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# **Nature's alchemy:**
# Harmonising heart health and longevity

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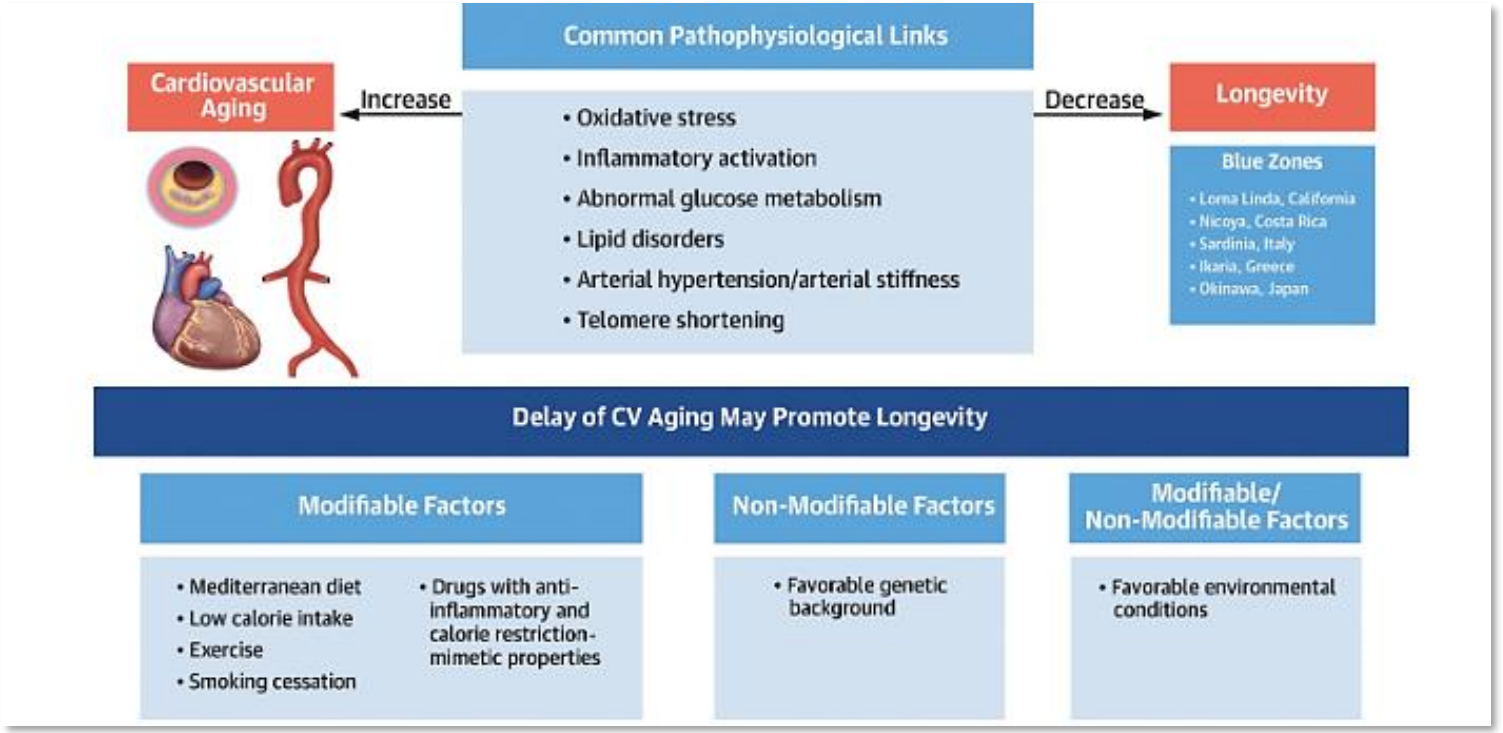
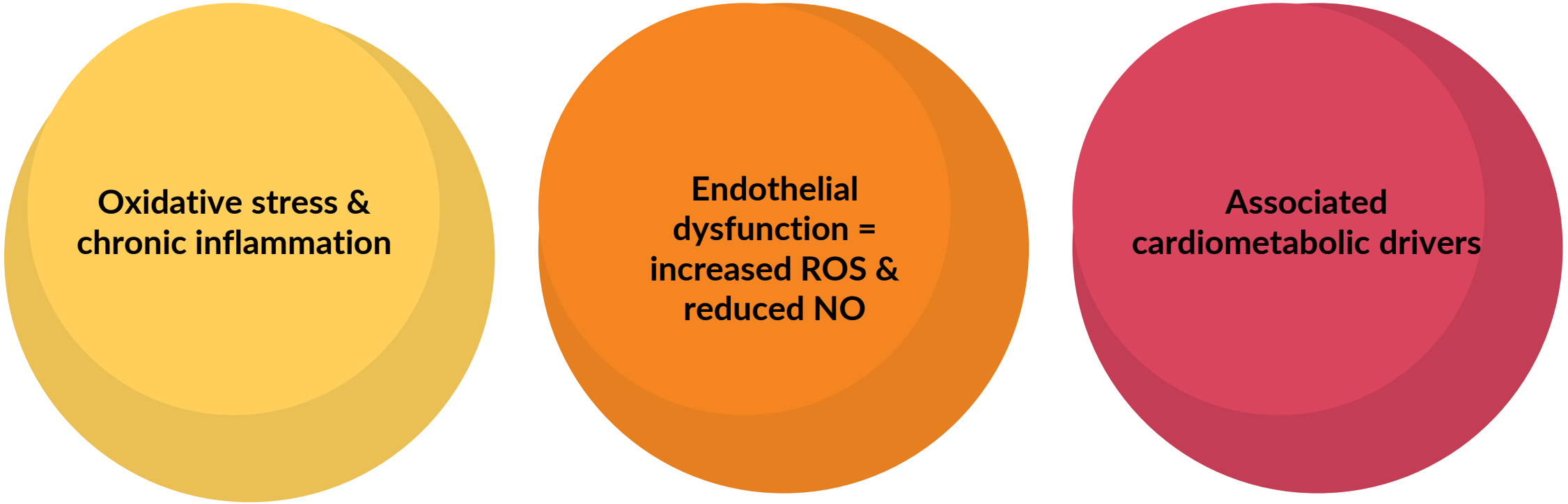
Cardiovascular disease & longevity share common mechanisms

