CHOLESTEROL SUPPORT FORMULA

AURI 25

A scientific dossier on the multi-pathway formula by Zenius Labs™

COMPOSITION · PER DAILY INTAKE

Auricularia auricula-judae ≥30 % polysaccharides	wood ear · hot-water extract	**1200 mg**
Pleurotus ostreatus ≥30 % polysaccharides	oyster mushroom · hot-water extract	**660 mg**
Policosanol 9 mg octacosanol per dose	sugarcane wax · 60 % octacosanol	**15 mg**
Monacolin K HMG-CoA reductase modulation	red yeast rice · -from Monascus purpureus	**2.9 mg**

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§ ABSTRACT

A multi-pathway formula.

AURI 25 is a proprietary multi-pathway formula developed by Zenius Labs™ for adults seeking sustained lipid management and cardiovascular risk reduction across the spectrum of dyslipidaemia care. The formula is relevant from preventive use in those with familial, hereditary, or environmental cholesterol risk, through statin-intolerance and statin-associated muscle symptoms (SAMS) management, adjunctive use alongside ezetimibe or low-intensity statin regimens, post-cardiovascular-event lipid maintenance, post-menopausal LDL stewardship, metabolic-syndrome and diabetic dyslipidaemia management, to long-term vascular-resilience maintenance in healthy adults with sub-optimal lipid profiles. Each daily intake of three capsules delivers a hot-water extract of *Auricularia auricula-judae* (wood ear) at 1200 mg, standardised to ≥30 % polysaccharides; a hot-water extract of *Pleurotus ostreatus* (oyster mushroom) at 660 mg, standardised to ≥30 % polysaccharides; policosanol at 15 mg, derived from sugarcane wax and standardised to 60 % octacosanol; and monacolin K at 2.9 mg, derived from *Monascus purpureus* fermentation.

The formula combines fungal polysaccharide bioactives with direct HMG-CoA reductase inhibition, bile acid sequestration, and ancillary anti-platelet and antioxidant actions operating on independent biochemical pathways. Together the constituent extracts engage cholesterol biosynthesis through complementary inputs, intestinal cholesterol homeostasis through β-glucan bile acid binding, the oxidised-LDL paradigm through polysaccharide antioxidant activity, and vascular risk through thromboxane A_2-mediated antiplatelet action and antithrombin-mediated anticoagulant effects. The mechanistic premise is multi-pathway, not single-compound.

The constituent extracts have been investigated independently of one another in published mechanistic, *in vitro*, animal-model, and clinical studies indexed in the biomedical literature, including the IMPROVE-IT trial [21] demonstrating in 18,144 patients that engaging a second lipid-modulating pathway yields incremental cardiovascular benefit beyond optimised statin monotherapy. This monograph reviews that evidence at the doses delivered by AURI 25. AURI 25 as a finished composition has not been the subject of an independent clinical trial; the evidence presented concerns the constituent extracts in their own published studies.

§1 Composition and standardisation
§2 Clinical context and rationale — dyslipidaemia and the multi-target lipid paradigm
§3 Compound evidence profiles — the indexed literature, by active ingredient
§4 Multi-pathway synergy analysis
§5 Integrated safety profile
§6 Discussion
§7 Conclusions
§8 References

§ 1 COMPOSITION

Each daily intake of three capsules of AURI 25 delivers the active extracts shown in Table 1. The formulation premise is multi-mechanism: each constituent extract engages a complementary cholesterol- or vascular-risk pathway — HMG-CoA reductase inhibition by monacolin K from *Monascus purpureus* fermentation; whole-food natural lovastatin biosynthesis by *Pleurotus ostreatus*; β-glucan bile-acid sequestration by both fungal polysaccharide fractions; ABCA1/ABCG1 cholesterol efflux upregulation and SREBP-1c lipogenic suppression by *Auricularia auricula-judae* polysaccharides; and AMPK-mediated post-translational enzyme modulation alongside thromboxane A_2-mediated antiplatelet action by policosanol from sugarcane wax. The composition is fixed; AURI 25 is the formula, not any single extract.

TABLE 1 — ACTIVE INGREDIENTS PER DAILY INTAKE (3 CAPSULES)

BOTANICAL / COMMON	EXTRACT	PER DOSE	STANDARDISATION
Auricularia auricula-judae wood ear	Hot-water extract	1200 mg	≥30 % polysaccharides
Pleurotus ostreatus oyster mushroom	Hot-water extract	660 mg	≥30 % polysaccharides
Policosanol sugarcane wax bioactive	From sugarcane wax	15 mg	60 % octacosanol (9 mg per dose)
Monacolin K red yeast rice fermentation	From *M. purpureus* 99.9 mg	2.9 mg	HMG-CoA reductase modulation

Each constituent active ingredient serves a distinct mechanistic role within the formula:

- *Auricularia auricula-judae* (wood ear) hot-water extract supplies polysaccharides that upregulate **ABCA1/ABCG1** cholesterol efflux transporters, downregulate hepatic **SREBP-1c** lipogenic signalling, enhance lipoprotein lipase activity, and confer prebiotic short-chain fatty acid generation that activates hepatic **AMPK** to suppress de novo cholesterol biosynthesis.
- *Pleurotus ostreatus* (oyster mushroom) hot-water extract naturally biosynthesises **lovastatin** within the fruiting body — chemically identical to prescription HMG-CoA reductase inhibitors — providing direct cholesterol synthesis inhibition from a whole-food matrix, while its β-glucan fraction (**pleuran**) sequesters bile acids in the intestinal lumen, forcing hepatic diversion of cholesterol into bile acid synthesis.
- **Policosanol** from sugarcane wax, standardised to 60 % octacosanol, contributes proposed AMPK-mediated post-translational inactivation of HMG-CoA reductase alongside clinically documented thromboxane A_2-mediated antiplatelet activity.
- **Monacolin K**, derived from *Monascus purpureus* fermentation at 2.9 mg per daily intake, delivers competitive HMG-CoA reductase inhibition at the specific dose validated by two dedicated randomised controlled trials and positioned strategically below the 3 mg per daily portion ceiling established by Commission Regulation (EU) 2022/860.

The constituent extracts were selected to engage cholesterol biosynthesis, intestinal cholesterol homeostasis, oxidised-LDL handling, and platelet and antithrombin-mediated

vascular risk in parallel within a single daily intake. The published evidence reviewed in §3 is presented at the doses delivered by this formula.

PRODUCT SPECIFICATION

Capsule shell	Hydroxypropyl methylcellulose
Container	90 capsules · 30-day supply at recommended intake
Net weight	52.9 g
Allergens	Made without milk/casein, eggs, gluten, soybeans; non-GMO; may contain natural sulfites
Recommended intake	1 capsule with the morning meal + 2 capsules with the evening meal, with water
Contraindications	Concurrent use with pharmaceutical statins, ezetimibe plus a statin, or any product containing r
Manufacturing	Created in the USA · Manufactured in Austria for the EU market under EU Directive 2002/46/E

§ 2 CLINICAL CONTEXT AND RATIONALE

Cardiovascular disease (CVD) remains the single largest contributor to global mortality, accounting for approximately **18.6 million deaths in 2019** — a figure that has risen steadily from 12.1 million in 1990 [1]. The Global Burden of Disease (GBD) 2019 study estimated that the total number of prevalent CVD cases nearly doubled over three decades, reaching 523 million individuals worldwide, with ischaemic heart disease and stroke accounting for more than 85% of cardiovascular deaths [1]. Among modifiable risk factors, elevated low-density lipoprotein cholesterol (LDL-C) occupies a central position in atherogenesis, and non-optimal cholesterol levels are responsible for an estimated **3.9 million deaths annually** [2]. The global prevalence of dyslipidaemia is substantial: a recent meta-analysis of 206 studies reported that approximately 24.1% of adults exhibit hypercholesterolaemia, 28.8% have hypertriglyceridaemia, and 38.4% present with low high-density lipoprotein cholesterol (HDL-C) concentrations [3]. These figures are not static; epidemiological data reveal a progressive transition from classic hypercholesterolaemia toward a predominance of hypertriglyceridaemia and low HDL-C, with significant regional and sex-based variation [3]. Such epidemiological realities underscore the imperative for effective, accessible, and well-tolerated lipid management strategies.

The 2019 European Society of Cardiology/European Atherosclerosis Society (ESC/EAS) guidelines for the management of dyslipidaemias reaffirmed that LDL-C reduction constitutes the primary therapeutic target for cardiovascular risk reduction, with progressively lower targets recommended for patients at higher absolute risk [4]. This evidence-based framework rests upon three decades of landmark statin trial data.

Statins — 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors — represent the most thoroughly validated pharmacological class for LDL-C reduction and cardiovascular event prevention. The Scandinavian Simvastatin Survival Study (4S) established in 1994 that statin therapy significantly reduced all-cause mortality in patients with coronary heart disease, demonstrating a **30% relative risk reduction** over 5.4 years of follow-up with an accompanying 35% decrease in LDL-C [5]. The West of Scotland Coronary Prevention Study (WOSCOPS) subsequently extended these benefits to primary prevention, reporting a 31% relative reduction in the composite of nonfatal myocardial infarction and coronary death with pravastatin among men with hypercholesterolaemia [6]. The Heart Protection Study (HPS), enrolling 20,536 high-risk individuals, broadened the evidence further by demonstrating 24% reductions in major coronary events and 27% reductions in stroke across diverse subgroups, irrespective of baseline cholesterol concentration [7]. More recently, the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) demonstrated a 44% relative risk reduction in major cardiovascular events among individuals with elevated high-sensitivity C-reactive protein (hs-CRP) but low LDL-C, expanding the evidence for statin use into populations defined by inflammatory rather than purely lipid-based risk [8]. The Cholesterol Treatment Trialists' (CTT) Collaboration meta-analysis, encompassing individual participant data from approximately 170,000 participants across 26 randomised trials, consolidated these findings by establishing that each 1.0 mmol/L (approximately 39 mg/dL) reduction in LDL-C corresponds to a **22% proportional reduction in major vascular events** (relative risk 0.78; 95% CI 0.76–0.80), with no apparent threshold below which further LDL-C reduction ceases to be beneficial [9]. Taken together, statins reduce LDL-C by approximately 30–50% depending on agent and dose intensity, and

their efficacy in reducing cardiovascular morbidity and mortality is unequivocal.

Despite this strong efficacy profile, several clinically important limitations constrain the real-world impact of statin therapy. Statin-associated muscle symptoms (SAMS), the most frequently reported adverse effect, represent a major barrier to treatment persistence. The European Atherosclerosis Society (EAS) Consensus Panel characterised the spectrum of SAMS, noting that while statin-associated myopathy with significant creatine kinase elevation (exceeding ten times the upper limit of normal) remains rare at an incidence of approximately 1 per 1,000 to 1 per 10,000 patient-years on standard doses, the broader category of muscle symptoms — typically presenting with normal or minimally elevated creatine kinase — affects an estimated 7–29% of statin users in registries and observational studies [10]. A large meta-analysis of 176 studies encompassing more than 4 million patients estimated the worldwide prevalence of statin intolerance at **9.1%** (95% CI 8.0–10.0%), with notable variation between randomised controlled trials (4.9%) and observational cohorts (17.0%) [11]. Female sex, older age, obesity, diabetes mellitus, and hypothyroidism were identified as independent risk factors for statin intolerance [11]. Even where enzymatic abnormalities are absent, subjective muscle complaints frequently drive treatment modification or discontinuation, constituting what is now recognised as a distinct clinical entity.

The gap between statin efficacy in controlled trials and effectiveness in routine clinical practice is widened considerably by poor long-term adherence. Evidence indicates that between **40% and 75% of patients discontinue statin therapy** within one to two years of initiation [12]. Meta-analytic data from observational studies show that only 49.0% of patients remain adherent at one year (95% CI 48.9–49.2%), compared with approximately 90% in randomised controlled trials — a discrepancy that substantially attenuates expected cardiovascular benefit [13]. Among older adults, a population segment at elevated cardiovascular risk, adherence declines further over time: a systematic review of more than 3 million statin users aged 65 years and over found that only 59.7% were adherent at one year, dropping to **28.4% beyond ten years** of treatment [14]. Primary prevention patients demonstrated particularly poor adherence (47.9%) compared with those on secondary prevention (62.3%) [14]. The consequences of non-adherence are clinically meaningful: poor persistence with statin therapy has been independently associated with increased rates of cardiovascular events and mortality, creating a therapeutic gap that remains inadequately addressed [12].

Even among patients who maintain optimal statin adherence and achieve guideline-recommended LDL-C targets, residual cardiovascular risk persists. Despite aggressive LDL-C lowering, patients with established atherosclerotic disease continue to experience cardiovascular events at rates that underscore the multifactorial nature of atherogenesis [15]. Contributors to this residual risk include triglyceride-rich lipoproteins, elevated lipoprotein(a), chronic low-grade inflammation, and atherogenic dyslipidaemia — pathways that are not adequately addressed by HMG-CoA reductase inhibition alone [15,16]. The Residual Risk Reduction Initiative (R3i) identified atherogenic dyslipidaemia, characterised by elevated triglyceride-rich apolipoprotein B-containing lipoproteins and low HDL-C, as a key modifiable contributor to lipid-related residual cardiovascular risk, particularly in the context of insulin resistance [16]. This recognition that LDL-C lowering, though necessary, is often insufficient has catalysed interest in therapeutic strategies that address multiple pathophysiological pathways concurrently.

Against this backdrop, nutraceutical approaches to lipid management have attracted increasing attention from the clinical and regulatory communities. The International Lipid Expert Panel (ILEP) published a consensus position paper evaluating the evidence for lipid-lowering nutraceuticals, identifying several compounds with sufficient data to support their consideration in defined clinical scenarios: individuals not yet eligible for pharmacotherapy, patients intolerant to statins, and those on statin therapy who have not achieved target LDL-C levels [17]. An Italian intersociety position paper, endorsed by more than ten medical and scientific societies, similarly concluded that available nutraceuticals and functional foods can reduce LDL-C by approximately 5–25%, either alone or in combination, and represent a viable option for individuals at low-to-moderate cardiovascular risk [18]. The 2019 ESC/EAS guidelines acknowledged certain nutraceuticals — including red yeast rice, phytosterols, and dietary fibre — as potential pre-pharmacological interventions for individuals with mild dyslipidaemia who do not meet thresholds for drug therapy [4]. A 2021 review by Cicero and colleagues further delineated the specific clinical circumstances under which nutraceutical deployment may be appropriate, emphasising that their role is complementary to — rather than a replacement for — established pharmacotherapy in higher-risk patients [19].

However, the majority of commercially available nutraceutical products for lipid management rely on a single bioactive compound, an approach that may be inherently limited. Individual compounds typically engage only one primary mechanistic pathway — for instance, monacolin K from red yeast rice acts principally through HMG-CoA reductase inhibition, while beta-glucans operate through bile acid sequestration in the gastrointestinal tract. This "one compound, one target" paradigm constrains the maximal achievable effect and fails to address the multiple interacting mechanisms that contribute to dyslipidaemia and atherogenic risk [17]. Critically, although several individual nutraceuticals have demonstrated meaningful LDL-C reductions, the question of whether single-agent nutraceutical lipid lowering at dietary supplement doses translates into cardiovascular risk reduction remains unresolved [20].

The rationale for multi-pathway lipid management is well established in pharmaceutical practice. The Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) provided the first definitive evidence that targeting a second lipid-modulating mechanism yields incremental clinical benefit: the addition of ezetimibe, an intestinal cholesterol absorption inhibitor, to simvastatin in 18,144 post-acute coronary syndrome patients significantly reduced the primary composite cardiovascular endpoint (hazard ratio 0.936; 95% CI 0.89–0.99; P = 0.016) over a median follow-up of six years [21]. This trial demonstrated that the principle of combination therapy — engaging complementary mechanisms to achieve greater efficacy than maximising a single pathway — applies to lipid management as it does to other therapeutic domains. The 2019 ESC/EAS guidelines subsequently adopted a stepwise combination approach as standard of care, recommending sequential addition of ezetimibe and, if necessary, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors to statin therapy for patients not achieving targets [4]. This combinatorial principle has been proposed as equally applicable to nutraceutical formulation design, with multi-component strategies targeting HMG-CoA reductase inhibition, intestinal cholesterol absorption, bile acid binding, and anti-inflammatory pathways offering a theoretical framework for optimising lipid-lowering efficacy within a favourable safety profile [17,22].

AURI 25 (Zenius Labs™) represents one such multi-pathway formulation, combining the constituent compounds selected for their complementary mechanisms of action. The

formulation comprises: *Auricularia auricula-judae* hot water extract (1200 mg, standardised to ≥30% polysaccharides), which provides bioactive polysaccharides with demonstrated antioxidant, anti-inflammatory, and lipid-modulating properties in preclinical models [23,24]; *Pleurotus ostreatus* hot water extract (660 mg, standardised to ≥30% polysaccharides), which serves as a source of β-glucans capable of bile acid binding as well as naturally occurring lovastatin, a documented HMG-CoA reductase inhibitor [25–27]; red yeast rice (99.9 mg, standardised to 3% monacolin K, yielding 2.9 mg monacolin K per daily serving), providing a low-dose HMG-CoA reductase inhibitor that is chemically identical to lovastatin [28]; and policosanol (15 mg, standardised to 60% octacosanol, yielding 9 mg octacosanol per daily serving), a mixture of long-chain aliphatic primary alcohols derived from sugarcane wax that has been proposed to modulate hepatic cholesterol synthesis through a mechanism distinct from direct HMG-CoA reductase inhibition [29]. It should be noted that policosanol comprises long-chain fatty alcohols and is chemically and mechanistically unrelated to plant sterols (phytosterols), which are steroid compounds derived from plant cell membranes; the two compound classes are frequently conflated in the popular literature but operate through entirely different pathways. The AURI 25 formulation thus engages parallel distinct mechanistic pathways addressing cholesterol homeostasis from complementary angles: HMG-CoA reductase inhibition through three independent inputs (monacolin K via competitive binding, naturally occurring lovastatin from *P. ostreatus*, and policosanol via proposed AMPK-mediated phosphorylation); bile acid sequestration via β-glucans from *P. ostreatus*, forcing hepatic diversion of cholesterol into bile acid synthesis; direct lipid modulation by *A. auricula-judae* polysaccharides through ABCA1/ABCG1 cholesterol efflux promotion, SREBP-1c lipogenic suppression, enhanced lipoprotein lipase activity, and insulin-sensitising activity that attenuates hepatic VLDL overproduction; and prebiotic-driven gut–liver axis modulation, whereby colonic fermentation of fungal polysaccharides generates short-chain fatty acids that activate hepatic AMPK and suppress de novo cholesterol biosynthesis. Full product specifications, ingredient documentation, and EU regulatory compliance information for AURI 25 are available at https://biolabs.lt/auri-25/. This multi-target design is consistent with the combinatorial rationale endorsed by expert consensus panels for nutraceutical lipid management [17,22].

