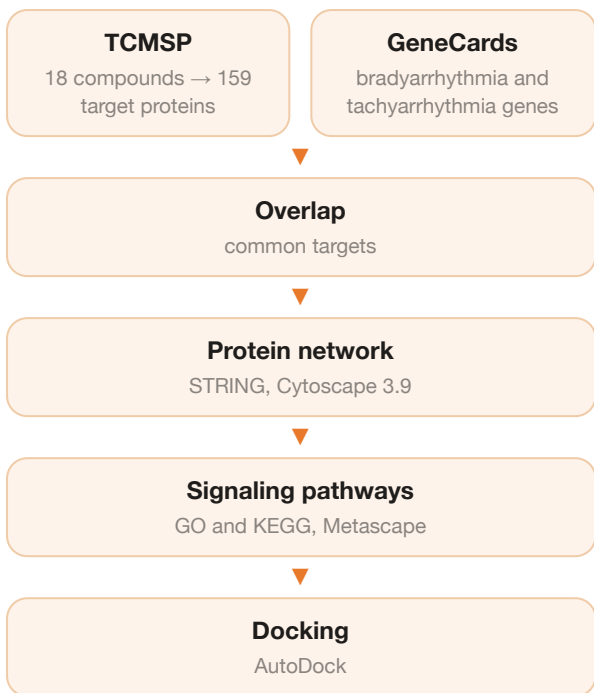
Everything in this section is a calculation based on databases. The article itself contains no experiments on cells or animals.

[in silico]

IN THIS SECTION

- **CALCULATION PIPELINE**
- **TARGET OVERLAP**
- **PROTEIN NETWORK**
- **SIGNALING PATHWAYS**
- **DOCKING**

CALCULATION PIPELINE



IN PLAIN WORDS

TCMSP and GeneCards are databases of compounds and genes; STRING is a database of protein interactions; GO and KEGG are a dictionary of gene functions and an atlas of signaling pathways.

Network pharmacology compares lists from databases: “which proteins the herb's compounds might act on” and “which genes are linked to the disease.” Matches are treated as mechanism candidates.

[in silico]

WHERE THE COMPOSITION COMES FROM

- Cordyceps compounds were taken from the TCMSP database — a systems pharmacology platform for traditional Chinese medicine.
- Selection: $OB \geq 30\%$ and $DL \geq 0.18$. Some compounds that did not meet the threshold but, in the authors' view, had significant pharmacological activity were also selected.
- The list of 18 compounds is given in the supplement (Table S2). The text names caffeine, arachidonic and nicotinic acids, and beta-sitosterol.

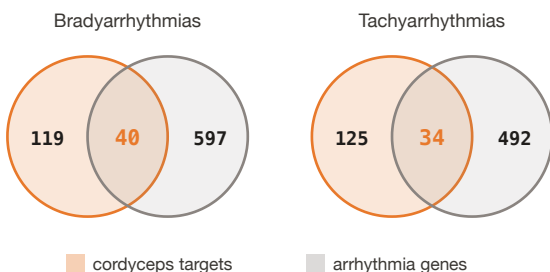
IN PLAIN WORDS

OB — calculated oral bioavailability, **DL** — calculated “drug-likeness” of the molecule.

The composition was taken from a database for “cordyceps” in general. The article contains no analysis of the composition of Ningxinbao capsules.

COMMON TARGETS

From Figure 2 of the article



IN PLAIN WORDS

Of 159 possible cordyceps targets, 40 matched bradyarrhythmia genes and 34 matched tachyarrhythmia genes. A match only means that the protein is on both lists.

[in silico]

THE NUMBERS DON'T MATCH

WHAT

TEXT FIGURES

Common with bradyarrhythmias	34	40
Common with tachyarrhythmias	40	34
Bradyarrhythmia genes	467	637

637 = 40 + 597 per the diagram. In the Figure 2 legend both parts are labeled “tachyarrhythmia,” and the second gives 647 genes.

IN PLAIN WORDS

The overall picture — a few dozen matches — does not change. But the numbers in this part of the article call for caution: which list belongs to which arrhythmia cannot be determined unambiguously from the text.

