

Berberine: A Review of the Evidence and a Practical Approach for Cardiometabolic Disorders

Jorg Nienhaus, MSc

Acupuncturist and physiotherapist

Praktijk aan het IJ, Mensendieck & Physiotherapy, Acupuncture & Shiatsu

Amsterdam, the Netherlands

www.praktijkaanhetij.nl

October 2026

Declarations

Conflict of interest

The author declares no conflict of interest. This review was not commissioned, funded or sponsored, and the author has no financial or commercial relationship with any manufacturer, importer or supplier of berberine, red yeast rice, or any other product named in this article.

Funding

This work received no external funding.

Declaration of generative AI and AI-assisted technologies in the writing process

In preparing this article the author used Claude (Anthropic, models Claude Opus 5 and Claude Opus 5.5) and, at earlier stages of the project, other general-purpose AI assistants. These tools were used to search and extract verbatim passages from the source literature, to build and query a structured database of those sources, to check the statements in the text against them, and to assist with drafting, editing and document production.

The author reviewed and edited all AI-assisted output, verified the factual claims and citations against the primary sources, and takes full responsibility for the content, the interpretation and the conclusions of this article. AI tools are not listed as authors, in line with the recommendations of the International Committee of Medical Journal Editors, because they cannot be responsible for the accuracy, integrity or originality of the work. Appendices 2 and 3 were drafted with AI assistance and reviewed by the author less closely than the main text, as is stated at the head of each.

Scope and intended use

This article is written for Dutch general practice and is a review, not a clinical guideline. It does not replace the NHG standards or individual clinical judgement, and nothing in it should be read as a recommendation to start, stop or alter treatment in an individual patient. The regulatory position described here is current as of September 2026 and is expected to change.

Copyright

© 2026 J. Nienhaus. Praktijk aan het IJ, Mensendieck & Physiotherapy, Acupuncture & Shiatsu, Amsterdam, the Netherlands

www.praktijkaanhetij.nl. All rights reserved. This article may be shared unaltered, with attribution, for individual educational and clinical use.

Table of Contents

Key clinical and scientific takeaways	5
When to consider berberine	5
Measured effect sizes	5
How berberine works	6
When NOT to use berberine.....	6
Dose, duration and monitoring	6
Overview: one compound, a synergistic network.....	6
Elaborate summary	7
What makes berberine clinically relevant	7
Background	7
Metabolic disorders.....	8
Cardiovascular disorders.....	10
Neurological, anti-inflammatory, antineoplastic and other disorders	11
Mechanisms of action.....	12
Safety and drug interactions	12
Conclusion and discussion.....	13
1. Introduction and Background.....	16
2. Clinical Evidence: Metabolic Disorders	19
2.1 Type 2 diabetes: the meta-analytic evidence.....	19
2.2 How berberine compares with metformin	20
2.3 Metabolic syndrome	21
2.4 Non-alcoholic fatty liver disease	22
2.5 Obesity.....	22
3. Clinical Evidence: Cardiovascular Disorders	24
3.1 Lipid lowering through a non-statin mechanism.....	24
3.2 Vascular endpoints and atherosclerosis	25
3.3 Arrhythmia	26
3.4 The limits of the cardiovascular evidence.....	26
4. Clinical Evidence: Antineoplastic, Anti-inflammatory, Reproductive and Neurological Effects ...	27
4.1 Antineoplastic activity: the strongest clinical-outcome evidence	27
4.2 Anti-inflammatory and immunomodulatory effects	28
4.3 Polycystic ovary syndrome (PCOS, recently renamed polyendocrine metabolic ovarian syndrome (PMOS))	28
4.4 Helicobacter pylori eradication.....	28
4.5 Neurological conditions.....	29
5. Safety and Drug Interactions.....	29
6. Pharmacology and Mechanisms of Action	32
6.1 Mechanisms of action	32

6.2 Synthesis: bioavailability, synergy, and durability	33
6.3 Comparison with single-target pharmaceuticals.....	34
6.4 Co-evolutionary context and what remains unknown	34
6.5 Berberine as a hormetic stressor (mitohormesis)	35
7. Discussion	36
7.1 The evidence in context: limitations and how to read them.....	36
7.2 Therapeutic positioning: where berberine fits.....	37
7.3 An interpretive point: how multi-target natural compounds are evaluated.....	38
8. A Practical 12-Week Approach for a Cardiometabolic Intervention in Primary Care	40
8.1 The rationale: why a structured intervention fits the NHG framework	40
8.2 Patient selection: a stepwise decision	40
8.3 The protocol, step by step	42
8.4 What this approach is, and is not.....	43
9. Conclusion.....	44
Appendix 1. References	45
Appendix 2. Berberine and red yeast rice: a practical comparison for general practice	50
A2.1 The two compounds side by side	50
A2.2 The decisive point: dose collapse under European law	50
A2.3 Where berberine is clearly stronger.....	51
A2.4 Where red yeast rice remains ahead.....	51
A2.5 Can the two be combined?	51
A2.6 The regulatory position, including berberine's own.....	52
A2.7 Practical guidance	52
A2.8 References for this appendix	53
Appendix 3. Glossary: terms, values and abbreviations explained.....	55
A3.1 Laboratory and clinical values	55
A3.2 Research and statistical terms	56
A3.3 Medical and pharmacological terms	57
A3.4 Abbreviations at a glance	59

Key clinical and scientific takeaways

Berberine acts on several targets at once, which is why its effects span several biomarkers and indications. Because cardiometabolic disease is driven by several risk factors together, modest effects on many of them, partly synergistic, can be expected to add up to a larger long-term benefit than a similar effect on a single risk factor. The evidence comes from roughly 100 trials and an estimated 20,000 participants, with overlap between the meta-analyses. The evidence gives a clear signal; as for many treatments in everyday medicine, more confirmation is needed for greater scientific certainty. With strong safety evidence, the balance of likely benefit against risk is favourable. The evidence fits the framework of systems biology and the related idea of xenohormesis, both of which echo the holistic, multi-component logic of the Chinese medicine from which berberine's use originates. A monitored, time-limited intervention is proposed here as a cautious option within the logic of the NHG standards, which do not mention berberine.

When to consider berberine

- Lower- and moderate-risk patients with mild dyslipidaemia, prediabetes, early type 2 diabetes or metabolic syndrome, including those who prefer a defined non-prescription step first.
- As an add-on: to a statin (insufficient LDL response and/or reduce statin side effects)
- As an add-on: to metformin, DPP-4 inhibitors or sulphonylureas.
- As an adjunct in H. pylori triple therapy and ulcerative colitis, and after polypectomy to prevent new adenomas.
- As well-tolerated prevention for all of the above, and possibly, though unproven, for healthy ageing.

Measured effect sizes

Pooled meta-analyses unless stated otherwise.

- HbA1c: ≈ 0.6 to 0.7 points lower than control, similar to metformin at the modest doses used in head-to-head trials; ≈ 0.6 to 0.9 points extra when added to other oral drugs.
- Fasting glucose: ≈ 0.6 to 0.9 mmol/L lower than placebo.
- Lipids versus placebo: LDL-cholesterol and triglycerides each roughly 15% lower (≈ 0.5 and ≈ 0.37 mmol/L), total cholesterol roughly 7%; the original trial found 20 to 35% from baseline. Added to a statin, meta-analyses mostly show further lowering.
- Waist: ≈ 3 cm smaller in metabolic syndrome, ≈ 1.8 cm in broader obesity trials.
- Fatty liver: lipids and HbA1c improve; liver fat $\approx 52\%$ lower with berberine plus lifestyle versus 36% with lifestyle alone (one trial).
- Inflammation: large falls in CRP, IL-6 and TNF- α .
- Colorectal adenoma (one large trial): about a third fewer patients with new adenomas 6 years after stopping (34.7% vs 52.1%). This is the strongest clinical-outcome result so far.
- Other add-on effects: H. pylori eradication 22% higher, ulcerative colitis response 22% higher, response in premature ventricular contractions 26% higher. In PCOS hormonal markers improve; stop berberine if pregnancy is planned or confirmed.
- Chronic schizophrenia (one 3-month trial): fewer negative symptoms when added to antipsychotics, with lower IL-6 and TNF- α .

How berberine works

Six mechanisms act in parallel and reinforce one another, mostly in the gut and liver:

- AMPK activation, as with metformin.
- More LDL receptors and less PCSK9.
- Gut-microbiome and bile-acid effects.
- GLP-1 release via bitter receptors.
- Inhibition of the inflammatory switches NF-κB and NLRP3.
- A mild, fasting-like cell stress (mitohormesis).

When NOT to use berberine

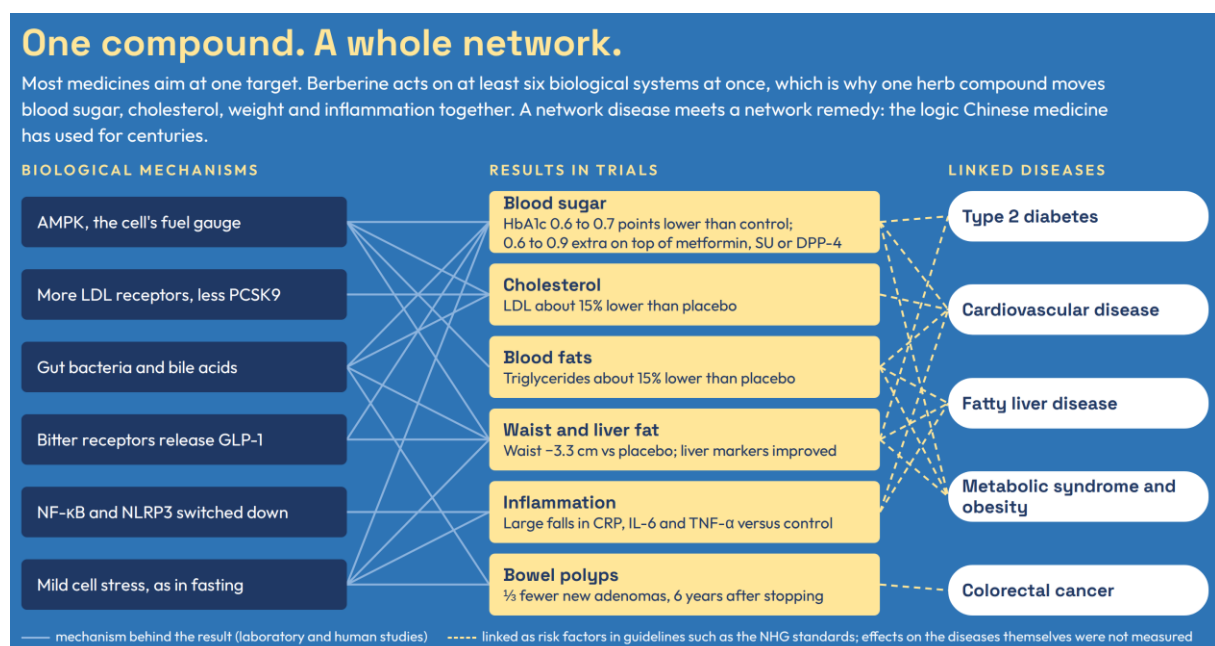
- Pregnancy, breastfeeding and neonates; known or suspected G6PD deficiency.
- eGFR below 30: discuss individually (a precaution).
- Interactions: proven with ciclosporin; expected with tacrolimus and CYP3A4-metabolised statins (simvastatin, atorvastatin, lovastatin); theoretical with warfarin (monitor INR) and with macrolides (arrhythmia risk).

Dose, duration and monitoring

- 500 mg twice daily with meals, taken at consistent times relative to food.
- A 12-week intervention: HbA1c, lipids, ALT and eGFR at baseline and at 12 weeks, then continue, combine or escalate following the NHG logic (Section 8).
- Side effects: mild, transient stomach and bowel complaints, usually settling within 2 to 4 weeks.

Overview: one compound, a synergistic network

Figure 1. Berberine's six mechanisms, the results measured in trials, and the diseases these results are linked to in guidelines. The links to diseases were not measured for berberine itself.



Elaborate summary

What makes berberine clinically relevant

Berberine is a plant alkaloid increasingly used by patients as a self-purchased supplement, often for diabetes, dyslipidaemia or weight concerns. This elaborate summary outlines what the current evidence does and does not support, places berberine accurately within a risk-stratified treatment framework, and aims to help it be used for patients' benefit, avoiding the two opposite errors of dismissing it as an unproven health trend or accepting it as a substitute for guideline-indicated therapy. This question is likely to arise more often from 2027, when the expected EU prohibition on monacolins removes red yeast rice, the lipid-lowering supplement patients most often turn to, from the market (see Appendix 2).

Berberine occupies a specific and clinically useful niche. Its combination of measurable biomarker benefits, a favourable safety profile, and a long history of human use makes it most defensible as a preventative and complementary, well-tolerated, biomarker-effective option in patients whose baseline cardiovascular risk is low enough that biomarker improvement, rather than rapid event reduction, is the goal: lower- and moderate-risk patients, statin-intolerant patients, and those preferring a defined non-prescription step before committing to long-term medication. It is not a substitute for guideline-indicated therapy in high- or very-high-risk patients, where the long-term outcome evidence of statins and metformin is decisive; in such patients it could be considered only as an add-on to that therapy, on the strength of its biomarker evidence.

Background

Berberine is a yellow and very bitter isoquinoline alkaloid extracted from the rhizome of *Coptis chinensis* (Huang Lian, the Chinese herb that gave berberine its name) and from several *Berberis* species. It has been used in Chinese medicine for over a thousand years, traditionally for gastrointestinal and inflammatory conditions. Modern pharmacological interest dates from the 1980s, with glycaemic and lipid effects systematically demonstrated from the early 2000s onward.

The evidence base for berberine is now substantial. In summary:

- Total evidence base: roughly 100 trials and an estimated 20,000 participants, though the meta-analyses overlap substantially in the primary trials they pool.
- Largest disease-specific meta-analyses: in type 2 diabetes, two largely overlapping pooled analyses cover 46 to 50 RCTs and about 4,150 participants each; in cardiovascular disease, a separate meta-analysis covers 44 RCTs and 4,606 participants.
- Three umbrella reviews: one synthesises 11 prior meta-analyses with 15,297 pooled participants for glycaemic and inflammatory outcomes.
- Empirical caveats: the individual underlying trials are typically small (most 60 to 200 participants) and short (mostly 4 to 24 weeks, range a week to 2 years). Most research is conducted in Chinese populations. Methodological quality of the reviews is mostly rated low to critically low, and most outcomes are graded low or very low for certainty. This is normal across medicine, where high-quality evidence is the exception (see Section 7.1). Eight outcomes reach HIGH-quality GRADE evidence in the most recent umbrella review: *Helicobacter pylori* eradication and its related outcomes (ulcer healing, symptom relief, fewer side-effects), body weight and BMI in cardiovascular disease, BMI in obesity, and the safety profile in type 2 diabetes. These are outcomes we can be confident are real; all eight are intermediate outcomes. Separately, the only patient-relevant clinical outcome so far, at moderate certainty, is colorectal-adenoma chemoprevention, where a placebo-

controlled RCT of 1,108 patients showed a reduction in adenoma recurrence that persisted through a 6-year post-treatment follow-up.

- Direction of effect: consistent and clinically meaningful on the biomarkers that matter in cardiometabolic disease (HbA1c, fasting plasma glucose, insulin resistance, lipids/cholesterol, anthropometric measures like BMI and inflammatory markers).

Metabolic disorders

The metabolic conditions below are not four separate diseases but overlapping expressions of one underlying process: insulin resistance and disordered glucose and lipid metabolism. Central obesity drives it; type 2 diabetes is its end-stage hyperglycaemic form; metabolic syndrome is the broader, earlier-stage cluster diagnosis and non-alcoholic fatty liver disease (NAFLD) is its hepatic manifestation. Because berberine acts on the shared upstream biology, it shows benefit across all four, though the strength of evidence and the size of effect differ. One consequence of this overlap is that the supporting meta-analyses draw on similar trial pools and the same biomarkers, so the four blocks are best read as consistent readings of one effect rather than four fully independent confirmations.

Type 2 diabetes

This is the largest and most robust body of metabolic evidence. The largest meta-analysis (50 RCTs, 4,150 participants; individual trials typically lasting 4 to 24 weeks, range 2 weeks to 6 months) distinguishes how berberine performs on its own and how much it adds on top of conventional therapy.

Pooled across all trials, berberine lowers HbA1c by about 0.6 to 0.7 percentage points, fasting glucose by about 0.8 to 0.9 mmol/L and two-hour glucose by about 1.2 mmol/L versus control; the largest glucose-focused meta-analysis grades the HbA1c and fasting-glucose effects as moderate certainty. The effect is present when berberine is used on its own (HbA1c about 0.4 to 0.7 points lower than placebo) and is largest when it is added to metformin, sulphonylureas or DPP-4 inhibitors (a further 0.6 to 0.9 points); with insulin the added effect was small and not significant. Pooled head-to-head trials, mostly against metformin at 1.5 g a day or less, found no significant difference, although metformin's own trials suggest berberine alone is somewhat less potent than full-dose metformin. Trials differ widely, and nearly all were short and Chinese. Each biomarker below is shown first as berberine alone versus placebo, then as berberine added to a conventional agent versus that agent alone:

- HbA1c: as monotherapy, $\approx$ 0.4 to 0.7 percentage point reduction versus placebo; added to conventional therapy, a further $\approx$ 0.6 to 0.9 percentage points.
- Fasting glucose: as monotherapy, $\approx$ 0.6 to 0.9 mmol/L lower versus placebo; added to conventional therapy, $\approx$ 0.7 to 1.1 mmol/L lower.
- 2-hour post-prandial glucose: as monotherapy, $\approx$ 1.5 to 1.9 mmol/L lower versus placebo; added to conventional therapy, $\approx$ 1.0 to 1.3 mmol/L lower.
- Insulin sensitivity: added to conventional therapy, a large improvement (fasting insulin and HOMA-IR both fall, SMD around -1); in the berberine-alone trials, most of which compared berberine with metformin rather than placebo, no significant difference from the control treatment.
- Inflammatory markers: as monotherapy, single-study signal only; added to conventional therapy, large reductions in CRP (SMD ≈ -1.4), IL-6 (≈ -1.8) and TNF- α (≈ -1.6).
- Synergy: clearest when berberine is combined with metformin, DPP-4 inhibitors or sulphonylureas; weaker or absent with insulin.

In short, berberine alone lowers HbA1c somewhat less than full-dose metformin does against placebo, performed similarly to metformin at the doses used in direct trials, and adds about as much as a second oral agent when combined; the decisive difference remains that metformin has long-term outcome data (UKPDS) while berberine does not, at least not yet.

Metabolic syndrome

A dedicated meta-analysis (12 placebo-controlled RCTs, 889 patients) reported the following pooled effects versus placebo, at berberine 300 to 1,500 mg/day for 12 to 20 weeks:

- Fasting plasma glucose: ≈ 0.5 mmol/L reduction.
- 2-hour oral glucose tolerance: ≈ 1.6 mmol/L reduction.
- Waist circumference: ≈ 3 cm reduction (in this metabolic-syndrome population; see the obesity block below for the separate, smaller figure from broader obesity trials).
- HDL-cholesterol and blood pressure: no significant effect.
- Adverse events: no excess versus placebo.

NAFLD (non-alcoholic fatty liver disease)

A meta-analysis of 6 RCTs (501 patients) found lower total and LDL-cholesterol and lower HbA1c, and the most recent umbrella review found 13 of 15 NAFLD outcomes significantly improved. Liver fat itself was measured directly in one 16-week RCT in 184 patients with NAFLD and impaired glucose regulation, randomised to three arms: lifestyle intervention alone, lifestyle plus pioglitazone, or lifestyle plus berberine 1.5 g/day (about 60 patients per arm):

- Hepatic fat content: reduced by 52.7% with berberine plus lifestyle versus 36.4% with lifestyle alone. Berberine matched the pioglitazone intervention on hepatic fat and glucose control, and beat it on body weight and lipids; no heart failure or bone fractures, known risks of pioglitazone, were observed in either group.

Obesity

A dose-response meta-analysis (9 RCTs, roughly 1,000 participants) measured body metrics change versus control.

- BMI: ≈ 0.3 kg/m² reduction.
- Waist circumference: ≈ 1.8 cm reduction overall, rising to about 2.4 cm in women and at doses above 1 g/day. This is measured in a broader, mixed obesity population and is a different figure from the ≈ 3 cm reported in the metabolic-syndrome block above; the two do not conflict, they simply come from different trial populations.
- Effect modifiers: greater with baseline BMI above 30 kg/m², doses above 1 g/day, and treatment longer than 12 weeks.

Cardiovascular disorders

Berberine's cardiovascular evidence comes from two distinct bodies of work: monotherapy lipid trials, and trials of berberine added to conventional therapy that measure vascular and inflammatory endpoints. The two are reported separately below.

The lipid evidence comes from a meta-analysis of placebo-controlled trials (8 trials for LDL-cholesterol, 9 for triglycerides) and from the foundational placebo-controlled trial in hypercholesterolaemia (91 patients, 63 on berberine, no statin co-treatment), which reported two sets of figures: the whole treated cohort, and a cleaner subgroup of patients on no other drugs, herbs or special diets.

Lipid outcomes

Berberine lowers lipids through a mechanism distinct from statins: it stabilises hepatic LDL receptors and downregulates PCSK9.

- Total cholesterol: $\approx$ 7% lower than placebo in pooled trials; in the original trial $\approx$ 18% from baseline in the full group, $\approx$ 29% in the berberine-alone subgroup.
- LDL-cholesterol: $\approx$ 15% lower than placebo in pooled trials; in the original trial $\approx$ 20% and $\approx$ 25%.
- Triglycerides: $\approx$ 15% lower than placebo in pooled trials ($\approx$ 22% in patients with raised lipids); in the original trial $\approx$ 28% and $\approx$ 35%.
- HDL-cholesterol: unchanged.
- Combined effect: added to statins or other lipid-lowering drugs, meta-analyses mostly show further lowering of total cholesterol and triglycerides; the extra LDL effect is less consistent.
- Statin combination: lower incidence of muscle pain (myalgia) and lower elevated transaminases (ALT, AST) than statin alone, making berberine a useful add-on where statins are poorly tolerated.

Put in context: berberine's LDL-C reduction (roughly 15% against placebo in pooled trials, 20 to 25% from baseline in the original trial) is at or below the level of a low-intensity statin and smaller than moderate- or high-intensity statins, which lower LDL-C by roughly 30 to 49% or more, and it is achieved through a complementary mechanism. This compares lipid lowering only. Statins have cardiovascular outcome trials behind them and berberine does not, so similar movement in LDL-C should not be read as similar protection against cardiovascular events. Because the mechanisms do not overlap, berberine and statins can be combined.