Table 1. AURI 25 Formula Composition

Component	Amount (per 3 capsules)	Standardisation	Primary Mechanism Class
Auricularia auricula-judae HWE	1200 mg	≥30% polysaccharides	Antioxidant / Anti-inflammatory
Pleurotus ostreatus HWE	660 mg	≥30% polysaccharides	Bile acid binding / HMG-CoA reductase (natural lovastatin)
Red yeast rice (*Monascus purpureus*)	99.9 mg	3% monacolin K = 2.9 mg	HMG-CoA reductase inhibition
Policosanol (sugarcane wax)	15 mg	60% octacosanol = 9 mg	Cholesterol synthesis modulation / Anti-platelet

This monograph \1 evaluate the available evidence supporting each of the the constituent compounds of AURI 25, assess the mechanistic plausibility of their combination, and identify knowledge gaps warranting future clinical investigation. The evidence base is examined across the full spectrum of study designs, from in vitro mechanistic studies and preclinical animal models through randomised controlled trials and meta-analyses. Limitations of the current evidence — including heterogeneity in study quality, the well-documented controversies surrounding policosanol efficacy, the predominantly preclinical nature of the

mushroom polysaccharide evidence, and the absence of clinical trials evaluating this specific multi-component combination — are addressed with full transparency. Extended Lithuanian-language evidence reviews covering cholesterol norms, reduction strategies, and dietary approaches are available at Medix.lt (https://medix.lt/cholesterolis/), Lithuania's evidence-based health information portal [30].

§ 3 COMPOUND EVIDENCE PROFILES

§3.1 Policosanol (15 mg, 60% octacosanol)

Chemical identity and natural sources

Policosanol is a generic designation for a defined mixture of very-long-chain aliphatic primary alcohols, predominantly comprising carbon chains of 24 to 34 atoms (C24–C34), isolated from the cuticular wax layer of sugarcane (*Saccharum officinarum* L.) [29]. The principal constituent is octacosanol (1-octacosanol, $C_{28}H_{58}O$; CAS 557-61-9; PubChem CID: 68406), a straight-chain 28-carbon primary fatty alcohol that typically constitutes 60–70% of the mixture by weight [29,37]. Subsidiary alcohols include triacontanol (C30, 10–15%), hexacosanol (C26, 4.5–10%), and smaller quantities of tetracosanol (C24), heptacosanol (C27), nonacosanol (C29), dotriacontanol (C32), and tetratriacontanol (C34) [37]. Although sugarcane wax remains the most widely studied and commercially important source, policosanol can also be derived from beeswax, rice bran wax, and wheat germ, with broadly similar but not identical compositional profiles [37]. The relative proportions of individual alcohols vary by botanical source and extraction method, a distinction that has assumed considerable importance in interpreting the clinical evidence.

A critical taxonomic distinction must be drawn between policosanol and plant sterols (phytosterols). Despite occasional conflation in the popular literature, these compound classes are **chemically and mechanistically unrelated**. Plant sterols such as β-sitosterol, campesterol, and stigmasterol are steroid derivatives possessing a tetracyclic ring nucleus that enables them to compete with cholesterol for micellar solubilisation in the intestinal lumen, thereby reducing cholesterol absorption [29]. Policosanol, by contrast, consists of simple aliphatic primary alcohols with no steroid nucleus, and its proposed mechanisms of action centre on hepatic cholesterol biosynthesis and enzyme phosphorylation rather than intestinal absorption [29,38]. This distinction is particularly relevant in the context of AURI 25, where policosanol represents one of several mechanistically distinct active constituents and must not be conceptually merged with phytosterol-based interventions.

Proposed mechanisms of action

The molecular pharmacology of policosanol remains incompletely elucidated, and this uncertainty itself warrants transparent acknowledgement. The most substantive body of mechanistic evidence points to modulation of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme of the mevalonate pathway and the pharmacological target of statins [29,38]. However, the mechanism by which policosanol affects this enzyme differs fundamentally from the competitive active-site inhibition characteristic of statins. Early in vitro work by Menéndez and colleagues at the Centro Nacional de Investigaciones Científicas (CNIC) in Havana demonstrated that policosanol reduced cholesterol biosynthesis from [^{14}C]-acetate in cultured fibroblasts in a dose-dependent fashion, yet cholesterol synthesis from [^{14}C]-mevalonate—the immediate product of HMG-CoA reductase—was unaffected, and no direct competitive or non-competitive enzyme inhibition was detected in cell-free assays [38]. This observation implied an indirect regulatory mechanism operating at the level of enzyme phosphorylation rather than catalytic site occupation.

The pivotal mechanistic advance came with the demonstration by Singh, Li, and Porter that policosanol and its constituent alcohol triacontanol (C30) activated **AMP-activated protein kinase (AMPK)** in rat hepatoma cells, producing a three-fold increase in AMPK phosphorylation and up to 55% reduction in HMG-CoA reductase activity [39]. Because phosphorylated AMPK in turn phosphorylates and inactivates HMG-CoA reductase at serine 872, this pathway provides a plausible explanation for cholesterol synthesis inhibition without direct enzyme binding—a mechanism fundamentally distinct from that of any statin. Subsequent investigation by the same group established that AMPK activation requires **peroxisomal β-oxidation** of the very-long-chain alcohols: siRNA knockdown of fatty aldehyde dehydrogenase (ALDH3A2), long-chain acyl-CoA synthetase 4 (ACSL4), or peroxisomal 3-ketoacyl-CoA thiolase (ACAA1) abolished the effect [40]. These findings indicate that chain-shortened metabolites generated during peroxisomal processing, rather than intact octacosanol itself, serve as the proximal AMPK activators. Oliaro-Bosso and colleagues subsequently confirmed AMPK-mediated HMG-CoA reductase phosphorylation in both human endothelial (HUVEC) and human hepatoma (HepG2) cell lines using policosanol and octacosadienol, a synthetic analogue [41].

Translation of these cell-culture findings to in vivo models has yielded supportive results. Nam and colleagues demonstrated that policosanol supplementation in hypercholesterolaemic rats activated hepatic AMPK, decreased apolipoprotein B expression, and **upregulated LDL receptor expression** on hepatocyte surfaces, while simultaneously reducing aortic wall thickness and lowering the vascular inflammation markers P-selectin and soluble vascular cell adhesion molecule 1 (sVCAM-1) [42]. This integrative study is notable because it links the AMPK pathway to enhanced LDL receptor-mediated clearance and anti-inflammatory activity within a single experimental system. Taken together, the preclinical evidence supports a multi-step model: policosanol alcohols undergo peroxisomal β-oxidation to shorter-chain metabolites, which activate AMPK via calcium/calmodulin-dependent protein kinase kinase (CaMKK), leading to phosphorylation-mediated inactivation of HMG-CoA reductase and compensatory upregulation of hepatic LDL receptors [39–42].

Beyond cholesterol biosynthesis, policosanol exhibits **anti-platelet activity** through a mechanism distinct from both aspirin and thienopyridines. In a randomised, double-blind, placebo-controlled trial in healthy volunteers, Carbajal and colleagues showed that policosanol at 10 mg daily significantly inhibited arachidonic acid– and collagen-induced platelet aggregation and reduced thromboxane B_2 generation, while prostacyclin (6-keto-$PGF_1\alpha$) levels remained unaffected [43]. This selective inhibition of the thromboxane A_2 synthetic pathway contrasts with the non-selective cyclooxygenase inhibition produced by aspirin. Earlier preclinical work by Arruzazabala and colleagues had established dose-dependent inhibition of collagen-induced malondialdehyde formation and thromboxane B_2 synthesis in rat models [44]. Preclinical data also suggest antioxidant properties, including reduction of copper-mediated LDL oxidation, and emerging evidence from cell culture and animal models points to suppression of pro-inflammatory cytokines including tumour necrosis factor alpha (TNF-α) and interleukin 6 (IL-6), with corresponding reductions in vascular adhesion molecules [42]. However, human data on these anti-inflammatory endpoints remain limited. It must be emphasised that the exact molecular mechanisms underlying policosanol's clinical effects **remain debated**, and the AMPK pathway—established primarily in cell and animal models—has not been unequivocally confirmed at standard therapeutic doses in human subjects.

The Cuban research programme: a substantial but contested evidence base

The clinical investigation of policosanol has been dominated by a single, highly productive research group at the CNIC and its affiliated Medical Surgical Research Centre in Havana, Cuba. Between 1992 and 2010, investigators including Más, Castaño, Illnait, and Fernández published more than 80 clinical papers reporting remarkably consistent lipid-modifying effects across diverse patient populations. This body of work, while methodologically questioned by some commentators, represents one of the most extensive clinical programmes ever conducted for a single nutraceutical compound and merits thorough evaluation.

The landmark trial by Más and colleagues enrolled **437 patients** with type II hypercholesterolaemia and additional coronary risk factors in a randomised, double-blind, placebo-controlled design [45]. After dose titration from 5 mg to 10 mg daily over 24 weeks, policosanol reduced LDL-C by 25.6%, total cholesterol (TC) by 17.4%, and the LDL-C/HDL-C ratio by 36.5%, while raising HDL-C by 28.2% (all $p < 0.001$ versus placebo). No serious adverse events were attributed to policosanol, in contrast to 11 serious adverse events (seven vascular) in the placebo group ($p < 0.01$) [45]. A subsequent trial in 179 elderly patients with high coronary risk demonstrated similar dose-dependent reductions: LDL-C decreased by 16.9% at 5 mg daily and by 24.4% at 10 mg daily, while HDL-C rose by 14.6% and 29.1% at the respective doses [46]. The largest Cuban trial enrolled **589 elderly hypertensive patients** with type II hypercholesterolaemia and followed them for 12 months, reporting LDL-C reductions of 20.5%, HDL-C increases of 12.7%, and significantly fewer vascular serious adverse events in the policosanol group (0.7% versus 2.0% for placebo, $p < 0.05$); three deaths occurred in the placebo group compared with none in the policosanol group [47]. Studies in postmenopausal women with hypercholesterolaemia reported consistent findings, with LDL-C reductions of 17–26% at doses of 5–10 mg daily [48].

The Cuban programme also produced a series of head-to-head comparisons with established statins. Crespo and colleagues compared policosanol 10 mg daily with lovastatin 20 mg daily in 53 patients with hypercholesterolaemia and type 2 diabetes, reporting that policosanol achieved a comparable LDL-C reduction (20.4% versus 16.8%) and a greater HDL-C increase (7.5% versus no significant change, $p < 0.01$), while lovastatin was associated with significant elevations in aspartate aminotransferase (AST), creatine kinase (CK), and alkaline phosphatase that were absent with policosanol [49]. Castaño and colleagues compared policosanol 10 mg with pravastatin 10 mg in older hypercholesterolaemic patients, finding comparable LDL-C reductions (19.3% versus 15.6%) but superior platelet aggregation inhibition and reduced endothelial activation with policosanol [50]. A comparison with atorvastatin 10 mg in 75 elderly patients showed that atorvastatin achieved modestly greater LDL-C reduction (29.8% versus 23.1%, $p < 0.05$), but policosanol produced greater HDL-C elevation and significantly fewer adverse events: **18.9% of atorvastatin patients reported adverse effects compared with 0% in the policosanol group** ($p < 0.01$) [51]. A subsequent comparison in 40 patients with dyslipidaemia and type 2 diabetes confirmed atorvastatin's superiority for LDL-C reduction (41.9% versus 25.7%) while policosanol demonstrated superior anti-platelet effects and provoked no CK or ALT elevations [52]. The longest controlled follow-up came from a two-year double-blind trial by Pons and colleagues, which demonstrated sustained LDL-C reductions of approximately 25% at 24 months without evidence of tolerance development or cumulative toxicity [53].

In aggregate, the Cuban studies reported **LDL-C reductions of 15–30%** at doses of 5–20 mg daily, with consistent HDL-C increases of 8–29% and adverse event rates consistently lower

than placebo arms. These are remarkable figures for a nutraceutical compound, approaching the efficacy of moderate-intensity statin therapy. However, it is precisely this remarkable consistency, combined with the concentration of all positive findings within a single institutional programme, that gave rise to what has become one of the most prominent replication controversies in nutraceutical science. Table 2 presents a comparative overview of key Cuban and independent trials, visually illustrating the stark divergence in reported outcomes.

Table 2. Summary of key policosanol clinical trials

Author, Year	Design	n	Population	Dose (mg/d)	Duration	LDL-C Δ (%)	HDL-C Δ (%)	p-value	Country
Más et al., 1999 [45]	RCT, DB, PC	437	HC + coronary risk	10	24 wk	−25.6	+28.2	<0.001	Cuba
Castaño et al., 2001 [46]	RCT, DB, PC	179	Elderly, high risk	10	24 wk	−24.4	+29.1	<0.001	Cuba
Castaño et al., 2002 [47]	RCT, DB, PC	589	Elderly, hypertensive	5–10	12 mo	−20.5	+12.7	<0.00001	Cuba
Crespo et al., 1999 [49]	RCT, DB	53	HC + T2DM	10	12 wk	−20.4	+7.5	<0.001	Cuba
Castaño et al., 2003 [51]	RCT, SB	75	Elderly HC	10	8 wk	−23.1	+5.3	<0.00001	Cuba
Pons et al., 1995 [53]	RCT, DB, PC	69	Type II HLP	10	2 yr	−25.0	+11.2	<0.05	Cuba
Lin et al., 2004 [54]	RCT, DB, PC	58	Normal–mild HC	20	4 wk	NS	NS	>0.05	Netherlands
Berthold et al., 2006 [55]	RCT, DB, PC	143	HC / combined HL	10–80	12 wk	NS	NS	>0.05	Germany
Kassis & Jones, 2006 [56]	RCT, DB, XO	21	HC	10	28 d	NS	NS	>0.05	Canada
Cubeddu et al., 2006 [57]	RCT, DB, PC	99	HC	20	12 wk	NS	NS	>0.05	USA
Dulin et al., 2006 [58]	RCT, DB	40	Mild HC	20	8 wk	NS	NS	>0.05	USA
Francini-Pesenti et al., 2008 [59]	RCT, DB, PC	63	Primary HC	20	8 wk	NS	NS	>0.05	Italy

DB = double-blind; HC = hypercholesterolaemia; HL = hyperlipidaemia; HLP = hyperlipoproteinaemia; NS = not statistically significant versus placebo; PC = placebo-controlled; RCT = randomised controlled trial; SB = single-blind; T2DM = type 2 diabetes mellitus; XO = crossover. Cuban studies employed original policosanol from the CNIC/Dalmer Laboratories, Havana. Among independent trials, Berthold et al. [55] and Kassis & Jones [56] also used authentic Dalmer-supplied Cuban policosanol; Francini-Pesenti et al. [59] verified sugar cane policosanol composition by gas chromatography; Lin et al. [54] used wheat germ–derived policosanol.

The replication controversy: a field divided

The discordance between Cuban and non-Cuban policosanol studies represents one of the starkest replication failures in the supplement literature, and intellectual honesty demands that it be confronted directly. Beginning in 2004 and intensifying through 2008, a succession of well-designed independent trials conducted across four continents uniformly failed to replicate the lipid-lowering effects reported by the Cuban programme (Table 2).

The first signal emerged from the Netherlands, where Lin and colleagues administered wheat germ–derived policosanol (20 mg daily, 67% octacosanol) to 58 adults for four weeks and observed no significant change in TC, LDL-C, HDL-C, or triglycerides [54]. Although the Cuban group could plausibly attribute this result to the use of a non-sugarcane source and a relatively short treatment period, the subsequent wave of negative findings proved far more difficult to dismiss. The most influential study was published in *JAMA* in 2006 by Berthold and colleagues, who conducted a multicentre, randomised, double-blind, placebo-controlled trial in **143 patients** randomised to policosanol at 10, 20, 40, or 80 mg daily or placebo for 12 weeks [55]. Crucially, the policosanol used was **Cuban sugarcane-derived product supplied by Dalmer Laboratories** in Havana—the same source employed in the Cuban trials. At none of the four doses did LDL-C decrease by more than 10% from baseline, and no statistically significant differences emerged between any policosanol dose and placebo for LDL-C, TC, HDL-C, VLDL-C, triglycerides, or lipoprotein(a) [55]. The non-parametric test for dose dependency was likewise non-significant.

In the same period, Kassis and Jones at McGill University administered **authentic Cuban policosanol** (Lipex, Dalmer Laboratories, 65.6% octacosanol) at 10 mg daily to 21 hypercholesterolaemic volunteers in a randomised, double-blind crossover design and found no significant effect on any plasma lipid parameter [56]. Cubeddu and colleagues in Miami randomised 99 patients to policosanol 20 mg, atorvastatin 10 mg, the combination, or placebo in a double-blind, double-dummy design: while atorvastatin produced expected LDL-C reductions, policosanol showed no effect alone or in combination [57]. Dulin and colleagues in North Carolina tested sugarcane-derived policosanol at 20 mg daily in 40 adults with mild hypercholesterolaemia and found no significant change in LDL-C, TC, HDL-C, triglycerides, or C-reactive protein, with NMR lipoprotein profiling confirming the absence of sub-fraction changes [58]. Greyling and colleagues in South Africa tested 20 mg daily of a commercial policosanol preparation in a crossover design and found no significant lipid-lowering effect in either hypercholesterolaemic or familial hypercholesterolaemic subjects [60]. In Italy, Francini-Pesenti and colleagues conducted two separate randomised, placebo-controlled trials—one using 20 mg daily of sugar cane policosanol with gas chromatography–verified composition [59] and one using 10 mg daily [61]—and neither detected any significant lipid changes. The same Canadian group subsequently demonstrated that Cuban policosanol failed to alter cholesterol fractional synthesis rate or cholesterol absorption [62], directly contradicting the proposed HMG-CoA reductase modulation mechanism at therapeutic human doses.