PROTEIN NETWORK

40

proteins and 321 links
· bradyarrhythmias

33

proteins and 207 links
· tachyarrhythmias

KEY TARGETS PER THE ARTICLE

IL6 · TNF · TP53 · CASP3 · CTNNB1
· EGF · NOS3

IN PLAIN WORDS

PPI network (protein–protein interaction) — a map of known protein interactions from the STRING database. Proteins with the most connections sit at the center; these are the ones called “key.”

A central position in the network is a property of the database, not proof that cordyceps acts on that protein. [in silico]

SEVEN TARGETS

GENE	PROTEIN
IL6	interleukin-6, an inflammation signal
TNF	tumor necrosis factor, an inflammation signal
TP53	p53, a transcription regulator and tumor suppressor
CASP3	caspase-3, an enzyme of programmed cell death
CTNNB1	β -catenin, a cell-to-cell junction protein
EGF	epidermal growth factor
NOS3	endothelial nitric oxide synthase

IN PLAIN WORDS

Two inflammation signals, two regulators of cell life and death, a protein that “glues” heart cells together, a growth factor, and an enzyme of the vessel wall. How each relates to heart rhythm is covered on the next pages.

TARGETS AND RHYTHM · 1

What the authors cite about the targets

- **IL6:** in rats, IL-6 injection increased susceptibility to atrial fibrillation; in isolated rat hearts, it recapitulated part of the calcium handling abnormalities (Liao et al., 2021).
[animals]
- **TNF:** rapidly increased spontaneous calcium release in mouse atrial cells (Zuo et al., 2019). [in vitro]
- **NOS3:** mice lacking this gene have more arrhythmias (Wang et al., 2008). [animals]

IN PLAIN WORDS

Calcium is the main “switch” for contraction of heart cells. A disturbance in its handling can cause extra beats.

None of these studies examined cordyceps.

[not cordyceps]

TARGETS AND RHYTHM · 2

- **CASP3:** in bradyarrhythmia induced by trimethyltin chloride, Na^+/K^+ -ATPase activity may be closely correlated with CASP3 expression (Liu et al., 2020). [experiment]
- **CTNNB1:** essential for cardiac conduction; loss of the cell-to-cell “junction” proteins disrupts the intercalated discs and leads to arrhythmias (Swope et al., 2012). [experiment]
- **TP53:** based on left ventricular tissue data, presumably linked to ventricular arrhythmias (Huizar 2019; Haywood 2020). [tissue]
- **EGF:** according to experimental data, presumably protects the heart from the deleterious effects of adrenaline (Lorita et al., 2002; rodents, per the title). [animals]

IN PLAIN WORDS

Na^+/K^+ -ATPase — a pump that maintains the charge of the cell membrane. These are data on the role of the proteins themselves in the heart. None of the studies examined cordyceps. [not cordyceps]

SIGNALING PATHWAYS

Leading KEGG pathways per the article

BRADYARRHYTHMIAS

PI3K-Akt

**Adrenergic
signaling in
cardiomyocytes**

**Fluid shear stress
and atherosclerosis**

mTOR · Rap1

TACHYARRHYTHMIAS

PI3K-Akt

**AGE-RAGE in
diabetic
complications**

**Fluid shear stress
and atherosclerosis**

MAPK · FOXO

IN PLAIN WORDS

KEGG (Kyoto Encyclopedia of Genes and Genomes) — an atlas of cellular signaling pathways. **PI3K-Akt** — the phosphoinositide 3-kinase and protein kinase B pathway; according to the article, a key pathway of cardiac protection under stress and a regulator of calcium current. Adrenergic signaling — the response of heart cells to adrenaline. [in silico]

GENE FUNCTIONS (GO)

- **Bradyarrhythmias:** two of the top ten processes are associated with adrenergic receptors; others include negative regulation of smooth muscle contraction, vasodilation, and release of cytochrome c from mitochondria. The leading molecular function is adrenergic receptor activity.
- **Tachyarrhythmias:** protein kinase B and phosphatidylinositol 3-kinase signaling, response to oxidative stress, macrophage-derived foam cell differentiation. [in silico]

IN PLAIN WORDS

GO (gene ontology) — a dictionary of gene functions: which processes a protein takes part in, where in the cell it is located, and what it does. Selection used a nominal $p < 0.05$.