Early intervention alters the course of disease & promotes healthy ageing




https://doi.org/10.1016/j.jacc.2020.11.023

# What are the challenges?



# Hypertension

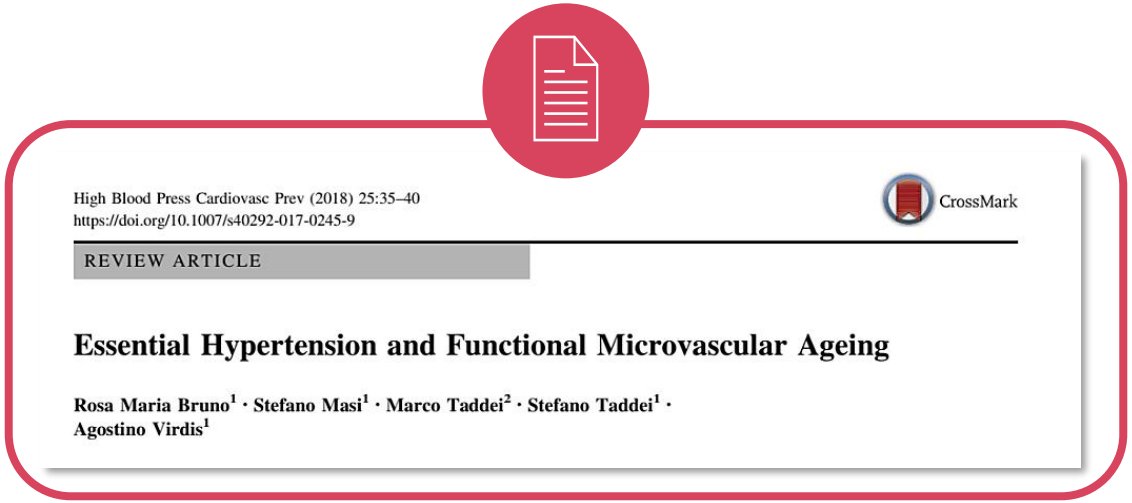
***The primary vascular disorder associated with ageing***

1. ↑ Reactive oxygen species
2. ↓ Arterial elasticity & tissue injury
3. ↓ Nitric oxide bioavailability

**Accelerates the vascular changes that lead to neurodegeneration, retina damage and kidney decline**

https://doi.org/10.1007/s40292-017-0245-9

# Research



High Blood Press Cardiovasc Prev (2018) 25:35–40
https://doi.org/10.1007/s40292-017-0245-9

REVIEW ARTICLE

**Essential Hypertension and Functional Microvascular Ageing**

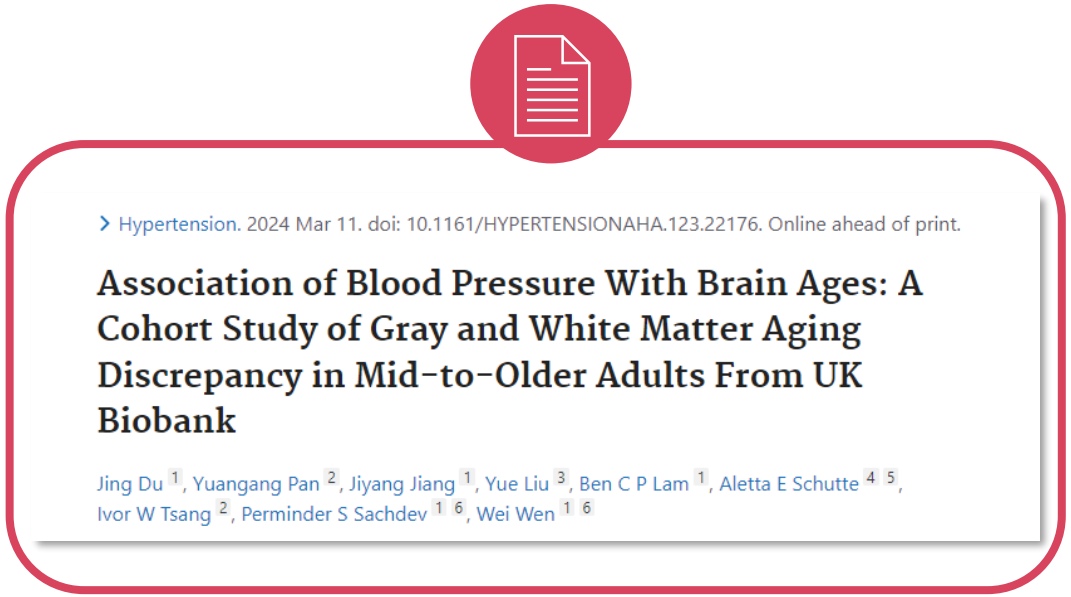
Rosa Maria Bruno[1] · Stefano Masi[1] · Marco Taddei[2] · Stefano Taddei[1] · Agostino Virdis[1]

Beyond its relaxing activity, other NO-related protective activities are impaired, including:

- **inhibition of platelet adhesion & aggregation**
- **leukocyte adhesion & migration**
- **smooth muscle cell proliferation**

*"A dysfunctioning endothelium is considered a contributor to the progression of atherosclerosis and cardiovascular events."*

# Research



> Hypertension. 2024 Mar 11. doi: 10.1161/HYPERTENSIONAHA.123.22176. Online ahead of print.

**Association of Blood Pressure With Brain Ages: A Cohort Study of Gray and White Matter Aging Discrepancy in Mid–to–Older Adults From UK Biobank**

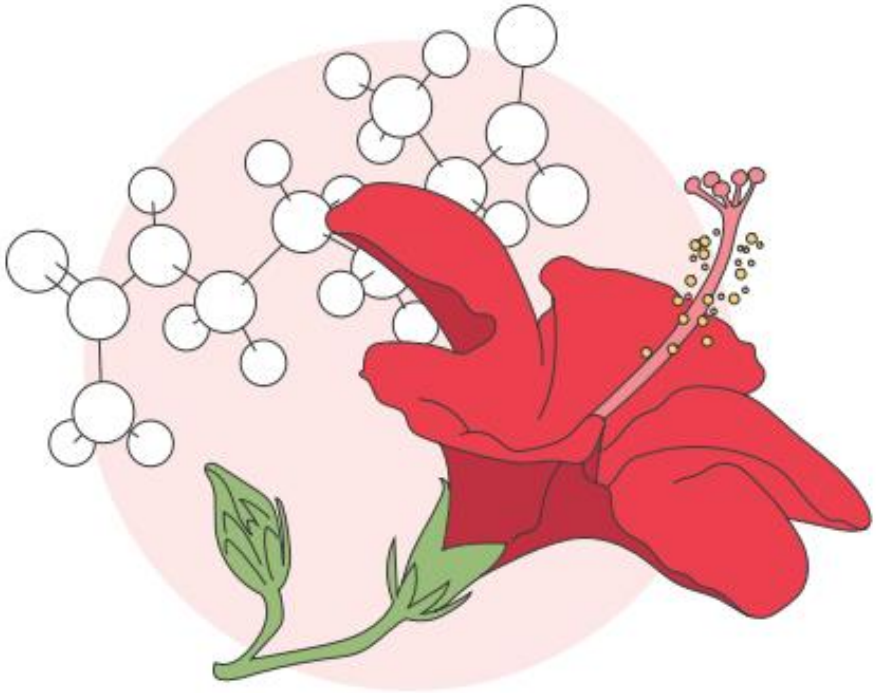
Jing Du [1], Yuangang Pan [2], Jiyang Jiang [1], Yue Liu [3], Ben C P Lam [1], Aletta E Schutte [4 5], Ivor W Tsang [2], Perminder S Sachdev [1 6], Wei Wen [1 6]