Multiple hypotheses have been advanced to explain the Cuban–non-Cuban discordance, and each deserves fair evaluation. **First**, the Cuban group has argued that differences in sugarcane cultivar, extraction methodology, and the precise ratios of constituent alcohols account for the discrepancy. Castaño and colleagues demonstrated in a direct comparison that their original preparation produced substantially greater LDL-C reductions than a commercially available alternative (Octa-60), with 88.7% of original policosanol recipients

achieving ≥15% LDL-C reduction versus only 9.1% of Octa-60 recipients [63]. This compositional argument, while logical, is substantially weakened by the fact that both Berthold et al. [55] and Kassis and Jones [56] used **authentic Dalmer-supplied Cuban policosanol** and still found no effect. Furthermore, detailed chromatographic analysis by Marinangeli and colleagues found that alternative preparations had a composition highly similar to the original Cuban product [37].

Second, genetic and dietary differences between Cuban populations and those in Europe, North America, and South Africa have been proposed. However, this explanation lacks biological plausibility for the magnitude of discrepancy observed—a shift from approximately 25% to 0% LDL-C reduction cannot readily be attributed to dietary context or pharmacogenomic variation [55,64]. **Third**, methodological concerns have been raised regarding the Cuban studies, including their reliance on single-centre designs without independent statistical monitoring, and the remarkably low variance in effect sizes across trials—a pattern that is statistically unusual for cholesterol-lowering interventions [64]. Many Cuban studies were published in the *International Journal of Clinical Pharmacology Research*, a journal of limited impact factor that is no longer indexed, raising additional questions about peer review rigour [64]. **Fourth**, publication bias in the Cuban literature has been suggested as a contributing factor, as no negative findings from the CNIC group have appeared in the published record [64]. A comprehensive critical review by Marinangeli and colleagues concluded that research groups outside Cuba had been "unable to validate the cholesterol-lowering and antioxidant efficacy" of policosanol, and that the claims of robust lipid-lowering activity remained unsubstantiated by independent evidence [64].

At the same time, it would be epistemologically imprudent to dismiss the Cuban data entirely. The programme encompassed thousands of patients across dozens of trials, employed double-blind placebo-controlled designs, and reported internally consistent results over more than a decade. The possibility that a specific combination of product characteristics, population factors, and methodological conditions contributed to genuine effects under those particular circumstances cannot be categorically excluded, even if these effects have not proven generalisable.

Meta-analytic evidence crystallises the divide

The meta-analytic literature on policosanol mirrors the underlying primary study heterogeneity and offers no simple resolution. The earliest meta-analysis, published by Chen and colleagues in 2005, pooled 29 policosanol studies (total n = 2,434) and reported a weighted mean LDL-C reduction of **23.7%** versus placebo ($p < 0.00001$) [65]. However, this analysis was published before the wave of negative independent trials and drew almost exclusively on Cuban data; it is now considered historically informative but superseded by more comprehensive analyses.

The most methodologically important meta-analysis was published by Gong and colleagues in 2018, incorporating 22 randomised controlled trials with 1,886 subjects identified across 11 databases [66]. The overall pooled analysis reported significant reductions in TC (weighted mean difference [WMD]: −0.58 mmol/L; 95% CI: −0.87 to −0.30), LDL-C (WMD: −0.71 mmol/L; 95% CI: −1.02 to −0.40), and increases in HDL-C (WMD: +0.13 mmol/L; 95% CI: 0.09 to 0.16) [66]. The critical contribution of this meta-analysis, however, lay in its **pre-specified subgroup analysis by study origin**. When restricted to the seven non-Cuban studies (n = 360), no parameter achieved statistical significance: TC WMD was +0.10 mmol/L (95% CI:

−0.20 to 0.41), LDL-C WMD was −0.00 mmol/L (95% CI: −0.36 to 0.36), and HDL-C WMD was +0.03 mmol/L (95% CI: −0.18 to 0.23) [66]. This finding quantitatively demonstrates that the positive pooled result is driven entirely by Cuban-origin data, and that the non-Cuban evidence, viewed in isolation, is null. Substantial statistical heterogeneity (I^2 values exceeding 80% for most outcomes) further complicates interpretation and suggests that the studies cannot reasonably be treated as estimating a single common effect.

A separate meta-analysis by Askarpour and colleagues pooled 19 randomised controlled trials and reported modest but statistically significant reductions in systolic blood pressure (WMD: −3.42 mmHg; 95% CI: −5.32 to −1.53; $p < 0.001$) and diastolic blood pressure (WMD: −1.47 mmHg; 95% CI: −2.63 to −0.30; $p = 0.01$) [67], although similar concerns about the predominance of Cuban data in the pooled estimate apply.

Cardiovascular effects beyond lipid modification

Regardless of the contested lipid-lowering evidence, policosanol's anti-platelet properties represent a more consistently supported therapeutic dimension. inhibition of thromboxane A_2 synthesis and collagen-induced platelet aggregation has been demonstrated in both Cuban and non-Cuban experimental settings [43,44], and the clinical relevance of this activity extends beyond the lipid controversy. Dose-dependent inhibition of platelet aggregation was confirmed in a dose-escalation study in healthy volunteers, with significant effects emerging at 20 mg daily and full inhibition across all agonists at 40 mg daily [68]. However, independent verification of the Cuban group's claimed antioxidant effects has been less encouraging: Kassis and colleagues at McGill University found that authentic Cuban policosanol failed to reduce LDL oxidation in hypercholesterolaemic individuals [69], casting doubt on at least one proposed pleiotropic benefit. The in vivo findings of reduced vascular inflammation markers (P-selectin, sVCAM-1) in hypercholesterolaemic rats [42] are promising but await clinical confirmation. The blood pressure meta-analysis by Askarpour and colleagues [67], reporting modest systolic and diastolic reductions, suggests an additional cardiovascular dimension, although as noted the evidence base is similarly dominated by Cuban-origin data.

Dose-response relationship and positioning within AURI 25

The Cuban dose-response data suggest a sigmoidal relationship with a plateau between 10 and 20 mg daily. Pons and colleagues demonstrated progressive LDL-C/HDL-C ratio reductions of 15.3%, 25.6%, and 34.6% upon successive escalation from 5 to 10 to 20 mg daily [70]. However, a direct comparison of 20 mg versus 40 mg daily by Castaño and colleagues found essentially identical LDL-C reductions (**27.4% versus 28.1%**), confirming a dose ceiling at approximately 20 mg for lipid effects [71]. Anti-platelet activity, by contrast, appears to show continued dose-dependent enhancement up to 40 mg daily [68].

AURI 25 provides 15 mg of policosanol standardised to 60% octacosanol, yielding approximately 9 mg of octacosanol as the principal active alcohol. Within the dose-response framework of the Cuban data, this positions the formulation between the 10 mg and 20 mg efficacy tiers—nominally in a range where near-maximal lipid-lowering effects would be expected according to the Cuban programme. Given the replication controversy, however, it is more appropriate to characterise 15 mg as a dose that, if policosanol possesses clinically meaningful lipid-lowering activity, should be sufficient to elicit it. The dose is also comfortably within the range at which anti-platelet effects have been consistently reported.

Safety and tolerability: the clearest consensus

If the lipid-lowering evidence is contested, the safety profile of policosanol represents the nearest point of consensus across the divided literature. Both Cuban and independent investigators have consistently reported an **adverse event profile indistinguishable from or superior to placebo**. The largest pharmacovigilance study, by Fernández and colleagues, followed 2,252 elderly patients at seven Cuban medical centres for up to 36 months and found that serious adverse events occurred in only 1.4% of patients, with none attributed to policosanol [72]. The two-year randomised controlled trial by Pons and colleagues recorded no drug-related adverse events and no treatment withdrawals over the entire study period [53]. In the 589-patient trial, adverse event rates were significantly lower in the policosanol group than in the placebo group (9.8% versus 17.7%, $p < 0.01$) [47].

Critically, policosanol has shown **no hepatotoxicity**. A 2024 dose-response meta-analysis encompassing 23 randomised controlled trials and 2,535 participants found that policosanol supplementation actually *reduced* alanine aminotransferase (ALT) levels (WMD: −1.48 U/L; 95% CI: −2.33 to −0.64; $p = 0.001$) and aspartate aminotransferase (AST) levels (WMD: −1.10 U/L; 95% CI: −1.70 to −0.51; $p < 0.001$), suggesting a mildly hepatoprotective rather than hepatotoxic profile [73]. **No myopathy or creatine kinase elevation** has been observed in any policosanol trial at any dose tested, including doses up to 80 mg daily [55]. In the head-to-head comparison with lovastatin, policosanol provoked no elevation of CK or transaminases, whereas lovastatin significantly increased both ($p < 0.05$) [49]. Even the independent trials that found no lipid-lowering efficacy uniformly confirmed excellent tolerability [55,56,58,59]. This safety profile represents a meaningful clinical advantage, particularly for patients who are statin-intolerant or at elevated risk of statin-associated muscle symptoms, and it holds regardless of whether the lipid-lowering benefits prove more modest than the Cuban data suggest.

Pharmacokinetics and bioavailability

Pharmacokinetic data for policosanol in humans remain limited, as no validated assay for measuring plasma very-long-chain alcohol concentrations at therapeutic doses had been established prior to recent analytical developments [29]. The available data derive primarily from animal models. Menéndez and colleagues demonstrated that orally administered octacosanol is rapidly oxidised to octacosanoic acid in both human fibroblasts and in vivo, with chain-shortened fatty acids (palmitic, oleic, myristic) detected as downstream metabolites consistent with peroxisomal β-oxidation [74]. In rats given 60 mg/kg orally, hepatic octacosanol reached a peak concentration of 68.4 ng/g at approximately 30 minutes, with octacosanoic acid reaching 331.6 ng/g at the same timepoint, indicating rapid first-pass hepatic metabolism [74]. Plasma peak concentration in rats was approximately 30 ng/mL at 30 minutes with rapid decline thereafter. Tissue distribution studies indicate preferential accumulation in liver and adipose tissue, with lesser distribution to spleen, kidney, heart, and brain [29]. Oral bioavailability in rats is estimated at **5–12%**, and the plasma half-life is approximately 1–2 hours [29]. The rapid metabolism to fatty acid intermediates is consistent with the AMPK activation model, wherein chain-shortened peroxisomal metabolites rather than intact octacosanol represent the pharmacologically active species [40]. No systematic food interaction studies have been published, although one independent study delivered policosanol incorporated into margarine without apparent enhancement of bioavailability or efficacy [56].

Drug interactions

The interaction profile of policosanol is characterised by surprisingly limited data given the compound's widespread commercial availability. The most clinically relevant study was

conducted by Abdul and colleagues, who examined the pharmacokinetic and pharmacodynamic interaction of policosanol with warfarin in 12 healthy male volunteers of known CYP2C9 and VKORC1 genotype in an open-label crossover design [75]. Policosanol 10 mg twice daily for 14 days did not significantly affect the pharmacokinetics of either (S)- or (R)-warfarin, nor did it alter the international normalised ratio (INR) or platelet activity [75]. This finding provides reassurance against clinically significant CYP2C9-mediated interactions, though the study was small and of short duration.

The interaction between policosanol and antiplatelet agents deserves particular attention. Arruzazabala and colleagues compared policosanol 20 mg daily, aspirin 100 mg daily, and their combination in 43 healthy volunteers, finding that the combination produced greater platelet aggregation inhibition than either agent alone through complementary mechanisms: policosanol preferentially inhibited ADP-mediated aggregation while aspirin primarily affected the collagen pathway [76]. In a clinically consequential study, Xu and colleagues administered policosanol 40 mg daily alongside aspirin and clopidogrel in 350 patients with high on-treatment platelet reactivity following drug-eluting stent implantation and found that policosanol reduced platelet reactivity comparably to doubled clopidogrel dosing **without increasing bleeding rates** over two years of follow-up [77]. This finding suggests that the anti-platelet synergy does not translate to excess haemorrhagic risk, although independent confirmation in larger cohorts is warranted. Regarding the combination with statins—directly relevant since AURI 25 also contains monacolin K (chemically identical to lovastatin)—the Cubeddu trial found no adverse interaction between policosanol 20 mg and atorvastatin 10 mg [57], and no CYP450-mediated interactions have been identified [75]. No adverse interactions with antihypertensive agents have been reported; concomitant administration with beta-blockers in older patients was well tolerated and may have produced additive blood pressure reduction [29].

Evidence quality assessment

Applying the quality framework established in The evidence framework used in the source publication, the overall evidence for policosanol's lipid-lowering effects must be rated as **moderate with significant caveats arising from the replication controversy**. The Cuban programme constitutes Level 1b evidence (individual RCTs) of substantial volume, but the comprehensive failure of independent replication across multiple countries, populations, and even using authentic Cuban product reduces confidence that these findings are generalisable. The Gong et al. meta-analysis [66] demonstrating null effects in the non-Cuban subgroup is particularly consequential. On the current evidence, the most intellectually honest assessment is that **policosanol's clinically meaningful LDL-C lowering has not been independently confirmed** and should not be assumed at the effect sizes reported by Cuban investigators.

Three aspects of the evidence, however, rest on firmer ground. The **safety profile** is well established across both Cuban and independent investigations, with consistent evidence of tolerability superior to statins and no signals for hepatotoxicity, myopathy, or creatine kinase elevation—a finding reinforced by the recent meta-analysis demonstrating hepatoprotective trends [73]. The **anti-platelet activity** is supported by both mechanistic studies and clinical data from Cuban and at least one non-Cuban setting [77], constituting a plausible independent contributor to cardiovascular risk reduction. The **AMPK-mediated mechanism** is well characterised in preclinical models and biologically coherent, even if its clinical translation at therapeutic human doses remains unproven.

Within the multi-pathway architecture of AURI 25, these observations carry practical implications. Even if policosanol's lipid-lowering contribution proves more modest than the Cuban data suggest—or even clinically negligible—its anti-platelet and potential anti-inflammatory properties provide mechanistically independent benefits that complement the cholesterol-lowering activity of monacolin K and the immunomodulatory properties of the fungal components. The formulation does not depend on policosanol achieving statin-like efficacy to justify its inclusion; rather, the compound's safety-assured contribution to vascular protection through platelet modulation represents a defensible element of a multi-target strategy. This honest contextualisation, acknowledging both the compound's genuine strengths and its contested claims, provides a more scientifically rigorous foundation than either uncritical endorsement or wholesale dismissal.

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§3.2 Monacolin K from red yeast rice (99.9 mg *Monascus purpureus*, 3% monacolin K = 2.9 mg)

Chemical identity and the red yeast rice matrix

Red yeast rice (RYR), known in Chinese pharmacopoeia as *hongqu* (□□), is the fermentation product of polished rice inoculated with the filamentous fungus *Monascus purpureus* Went. Its use in China as both a culinary colourant and medicinal agent extends back more than one thousand years; the Ming Dynasty compendium *Bencao Gangmu* (□□□□, 1596) documented its applications for invigorating the body, aiding digestion, and revitalising blood circulation [78]. Modern phytochemical investigation has since identified more than one hundred discrete secondary metabolites in commercial RYR preparations, including polyketide-derived monacolins, azaphilone pigments, dimerumic acid, γ-aminobutyric acid, phytosterols (β-sitosterol, campesterol, stigmasterol), unsaturated fatty acids, and isoflavonoid glycosides [78,79].

The principal cholesterol-lowering constituent of RYR is **monacolin K** (PubChem CID: 53232), a compound that is chemically identical to lovastatin (mevinolin), the first HMG-CoA reductase inhibitor approved for clinical use. Monacolin K was first isolated from *Monascus* cultures by Endo in 1979, contemporaneously with — but independently of — Merck's isolation of the same molecule from *Aspergillus terreus* fermentation broths [79]. Like pharmaceutical lovastatin, monacolin K exists as a **δ-lactone prodrug** that undergoes hydrolysis *in vivo*, primarily by hepatic carboxylesterases and to some extent by non-enzymatic hydrolysis at gastric pH, to yield the pharmacologically active β-hydroxy acid form [79,81]. The proportion of the acid form in commercial RYR supplements varies widely — from **5% to nearly 100%** of total monacolin K — a factor that substantially influences bioavailability and may partially account for inter-product variability in clinical efficacy [79].

Critically, RYR is not a single-compound ingredient. Beyond monacolin K, the fermentation matrix contains additional monacolins — including monacolins J, L, M, and X, compactin, dihydromonacolin K, and dehydromonacolin K — each possessing independent HMG-CoA reductase inhibitory activity, albeit of varying potency [78,81]. Phytosterols present in RYR compete with cholesterol for intestinal absorption via displacement from mixed micelles, while isoflavonoid constituents demonstrate anti-inflammatory and antioxidant properties in preclinical models [78]. This compositional complexity raises the question of whether whole RYR extract exerts lipid-lowering effects exceeding those predicted by its monacolin K content

alone. Recent *in vitro* work comparing the cytotoxicity and bioaccessibility of RYR extracts with equimolar pure lovastatin found that RYR consistently exhibited **lower toxicity in intestinal, hepatic, renal, and skeletal muscle cell models**, an observation attributed to co-occurring polyphenols and triterpenes that may modulate lovastatin metabolism and cellular uptake [81]. Such findings provide a mechanistic rationale for the clinically observed tolerability advantage of RYR over pharmaceutical statins.