HOW TO INTERPRET THIS

**Genes in
the overlap**

known

**Pathways
of these
genes**

calculated

**Effect of
cordyceps
on the
pathway**

not tested

- The same top-20 pathway lists include “type 2 diabetes mellitus,” “insulin secretion,” and “salivary secretion” in Figure 4, and “rheumatoid arthritis” and “inflammatory bowel disease” in Figure 5.

IN PLAIN WORDS

Enrichment analysis shows which pathways the genes on the list belong to, not that the compound acts on them. Pathways far removed from the heart in the same tables illustrate this well.

MOLECULAR DOCKING

Calculated binding energy, kcal/mol

COMPOUND	PROTEIN	ENERGY
Beta-sitosterol	CASP3	-7.0
Caffeine	TP53	-6.3
Arachidonic acid	NOS3	-5.6
Nicotinic acid	NOS3	-5.4
Caffeine	CASP3	-5.3
Caffeine	IL6	-5.1
Caffeine	TNF	-5
Caffeine	CTNNB1	-4.9
Arachidonic acid	EGF	-4.0
Arachidonic acid	CASP3	-3.9

IN PLAIN WORDS

Docking — a computer “fitting” of a molecule into a pocket of a protein. The more negative the number, the tighter the calculated fit. [in silico]

WHAT DOCKING DOES NOT SHOW

- The authors write of 11 binding complexes but list and display 10.
- All values are said to indicate “a stable combination”; the threshold above which binding is considered stable is not stated.
- Caffeine appears in 5 of the 10 pairs. The article does not say how much of it Ningxinbao capsules contain.

ASSESSMENT

Docking does not show that a compound is absorbed, reaches the heart at the required concentration, and changes how the protein works. That is tested in cells and animals — the article contains no such experiments.

IN PLAIN WORDS

A key that fits a lock on a computer has not yet opened a single door.

THE AUTHORS' SCHEME

From Figure 7 of the article

Cordyceps



Fig. 7 shows an inhibition symbol

**Adrenergic
signaling**

in cardiomyocytes

PI3K-Akt pathway

TNF, IL6, EGF → PI3K →
AKT



“Improved rhythm”

hypothesis

IN PLAIN WORDS

This is the final picture of the calculations. The authors themselves write that the mechanisms were predicted only by network pharmacology and require experimental confirmation. [hypothesis]

06

SECTION

AUTHORS' EXPLANATIONS

WHAT THIS SECTION COVERS

How the authors explain the “bidirectional” effect and which studies they rely on.

Most of the references concern other substances, the proteins themselves, or animal experiments. Only one cited study is an experiment with cordyceps itself (Mei et al., 1989, in animals).

IN THIS SECTION

- **WHERE “BIDIRECTIONALITY” COMES FROM**
- **CORDYCEPS IN RATS**
- **THE CAFFEINE HYPOTHESIS**
- **OTHER SUBSTANCES**
- **BRADYCARDIA AND THE PI3K-AKT PATHWAY**

WHERE “BIDIRECTIONALITY” COMES FROM

BRADYARRHYTHMIAS

Effectiveness ↑

RR 1.24



Average HR ↑

SMD 1.10 · 2 RCTs

TACHYARRHYTHMIAS

Effectiveness ↑

RR 1.27–1.40



**HR — no significant
change**

SMD -1.14 · p 0.19

IN PLAIN WORDS

The claim that “one remedy both speeds up and slows down the rhythm” rests mainly on the “total effectiveness rate” in both groups. Direct heart rate measurement in tachyarrhythmias did not show significant slowing. [hypothesis]

CORDYCEPS IN RATS

MEI ET AL., 1989

- A petroleum ether extract of cordyceps improved aconitine-induced arrhythmia: it prolonged the time to its onset and reduced its duration and severity.