Vascular outcomes

Vascular outcomes come from a different and larger body of evidence: the largest cardiovascular meta-analysis (44 RCTs, 4,606 participants), in which berberine was added to conventional therapy across ischaemic stroke, coronary heart disease and atherosclerosis.

- Inflammatory markers (in the stroke-adjunct trials specifically): significantly reduced.
- Lipids: adding berberine to routine therapy produces further reductions in total cholesterol, LDL-C and triglycerides, with HDL-C unchanged. (Where berberine was used alone instead of routine therapy or a statin, the lipid differences were not statistically significant.)
- Carotid intima-media thickness: reduced (SMD $\approx$ -0.52), a marker of subclinical atherosclerosis, independently replicated in post-stroke patients; stroke severity on the NIHSS fell markedly (SMD $\approx$ -1.24).

- Arrhythmia (premature ventricular contractions): added to antiarrhythmic therapy, $\approx$ 26% more patients responded than with antiarrhythmic therapy alone, with no change in PR, QRS or QT intervals (unlike many conventional antiarrhythmics). In the subgroup where berberine replaced the conventional drug, both adverse reactions and recurrence were roughly 60% lower than with the conventional drug.

Hard cardiovascular endpoint data, however, remain scarce: the single available heart-failure mortality trial predates modern guideline-directed therapy (the contemporary four-pillar regimen was only fully assembled by 2021) and is not directly applicable to current Dutch practice, although the biomarkers berberine does improve are those the Dutch NHG guidelines are built around.

Neurological, anti-inflammatory, antineoplastic and other disorders

This domain spans neurological, anti-inflammatory and antineoplastic indications. The evidence quality varies sharply by indication, from the strongest clinical-outcome evidence in the whole berberine corpus down to predominantly preclinical work.

Colorectal-adenoma chemoprevention (the strongest clinical-outcome evidence)

A placebo-controlled RCT of 1,108 patients receiving berberine 0.3 g twice daily for 2 years after polypectomy reduced adenoma recurrence from 47% to 36% at 2 years. In a post-treatment follow-up of the same cohort over a median of 6 years, recurrence was 34.7% with berberine versus 52.1% with placebo, with an adjusted hazard ratio of 0.58 (95% CI 0.45 to 0.74); at 6.9 years after randomisation, 43.0% of berberine patients versus 18.5% of placebo patients remained completely adenoma-free, despite treatment having stopped years earlier.

Ischaemic stroke (the main clinical neurological signal)

In acute ischaemic stroke, berberine added to conventional therapy improved inflammatory and vascular markers (17 RCTs, 1,670 patients): carotid intima-media thickness was reduced and stroke severity on the NIHSS fell by about 1.4 points (5 trials).

Anti-inflammatory effects across domains

Berberine consistently reduces CRP, IL-6 and TNF- α . Clinical anti-inflammatory effects have been demonstrated in ulcerative colitis (meta-analysis of 10 RCTs, 952 patients; clinical response about 22% higher, with reduced endoscopic Baron and disease-activity scores) and in chronic schizophrenia (3-month RCT of 134 patients; berberine 900 mg/day added to existing antipsychotic therapy reduced negative-symptom scores by $\approx$ 10 points on the SANS scale, with parallel reductions in IL-1 β , IL-6 and TNF- α).

Polycystic ovary syndrome (PCOS, recently renamed polyendocrine metabolic ovarian syndrome (PMOS))

12 RCTs, 1,544 women (berberine 900 to 2,000 mg/day). Fertility outcome depends on the comparator: live birth rates were similar to placebo and to metformin, but lower than with letrozole ($\approx$ 39% fewer live births and $\approx$ 21% lower ovulation per subject). It improved endocrine markers versus placebo (lower total testosterone $\approx$ 0.34 nmol/L, lower LH and LH/FSH; higher SHBG) and outperformed metformin on testosterone, waist measures and SHBG with comparable glucose control.

Helicobacter pylori eradication

In a meta-analysis of 13 randomised trials in Chinese populations, berberine added for the 7 to 14 days of standard triple therapy (a proton pump inhibitor plus two antibiotics) improved eradication by $\approx 22\%$, with better ulcer healing and symptom relief, and reduced treatment side-effects by $\approx 35\%$.

Alzheimer's, Parkinson's, post-stroke depression and neuropathy

Evidence here is predominantly preclinical, with no published human RCTs of meaningful size, but the direction is consistent: in animal and cell models berberine reduces amyloid- β and tau pathology and neuroinflammation (Alzheimer's models), limits α -synuclein aggregation and dopaminergic-neuron loss (Parkinson's models), and shows antidepressant and nerve-protective effects in post-stroke-depression and neuropathy models. These findings are mechanistically encouraging but remain unproven in humans.

Mechanisms of action

Berberine acts on six mechanisms in parallel, most of them in the gut and liver rather than via systemic absorption:

- AMPK activation: shifts cells toward energy production; more glucose uptake, fat burning and mitochondrial adaptation, less fat/cholesterol synthesis and growth signalling. With repeated activation, it supports improved mitochondrial function, metabolic flexibility, and insulin sensitivity.
- Hepatic LDL-receptor stabilisation and PCSK9 downregulation: berberine's predominant lipid action is to increase LDL clearance from the blood rather than to block cholesterol synthesis as statins do, a complementary (non-duplicating) mechanism; it also modestly reduces lipid synthesis indirectly through AMPK activation.
- Gut microbiome and bile-acid modulation: gut bacteria convert berberine to more absorbable metabolites and shift the microbial community toward producers of short-chain fatty acids such as butyrate, with downstream metabolic effects via the gut-liver axis.
- Bitter-taste receptor (TAS2R) signalling on gut enteroendocrine cells: releasing GLP-1, the same hormone targeted by GLP-1 receptor agonists.
- NF- κ B and NLRP3 inflammasome inhibition: the principal switches of chronic low-grade inflammation, plausibly contributing to the consistent inflammation biomarker reductions (CRP, IL-6 and TNF- α) seen across trials.
- Xenohormesis and mitohormesis: berberine acts partly as a mild metabolic stressor (mitohormesis), the same adaptive response triggered by fasting and exercise. This links to the broader, still-unproven hypothesis of xenohormesis, that plant stress-compounds activate protective responses in those who consume them, and offers a rationale for why whole-plant preparations may capture effects that isolated berberine misses.

Safety and drug interactions

Berberine has a favourable safety profile. This is also one of its best-supported findings: the adverse-event evidence in type 2 diabetes is graded HIGH in the most recent umbrella review. Across the largest meta-analysis (50 RCTs, 4,150 participants) no serious adverse events were reported in the 16 trials that reported adverse-event data, and no hepatotoxicity signal has emerged. The commonest adverse effects are mild, transient gastrointestinal symptoms (diarrhoea, constipation, abdominal discomfort), dose-related and usually subsiding within 2 to 4 weeks. Notably, in berberine-statin

combinations the combined regimen produced a lower incidence of muscle pain and elevated transaminases than statin monotherapy, an unusual safety advantage of particular interest in statin-intolerant patients. In its 2026 draft opinion, however, EFSA could not establish a safe intake for berberine preparations (Appendix 2).

Five practical cautions:

- Pregnancy, lactation, neonates: avoid, because of kernicterus risk from bilirubin displacement; also avoid in known or suspected G6PD deficiency, where a single case report describes acute haemolysis after exposure to a berberine-containing preparation.
- Renal impairment (eGFR < 30 mL/min/1.73 m²): no dose-adjustment data exist for severe renal impairment, so this inclusion for safety is precautionary rather than based on a demonstrated harm; discuss individually before initiation.
- Drug interactions: three tiers. Proven in clinical data: berberine raises cyclosporine blood levels (transplant recipients). Theoretical: warfarin is a CYP2C9 substrate, but controlled human studies of the combination are lacking; monitor INR where it cannot be avoided. Expected from its pharmacology: it inhibits CYP3A4, CYP2C9, CYP2D6 and P-glycoprotein and can raise levels of drugs cleared by these routes, with the same interaction anticipated for tacrolimus (not tested directly). Most important to watch, though theoretical: with macrolide antibiotics or statins berberine could in principle inhibit the hERG cardiac channel and affect arrhythmia risk, but this is a mechanistic caution, not a harm seen in the available trials, where the cardiac and combination data have in fact been reassuring (no QT change, and fewer muscle and liver effects with berberine-statin combination). Monitor when co-prescribing.
- Glucose-lowering combinations: berberine's own risk of hypoglycaemia is low, and in combination trials with metformin, sulphonylureas, DPP-4 inhibitors, GLP-1 receptor agonists or insulin only mild hypoglycaemia has been reported; additive hypoglycaemia is therefore possible but uncommon. Monitor when combining with agents that themselves carry hypoglycaemia risk.
- Supplement quality: product content is not formally guaranteed; advise patients to choose standardised berberine extracts from reputable manufacturers with independent testing.

Conclusion and discussion

Berberine's evidence base is now substantial, internally consistent and clinically meaningful on the biomarkers that matter in cardiometabolic disease, with eight outcomes reaching HIGH-quality GRADE evidence (*Helicobacter pylori* eradication and related outcomes, body weight and BMI, and safety in type 2 diabetes) and with one indication, colorectal-adenoma chemoprevention, reaching a patient-relevant clinical outcome rather than a biomarker. Its multi-target pharmacology complements the statins and partly overlaps with metformin, and its safety profile is favourable. The biomarker evidence rests on roughly 100 trials and an estimated 20,000 participants, with clear empirical limitations, yet across this heterogeneous base the direction and size of effect are consistent. When many differently designed trials point the same way, the underlying signal is likely real. Used carefully, with the knowledge this paper provides, berberine is compatible with conventional drugs and a reasonable, potentially valuable additional option in primary care.

One interpretive point deserves emphasis. Modern research is built to detect single-target drugs through short trials measuring one or two biomarkers, a powerful design that systematically under-detects interventions, natural compounds, lifestyle measures, microbiome-directed strategies, that act across several interacting systems and accumulate over time. Chronic cardiometabolic disease is itself a networked process spanning metabolism, immunity, vascular biology and the gut, and a multi-target agent acting modestly on each may yield integrated long-term benefit that no single short-term trial captures. This argues for longer, outcome-based trials and fair consideration in clinical decisions, not for claiming unmeasured benefits.

This thinking is not new. Traditional Chinese Medicine has long treated chronic disease as a disturbance of multiple interacting subsystems, favouring whole herbs over isolated compounds, multi-herb formulas, and treatment matched to the individual's pattern. Berberine's modern pharmacology, including its action as a mild hormetic stressor, in many respects vindicates that systems-level approach, which is worth recognising as a methodological resource rather than a historical curiosity, a framing that complements rather than replaces the conventional evidence on which berberine's positioning rests.

The main article text elaborates on this summary and translates the evidence into a monitored addition intended to sit within the logic of the existing NHG framework: a structured 12-week intervention for selected low- and moderate-risk patients with mild dyslipidaemia, prediabetes or early type 2 diabetes, with baseline bloodwork, a defined dose and duration, parallel lifestyle advice, and a pre-agreed decision at 12 weeks to continue, combine, or escalate to guideline-indicated medication.

Main text

1. Introduction and Background

Berberine is a plant alkaloid that an increasing number of patients in the Netherlands buy and use on their own initiative, usually for cardiometabolic concerns: type 2 diabetes, raised cholesterol, metabolic syndrome, weight management. It is sold as a food supplement rather than a registered medicine, and online it is sometimes incorrectly marketed as “natural Ozempic” or “poor man’s Ozempic”. This means it sits outside the prescribing pathway a GP normally works within, but it does not sit outside the consultation. Patients may ask about it, take it alongside prescribed drugs, and sometimes use it instead of starting a statin or metformin. This is also about to become a more frequent question. Red-yeast-rice supplements, long used for self-treatment of raised cholesterol, are being removed from the EU market after EFSA concluded in 2025 that no safe intake of their active monacolins could be identified, and patients who used them are likely to look for a replacement, berberine among the most obvious. That history is worth keeping in view: monacolin K is chemically a statin that was sold as a supplement, and its withdrawal illustrates what is at stake when a pharmacologically active compound is taken at drug-like doses outside medical supervision. The same consideration applies to berberine, and is part of the reason this article sets out a supervised, time-limited protocol rather than a recommendation to use it. A working knowledge of what berberine is, what it does, and where its evidence is strong or weak is therefore useful for patients and primary-care practice.

This article has three purposes. The first is to give a balanced, evidence-based account of what berberine has been shown to do across the major disease domains in which it has been studied, with attention to the quality of that evidence and to the points a patient or a GP needs for patient counselling and safety. The second is to translate that evidence into something practical: a structured, time-limited way of using berberine that fits within the existing Dutch guideline framework rather than competing with it. The article closes with a 12-week approach for carefully selected patients, set out in enough detail to be used in practice. Lastly, this article aims to show how the systems theory of the centuries-old knowledge of Traditional Chinese Medicine can contribute to modern clinical practice and medical science.

The clinical evidence on berberine is now substantial. The largest single trial-level meta-analyses are those of Wang et al. (2024) in type 2 diabetes (50 RCTs, 4,150 participants), Guo et al. (2021), also in type 2 diabetes (46 RCTs, approximately 4,158 participants), and Yang et al. (2023) in cardiovascular disease (44 RCTs, 4,606 participants). Above these sit three umbrella reviews (Nazari et al., 2024; Li et al., 2023; Shi et al., 2025), synthesising prior meta-analyses across the metabolic, cardiovascular, inflammatory and gastrointestinal domains. These umbrella reviews are themselves valuable for their evidence-quality grading: Li et al. (2023) and Shi et al. (2025) both apply AMSTAR-2 and GRADE systematically to the underlying systematic reviews and consistently rate methodological quality as predominantly low to critically low. Shi et al. (2025) applied GRADE systematically and rated eight berberine outcomes as HIGH-quality evidence: in *Helicobacter pylori* therapy (eradication, peptic-ulcer healing, symptom relief, and fewer treatment side-effects), in body weight and BMI in cardiovascular disease, in BMI in obesity, and in the safety profile in type 2 diabetes. The large majority of the remaining outcomes were graded low or very low, as is common across medicine (see Section 7.1). These eight are outcomes we can be confident are real; without exception they are intermediate outcomes (mostly biomarkers and blood markers). Colorectal-adenoma recurrence

stands apart: a cancer-precursor outcome from a large placebo-controlled RCT, with benefit persisting through a 6-year post-treatment follow-up, and the only place in the berberine literature where moderate-certainty evidence attaches to a patient-relevant clinical outcome. This evidence-quality picture is the empirical anchor for the limitations discussion in Section 7. Cumulatively, the evidence covers roughly 100 trials and an estimated 20,000 participants, though the meta-analyses overlap in the primary trials they pool (Wang et al., 2024 alone contributes 4,150 participants, Guo et al., 2021 a substantially overlapping 4,158, Yang et al., 2023 in cardiovascular disease 4,606, with additional non-overlapping participants from the disease-specific meta-analyses and stand-alone RCTs in PCOS, *H. pylori*, obesity, NAFLD, ulcerative colitis, schizophrenia and colorectal adenoma). Across this heterogeneous evidence base the direction and magnitude of effect on the key outcomes (HbA1c, fasting plasma glucose, insulin resistance, blood lipids, anthropometric measures, and inflammatory markers) is consistent, and clinically meaningful rather than trivial; when many differently designed trials point the same way, the underlying signal is likely to be real.

Throughout, a deliberate distinction is maintained between three kinds of evidence: findings from randomised controlled trials (RCTs) and meta-analyses in humans; mechanistic or preclinical work in cells and animals; and the traditional use of the parent herb in Chinese medicine. These are not interchangeable, and misinterpreting them is the most common way berberine is either oversold or unfairly dismissed.

Chemically, berberine is an isoquinoline alkaloid found in several plant families, with the highest concentrations in the rhizome of *Coptis chinensis* (Huang Lian), as well as in various *Berberis* species. In Traditional Chinese Medicine (TCM), *Coptis Rhizoma* has been used for centuries, principally for gastrointestinal infections and other inflammatory conditions classified in the TCM framework as “damp-heat” syndromes (Lan et al., 2015; Ai et al., 2021). In TCM, herbal (and other) interventions are tailored to the patient’s diagnosed TCM pattern (the theoretical holistic TCM model evaluating a person, its environment and its characteristics, signs and symptoms) in combination with the disease, rather than to the disease alone. In modern China the herb has also been available for decades as an inexpensive over-the-counter remedy for bacterial diarrhoea (Kong et al., 2004; Yin et al., 2008). This long record of human use is relevant to the safety discussion later in this article, but it is not in itself evidence of efficacy for cardiometabolic or other disease; that case rests on the modern trial literature.

Table 1. Berberine evidence by indication, ordered by strength of evidence.

Indication / outcome	Evidence base	Main effect	Strength (GRADE) HIGH means we can be confident the effect is real, not that it is large; LOW and MODERATE are the usual grades across medicine	What this means
H. pylori: eradication, ulcer healing, symptom relief (adjunct)	13 RCTs, 7 to 14 days (Hu 2020); umbrella GRADE (Shi 2025)	Eradication ~22% higher; ulcer healing +15%; symptoms +11%; side-effects -35%	HIGH	High-certainty intermediate outcomes (not a hard endpoint)
Body-mass index and body weight	Umbrella GRADE (Shi 2025); CVD & obesity meta-analyses	Modest but reliable reduction in BMI (~0.3 kg/m ²) and body weight	HIGH	High certainty of a modest effect
Safety / adverse events in type 2 diabetes	Umbrella GRADE (Shi 2025)	Favourable safety profile; no serious harm signal	HIGH	High-certainty safety evidence
Colorectal-adenoma recurrence	1 large RCT, n=1,108, 2-yr treatment (Chen 2020) + 6-yr post-treatment follow-up (Tan 2025)	Recurrence ~23% lower at 2 yr; at 6 yr, 34.7% vs 52.1%, adjusted HR 0.58; effect persists after stopping	MODERATE	The only patient-relevant clinical outcome; moderate certainty
Type 2 diabetes (add-on)	50 RCTs, n=4,150, 2 wks to 6 mo (Wang 2024)	Added to conventional therapy: HbA1c -0.7 pp; fasting glucose -1.0 mmol/L	MODERATE	Large consistent sample; typical of accepted treatments
Dyslipidaemia (LDL, triglycerides)	44 RCTs, n=4,606, 7 d to 2 yr (Yang 2023); Liu 2025, 12 placebo-controlled RCTs; Kong 2004, 3 mo	LDL and triglycerides each ~15% lower than placebo (Liu 2025); -20 to -25% and -28 to -35% from baseline (Kong 2004)	MODERATE	Consistent across trials; short durations
Cardiovascular biomarkers	44 RCTs, n=4,606, 7 d to 2 yr (Yang 2023)	Improved CRP, lipids, carotid thickness	MODERATE	Biomarker-level, no hard-outcome data yet
Metabolic-inflammatory (umbrella)	11 meta-analyses, 15,297 (Nazari 2024)	Significant ↓ HbA1c, glucose, HOMA-IR, CRP, IL-6	MODERATE	Broad, consistent biomarker benefit
Metabolic syndrome	12 RCTs, n=889, 12 to 20 wks (Liu 2025)	Waist -3.3 cm; triglycerides, glucose, LDL improved	LOW-MODERATE	Smaller trials; consistent direction
Ulcerative colitis (adjunct)	10 RCTs, n=952, duration not reported (Li 2024)	Clinical response ~22% higher	LOW-MODERATE	Add-on benefit; modest trial base
PCOS / PMOS	12 RCTs, 3 to 24 wks (Xie 2019)	Ovulation ~51% higher vs no treatment, not vs placebo; androgens and SHBG improved	LOW-MODERATE	Coherent endocrine effect; reproductive endpoints less robust
Premature ventricular contractions	10 RCTs, n=896, 7 to 30 days (Qiao 2023)	Response ~26% higher as add-on; no QT prolongation	LOW-MODERATE	Adjunctive benefit only
Ischaemic stroke (adjunct)	17 RCTs, n=1,670, 8 d to 6 mo (Luo 2023)	↓ stroke severity (NIHSS), ↓ carotid thickness, ↓ inflammation	LOW-MODERATE	Add-on; heterogeneous trials
NAFLD (fatty liver)	6 RCTs, n=501 (meta-analysis in Li 2023); liver fat: 1 RCT, n=184, 16 wks (Yan 2015)	Lipids and HbA1c improved; liver fat -53% with berberine plus lifestyle vs -36% with lifestyle alone (1 RCT)	LOW	Pooled biomarkers consistent; liver-fat result from one trial
Cardiovascular events / mortality	1 small trial, 8 wks treatment, up to 9 yr follow-up (Zeng 2003)	No reliable estimate	VERY LOW	Not a basis for hard-outcome claims

Reading the Strength column: **HIGH** means we can be confident the effect is real; it does not mean the effect is large, or that the outcome is a hard clinical endpoint. **LOW** and **MODERATE** are the usual grades across medicine and are not by themselves a sign of weak evidence (see Section 7.1). Berberine reaches **HIGH** for eight outcomes, all of them intermediate; colorectal-adenoma recurrence, graded **MODERATE**, is the only patient-relevant clinical outcome in a contemporary treatment setting.

2. Clinical Evidence: Metabolic Disorders

The metabolic domain, which covers type 2 diabetes, insulin resistance, metabolic syndrome and non-alcoholic fatty liver disease, is where berberine has been studied most extensively and where the evidence is strongest. This section sets out that evidence and places the effect sizes in context.

2.1 Type 2 diabetes: the meta-analytic evidence

The trial evidence answers three different questions, which are best kept apart. On its own, berberine lowers glucose: against placebo or lifestyle advice alone, HbA1c fell by 0.38 percentage points in Guo et al. (2021; 9 trials, 786 patients), by 0.68 points in the placebo-controlled trials of Wang et al. (2024) and by 0.71 points in Lan et al. (2015; 5 trials), with fasting glucose 0.58 to 0.90 mmol/L lower. Added to conventional glucose-lowering drugs, berberine lowers HbA1c further: by 0.58 points in Lan et al. (2015; 7 trials), 0.69 points in Wang et al. (2024; 25 trials) and 0.91 points in Guo et al. (2021; 27 trials, about 2,500 patients). In Wang et al. (2024) the added effect was 0.79 points on top of metformin, 0.79 on top of DPP-4 inhibitors, 0.68 on top of sulphonylureas and 0.60 on top of metformin plus a sulphonylurea, but only 0.29 points, not statistically significant, on top of insulin. Compared directly with oral glucose-lowering drugs, mostly metformin, berberine showed no significant difference (Section 2.2). Across 37 trials and 3,048 patients, Xie et al. (2022) graded the certainty of the HbA1c and fasting-glucose effects as moderate, and found larger falls when baseline HbA1c was 9% or higher (0.79 versus 0.58 points); the umbrella reviews grade the same outcomes low to very low (Li et al., 2023; Shi et al., 2025). Heterogeneity between trials is high throughout, and the meta-analyses overlap in the trials they pool.