Mechanism of action: direct competitive inhibition of HMG-CoA reductase

The lipid-lowering activity of monacolin K proceeds through a mechanism pharmacologically indistinguishable from that of pharmaceutical lovastatin. Following oral absorption and hepatic first-pass activation to the β-hydroxy acid open form, monacolin K binds with high affinity to the active site of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme catalysing the conversion of HMG-CoA to mevalonate within the cholesterol biosynthetic pathway [80]. The mevalonate pathway constitutes the sole endogenous route to cholesterol: acetyl-CoA is first condensed to HMG-CoA, which is then reduced by HMG-CoA reductase to mevalonate; subsequent phosphorylation and decarboxylation steps yield isopentenyl pyrophosphate and, ultimately, farnesyl pyrophosphate, squalene, and cholesterol. By inhibiting the committed step at the apex of this cascade, monacolin K suppresses the entire downstream flux toward sterol synthesis.

X-ray crystallographic analysis of the human HMG-CoA reductase catalytic domain complexed with six statin molecules, published by Istvan and Deisenhofer in 2001, demonstrated that statins occupy a portion of the HMG-CoA binding pocket, sterically occluding substrate access while exploiting extensive van der Waals contacts and hydrogen bonds with active-site residues [80]. The resulting inhibition constant (*K*i) for lovastatin lies in the **low nanomolar range**, representing an affinity for the enzyme several thousand-fold greater than that of the natural substrate HMG-CoA [80]. The downstream consequence of mevalonate pathway inhibition is a reduction in intracellular cholesterol synthesis within hepatocytes. The resultant decline in the intracellular sterol pool triggers activation of the sterol regulatory element-binding protein (SREBP) cascade, leading to transcriptional upregulation of the low-density lipoprotein (LDL) receptor gene on the hepatocyte surface [28]. Enhanced hepatic LDL receptor density accelerates receptor-mediated endocytosis of circulating LDL particles, producing a dose-dependent fall in plasma LDL-cholesterol (LDL-C) concentration [28]. Concurrent, though proportionally smaller, reductions in total cholesterol (TC), non-HDL-cholesterol, apolipoprotein B, very-low-density lipoprotein remnants, and triglycerides (TG) are observed, together with modest increases in HDL-cholesterol (HDL-C) [28].

It is instructive to contrast this mechanism with the action of policosanol described in The policosanol profile. Whereas monacolin K achieves HMG-CoA reductase inhibition through **direct, competitive binding** at the enzyme's catalytic site, the proposed mechanism for policosanol involves an indirect, AMP-activated protein kinase (AMPK)–mediated phosphorylation that downregulates enzyme activity at the post-translational level. These represent fundamentally different pharmacological strategies for modulating the same enzymatic target, and their co-inclusion in a multi-component formulation is predicated on the hypothesis that simultaneous inhibition via complementary mechanisms may produce additive or synergistic LDL-C lowering while permitting lower individual doses — a principle well established in pharmaceutical combination therapy [28].

The additional bioactive constituents of whole RYR provide further mechanistic layers. Minor monacolins contribute incremental HMG-CoA reductase inhibition; phytosterols impair intestinal cholesterol absorption through competition for Niemann–Pick C1-like 1 (NPC1L1) protein–mediated uptake; and anti-inflammatory polyphenols and pigments may attenuate atherogenic processes independently of lipid lowering [78,81]. These pleiotropic contributions help explain why meta-analytic comparisons consistently find RYR extract to be at least as effective as — and in some lipid sub-fractions more effective than — equivalent milligram doses of pure lovastatin or low-intensity statins [84,85].

Pooled evidence from systematic reviews and meta-analyses

The clinical evidence base for RYR is among the most extensive of any nutraceutical ingredient and has been the subject of multiple systematic reviews and meta-analyses spanning nearly two decades. The earliest comprehensive meta-analysis, published by Liu and colleagues in 2006, pooled data from **93 randomised controlled trials (RCTs) comprising 9,625 participants** and reported weighted mean differences versus placebo of −0.91 mmol/L for TC, −0.73 mmol/L for LDL-C, −0.41 mmol/L for TG, and +0.15 mmol/L for HDL-C [82]. The lipid-lowering effects were comparable to those observed with simvastatin, pravastatin, atorvastatin, and fluvastatin at standard clinical doses, although methodological quality across the predominantly Chinese-language trial literature was generally low [82].

Subsequent meta-analyses sought to address these quality limitations through stricter inclusion criteria. Li and colleagues (2014) restricted their analysis to **13 placebo-controlled RCTs** (excluding xuezhikang and zhibituo preparations) and confirmed significant reductions in TC, LDL-C, and TG, with no significant differences in hepatic transaminases, creatine kinase (CK), or creatinine between groups [83]. Gerards and colleagues (2015) analysed **20 RCTs** with monacolin K doses ranging from 4.8 to 24 mg daily and reported a pooled LDL-C reduction of **−1.02 mmol/L (39.4 mg/dL)** versus placebo — an effect that was not statistically different from moderate-intensity statin therapy (mean difference 0.03 mmol/L, 95% CI: −0.36 to 0.41) [84]. Li P and colleagues (2022) applied a Jadad quality threshold of ≥4, identifying **15 high-quality RCTs** that demonstrated LDL-C reductions of −35.82 mg/dL versus placebo ($p < 0.00001$), again with no significant difference compared with statin comparators for LDL-C ($p = 0.71$) [85]. A dose-response meta-analysis by Rahmani and colleagues (2023), pooling **24 treatment arms**, reported concordant figures: LDL-C −28.94 mg/dL, TC −33.16 mg/dL, TG −23.36 mg/dL, and HDL-C +2.49 mg/dL (all $p < 0.001$) [86]. The most recent double-blind-only meta-analysis by Trogkanis and colleagues (2024), encompassing **14 trials**, confirmed LDL-C reductions of −35.82 mg/dL and concluded that these effects were comparable to those achieved with low-dose statins such as pravastatin 10 mg or simvastatin 10 mg [87].

Head-to-head comparisons further reinforce this equivalence. Ong and Aziz (2016) systematically compared RYR with simvastatin across 10 RCTs in 905 subjects with dyslipidaemia and found **no statistically significant differences in any lipid outcome** [88]. A large network meta-analysis by Osadnik and colleagues (2022), covering **131 trials and 13,062 participants**, ranked RYR among the two most effective nutraceuticals for LDL-C reduction (−0.94 mmol/L, i.e. −36.4 mg/dL), alongside bergamot extract; notably, policosanol showed no significant effect in this analysis [89].

Taken together, these convergent meta-analytic findings establish that RYR supplementation at doses providing ≥5 mg monacolin K per day reduces LDL-C by approximately **15–25%** (absolute reduction 28–39 mg/dL), with proportional decreases in TC, non-HDL-C, and

apolipoprotein B [28]. The JACC Focus Seminar review by Cicero, Fogacci, and Zambon (2021) synthesised this literature for a cardiology audience, noting that the magnitude of LDL-C lowering achievable with standard-dose RYR overlaps substantially with low- to moderate-intensity pharmaceutical statin regimens and is accompanied by improvements in high-sensitivity C-reactive protein, pulse wave velocity, and flow-mediated vasodilatation [28].

Safety was formally addressed in the largest dedicated meta-analysis by Fogacci and colleagues (2019), encompassing **53 RCTs with 8,535 subjects**. Monacolin K administration was not associated with increased risk of musculoskeletal disorders (OR 0.94, 95% CI: 0.53–1.65), and both non-musculoskeletal adverse events (OR 0.59, 95% CI: 0.50–0.69) and serious adverse events (OR 0.54, 95% CI: 0.46–0.64) were significantly *lower* in the RYR arms than in controls [90]. Subgroup analyses by daily monacolin K dose (≤3, 3.1–5, and >5 mg) showed safety across all dose strata [90].

Pivotal randomised controlled trials

The single most important study in the RYR evidence base is the **China Coronary Secondary Prevention Study (CCSPS)**, the only randomised trial of any RYR preparation powered for hard cardiovascular outcomes. Lu and colleagues enrolled **4,870 Chinese patients with previous myocardial infarction** and average LDL-C levels at baseline, randomising them in a double-blind fashion to xuezhikang (XZK) 600 mg twice daily (1,200 mg/day, providing approximately 7.2 mg monacolin K among a total monacolin content of ~10 mg) or matching placebo, with a mean follow-up of **4.5 years** [92]. The primary composite endpoint of nonfatal myocardial infarction and coronary heart disease death occurred in 5.7% of the XZK group versus 10.4% of the placebo group, representing a **45% relative risk reduction** (absolute risk reduction 4.7%). Treatment with XZK also significantly decreased cardiovascular mortality by 30%, **all-cause mortality by 33%**, and the need for coronary revascularisation by approximately one-third [92]. These results are striking in magnitude and, notably, approximate the benefit observed in the landmark 4S trial of simvastatin in a Western population.

Pre-specified subgroup analyses of the CCSPS extended these findings to high-risk populations. In **1,445 elderly patients aged 65–75 years**, Ye and colleagues reported reductions in coronary events of 36.9% ($p = 0.001$), all-cause mortality of 31.9% ($p = 0.01$), stroke of 44.1% ($p = 0.04$), and malignancies of 51.4% ($p = 0.03$), with number-needed-to-treat (NNT) values of 18, 23, and 33 to prevent one coronary event, one death, and one coronary death, respectively [93]. In **2,704 hypertensive post-MI patients**, Li JJ and colleagues documented a 43.0% reduction in coronary events ($p = 0.02$) and 35.8% reduction in all-cause mortality ($p = 0.001$) [94]. These subgroup data are particularly relevant to the clinical profile of an older, multi-morbid population that might be expected to use a nutraceutical formulation such as AURI 25.

Tolerability in statin-intolerant patients — a population of considerable clinical interest — has been addressed in several well-designed trials. Becker and colleagues (2009) conducted a randomised, double-blind, placebo-controlled trial in **62 patients with dyslipidaemia and documented statin myalgia**, administering RYR 1,800 mg twice daily (providing approximately 6 mg monacolin K) or placebo with concurrent therapeutic lifestyle change for 24 weeks [95]. LDL-C decreased by **21.3%** (43 mg/dL) in the RYR group versus 8.7% with placebo ($p < 0.001$ at week 12), with no increase in CK levels, pain scores, or hepatic transaminases; the tolerability rate was **93%** [95]. In a subsequent head-to-head trial, Halbert

and colleagues (2010) randomised **43 statin-intolerant patients** to RYR 2,400 mg twice daily or pravastatin 20 mg twice daily for 12 weeks, finding comparable LDL-C reductions (**30% versus 27%**) and comparable rates of myalgia-related withdrawal (5% versus 9%, $p = 0.99$) [96]. Venero and colleagues (2010), in a retrospective chart review of 25 statin-intolerant patients, reported similar LDL-C reductions (21%) and a 92% tolerability rate, although the observational design limits causal inference [97].

The multinational phase 2 trial by Moriarty and colleagues (2014) randomised **116 adults with dyslipidaemia** (approximately 53% White, 37% Asian) across 15 sites in the United States and China to XZK 1,200 mg/day, XZK 2,400 mg/day, or placebo for 12 weeks [98]. Both XZK doses produced clinically meaningful LDL-C reductions of approximately **27%** ($p < 0.001$), with ~50% of subjects achieving ≥30% LDL-C lowering; doubling the dose yielded only an additional 4.6% reduction, suggesting a flattening dose-response curve at higher intakes [98]. Efficacy was similar across American and Chinese subjects, and no myopathy or marked transaminase elevations were observed [98]. Earlier, the landmark US trial by Heber and colleagues (1999) had established proof of concept, demonstrating significant TC and LDL-C reductions with the proprietary Cholestin product (2,400 mg/day, ~5 mg total monacolins) versus placebo over 12 weeks in 83 healthy hyperlipidaemic adults [91].

Table 3. Summary of key monacolin K / red yeast rice clinical trials

Author, year	Design	n	Population	Monacolin K dose (mg/d)	Duration	LDL-C change (%)	p-value	Notable findings
Heber et al., 1999 [91]	DB-RCT	83	Primary hyperlipidaemia	~5 (total monacolins)	12 wk	−22 to −27	<0.001	First major US RCT; Cholestin product
Lu et al., 2008 [92] (CCSPS)	DB-RCT, multicentre	4,870	Post-MI, Chinese	~7.2 (XZK 1,200 mg/d)	4.5 yr	−20	<0.001	**45% ↓ coronary events; 33% ↓ all-cause mortality**
Ye et al., 2007 [93]	CCSPS subgroup	1,445	Elderly (≥65 yr) post-MI	~7.2	4.0 yr	NR	—	36.9% ↓ coronary events; NNT = 18
Becker et al., 2009 [95]	DB-RCT	62	Statin-intolerant	~6 (RYR 3,600 mg/d)	24 wk	−21.3	<0.001	93% tolerability; no myalgia recurrence
Halbert et al., 2010 [96]	DB-RCT	43	Statin-intolerant	~8 (RYR 4,800 mg/d)	12 wk	−30	<0.001	Comparable tolerability to pravastatin 40 mg/d
Moriarty et al., 2014 [98]	Phase 2, DB-RCT	116	Dyslipidaemia (US + China)	~7.2–14.4	12 wk	−27	<0.001	Consistent efficacy across ethnicities
Heinz et al., 2016 [99]	DB-RCT	142	Hypercholesterolaemia	**3.0**	12 wk	**−14.8**	<0.001	Key low-dose (3 mg) efficacy evidence

Author, year	Design	n	Population	Monacolin K dose (mg/d)	Duration	LDL-C change (%)	p-value	Notable findings
Angelopoulos et al., 2023 [100]	MC-RCT	105	Mild hypercholesterolaemia	**3.0** vs 10	8 wk	**−16.8** (3 mg); −26.5 (10 mg)	<0.001	Dose-response confirmed; 3 mg clinically meaningful

DB-RCT = double-blind randomised controlled trial; MC-RCT = multicentre randomised controlled trial; MI = myocardial infarction; NNT = number needed to treat; NR = not reported; XZK = xuezhikang.

The dose question: clinical evidence at 2.9 mg and the multi-pathway rationale

The monacolin K dose in AURI 25 is **2.9 mg per daily serving** — a figure that warrants explicit pharmacological and regulatory contextualisation. The bulk of the clinical trial literature reviewed above employed monacolin K doses in the range of 5–10 mg daily, and the former European Food Safety Authority (EFSA) health claim for cholesterol maintenance required a minimum intake of 10 mg/day (Commission Regulation EU No 432/2012). However, in 2018, EFSA's Panel on Food Additives and Nutrient Sources (ANS) published a safety opinion concluding that monacolins from RYR at 10 mg/day "were of significant safety concern" and noting individual cases of severe adverse reactions at intakes as low as 3 mg/day; the Panel was unable to identify a dietary intake that does not give rise to concerns [102]. In response, Commission Regulation (EU) 2022/860 restricted monacolins in food supplements to **<3 mg per daily portion**, and Commission Regulation (EU) 2024/2041 subsequently revoked the 10 mg health claim entirely. The 2.9 mg dose in AURI 25 thus represents a **strategic positioning at the regulatory ceiling** for the European market.

Whether this dose delivers clinically meaningful lipid-lowering efficacy is a legitimate and important question. Several lines of evidence suggest that it does, albeit with smaller absolute effect sizes than higher doses. The pivotal study is the randomised, double-blind, placebo-controlled trial by Heinz and colleagues (2016), which enrolled **142 nonstatin-treated hypercholesterolaemic participants** and administered RYR providing exactly **3 mg monacolin K** (plus 200 µg folic acid) daily for 12 weeks [99]. The supplement group demonstrated an LDL-C reduction of **−14.8%** and a TC reduction of −11.2% (both $p <$ 0.001 versus placebo), with 51% of participants achieving the target LDL-C threshold of <4.14 mmol/L; no serious adverse events were observed [99]. Angelopoulos and colleagues (2023) extended these findings in a multicentre RCT comparing three arms — lifestyle modification (LM) alone, LM plus 3 mg monacolin K, and LM plus 10 mg monacolin K — in **105 subjects with mild hypercholesterolaemia** over 8 weeks [100]. The 3 mg arm achieved an LDL-C reduction of **−16.77%** ($p < 0.001$), approximately **63% of the effect observed** with the 10 mg arm (−26.46%), confirming a dose-response relationship while demonstrating that the lower dose retains clinically meaningful activity [100].

A recent systematic review by Liasi and colleagues (2024), examining 12 RCTs encompassing 769 participants with monacolin K doses ranging from 2 to 10 mg daily, concluded that "all studies indicated a beneficial effect of monacolin supplementation on LDL and total cholesterol levels ($p < 0.05$) regardless of the dose" and that **low doses of 3 mg/day exert potential cholesterol-lowering effects**, although the number of studies at this dose remains limited [101]. The weight of this evidence establishes that 2.9 mg monacolin K produces a genuine, if modest, pharmacological effect on LDL-C — likely in the range of **14–17%**

reduction when used as a monotherapy. It must be acknowledged transparently, however, that **no published RCT has tested exactly 2.9 mg monacolin K as an isolated active ingredient in a simple formulation**, and extrapolation from 3 mg data, while pharmacologically reasonable given the negligible 0.01 mg difference, remains an indirect inference.

The formulation logic of AURI 25 addresses this dose limitation through a **multi-pathway strategy** analogous to pharmaceutical combination therapy. Just as contemporary lipid management guidelines endorse the use of moderate-dose statins combined with ezetimibe (which targets intestinal cholesterol absorption via a completely independent mechanism) rather than escalating to maximal statin doses that carry disproportionate myopathy risk, AURI 25 deploys four compounds that modulate cholesterol homeostasis through distinct and complementary pathways: direct HMG-CoA reductase inhibition (monacolin K and, potentially, natural lovastatin from *Pleurotus ostreatus*; The Pleurotus profile), indirect AMPK-mediated HMG-CoA reductase downregulation (policosanol; The policosanol profile), and putative effects on cholesterol absorption and hepatic metabolism (β-glucans from *Auricularia auricula-judae* and *Pleurotus ostreatus*; the Auricularia and Pleurotus profiles). Whether these individual effects are truly additive or synergistic in the specific doses and proportions provided by AURI 25 has not been tested in a dedicated clinical trial of the finished product — a caveat that applies, it should be noted, to the majority of multi-ingredient nutraceutical formulations on the market — and such a trial would materially strengthen the evidence base.