[animals]

- The extract had an antagonistic effect on arrhythmia induced by barium chloride. [animals]

- Possible mechanism — regulation of ion channel transport in the cell membrane. [hypothesis]

IN PLAIN WORDS

Aconitine and barium chloride are poisons used to induce arrhythmia in animal experiments. This is the only cited study of cordyceps itself (*Cordyceps sinensis*, per the title) in animals.

THE CAFFEINE HYPOTHESIS

- Low doses of caffeine reduced HR during submaximal cycle ergometry (Flueck et al., 2016). [not cordyceps]
- A high dose (150 mg) increased HR in healthy people (Vukovich et al., 2005; caffeine together with ephedra, per the title). [not cordyceps]
- Caffeine before aerobic exercise delayed the recovery of autonomic control of HR (Gonzaga et al., 2017). [not cordyceps]

ASSESSMENT

The statement that caffeine “plays an important role in preventing and treating arrhythmia” is given without a reference. The caffeine content of the capsules is not reported.

IN PLAIN WORDS

The authors suggest that a low dose of caffeine slows the pulse and a high dose speeds it up; in their view, this may be one of the reasons for “bidirectionality.” This was not tested in patients. [hypothesis]

OTHER SUBSTANCES

- **Beta-sitosterol** inhibited arrhythmias induced by aconitine, ouabain, and myocardial ischemia (Zhang et al., 2013; a study of the Guangzao remedy, per the title). [not cordyceps]
- **Arachidonic and linoleic acids** given intravenously had strong antiarrhythmic effects in three experimental arrhythmia models (Forster et al., 1976; Xiao et al., 2004). [not cordyceps]

IN PLAIN WORDS

These are data on pure substances in experiments; the fatty acids were given intravenously. The article did not measure what concentrations of these substances the capsules produce when taken by mouth.

MECHANISMS IN BRADYCARDIA

As listed by the authors (cited from Zeng, 2015;
Das et al., 2020)

1. Increases the sinus heart rate and improves the electrical activity of the sinus node and AV conduction.
2. May increase blood flow to the heart and brain, improve microcirculation, and stabilize blood pressure.
3. May promote fibrinolysis and reduce blood viscosity.
4. May increase superoxide dismutase activity and inhibit the production of lipid peroxides and free radicals.

ASSESSMENT

The article's results contain no measures of conduction (sinus node, AV node). Item 1 is presented as a finding in the Discussion, but the meta-analysis results contain no such data.

IN PLAIN WORDS

Fibrinolysis — the dissolution of blood clots.

Superoxide dismutase — an enzyme that neutralizes free radicals. Apart from the increase in average HR (2 RCTs), none of these effects is reported in the article's results. [hypothesis]

THE PI3K-AKT PATHWAY

- Mice with reduced cardiac PI3K-Akt activity are very susceptible to atrial fibrillation; in surgical specimens from patients with atrial fibrillation, activity is lower than in patients with sinus rhythm (Pretorius et al., 2009). [animals; tissue]
- Increased PI3K-Akt activity improved the function of failing hearts in mouse models of heart failure (McMullen et al., 2014). [animals]
- PI3K α is the main regulator of calcium current in heart cells (Liang et al., 2010; mice, per the title). [animals]

IN PLAIN WORDS

These studies show that the pathway matters for heart rhythm. They do not show that cordyceps affects it. [not cordyceps]

07

SECTION

SUMMARY

WHAT THIS SECTION COVERS

What the article shows, what it does not show, which limitations the authors themselves acknowledge, and where the text diverges from the numbers.

At the end — what this means in practice.