Pooling all comparisons together, the largest meta-analyses report a reduction in HbA1c of roughly 0.6 to 0.7 percentage points, accompanied by parallel reductions in fasting plasma glucose, markers of insulin resistance, blood lipids, and inflammatory markers (Nazari et al., 2024; Guo et al., 2021). The umbrella meta-analysis by Nazari et al. (2024) synthesised 11 prior meta-analyses (15,297 pooled participants) across type 2 diabetes, prediabetes, metabolic syndrome, fatty liver disease and polycystic ovary syndrome, and reported significant reductions in HbA1c, fasting glucose, fasting insulin, insulin resistance (HOMA-IR), and the inflammatory markers CRP, IL-6 and TNF- α . Guo et al. (2021), pooling 46 RCTs of 4 weeks to 6 months duration, reported an HbA1c reduction of 0.73% and a fasting glucose reduction of 0.86 mmol/L, in Guo's own subgroup analysis, promising fasting-glucose effects at doses below 1 g/day; the HbA1c effect was strongest in trials of eight to twelve weeks, while the two-hour glucose effect was larger in longer trials.

This dose-and-duration pattern in Guo et al. (2021) is a gradient observed within the berberine trials themselves: the effect builds over the first months of treatment, but it is not simply larger at higher doses: lower doses did at least as well for fasting glucose. It is not a comparison with metformin and does not indicate a time-course unique to berberine. Most oral glucose-lowering agents, including metformin, show a comparable build-up of effect over the first weeks to months of treatment; the available evidence does not include head-to-head data on whether berberine's effect beyond three months differs from metformin's. The genuinely distinctive durable effect documented for berberine lies in a different domain, colorectal-adenoma chemoprevention, and is discussed in Section 4.1.

The most recent and most clinically detailed synthesis is Wang et al. (2024), which pooled 50 RCTs and 4,150 participants. Its most useful contribution is its analysis of berberine as an add-on therapy. In the 33 trials in which berberine was added on top of a conventional glucose-lowering drug, every measured outcome improved relative to the conventional drug alone: HbA1c fell by a mean of 0.69 percentage points, fasting glucose by 0.99 mmol/L, two-hour postprandial glucose by 1.07 mmol/L, with further improvements in fasting insulin, insulin resistance, the full lipid panel, and inflammatory markers. The synergy was clearest when berberine was combined with metformin, with DPP-4 inhibitors, or with sulphonylureas; when combined with insulin, the additional benefit was smaller and less consistent. In the 17 berberine-alone trials of the same analysis, most of which compared berberine with another drug rather than with placebo, the overall HbA1c difference was not significant (0.24 percentage points); against placebo it was 0.68 points in favour of berberine, and against metformin 0.05 points, essentially no difference.

One practical nuance from the same analysis concerns dose. In the combination setting specifically, lower berberine doses (at or below 0.9 g/day) performed at least as well as higher doses for several outcomes, including fasting insulin, LDL-cholesterol and HDL-cholesterol (Wang et al., 2024). This finding applies only to combination therapy; it is not a general statement about berberine monotherapy, where the evidence, including the Guo et al. (2021) dose gradient above, points the same way: lower doses perform at least as well. The most plausible explanation offered for the combination finding is a pharmacokinetic one: at higher doses berberine may inhibit drug-metabolising enzymes and so alter the handling of the co-administered drug. The point is returned to in the dosing guidance in Section 8.

2.2 How berberine compares with metformin

Meta-analyses establish that berberine works, this section compares it to the drug that would otherwise be prescribed. Three meta-analyses have pooled trials that compared berberine directly with an oral glucose-lowering drug, and none found a significant difference. Lan et al. (2015) pooled seven such trials, against metformin, sulphonylureas, rosiglitazone and other agents, with about 500 patients: HbA1c differed by 0.1 percentage points (95% CI -0.33 to 0.14). In Guo et al. (2021) all four head-to-head trials used metformin as the comparator (275 patients): HbA1c differed by 0.06 points (95% CI -0.26 to 0.37) and fasting glucose by 0.25 mmol/L (95% CI -0.18 to 0.68). Wang et al. (2024) identified six trials against metformin: HbA1c differed by 0.05 points (95% CI -0.59 to 0.69). The meta-analyses share several of these trials, and the umbrella review of Li et al. (2023) rates the comparisons with metformin, on fasting glucose, post-meal glucose, fasting insulin and insulin resistance, as low to very low certainty.

The best-documented single head-to-head trial is Yin et al. (2008). In the monotherapy arm of that study, 36 adults with newly diagnosed type 2 diabetes were randomised to either berberine 500 mg three times daily or metformin 500 mg three times daily, for 13 weeks. The glucose-lowering effect of berberine was similar to that of metformin: in the berberine group, HbA1c fell from 9.5% to 7.5%, fasting glucose from 10.6 to 6.9 mmol/L, and postprandial glucose from 19.8 to 11.1 mmol/L. Because it is randomised and reports the fullest data, it carries real weight. With 36 patients randomised, of whom 31 completed the study, and no blinding reported, it was not designed to prove equivalence: it shows the two performed similarly, not that they are interchangeable. A

second arm of the same study added berberine to existing therapy in 48 patients with poorly controlled diabetes, where it further reduced HbA1c from 8.1% to 7.3% and reduced fasting insulin and insulin resistance.

Two caveats keep these results from being read as equivalence. First, most of the direct comparisons used metformin at 1.5 g per day or less, and in the metformin trials themselves higher doses lowered HbA1c by a further 0.26 percentage points compared with lower doses, up to 2,000 mg per day (Hirst et al., 2012). Second, the indirect comparison points the same way: in 35 randomised trials, metformin monotherapy lowered HbA1c by 1.12 percentage points versus placebo, and by 0.95 points when added to another oral drug (Hirst et al., 2012), against about 0.4 to 0.7 and 0.6 to 0.9 points for berberine (Section 2.1). Such indirect comparisons across different trial populations are approximate. On this evidence berberine alone is likely somewhat less potent than full-dose metformin, performs similarly at the doses used in the direct trials, and as an add-on contributes an effect of the same order as adding a second oral drug.

Placed in clinical context, this is a meaningful effect. The common second-line oral agents add a further 0.5 to 1.0 percentage points to metformin, so berberine's add-on effect of about 0.6 to 0.9 points falls within the range of established oral hypoglycaemic therapy. The honest and important qualification is one of evidence type, not effect size: metformin's place in therapy rests not only on its HbA1c effect but on decades of clinical-endpoint data, including reduced mortality and myocardial infarction in long-term outcome trials. Berberine has no equivalent body of clinical-endpoint outcome evidence in diabetes yet. The two performed similarly on the biomarker, but they are not comparable on proven long-term outcomes: there is no trial evidence that berberine's biomarker effects translate into the same clinical-endpoint benefits that have been demonstrated for metformin.

On tolerability, the head-to-head trial does not allow a direct comparison with metformin. In that study, 20 of 58 berberine-treated patients (34.5%) experienced transient gastrointestinal effects (diarrhoea, constipation, flatulence, abdominal pain), counted across the monotherapy and add-on parts of the study together, and no rate was reported for the metformin group; the protocol reduced berberine to 300 mg three times daily where gastrointestinal effects were heavy. Wang et al. (2024) reported no serious adverse events in the 16 trials reporting adverse-event data, with adverse-event rates in three of the included trials actually lower with berberine than with the comparator drug.

2.3 Metabolic syndrome

In metabolic syndrome specifically, a 2025 meta-analysis of 12 placebo-controlled trials (889 participants; Liu et al., 2025) gave pooled estimates for berberine at 300 to 1,500 mg/day for 12 to 20 weeks; Liu's subgroup analysis found short-term treatment (≤ 90 days) more effective than longer treatment for LDL- and HDL-cholesterol, although duration findings differ between meta-analyses (Wang et al., 2024, found the LDL-cholesterol effect of monotherapy only in trials of three months or longer). Triglycerides fell by 0.37 mmol/L, fasting plasma glucose by 0.52 mmol/L, and waist circumference by 3.3 cm (all significant). On the secondary indicators, LDL-cholesterol fell by 0.50 mmol/L, total cholesterol by 0.45 mmol/L, BMI by 0.4 kg/m², and 2-hour oral glucose tolerance by

1.6 mmol/L (all significant). Not every trial measured every outcome: the triglyceride estimate pools 9 trials (666 participants) and the LDL-cholesterol estimate 8 (750 participants). In participants with dyslipidaemia the triglyceride reduction was larger (0.51 mmol/L) than in other populations (0.26 mmol/L). Liu reports these effects in mmol/L only; set against the starting levels in Kong et al. (2004), one of the included trials (LDL-cholesterol 3.2 to 3.7, triglycerides 2.2 to 2.3, total cholesterol 5.9 to 6.1 mmol/L), they correspond to roughly 15% for LDL-cholesterol and triglycerides, about 22% for triglycerides in dyslipidaemia, and about 7% for total cholesterol. No significant effect was seen on HDL-cholesterol or blood pressure, and adverse events were not more frequent than with placebo. The cluster of effects is coherent: berberine improves several components of the metabolic syndrome simultaneously rather than acting on one in isolation, which is consistent with its multi-target pharmacology.

2.4 Non-alcoholic fatty liver disease

Non-alcoholic fatty liver disease (NAFLD; increasingly termed metabolic dysfunction-associated steatotic liver disease) is closely tied to insulin resistance and is a common, often unaddressed finding in patients with metabolic syndrome. Pooled evidence comes from a meta-analysis of 6 RCTs (501 patients), summarised in the umbrella review of Li et al. (2023), which found lower total cholesterol (by about 0.48 mmol/L), LDL-cholesterol (about 0.45 mmol/L) and HbA1c (about 0.35 percentage points), graded low certainty, and from the umbrella overview of Shi et al. (2025), in which 13 of 15 NAFLD outcomes for berberine were significantly improved. Liver fat itself was measured directly in one trial, the three-arm RCT by Yan et al. (2015), which randomised 184 patients with NAFLD and impaired glucose regulation to lifestyle intervention alone, lifestyle plus pioglitazone, or lifestyle plus berberine 1.5 g/day, for 16 weeks. Hepatic fat content was measured directly and objectively by magnetic resonance spectroscopy.

Berberine added to lifestyle reduced hepatic fat content by 52.7%, compared with 36.4% for lifestyle alone ($p = 0.008$), a statistically significant difference, and to a degree comparable to pioglitazone. Berberine also produced greater improvements in body weight, insulin resistance and lipids than lifestyle alone, and the trial indicated it reduced liver fat beyond what its weight-loss effect alone would explain, pointing to a direct hepatic action. The comparison with pioglitazone deserves emphasis for a GP audience: In this trial berberine matched pioglitazone on hepatic fat and glucose while outperforming it on body weight and lipids, and no congestive heart failure or bone fractures were observed in either group. Berberine matched it on the efficacy endpoint without carrying pioglitazone's known side-effect burden (Yan et al., 2015). This is one of the clearer illustrations in the whole evidence base of berberine's favourable balance of effect and risk; it is the same risk-and-benefit theme that runs through the metformin comparison in Section 2.2 and the therapeutic positioning in Section 7.

2.5 Obesity

Obesity is the upstream driver of much of the metabolic dysfunction discussed above, and berberine has been assessed here in a dose-response meta-analysis of 9 RCTs and roughly 1,000 participants, with trial durations from 4 to 52 weeks (Xiong et al., 2020). Berberine produced a small but significant reduction in body mass index (0.29 kg/m^2) and in waist circumference (1.78 cm), with the waist effect larger in women and at doses above 1 g/day (about 2.4 cm in each of those subgroups).

Pooled body weight, by contrast, did not change significantly (-0.11 kg). This is not a true dissociation, since BMI and weight are mathematically linked for a fixed height; rather, the three measures were reported by different and only partly overlapping subsets of trials (BMI from 9 trials and 983 participants, waist from 7 trials, but body weight from only 5 trials and 378 participants (participant totals calculated from Xiong's trial table)), and the body-weight analysis rested on the smallest, least-powered sample. The most that can be said is that berberine's effect on body size is modest, most reliably detected as a reduction in BMI and in abdominal (waist) measurement. The effect was greater in patients with a baseline BMI above 30 kg/m^2 , at doses above 1 g/day , and with treatment longer than 12 weeks. The waist-circumference figure here (about 1.8 cm) is a different and smaller estimate than the roughly 3 cm reported in the dedicated metabolic-syndrome population (Section 2.3); the two come from different trial populations rather than being in conflict. Notably, body-mass index and body weight are among the eight outcomes the Shi et al. (2025) umbrella review rated as HIGH-quality GRADE evidence: the certainty that berberine produces these anthropometric reductions is high, even though the magnitude of the weight effect is modest.

3. Clinical Evidence: Cardiovascular Disorders

3.1 Lipid lowering through a non-statin mechanism

Berberine's cardiovascular relevance begins with its effect on blood lipids, and the foundational study is Kong et al. (2004), which identified berberine as a cholesterol-lowering compound working through a mechanism distinct from that of statins. Statins inhibit cholesterol synthesis; berberine instead increases the liver's capacity to clear LDL-cholesterol from the blood, by stabilising the messenger RNA for the hepatic LDL receptor and thereby raising the number of LDL receptors on the liver-cell surface. Later mechanistic work added that berberine also downregulates PCSK9, a liver protein that would otherwise degrade LDL receptors, and which is itself the target of the injectable PCSK9 inhibitors (alirocumab, evolocumab) used in specialist lipid practice (Feng et al., 2019). The two mechanisms, more LDL receptors made and fewer destroyed, both push in the same direction.

On the clinical effect size, the pooled placebo-controlled trials of Liu et al. (2025) show LDL-cholesterol and triglycerides each roughly 15% lower than placebo (Section 2.3). The foundational trial, Kong et al. (2004; 91 patients randomised, 63 to berberine and 28 to placebo), reported two sets of larger figures, and the difference between them is simply the patient group each describes. In the whole group of 63 patients who received berberine, three months of treatment reduced total cholesterol by about 18%, triglycerides by about 28%, and LDL-cholesterol by about 20%. The larger, often-quoted figures, namely a reduction of about 29% in total cholesterol, 35% in triglycerides, and 25% in LDL-cholesterol, come from a cleaner subgroup of 32 of those patients who were taking no other lipid-lowering drugs, herbs, or special diets, and who therefore isolate berberine's effect on its own. The larger figures are thus the confounder-free estimate; the more conservative figures are all treated patients, some of whom were on other treatments. Both sets are changes from baseline within the berberine arm rather than placebo-adjusted between-group differences, and Kong does not report a between-group estimate with a confidence interval, so they are best read as the size of the change seen on treatment rather than as an effect attributable to berberine alone. The pooled placebo-controlled estimate above is therefore the better guide to the size of the effect. Either way, two features are consistent. First, berberine's LDL-cholesterol effect is real and clinically useful, though smaller than that of a moderate-intensity statin (for example atorvastatin 10 to 20 mg, rosuvastatin 5 to 10 mg, or simvastatin 20 to 40 mg daily), which typically lowers LDL-cholesterol by 30 to 49%. Second, berberine's effect on triglycerides is proportionally large in this trial; across the pooled placebo-controlled trials it is roughly 15%, and about 22% in patients with dyslipidaemia, comparable to or somewhat above the 10 to 20% reduction usually seen with statins. These statin figures are established properties of statins in clinical use rather than findings from the berberine literature (Nederlands Huisartsen Genootschap, 2024). Because berberine and statins act through non-overlapping mechanisms, the two can be combined: a controlled human study of berberine 1.0 g/day plus simvastatin 0.02 g/day (Kong et al., 2008) reported additive lipid lowering, and meta-analyses of berberine added to lipid-lowering drugs mostly confirm further lowering (Lan et al., 2015; Yang et al., 2023), although one pooled analysis found no significant additional LDL effect (Zhang et al., 2019, as summarised by Li et al., 2023). Separately, the combination has been associated with a lower incidence of muscle pain and elevated transaminases (ALT, AST) than control (Li et al., 2023). Berberine-statin combination preparations (for example marketed European products combining berberine with red yeast rice, the natural source of monacolin K) have been used in statin-intolerant patients with acceptable safety, but their availability in the EU is ending: EFSA concluded in 2025 that

no safe daily intake of monacolins from red yeast rice could be identified, and a Commission regulation prohibiting monacolins in food supplements was approved by the Member States in May 2026 and is expected to apply after a transitional period (position as of September 2026). The drug-interaction picture is dose-dependent. At a dose close to the one this article recommends, berberine 300 mg three times daily (900 mg/day) for two weeks decreased the activity of several cytochrome P450 enzymes (CYP3A4, CYP2C9 and CYP2D6), the liver's main drug-processing system, in healthy volunteers, raising exposure (AUC) to the CYP3A4 probe drug midazolam by about 40% (Guo et al., 2012). Simvastatin, atorvastatin and lovastatin are themselves CYP3A4 substrates, as is monacolin K, which is chemically lovastatin. Combining berberine with a statin is therefore reasonable on mechanistic grounds, but it is a reason for dose caution and for the muscle- and liver-related monitoring set out in Section 8, not a reason to assume no interaction. What is missing from the evidence base is not the combination data itself but a dedicated cardiovascular-outcome trial. The available evidence is at the level of blood lipids and biomarkers, not clinical events.

3.2 Vascular endpoints and atherosclerosis

Beyond the lipid panel, the largest cardiovascular meta-analysis to date (Yang et al., 2023; 44 RCTs, 4,606 participants, with treatment lasting from 7 days to 2 years) examined berberine added to conventional therapy across ischaemic stroke, coronary heart disease and atherosclerosis. It reported improved clinical efficacy across all three, with consistent reductions in inflammatory markers (hs-CRP, IL-6, TNF- α), in lipid markers, and in carotid intima-media thickness, a measurement of arterial-wall thickness used as a marker of subclinical atherosclerosis. On the atherosclerotic-plaque markers, berberine, most clearly when added to statins, reduced carotid intima-media thickness, the Crouse score, and the number of unstable plaques. These vascular findings were independently replicated in a post-stroke meta-analysis (Luo et al., 2023; 17 RCTs, 1,670 participants, treatment from 8 days to 6 months). That two separate meta-analyses, each a study that statistically pools the results of many individual trials, arrive at the same vascular signal, drawing on largely different underlying trials, makes the finding more credible than either would be alone.

It is worth setting this against the established comparator. A useful reference point is the meta-analysis of statin therapy and carotid intima-media thickness by Huang et al. (2013; 21 RCTs, 6,317 participants), which found that statins reduce carotid wall thickness by a pooled weighted mean difference of about 0.029 mm versus placebo. That analysis also found, through meta-regression, that the strongest single lipid predictor of carotid regression was triglyceride reduction. This is an interesting point of contact: berberine has a substantial effect on triglycerides, particularly in patients with raised lipids. It raises the plausible, but not yet proven, hypothesis that the carotid findings seen with berberine and the established carotid effect of statins may share a triglyceride-lowering common pathway. This should be read as a mechanistic hypothesis worth investigating, not as proof that berberine and statins produce the same vascular effect. The two bodies of evidence are also not matched for duration: Huang's analysis required a minimum of six months of follow-up, whereas the berberine trials range from a week to two years, so the comparison is indicative rather than like-for-like.

3.3 Arrhythmia

A meta-analysis of 10 RCTs (896 participants) found that berberine added to standard antiarrhythmic therapy reduced premature ventricular contractions and improved clinical efficacy, with no QT-interval prolongation reported in any included trial (Qiao et al., 2023). That reassurance is bounded by duration. Every included trial ran between 7 and 30 days, and Qiao's authors note that properly assessing antiarrhythmic efficacy requires longer follow-up than any of the pooled trials provided. The absence of QT prolongation over a month does not establish arrhythmia safety over a year. The absence of QT prolongation is the clinically relevant safety point: many conventional antiarrhythmic drugs lengthen the QT interval and thereby carry a risk of dangerous arrhythmia, so an add-on agent that reduces extra (ectopic) heartbeats, that is, beats arising outside the heart's normal pacemaker, without that liability is of genuine interest. This is the same favourable balance seen elsewhere in this article: a useful effect achieved without the specific risk that limits the conventional comparator. As with the other cardiovascular findings, however, this is a positive but biomarker-level result, not an outcome trial. Where berberine replaced rather than supplemented the antiarrhythmic drug, the incidence of adverse reactions and the recurrence rate were each roughly 60% lower than with the conventional drug (Qiao et al., 2023).

3.4 The limits of the cardiovascular evidence

The cardiovascular evidence for berberine is consistent and mechanistically coherent, but it stops short of hard endpoints. The one trial reporting a mortality outcome is Zeng et al. (2003), a small Chinese trial of 156 patients with chronic congestive heart failure, in which berberine added to standard therapy for 8 weeks was associated with reduced symptoms, improved cardiac function, and lower mortality (7 deaths vs 13, $p < 0.02$) over a follow-up ranging from 6 months to 9 years (mean 24 ± 58 months), at 1.2-2.0 g/day, above the range used in the metabolic trials. This finding has never been replicated. More importantly for the Dutch situation, the trial was conducted on a heart-failure treatment backbone that predates modern guideline-directed therapy, it long precedes the routine use of ARNIs, SGLT2 inhibitors and mineralocorticoid-receptor antagonists. It should be regarded as hypothesis-generating only, and it is not a basis for using berberine in the management of heart failure in current practice.

4. Clinical Evidence: Antineoplastic, Anti-inflammatory, Reproductive and Neurological Effects

This section covers the domains outside the metabolic and cardiovascular systems: the antineoplastic evidence, which is the strongest clinical-outcome finding in the whole berberine literature; the anti-inflammatory and immunomodulatory effects; the reproductive-endocrine evidence in polycystic ovary syndrome; the gastrointestinal evidence in *Helicobacter pylori* eradication; and the neurological evidence, which remains largely preclinical. The evidence quality varies sharply across these indications, and they are presented here strongest-first.

4.1 Antineoplastic activity: the strongest clinical-outcome evidence

The single strongest piece of clinical-outcome evidence in the entire berberine literature is in colorectal-adenoma chemoprevention, and it is the one indication in this review that reaches a patient-relevant clinical outcome rather than a biomarker. Adenoma recurrence is a precursor of cancer rather than cancer itself, so it is best described as a clinically relevant outcome rather than as a hard endpoint such as death or a diagnosed cancer. Chen et al. (2020) conducted a large multicentre, double-blind, placebo-controlled RCT in which 1,108 patients who had had colorectal adenomas removed were randomised to berberine 0.3 g twice daily or placebo for two years, with follow-up colonoscopy. In the analysed population, recurrent adenoma occurred in 36% of the berberine group versus 47% of the placebo group, about 23% lower (significant), with constipation as the only notable adverse effect and no serious adverse events reported.