- High BP is an independent risk factor for **accelerated ageing of white brain matter**
- Mid-adulthood hypertension associated with **65% increase in dementia**

***"Early onset correlates with significantly greater CVD risk than late onset"***

# Hibiscus and citrulline:

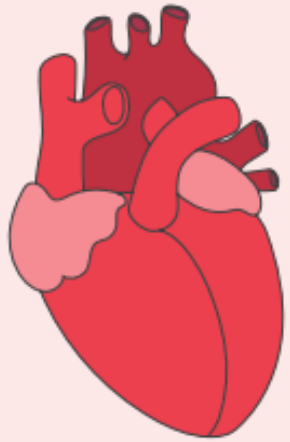
*A dynamic duo with benefits beyond hypertension*



# Pretty polyphenols: anthocyanins' diverse influence on heart health

With is **vibrant crimson hue,** this botanical beauty has emerged as a **potent defender against mild to moderate hypertension.** A growing body of evidence has confirmed its remarkable cardiovascular advantages due to **its rich cocktail of bioactive compounds.**[1]

**Vasodilatory actions** - stimulates vascular $Na^+$-$K^+$ ATPase activity and inhibits $Ca^{2+}$ influx, dilating blood vessels and lowering BP.[1,3]



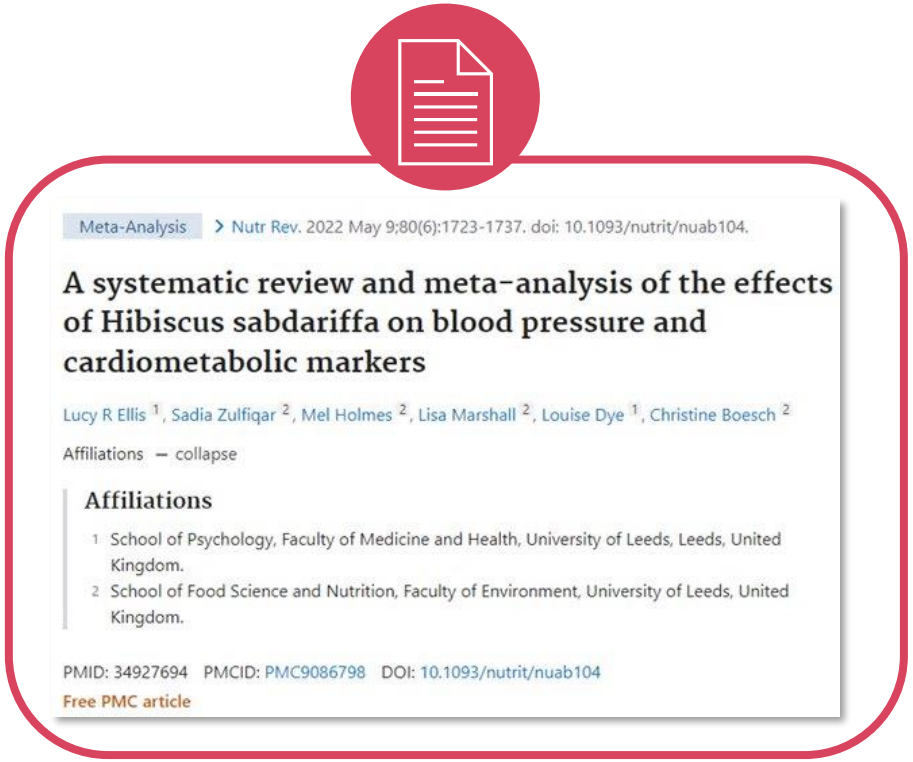
**Anti-inflammatory** - inhibits NF-κB and COX-2 enzymes in vascular smooth muscle cells; decreases migration of immune cells.[3]

**Delivers the actions of antihypertensives,** without undesirable side effects

**Diuretic actions** - eliminates excess sodium, chloride and fluid by inhibiting RAAS and reducing arterial pressure.[4]

**Antioxidant** - quenches ROS; improves endothelial function via increased NO synthase.[3,4]

# Hibiscus: a viable alternative



Meta-Analysis > Nutr Rev. 2022 May 9;80(6):1723-1737. doi: 10.1093/nutrit/nuab104.

**A systematic review and meta-analysis of the effects of Hibiscus sabdariffa on blood pressure and cardiometabolic markers**

Lucy R Ellis [1], Sadia Zulfiqar [2], Mel Holmes [2], Lisa Marshall [2], Louise Dye [1], Christine Boesch [2]

Affiliations – collapse

Affiliations

1 School of Psychology, Faculty of Medicine and Health, University of Leeds, Leeds, United Kingdom.
2 School of Food Science and Nutrition, Faculty of Environment, University of Leeds, United Kingdom.

PMID: 34927694 PMCID: PMC9086798 DOI: 10.1093/nutrit/nuab104

Free PMC article

2022 systematic review and meta-analysis, the most recent evidence

17 studies

Results:

- ✓ Hibiscus considered a viable alternative to pharmaceutical treatment
- ✓ Mean reduction SBP (-10.05 mmHg)
- ✓ > 4 weeks showed most significant BP lowering effect

# Hibiscus: reducing stroke risk

12g/d

Meta-Analysis > Nutr Rev. 2022 May 9;80(6):1723-1737. doi: 10.1093/nutrit/nuab104.