IN THIS SECTION

- **WHAT IS SHOWN**
- **WHAT IS NOT SHOWN**
- **LIMITATIONS PER THE AUTHORS**
- **INCONSISTENCIES**
- **PRACTICAL IMPLICATIONS**

WHAT IS SHOWN

- Adding Ningxinbao to routine therapy increased the share of “responders” in bradyarrhythmias (RR 1.24) and tachyarrhythmias (RR 1.27–1.40).
[meta-analysis of RCTs]
- In bradyarrhythmias, average HR increased (SMD 1.10). [2 RCTs]
- AEs in the Ningxinbao group are described as less frequent; no serious AEs were noted.
[RCTs, partly no numbers]
- Genes shared by cordyceps targets and arrhythmias belong to the PI3K-Akt and adrenergic signaling pathways. [in silico]

IN PLAIN WORDS

There is a signal of benefit in small Chinese trials with a vague criterion of success, plus a calculated hypothesis of the mechanism.

WHAT IS NOT SHOWN · 1

- Effect on mortality, stroke, hospitalizations — the article has no data.
- Long-term outcomes — unknown; the authors say so directly.
- Effect of the capsules without routine therapy — not studied.
- Which arrhythmias respond better — the subgroups are small, and they are not compared with one another.
- Changes in cardiac conduction — not reported in the results.

IN PLAIN WORDS

“Not shown” does not mean “does not work.” It means that the article does not answer these questions.

WHAT IS NOT SHOWN · 2

- What counted as a “response to treatment” — not defined.
- How many people benefited in absolute numbers — not reported.
- Results outside China — not a single trial.
- Effect of the compounds on cells and animals — not tested in the article.
- Capsule composition and caffeine content — not analyzed.
- Applicability to other cordyceps products — no basis: a single standardized product was studied.
- Contraindications, safety in pregnancy, in children, in liver and kidney disease — not considered in the article.

IN PLAIN WORDS

The result applies to Ningxinbao capsules at 0.5 g 3 times a day alongside treatment by a physician, not to cordyceps in general.

LIMITATIONS PER THE AUTHORS

1. All trials were published in Chinese; sample sizes were small.
2. All were conducted in China — geographic bias limits generalization to other countries.
3. All reported positive results — publication bias is possible.
4. The mechanisms were predicted only by network pharmacology and require experiments.

WHAT IS NEEDED, ACCORDING TO THE AUTHORS

Strictly designed multicenter RCTs to assess efficacy and safety, especially with long-term “hard” endpoints.

IN PLAIN WORDS

Publication bias — unsuccessful trials are published less often, so a review sees only the successful ones. **A hard endpoint** is an event that matters to the patient: death, stroke, hospitalization.

INCONSISTENCIES · 1

Clinical part

- Effect measures: OR and MD in the methods, RR and SMD in the results.
- HR in tachyarrhythmias: “significant increase” and I^2 0% in the text; SMD -1.14 , $p = 0.19$, I^2 97% in the table.
- Minimal HR in bradyarrhythmias is called significantly increased at $p = 0.19$.
- 11 trials with the “effectiveness” outcome in tachyarrhythmias, but $5 + 4 + 4 = 13$ in the subgroups.
- “8 trials” with AEs in tachyarrhythmias — the list has 9 references, one of them repeated twice.

IN PLAIN WORDS

Minor discrepancies do not cancel the main result, but they suggest that the article was not prepared very carefully.

INCONSISTENCIES · 2

Computational part and conclusions

- Common targets: 34 with bradyarrhythmias and 40 with tachyarrhythmias in the text; the reverse in the figures.
- Bradyarrhythmia genes: 467 in the text, 637 in the Fig. 2 diagram, 526 in its legend; tachyarrhythmia genes: 526 in the text and the diagram, 647 in the legend.
- Docking: “11 binding complexes,” 10 shown.
- The Discussion claims improved “sinus node and atrioventricular conduction”; the results contain no such data.
- The conclusion that cordyceps is “effective in stabilizing heart rates” — despite nonsignificant changes in average HR in tachyarrhythmias and minimal HR in bradyarrhythmias ($p = 0.19$).

IN PLAIN WORDS

The conclusions in the Discussion section are at times stronger than the data in the Results section. When reading the article, rely on the tables.

PRACTICAL IMPLICATIONS ·

1

- In all trials, Ningxinbao was only added to routine treatment. There are no data on taking it instead of antiarrhythmic drugs.
- Participants were also receiving amiodarone, propafenone, verapamil, metoprolol, trimetazidine, and other drugs. The meta-analysis did not separately analyze compatibility; only one trial (Liu, Chen, 2018), judging by its title, assessed the safety of the combination.