A post-treatment follow-up of the same cohort (Tan et al., 2025), the CBAR Follow-up Extension study, examined 648 of the original participants over a median of 6 years and found the protective effect was not only durable but had strengthened after treatment stopped. Adenoma recurrence over the extended follow-up occurred in 34.7% of the berberine group (109 of 314) versus 52.1% of the placebo group (174 of 334), with an adjusted hazard ratio of 0.58 (95% CI 0.45 to 0.74; $p < 0.001$). The figure of 42% sometimes quoted for this result is the reduction in hazard, not a reduction in the recurrence rate: the rates themselves differ by 17.4 percentage points, a relative reduction of about a third. Because these proportions come from a subset of the original cohort followed for much longer, they are not directly comparable with the raw 36% versus 47% figure from the 2-year colonoscopy in Chen et al. (2020). The protective effect reached statistical significance from year 3 after treatment and remained stable from year 5 onwards; on Kaplan-Meier analysis at 6.9 years, 43.0% of the berberine group remained free of adenoma versus 18.5% of the placebo group. Occurrence of any neoplasm was also reduced, by about 25% (significant). The follow-up did not itself analyse gut microbiota or bile-acid profiles, although a durable microbiome shift is one plausible explanation of the long time effects. A two-year course of berberine therefore produced a chemopreventive effect that persisted, and continued to widen, for at least six years without further treatment. This is a genuine clinical-outcome result, in a Western-relevant indication, from a well-conducted trial, and it stands apart from the rest of the evidence base in quality: on the GRADE assessment in Section 7 it is the only moderate-certainty finding that is also a patient-relevant clinical outcome. It is a follow-up of a randomised trial rather than a randomised comparison in its own right, which is why it is reported here separately from the two-year trial result.

Beyond this specific indication, berberine's broader anticancer activity rests on preclinical work, with mechanisms including cellular energy depletion (Fan et al., 2013) and interference with homologous-recombination DNA repair (Hou et al., 2017). Outside colorectal-adenoma chemoprevention, human oncology data are limited and exploratory.

4.2 Anti-inflammatory and immunomodulatory effects

One of the most consistent findings across the whole berberine literature is a reduction in the inflammatory markers CRP, IL-6 and TNF- α , seen repeatedly in cardiometabolic populations (Nazari et al., 2024; Guo et al., 2021; Wang et al., 2024). In the Nazari et al. (2024) umbrella synthesis these reductions are large by conventional standards (standardised mean differences of approximately -1.7 for CRP, -1.2 for IL-6 and -1.0 for TNF- α , where an SMD above 0.8 is considered a large effect). Because chronic low-grade inflammation is a shared mechanism across metabolic, vascular and other chronic disease, this is mechanistically important rather than incidental. The anti-inflammatory effect has also been demonstrated in clinical settings outside cardiometabolic disease. In ulcerative colitis, a meta-analysis of 10 RCTs (952 participants), which does not report the treatment durations of the pooled trials, found that berberine added to standard 5-aminosalicylic acid therapy improved clinical response by about 22% and improved endoscopic (Baron) and disease-activity scores (Li et al., 2024). In chronic schizophrenia, a 3-month randomised trial (Pu et al., 2023; 134 randomised, 106 completers) found that berberine 900 mg/day added to existing atypical antipsychotic therapy reduced negative-symptom scores on the SANS scale (by about 10 points, significant) and produced concurrent significant reductions in IL-1 β , IL-6 and TNF- α , with the cytokine reductions statistically predicting the clinical improvement.

4.3 Polycystic ovary syndrome (PCOS, recently renamed polyendocrine metabolic ovarian syndrome (PMOS))

In polycystic ovary syndrome (PCOS), a meta-analysis of 12 RCTs (1,544 women overall, with up to 577 participants pooled per individual outcome; Xie et al., 2019) assessed berberine at 900 to 2,000 mg/day over 3 to 24 weeks. Berberine reduced total testosterone (by about 0.34 nmol/L) and luteinising hormone, increased sex-hormone-binding globulin, and lowered the LH/FSH ratio. It improved ovulation per cycle against no treatment (RR 1.51, 95% CI 1.23 to 1.86), though not against placebo (RR 1.03, 95% CI 0.95 to 1.11). The reproductive effect depended on the comparator: live birth rates were similar to placebo and to metformin, but lower than with letrozole, which outperformed berberine on live birth (RR 0.61, 95% CI 0.44 to 0.82), pregnancy (RR 0.57) and ovulation per subject (RR 0.79). Against metformin, berberine produced a greater reduction in total testosterone and a greater rise in SHBG, with greater reductions in waist circumference and waist-to-hip ratio and comparable glucose control. The rate of gastrointestinal events was essentially unchanged versus placebo. This is a coherent endocrine-metabolic profile consistent with berberine's action elsewhere, though the reproductive endpoints remain less robust than its metabolic ones. Xie's own conclusion is that there is no solid evidence that berberine improves live birth or other clinical reproductive outcomes, while it does improve insulin resistance, dyslipidaemia, androgen levels and the LH/FSH ratio.

4.4 *Helicobacter pylori* eradication

In *Helicobacter pylori* eradication, a meta-analysis of 13 randomised trials in Chinese populations (Hu et al., 2020) found that berberine added, for the 7 to 14 days of a standard triple-therapy course (a proton pump inhibitor plus two antibiotics), improved eradication by about 22%, with about 15% better peptic-ulcer healing and about 11% better symptom relief, and reduced treatment side-effects by about 35%. The *H. pylori* outcomes are, in fact, the largest cluster of HIGH-quality evidence in the whole berberine literature: the Shi et al. (2025) umbrella review rated four gastrointestinal outcomes as HIGH-quality GRADE evidence, namely the eradication rate, the peptic-ulcer healing rate, the symptom-relief rate, and the reduction in treatment adverse events. These four are the largest single block of the eight HIGH-rated berberine outcomes in that review (the others being body-mass index and body weight in cardiovascular disease, BMI in obesity, and the safety profile in type 2 diabetes). A cluster of four HIGH-rated outcomes in a single indication is notable. These are clinically useful treatment outcomes, but short-term ones, unlike the longer-term clinical outcome measured in the

colorectal-adenoma trial and its follow-up. All the included trials were conducted in China, which limits direct generalisation to Dutch practice.

4.5 Neurological conditions

The neurological evidence for berberine is mostly preclinical and should be viewed as such. The one area with meaningful clinical data is acute ischaemic stroke, where the meta-analysis already cited (Luo et al., 2023; 17 RCTs, 1,670 participants) found that berberine added to conventional therapy reduced inflammatory and vascular markers and improved lipid profiles, without increasing adverse events; on the NIHSS stroke-severity scale the score fell by about 1.4 points (5 trials, 580 participants). For the other neurological conditions, namely Alzheimer's disease, Parkinson's disease, post-stroke depression and neuropathy, the evidence is predominantly preclinical. A 2024 review (Sunhe et al., 2024) synthesised mechanistic work showing that, in cell and animal models, berberine reduces oxidative stress, neuroinflammation and cellular stress responses, and limits amyloid- β and tau pathology in Alzheimer's models. In a Parkinson's cell model, berberine reduced the neurotoxicity of alpha-synuclein, the protein centrally involved in Parkinson's pathology (Lin et al., 2024). In experimental stroke models it reduces the pathological breakdown of the blood-brain barrier that contributes to secondary injury. These findings are mechanistically encouraging but, apart from acute ischaemic stroke, remain unproven in humans and should be described to patients as investigational, not established.

5. Safety and Drug Interactions

Berberine's safety profile is one of its most clinically attractive features, and it is well documented in two complementary ways. The first is the long record of human use referred to in Section 1: in China the herb has been an inexpensive over-the-counter remedy for bacterial diarrhoea for decades and a TCM material for centuries, with no signal of substantial harm from this long-term, large-population exposure. The second is the modern trial literature: in the Wang et al. (2024) meta-analysis of 50 RCTs and 4,150 participants, no serious adverse events were reported in any of the 16 trials that reported adverse-event data. The most common adverse effects are mild, transient gastrointestinal symptoms (diarrhoea, constipation, abdominal discomfort), typically occurring early in treatment and often settling. In the head-to-head trial by Yin et al. (2008), about one third of berberine-treated patients experienced such symptoms (no rate was reported for metformin), and no liver or kidney damage was seen. Where gastrointestinal symptoms are troublesome, the trial evidence indicates they can usually be managed by temporarily reducing the dose. Notably, this favourable safety profile is one of the eight outcomes that reached HIGH-quality GRADE evidence in the Shi et al. (2025) umbrella review, so it is not merely reassuring but among the best-supported findings in the entire berberine literature. Clinical tolerability is therefore well documented; however, in its 2026 draft opinion EFSA could not establish a safe intake for berberine preparations, chiefly because of in-vitro genotoxicity data (Appendix 2, A2.6).

This favourable profile does not mean berberine is free of cautions. Five matter in primary care:

1. Pregnancy and breastfeeding: Berberine should be avoided. It can displace bilirubin from albumin, an effect nearly ten times that of phenylbutazone, creating a theoretical risk of kernicterus in the neonate (Feng et al., 2019). This caution should be given actively, since patients using a supplement may not think to ask. Berberine should also be avoided in patients with known or suspected glucose-

6-phosphate dehydrogenase (G6PD) deficiency, in whom a single case report (conference abstract) describes haemolysis on exposure to a berberine-containing preparation (Khan et al., 2021).

2. Renal function: No formal dose adjustment for renal impairment has been established, and the available trial data are predominantly in patients without significant renal disease. Berberine and its metabolites are excreted largely via the gastrointestinal route rather than the kidneys, so the conventional concerns that drive dose adjustment for many oral agents are less acute here, but the evidence base is also too thin to give a confident recommendation in patients with eGFR below 30 mL/min/1.73 m²; in such patients the conservative approach, in the absence of dedicated trial data, is to discuss the decision individually before initiation.

3. Drug interactions: Berberine raises blood levels of cyclosporine: a controlled trial in renal-transplant recipients (Wu et al., 2005) found that adding berberine markedly increased cyclosporine trough concentrations, an effect attributed to inhibition of CYP3A4. The same interaction is expected with tacrolimus, which shares CYP3A4 and P-glycoprotein metabolism, though it has not been tested directly. More broadly, in healthy volunteers, berberine 300 mg three times daily for two weeks decreased CYP2D6, CYP2C9 and CYP3A4 activities, with CYP2D6 most affected (Guo et al., 2012), and it modulates P-glycoprotein, so it can raise levels of drugs cleared by these routes. Berberine also induces CYP3A4 transcriptionally, so the net effect in humans is not one-directional. Warfarin is a CYP2C9 substrate and therefore at theoretical risk, but controlled human studies of the combination are lacking; INR monitoring is sensible where it cannot be avoided (Dumitru et al., 2025). The most important cardiac-safety signal is that berberine combined with macrolide antibiotics, or with statins, can inhibit the hERG potassium channel and so increase the risk of arrhythmia and cardiotoxicity. This rests on in-vitro work rather than on human data, so it remains a theoretical signal, but given the consequence these combinations warrant caution or monitoring. A modest additional blood-pressure-lowering effect is mechanistically expected when berberine is combined with antihypertensive medication, so routine blood-pressure monitoring is sensible, particularly in patients already near target.

A reassuring counter-example is the antiarrhythmic setting: in the Qiao et al. (2023) meta-analysis, berberine added to standard antiarrhythmic therapy did not prolong QT in any included trial, so unlike many conventional antiarrhythmic agents berberine does not appear to carry torsadogenic risk (torsadogenic = capable of provoking torsades de pointes, a potentially fatal polymorphic ventricular tachycardia precipitated by QT prolongation).

A second positive interaction example is the berberine-statin combination, where the combined regimen has been associated with a lower incidence of muscle pain (myalgia) and lower transaminase elevations than statin monotherapy (Li et al., 2023), a moderation of statin side-effects that is clinically valuable in statin-intolerant patients.

4. Hypoglycaemia: Berberine's own risk of hypoglycaemia is low, but additive hypoglycaemia is mechanistically possible. Across the 50 RCTs and 4,150 participants in Wang et al. (2024), 33 of which combined berberine with conventional hypoglycaemics, no serious adverse events were reported in

the 16 trials with adverse-event data and only mild hypoglycaemia was seen; in the head-to-head trial of Yin et al. (2008) berberine produced no hypoglycaemia even at HbA1c-lowering doses. Additive hypoglycaemia is therefore mechanistically possible but uncommon. Routine glucose monitoring is nonetheless sensible, particularly with sulphonylureas or insulin, which carry intrinsic hypoglycaemia risk.

5. Supplement quality. Because berberine is sold as a food supplement rather than a registered medicine, the actual content and purity of commercial products is not formally guaranteed in the way it is for a prescription drug. Patients should be advised to choose products from reputable manufacturers, ideally with independent quality testing. As discussed in the protocol below, inconsistent product quality tends to show up as an inadequate biomarker response and is therefore detectable through the same monitoring used to judge effectiveness. A related caveat applies to the type of preparation: the clinical-trial literature summarised in this article overwhelmingly used standardised berberine extracts (often berberine hydrochloride). The findings are not directly applicable to whole-herb Coptis preparations or multi-herb traditional formulas, which contain berberine in much smaller amounts alongside other compounds, and which have a different and substantially weaker evidence base.

This incompleteness is not peculiar to berberine. Across 1,567 interventions in Cochrane reviews, harms were measured for only 36.8%, and safety is assessed more rarely than benefit throughout the evidence base (Howick et al., 2022).

Box 1. Practical safety summary for primary care

Caution	Practical action
Pregnancy, breastfeeding, neonates	Avoid. Theoretical kernicterus risk from bilirubin displacement; lactation safety not established. Avoid in known or suspected G6PD deficiency: one case report (conference abstract) describes acute haemolysis after exposure to a berberine-containing preparation.
Renal impairment (eGFR <30 mL/min/1.73 m²)	No formal dose adjustment established. Discuss individually before initiation; GI excretion route makes this less acute than for renally cleared drugs.
Narrow-therapeutic-index drugs (warfarin, cyclosporine, tacrolimus)	Berberine inhibits CYP3A4 and P-glycoprotein. Monitor INR / drug levels when combination cannot be avoided.
Glucose-lowering drugs (sulphonylureas, insulin, DPP-4 inhibitors, GLP-1 RAs)	Berberine's own hypoglycaemia risk is low; additive hypoglycaemia is possible but uncommon, with only mild hypoglycaemia reported in combination trials. Continue routine glucose monitoring; counsel hypoglycaemia awareness, particularly with sulphonylureas or insulin.
Supplement quality and product type	Choose standardised berberine extracts from reputable manufacturers with independent testing. Trial evidence does not generalise to whole-herb Coptis or multi-herb traditional formulas.

6. Pharmacology and Mechanisms of Action

Berberine is taken orally, typically at a total dose of 900 to 1,500 mg per day divided over two or three doses with meals. Its oral bioavailability is very low; under 1% in animal studies, with plasma concentrations in humans in the low ng/mL range (Dumitru et al., 2025). Absorption is not fixed, however: a high-fat meal raised berberine C_{max} by a factor of 2.97 and AUC by 2.69 in healthy volunteers (Persiani et al., 2014). Ordinarily a compound that is barely absorbed would not be a serious candidate for clinical effect; yet berberine consistently produces measurable changes in glucose, lipids, inflammation, and other biomarkers and endpoints across roughly 100 randomised trials. Resolving that paradox is the work of the rest of this section. The short answer is that berberine acts through several mechanisms operating in parallel, most of them anchored in the gut and the liver rather than depending on high systemic concentrations, and together they account for the trial-level effects observed clinically.

6.1 Mechanisms of action

Five mechanisms have substantive evidence behind them. They are presented separately for clarity, but in practice they act simultaneously and interactively.

1. AMPK activation. Berberine activates AMP-activated protein kinase (AMPK) in liver, muscle, and adipose tissue, the same energy-sensing pathway through which metformin produces much of its glycaemic effect (Turner et al., 2008). AMPK activation suppresses hepatic gluconeogenesis, increases peripheral glucose uptake, and reduces lipogenesis. This is one of the most clearly metformin-like aspects of berberine and helps explain why berberine and metformin performed similarly on HbA1c and fasting glucose in the randomised head-to-head trial and in meta-analyses of other direct comparisons (Section 2.2).

2. Hepatic LDL-receptor stabilisation and PCSK9 downregulation. Berberine increases the number of functional LDL receptors on liver cells and downregulates PCSK9, the liver protein that would otherwise degrade those receptors. The latter target is the same one addressed by the injectable PCSK9 inhibitors (alirocumab, evolocumab) used in specialist lipid practice (Feng et al., 2019). This is a lipid-lowering route entirely separate from the cholesterol-synthesis blockade of statins, which is why the two drug classes can be combined for additive effect, as discussed in Section 3 above.

3. Gut microbiome and bile acid modulation (including conversion to more absorbable metabolites). Because most berberine remains in the intestinal lumen, its action on and through the gut microbiome is central rather than incidental. Berberine shifts microbiome composition and alters bile acid metabolism, with downstream effects on gut-derived hormones and metabolic homeostasis (Wang et al., 2022; Li et al., 2023). One specific route operates within this broader pathway: gut bacterial nitroreductases convert berberine to dihydroberberine, which is absorbed roughly five times more efficiently and is then re-oxidised back to berberine in intestinal tissue (Feng et al., 2015; Wang et al., 2017). Berberine's conversion and activity both depend on the gut flora the patient happens to have, which is one plausible mechanistic basis for the inter-patient variability seen in clinical response.

4. Bitter-taste receptor signalling and GLP-1 release. Berberine, being very bitter, activates bitter-taste receptors (TAS2Rs) expressed not on the tongue but on enteroendocrine cells of the gut, and through this pathway stimulates the release of glucagon-like peptide-1 (GLP-1), the same hormone targeted by modern incretin-based diabetes drugs (Yu et al., 2015; Sun et al., 2022). This route does not require berberine to enter the systemic circulation at all and is preserved when bitter compounds are delivered intragastrically rather than tasted in the mouth, as is the case for capsule administration (Bitarafan et al., 2020; Mohammadpour et al., 2024).

5. Anti-inflammatory signalling. Berberine inhibits the NF- κ B and NLRP3 inflammasome pathways, two of the principal switches controlling inflammatory cytokine production, and supports the protective Nrf2 pathway (Feng et al., 2019; Sunhe et al., 2024). This mechanism underlies the consistent reductions in CRP, IL-6 and other inflammatory markers observed across trials, and is itself part of how berberine improves the cardiometabolic profile.

6.2 Synthesis: bioavailability, synergy, and durability

These five mechanisms together resolve the bioavailability paradox that opens this section. Berberine produces clinical effects despite negligible systemic absorption because most of its action does not require systemic exposure. The TAS2R pathway acts on the gut wall without needing the compound to leave the lumen; the gut-microbiome and bile-acid routes act on the gut ecosystem itself; the dihydroberberine and demethylated-metabolite routes turn the bioavailability problem on its head by using gut bacteria to produce more absorbable forms of the compound. What systemic exposure does occur is therefore enriched in bioactive metabolites rather than parent berberine alone, and in humans, higher faecal nitroreductase activity is associated with higher circulating berberine (Wang et al., 2017). This is one plausible mechanistic basis for the inter-patient variability seen in clinical trials, and it is also a striking modern echo of the pattern-based individualisation that TCM has long applied: the same compound interacts differently with different patients depending on their underlying biology.

The mechanisms also interact synergistically. AMPK activation lowers hepatic glucose output; GLP-1 release from bitter-receptor signalling slows gastric emptying and increases insulin secretion; the microbiome shifts produce short-chain fatty acids that themselves activate AMPK and reduce inflammation; PCSK9 downregulation and the gut-bile-acid axis both contribute to lipid lowering through non-overlapping routes. The clinical picture, modest improvements across several biomarkers simultaneously rather than a large effect on any single one, is what one would predict from a compound acting on this many interacting systems.

One line of evidence suggests the effects are durable rather than transient. In the colorectal-adenoma chemoprevention follow-up (Tan et al., 2025), the chemopreventive effect itself persisted, and even strengthened, for at least six years after treatment had stopped (see Section 4.1). That trial did not measure gut microbiota or bile-acid profiles, so the biological basis of the durable effect was not directly established; however, berberine's known and sustained remodelling of the gut ecosystem in other studies is a plausible mechanism, and this kind of long-tail benefit is not what one would expect from a drug working only by direct receptor occupancy.

6.3 Comparison with single-target pharmaceuticals

Most modern Western chemical pharmaceuticals, including the statins, are single-target by design: each is developed to bind one molecular target with high affinity and selectivity. Berberine sits at the opposite end of this spectrum, acting on several targets in parallel, and a compound of this kind is poorly served by trial designs optimised to detect a single large effect on a single biomarker. Because cardiometabolic risk has several drivers, modest effects on many of them can be expected to add up to a larger long-term benefit than a similar effect on one. This methodological mismatch is taken up further in Section 7.

6.4 Co-evolutionary context and what remains unknown

A further observation belongs here rather than among the established human pharmacology. In broiler chickens, acetogenic *Blautia* species demethylate berberine mainly to thalifendine, which the authors hypothesise may stimulate production of the short-chain fatty acids acetate and butyrate (Dehau et al., 2023). Whether the same route operates in humans has not been tested.

Plant-derived compounds, including berberine, were never designed for pharmacological selectivity, and their broad action profiles reflect both their original biological role (typically plant defence) and the long evolutionary history during which animal physiology developed mechanisms for handling them. The bitter-taste receptor system itself is a clear example: humans have twenty-five functional TAS2R subtypes, expressed throughout the gut and not only on the tongue, evolved in part to detect the diversity of bitter plant alkaloids that ancestral diets contained. Gut bacterial enzymes such as the nitroreductases and methyltransferases described above are similarly broad-spectrum, plausibly shaped by the same long history of plant-compound exposure. The biological machinery that handles berberine, in other words, is not new and is not narrowly specific to it.