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PMID: 34927694 PMCID: PMC9086798 DOI: 10.1093/nutrit/nuab104

Free PMC article

10 mmHg decrease in usual systolic blood pressure or 5 mmHg decrease in usual diastolic blood pressure is associated with:

- **40% lower risk of stroke death**
- **30% lower risk of death from ischaemic heart disease or other vascular causes throughout middle age**

# Hibiscus: Immediate results

**Results**: SBP decreased by 17.08 (±5.12) mmHg from 150.88 mmHg to 133.80 mmHg

Statistical results begin at 2 weeks, **best effect at 4 weeks**

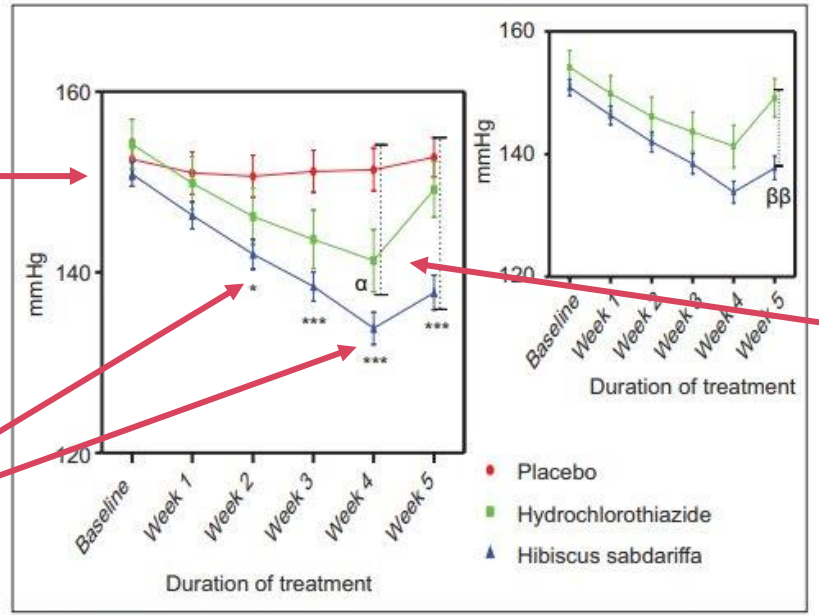
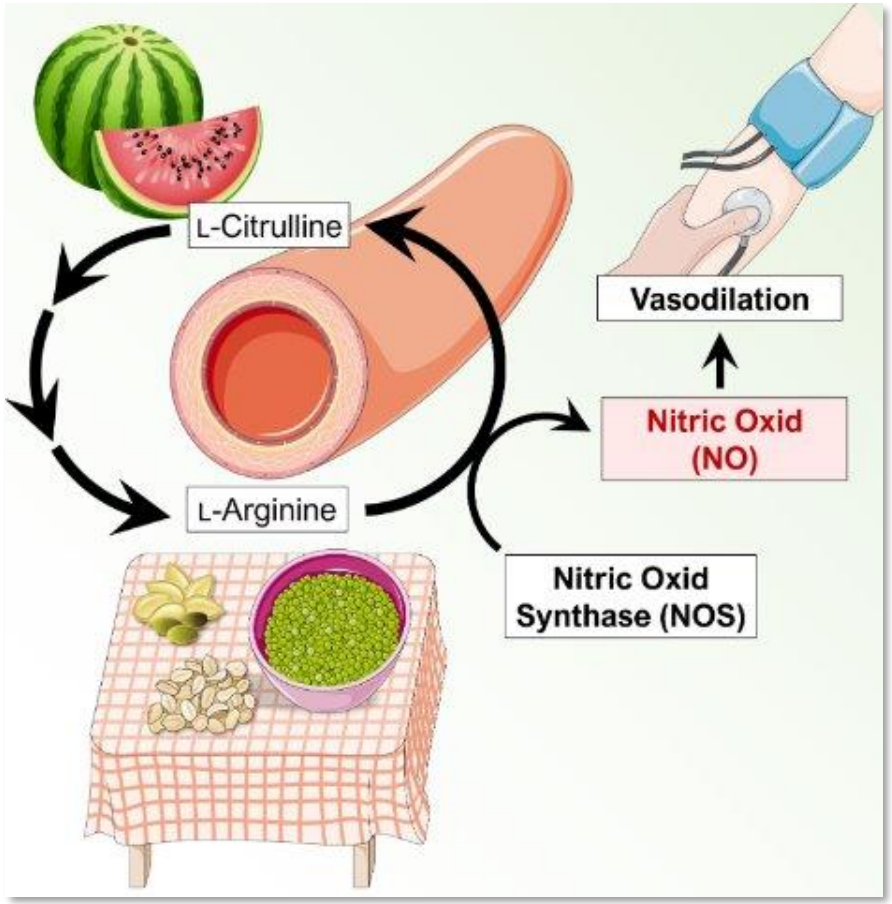



**Figure 1:** Systolic blood pressure measurements following the administration ofplacebo (control), hydrochlorothiazide andHibiscus sabdariffa on mild to moderate hypertensive subjects. Each point on the graph represents the average of atleast 25 independent measurements. Error bars are SEM; $^{*}P<0.05$, $^{**}P<0.01$, $^{***}P<0.001$, $^{\alpha}P<0.05$, $^{\beta\beta}P<0.01$ (two way ANOVA with Bonferroni posttest, using Graphpad prism 5.0). Inset is a comparison of thetreatment groups

**Better results than pharmaceutical medication**

doi: 10.4103/1119-3077.163278

# L-citrulline




3g/day

- L-citrulline effectively bypasses metabolism by the intestines and liver, enabling it to reach the kidneys, where it is converted into arginine
- **Arginine is a substrate for the synthesis of nitric oxide**
- **Nitric oxide regulates BP by inducing vasodilation**

# Protection from vascular ageing

## Taurine

1-6/g day

An important amino in controlling cardiovascular disease, taurine has a direct effect on blood vessel function, inducing vasorelaxation and regulating RAAS. Multiple mechanisms include: [8]

- ✓ Activates the protective arm of RAAS by increasing ACE2 expression; relaxing blood vessels
- ✓ Inhibits the adverse components of RAAS by reducing angiotensin II production
- ✓ Regulates electrolyte balance
- ✓ Reduces ROS-induced endothelial and vascular inflammation
- ✓ Nephroprotective and restores mitochondrial function

## Vitamin C

500mg /day

Evaluation of clinical trials confirm that dosing at 250mg twice daily significantly lowers blood pressure, with plasma concentrations inversely correlated with systolic and diastolic blood pressure and heart rate.[7]

- ✓ Diuretic activity, inducing sodium excretion
- ✓ Improves endothelial function and arterial compliance
- ✓ Recycles vitamin E
- ✓ Increases NO, PGI2, SOD and cyclic GMP
- ✓ Improves sympathovagal balance and aortic elasticity
- ✓ Enhances the efficacy of amlodipine, a calcium channel blocker