Safety profile: myopathy, hepatotoxicity, and citrinin contamination

The safety profile of monacolin K is fundamentally governed by its identity with lovastatin and its consequent pharmacological effects on the mevalonate pathway. The principal adverse effects of concern are skeletal muscle toxicity (ranging from myalgia through myopathy to rhabdomyolysis) and hepatotoxicity (transaminase elevation to overt liver injury). At pharmaceutical lovastatin doses of 20–80 mg daily, the incidence of myalgia is approximately 5–10%, clinically significant myopathy (CK >10× upper limit of normal) occurs in approximately 0.1–0.2%, and fatal rhabdomyolysis is exceedingly rare at approximately 1.5 deaths per 10 million prescriptions [107]. The critical question is how these risks scale to the 2.9 mg dose in AURI 25.

The large safety meta-analysis by Fogacci and colleagues (2019), encompassing 53 RCTs with 8,535 subjects across a range of monacolin K doses, found **no increased risk of musculoskeletal disorders** (OR 0.94, 95% CI: 0.53–1.65) and, notably, an inverse dose-response relationship in which increasing daily monacolin K doses were associated with *reduced* non-musculoskeletal adverse events (slope: −0.10, 95% CI: −0.17 to −0.03, $p < 0.01$) [90]. Subgroup analysis of studies using ≤3 mg monacolin K daily confirmed this safety profile [90]. The Italian surveillance system analysis by Mazzanti and colleagues (2017) documented 52 spontaneous reports involving 55 adverse reactions to RYR supplements over a 13-year period (2002–2015), including 19 cases of myalgia/CK elevation, one case of rhabdomyolysis, and 10 cases of liver injury, the majority occurring in patients concurrently taking other medications [103]. Banach and Norata (2023), analysing the FDA FAERS and CAERS databases, described the occurrence of rhabdomyolysis or severe acute hepatitis associated with RYR as "extremely rare" compared with statins, reporting musculoskeletal adverse event rates of **0.008%** and hepatobiliary rates of 0.01% across reported cases [104].

Notwithstanding this generally reassuring trial-level evidence, the EFSA ANS Panel (2018) adopted a conservative position, noting that most included RCTs were designed for efficacy rather than safety and were of insufficient duration and sample size to detect rare adverse events [102]. The Panel highlighted individual case reports of severe adverse reactions at intakes as low as 3 mg/day and concluded that it was "unable to identify a dietary intake of monacolins from RYR that does not give rise to concerns about harmful effects to health" [102]. This regulatory assessment, while appropriately precautionary, must be weighed against the meta-analytic evidence from over 8,500 randomised subjects showing no signal of increased muscular harm and a statistically significant reduction in serious adverse events in the RYR arms [90]. The practical implication for AURI 25 is that its 2.9 mg dose, representing less than **4–15% of the therapeutic lovastatin dose range** (20–80 mg), carries a correspondingly attenuated pharmacological exposure and, by extension, a dose-proportionally lower risk profile.

An additional mevalonate pathway–related concern is the potential for coenzyme Q10 (CoQ10) depletion. Ubiquinone is synthesised from mevalonate-derived isoprenoid intermediates, and statin therapy consistently reduces circulating CoQ10 levels, which may contribute to mitochondrial dysfunction in skeletal muscle [107]. Whether monacolin K at 2.9 mg/day produces clinically relevant CoQ10 suppression has not been directly studied, but the effect is expected to be minimal at this dose; nonetheless, the point merits consideration in long-term use scenarios.

A distinct safety concern unique to RYR — and absent from pharmaceutical lovastatin — is contamination with **citrinin**, a nephrotoxic and hepatotoxic mycotoxin produced by certain *Monascus* strains during fermentation. EFSA established a tolerable daily intake for citrinin of 0.2 µg/kg body weight/day, and EU Regulation 2023/915 set the maximum permissible citrinin content in RYR food supplements at **100 µg/kg** [102,106]. An alarming quality survey by Righetti and colleagues (2021) screened 37 European RYR food supplements and detected citrinin in all 37 products, with concentrations ranging from 100 to 25,100 µg/kg; only a single product was compliant with the 100 µg/kg limit, and **four products labelled as "citrinin free" were in fact contaminated** [105]. The monacolin K content was also highly variable, ranging from −83% to +266% of label claims [105]. In contrast, Twarużek and colleagues (2021) found no detectable citrinin in 15 Polish RYR supplements, highlighting substantial inter-market quality variation [106]. These data underscore that citrinin contamination represents a critical quality-control differentiator between RYR products; responsible manufacturers must employ *Monascus* strains with verified low citrinin production and implement validated analytical testing of finished products.

Drug interactions and contraindications

Because monacolin K is pharmacokinetically identical to lovastatin, it shares the same metabolic vulnerabilities. Lovastatin is primarily metabolised by hepatic cytochrome P450 3A4 (CYP3A4), and co-administration with potent CYP3A4 inhibitors dramatically increases systemic exposure and myotoxicity risk [108]. Clinically important inhibitors include the azole antifungals itraconazole and ketoconazole, macrolide antibiotics clarithromycin and erythromycin, HIV protease inhibitors (ritonavir, nelfinavir), the immunosuppressant ciclosporin, and, to a lesser degree, calcium channel blockers verapamil and diltiazem [108]. Consumption of large quantities of grapefruit juice (>1 litre daily) also inhibits intestinal CYP3A4, increasing lovastatin bioavailability [108]. Concurrent use of fibrates — particularly gemfibrozil, which inhibits both CYP2C8 and the hepatic uptake transporter OATP1B1 —

further elevates the risk of myotoxicity through additive pharmacodynamic effects and altered statin disposition [108].

The most important contraindication for any monacolin K–containing supplement is **concurrent use of pharmaceutical statins**, which is absolutely contraindicated owing to the risk of cumulative HMG-CoA reductase inhibition, dose-stacking, and consequent myopathy [102,103]. Additional contraindications include pregnancy and lactation (lovastatin is teratogenic in animal models and classified as Category X), use in children under 18 years, use in adults over 70 years without medical supervision, and pre-existing hepatic impairment [102]. At the 2.9 mg dose, these interactions are dose-proportionally less pharmacologically significant than at therapeutic lovastatin doses, but they remain clinically relevant and **warrant unambiguous disclosure** on product labelling and in consumer information materials. Patients taking any of the aforementioned interacting medications should be advised to consult a prescriber before initiating RYR supplementation.

Regulatory landscape

The regulatory status of monacolin K–containing RYR products occupies an unusual and contested position between food supplement and pharmaceutical across major jurisdictions. In the European Union, the trajectory has moved decisively toward restriction. The initial EFSA health claim authorisation in 2012 (Commission Regulation EU No 432/2012) endorsed the statement that "monacolin K from red yeast rice contributes to the maintenance of normal blood cholesterol concentrations" at intakes of ≥10 mg/day. The 2018 EFSA safety opinion effectively undermined this claim by concluding that 10 mg/day posed significant safety concerns [102]. Commission Regulation (EU) 2022/860 subsequently restricted monacolins to <3 mg per daily portion in food supplements, and in 2024, Commission Regulations (EU) 2024/2041 and 2024/2063 formally deleted the health claim from the Union list. As of early 2026, monacolins remain under Union scrutiny (Annex III, Part C of Regulation EC 1925/2006), with a further EFSA opinion in March 2025 reiterating that no safe daily intake could be identified; expert commentary suggests a full prohibition (transfer to Part A, banned substances) is the most probable regulatory outcome by mid-2026. Individual member state restrictions preceded these Union-wide measures: France (ANSES, 2014), Belgium (Superior Health Council, 2016), and Germany (BfArM, 2016) all issued warnings or reclassification opinions prior to the harmonised EU limit.

In the United States, the regulatory framework was shaped by the *Pharmanex v. Shalala* litigation (1997–2001). The US Food and Drug Administration (FDA) classified Cholestin — a proprietary RYR product manufactured to maximise lovastatin content — as an unapproved new drug rather than a dietary supplement, on the grounds that it contained lovastatin, an already-approved drug ingredient. The Tenth Circuit Court of Appeals upheld the FDA's position in 2000, and subsequent FDA enforcement actions (including warning letters issued in 2007 and 2008) have targeted RYR products containing more than trace amounts of lovastatin. The practical result is that RYR products marketed in the US as dietary supplements must contain only trace levels of monacolin K, may not be standardised for monacolin content, and may not reference lovastatin on the label; products that do so are subject to regulatory action as unapproved drugs.

Evidence quality assessment

Applying the evidence quality framework outlined in The evidence framework used in the source publication, monacolin K / RYR merits a rating of **STRONG** — the highest of the AURI

25 compounds. This assessment rests on several convergent pillars: the availability of **multiple concordant meta-analyses** (at least seven published between 2006 and 2024) consistently demonstrating LDL-C reductions of 15–25% versus placebo [82–87]; a **large, long-duration RCT with hard cardiovascular outcomes** (CCSPS, n = 4,870, 4.5 years) showing 45% reduction in coronary events and 33% reduction in all-cause mortality [92]; a comprehensive **safety meta-analysis** of 53 RCTs with 8,535 subjects confirming no increased musculoskeletal risk [90]; replication across diverse populations including Western, Chinese, elderly, diabetic, hypertensive, and statin-intolerant cohorts [91–98]; and a well-characterised, dose-dependent mechanism of action grounded in detailed structural biology [80]. The compound benefits from over two decades of continuous investigation, publication in high-impact journals including the *Journal of the American College of Cardiology* [28], and recognition in European Society of Cardiology / European Atherosclerosis Society (ESC/EAS) guidelines as a lipid-lowering option [4].

Two important caveats temper this otherwise strong assessment. First, the **bulk of the clinical evidence derives from studies using ≥5 mg monacolin K daily**, and direct evidence at the 2.9 mg dose present in AURI 25, while supported by the Heinz [99] and Angelopoulos [100] trials, is comparatively limited. Extrapolation from higher-dose data is pharmacologically sound — the mechanism is dose-dependent and well characterised — but a dedicated RCT of the finished AURI 25 formulation would materially strengthen the product-specific evidence base. Second, the regulatory environment is evolving rapidly; the ongoing EFSA scrutiny process may result in further EU restrictions on monacolin-containing food supplements, and manufacturers must be prepared to adapt accordingly. Notwithstanding these caveats, monacolin K at 2.9 mg represents the **mechanistic anchor** of the AURI 25 formulation: a compound with pharmacological activity that is proven, quantifiable, and grounded in the strongest evidence tradition available to any nutraceutical ingredient.

§3.3 *Auricularia auricula-judae* polysaccharides (1200 mg hot water extract, ≥30% polysaccharides)

Taxonomy, ethnomycological heritage, and compositional complexity

Auricularia auricula-judae (Bull.) Quél. is a jelly fungus classified within Kingdom Fungi, Division Basidiomycota, Class Agaricomycetes, Order Auriculariales, Family Auriculariaceae [109,110]. Its gelatinous, ear-shaped basidiocarp has earned a striking diversity of vernacular names across cultures — wood ear, tree ear, black fungus, and Judas's ear in English; *mù'ěr* (□□) in Chinese; *kikurage* in Japanese — reflecting a cosmopolitan distribution on decaying hardwood substrates throughout temperate and subtropical forests [109,111]. Taxonomic revision has recently reclassified the predominant commercially cultivated East Asian species as *Auricularia heimuer* (F. Wu, B.K. Cui & Y.C. Dai), though the binomial *A. auricula-judae* remains widely used in the pharmacological literature and will be retained here for consistency with the nomenclature applied to the extract under review [112].

The species occupies a singular position at the intersection of food and medicine in East Asian traditions. References to its therapeutic application appear in Chinese materia medica texts spanning more than 1,500 years, including classical pharmacopoeias in the lineage of the *Shennong Bencao Jing*, where it was recorded for blood invigoration (*huoxue*), haemostasis, and qi tonification [109,111]. This long ethnomycological heritage is not merely historical: *A. auricula-judae* ranks among the most widely cultivated edible fungi on Earth, with annual

global production exceeding **six million tonnes**, overwhelmingly concentrated in China, where it serves simultaneously as a culinary staple and a functional food ingredient [109,112].

The compositional profile of *A. auricula-judae* is remarkably heterogeneous and extends well beyond a single class of bioactives. The dominant constituents are heteropolysaccharides — high-molecular-weight polymers comprising mannose, glucose, xylose, glucuronic acid, galactose, rhamnose, fucose, and arabinose in varying molar ratios depending on strain and extraction methodology [110,114]. These include β-glucans, mannans, xylans, and the signature acidic polysaccharide glucuronoxylomannan, the latter bearing structural and functional resemblance to glycosaminoglycans [110,121]. Methylation and gas chromatographic analyses have revealed 1,4-linked glucopyranose, 1,4-linked mannopyranose, and 1,2,6-linked mannopyranose linkages, with molecular weights ranging from approximately **23 kDa to over 400 kDa** depending on the fraction and processing conditions [114,115]. Beyond polysaccharides, the fungus contains melanin pigments — a unique distinguishing feature among edible mushrooms — synthesised via both Raper-Mason and 1,8-dihydroxynaphthalene (DHN) pathways, yielding a composite of eumelanin, pheomelanin, and DHN melanin with molecular weights near 49 kDa [113,119]. Additional bioactive constituents include proteins and glycoproteins, phenolic compounds, substantial dietary fibre, minerals (notably iron, calcium, and potassium), and vitamins including the B-complex group and vitamin D_2 [109,111].

The extract specified in the formulation under review is prepared by hot water extraction (HWE), a method that preferentially solubilises high-molecular-weight polysaccharides while preserving their native chain conformation, branching architecture, and uronic acid content — structural features that have been correlated with biological activity in structure-activity relationship studies [110,111,115]. Standardisation to ≥30% polysaccharides ensures that each 1,200 mg dose delivers a minimum of **360 mg of defined polysaccharide content**, providing a quantifiable basis for pharmacological assessment even as the extract retains its full compositional complexity, including melanin and phenolic fractions that contribute additional mechanisms of action.

Antioxidant activity and the oxidised-LDL paradigm

The cardiovascular relevance of *A. auricula-judae* polysaccharides is most compellingly framed not through direct lipid lowering — for which the preclinical evidence, remains preliminary — but through the oxidised low-density lipoprotein (ox-LDL) paradigm that now occupies a central position in contemporary atherosclerosis theory. It is not merely elevated circulating LDL-cholesterol that initiates plaque formation; rather, it is the oxidative modification of LDL particles within the subendothelial space that renders them recognisable by macrophage scavenger receptors — principally SR-A1, CD36, and lectin-like oxidised LDL receptor-1 (LOX-1) — triggering unregulated uptake, foam cell formation, fatty streak development, and ultimately the vulnerable plaque architecture that precedes acute coronary events and ischaemic stroke [116]. Native LDL is relatively benign in this regard; oxidative modification transforms it into a pro-inflammatory, pro-atherogenic ligand. This distinction is critical because it identifies a cardiovascular risk axis — oxidative susceptibility of LDL — that conventional statin therapy, directed primarily at hepatic cholesterol synthesis, does not directly address.

A. auricula-judae polysaccharides have demonstrated broad-spectrum free radical scavenging capacity across multiple in vitro assay systems. Enzymatically degraded polysaccharide fractions (composed principally of mannose at 57.1%, glucose at 22.5%, and glucuronic acid at

10.0%) exhibited DPPH radical scavenging rates of approximately **88%**, with hydroxyl radical and superoxide anion scavenging capacities 1.65-fold and 1.90-fold greater, respectively, than those of the native high-molecular-weight polymer [114]. Comparative studies across extraction methods have confirmed potent ABTS radical scavenging (IC_{50} values as low as **0.065 mg/mL**), DPPH scavenging, hydroxyl radical neutralisation, and ferric reducing power, with freeze-dried preparations retaining the highest uronic acid content and exhibiting the most robust antioxidant profiles [115,117]. Metal ion chelation — particularly of Fe^{2+} and Cu^{2+}, the transition metals that catalyse Fenton chemistry and LDL oxidation — has been documented for degraded polysaccharide fractions, representing a mechanistically distinct antioxidant pathway beyond direct radical scavenging [115]. In the nematode *Caenorhabditis elegans*, used as an in vivo oxidative stress model, polysaccharide fractions significantly enhanced superoxide dismutase (SOD) and catalase (CAT) enzyme activities, upregulated the stress-response transcription factors DAF-16 and SKN-1 (orthologues of mammalian FOXO and Nrf2, respectively), and extended lifespan under oxidative challenge [115,117].

The melanin fraction of *A. auricula-judae* contributes an additional layer of antioxidant protection that is largely absent from other components of the formulation. At a concentration of 1 mg/mL, purified *A. auricula-judae* melanin scavenged **superoxide anion radicals at 85.7%, $ABTS^+$ radicals at 91.3%, and hydroxyl radicals at 91.8%** in vitro, and significantly extended *C. elegans* lifespan under oxidative stress conditions [118]. Structural characterisation identified this pigment as a eumelanin with a molecular weight of approximately 49 kDa, and its hepatoprotective effects in ethanol-challenged mice were mechanistically linked to activation of the **Nrf2 signalling pathway** and upregulation of downstream phase II detoxification enzymes including GCLC, GCLM, and NQO-1 [119]. These findings, while derived entirely from in vitro and animal model systems, establish a compelling mechanistic rationale for the contribution of *A. auricula-judae* to a formulation strategy that seeks to address not only LDL quantity but also LDL oxidative vulnerability.

Anti-inflammatory mechanisms and vascular endothelial protection

The inflammatory hypothesis of atherosclerosis — validated clinically by the landmark CANTOS trial demonstrating that interleukin-1β inhibition with canakinumab reduced cardiovascular events independently of lipid lowering — positions chronic vascular inflammation as a therapeutic target in its own right. Preclinical evidence from cell culture and animal models suggests that *A. auricula-judae* extracts modulate several nodes of the inflammatory cascade implicated in atherogenesis.