This co-evolutionary picture has been formalised in the hypothesis of xenohormesis, proposed by Howitz and Sinclair: the idea that animals evolved to sense stress-induced chemical cues produced by plants, and to mount pre-emptive protective responses on detecting them (Howitz and Sinclair, 2008). On this view, compounds such as berberine are not merely tolerated by the consuming organism but are read as signals of environmental adversity, activating the same conserved defensive and energy-regulation pathways described above. The hypothesis fits berberine's profile well, although the strong evolutionary claim, that these responses were specifically selected to detect plant stress-metabolites, remains unproven and is best treated as a useful interpretive frame rather than established fact. One observation does lend it weight in berberine's case. Berberine's principal source plant, *Coptis chinensis*, does not produce berberine in isolation but a coordinated mixture of related protoberberine alkaloids (coptisine, palmatine, jatrorrhizine, epiberberine, columbamine) together with phenolic constituents including chlorogenic and ferulic acid; 128 chemical constituents in total (Wang et al., 2019), together with a minor fraction of stress-induced polyphenols such as chlorogenic and ferulic acids, the very compound class on which the xenohormesis hypothesis was originally built. Isolating the single molecule discards this evolved ensemble. That offers a mechanistic, evolution-grounded rationale for why a whole-plant or systems-level preparation, of the kind traditional Chinese medicine has always used, might capture effects that purified single-compound pharmacology misses. This remains a hypothesis to be tested rather than a demonstrated superiority, but it is a coherent one, and it connects berberine's modern pharmacology to the multi-component logic of its traditional use.

The mechanisms described in this section are the ones for which there is reasonable evidence, but they should not be presumed to be the complete account. Several other plausible routes, for example gut-to-brain signalling via the vagus nerve through short-chain fatty acid effects on vagal afferents, and inhibition of microbial trimethylamine-N-oxide production with downstream cardiovascular implications, have preliminary evidence but are not developed here. It is reasonable to expect that further mechanisms will be characterised over time. None of this changes the clinical evaluation, which rests on the trial-level evidence summarised in the preceding sections, but it does support the broader point made in Section 6.3 and Section 7: a multi-mechanism, network-acting compound is not best understood as a less-precise version of a single-target drug, but as a different kind of intervention that calls for a different evaluative framework.

6.5 Berberine as a hormetic stressor (mitohormesis)

Underlying several of the mechanisms above is a single unifying principle that is worth making explicit: berberine acts, in part, as a mild metabolic stressor. It accumulates in mitochondria and mildly inhibits respiratory-chain complex I, reducing the efficiency of ATP production and raising the intracellular AMP-to-ATP ratio, with a modest increase in reactive oxygen species and in the NAD⁺-to-NADH ratio (Turner et al., 2008; Zhu et al., 2020). Rather than damaging the cell, this controlled, low-grade stress switches on a coordinated adaptive response: AMPK activation (the route described in 6.1), NAD⁺-dependent sirtuin signalling (SIRT1 and SIRT3) that promotes mitochondrial biogenesis, and antioxidant and protein-quality-control programmes. This is the phenomenon known as mitohormesis, in which a sub-toxic mitochondrial stress produces a net protective, health-promoting adaptation (Zhu et al., 2020).

Two points follow that matter clinically. First, this is the same mechanism by which metformin is thought to act, and it explains at a deeper level why berberine and metformin have broadly similar effects on blood glucose: both are mild complex-I inhibitors that work largely through the resulting adaptive signalling rather than through a single receptor. It is also the mechanistic link to the broader family of caloric-restriction-mimetic and exercise-mimetic compounds, and the basis for berberine's tentative interest in healthy-ageing research, where the NAD⁺-to-SIRT1 axis is central. Second, because the effect is hormetic, it is dose-dependent in a biphasic way: the adaptive, cytoprotective response occurs at low, physiological doses, whereas at high concentrations the same mitochondrial action becomes pro-apoptotic. This dual nature is what reconciles berberine's apparently contradictory profile, cytoprotective in metabolic and neuronal tissue yet pro-apoptotic in cancer cells, and it carries a practical caution: the relationship between dose and effect is not simply linear, and more is not necessarily better. Zhu et al. (2020) also note that, at certain low concentrations in laboratory models, berberine may promote rather than suppress cancer-cell proliferation and attenuate the activity of chemotherapeutic agents in combination regimens (Zhu et al., 2020), which is one reason the antineoplastic clinical evidence in 4.1 should not be over-extrapolated to a general anticancer claim.

7. Discussion

Three findings about berberine are reasonably firm, and a fourth decides what to do with them. The effects are consistent and, in places, substantial: across roughly 100 randomised trials berberine lowers HbA1c, glucose, LDL-cholesterol, triglycerides and inflammatory markers, performing similarly to metformin on glycaemia in one small randomised head-to-head trial and in meta-analyses of other direct comparisons, and lowering triglycerides about as much as statins typically do, somewhat more in patients with raised lipids. Yet the evidence behind these numbers is not always strong, often resting on small, short, mostly Chinese trials of variable methodological quality, with colorectal-adenoma chemoprevention the only patient-relevant clinical outcome. The crucial distinction is that what is modest here is the evidence, not the effect: berberine moves the biomarkers substantially, but the trials stop at biomarkers rather than outcomes, so the open question is one of statistical confidence, not of magnitude. One feature of that modest evidence base partly offsets it. The trials are numerous and heterogeneous in design, dose and setting, and yet they point consistently in the same direction; convergence of many differently constructed studies is harder to explain as artefact than a single clean result would be, and it makes the underlying effect more likely to be real. This is corroboration rather than proof, and it carries weight here only because the one formal check for publication bias, in the largest meta-analysis, left the main effects essentially unchanged. The fourth point, and the one that should govern the clinical decision, is balance. That real biomarker benefit is set against an unusually low burden of risk: berberine is well tolerated, inexpensive, easily stopped, and carries only a few predictable drug interactions. A genuine effect weighed against low risk and low cost is what makes a monitored usage reasonable in a lower-risk patient, where the downside of being wrong is small; the same balance is why berberine cannot substitute for proven therapy in higher-risk patients, where the evidence gap matters and outcome-changing drugs already exist. The sections that follow develop this in turn: the limitations that bound any conclusion, the positioning that follows from them, and an interpretive point about how a multi-target natural compound should be judged in the first place.

7.1 The evidence in context: limitations and how to read them

Before turning to the limitations, it is worth stating plainly what the preceding sections have established, because the qualifications that follow should not be allowed to obscure it: across roughly 100 trials, though these meta-analyses overlap in the trials they pool, berberine produces consistent, and in places substantial, improvements in the biomarkers that define cardiometabolic risk, it has eight outcomes rated HIGH-quality under GRADE, and separately it has one patient-relevant clinical-outcome result (colorectal-adenoma prevention, moderate certainty). With that firmly in view, four limitations of the evidence base bear on clinical use. First, although the pooled meta-analytic samples are large, the underlying individual RCTs are mostly small and short, and the largest recent meta-analysis (Wang et al., 2024) detected statistical evidence of publication bias for several outcomes; reassuringly, when the authors corrected for this, the main effects on HbA1c, cholesterol and triglycerides were essentially unchanged. Second, methodological quality is variable; the umbrella reviews of Li et al. (2023) and Shi et al. (2025) rated many of the underlying reviews as low or critically low quality. Third, the evidence is overwhelmingly Chinese, since 49 of the 50 trials in Wang et al. (2024) were conducted in China, so its direct transferability to Dutch and other European populations, with different diets, genetics and background care, is genuinely uncertain. Fourth, patient-relevant clinical outcomes are largely absent, the colorectal-adenoma trial and its follow-up being the principal exception; for the metabolic and cardiovascular domains, the evidence rests on biomarkers such as HbA1c, lipids and inflammatory markers, and an improvement in a biomarker is not in itself a guarantee of improved long-term outcomes.

These limitations do not contradict the biomarker findings; they bound the confidence with which those findings can be extrapolated to long-term outcomes. They are the reason the practical approach in Section 8 is structured, monitored and time-limited, and is restricted to lower-risk patients in whom the consequences of an incomplete evidence base are small.

There is, however, an important qualification to the “biomarker only” concern. In Dutch primary care the biomarkers berberine improves, LDL-cholesterol and HbA1c, are not merely surrogates awaiting validation; they are the target values (“streefwaarden”) that the NHG standards for cardiovascular risk management and type 2 diabetes instruct clinicians to treat towards. Those standards are built on a lifestyle-first logic: non-pharmacological measures are tried first, and medication is added only when the biomarker target is not reached. Within that framework, reaching or approaching the guideline’s own target with a well-tolerated agent is not a lesser outcome awaiting endpoint data; it is precisely what first-line management aims to achieve.

These limitations should also be read in proportion. Under GRADE, LOW and MODERATE grades are ordinary across medicine and high-quality evidence is the exception (Fleming et al., 2016; Howick et al., 2020, 2022), so a low grade is not by itself a sign that berberine’s evidence is unusually weak. A second, separate limitation is duration: across the indications reviewed here the trials are short. Most pooled trials run between one and six months, the arrhythmia trials no longer than 30 days, and the *Helicobacter pylori* trials one to two weeks. The colorectal-adenoma trial is the main exception: it treated patients for two years and followed them for a median of 6 years afterwards, and it is the only one measuring a patient-relevant clinical outcome in a contemporary treatment setting.

Two consequences follow for how berberine should be judged. First, insufficient high-quality evidence is not the same as evidence of no effect: it marks a treatment as not yet adequately tested, an absence of proof rather than proof of absence. This is precisely why the confidence-graded presentation used throughout this article, separating what is shown in human trials from what rests on mechanism or tradition, is more honest than a binary verdict of proven or unproven. The full list of its eight HIGH-rated outcomes, and the *H. pylori* cluster in particular, is given in Section 4.4.

Second, where no single trial is decisive, rational confidence can still be built from the convergence of independent lines of evidence: basic mechanism, animal work, epidemiology, human trials, and reasoning about the body as an interacting system. This review’s separation of mechanistic from clinical sources is a version of that logic. The argument has a clear and important limit, and it must not be overstated. Convergence across several weaker forms of evidence is not equivalent to a single robust randomised trial, and for berberine it remains the human-outcome studies, the diabetes and lipid trials and above all the colorectal-adenoma result, that carry the real weight. The philosophy licenses honest hedging in proportion to the evidence; it does not convert mechanistic plausibility into proof. The purpose of this note is therefore not to excuse berberine’s evidence gaps but to calibrate them: to ensure that a LOW or MODERATE grade is read as a statement about confidence rather than a verdict of no effect, and that the genuinely exceptional finding in this evidence base is recognised as such.

7.2 Therapeutic positioning: where berberine fits

Drawing the clinical sections together, berberine can be positioned with reasonable precision. On glycaemic control, its effect falls within the range of established oral hypoglycaemic agents, and it performed similarly to metformin in one small randomised head-to-head trial and in meta-analyses of other direct comparisons. On lipids, it produces clinically meaningful reductions in LDL-cholesterol and triglycerides, through a mechanism that complements rather than duplicates statins. It has a consistent anti-inflammatory effect, a favourable and well-documented safety profile, and, in the

single specific indication of colorectal-adenoma chemoprevention, genuine patient-relevant clinical-outcome evidence.

Against this, berberine lacks the long-term cardiovascular and mortality outcome data that underpin the first-line use of statins and metformin in higher-risk patients. The reasonable conclusion is not that berberine is ineffective, nor that it should replace guideline-based therapy, but that it occupies a specific and useful niche, defined by two features. The first follows from the risk-benefit balance set out above: because a well-documented, low-burden safety profile sits alongside real biomarker effects, the cost of a properly monitored therapeutic attempt is low, and this compares favourably with first-line synthetic drugs specifically in patients whose cardiovascular risk is low enough that biomarker improvement, rather than rapid event reduction, is the goal. The second is that berberine can be combined with conventional drugs, or tried for a defined period in an individual patient, which fits the clinical reality that patients differ in how they respond to any treatment. Berberine is therefore most defensible as a complementary, well-tolerated, biomarker-effective option in lower- and moderate-risk patients, in patients intolerant of first-line drugs, and as an add-on where conventional therapy alone is insufficient.

7.3 An interpretive point: how multi-target natural compounds are evaluated

One interpretive issue deserves explicit attention, because it bears directly on how berberine, and natural agents like it, should be valued, and because it is easy to get wrong in both directions.

Modern biomedical research is, by design, built to detect single-target drugs. Its central tool, the randomised controlled trial, is at its most powerful when one well-defined intervention is tested against one comparator over a defined period, with one or two pre-specified biomarkers as the outcome. This design has been extraordinarily successful and is the basis of evidence-based medicine. But it has a structural blind spot. An intervention that acts gently across several interacting systems at once, producing measurable effects on glucose, lipids, and inflammation, together with shifts in the microbiome, is poorly served by a method optimised to detect a single large effect on a single variable. Each individual effect may look modest when isolated, and a trial measuring only one of them will capture only part of the action.

This matters because chronic cardiometabolic disease is itself, like the whole biological system of the human body and mind, a networked process. It is also plausible that, given our evolutionary history of dietary exposure to plant compounds, humans are predisposed to respond to such substances in a systemic, multi-system way. Type 2 diabetes, atherosclerosis, metabolic syndrome and fatty liver disease are not single-pathway faults; they are disturbances spanning metabolism, immunity, vascular biology and the gut, with those systems interacting continuously. An agent that nudges several of these systems modestly and in a coherent direction may, over time, produce an integrated benefit that is larger than any single short-term biomarker reflects. This is a reasoning step, not a measured result, and it should be labelled as such; but it is not arbitrary. It follows the same logic that established medicine already relies on when it combines mechanisms, for instance adding a second lipid-lowering agent with a different mechanism to a statin, or adding structured lifestyle change to drug therapy, on the expectation of benefit beyond single-agent treatment. The

cardiovascular polypill rests on the same reasoning: Wald and Law (2003) estimated that one daily pill combining several drugs, each lowering a different risk factor, could prevent more than 80% of heart attacks and strokes, and in the TIPS-3 trial, in 5,713 people without cardiovascular disease followed for an average of 4.6 years, a polypill taken with aspirin reduced cardiovascular events by about 31% (Yusuf et al., 2021). The argument is offered here as a way of interpreting an incomplete evidence base, not as a substitute for the outcome trials that would be needed to confirm it.

The conclusion to draw from this is balanced, and the balance matters. Berberine's profile of broad, mechanistically coherent effects across several interacting systems is well matched to the networked nature of human biology and the chronic diseases it is used for, and the conventional trial apparatus is liable to undervalue exactly this kind of agent. As Section 6.4 argued, this multi-mechanism action is not incidental: it reflects both berberine's biological origin as a plant compound and the long evolutionary history during which animal physiology developed the machinery to detect, metabolise, and respond to compounds of this class. The honest qualification is that this argues for proper investigation, with longer, outcome-based, multi-system trials, and for fair consideration in clinical decisions, but it is not a substitute for the outcome evidence that, for now, only the conventional agents possess. This is precisely the reasoning that motivates a structured therapeutic attempt rather than either dismissal or uncritical enthusiasm.

This way of thinking is not new. Traditional Chinese Medicine has, for centuries, worked from the assumption that disease is a disturbance of multiple interacting subsystems and that effective therapy is usually multi-target: a whole herb rather than a single isolated compound; a formula combining several herbs whose actions complement each other; treatment chosen for the patient's overall pattern rather than for a single biomarker. The modern pharmacology research of berberine, taken as a whole, is largely a confirmation of that approach. Berberine is in fact the principal active alkaloid of a multi-component herb, *Coptis chinensis*, which itself is most often prescribed in classical formulas alongside other herbs; the systemic, multi-target, gut-and-liver pharmacology described in Section 6 of this article is precisely the kind of action TCM has long sought to harness. This does not mean classical TCM theory and modern biomedicine are interchangeable, and it does not mean every traditional claim is supported by modern evidence. It does mean that, for chronic diseases involving several interacting systems at once, the methodological habits of TCM, namely treating whole-organism patterns, combining agents and interventions rather than relying on single molecules, and judging therapy over longer time scales, are themselves a useful complement to the standard short-trial single-target paradigm. Taking these habits seriously, and designing research that can accommodate them, is a possible productive direction for integrative cardiometabolic care.

8. A Practical 12-Week Approach for a Cardiometabolic Intervention in Primary Care

This final section translates the evidence into a concrete, actionable approach: a monitored 12-week berberine intervention for carefully selected patients. It is designed to fit within the existing Dutch NHG-guideline framework, not to bypass it. The clinical evidence cited throughout is drawn from the scientific evidence presented earlier in this article; the guideline structure, meaning risk categories, thresholds, and treatment logic, is drawn from the NHG-Standaard Cardiovasculair Risicomanagement (CVRM) and the NHG-Standaard Diabetes mellitus type 2 (Nederlands Huisartsen Genootschap, 2024, 2025).

8.1 The rationale: why a structured intervention fits the NHG framework

The NHG guidelines for both cardiovascular risk management and type 2 diabetes are built on a lifestyle-first logic. Lifestyle modification is offered first; medication is added when biomarker targets are not met. Crucially, the guidelines treat successful non-pharmacological control of biomarkers as a legitimate end-state. The 2025 revision of the diabetes standard formally recognises “type 2 diabetes in remission”, defined as a fasting glucose below 7 mmol/L and an HbA1c below 48 mmol/mol maintained for at least three months without medication. In day-to-day practice, the GP assesses whether an intervention has worked using the same tool regardless of what the intervention was: HbA1c, the lipid panel, blood pressure.

A monitored 12-week berberine intervention fits naturally into this existing logic. It is an additional, time-limited step alongside the standard lifestyle advice, assessed by the same before-and-after bloodwork the GP already uses, with a defined review point and a pre-agreed rule for what happens next. Berberine’s safety, which reached HIGH-quality GRADE evidence for adverse events in type 2 diabetes and in gastrointestinal indications, its measurability through routine bloodwork, and its combinability with metformin and statins are what make this approach reasonable. It is, in effect, treating berberine the way the guidelines already treat a defined period of intensified lifestyle change: a monitored attempt to reach target without committing the patient to long-term medication, with that medication still available if needed.

8.2 Patient selection: a stepwise decision

The single most important safeguard is correct patient selection. Rather than a long list of criteria, the decision can be made as a short sequence of steps. Cardiovascular risk should be categorised using SCORE2 for patients under 70, and SCORE2-OP for patients aged 70 and over; these are the risk models embedded in the NHG-CVRM. Both estimate the 10-year risk of fatal and non-fatal cardiovascular disease from age, sex, smoking status, systolic blood pressure and non-HDL cholesterol. The four steps below are worked through in order; the patient is eligible only if Steps 1 to 3 are all cleared.

Step 1. Is there a condition that makes medication first-line in its own right? If the patient has established atherosclerotic cardiovascular disease, heart failure of any ejection fraction, familial hypercholesterolaemia, severe chronic kidney disease, or type 2 diabetes with target-organ damage

or clustered risk factors, then guideline-indicated medication should be started without delay. A medication-sparing berberine intervention is not appropriate. (Berberine may still be added on top of that medication, as noted below, but it must not delay it.)

Step 2. What is the SCORE2 / SCORE2-OP category? Using the age-appropriate threshold, a patient at high or very high risk should start guideline-indicated medication promptly; a 12-week delay carries real risk. Only patients at low-to-moderate risk proceed. The NHG-CVRM thresholds are as follows. Under age 50: low-to-moderate below 2.5%, high 2.5% to under 7.5%, very high 7.5% or above. Age 50 to 69: low-to-moderate below 5%, high 5% to under 10%, very high 10% or above. Age 70 and over (SCORE2-OP): low-to-moderate below 7.5%, high 7.5% to under 15%, very high 15% or above. A markedly raised lipoprotein(a), a high coronary-calcium score, or a strong family history of premature cardiovascular disease can move a patient into a higher category and should prompt the same caution.

Step 3. Is there a safety or interaction reason to exclude? Exclude if the patient is pregnant, planning pregnancy, or breastfeeding; if the patient has known or suspected G6PD deficiency; if the patient is a transplant recipient on cyclosporine or tacrolimus; or if the patient takes warfarin, where the interaction is theoretical but the consequence of being wrong is serious. Review concurrent prescribing for macrolides and other QT-prolonging drugs, and discuss individually if eGFR is below 30 mL/min/1.73 m². These follow directly from the cautions in Section 5.

Step 4. Is there an appropriate indication? If Steps 1 to 3 are cleared, the patient is eligible when there is mild-to-moderate dyslipidaemia, a modestly raised HbA1c (roughly 42 to 53 mmol/mol, i.e. prediabetes or very early type 2 diabetes, the diagnostic threshold being 48 mmol/mol), mixed dyslipidaemia in which raised triglycerides are prominent (berberine's triglyceride effect is largest in patients with raised lipids), or statin intolerance with residual lipid abnormality at moderate risk. A patient who, after shared decision-making, prefers a defined non-prescription step before committing to long-term medication, and in whom the GP agrees this is clinically reasonable, also qualifies.

Two points make the selection logic less rigid than a simple yes/no. First, the “not eligible” outcome of Steps 1 and 2 means not eligible for a medication-sparing intervention; that is, berberine should not be used as a way of postponing medication the patient needs. It does not mean berberine can never be used in that patient: as Section 2.1 showed, berberine’s strongest evidence is precisely as an add-on, and a higher-risk patient who has started guideline-indicated medication may still add berberine on top, with the same monitoring, if they wish. What is not acceptable is allowing a berberine step to delay indicated treatment. Second, the eligible categories are not mutually exclusive, and clinical judgement still applies within them.

Figure 2. Stepwise selection for the 12-week berberine intervention

Step	Decision	If YES	If NO
1	Established ASCVD, heart failure, familial hypercholesterolaemia, severe CKD, T2DM with target-organ damage or clustered risk factors, or other condition where first-line medication is indicated?	Start guideline-indicated medication. Berberine only as an add-on, never as a delay.	Continue to Step 2.
2	SCORE2 / SCORE2-OP risk high or very high?	Start guideline-indicated medication promptly.	Continue to Step 3.
3	Pregnancy or breastfeeding, G6PD deficiency, cyclosporine or tacrolimus, or warfarin? (Review macrolides and QT-prolonging drugs; eGFR <30: discuss individually.)	Berberine not appropriate. Counsel patient and pursue alternatives.	Continue to Step 4.
4	Mild-to-moderate dyslipidaemia, HbA1c roughly 42 to 53 mmol/mol, triglyceride-prominent mixed dyslipidaemia, statin intolerance at moderate risk, or informed patient preference?	Start the 12-week intervention. Document baseline.	Standard NHG care.
At 12 weeks: biomarker at or moving towards the NHG target, and well tolerated? Yes: continue with periodic monitoring. Partly: add berberine to a lower-dose conventional drug. No: escalate to guideline-indicated medication.			