WHAT TO DO

Discuss with your physician whether to take cordyceps for arrhythmia and whether to combine it with medications. Do not stop prescribed treatment on the basis of this article: it did not study that.

IN PLAIN WORDS

In the trials, the capsules were an add-on to treatment by a cardiologist, not a replacement for it. Any changes to your regimen — only together with your physician.

PRACTICAL IMPLICATIONS . 2

- 14 trials described skin allergy, nausea, vomiting, abdominal discomfort, and other reactions; the article does not say in which group they occurred.
- In the three RCTs with numbers, AEs were more frequent in the control group. [3 RCTs]
- The trials were small and short (from 2 weeks to 1.5 years); rare AEs may not show up in such samples.

IN PLAIN WORDS

The list of adverse reactions in the article is incomplete and not linked to a group. If such symptoms appear while taking the capsules, discuss with your physician whether to continue.

CONCLUSION

LEVEL OF EVIDENCE

A meta-analysis of 19 small Chinese RCTs with an undefined surrogate outcome shows a signal of benefit from Ningxinbao capsules as an add-on to arrhythmia treatment. The mechanism is a calculated hypothesis without experimental confirmation. This is a basis for rigorous trials, not a proven treatment.

**Signal in
RCTs**

present

Mechanism

calculation

**Hard
outcomes**

no data

IN PLAIN WORDS

The authors conclude that the study “confirmed that Cordyceps has a certain positive effect” and that it “is effective in stabilizing heart rates.” However, in tachyarrhythmias HR did not change significantly ($p = 0.19$). The authors also acknowledge that the effect on long-term outcomes is unknown.

GLOSSARY · HEART

Arrhythmia — a disturbance in the normal activation or beating of the heart.

Bradyarrhythmia / tachyarrhythmia — a rhythm slower than 60 / faster than 100 beats per minute.

HR — heart rate.

Sinus node — the heart's natural “pacemaker”; **SSS** — sick sinus syndrome.

AV block — a delay of the signal from the atria to the ventricles; sinoatrial block — a delay of the signal's exit from the sinus node.

Premature beat (extrasystole) — an out-of-turn contraction; **PVC** — a premature ventricular contraction.

Fibrillation, flutter — chaotic or very rapid contraction of the atria or ventricles.

CHD — coronary heart disease.

Cardiomyocyte — a heart muscle cell.

GLOSSARY · STATISTICS

RCT — randomized controlled trial.

Meta-analysis — pooling the results of several trials into a single estimate.

RR / OR — relative risk / odds ratio; 1 — no difference.

SMD / MD — standardized / simple mean difference; 0 — no difference.

95% CI — confidence interval; **p** — the probability of a chance result when there is no effect.

I² — the share of differences between trials not explained by chance.

Jadad scale — a point score of the methodological quality of an RCT.

Surrogate / hard endpoint — an intermediate measure / an event that matters to the patient.

AE — adverse event.

Publication bias — a distortion caused by unsuccessful trials being published less often.

Fail-safe number — how many unpublished “null” trials would be needed for the result to stop being significant.

Chi-square — a test of whether differences between trials are due to chance.

GLOSSARY · CALCULATIONS

In silico — computer calculation; **in vitro** — an experiment on cells outside the body.

Network pharmacology — matching “compound — protein” and “gene — disease” databases.

TCMSP — the Traditional Chinese Medicine Systems Pharmacology database; **GeneCards** — a gene database; **STRING** — a database of protein interactions.

OB / DL — calculated oral bioavailability / “drug-likeness.”

PPI — protein–protein interaction network.

GO / KEGG — a dictionary of gene functions / an atlas of signaling pathways.

Docking — calculation of how a molecule fits into a protein pocket, kcal/mol.

PI3K-Akt, mTOR, MAPK, FOXO, Rap1, AGE-RAGE — intracellular signaling pathways.

IL6, TNF, hs-CRP — inflammation markers.

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