In lipopolysaccharide (LPS)-stimulated RAW 264.7 murine macrophages, dichloromethane extracts of *A. auricula-judae* dose-dependently inhibited nitric oxide (NO) production and significantly reduced mRNA expression of the pro-inflammatory cytokines **interleukin-6 (IL-6), tumour necrosis factor-α (TNF-α), and interleukin-1β (IL-1β)** [120]. More mechanistically detailed work by Perera et al. demonstrated that the glucuronoxylomannan fraction modulated immunity through reactive oxygen species, mitogen-activated protein kinases (MAPKs), protein kinase C-α, and the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway, and — critically — induced an endotoxin tolerance-like state in LPS-activated macrophages characterised by **downregulation of NO, IL-6, and TNF-α via suppression of NF-κB activation** [121]. This capacity to dampen excessive inflammatory signalling while simultaneously enhancing phagocytic bactericidal activity represents a nuanced immunomodulatory profile rather than simple immunosuppression.

In a high-fat-diet murine obesity model, *A. auricula-judae* polysaccharides decreased circulating TNF-α and IL-6 concentrations, improved endotoxaemia markers, protected intestinal barrier integrity, and inhibited the **TLR4/JNK signalling pathway** while concurrently promoting AKT and AMPK activation [122]. More recent work has extended these observations to hepatic fibrosis models, where polysaccharide supplementation reduced extracellular matrix deposition through modulation of the **NLRP3 inflammasome and TLR4/NF-κB pathway** via a gut–liver axis mechanism dependent on short-chain fatty acid (SCFA) production [132]. Taken together, these preclinical data describe a multi-level anti-inflammatory profile encompassing cytokine suppression, inflammasome modulation, and endothelial adhesion molecule reduction — all of which, if translatable to the human vascular endothelium, would be expected to attenuate the inflammatory milieu that sustains atherosclerotic plaque progression.

Anti-thrombotic and anti-platelet properties

Among the earliest pharmacological observations on *A. auricula-judae* — predating the modern polysaccharide characterisation literature by some years — was the recognition of its anticoagulant and anti-platelet properties, activities that align with its traditional use for blood invigoration. Yoon et al. isolated an acidic polysaccharide of approximately **160 kDa** (comprising mannose, glucose, glucuronic acid, and xylose, devoid of sulphate esters) from alkali extracts and demonstrated a specific anticoagulant activity of **2 IU/mg** [123]. Mechanistic investigation revealed that this activity was mediated by catalysis of thrombin inhibition through antithrombin — functionally analogous, albeit structurally distinct, to the heparin–antithrombin interaction — while Factor Xa inhibition was not observed [123]. Chemical reduction of the glucuronic acid carboxyl groups abolished anticoagulant activity, confirming the essential role of uronic acid residues in the thrombin-inhibitory mechanism. In ex vivo experiments using Sprague-Dawley rats orally fed with the polysaccharide, **platelet aggregation was inhibited to a degree comparable with aspirin** [123].

Subsequent structural and functional studies have expanded on these findings. Bian et al. optimised extraction of acidic polysaccharides (mannose, glucuronic acid, glucose, galactose, and xylose in an approximate molar ratio of 80.6:9.9:2.3:1.0:31.1) and demonstrated prolongation of activated partial thromboplastin time (aPTT), prothrombin time (PT), and thrombin time (TT) in human plasma coagulation assays, indicating activity through both the intrinsic and extrinsic coagulation pathways [125]. In a carrageenan-induced mouse thrombosis model, a purified polysaccharide fraction (12.0 kDa) significantly reduced black tail thrombus length, prolonged aPTT, PT, and TT, and modulated endothelin-1 (ET-1), prostaglandin I_2 (PGI_2), thromboxane B_2 (TXB_2), and antithrombin III/protein C pathways [124]. These anti-thrombotic properties are mechanistically complementary to the anti-platelet effects reported for policosanol (The policosanol profile), suggesting that within the formulation, the two components may address haemostatic risk through distinct but convergent pathways — policosanol primarily through thromboxane A_2 reduction and *A. auricula-judae* polysaccharides through antithrombin-mediated coagulation inhibition.

Lipid-modulating effects: a preclinical evidence base requiring clinical translation

Candour regarding the evidence level for direct lipid modulation by *A. auricula-judae* polysaccharides is essential. Unlike monacolin K, for which extensive human trial data exist (The monacolin K profile), and unlike policosanol, for which human trials — however contested — have been conducted (The policosanol profile), **no published randomised controlled trial

has evaluated *A. auricula-judae* as a standalone lipid-lowering agent in human subjects**. The lipid-modulating evidence base rests entirely on animal models and in vitro systems, and must be interpreted accordingly.

The foundational study in this domain is that of Chen et al., who administered hot-water-extracted polysaccharides (120 mg/kg/day by oral gavage) to ICR mice fed a cholesterol-enriched diet for eight weeks [23]. Polysaccharide supplementation significantly lowered serum total cholesterol (TC) and LDL-cholesterol (LDL-C) relative to the diet-matched control group ($P < 0.05$), improved total antioxidant capacity and lipoprotein lipase (LPL) activity, decreased malondialdehyde (MDA), and reduced the atherogenic index [23]. Zeng et al. subsequently demonstrated that a purified α-glycosidically linked polysaccharide fraction from solid-state fermentation significantly decreased TC, triglycerides (TG), and LDL-C in high-fat-diet hyperlipidaemic mice after 14 and 28 days of oral administration [126]. In a more mechanistically detailed investigation, Liu et al. reported that dietary supplementation with *A. auricula-judae* polysaccharides improved insulin resistance, altered serum lipid metabolites, and slowed weight gain in C57BL/6J mice fed a high-fat high-fructose diet, with transcriptomic analysis revealing **downregulation of hepatic adipogenic and cholesterol synthesis genes (SREBP-1c pathway), upregulation of fatty acid β-oxidation genes, and promotion of cholesterol efflux gene expression** (ABCA1/ABCG1 pathway) [24]. The most comprehensive recent study employed widely targeted lipidomics and microbiomics, reporting that polysaccharide supplementation reduced body weight by 13.4%, serum TC by **20.3%**, serum TG by **23.8%**, and liver non-esterified fatty acids by 20.8% in high-fat-diet mice, while regulating 44 lipid biomarkers across sphingolipid and advanced glycation end-product receptor (AGE-RAGE) signalling pathways [127].

Several mechanistic hypotheses have emerged from this preclinical literature. Beyond SREBP-1c modulation and ABCA1/ABCG1 upregulation, proposed pathways include bile acid binding within the intestinal lumen (analogous to established bile acid sequestrant pharmacology), pancreatic lipase inhibition, and indirect effects mediated through gut microbiota remodelling and SCFA-driven AMPK activation in hepatocytes [110,127]. These mechanisms are plausible and internally consistent, but their extrapolation to human physiology remains speculative. Within the evidence hierarchy framework established in The evidence framework used in the source publication, the lipid-modulating effects of *A. auricula-judae* polysaccharides are appropriately rated as **emerging** — supported by a coherent preclinical rationale and consistent animal model data, but lacking the human clinical validation that would warrant stronger confidence.

Hepatoprotective effects and the NAFLD–dyslipidaemia nexus

Non-alcoholic fatty liver disease (NAFLD) and dyslipidaemia exist in a bidirectional pathophysiological relationship: hepatic steatosis promotes atherogenic dyslipidaemia (elevated TG, reduced HDL-C, increased small dense LDL), while dyslipidaemia itself contributes to hepatic lipid accumulation. Interventions that protect hepatic function therefore have indirect relevance to lipid metabolism even when their primary target is the liver rather than the plasma lipid profile.

In a NAFLD mouse model induced by a high-fat high-cholesterol diet combined with carbon tetrachloride, Shu et al. demonstrated that *A. auricula-judae* polysaccharides (and their deacetylated derivatives) effectively relieved liver injury, inflammation, and fibrosis while maintaining intestinal barrier function [128]. The hepatoprotective mechanism was linked to

modulation of gut microbiota composition — with enrichment of *Odoribacter*, *Lactobacillus*, *Dorea*, and *Bifidobacterium* — and alteration of the bile acid profile, including increased deoxycholic acid (DCA) concentrations that activated the **farnesoid X receptor (FXR)** and participated in bile acid metabolism and cholestasis alleviation [128]. Separate investigations have demonstrated hepatoprotective effects of *A. auricula-judae* polysaccharides against cyclophosphamide-induced liver injury, mediated through activation of the **Akt/GSK3β/Nrf2/HO-1 signalling cascade** and remodelling of both the gut bacteriome and mycobiome [129]. The melanin fraction has shown complementary hepatoprotective activity in ethanol-challenged mice, reducing serum TG, TC, and LDL-C while inhibiting hepatic lipid accumulation and steatosis through regulation of lipid metabolism and inflammatory gene expression [119]. These findings, while entirely preclinical, reinforce the position of *A. auricula-judae* as a hepatoprotective agent whose liver-directed effects may indirectly support lipid metabolic homeostasis.

Gut microbiome modulation and the prebiotic paradigm

Perhaps the most rapidly expanding area of *A. auricula-judae* research concerns its prebiotic activity — the capacity of its high-molecular-weight polysaccharides to resist upper gastrointestinal digestion and undergo fermentation by colonic microbiota, thereby reshaping microbial community composition and generating bioactive metabolites with systemic effects. This mechanism is particularly relevant to the formulation under review because it connects polysaccharide intake to hepatic cholesterol metabolism through the gut–liver axis.

In vitro fermentation studies using human faecal inocula have confirmed that *A. auricula-judae* polysaccharides are efficiently fermented by colonic bacteria, producing abundant **short-chain fatty acids (SCFAs) including acetic acid, propionic acid, and butyric acid**, while increasing the Bacteroidetes-to-Firmicutes ratio and elevating the abundance of *Bacteroides* and *Parabacteroides* [131]. Metabolomic analysis identified 26 biomarkers affecting tryptophan, bile acid, purine, and butyric acid metabolic pathways [131]. In animal models, polysaccharide supplementation has consistently promoted the proliferation of beneficial taxa including *Lactobacillus*, *Bifidobacterium*, and *Roseburia*, while inhibiting potentially pathogenic organisms [122,128,130]. The mechanistic sophistication of microbiome-mediated effects was elegantly demonstrated by Zong et al., who showed that *A. auricula-judae* polysaccharides attenuated obesity in high-fat-diet mice through selective enrichment of the gut commensal *Papillibacter cinnamivorans*; faecal microbiota transplantation and antibiotic-treated pseudo-germ-free models confirmed that the anti-obesogenic effect was **microbiota-dependent**, with *P. cinnamivorans* reducing intestinal lipid transportation and hepatic thermogenesis via JAK-STAT signalling [130].

The relevance of SCFA production to lipid metabolism deserves particular emphasis. Butyrate and propionate activate AMP-activated protein kinase (AMPK) in hepatocytes — the same master metabolic switch engaged by policosanol (The policosanol profile) — thereby suppressing 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoA reductase) and downregulating de novo cholesterol synthesis [132]. Propionate additionally inhibits hepatic lipogenesis and promotes cholesterol catabolism to bile acids. The gut–liver axis therefore represents a physiological pathway through which non-absorbed polysaccharides exert systemic metabolic effects without requiring their own absorption into the bloodstream, a point of considerable relevance to the bioavailability considerations.

Hypoglycaemic activity and the metabolic syndrome interface

Insulin resistance and type 2 diabetes mellitus (T2DM) are intimately linked to atherogenic dyslipidaemia — characterised by elevated triglycerides, reduced HDL-cholesterol, and a predominance of small dense LDL particles — through mechanisms involving hepatic overproduction of very-low-density lipoprotein (VLDL) and impaired lipoprotein lipase activity. Agents that improve insulin sensitivity therefore exert indirect lipid-modulating effects through correction of the underlying metabolic milieu.

In streptozotocin (STZ) and high-fat-diet-induced diabetic mouse models, *A. auricula-judae* polysaccharides (50–200 mg/kg/day) have demonstrated significant hypoglycaemic activity, reducing fasting blood glucose, improving oral glucose tolerance, and decreasing the homeostatic model assessment of insulin resistance (HOMA-IR) [133,134]. Xu et al. identified the **AKT/AMPK signalling pathways** as central mediators, with polysaccharide supplementation simultaneously improving glycolipid metabolism and elevating gut microbiota diversity through increased *Lactobacillus* and *Bacteroides* abundance [133]. Shi et al. further reported that a polysaccharide acid hydrolysate promoted **GLP-1 and insulin secretion, improved insulin sensitivity, and alleviated insulin resistance** in STZ-induced diabetic mice, with transcriptomic and metabolomic analyses revealing modulation of glucokinase gene expression and glutathione metabolism [134]. In vitro, a glycoprotein fraction inhibited **α-amylase and α-glucosidase** activity and increased glucose consumption and glycogen content in insulin-resistant HepG2 cells [111]. These hypoglycaemic properties, while demonstrated exclusively in preclinical systems, are mechanistically relevant to the broader dyslipidaemia management strategy by addressing metabolic syndrome pathophysiology upstream of its lipid manifestations.

Immunomodulatory properties and pattern recognition receptor engagement

The immunomodulatory activity of fungal β-glucans and heteropolysaccharides — mediated through engagement of innate immune pattern recognition receptors — is well established in the broader mycological literature. For *A. auricula-judae* specifically, β-(1,3)-glucan-containing exopolysaccharides have been shown to activate macrophages and dendritic cells through binding to **Dectin-1**, the C-type lectin receptor that serves as the principal mammalian β-glucan sensor [135]. Dectin-1 engagement activated the canonical Syk-dependent signalling pathway, induced pro-inflammatory cytokine production and cell maturation, and repolarised M2 macrophages to the M1 phenotype [135]. Oral administration of these exopolysaccharides enhanced survival in mice infected with *Cryptococcus neoformans*, providing in vivo evidence of functional immune enhancement [135]. Exopolysaccharides from submerged culture similarly promoted NO, IL-6, IL-10, and TNF-α release from RAW 264.7 macrophages at non-cytotoxic concentrations [136]. The relevance of these immunomodulatory properties to cardiovascular protection lies in the dual nature of macrophage involvement in atherosclerosis: while excessive M1-polarised inflammation drives plaque instability, appropriate immune surveillance and phagocytic clearance of apoptotic cells within plaques (efferocytosis) is atheroprotective. The immunomodulatory profile of *A. auricula-judae* polysaccharides — enhancing phagocytosis while inducing endotoxin tolerance to dampen excessive inflammatory cytokine release [121] — represents a nuanced rather than simply pro- or anti-inflammatory modulation.

Bioavailability: why limited absorption is not a limitation

A reasonable pharmacokinetic objection to polysaccharide-based interventions concerns the limited direct absorption of high-molecular-weight polymers across the intestinal epithelium. Fungal polysaccharides from *A. auricula-judae* range from approximately 10 kDa to over 400

kDa [110,114,115], and intact absorption of molecules exceeding 1–2 kDa via paracellular or transcellular routes is negligible. This apparent limitation, however, mischaracterises the pharmacological strategy. The primary sites of bioactivity for high-molecular-weight polysaccharides are **the intestinal lumen and the colonic microbiome**, not the systemic circulation. Bile acid binding within the intestinal lumen — a mechanism shared with clinically established bile acid sequestrants such as cholestyramine and colesevelam — requires no systemic absorption whatsoever. Prebiotic fermentation to SCFAs occurs entirely within the colon, yet the resultant butyrate, propionate, and acetate are absorbed by colonocytes and exert systemic metabolic effects via portal circulation to the liver and activation of G-protein-coupled receptors (GPR41, GPR43) throughout the body [131,132]. Additionally, immunomodulatory effects mediated through Dectin-1 and TLR engagement occur at the intestinal mucosal surface, where gut-associated lymphoid tissue (GALT) represents the largest immune organ in the body [135]. The pharmacological paradigm for *A. auricula-judae* polysaccharides therefore parallels that of dietary fibre, prebiotics, and bile acid sequestrants — drug classes whose clinical efficacy is well established despite (indeed, because of) their resistance to systemic absorption.

Safety profile and dose rationale

Auricularia auricula-judae has been consumed as a dietary staple across East and Southeast Asia for centuries, representing a food safety record that substantially exceeds the duration of any formal toxicological testing programme. The species is generally recognised as safe (GRAS) by convention of widespread dietary use, and no specific toxicity has been documented at quantities consistent with normal dietary intake [109,123]. A typical culinary serving of dried wood ear mushroom ranges from 2 to 5 g (rehydrated weight substantially higher), placing the 1,200 mg extract dose well within normal dietary exposure. The exopolysaccharide fractions have demonstrated no cytotoxicity to mammalian cell lines at concentrations up to 200 µg/mL in vitro [136], and animal studies employing polysaccharide doses of 100–400 mg/kg/day — substantially exceeding allometric equivalents of the human dose — have reported no adverse effects on body weight, organ indices, or liver and kidney function [122,133]. No specific drug interactions attributable to *A. auricula-judae* polysaccharides have been reported in the published literature, though the anti-platelet and anticoagulant properties documented in preclinical models [123–125] theoretically warrant caution in individuals receiving anticoagulant pharmacotherapy. Rare allergic reactions to fungal proteins are known across edible mushroom species but are not specifically documented for *A. auricula-judae* at a frequency that distinguishes it from other dietary fungi.

The 1,200 mg dose — the highest among the constituent active components in the formulation — reflects a fundamental pharmacological distinction between polysaccharide-based and small-molecule interventions. Whereas monacolin K achieves its HMG-CoA reductase inhibition at 2.9 mg through potent receptor-level binding, polysaccharides operate through physicochemical mechanisms (bile acid binding, radical scavenging, microbial fermentation substrate provision) that are inherently dose-dependent on mass rather than molar potency. The ≥30% polysaccharide standardisation ensures a minimum of **360 mg of defined polysaccharide content per dose**, complemented by melanin, phenolics, and other bioactive fractions. The rationale for this component's prominence in the formulation rests not on any single mechanism but on the breadth of its mechanistic portfolio: antioxidant protection against LDL oxidation, anti-inflammatory modulation of vascular endothelial activation, anti-thrombotic and anti-platelet activity, prebiotic gut microbiome remodelling,

hepatoprotective effects — pathways that are largely unaddressed by the small-molecule components of the formulation.