8.3 The protocol, step by step

- 1. Confirm eligibility and counsel the patient.** Work through the four selection steps above and confirm the patient is eligible. Explain clearly that this is a defined 12-week intervention with a fixed review point; that conventional medication remains fully available and will be recommended if the preset goals are not met; and that the decision at 12 weeks will be guided by the bloodwork, not by preference alone.
- 2. Take baseline measurements.** Before starting, record: HbA1c; a fasting lipid panel (total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides) with non-HDL cholesterol; apolipoprotein B (ApoB) where locally available, since it reflects the number of atherogenic particles more reliably than LDL-cholesterol, particularly when triglycerides are raised; ALT and AST as a liver-safety baseline; eGFR; blood pressure; and weight and waist circumference. Document all current medication and, explicitly, any other supplements.
- 3. Start berberine at a defined dose.** A reasonable regimen, consistent with the trial evidence, is 500 mg twice daily (1,000 mg/day), taken with meals; a high-fat meal raises berberine exposure roughly threefold (Persiani et al., 2014), so consistency of timing relative to food matters more than the precise hour. Meta-analytic subgroup data do not show doses above 1 g/day to be

consistently superior for glycaemic or lipid outcomes. Where berberine is added to a sulphonylurea or insulin, warn the patient about hypoglycaemia and consider home glucose monitoring for the first four weeks. Advise the patient to choose a product from a reputable manufacturer with independent quality testing. If gastrointestinal symptoms occur, they can usually be managed by temporarily lowering the dose.

4. **Continue lifestyle advice in parallel.** The intervention is berberine plus standard NHG lifestyle advice, set against the alternative of starting medication now. It is not berberine instead of lifestyle change. Diet, physical activity, weight and smoking should be addressed exactly as they would be otherwise.
5. **Review at 12 weeks with repeat bloodwork.** Repeat the baseline panel. Twelve weeks is the minimum sensible interval: the trial evidence shows berberine's effects on HbA1c and lipids emerging over roughly 8 to 12 weeks, and HbA1c itself reflects the preceding 8 to 12 weeks of glycaemic control.
6. **Apply the pre-agreed decision rule.** If the relevant biomarker has reached, or moved substantially towards, the NHG target for that patient, and the patient is tolerating berberine well, continue, with the same periodic monitoring used for lifestyle-based management. If the biomarker has not moved meaningfully, escalate to guideline-indicated pharmacotherapy without further delay. For a partial response, adding berberine to a lower-dose conventional drug is a reasonable middle path, consistent with the combination evidence.
7. **Document and follow up.** Record the intervention, its result, and the decision in the patient file, so that subsequent care, by the GP or by anyone else involved, reflects what was tried and what happened.

8.4 What this approach is, and is not

This 12-week approach is proposed as a structured and monitored way, consistent with the logic of the NHG framework, of giving a well-tolerated intervention a defined chance to work in patients for whom the cost of a short, supervised attempt is low. It respects the NHG framework's own logic, in which biomarker control achieved without medication is a legitimate outcome. It keeps conventional therapy fully in reserve and brings it in promptly if the preset goals are not met. It is not a way of avoiding necessary medication in patients who need it. It is not appropriate for high- or very-high-risk patients, for whom outcome-proven drugs should be started without delay. And it is not a claim that berberine is equivalent to those drugs; on long-term outcomes, the evidence for that does not yet exist. Used within these limits, a monitored berberine intervention is a reasonable, evidence-aware option that fits the clinical reality of primary care: that patients differ in how they respond, that many prefer to try a non-pharmaceutical route first, and that a well-tolerated agent assessed against objective bloodwork can be offered honestly, monitored properly, and acted on either way.

9. Conclusion

Berberine could sit in a clinically useful but specific place in primary care. The evidence base is now substantial, internally consistent, and clinically meaningful on the biomarkers that matter in cardiometabolic disease, namely HbA1c, lipids, and markers of inflammation. Beyond the cardiometabolic core, berberine also has a genuine, if narrower, evidence base in several other areas: the prevention of colorectal-adenoma recurrence, adjunctive *Helicobacter pylori* eradication, ulcerative colitis, polycystic ovary syndrome, and, as an add-on, some cardiac-rhythm and post-stroke settings. Its multi-target pharmacology and gut-and-liver mechanism complement the statins and partly overlap with metformin, and its safety profile, documented in the 16 trials reporting adverse-event data and across roughly 100 trials overall, is favourable. Colorectal-adenoma chemoprevention is its only patient-relevant clinical-outcome result in a contemporary treatment setting, with an effect that persists for years after treatment has stopped.

These strengths do not equal the long-term mortality and event evidence that anchors first-line use of statins and metformin in higher-risk patients, and on current evidence berberine is not a substitute for guideline-indicated drug therapy in such patients. What it is, used carefully, is a reasonable additional option in primary care: well tolerated, measurable through routine bloodwork, combinable with metformin and statins, and with a balance of effect and risk that is itself a clinical argument in its favour, particularly in lower-risk patients and in those for whom first-line agents are unsuitable.

Beyond its specific clinical place, berberine is also a useful working example of something larger; it is a multi-target compound, drawn from a multi-component herb, embedded in a centuries-old tradition that has always treated chronic disease as a disturbance of several interacting systems at once. The modern evidence base for berberine, with its consistent effects across glucose, lipids, the microbiome, and inflammation, points in the same direction. There is a real opportunity, and arguably a clinical need, to take the systems-level habits of Traditional Chinese Medicine seriously as a methodological resource: studying whole herbs and combination formulas with the same rigour as single molecules, designing trials that measure several outcomes over longer time scales, and admitting that the agent best matched to a networked disease may be one with several modest effects rather than one large one. None of this requires accepting traditional theory at face value; it requires being willing to evaluate it on its own terms and on the modern outcomes that matter.

The structured 12-week approach proposed in Section 8 is the practical translation of the cardiometabolic evidence in this article. It treats berberine as a defined and monitored step within the existing NHG cardiometabolic framework, and resolves itself, one way or the other, against the patient's own bloodwork at the 12-week review. In miniature, it is also a practical example of what evidence-based TCM-integration in primary care can look like: an old remedy used on the basis of modern evidence, with modern monitoring, judged by modern criteria, in the service of a patient sitting in front of a Dutch GP.

Appendix 1. References

- Ai, X., Yu, P., Peng, L., Luo, L., Liu, J., Li, S., Lai, X., Luan, F., & Meng, X. (2021). Berberine: A review of its pharmacokinetics properties and therapeutic potential in cardiovascular diseases. *Frontiers in Pharmacology*, 12, 762654.
- Bitarafan, V., Fitzgerald, P. C. E., Little, T. J., Meyerhof, W., Jones, K. L., Wu, T., Horowitz, M., & Feinle-Bisset, C. (2020). Intra-gastric administration of the bitter tastant quinine lowers the glycemic response to a nutrient drink without slowing gastric emptying in healthy men. *American Journal of Physiology - Regulatory, Integrative and Comparative Physiology*, 318(2), R263–R273. <https://doi.org/10.1152/ajpregu.00294.2019>
- Chen, Y.-X., Gao, Q.-Y., Zou, T.-H., Wang, B.-M., Liu, S.-D., Sheng, J.-Q., Ren, J.-L., Zou, X.-P., Liu, Z.-J., Song, Y.-Y., Xiao, B., Sun, X.-M., Dou, X.-T., Cao, H.-L., Yang, X.-N., Li, N., Kang, Q., Zhu, W., Xu, H.-Z., ... Fang, J.-Y. (2020). Berberine versus placebo for the prevention of recurrence of colorectal adenoma: A multicentre, double-blinded, randomised controlled study. *The Lancet Gastroenterology & Hepatology*, 5(3), 267–275.
- Dehau, T., Cherlet, M., Croubels, S., Van De Vliet, M., Goossens, E., & Van Immerseel, F. (2023). Berberine-microbiota interplay: Orchestrating gut health through modulation of the gut microbiota and metabolic transformation into bioactive metabolites. *Frontiers in Pharmacology*, 14, 1281090. <https://doi.org/10.3389/fphar.2023.1281090>
- El Dib, R. P., Atallah, A. N., & Andriolo, R. B. (2007). Mapping the Cochrane evidence for decision making in health care. *Journal of Evaluation in Clinical Practice*, 13(4), 689–692. <https://doi.org/10.1111/j.1365-2753.2007.00886.x>
- Dumitru, C. N., Marcu, T., Dumitru, A. O., Tudor, S. S., Fertu, I. D., Elisei, A.-M., & Goroftei, L. (2025). Berberine-drug interactions: Mechanisms, clinical relevance and risk stratification: A narrative review. *Pharmaceuticals*, 19(1), 1313.
- Fan, L.-X., Liu, C.-M., Gao, A.-H., Zhou, Y.-B., & Li, J. (2013). Berberine combined with 2-deoxy-D-glucose synergistically enhances cancer cell proliferation inhibition via energy depletion and unfolded protein response disruption. *Biochimica et Biophysica Acta (General Subjects)*, 1830(11), 5175–5183. <https://doi.org/10.1016/j.bbagen.2013.07.010>
- Feng, R., Shou, J.-W., Zhao, Z.-X., He, C.-Y., Ma, C., Huang, M., Fu, J., Tan, X.-S., Li, X.-Y., Wen, B.-Y., Chen, X., Yang, X.-Y., Ren, G., Lin, Y., Chen, Y., You, X.-F., Wang, Y., & Jiang, J.-D. (2015). Transforming berberine into its intestine-absorbable form by the gut microbiota. *Scientific Reports*, 5, 12155. <https://doi.org/10.1038/srep12155>
- Feng, X., Sureda, A., Jafari, S., Memariani, Z., Tewari, D., Annunziata, G., Barrea, L., Hassan, S. T. S., Šmejkal, K., Malaník, M., Sychrová, A., Barreca, D., Ziberna, L., Mahomoodally, M. F., Zengin, G., Xu, S., Nabavi, S. M., & Shen, A.-Z. (2019). Berberine in cardiovascular and metabolic diseases: From mechanisms to therapeutics. *Theranostics*, 9(7), 1923–1951.
- Fleming, P. S., Koletsi, D., Ioannidis, J. P. A., & Pandis, N. (2016). High quality of the evidence for medical and other health-related interventions was uncommon in Cochrane systematic reviews. *Journal of Clinical Epidemiology*, 78, 34–42. <https://doi.org/10.1016/j.jclinepi.2016.03.012>
- Garrow, J. S. (2007). What to do about CAM: How much of orthodox medicine is evidence based? *BMJ*, 335(7627), 951. <https://doi.org/10.1136/bmj.39388.393970.1F>

- Guo, Y., Chen, Y., Tan, Z.-R., Klaassen, C. D., & Zhou, H.-H. (2012). Repeated administration of berberine inhibits cytochromes P450 in humans. *European Journal of Clinical Pharmacology*, 68(2), 213–217. <https://doi.org/10.1007/s00228-011-1108-2>
- Guo, J., Chen, H., Zhang, X., Lou, W., Zhang, P., Qiu, Y., Zhang, C., Wang, Y., & Liu, W. J. (2021). The effect of berberine on metabolic profiles in type 2 diabetic patients: A systematic review and meta-analysis of randomized controlled trials. *Oxidative Medicine and Cellular Longevity*, 2021, 2074610.
- Hirst, J. A., Farmer, A. J., Ali, R., Roberts, N. W., & Stevens, R. J. (2012). Quantifying the effect of metformin treatment and dose on glycemic control. *Diabetes Care*, 35(2), 446–454. <https://doi.org/10.2337/dc11-1465>
- Hou, D., Xu, G., Zhang, C., Li, B., Qin, J., Hao, X., Liu, Q., Zhang, X., Liu, J., Wei, J., Gong, Y., Liu, Z., & Shao, C. (2017). Berberine induces oxidative DNA damage and impairs homologous recombination repair in ovarian cancer cells to confer increased sensitivity to PARP inhibition. *Cell Death & Disease*, 8(10), e3070. <https://doi.org/10.1038/cddis.2017.471>
- Howick, J., Koletsis, D., Pandis, N., Fleming, P. S., Loef, M., Walach, H., Schmidt, S., & Ioannidis, J. P. A. (2020). The quality of evidence for medical interventions does not improve or worsen: A metaepidemiological study of Cochrane reviews. *Journal of Clinical Epidemiology*, 126, 154–159. <https://doi.org/10.1016/j.jclinepi.2020.08.005>
- Howick, J., Koletsis, D., Ioannidis, J. P. A., Madigan, C., Pandis, N., Loef, M., Walach, H., Sauer, S., Kleijnen, J., Seehra, J., Johnson, T., & Schmidt, S. (2022). Most healthcare interventions tested in Cochrane Reviews are not effective according to high quality evidence: A systematic review and meta-analysis. *Journal of Clinical Epidemiology*, 148, 160–169. <https://doi.org/10.1016/j.jclinepi.2022.04.017>
- Howitz, K. T., & Sinclair, D. A. (2008). Xenohormesis: Sensing the chemical cues of other species. *Cell*, 133(3), 387–391. <https://doi.org/10.1016/j.cell.2008.04.019>
- Hu, Q., Peng, Z., Li, L., Zou, X., Xu, L., Gong, J., & Yi, P. (2020). The efficacy of berberine-containing quadruple therapy on *Helicobacter pylori* eradication in China: A systematic review and meta-analysis of randomized clinical trials. *Frontiers in Pharmacology*, 10, 1694. <https://doi.org/10.3389/fphar.2019.01694>
- Huang, Y., Li, W., Dong, L., Li, R., & Wu, Y. (2013). Effect of statin therapy on the progression of common carotid artery intima-media thickness: An updated systematic review and meta-analysis of randomized controlled trials. *Journal of Atherosclerosis and Thrombosis*, 20(1), 108–121.
- Khan, S., Jamison, T., Nguyen, C., Namireddy, M., & Fisher, J. (2021). Berberine use unburies G6PD deficiency [Conference abstract 505]. SHM Converge 2021, Society of Hospital Medicine.
- Kong, W., Wei, J., Abidi, P., Lin, M., Inaba, S., Li, C., Wang, Y., Wang, Z., Si, S., Pan, H., Wang, S., Wu, J., Wang, Y., Li, Z., Liu, J., & Jiang, J.-D. (2004). Berberine is a novel cholesterol-lowering drug working through a unique mechanism distinct from statins. *Nature Medicine*, 10(12), 1344–1351.
- Kong, W.-J., Wei, J., Zuo, Z.-Y., Wang, Y.-M., Song, D.-Q., You, X.-F., Zhao, L.-X., Pan, H.-N., & Jiang, J.-D. (2008). Combination of simvastatin with berberine improves the lipid-lowering efficacy. *Metabolism*, 57(8), 1029–1037. <https://doi.org/10.1016/j.metabol.2008.01.037>
- Lan, J., Zhao, Y., Dong, F., Yan, Z., Zheng, W., Fan, J., & Sun, G. (2015). Meta-analysis of the effect and safety of berberine in the treatment of type 2 diabetes mellitus, hyperlipemia and hypertension. *Journal of Ethnopharmacology*, 161, 69–81.

- Li, J., Zhang, C., Xu, Y., & Yang, L. (2024). The efficacy and safety of berberine in combination with 5-aminosalicylic acid in the treatment of ulcerative colitis: A systematic review and meta-analysis. *PLOS ONE*, 19(9), e0309144. <https://doi.org/10.1371/journal.pone.0309144>
- Li, Z., Wang, Y., Xu, Q., Ma, J., Li, X., Tian, Y., Wen, Y., & Chen, T. (2023). Berberine and health outcomes: An umbrella review. *Phytotherapy Research*, 37(5), 2051–2066. <https://doi.org/10.1002/ptr.7806>
- Lin, C.-H., Wu, Y.-R., Chao, C.-Y., Chang, K.-H., Chen, C.-M., Chen, W.-L., Yang, P.-N., & Lee-Chen, G.-J. (2024). Protective effects of *Coptis chinensis* rhizome extract and its constituents (berberine, coptisine, and palmatine) against α -synuclein neurotoxicity in dopaminergic SH-SY5Y cells. *Biological and Pharmaceutical Bulletin*, 47(4), 837–849. <https://doi.org/10.1248/bpb.b23-00758>
- Liu, D., Zhao, H., Zhang, Y., Hu, J., & Xu, H. (2025). Efficacy and safety of berberine on the components of metabolic syndrome: A systematic review and meta-analysis of randomized placebo-controlled trials. *Frontiers in Pharmacology*, 16, 1572197. <https://doi.org/10.3389/fphar.2025.1572197>
- Luo, D., Yu, B., Sun, S., Chen, B., Harkare, H. V., Wang, L., Pan, J., Huang, B., Song, Y., Ma, T., & Shi, S. (2023). Berberine in the treatment of acute ischemic stroke: A systematic review and meta-analysis. *Phytotherapy Research*, 37(9), 3820–3838. <https://doi.org/10.1002/ptr.7920>
- Mohammadpour, Z., Heshmati, E., Heilbronn, L. K., Hendrie, G. A., Brooker, P. G., & Page, A. J. (2024). The effect of post-oral bitter compound interventions on the postprandial glycemia response: A systematic review and meta-analysis of randomised controlled trials. *Clinical Nutrition*, 43(11), 31–45. <https://doi.org/10.1016/j.clnu.2024.09.027>
- Nazari, A., Ghotbabadi, Z. R., Kazemi, K. S., Metghalchi, Y., Tavakoli, R., Rahimabadi, R. S., & Salmani, F. (2024). The effect of berberine supplementation on glycaemic control and inflammatory biomarkers in metabolic disorders: An umbrella meta-analysis of randomized controlled trials. *Clinical Therapeutics*, 46(2), e64–e72.
- Nederlands Huisartsen Genootschap. (2024). NHG-Standaard Cardiovasculair risicomanagement (CVRM). Utrecht: NHG.
- Nederlands Huisartsen Genootschap. (2025). NHG-Standaard Diabetes mellitus type 2. Utrecht: NHG.
- Persiani, S., Sala, F., Zangarini, M., Manzotti, C., Colovic, M., Donazzolo, Y., Barbetta, B., Vitalini, C., Giacobelli, G., Benvenuti, C., & Rovati, L. C. (2014). Effect of food on the oral bioavailability of berberine and monacolin administered in combination in healthy male volunteers. *Journal of Pharmacy and Pharmacology*, 2(12), 703–712. <https://doi.org/10.17265/2328-2150/2014.12.003>
- Pu, Z., Wen, H., Jiang, H., Hou, Q., & Yan, H. (2023). Berberine improves negative symptoms and cognitive function in patients with chronic schizophrenia via anti-inflammatory effect: A randomized clinical trial. *Chinese Medicine*, 18, 41. <https://doi.org/10.1186/s13020-023-00746-4>
- Qiao, M., Lei, C., Tan, C., Lu, C., Chen, Z., Zhang, Q., & Wang, Z. (2023). Efficacy and safety of berberine for premature ventricular contractions: A meta-analysis and systematic review of randomized controlled trials. *Pharmaceutical Biology*, 61(1), 1474–1483. <https://doi.org/10.1080/13880209.2023.2248167>
- Shi, L., Wang, W., Jing, C., Hu, J., Liao, X., & Wang, J. (2025). Berberine and health outcomes: An overview of systematic reviews. *BMC Complementary Medicine and Therapies*, 25, 147. <https://doi.org/10.1186/s12906-025-04872-4>

- Sun, S., Yang, Y., Xiong, R., Ni, Y., Ma, X., Hou, M., Chen, L., Xu, Z., Chen, L., & Ji, M. (2022). Oral berberine ameliorates high-fat diet-induced obesity by activating TAS2Rs in tuft and endocrine cells in the gut. *Life Sciences*, 311, 121141. <https://doi.org/10.1016/j.lfs.2022.121141>
- Sunhe, Y.-X., Zhang, Y.-H., Fu, R.-J., Xu, D.-Q., & Tang, Y.-P. (2024). Neuroprotective effect and preparation methods of berberine. *Frontiers in Pharmacology*, 15, 1429050. <https://doi.org/10.3389/fphar.2024.1429050>
- Tan, Y.-J., Zou, T.-H., Yu, K., Sheng, J.-Q., Jin, P., Zhang, M.-J., Zou, X.-P., Dou, X.-T., Liu, S.-D., Huang, S.-H., Ren, J.-L., Yang, X.-N., Liu, Z.-J., Sun, X.-M., Wang, B.-M., Cao, H.-L., Zhang, Y.-X., Gao, Q.-Y., Chen, H.-M., ... Fang, J.-Y. (2025). Berberine prevents colorectal adenoma recurrence: A 6-year extended follow-up of a randomised controlled trial. *Cell Reports Medicine*, 6, 102293.
- Turner, N., Li, J.-Y., Gosby, A., To, S. W. C., Cheng, Z., Miyoshi, H., Taketo, M. M., Cooney, G. J., Kraegen, E. W., James, D. E., Hu, L.-H., Li, J., & Ye, J.-M. (2008). Berberine and its more biologically available derivative, dihydroberberine, inhibit mitochondrial respiratory complex I: A mechanism for the action of berberine to activate AMP-activated protein kinase and improve insulin action. *Diabetes*, 57(5), 1414–1418. <https://doi.org/10.2337/db07-1552>
- Wald, N. J., & Law, M. R. (2003). A strategy to reduce cardiovascular disease by more than 80%. *BMJ*, 326(7404), 1419–1423. <https://doi.org/10.1136/bmj.326.7404.1419>
- Wang, J., Wang, L., Lou, G.-H., Zeng, H.-R., Hu, J., Huang, Q.-W., Peng, W., & Yang, X.-B. (2019). *Coptidis Rhizoma*: A comprehensive review of its traditional uses, botany, phytochemistry, pharmacology and toxicology. *Pharmaceutical Biology*, 57(1), 193–225. <https://doi.org/10.1080/13880209.2019.1577466>
- Wang, H., Zhang, H., Gao, Z., Zhang, Q., & Gu, C. (2022). The mechanism of berberine alleviating metabolic disorder based on gut microbiome. *Frontiers in Cellular and Infection Microbiology*, 12, 854885. <https://doi.org/10.3389/fcimb.2022.854885>
- Wang, J., Bi, C., Xi, H., & Wei, F. (2024). Effects of administering berberine alone or in combination on type 2 diabetes mellitus: A systematic review and meta-analysis. *Frontiers in Pharmacology*, 15, 1455534.
- Wang, Y., Tong, Q., Shou, J.-W., Zhao, Z.-X., Li, X.-Y., Zhang, X.-F., Ma, S.-R., He, C.-Y., Lin, Y., Wen, B.-Y., Guo, F., Fu, J., & Jiang, J.-D. (2017). Gut microbiota-mediated personalized treatment of hyperlipidemia using berberine. *Theranostics*, 7(9), 2443–2451. <https://doi.org/10.7150/thno.18290>
- Wu, X., Li, Q., Xin, H., Yu, A., & Zhong, M. (2005). Effects of berberine on the blood concentration of cyclosporin A in renal transplanted recipients: Clinical and pharmacokinetic study. *European Journal of Clinical Pharmacology*, 61(8), 567–572. <https://doi.org/10.1007/s00228-005-0952-3>
- Xie, L., Zhang, D., Ma, H., He, H., Xia, Q., Shen, W., Chang, H., Deng, Y., Wu, Q., Cong, J., Wang, C. C., & Wu, X. (2019). The effect of berberine on reproduction and metabolism in women with polycystic ovary syndrome: A systematic review and meta-analysis of randomized control trials. *Evidence-Based Complementary and Alternative Medicine*, 2019, 7918631. <https://doi.org/10.1155/2019/7918631>
- Xie, W., Su, F., Wang, G., Peng, Z., Xu, Y., Zhang, Y., Xu, N., Hou, K., Hu, Z., Chen, Y., & Chen, R. (2022). Glucose-lowering effect of berberine on type 2 diabetes: A systematic review and meta-analysis. *Frontiers in Pharmacology*, 13, 1015045. <https://doi.org/10.3389/fphar.2022.1015045>