# Clinical investigations:

## General Pathology

| Investigation (Serum) | Important indices | Clinical significance |
|---|---|---|
| **Full blood count** | • Elevated WBC, CRP | • Underlying infection or inflammation |
| | • Haematocrit | • *Anaemia is a marker of polycythemia* |
| **Lipid analysis** | • Elevated triglycerides, LDL and/or HDL | • Greater risk for CVD, metabolic syndrome |
| **Electrolytes** | • Potassium (K+) | • K+ is important for CV function, hormonal regulation (hypokalaemia can indicate hyperaldosteronism) |
| | • Sodium (Na+) | • Some medications (diuretics) may deplete K+ |
| | • Calcium and phosphate | • Low Na+ requires immediate intervention, associated with developed CV conditions<br>• Markers for hyperparathyroidism |
| **Metabolites** | • Elevated creatinine<br>• Elevated urea | • Associated with renal dysfunction |
| | • Fasting glucose | • Hyperglycaemia is associated with secondary hypertension causes (Cushing's syndrome, primary aldosteronism) |
| **Homocysteine** | • Elevation | • Greater risk for HTN |
| **Vitamin D** | • Deficiency | • Can contribute to HTN, CVD |
| **Urinalysis** | • Glucose | • Associated with diabetes |
| | • Albuminuria<br>*Albumin: creatinine ratio* | • Sign of kidney disease, linked with HTN, kidney inflammation, and diabetes |
| | • Haematuria | • Can indicate infection, inflammation, kidney disease |

# Functional testing

| Functional testing | Clinical significance |
|---|---|
| **Essential fatty acids (EFA)** | • Deficient or imbalanced in HTN/CVD |
| **Total antioxidant status** | • High free radical load is shown with HTN; can be indicative of compromised liver function |
| **Functional liver detoxification profile** | • Compromised capacity will create extra burden on the heart, liver and kidneys; impacts EFA status |
| **Toxic nutrient screen** | • Heavy metal toxicity is implicated in HTN and will affect kidneys (as end-organ target) |
| **Electrocardiogram (ECG)** | • Indicative of hypertensive heart disease; identifies arrhythmias; screens for LVH |
| **Magnetic resonance imaging (MRI)** | • Considered in patients with neurologic disturbances, cognitive decline, and memory loss, to rule out TIA or stroke; to identify subclinical changes associated with elevated BP |

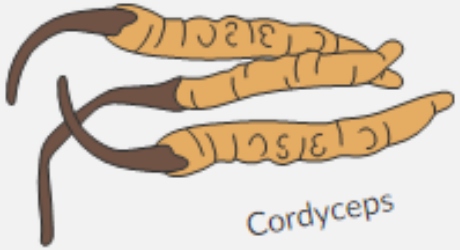
**CLINICAL NOTE**

A higher aldosterone-to-renin (ARR) ratio is a predictive measurement in normotensive patients for the development of HTN (within a 5-year period) - ARR imbalance is associated with new-onset HTN or incidental HTN.[59,60]

Shiitake

Maitake

Snow fungus



Cordyceps

Reishi

Turkey Tail

Poria

# Mycelial magic:
# Shielding the ageing heart and brain

**Mushrooms are miniature pharmaceutical factories, and of the thousands of mushroom species in nature, our ancestors and modern scientists have identified several dozen that have a unique combination of talents that improve our health.**

- Paul Stamets, American mycologist

# Reishi

## *(Ganoderma lucidum)*

- ✓ Antioxidative
- ✓ Antihypertensive
- ✓ Hypoglycaemic
- ✓ Lipid-lowering
- ✓ Anti-inflammatory
- ✓ Adaptogen

# Insulin resistance & Type 2 Diabetes

Study design:

- 71 patients with T2D
- 2 groups – **1800mg Reishi TDS** or placebo for 12 weeks

Results:

- ✓ **Significantly reduced HbA1c, fasting plasma glucose, postprandial glucose**
- ✓ Improvements seen in insulin and C-peptide levels, indicating **enhanced glucose metabolism**
- ✓ Values demonstrated no change or increased in the placebo group

# Shiitake
## *(Lentinula edodes)*

- ✓ Antioxidant
- ✓ Hepatoprotective
- ✓ Anti-hypertensive
- ✓ Lipid-lowering
- ✓ Anti-inflammatory
- ✓ Immunomodulatory
- ✓ Nutrient rich

# Research

- **Reduced lipidaemia-related factors** in serum, including total cholesterol, HDL cholesterol, non-HDL cholesterol
- **Significantly decreased (55%) serum triglyceride concentrations** relative to the control groups
- **62% reduction in serum leptin concentrations**
- Lowered pro-oxidative status & improved metabolic profiles

doi: 10.3945/jn.116.239806

# Cordyceps
## (*Cordyceps sinensis)*

- ✓ Anti-inflammatory
- ✓ Adaptogen
- ✓ Immunomodulating
- ✓ Regulates intestinal bacteria
- ✓ Antioxidant
- ✓ Anti-ageing
- ✓ Anti-hyperglycaemic
- ✓ Renal protection

# Research

Acta Pharmacol Sin. 2014 May;35(5):697-706. doi: 10.1038/aps.2013.186. Epub 2014 Mar 17.

## Cordyceps sinensis protects against liver and heart injuries in a rat model of chronic kidney disease: a metabolomic analysis

Xia Liu [1], Fang Zhong [2], Xu-long Tang [1], Fu-lin Lian [1], Qiao Zhou [2], Shan-mai Guo [2], Jia-fu Liu [3], Peng Sun [1], Xu Hao [2], Ying Lu [2], Wei-ming Wang [2], Nan Chen [2], Nai-xia Zhang [1]

Modulates metabolism in the extrarenal organs of CKD

**Significantly rescued liver and heart function** by reversing disrupted metabolite levels

Key findings:

- **Increased glutathione turnover**
- **Increased energy metabolism**
- **Restored key amino acids in the heart & liver**

# Snow Fungus

## *(Tremella fuciformis)*

- ✓ Anti-inflammatory
- ✓ Antioxidant
- ✓ Anti-ageing
- ✓ Lipid-lowering
- ✓ Hypoglycaemic
- ✓ Immunomodulatory
- ✓ Anti-cancer

# Mushrooms for the mind:

## *Fungi rescue the ageing brain*

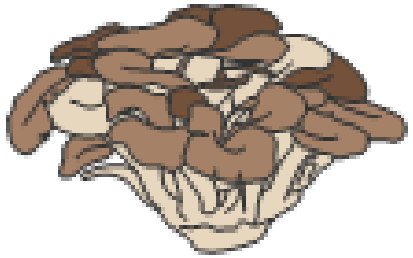
Review > Crit Rev Biotechnol. 2015;35(3):355-68. doi: 10.3109/07388551.2014.887649.