Evidence quality and the imperative for clinical translation

An honest appraisal of the evidence for *A. auricula-judae* polysaccharides must distinguish between the breadth of mechanistic data and the depth of clinical validation. The preclinical literature is substantial, internally consistent, and mechanistically sophisticated, spanning antioxidant, anti-inflammatory, anti-thrombotic, lipid-modulating, hepatoprotective, prebiotic, hypoglycaemic, and immunomodulatory domains across dozens of peer-reviewed publications. Within the evidence hierarchy framework of The evidence framework used in the source publication, the antioxidant and anti-inflammatory properties rest on the strongest preclinical foundations, supported by convergent data from multiple independent research groups using diverse model systems. The anti-thrombotic properties are well characterised mechanistically, with the seminal observation of antithrombin-mediated anticoagulation now replicated and extended across several studies. The lipid-modulating effects are appropriately rated as **emerging to limited** — consistent in direction across animal models but entirely lacking human clinical validation. No randomised controlled trial, crossover study, or even uncontrolled pilot study has evaluated *A. auricula-judae* polysaccharides as a standalone lipid-lowering intervention in human dyslipidaemia.

This evidence gap does not invalidate the inclusion of the extract in a multi-component formulation; rather, it reframes its contribution. The justification for *A. auricula-judae* rests on the provision of mechanistic pathways — antioxidant suppression of LDL oxidation, anti-inflammatory attenuation of vascular endothelial activation, anti-thrombotic reduction of coagulation and platelet aggregation risk, and prebiotic modulation of the gut–liver metabolic axis — that are not provided by the other formulation components. **A dedicated clinical trial evaluating the lipid-modulating effects of *A. auricula-judae* polysaccharides in human subjects represents an important evidence gap** that, if addressed, would substantially strengthen the scientific basis for this ingredient's inclusion in cardiovascular risk management strategies.

Table 4. Summary of *Auricularia auricula-judae* bioactivity studies

Author (Year)	Model System	Compound / Dose	Primary Finding	Mechanism	Evidence Level
Yoon et al. (2003) [123]	In vitro (human plasma); ex vivo (Sprague-Dawley rats, oral)	Acidic polysaccharide, ~160 kDa; 2 IU/mg	Anticoagulant activity; platelet aggregation inhibition comparable to aspirin	Antithrombin-mediated thrombin inhibition; glucuronic acid residues essential	Preclinical
Chen et al. (2008) [23]	ICR mice, cholesterol-enriched diet, 8 wk (n = 12/group)	HWE polysaccharide, 120 mg/kg/day oral gavage	Significant reduction in serum TC and LDL-C ($P < 0.05$); improved atherogenic index	↑ Lipoprotein lipase activity; ↑ total antioxidant capacity; ↓ MDA	Preclinical
Damte et al. (2011) [120]	RAW 264.7 macrophages, LPS-stimulated	DCM extract, 10–100 µg/mL	Dose-dependent inhibition of NO; reduced IL-6, TNF-α, IL-1β mRNA	Suppression of pro-inflammatory cytokine transcription	Preclinical
Zeng et al. (2013) [126]	Mice, high-fat-diet-induced hyperlipidaemia, 14–28 d	Purified polysaccharide (AAP-I), oral	Significant decrease in TC, TG, and LDL-C	Hypolipidaemic; mechanism not fully elucidated	Preclinical

Author (Year)	Model System	Compound / Dose	Primary Finding	Mechanism	Evidence Level
Perera et al. (2020) [121]	RAW 264.7 macrophages, LPS-activated	Glucuronoxylomannan (AAPS)	Endotoxin tolerance; ↓ NO, IL-6, TNF-α; ↑ phagocytosis	NF-κB downregulation; ROS, MAPKs, PKC-α modulation	Preclinical
Basso et al. (2020) [135]	RAW 264.7; dendritic cells; C57BL/6J mice (*C. neoformans* infection)	β-(1,3)-glucan EPS, oral	Macrophage/DC activation; M2→M1 repolarisation; enhanced survival in vivo	Dectin-1/Syk-dependent pathway	Preclinical
Bian et al. (2020) [125]	In vitro (human plasma coagulation assays)	Acidic polysaccharide (aAAP-1)	Prolonged aPTT, PT, and TT	Intrinsic and extrinsic coagulation pathway inhibition	Preclinical
Xiao et al. (2021) [117]	*C. elegans*; in vitro radical scavenging	Enzymatic polysaccharide (AAP3), 0.25 mg/mL	86% $ABTS^+$ scavenging; ↑ SOD, CAT; ↓ body fat and TG in *C. elegans*	↑ daf-16, skn-1 mRNA (Nrf2/FOXO orthologues)	Preclinical
Chen Y et al. (2021) [118]	In vitro; *C. elegans*	Melanin, 1 mg/mL	91.3% ABTS, 91.8% OH·, 85.7% O_2^- scavenging; extended lifespan	Radical scavenging; eumelanin structure	Preclinical
Xu et al. (2021) [133]	C57BL/6J mice, HFD + STZ-induced T2DM	Polysaccharide, 50–100 mg/kg/day	↓ Fasting blood glucose; ↓ inflammation; improved glycolipid metabolism	AKT/AMPK activation; ↑ *Lactobacillus*, *Bacteroides*	Preclinical
Bian et al. (2022) [124]	Carrageenan-induced thrombosis mouse model	Purified polysaccharide (AAP-b2), 12 kDa	↓ Black tail thrombus length; prolonged aPTT, PT, TT; ↓ platelet aggregation	eNOS, ET-1, PGI_2, TXB_2 regulation; AT-III/Protein C pathways	Preclinical
Liu Q et al. (2022) [24]	C57BL/6J mice, HFFD	AAP dietary supplementation	Improved insulin resistance; altered lipid metabolites; ↓ weight gain	↓ SREBP-1c; ↑ fatty acid β-oxidation genes; ↑ ABCA1/ABCG1	Preclinical
Zhou et al. (2023) [122]	Mice, high-fat-diet obesity	AAP, oral	↓ TNF-α, IL-6; improved endotoxaemia; protected intestinal barrier	TLR4/JNK inhibition; ↑ AKT, AMPK; ↑ *Lactobacillus*, *Roseburia*	Preclinical
Shu et al. (2023) [128]	C57BL/6J mice, NAFLD (HFC + CCl_4)	Polysaccharides and deacetylated derivatives	Alleviated liver injury, inflammation, fibrosis; maintained intestinal barrier	Gut microbiota modulation; FXR/bile acid metabolism; ↑ *Bifidobacterium*	Preclinical
Zong et al. (2023) [130]	C57BL/6J mice, HFD; FMT; pseudo-germ-free model	AAP, oral	↓ Weight gain; ↓ fat deposition; ↑ glucose tolerance	Microbiota-dependent: *P. cinnamivorans* ↓ intestinal lipid transport via JAK-STAT	Preclinical
Shi et al. (2024) [134]	STZ-induced diabetic mice	Polysaccharide acid hydrolysate, 100 mg/kg	↓ Blood glucose, ↓ serum lipids; ↑ GLP-1, insulin secretion	Glucokinase modulation; glutathione metabolism regulation	Preclinical
Wu et al. (2024) [127]	Mice, high-fat-diet	Polysaccharide, oral	↓ TC 20.3%, ↓ TG 23.8%; ↑ SCFA 119.4%; regulated 44 lipid biomarkers	Sphingolipid/AGE-RAGE pathways; gut microbiome remodelling	Preclinical

Author (Year)	Model System	Compound / Dose	Primary Finding	Mechanism	Evidence Level
Liu N et al. (2025) [131]	In vitro human faecal fermentation	AAP	Abundant SCFA production (acetic, propionic, butyric acid); ↑ Bacteroidetes/Firmicutes	Prebiotic fermentation; 26 metabolic biomarkers identified	Preclinical
Zhang et al. (2025) [132]	C57BL/6J mice, hepatic fibrosis	AAP, oral	↓ ECM deposition; anti-fibrotic; enhanced SCFA metabolism	NLRP3 inflammasome; TLR4/NF-κB; gut–liver axis (microbiota-dependent)	Preclinical

All studies listed above represent preclinical evidence (in vitro, *C. elegans*, or rodent models). No human randomised controlled trials evaluating *A. auricula-judae* polysaccharides as a standalone lipid-modulating agent have been published to date.

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§3.4 *Pleurotus ostreatus* polysaccharides (660 mg hot water extract, ≥30% polysaccharides)

Taxonomy, global significance, and nutritional profile

Pleurotus ostreatus (Jacq.) P. Kumm., commonly known as the oyster mushroom, is a white-rot basidiomycete classified within the phylum Basidiomycota, class Agaricomycetes, order Agaricales, and family Pleurotaceae [25,137]. The genus *Pleurotus* is among the most economically important groups of cultivated edible fungi worldwide, ranking second only to *Agaricus bisporus* in global production volume and occupying a central position in the culinary traditions of Europe, East Asia, South-east Asia, and the Americas [138]. The species is saprophytic and ligninolytic, colonising a broad spectrum of agricultural substrates including wheat straw, cotton-seed hulls, coffee pulp, and agro-industrial by-products, a versatility that has facilitated its rapid expansion across both industrial and small-holder cultivation systems [139].

From a nutritional standpoint, *P. ostreatus* fruiting bodies present an unusually favourable macronutrient composition for a fungal organism. Protein content ranges from approximately 19 to 35% on a dry-weight basis, with a complete essential amino acid profile; carbohydrate content—predominantly dietary fibre—constitutes 40–60% of dry mass, whereas lipid content remains low at 1–5% [138,140]. Beyond macronutrients, the fruiting bodies are notable reservoirs of micronutrients and bioactive small molecules. Cohen et al. (2014) reported that *P. ostreatus* fruiting bodies were among the richest mushroom sources of **ergothioneine** (2,444 µg g^{-1} dry weight) and γ-aminobutyric acid (GABA; 1,305 µg g^{-1}), alongside appreciable concentrations of B-group vitamins (particularly niacin, riboflavin, and pantothenic acid), ergosterol (the vitamin D_2 precursor), and the trace elements selenium and zinc [138]. The capacity of *Pleurotus* species to accumulate selenium from enriched substrates through biofortification has been independently confirmed, suggesting that cultivation conditions can be optimised to enhance micronutrient density [140,141]. This nutritional richness underpins the species' extensive ethnomycological history and, more recently, its growing recognition as a functional food ingredient.

For the purposes of the AURI 25 formulation, the distinguishing pharmacological attribute of *P. ostreatus* is its **dual mechanistic contribution** to cholesterol homeostasis. The species simultaneously provides (i) natural lovastatin—an endogenous HMG-CoA reductase inhibitor

identical to the monacolin K reviewed in The monacolin K profile—and (ii) β-glucan polysaccharides (pleuran) capable of binding bile acids in the intestinal lumen. This convergence of a cholesterol synthesis inhibitor and an absorption inhibitor within a single botanical extract is pharmacologically noteworthy and constitutes the principal rationale for the inclusion of *P. ostreatus* in AURI 25.

The natural lovastatin discovery and its quantitative variability

The landmark observation that *Pleurotus* fruiting bodies contain lovastatin was made by Gunde-Cimerman and Cimerman in a series of studies conducted in the early 1990s. In their initial report, these investigators demonstrated through thin-layer chromatography, high-performance liquid chromatography, and mass spectrometry that crude methanol extracts from *P. ostreatus*, *P. sapidus*, and *P. saca* mycelium contained mevinolin (lovastatin), and that these extracts competitively inhibited solubilised microsomal HMG-CoA reductase from Chinese hamster ovary cells [142]. A subsequent study extended this finding to the fruiting body itself, tracking lovastatin accumulation through successive developmental stages—vegetative mycelium, primordia, and mature sporocarps—and demonstrating that concentrations were generally higher in pilei than in stipes, with lower amounts detected in lamellae and basidiospores [25]. These discoveries established that *P. ostreatus* is a natural biological source of the same pharmacophore used in one of the most widely prescribed classes of cardiovascular medications.

The lovastatin content of *P. ostreatus* is, however, subject to pronounced variability. Strain genotype, growth substrate, developmental stage, and post-harvest processing all exert significant influence. Piskov et al. (2018) compared freeze-dried and convection-dried *P. ostreatus* material and reported lovastatin concentrations of **342 ± 9 mg kg⁻¹** and **190 ± 6 mg kg⁻¹** dry weight, respectively, illustrating that thermal processing alone can halve the recovered statin content [143]. Tsiantas et al. (2021), employing validated LC-MS methodology, found that substrate composition critically influenced lovastatin yield, with *P. ostreatus* grown on grape marc–wheat straw mixtures achieving the highest levels among the substrates tested [144]. Conversely, Lam and Okello (2015) reported undetectable lovastatin in commercially sourced *P. ostreatus* from UK retail outlets, underscoring that not all market-available material can be assumed to contain pharmacologically relevant quantities [145]. Krakowska et al. (2020) confirmed this heterogeneity across six *Pleurotus* species, noting that mycelia from in vitro culture frequently contained higher lovastatin concentrations than corresponding fruiting bodies [141].

These data carry two implications for the AURI 25 formulation. First, the **660 mg hot water extract standardised to ≥30% polysaccharides** cannot be assumed to deliver a precisely quantified lovastatin dose without specific analytical verification. Hot water extraction preferentially solubilises polysaccharides and water-soluble compounds, and lovastatin—being a moderately lipophilic lactone—may partition only partially into the aqueous phase. Nevertheless, even trace quantities of lovastatin in the extract provide an additional biological source of HMG-CoA reductase inhibition beyond the 2.9 mg monacolin K delivered by the red yeast rice component (The monacolin K profile). The total HMG-CoA reductase inhibitory load in AURI 25 therefore derives from **two independent biological sources**—a pharmacological redundancy that may confer robustness to the cholesterol synthesis-blocking arm of the formulation [139].

β-Glucan composition: pleuran as a structurally distinct polysaccharide

The polysaccharide fraction of *P. ostreatus* is dominated by pleuran, an insoluble β-1,3/1,6-D-glucan whose structural characteristics differ substantively from the cereal β-glucans for which regulatory health claims have been established [26,146]. Vetter (2023) reviewed the structural biology of mushroom glucans and described pleuran as a high-molecular-weight polymer (10^4–10^6 Da) with a β-1,3-linked glucose backbone carrying β-1,6-linked glucose side chains at regular intervals, a branching pattern that favours triple-helical conformations in solution [26]. This architecture contrasts with oat and barley β-glucans, which consist of β-1,3 and β-1,4 linkages in a linear, unbranched chain and which rely principally on high molecular weight and viscosity for their physiological effects [146,147]. Cerletti et al. (2021) explicitly compared these two classes, noting that the β-1,6 branching of fungal glucans confers distinct receptor-binding properties relevant to immunomodulation (discussed in The Pleurotus profile.6), whereas both classes share the capacity to increase luminal viscosity and interact with bile acids [146].

The β-glucan content of *P. ostreatus* fruiting bodies is notably high. Belobrajdic et al. (2024) reported that freeze-dried oyster mushrooms contained **32.5–37.4 g β-glucan per 100 g**—approximately five-fold greater than *Agaricus bisporus* (4.5–8.1 g per 100 g) and markedly exceeding the 7.6 g per 100 g measured in raw oats [148]. For the AURI 25 extract, the ≥30% polysaccharide standardisation ensures that the 660 mg dose delivers a minimum of approximately **198 mg total polysaccharides**, of which a substantial proportion is expected to comprise pleuran. While this quantity falls well below the 3 g day^{-1} threshold established for oat β-glucan health claims by EFSA and the FDA [147,149], the mechanistic pathway—bile acid binding in the intestinal lumen—operates on the same pharmacological principle and contributes an absorption-blocking mechanism that complements the synthesis-blocking activity of monacolin K and endogenous lovastatin.

Mechanism 1: HMG-CoA reductase inhibition via natural lovastatin

The mechanism by which natural lovastatin from *P. ostreatus* inhibits cholesterol biosynthesis is identical to that described for monacolin K in The monacolin K profile, as the two compounds are the same molecule. In its active hydroxy-acid form, lovastatin binds the active site of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase—the rate-limiting enzyme catalysing the conversion of HMG-CoA to mevalonate—with nanomolar affinity, acting as a competitive inhibitor that mimics the tetrahedral intermediate of the natural substrate [139]. Sadowska et al. (2023) traced the history of statin pharmacology from the initial isolation of mevastatin from *Penicillium citrinum* through the development of lovastatin from *Aspergillus terreus* and noted that the HMG-CoA-like moiety shared by all natural statins is responsible for their competitive binding at the reductase active site [139]. Wongkhieo et al. (2023) demonstrated in a liver-spheroid model that crude mushroom extracts containing lovastatin exhibited HMG-CoA reductase inhibitory activity and, notably, enhanced HDL production to a greater degree than equimolar pure lovastatin, suggesting that co-extracted bioactive compounds may exert synergistic effects [150].

For the AURI 25 formulation, the practical significance is that any lovastatin present in the *P. ostreatus* hot water extract adds incrementally to the **2.9 mg monacolin K** from red yeast rice, creating a combined HMG-CoA reductase inhibitory input from two phylogenetically unrelated fungal sources. While the absolute lovastatin contribution from 660 mg of extract is likely modest—substantially below the 20–40 mg therapeutic doses used in pharmaceutical lovastatin prescriptions—the addition operates on the steep portion of the dose–response curve where even small increments in enzyme occupancy can translate to measurable

reductions in hepatic cholesterol synthesis.

Mechanism 2: bile acid binding and cholesterol absorption inhibition

The second and arguably more consequential mechanism contributed by *P. ostreatus* polysaccharides is the binding of bile acids within the intestinal lumen, thereby disrupting the enterohepatic circulation of cholesterol. This mechanism is pharmacologically analogous to the action of bile acid sequestrant drugs (cholestyramine, colesevelam) and operates independently of HMG-CoA reductase inhibition [146,151]. Naumann et al. (2020) reviewed the mechanisms by which dietary fibres including β-glucans interact with bile acids and concluded that the primary mode of action involves **viscosity-mediated entrapment**: soluble and gel-forming polysaccharides increase the viscosity of the intestinal chyme, reducing the diffusion and micellar mobility of bile acids and thereby diminishing their reabsorption in the terminal ileum [151]. As a consequence, bile acids are lost in faecal excretion, and the liver compensates by upregulating the conversion of cholesterol to new bile acids via the classical (CYP7A1-mediated) pathway, producing a net reduction in circulating cholesterol.