- Xiong, X., Wang, X., Li, B., Chowdhury, S., Lu, Y., Hu, J., & Zhang, J. (2020). Berberine in the treatment of obesity: A dose-response meta-analysis. *Complementary Therapies in Clinical Practice*, 39, 101113. <https://doi.org/10.1016/j.ctcp.2020.101113>
- Yan, H.-M., Xia, M.-F., Wang, Y., Chang, X.-X., Yao, X.-Z., Rao, S.-X., Zeng, M.-S., Tu, Y.-F., Feng, R., Jia, W.-P., Liu, J., Deng, W., Jiang, J.-D., & Gao, X. (2015). Efficacy of berberine in patients with non-alcoholic fatty liver disease. *PLOS ONE*, 10(8), e0134172.
- Yang, L., Zhu, W., Zhang, X., Zhou, X., Wu, W., & Shen, T. (2023). Efficacy and safety of berberine for several cardiovascular diseases: A systematic review and meta-analysis of randomized controlled trials. *Phytomedicine*, 112, 154716. <https://doi.org/10.1016/j.phymed.2023.154716>
- Yin, J., Xing, H., & Ye, J. (2008). Efficacy of berberine in patients with type 2 diabetes mellitus. *Metabolism*, 57(5), 712–717.
- Yu, Y., Hao, G., Zhang, Q., Hua, W., Wang, M., Zhou, W., Zong, S., Huang, M., & Wen, X. (2015). Berberine induces GLP-1 secretion through activation of bitter taste receptor pathways. *Biochemical Pharmacology*, 97(2), 173–177. <https://doi.org/10.1016/j.bcp.2015.07.012>
- Yusuf, S., Joseph, P., Dans, A., Gao, P., Teo, K., Xavier, D., López-Jaramillo, P., Yusoff, K., Santoso, A., Gamra, H., Talukder, S., Christou, C., Girish, P., Yeates, K., Xavier, F., Dagenais, G., Rocha, C., McCready, T., Tyrwhitt, J., ... Pais, P. (2021). Polypill with or without aspirin in persons without cardiovascular disease. *The New England Journal of Medicine*, 384(3), 216–228. <https://doi.org/10.1056/NEJMoa2028220>
- Zeng, X.-H., Zeng, X.-J., & Li, Y.-Y. (2003). Efficacy and safety of berberine for congestive heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. *The American Journal of Cardiology*, 92(2), 173–176.
- Zhu, X., Wei, Y., Yang, B., Yin, X., & Guo, X. (2020). The mitohormetic response as part of the cytoprotection mechanism of berberine. *Molecular Medicine*, 26(1), 10. <https://doi.org/10.1186/s10020-020-0136-8>

Appendix 2. Berberine and red yeast rice: a practical comparison for general practice

Please note this appendix is AI generated and only briefly reviewed by the author

Why this appendix

Red yeast rice (RYR) is among the lipid-lowering supplements most often used by patients who decline or cannot tolerate a statin. Its active constituent, monacolin K, is chemically identical to lovastatin. During 2026 the European Commission has been completing a procedure that will remove monacolins from the European supplement market. Patients who use RYR, and the general practitioners advising them, will need an alternative, and berberine is the most likely one they will reach for. This appendix compares the two compounds, sets out where berberine is and is not the better option, and states plainly that berberine is itself now under European safety review.

A2.1 The two compounds side by side

	Berberine	Red yeast rice (monacolin K)
Mechanism	Raises the number of hepatic LDL receptors: stabilises LDL-receptor mRNA and suppresses PCSK9 through HNF1 α . Does not inhibit cholesterol synthesis.	Monacolin K is lovastatin. Inhibits HMG-CoA reductase; a weak, reversible statin.
LDL-cholesterol	Roughly 15% against placebo in pooled trials (Liu et al., 2025); 20 to 25% from baseline (Kong et al., 2004)	15 to 25% within 6 to 8 weeks at full dose (Cicero et al., 2021). In the EU the legal dose is capped below 3 mg/day.
Triglycerides	Roughly 15% against placebo in pooled trials, about 22% with raised lipids (Liu et al., 2025); 28 to 35% from baseline (Kong et al., 2004)	Modest; falls roughly in proportion to LDL-cholesterol
Beyond lipids	HbA1c reduction similar to metformin at the doses used in direct trials; effects on body weight, hepatic steatosis and inflammatory markers	None established; hs-CRP falls in proportion to LDL-cholesterol
Patient-relevant clinical outcomes	None. The berberine lipid evidence stops at biomarkers.	Secondary-prevention event data from the Chinese CCSPS trial: 45% relative reduction in major coronary events over 4.5 years (Cicero et al., 2021)
Typical dose	500 mg twice daily (1,000 mg/day) with meals, up to 1,500 mg/day	3 to 10 mg monacolin K daily
Main adverse effects	Mild, transient gastrointestinal symptoms (diarrhoea, constipation, abdominal discomfort), usually early and often settling	Statin-type myalgia; raised transaminases; variable monacolin content between products; citrinin contamination
EU regulatory status (September 2026)	Available, but under EFSA Article 8 safety review; Belgium already caps isoquinoline alkaloids at 10 mg/day	Capped below 3 mg/day since 2022; full prohibition approved by the Member States in May 2026, awaiting publication

A2.2 The decisive point: dose collapse under European law

The efficacy figures quoted for RYR in the international literature rest on doses that are no longer legal in the Netherlands. The EFSA health claim for monacolin K and blood cholesterol was substantiated at 10 mg per day. Since Regulation (EU) 2022/860 took effect, supplements providing 3 mg per day or more of monacolins may not be placed on the market.

A Dutch patient buying RYR today therefore receives roughly a third of the dose on which the published efficacy rests, and a realistic expectation is an LDL-cholesterol reduction at the bottom of the 15 to 25% band. Berberine at 1,000 to 1,500 mg per day delivers its full effect: roughly 15% against placebo in pooled trials, 20 to 25% from baseline in the original trial.

At the doses actually available to Dutch patients, berberine lowers LDL-cholesterol about as much as RYR, and it is the only one of the two that also lowers triglycerides substantially and improves glycaemic control.

A2.3 Where berberine is clearly stronger

- Triglycerides. Roughly 15% against placebo in pooled trials and about 22% in patients with raised lipids (28 to 35% from baseline in the original trial), comparable to or somewhat above statins and clearly larger than RYR's. In the typical dyslipidaemic patient with metabolic syndrome this is often the more relevant abnormality.
- Glycaemic control. An HbA1c reduction similar to metformin at the doses used in direct comparisons, discussed in Section 2.2. RYR does nothing here.
- Statin-type adverse effects. Monacolin K carries the statin adverse-effect profile, including myalgia and, rarely, rhabdomyolysis, which is part of why EFSA moved against it. Berberine's adverse effects are predominantly gastrointestinal.

A2.4 Where red yeast rice remains ahead

Three points should be stated plainly, so the comparison is not read as promotional.

First, RYR has clinical-event data. In the Chinese CCSPS secondary-prevention trial, RYR treatment was associated with a 45% relative reduction in major coronary events over 4.5 years, with the event rate falling from 10.4% to 5.7% (Cicero et al., 2021). These data come from Chinese Xuezhikang trials rather than from Western supplements. Berberine has no equivalent cardiovascular-outcome trial; its evidence stops at lipids and biomarkers, as Section 3.4 sets out.

Second, at unrestricted dose (10 mg monacolin K) the LDL-cholesterol effect of RYR is at least as large as berberine's, and probably larger. That berberine now matches it follows from European dose restriction, not from superior intrinsic potency.

Third, monacolin K's toxicology is the familiar toxicology of a statin. Berberine's is less well characterised, and the open questions are set out in A2.6.

A2.5 Can the two be combined?

Mechanistically the combination is attractive. Statins raise PCSK9 as well as LDL receptors, which partly undoes their own effect. In hepatocytes, berberine reduced HNF1 α protein to about 40% of control, suppressed PCSK9 transcription, and abolished the rise in PCSK9 messenger RNA produced by fluvastatin, lovastatin and simvastatin, while leaving LDL-receptor expression intact (Li et al., 2009). Monacolin K opens the tap; berberine closes the drain. This is cell-culture work, so it is mechanistic plausibility rather than demonstrated clinical benefit, and at least one animal study reports the opposite direction for circulating PCSK9.

Two caveats follow. Berberine inhibits CYP3A4, which metabolises monacolin K: at 900 mg per day it raised exposure to a CYP3A4 probe drug by about 40% (Guo et al., 2012), so monacolin K exposure, and with it myopathy risk, would be expected to rise in precisely the statin-intolerant patients most likely to use the combination. And the marketed European combination products deliberately pair sub-therapeutic doses of both: a meta-analysis of 11 randomised trials and 3,924 patients found pooled reductions of 9.9% in total cholesterol, 13.7% in LDL-cholesterol and 7.0% in triglycerides (Millán et al., 2016), similar to berberine alone for LDL-cholesterol and less than berberine alone for triglycerides.

For practical purposes the combination question is closing, because monacolin-containing products are being withdrawn.

A2.6 The regulatory position, including berberine's own

EFSA concluded in 2025 that the data submitted during the scrutiny period did not establish the safety of monacolins from RYR below 3 mg per day, and that no daily intake could be identified that does not raise safety concerns for the general population or vulnerable subgroups (EFSA NDA Panel, 2025). On 4 March 2026 the Commission notified the World Trade Organization of a draft regulation moving monacolins from Part B (restricted) to Part A (prohibited) of Annex III to Regulation (EC) No 1925/2006. On 13 May 2026 the Member States' Standing Committee approved the prohibition. A transitional period of twelve months is expected for products already on the market, so full application is estimated between late 2027 and early 2028. Publication in the Official Journal had not been confirmed at the time of writing. The prohibition covers monacolins rather than red yeast rice itself, so monacolin-free RYR products may appear; these will have no cholesterol-lowering effect.

Berberine is not outside this process. During 2026 EFSA published for public consultation a draft opinion on plant preparations containing berberine and protoberberines, concluding that the available data do not allow a safe intake for humans to be established for any of the preparations assessed. The draft reports in-vitro evidence of genotoxicity, indicating gene mutation and chromosomal damage, without in-vivo confirmation at the sites of contact; it identifies goldenseal (*Hydrastis canadensis*) preparations as showing carcinogenic activity in rodents, chiefly liver adenomas; and it notes hepatotoxicity cases associated with greater celandine (*Chelidonium majus*). France's ANSES had earlier been unable to establish a toxicity reference value and advised against use by children, adolescents, pregnant and breastfeeding women and other vulnerable groups (ANSES, 2019). Belgium caps isoquinoline alkaloids in supplements at 10 mg per day. A final EFSA opinion is expected in 2027, after which the Commission will decide whether berberine is listed under Annex III Part A (prohibition), Part B (restriction) or Part C (Union scrutiny).

Two qualifications matter for reading this. The trials on which this paper rests used purified berberine hydrochloride derived from *Berberis* or *Coptis* species, not goldenseal or greater celandine, and the carcinogenicity finding attaches specifically to goldenseal. But the genotoxicity signal attaches to berberine itself, and EFSA's inability to establish a safe intake applies across the preparations assessed. A practitioner advising berberine in 2027 should expect this question to be live, and should not present berberine as the regulatorily secure option.

A2.7 Practical guidance

- Patients currently using RYR. Supplies will disappear during the transitional period. Reassess cardiovascular risk now rather than at the point of withdrawal.
- If a statin is indicated and tolerated, prescribe it. Neither supplement substitutes for a statin in secondary prevention or in high-risk primary prevention.
- If a statin is declined or not tolerated, berberine 500 mg twice daily with meals is the more broadly effective of the two options under current European dose limits (similar LDL-cholesterol lowering, plus effects on triglycerides and glucose), used within the 12-week structured approach set out in Section 8.
- Favour berberine particularly where triglycerides are raised, or where there is impaired glucose tolerance, type 2 diabetes or hepatic steatosis.

- Check interactions. Berberine inhibits CYP2D6, CYP2C9 and CYP3A4 and modulates P-glycoprotein. Review comedication, especially statins, cyclosporine, tacrolimus, warfarin, macrolides and QT-prolonging drugs.
- Observe the contraindications set out in Section 5: pregnancy, breastfeeding and neonates; known or suspected G6PD deficiency; eGFR below 30 mL/min/1.73 m² is a precaution to be discussed individually.
- Monitor the lipid panel, HbA1c, ALT and eGFR at baseline and after 12 weeks, as set out in Section 8.
- Mention the regulatory position. Berberine is itself under EFSA review, and its status in the EU may change.

Bottom line

Monacolin K has been the most effective lipid-lowering nutraceutical available in Dutch practice. European regulation has already cut its usable dose by roughly two-thirds and is about to remove it altogether. On the pooled placebo-controlled data, berberine at legally available doses lowers LDL-cholesterol about as much, lowers triglycerides substantially more, improves glycaemic control, and does not carry the statin adverse-effect profile. For the patient losing access to red yeast rice, berberine is the most plausible successor. Two caveats belong with that conclusion: neither compound has the outcome evidence a statin has, and berberine's own European safety review is unresolved. One further consideration belongs in this comparison. Cardiometabolic disease is not a single defect but a network of linked disturbances in glucose handling, lipid transport, body composition and low-grade inflammation, each reinforcing the others. Against a target of that shape, an agent acting at several nodes at once has an advantage that a single-target drug does not. Berberine acts on glucose, lipids, body weight and inflammation together, whereas monacolin K acts on one. This is an argument about biological plausibility and breadth of effect, not about strength of evidence, and it does not offset berberine's lack of outcome data.

A2.8 References for this appendix

These sources support this appendix only and are not held in the paper's source corpus. Guo et al. (2012), Kong et al. (2004) and Liu et al. (2025) also appear in Appendix 1.

ANSES. (2019). Opinion on the use of berberine-containing plants in food supplements (Opinion No. 2018-SA-0095). French Agency for Food, Environmental and Occupational Health and Safety.

Cicero, A. F. G., Fogacci, F., & Zambon, A. (2021). Red yeast rice for hypercholesterolemia: JACC focus seminar. *Journal of the American College of Cardiology*, 77(5), 620–628.
<https://doi.org/10.1016/j.jacc.2020.11.056>

EFSA Panel on Nutrition, Novel Foods and Food Allergens. (2025). Scientific opinion on additional scientific data related to the safety of monacolins from red yeast rice submitted pursuant to Article 8(4) of Regulation (EC) No 1925/2006. *EFSA Journal*, 23(3), e9276.
<https://doi.org/10.2903/j.efsa.2025.9276>

EFSA Panel on Nutrition, Novel Foods and Food Allergens. (2026). Draft scientific opinion on the safety of berberine, protoberberines and plant preparations containing these substances [Draft for public consultation]. European Food Safety Authority.

European Commission. (2022). Commission Regulation (EU) 2022/860 of 1 June 2022 amending Annex III to Regulation (EC) No 1925/2006 as regards monacolins from red yeast rice. *Official Journal of the European Union*, L 151, 37–39.

- Guo, Y., Chen, Y., Tan, Z.-R., Klaassen, C. D., & Zhou, H.-H. (2012). Repeated administration of berberine inhibits cytochromes P450 in humans. *European Journal of Clinical Pharmacology*, 68(2), 213–217. <https://doi.org/10.1007/s00228-011-1108-2>
- Kong, W., Wei, J., Abidi, P., Lin, M., Inaba, S., Li, C., Wang, Y., Wang, Z., Si, S., Pan, H., Wang, S., Wu, J., Wang, Y., Li, Z., Liu, J., & Jiang, J.-D. (2004). Berberine is a novel cholesterol-lowering drug working through a unique mechanism distinct from statins. *Nature Medicine*, 10(12), 1344–1351. <https://doi.org/10.1038/nm1135>
- Li, H., Dong, B., Park, S. W., Lee, H.-S., Chen, W., & Liu, J. (2009). Hepatocyte nuclear factor 1 α plays a critical role in PCSK9 gene transcription and regulation by the natural hypocholesterolemic compound berberine. *Journal of Biological Chemistry*, 284(42), 28885–28895. <https://doi.org/10.1074/jbc.M109.052407>
- Liu, D., Zhao, H., Zhang, Y., Hu, J., & Xu, H. (2025). Efficacy and safety of berberine on the components of metabolic syndrome: A systematic review and meta-analysis of randomized placebo-controlled trials. *Frontiers in Pharmacology*, 16, 1572197. <https://doi.org/10.3389/fphar.2025.1572197>
- Millán, J., Cicero, A. F. G., Torres, F., & Anguera, A. (2016). Effects of a nutraceutical combination containing berberine, policosanol and red yeast rice on lipid profile in hypercholesterolemic patients: A meta-analysis of randomised controlled trials. *Clínica e Investigación en Arteriosclerosis*, 28(4), 178–187. <https://doi.org/10.1016/j.arteri.2016.03.002>

Appendix 3. Glossary: terms, values and abbreviations explained

Please note this appendix is AI generated and only briefly reviewed by the author

How to use this glossary

This appendix is written for readers with or without a medical background, so that the main text can also be read without prior knowledge. It has five parts. A3.1 lists the laboratory and clinical values that appear in the paper, each with the range that counts as normal or the target a Dutch guideline sets, so that a figure reported in a trial can be judged against something. A3.2 explains the research and statistical vocabulary. A3.3 explains the medical and pharmacological terms. A3.4 is a quick look-up list of abbreviations. A3.5 gives notes for clinicians working outside these fields.

Two cautions about the reference values. Laboratories differ, and the range printed on your own result sheet takes precedence over the general figures given here. And a target is not the same thing as a normal value: for cholesterol in particular, the numbers below are treatment targets that depend on a person's overall risk, not a line between healthy and unhealthy.

A3.1 Laboratory and clinical values

Measure (unit)	What it measures, in plain words	Normal range or guideline target
HbA1c (mmol/mol)	Average blood sugar over the previous 8 to 12 weeks. It measures how much sugar has attached itself to the haemoglobin inside red blood cells, so a single good or bad day cannot distort it.	Below 42 normal. 42 to 47 raised (prediabetes). 48 and above means diabetes. Dutch treatment target is usually 53 or below under age 70, and 54 to 64 for older patients on more than one drug. Roughly: 42 = 6.0%, 48 = 6.5%, 53 = 7.0% on the older percentage scale.
Fasting plasma glucose (mmol/L)	Blood sugar measured after a night without food.	Below 6.1 normal. 6.1 to 6.9 impaired fasting glucose. 7.0 and above, on two separate occasions, means diabetes.
LDL-cholesterol (mmol/L)	Cholesterol carried in the particles that deposit fat in artery walls. Often called bad cholesterol.	No fixed normal value: lower is better. Dutch targets on lipid-lowering treatment are below 1.8 with established cardiovascular disease and below 2.6 for other treated high-risk groups.
HDL-cholesterol (mmol/L)	Cholesterol carried in the particles that return fat to the liver. Often called good cholesterol.	Desirable above 1.0 in men and above 1.3 in women. A low value counts towards metabolic syndrome.
Total cholesterol (mmol/L)	All cholesterol in the blood added together, harmful and protective fractions combined.	Often quoted as desirable below 5.0. On its own it is a weak guide; the split between LDL and HDL matters more.
Triglycerides (mmol/L)	The main form of fat circulating in the blood. Strongly affected by recent food, alcohol and insulin resistance.	Below 1.7 desirable. 1.7 to 2.2 borderline. 2.3 and above raised. Measured fasting.
Non-HDL cholesterol (mmol/L)	Total cholesterol minus HDL: everything capable of contributing to plaque, in a single number.	Usually about 0.8 mmol/L above the LDL target, so below 2.6 or below 3.4 depending on the risk group.
Apolipoprotein B, ApoB (g/L)	A protein carried one per particle on every fat particle that can enter an artery wall, so it counts the particles rather than the cholesterol inside them.	Roughly below 0.8 g/L at high risk and below 1.0 g/L at moderate risk. Not measured in every Dutch laboratory.
Body mass index, BMI (kg/m ²)	Weight in kilograms divided by height in metres squared. A crude measure of body size that cannot tell muscle from fat.	Below 18.5 underweight. 18.5 to 24.9 healthy. 25 to 29.9 overweight. 30 and above obesity.
Waist circumference (cm)	Measured around the waist at navel level. Reflects fat around the organs, which carries more metabolic risk than fat under the skin.	Raised above 102 cm in men and above 88 cm in women. These are the metabolic-syndrome cut-offs.
eGFR (mL/min/1.73 m ²)	Estimated glomerular filtration rate: how much blood the kidneys clean each minute, adjusted for body size. Calculated from creatinine, age and sex rather than measured directly.	90 and above normal. 60 to 89 mildly reduced. 45 to 59 and 30 to 44 moderately reduced. 15 to 29 severely reduced. Below 15 kidney failure. Below 30, this paper advises discussing berberine individually.
ALT and AST (U/L)	Enzymes released from liver cells when those cells are irritated or damaged. ALT is the more specific of the two for the liver.	Reference ranges differ between laboratories, typically up to about 45 U/L in men and about 35 U/L in women. A rise to three times the upper limit usually prompts stopping the suspected cause.