**Therapeutic potential of culinary-medicinal mushrooms for the management of neurodegenerative diseases: diversity, metabolite, and mechanism**

Chia-Wei Phan [1], Pamela David, Murali Naidu, Kah-Hui Wong, Vikineswary Sabaratnam

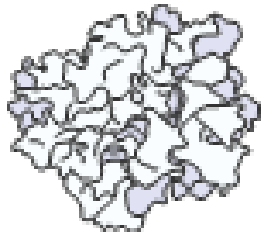
**Cordyceps:**

- Stimulates nerve growth synthesis
- Polysaccharides reduce free radicals and lipid peroxidation



**Maitake:**

- Enhances neurotrophic activity
- Attenuates neurotoxicity
- Supports neuronal cell repair, proliferation and survival



**Snow fungus:**

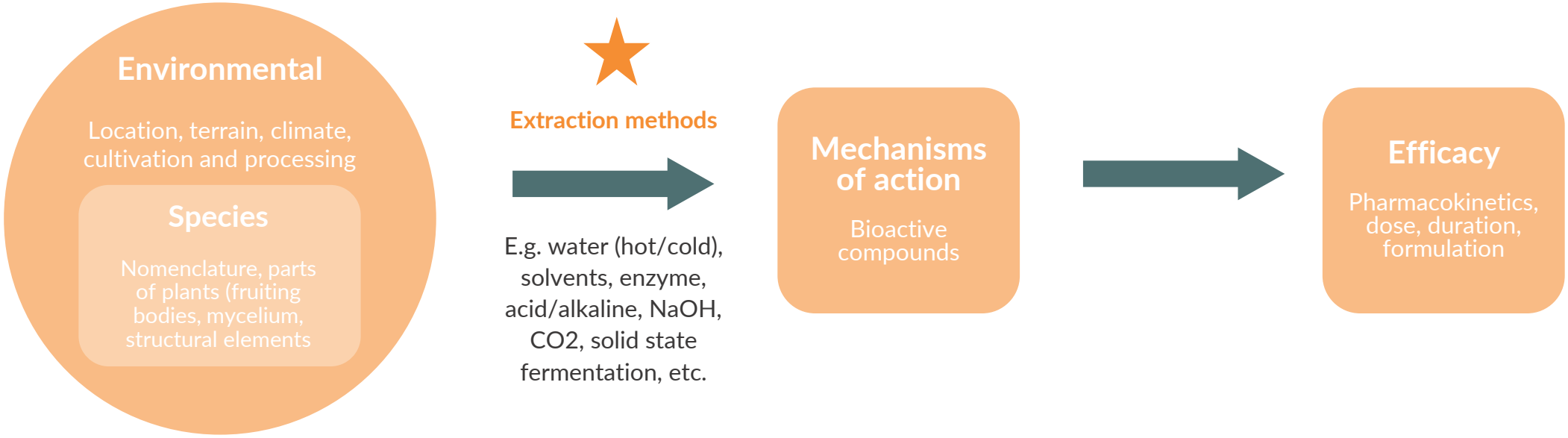
- Reverses memory deficits
- Promotes neurite outgrowth

**Reishi:**

- Suppresses reactive oxygen damage
- Enhances neurotrophic activity
- Attenuates microglial activity

# Making Medicinal Mushrooms Therapeutic

**Factors to consider if medicinal mushrooms are to be used for therapeutic and treatment purposes**




Extraction methods employed to isolate bioactive compounds must be a primary consideration in elucidating effects and mechanisms of action, and thus, efficacious targeting of physiological endpoints

doi:10.3390/molecules27072302

# Herbal alchemists for cardiometabolic prevention & treatment

*Nigella, Pomegranate & Garlic*



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# Nigella *(Nigella sativa)*

## Look for:

Plant part: Seed oil
Standardised for active constituent Thymoquinone (TQ)

## Required for:

- ✓ Antioxidant
- ✓ Anti-inflammatory
- ✓ Anti-hypertensive
- ✓ Anti-hepatotoxic
- ✓ Hypoglycaemic
- ✓ Lipid-lowering actions

# Broad scope of cardioprotective activity

| Therapeutic action | Mechanism |
|---|---|
| **Antioxidant/Anti-hypertensive** | Free radical scavenging activity = reduced ROS<br>Increases SOD, catalase and glutathione reductase |
| **Anti-inflammatory** | Reduces:<br>• NO synthase<br>• Pro-inflammatory cytokines via NF-κB pathway<br>• COX-2 |
| **Anti-dyslipidaemic** | ⇩ HMG-CoA reductase expression<br>⇧ LDL receptor expression, reducing cholesterol |
| **Anti-diabetic** | PPAR-γ agonist = improved insulin resistance<br>Inhibits α-glucosidase<br>Increases AMPK & GLUT4 receptors<br>Supports integrity & proliferation of β pancreatic cells |

# Clinical trial - dyslipidaemia

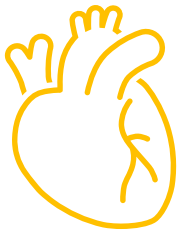
Randomised, placebo-controlled trial, 88 patients
18 years + with a total cholesterol concentration > 200mg/dl
Dose: **2g/day**
Duration: 4 weeks

**Significantly reduced:**

- **Total cholesterol ($p < 0.001$) 4.78%**
- **Low density lipoprotein (LDL) ($p < 0.001$) 7.6%**
- **Triglycerides ($p < 0.001$) 16.65%**

DOI: 10.5455/medarh.2012.66.198-200

# Clinical trial – CVD risk in hypertension



Randomised, double-blind, placebo-controlled trial
55 patients, managed with standard drug therapy
Dose: 2.5ml, BD - standardised for TQ
Duration: 8 weeks

**Significantly decreased:**

- Blood pressure ($p < 0.001$)
- Malondialdehyde ($p = 0.008$)
- Fasting blood sugar ($p < 0.001$)
- Cholesterol ($p = 0.009$)

**Significantly increased:**

- HDL ( $p= 0.007$)
- Glutathione reductase ($p < 0.001$)

# Pomegranate

**Look for:**

Plant part: Peel/hull

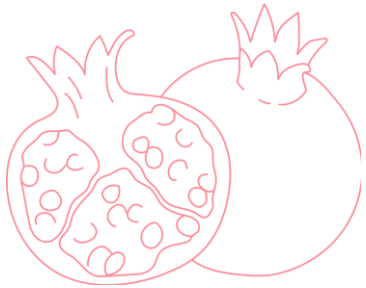
Standardised for active constituents:
- Punicalagins
- Ellagic acid