Measure (unit)	What it measures, in plain words	Normal range or guideline target
CRP and hs-CRP (mg/L)	C-reactive protein, made by the liver during inflammation. The high-sensitivity version detects the low levels relevant to cardiovascular risk.	For cardiovascular risk: below 1 low, 1 to 3 average, above 3 raised. Above 10 usually indicates infection or another acute illness rather than background inflammation.
IL-6 and TNF-alpha	Interleukin-6 and tumour necrosis factor alpha: chemical messengers that cells use to switch inflammation on.	No routine clinical reference range. These are research measures, and in this paper they appear only as changes relative to a comparison group.
Blood pressure (mmHg)	Pressure in the arteries, written as systolic (heart contracting) over diastolic (heart relaxing).	Generally treated to below 140 mmHg systolic in Dutch primary care, with a lower target in selected groups. Individualised, particularly in older patients.
SCORE2 and SCORE2-OP (%)	Risk calculators estimating the chance of a first fatal or non-fatal heart attack or stroke within ten years. SCORE2-OP is the version for people aged 70 and over.	Age 40 to 49: low-to-moderate below 2.5%, high 2.5% to under 7.5%, very high 7.5% or above. Age 50 to 69: low-to-moderate below 5%, high 5% to under 10%, very high 10% or above. Age 70 and over: low-to-moderate below 7.5%, high 7.5% to under 15%, very high 15% or above.
HOMA-IR	A calculated index of insulin resistance, derived from fasting glucose and fasting insulin together. Higher means the body needs more insulin for the same effect.	No universal cut-off, because it depends on the insulin assay used. Values around 2.5 and above are commonly taken to indicate insulin resistance.
NIHSS (points)	National Institutes of Health Stroke Scale: a bedside score of how disabling a stroke is, running from 0 to 42.	0 no symptoms. 1 to 4 minor. 5 to 15 moderate. 16 to 20 moderate to severe. 21 and above severe.
SHBG (nmol/L)	Sex hormone binding globulin, the carrier protein that holds sex hormones in the blood and keeps them inactive. When it is low, more free testosterone circulates.	Typically about 20 to 80 nmol/L in women, varying with laboratory and age. Often low in polycystic ovary syndrome.
Testosterone (nmol/L)	The main androgen hormone. Raised in polycystic ovary syndrome, where it drives acne, unwanted hair growth and irregular cycles.	In women usually below about 1.7 nmol/L. Laboratory-specific.
LH and FSH	Luteinising hormone and follicle-stimulating hormone, the two pituitary hormones driving the menstrual cycle. The ratio between them is often raised in polycystic ovary syndrome.	Both vary across the cycle, so they are read against the day of the cycle rather than a single range.
INR	International normalised ratio: how long blood takes to clot, expressed relative to normal. Used to monitor warfarin.	About 1.0 without anticoagulation. Usually a target of 2.0 to 3.0 on warfarin. Higher means thinner blood and more bleeding risk.
Carotid intima-media thickness (mm)	The thickness of the inner two layers of the neck artery wall, measured by ultrasound. A marker of silent, early hardening of the arteries.	Commonly regarded as raised above about 0.9 mm, though it increases with age and cut-offs vary between laboratories.
Crouse score	A summed ultrasound measure of the total plaque burden in the carotid arteries.	No single threshold. Used to compare before with after, or one group with another.
QT interval and QTc (ms)	The time the heart's electrical system takes to recover between beats, measured on an ECG. QTc is the value corrected for heart rate.	Prolonged above roughly 450 ms in men and 470 ms in women. A long QT raises the risk of a dangerous rhythm disturbance.
PR and QRS intervals (ms)	Two further ECG timings. PR is conduction from the upper to the lower chambers; QRS is the spread of the impulse through the lower chambers.	PR roughly 120 to 200 ms. QRS below about 120 ms.
Bilirubin (µmol/L)	A yellow pigment produced when red blood cells are broken down, then cleared by the liver. When it accumulates it causes jaundice.	Usually below about 17 µmol/L in adults. Newborns tolerate far less before treatment is needed, which is why the displacement risk described in Section 5 matters.
ng/mL and mg/L	Units of concentration in blood. A nanogram per millilitre is one thousandth of a milligram per litre.	Berberine blood levels in humans sit in the low ng/mL range, which is very low. This is why its poor absorption matters.
g/day and mg/day	The daily dose. One gram equals 1,000 milligrams.	The berberine doses discussed in this paper are 900 to 1,500 mg/day, that is 0.9 to 1.5 g/day.
Percentage point	The plain arithmetic difference between two percentages, as opposed to a relative change.	An HbA1c fall of 0.7 percentage point means, for example, 8.0% down to 7.3%. It does not mean a 0.7% relative reduction.

A3.2 Research and statistical terms

Term	What it means
Randomised controlled trial (RCT)	A study in which participants are allocated to treatment or comparison by chance. Randomising is what allows a difference in outcome to be attributed to the treatment rather than to how the groups differed beforehand.
Placebo, placebo-controlled	A dummy treatment indistinguishable from the real one. Comparing against placebo separates the effect of the drug from the effect of being treated and observed.

Term	What it means
Double-blind	Neither the participant nor the assessor knows who received the real treatment, so expectation cannot colour the result.
Meta-analysis	A statistical pooling of the results of several trials into one combined estimate. It buys precision, but it cannot repair weaknesses in the trials it pools.
Systematic review	A search of the literature conducted to a written protocol, so that the selection of studies is reproducible rather than selective.
Umbrella review	A review of existing systematic reviews and meta-analyses rather than of individual trials. It gives a wide view and is the usual place where evidence quality is graded.
GRADE	The standard system for rating how much confidence a result deserves, in four levels: HIGH, MODERATE, LOW and VERY LOW. It rates the certainty of the evidence, not the size of the effect. A LOW rating does not mean the treatment does not work; it means further research could well change the estimate.
AMSTAR-2	A checklist for judging the methodological quality of a systematic review, used alongside GRADE.
Standardised mean difference (SMD)	A way of expressing an effect when studies used different measuring scales, given in standard deviations. By convention about 0.2 is small, 0.5 moderate and 0.8 large. A negative sign means the measure fell.
Relative risk (RR)	How many times more or less likely an outcome is in one group than the other. An RR of 0.61 means a 39% lower chance.
95% confidence interval (CI)	The range within which the true value most plausibly lies. A narrow interval means a precise estimate. If the interval for a difference includes zero, or for a ratio includes 1, the result is not statistically significant.
Statistically significant	Unlikely to be explained by chance alone. It says nothing about whether the difference is large enough to matter to a patient.
n =	The number of participants. Larger numbers generally give more reliable estimates.
Subgroup analysis	Looking at the result within a slice of the participants, such as one dose band or one age group. Useful for generating ideas, unreliable as proof, because enough slices will always throw up an apparent difference.
Confounder	Something other than the treatment that differs between groups and could explain the result, such as diet or another medication.
Heterogeneity	The degree to which pooled trials disagree with one another. High heterogeneity makes a combined figure harder to trust.
Publication bias	The tendency for positive results to reach print more readily than negative ones, which inflates the apparent benefit in any pooled analysis.
Hard clinical endpoint	Something that happens to the patient and matters in itself: a heart attack, a stroke, a death, a cancer. The strongest kind of evidence. Colorectal-adenoma recurrence is not one: an adenoma is a precursor of cancer, so this review calls it a patient-relevant clinical outcome.
Intermediate or surrogate outcome	A measurement that stands in for a hard endpoint, such as a cholesterol level or an HbA1c. Useful, but improving a marker does not always translate into fewer events.
Monotherapy, adjunct, add-on	Monotherapy means the treatment is given on its own. Adjunct or add-on means it is given on top of existing treatment, and the comparison is with that existing treatment alone.
Dose-response	The pattern where a larger dose produces a larger effect. Its presence strengthens the case that the effect is real.
Primary and secondary prevention	Primary prevention is treating someone who has not yet had a cardiovascular event. Secondary prevention is treating someone who has, where the risk and therefore the case for medication is higher.

A3.3 Medical and pharmacological terms

Term	In plain words
Adenoma	A benign growth in the bowel lining that can, over years, turn into bowel cancer. Preventing its return is a cancer-precursor outcome.
Alkaloid, isoquinoline alkaloid	A class of nitrogen-containing plant compounds with strong biological activity. Berberine is one; so are morphine and quinine.
AMPK	An enzyme acting as the cell's fuel gauge. When energy runs low it switches the cell from storing to burning. Metformin works largely through it, and so does berberine.
Anthropometric	Relating to body measurements: weight, BMI, waist circumference.
Antineoplastic	Acting against tumours.
ARNI	Angiotensin receptor/neprilysin inhibitor, a modern class of heart-failure drug.
Arrhythmia	An abnormal heart rhythm, too fast, too slow or irregular.
Atherosclerosis, plaque	The build-up of fatty, fibrous deposits in artery walls. An unstable plaque is one liable to rupture and trigger a heart attack or stroke.
Bile acids	Detergent-like substances made by the liver to absorb fat. Gut bacteria modify them, and the modified forms act as signals affecting metabolism.
Bioavailability	The proportion of a swallowed dose that reaches the bloodstream intact. Berberine's is under 1%, which is why large doses are needed.

Term	In plain words
Bitter-taste receptor (TAS2R)	A receptor for bitterness, found not only on the tongue but in the gut wall. Berberine is intensely bitter, and activating these gut receptors releases appetite and glucose hormones.
Cardiotoxicity	Damage to the heart caused by a substance.
Cytochrome P450 (CYP)	The liver's main family of drug-processing enzymes. Individual members are numbered: CYP3A4 handles roughly half of all prescribed drugs, CYP2C9 handles warfarin, CYP2D6 handles many antidepressants and heart drugs. Blocking one of them makes the drugs it handles accumulate.
Damp-heat	A Traditional Chinese Medicine pattern description, not a Western diagnosis. It covers presentations with heaviness, heat and discharge, historically treated with the herb berberine comes from.
DPP-4 inhibitor	A class of diabetes tablet that prolongs the body's own gut hormone signal. Sitagliptin is an example.
Ejection fraction	The proportion of blood the left ventricle pumps out with each beat. A measure of how well the heart is pumping.
Enteroendocrine cells	Hormone-producing cells scattered through the gut lining that sense what is passing and signal to the rest of the body.
Familial hypercholesterolaemia	An inherited condition causing very high LDL-cholesterol from birth and early heart disease. It always requires medication.
G6PD deficiency	An inherited enzyme deficiency, common around the Mediterranean, Africa and Asia, in which red blood cells break apart when exposed to certain drugs and foods.
GLP-1	Glucagon-like peptide 1, a gut hormone released after eating that increases insulin, slows the stomach and reduces appetite. The drug class in Ozempic mimics it.
Gut microbiome	The community of bacteria living in the bowel. It influences metabolism, inflammation and how drugs are processed.
Haemolysis	The breaking apart of red blood cells, causing anaemia and jaundice.
hERG channel	A potassium channel that lets heart muscle cells reset electrically after a beat. Blocking it lengthens the QT interval and can provoke a dangerous rhythm.
HMG-CoA reductase	The rate-limiting enzyme in the body's own cholesterol production. Statins, and monacolin K, work by blocking it.
Hypoglycaemia	Blood sugar falling too low, causing sweating, shaking, confusion and, if severe, collapse. A risk mainly with insulin and sulphonylureas.
Insulin resistance	The state in which tissues respond poorly to insulin, so more of it is needed for the same effect. The central abnormality in type 2 diabetes and metabolic syndrome.
Ischaemic stroke	A stroke caused by a blocked artery cutting off blood supply to part of the brain, as distinct from a bleed.
Kernicterus	Brain damage in a newborn caused by very high bilirubin crossing into the brain. The reason bilirubin displacement matters in pregnancy and infancy.
LDL receptor	The docking point on liver cells that pulls LDL-cholesterol out of the blood. More receptors means lower blood cholesterol.
Lipid panel	The standard blood test set: total cholesterol, LDL, HDL and triglycerides.
Macrolide antibiotics	A family including azithromycin, clarithromycin and erythromycin. They can lengthen the QT interval and block CYP3A4.
Metabolic syndrome	A cluster of abdominal obesity, raised triglycerides, low HDL, raised blood pressure and raised fasting glucose. Three of the five make the diagnosis.
Metformin	The standard first-line tablet for type 2 diabetes, and the comparator used throughout this paper.
Mineralocorticoid-receptor antagonist	A drug class including spironolactone, part of modern heart-failure treatment.
Mitochondria, complex I	The compartments in which cells burn fuel for energy. Complex I is the first step of that chain, and berberine mildly inhibits it.
Mitohormesis	The principle that a mild, non-damaging stress to the mitochondria triggers a protective response that leaves the cell better off. Exercise and fasting work this way, and this paper argues berberine does too.
Monacolin K	The active substance in red yeast rice. Chemically the same molecule as the statin lovastatin.
Myalgia	Muscle pain. The commonest reason people stop taking statins.
NAFLD	Non-alcoholic fatty liver disease: fat accumulating in the liver in someone who does not drink heavily. Closely tied to insulin resistance.
NF-κB and the NLRP3 inflammasome	Two of the master switches that turn on chronic low-grade inflammation inside cells.
NHG-Standaard, CVRM	The Dutch College of General Practitioners' clinical guidelines. CVRM is the one covering cardiovascular risk management.
Nitric oxide	A short-lived gas made by the artery lining that relaxes blood vessels. Less of it means stiffer, less responsive arteries.
P-glycoprotein	A pump in the gut wall that ejects absorbed substances back into the bowel. It is one reason berberine is so poorly absorbed, and it also affects other drugs.

Term	In plain words
PCSK9	A liver protein that destroys LDL receptors. Blocking it leaves more receptors in place and lowers cholesterol. It is the target of the injectable cholesterol drugs used in specialist practice.
Pharmacokinetics	What the body does to a drug: absorption, distribution, processing and elimination. Distinct from what the drug does to the body.
Polycystic ovary syndrome (PCOS, PMOS)	A common hormonal condition combining irregular or absent ovulation, raised androgens and often insulin resistance. Recently renamed polyendocrine metabolic ovarian syndrome.
Proton pump inhibitor	A stomach-acid suppressing drug such as omeprazole, part of standard <i>Helicobacter pylori</i> treatment.
Red yeast rice	Rice fermented with a mould that produces monacolin K. Sold as a supplement, and the subject of Appendix 2.
Rhizome, <i>Coptis chinensis</i> (Huang Lian)	The underground stem of the plant that is berberine's richest natural source, used in Chinese medicine for centuries.
SANS scale	Scale for the Assessment of Negative Symptoms: a research measure of the withdrawn, flattened symptoms of schizophrenia.
SGLT2 inhibitor	A diabetes drug class that makes the kidneys excrete glucose, with proven heart and kidney benefits. Empagliflozin is an example.
Short-chain fatty acids	Compounds gut bacteria make from fibre. They feed the bowel lining and influence metabolism and inflammation.
Sirtuins (SIRT1, SIRT3) and NAD+	A repair and maintenance signalling system inside cells, dependent on the molecule NAD+, which is activated by energy stress.
Statin	The standard cholesterol-lowering drug class, working by blocking the body's own cholesterol production. Simvastatin, atorvastatin and rosuvastatin are the common ones.
Substrate	A drug that a particular enzyme processes. A CYP3A4 substrate is a drug whose breakdown depends on CYP3A4, so it accumulates if that enzyme is blocked.
Sulphonylurea	An older diabetes tablet class that pushes the pancreas to release insulin. Carries a real risk of hypoglycaemia. Gliclazide is the usual Dutch example.
Thiazolidinedione	A diabetes drug class improving insulin sensitivity. Pioglitazone is the surviving member.
Traditional Chinese Medicine (TCM), pattern differentiation	A system that classifies patients by a pattern of signs and symptoms rather than by disease alone, and matches the treatment to that pattern.
Transaminases	The liver enzymes ALT and AST, used to detect liver irritation.
Triple therapy	The standard <i>Helicobacter pylori</i> regimen: an acid-suppressing drug plus two antibiotics.
Ulcerative colitis	A chronic inflammatory disease of the large bowel causing bloody diarrhoea and flares.

A3.4 Abbreviations at a glance

Short form	Stands for	In plain words
ALT, AST	Alanine and aspartate aminotransferase	Liver enzymes measured in blood
AMPK	AMP-activated protein kinase	The cell's fuel gauge
ApoB	Apolipoprotein B	Counts harmful fat particles
ASCVD	Atherosclerotic cardiovascular disease	Disease caused by furred-up arteries
ATP, NAD+, NADH	Adenosine triphosphate; nicotinamide adenine dinucleotide, oxidised and reduced forms	The cell's energy currency and a key signalling molecule
BMI	Body mass index	Weight adjusted for height
CI	Confidence interval	The plausible range around an estimate
CKD	Chronic kidney disease	Long-term reduced kidney function
CRP, hs-CRP	C-reactive protein, high-sensitivity CRP	Blood marker of inflammation
CVD, CVRM	Cardiovascular disease; cardiovascular risk management	Heart and vessel disease, and the Dutch guideline for managing its risk
CYP3A4, CYP2C9, CYP2D6	Cytochrome P450 enzymes 3A4, 2C9, 2D6	The liver's main drug-processing enzymes
DPP-4	Dipeptidyl peptidase 4	Target of one class of diabetes tablet
eGFR	Estimated glomerular filtration rate	Kidney filtering capacity
EFSA	European Food Safety Authority	The EU's food and supplement safety body
FSH, LH	Follicle-stimulating and luteinising hormone	The two pituitary hormones driving the menstrual cycle
G6PD	Glucose-6-phosphate dehydrogenase	Enzyme whose deficiency makes red cells fragile
GLP-1	Glucagon-like peptide 1	Gut hormone controlling insulin and appetite
GRADE	Grading of Recommendations, Assessment, Development and Evaluation	The standard system for rating evidence certainty

Short form	Stands for	In plain words
HbA1c	Glycated haemoglobin	Average blood sugar over 8 to 12 weeks
HDL, LDL (HDL-C, LDL-C)	High- and low-density lipoprotein	Good and bad cholesterol carriers
hERG	human Ether-a-go-go Related Gene	A heart potassium channel; blocking it risks arrhythmia
HMG-CoA	3-hydroxy-3-methylglutaryl coenzyme A	The enzyme statins block
HOMA-IR	Homeostatic model assessment of insulin resistance	Calculated index of insulin resistance
IL-6, IL-1 β	Interleukin 6, interleukin 1 beta	Inflammatory messenger molecules
INR	International normalised ratio	Blood clotting measure used for warfarin
NAFLD	Non-alcoholic fatty liver disease	Fatty liver unrelated to alcohol
NF- κ B, NLRP3	Nuclear factor kappa B; NLR family pyrin domain containing 3	Master switches of chronic inflammation
NHG	Nederlands Huisartsen Genootschap	The Dutch College of General Practitioners
NIHSS	National Institutes of Health Stroke Scale	Score of stroke severity
PCOS, PMOS	Polycystic ovary syndrome; polyendocrine metabolic ovarian syndrome	The same condition, old and new names
PCSK9	Proprotein convertase subtilisin/kexin type 9	Liver protein that destroys LDL receptors
RCT, RCTs	Randomised controlled trial(s)	The standard fair-comparison study design
RR	Relative risk	How many times more or less likely an outcome is
SANS	Scale for the Assessment of Negative Symptoms	Research measure used in schizophrenia
SCORE2, SCORE2-OP	Systematic COronary Risk Evaluation 2, and the version for older persons	Ten-year cardiovascular risk calculators
SGLT2	Sodium-glucose cotransporter 2	Target of a modern diabetes drug class
SHBG	Sex hormone binding globulin	Carrier protein for sex hormones
SIRT1, SIRT3	Sirtuin 1 and sirtuin 3	Cell repair and maintenance signals
SMD	Standardised mean difference	Effect size on a common scale
T2DM	Type 2 diabetes mellitus	Adult-onset diabetes
TAS2R	Taste receptor type 2	Bitter-taste receptors, including those in the gut
TCM	Traditional Chinese Medicine	The classical Chinese medical system
TNF- α	Tumour necrosis factor alpha	Inflammatory messenger molecule
UKPDS	United Kingdom Prospective Diabetes Study	The long-term trial that established metformin's outcome benefit

A3.5 Notes for clinicians working outside these fields

Topic	What a clinician from another field may want to know
Reading GRADE in practice	GRADE rates how much the estimate is likely to change with more research, not how big or how useful the effect is. A LOW rating on a real effect and a LOW rating on a spurious one look the same. Read the GRADE level and the effect size together, and remember that most interventions across medicine sit at LOW or MODERATE.
What an umbrella review adds	An umbrella review pools systematic reviews rather than trials. It is the right tool for surveying a whole field and for grading evidence quality consistently, but it inherits every weakness of the reviews beneath it and cannot correct for trials that several reviews all included.
Overlap between meta-analyses	Three meta-analyses of 46, 50 and 44 trials do not represent 140 separate trials. They draw on a shared pool, so their participant counts cannot simply be added together. Allowing for this overlap, this article estimates the evidence base at roughly 100 trials and 20,000 participants.
Add-on versus monotherapy designs	An add-on trial asks whether berberine improves on existing treatment; a monotherapy trial asks whether it works alone. The two answer different clinical questions, and an add-on result says nothing about whether the agent could replace anything.
Per-cycle versus per-subject outcomes	In fertility research, an effect per cycle and an effect per woman can point in different directions, because women contribute different numbers of cycles. The per-subject figure is the one that matches what a patient experiences.
Chinese trial literature	Most berberine trials were conducted in China, in Chinese populations, often with treatment backbones that differ from Dutch practice. This affects generalisability rather than internal validity: the trials may be sound and still not transfer directly.
Why a biomarker change may not mean benefit	Lowering a marker is not the same as preventing an event. Several drug classes have improved biomarkers and failed on outcomes. This is the central limitation of the berberine evidence, and the reason the colorectal-adenoma trial carries disproportionate weight here.

Topic	What a clinician from another field may want to know
Relative versus absolute risk	A 39% relative reduction means very different things at 2% and at 40% baseline risk. Where this article gives relative figures, the underlying baseline risk should be considered before translating them to a patient.
HbA1c in both scales	Dutch laboratories report mmol/mol (IFCC); older literature and most international papers use percentages (DCCT). As a rough guide: 42 mmol/mol = 6.0%, 48 = 6.5%, 53 = 7.0%, 58 = 7.5%, 64 = 8.0%, 75 = 9.0%.
Lipids and glucose in both units	To convert mg/dL to mmol/L: divide by 38.7 for total, LDL and HDL cholesterol, by 88.6 for triglycerides, and by 18 for glucose. Much of the older berberine literature reports mg/dL.
Supplement regulation is not medicines regulation	A food supplement needs no proof of efficacy, no marketing authorisation and no pharmacovigilance system. Content and purity vary between products, and a dose shown to work in a trial is not necessarily the dose in the bottle. This is a different regulatory world from the one prescribing operates in.
TCM pattern differentiation, for Western-trained readers	Traditional Chinese Medicine matches treatment to a pattern of signs and symptoms as well as to the disease, so two patients with the same diagnosis may receive different herbs. The claim made in this article is narrow: that this multi-node way of describing a disturbance is a useful heuristic alongside the trial evidence, not a substitute for it.