**Required for:**

✓ Anti-inflammatory
✓ Antioxidant
✓ Anti-atherogenic actions

# The full potential of punicalagins in cardiometabolic disease

- Decreases lipid plaque deposition
- Increases autophagy & mitochondrial health
- Antiplatelet activity
- Positive effects on lipoprotein metabolism & lipid homeostasis



- Improves endothelial function
- Influences gut microbiota
- Antioxidant activity
- Attenuates pro-inflammatory mediators

# Ellagic acid for T2D and its complications

Received: 23 April 2020 | Revised: 30 July 2020 | Accepted: 23 August 2020
DOI: 10.1002/ptr.6867

RESEARCH ARTICLE

WILEY

**Randomized double-blind clinical trial examining the Ellagic acid effects on glycemic status, insulin resistance, antioxidant, and inflammatory factors in patients with type 2 diabetes**

Mahnaz Ghadimi[1] | Farshad Foroughi[2] | Sima Hashemipour[3] | Mohamadreza Rashidi Nooshabadi[4] | Mohammad Hossein Ahmadi[5] | Bahman Ahadi Nezhad[6] | Hossein Khadem Haghighian[1,3]

44 patients with T2D
Dose: **180mg** or placebo
Duration: 8 weeks

**Outcome:**

- ✓ **Significantly decreased: total cholesterol, triglycerides and LDL, blood sugar and insulin resistance, CRP, TNF-α and IL-6** ($p < 0.05$)
- ✓ **Raised SOD enzymes & GPx activity** ($p < 0.05$)

# Garlic

## Look for:

Plant part:  Fresh bulb
Standardised for active constituents:

- Allicin
- Alliin

## Required for:

- ✓ Anti-inflammatory
- ✓ Antioxidant
- ✓ Anti-diabetic
- ✓ Kidney and neuroprotection
- ✓ Lipid-lowering activity

PeerJ

# Antioxidant and anti-inflammatory effects of allicin in the kidney of an experimental model of metabolic syndrome

Abraham Said Arellano Buendia[1,2], Juan Gabriel Juárez Rojas[3], Fernando García-Arroyo[2], Omar Emiliano Aparicio Trejo[2],

"Allicin exerts its beneficial effects on metabolic syndrome by considerably **reducing systemic and renal inflammation as well as oxidative stress.** These effects were **mediated through the Nrf2 pathway**. The results suggest **allicin may be a therapeutic alternative for treating kidney injury induced by the metabolic syndrome risk factors**."

International Journal of Molecular Sciences

MDPI

Int J Mol Sci. 2017 Sep; 18(9): 1980.

Published online 2017 Sep 16. doi: 10.3390/ijms18091980

*Article*

# The Beneficial Effects of Allicin in Chronic Kidney Disease Are Comparable to Losartan

Ehécatl Miguel Ángel García Trejo [1], Abraham Said Arellano Buendía [1], Omegar Sánchez Reyes [1], Fernando Enrique García Arroyo [1], Raúl Arguello García [2], María Lilia Loredo Mendoza [3], Edilia Tapia [1], Laura Gabriela Sánchez Lozada [1] and Horacio Osorio Alonso [1,*]

- **Relieved renal dysfunction, hypertension & oxidative stress**
- **Effects comparable or greater than losartan on blood pressure and renal function**
- More effective at restoring SOD & NO expression
- Decreased nephrin expression, albuminuria & urinary NAG excretion
- Prevented downregulation of angiotensin II receptors

# Allicin annihilates advanced glycation end products


*molecules*

Published: 12 December 2022

MDPI

*Article*

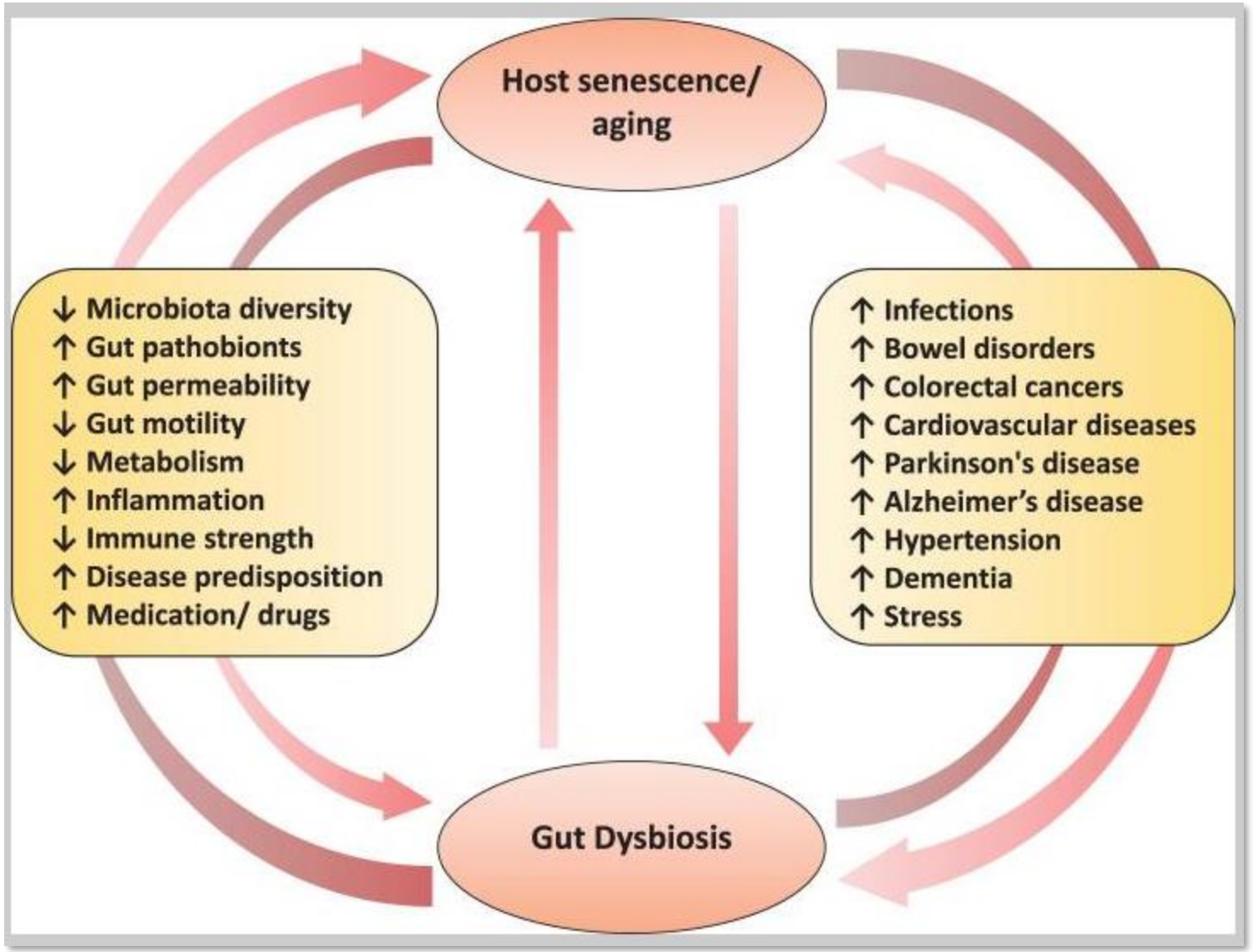
**Allicin Alleviates Diabetes Mellitus by Inhibiting the Formation of Advanced Glycation End Products**

Linzehao Li [1,†], Qinghe Song [2,†], Xiandang Zhang [3], Yan Yan [4,*] and Xiaolei Wang [1,*]

"Our research suggests that **allicin may alleviate diabetes** by inhibiting the formation of AGEs and **reducing RAGE levels to relieve oxidative stress** and **promote insulin secretion**."

# Gut Microbiome and Ageing

*Selective antimicrobials promote gut-driven metabolic shifts*



# Omega-3:

*An essential, but are we dosing high enough for clinical effect?*

**2-4g total (EPA & DHA)**:

- ✓ Improves arterial elasticity and reduces arterial stiffness
- ✓ Reduces inflammation, platelet aggregation and vasoconstriction
- ✓ Antagonises omega-6 derived proinflammatory eicosanoids
- ✓ Increases antioxidant activity, reduces lipid peroxidation and oxidative stress

# Current clinical perspectives

## Blood pressure

3g/day

Review > J Am Heart Assoc. 2022 Jun 7;11(11):e025071. doi: 10.1161/JAHA.121.025071. Epub 2022 Jun 1.

### Omega-3 Polyunsaturated Fatty Acids Intake and Blood Pressure: A Dose-Response Meta-Analysis of Randomized Controlled Trials

Xin Zhang [1], Jennifer A Ritonja [2], Na Zhou [1], Bingshu E Chen [2], Xinzhi Li [1]

Affiliations + expand

PMID: 35647665 PMCID: PMC9238708 DOI: 10.1161/JAHA.121.025071

## Dyslipidaemia

2-4g/day

Meta-Analysis > J Am Heart Assoc. 2023 Jun 6;12(11):e029512. doi: 10.1161/JAHA.123.029512. Epub 2023 Jun 2.

### Association Between Omega-3 Fatty Acid Intake and Dyslipidemia: A Continuous Dose-Response Meta-Analysis of Randomized Controlled Trials

Tianjiao Wang [1], Xin Zhang [1], Na Zhou [1], Yuxuan Shen [2], Biao Li [2], Bingshu E Chen [3], Xinzhi Li [1]

Affiliations + expand

PMID: 37264945 PMCID: PMC10381976 DOI: 10.1161/JAHA.123.029512

# No contraindications with common medications

**Common prescriptions**:

- Anticoagulants
- Antiplatelet agents
- ACE inhibitors
- Angiotensin II receptor blockers
- Beta blockers
- Calcium channel blockers
- Statins

**Bleeding risk is low** and seems not clinically relevant, even when antiplatelet therapy is concurrently administered

Natural Medicines Database: **Theoretical low to moderate interactions**
(risk of additive effects)

- **Separate dose by at least 2 hours** -

doi: 10.3389/fcvm.2021.802306

# What to look for: *purity from start to finish*

The quality and purity of fish oil supplements can **significantly alter** the **bioavailability** and **pharmacodynamics of its active ingredients.**

## Look for:

- ***When*** it has been tested
- ***What*** has been tested
- ***How low*** the testing goes

## How to compare like-for-like?

The simplest way to quantify that the highest standards possible have been checked at every box along the way **points straight back to test results *(see table below)*.**

1. Ask for independent 3rd party, **post-encapsulation** test results
2. Make sure important contaminants including **plasticisers, phthalates, and radioactive isotopes** have been included
3. Put the **results side-by-side** to choose the option that suits best

# Product highlights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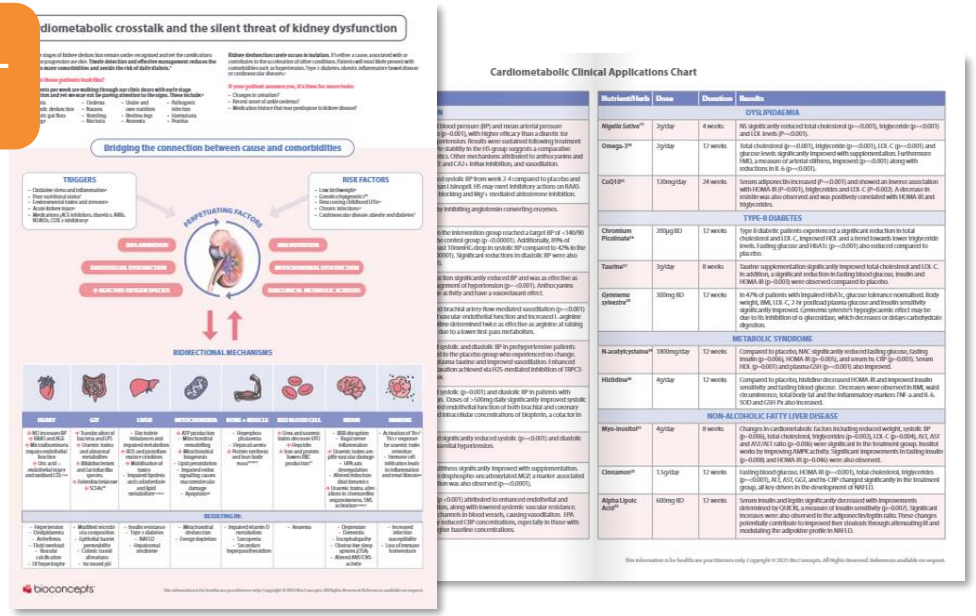
*Always read the label and follow the directions for use. Please note Orthoplex White products can only be purchased if you are an Orthoplex White approved customer.*

# Resources

**CLINICAL GUIDES**


**CLINICAL CHART**

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