Direct evidence for bile acid binding by *Pleurotus* polysaccharides was provided by Palanisamy et al. (2014), who used pressurised water extraction to obtain β-glucan-enriched fractions from *P. ostreatus*, *Lentinula edodes*, and *Agaricus bisporus* and demonstrated that certain fractions exhibited bile acid binding capacities comparable to those of cereal-derived β-glucans [152]. Belobrajdic et al. (2024) extended this monograph with a rigorous in vitro comparison, finding that while oyster mushroom β-glucan content (32.5–37.4%) far exceeded that of oats (7.6%), the bile acid binding capacity of raw oyster mushroom material (22%) was somewhat lower than that of raw oats (36%) [148]. Notably, however, thermal processing—boiling and frying—significantly increased the bile acid binding capacity of the mushroom material, a finding directly relevant to the hot water extraction process used in manufacturing the AURI 25 ingredient [148]. Schlörmann et al. (2021) further demonstrated that all β-glucan sources tested, regardless of origin, reduced bile acid concentrations in fermentation supernatants, although oat β-glucan exhibited the highest absolute cholesterol-binding capacity (65.9 ± 8.8 mg g^{-1}) [153].

The strategic importance of this mechanism within the AURI 25 formulation cannot be overstated. The combination of monacolin K (blocking cholesterol synthesis via HMG-CoA reductase) with *P. ostreatus* β-glucan (blocking cholesterol absorption via bile acid sequestration) **recapitulates the dual-pathway principle** validated in the landmark IMPROVE-IT trial, in which the addition of ezetimibe (an absorption inhibitor) to simvastatin (a synthesis inhibitor) produced a statistically significant reduction in cardiovascular events beyond statin monotherapy. While the doses and potencies in AURI 25 are of course far lower than those employed in IMPROVE-IT, the mechanistic logic—simultaneous attenuation of both cholesterol synthesis and cholesterol reclamation from the gut—is pharmacologically sound and represents the formulation's most distinctive design feature (see §4 (the synergy analysis) for integrative pathway analysis).

Mechanism 3: gut microbiome modulation and short-chain fatty acid production

Beyond their direct physicochemical interaction with bile acids, *P. ostreatus* polysaccharides exert prebiotic effects that indirectly influence lipid metabolism through modulation of the colonic microbiome. Andrade et al. (2024) subjected digested *P. ostreatus* powder to in vitro colonic fermentation using human faecal inocula and observed significant increases in *Bifidobacterium* spp. and *Lactobacillus* spp. (from 1.12% to 4.83% relative abundance),

Faecalibacterium spp. (0.59% to 1.85%), and *Akkermansia muciniphila* (0.37% to 1.88%), accompanied by enhanced production of lactic acid and short-chain fatty acids (SCFAs) [154]. Saxami et al. (2023) confirmed that *P. ostreatus* fermentation promoted *Bifidobacterium* proliferation and elevated butyrate concentrations after 24 hours of incubation [155]. In an in vivo context, Hu et al. (2022) demonstrated that *P. ostreatus* supplementation in high-fat-diet-fed mice ameliorated obesity, beneficially restructured the gut microbiota, and upregulated bile acid biosynthesis pathways—linking prebiotic effects directly to cholesterol elimination [156].

The SCFA profile generated by *P. ostreatus* polysaccharide fermentation is of particular mechanistic interest. Zavadinack et al. (2023) isolated β-1,3/1,6-glucans from *Pleurotus pulmonarius* with varying degrees of branching and solubility and showed that these structural variants produced distinct SCFA ratios, with propionate comprising 28.5–30.3% of total SCFAs [157]. Propionate is a well-characterised activator of AMP-activated protein kinase (AMPK) in hepatocytes, and its generation in the colon thus provides an indirect route to the same AMPK-mediated metabolic effects discussed in the context of policosanol (The policosanol profile). This mechanistic convergence—whereby the *P. ostreatus* prebiotic effect feeds into the AMPK signalling axis also targeted by policosanol—adds a further dimension of pathway integration within the AURI 25 formulation. The prebiotic profile of *P. ostreatus* may also complement that of *Auricularia auricula-judae* (The Auricularia profile), as the two species contribute structurally distinct polysaccharides (β-1,3/1,6-glucan versus β-1,3-glucan with mannose and xylose side chains) that are likely to be fermented by partially overlapping but non-identical microbial consortia, potentially broadening the overall prebiotic coverage.

Mechanism 4: immunomodulatory and anti-inflammatory activity

The β-1,3/1,6-glucan structure of pleuran is recognised by pattern-recognition receptors on innate immune cells, most notably **Dectin-1** (CLEC7A) and **complement receptor 3** (CR3; CD11b/CD18). Vetvicka et al. (2019) demonstrated that glucans extracted from *P. eryngii* competed with anti-Dectin-1 and anti-CR3 antibodies for binding, confirming dual receptor engagement, and that these glucans ameliorated dextran sodium sulphate–induced inflammatory bowel disease in a murine model by downregulating intestinal pro-inflammatory cytokines [158]. Ellefsen et al. (2023) showed that alkali-soluble β-glucans from *P. eryngii* fruiting bodies bound human Dectin-1a and activated Toll-like receptor 2 (TLR2)–TLR6 heterodimers, identifying a further immune-signalling pathway through which *Pleurotus* polysaccharides modulate innate immunity [159]. Downstream, these receptor interactions converge on NF-κB-dependent transcriptional programmes. Zhang et al. (2023) demonstrated that *Pleurotus* polysaccharides inhibited NF-κB and STAT3 signalling in a hyperlipidaemic rat model, reducing hepatic levels of tumour necrosis factor-α (TNF-α), interleukin-1β (IL-1β), IL-6, and IL-17A while increasing the anti-inflammatory cytokine IL-10 [160].

The immunomodulatory properties of pleuran have been most extensively characterised in the clinical programme led by Jesenak and colleagues in Slovakia. In a double-blind, placebo-controlled randomised trial involving 175 children with recurrent respiratory tract infections (RRTIs), oral pleuran significantly increased the proportion of infection-free children (36% versus 21% in the placebo group; $p < 0.05$) and modulated both humoral and cellular immune parameters [161]. A subsequent large-scale, multicentre, open-label study across seven countries enrolled 1,030 children and confirmed a significant reduction in total RTI frequency (from 7.07 ± 2.89 to 3.87 ± 3.19 episodes per year; $p < 0.001$), with a favourable safety profile [162]. While these immunological studies were not designed to assess

cardiometabolic endpoints, the anti-inflammatory activity of pleuran is relevant to the broader cardiovascular context, given that chronic low-grade inflammation is a recognised driver of atherosclerotic progression and that NF-κB activation in hepatocytes contributes to the metabolic dysfunction associated with non-alcoholic fatty liver disease (NAFLD).

Mechanism 5: hepatoprotective effects

Preclinical evidence suggests that *P. ostreatus* extracts confer hepatoprotective effects that extend beyond lipid-lowering per se. Dubey et al. (2023) administered aqueous *P. ostreatus* extract (250 and 500 mg kg⁻¹ body weight) to streptozotocin-induced diabetic rats and observed dose-dependent reversal of histopathological liver damage, including resolution of hepatic sinusoidal dilation, Kupffer cell proliferation, and necrosis [163]. Maheshwari et al. (2020) supplemented the diet of obese Zucker rats with 5% biotechnologically produced *Pleurotus sajor-caju* material and reported significant reductions in hepatic lipid accumulation and liver inflammation, demonstrating **anti-steatotic and anti-inflammatory effects** mediated through altered hepatic gene expression [27]. These findings, while confined to animal models, suggest that the polysaccharide and bioactive fractions of *Pleurotus* may attenuate the hepatic fat accumulation and inflammatory milieu characteristic of NAFLD—a condition that frequently coexists with the dyslipidaemia targeted by AURI 25.

Clinical evidence in human studies

The clinical evidence base for *P. ostreatus* as a lipid-modifying intervention was comprehensively appraised in a PRISMA-compliant systematic review by Dicks and Ellinger (2020), which identified eight clinical trials published across seven articles [164]. All eight trials reported beneficial effects on at least one index of glucose metabolism, and most observed reductions in total cholesterol, LDL-cholesterol, and/or triglycerides; HDL-cholesterol was unchanged across all studies [164]. However, the reviewers rated the **overall evidence quality as low**, primarily owing to small sample sizes, absence of blinding in most studies, lack of a priori sample size calculations, and the predominantly uncontrolled or non-randomised designs employed.

Among the trials identified, several merit individual discussion. Khatun et al. (2007) conducted a self-controlled study in 30 Bangladeshi patients with type 2 diabetes mellitus who consumed 150 g day⁻¹ of cooked *P. ostreatus* over two 7-day periods separated by a 7-day washout. Reductions in fasting plasma glucose (22–23%), total cholesterol (8–13%), and triglycerides (9–28%) were observed during mushroom-feeding periods, with partial reversal during washout [165]. While the magnitude of these effects was striking, the design lacked a separate control group, precluded blinding, and suffered a 66% dropout rate, severely limiting the confidence that can be placed in the results. Kajaba et al. (2008) administered 10 g day⁻¹ of lyophilised *P. ostreatus* powder to patients with combined dyslipidaemia in Slovakia and reported reductions in triglycerides of 36%, total cholesterol of 22%, and the total cholesterol/HDL-cholesterol ratio of 24% over six weeks, alongside favourable changes in antioxidant markers [166]. Again, however, the absence of a control group and blinding limits interpretability.

The only properly controlled randomised trial included in the Dicks and Ellinger review was that of Schneider et al., which randomised young adults with moderate untreated hyperlipidaemia to a soup providing 30 g day⁻¹ of lyophilised *P. ostreatus* or a mushroom-free tomato soup control for three weeks. Triglycerides decreased by 23% in the mushroom group while increasing by 25% in controls, yielding a statistically significant between-group

difference, though no significant changes in total or LDL-cholesterol were observed [164]. Notably, lovastatin was undetectable in the mushroom material used, suggesting that the lipid effects were attributable to the polysaccharide fraction rather than endogenous statin activity.

Subsequent to the systematic review, Dicks et al. (2022) published the highest-quality individual study identified in the literature: a double-blind, randomised, controlled crossover trial in 22 adults with impaired glucose tolerance. A single test meal fortified with 20 g of oven-dried *P. ostreatus* powder (providing 8.1 g of β-glucans) did not acutely alter postprandial glucose, insulin, or triglyceride concentrations relative to a control meal but significantly increased GLP-1 area under the curve by 17% ($p = 0.001$), decreased non-esterified fatty acids by 14% ($p = 0.026$), and reduced hunger sensation by 22% ($p = 0.031$) [167]. While this acute-feeding design cannot address chronic lipid outcomes, the GLP-1-stimulating effect is mechanistically relevant, as incretin signalling influences hepatic lipid metabolism and insulin sensitivity.

Jayasuriya et al. (2015) studied the hypoglycaemic activity of freeze-dried *P. ostreatus* at 50 mg kg^{-1} body weight in both healthy volunteers and type 2 diabetic patients in Sri Lanka, observing significant reductions in fasting glucose (6% after 14 days of chronic intake) and 2-hour post-oral-glucose-tolerance-test values (15–16% reduction) [168]. González-Bonilla et al. (2022) conducted a randomised trial in a rural Mexican community (n = 30), administering 1 kg per week of fresh *P. ostreatus* alongside a healthy diet for three months; the mushroom group demonstrated reductions in visceral fat, triglycerides, total cholesterol, and glucose compared with a diet-only control, though the small sample and dietary confounding temper the conclusions [169].

The HIV-associated dyslipidaemia study by Abrams et al. (2011) warrants specific mention, as it represents one of the few studies employing a defined *P. ostreatus* dose (15 g day^{-1} of freeze-dried material for eight weeks) in a population with pronounced lipid disturbances (non-HDL-cholesterol >160 mg dL^{-1} due to antiretroviral therapy). The primary endpoint—reduction in non-HDL-cholesterol—was not met, with a mean change of only −1.70 mg dL^{-1} (95% CI: −17.4, 14.0) [170]. Triglycerides showed a statistically significant but clinically modest decrease (−63.0 mg dL^{-1}; 95% CI: −120.9, −5.1). Importantly, **no adverse effects were recorded**, and hepatic and muscle enzyme profiles remained normal throughout, supporting the safety of high-dose *P. ostreatus* consumption [170]. A broader systematic review by Uffelman et al. (2023), encompassing all mushroom species and both experimental and observational studies, concluded that limited evidence supports mushroom consumption for reducing triglycerides and high-sensitivity C-reactive protein but found insufficient evidence for effects on other lipid parameters [171].

Table 5. Summary of *Pleurotus ostreatus* evidence for cardiometabolic outcomes

Author, Year	Model/Design	n	Compound/Dose	Key Finding	Proposed Mechanism	Evidence Level
Gunde-Cimerman & Cimerman, 1995 [25]	In vitro / analytical	—	Fruiting body methanol extract	Lovastatin identified in *P. ostreatus*; inhibits HMG-CoA reductase	HMG-CoA reductase competitive inhibition	Preclinical

Author, Year	Model/Design	n	Compound/Dose	Key Finding	Proposed Mechanism	Evidence Level
Belobrajdic et al., 2024 [148]	In vitro digestion model	—	Freeze-dried *Pleurotus* spp.	β-Glucan content 32.5–37.4%; bile acid binding 22% (raw), increased with cooking	Bile acid sequestration	Preclinical
Palanisamy et al., 2014 [152]	In vitro	—	β-Glucan-enriched fractions, PWE	Bile acid binding comparable to cereal β-glucans	Bile acid binding	Preclinical
Hu et al., 2022 [156]	HFD mice	—	*P. ostreatus* diet supplementation	Ameliorated obesity; modulated gut microbiota and bile acid pathways	Prebiotic / bile acid modulation	Preclinical
Maheshwari et al., 2020 [27]	Obese Zucker rats	—	5% *P. sajor-caju* diet	Reduced hepatic lipids and liver inflammation	Anti-steatotic; hepatic gene modulation	Preclinical
Dubey et al., 2023 [163]	STZ-diabetic rats	—	Aqueous extract, 250–500 mg kg^{-1}	Reversed hepatic histopathological damage	Hepatoprotective	Preclinical
Zhang et al., 2023 [160]	Hyperlipidaemic rats	—	*Pleurotus* polysaccharide PAPS1	Reduced hepatic TNF-α, IL-1β, IL-6; inhibited NF-κB/STAT3	Anti-inflammatory	Preclinical
Khatun et al., 2007 [165]	Self-controlled; T2DM	30	150 g day^{-1} cooked *P. ostreatus*, 2 × 7 d	TC ↓8–13%, TG ↓9–28%, FPG ↓22–23%	Multiple (fibre, lovastatin)	Clinical (low quality)
Kajaba et al., 2008 [166]	Uncontrolled; dyslipidaemia	—	10 g day^{-1} lyophilised powder, 6 wk	TC ↓22%, TG ↓36%, TC/HDL ratio ↓24%	Multiple	Clinical (low quality)
Abrams et al., 2011 [170]	Open-label Phase I/II; HIV/ART	20	15 g day^{-1} freeze-dried, 8 wk	Non-HDL-C unchanged; TG ↓63 mg dL^{-1}; safe	Multiple	Clinical (low quality)
Jayasuriya et al., 2015 [168]	Multiple sub-studies; healthy + T2DM	—	50 mg kg^{-1} lyophilised	FPG ↓6%, 2h-PG ↓15–16%	Polysaccharide, fibre	Clinical (moderate)
Dicks & Ellinger, 2020 [164]	Systematic review	8 trials	Various whole mushroom interventions	Beneficial glucose effects; lipid improvements in most; quality low	—	SR (low quality evidence)
González-Bonilla et al., 2022 [169]	RCT; rural community	30	1 kg wk^{-1} fresh *P. ostreatus*, 3 mo	↓Visceral fat, TG, TC, glucose (women)	Multiple	Clinical (moderate)
Dicks et al., 2022 [167]	DB-RCT crossover; IGT	22	20 g powder (8.1 g β-glucan), single meal	GLP-1 ↑17%, NEFAs ↓14%; no acute glucose/TG change	GLP-1 secretion, bile acid interaction	Clinical (high quality, acute)

Abbreviations: DB, double-blind; FPG, fasting plasma glucose; HFD, high-fat diet; IGT, impaired glucose tolerance; NEFA, non-esterified fatty acid; PWE, pressurised water extraction; RCT, randomised controlled trial; SR, systematic review; STZ, streptozotocin; T2DM, type 2 diabetes mellitus; TC, total cholesterol; TG, triglycerides.

Comparison with EFSA- and FDA-approved β-glucan health claims

The regulatory landscape for β-glucan cholesterol claims is presently dominated by cereal-derived polysaccharides. The European Food Safety Authority authorised a health claim (Commission Regulation EU 432/2012) stating that oat β-glucan contributes to the maintenance of normal blood cholesterol concentrations, with the beneficial effect obtained at a daily intake of 3 g of oat β-glucan [147]. The US Food and Drug Administration similarly permits a qualified health claim for soluble fibre from oat β-glucan at 3 g day⁻¹ in relation to coronary heart disease risk [149]. A meta-analysis of 28 randomised controlled trials by Whitehead et al. (2014) confirmed that **≥3 g day⁻¹ of oat β-glucan** reduced LDL-cholesterol by 0.25 mmol L⁻¹ and total cholesterol by 0.30 mmol L⁻¹ versus control, providing the quantitative basis for these regulatory positions [147].

Crucially, these approved claims pertain exclusively to cereal β-glucans, which possess β-1,3/1,4 linkages and a linear, unbranched structure [146,149]. Fungal β-glucans from *P. ostreatus*—with their β-1,3/1,6-linked, branched architecture—represent a structurally distinct class. Cerletti et al. (2021) identified this as a regulatory gap, noting that while mushroom β-glucans share the mechanistic capacity for bile acid binding with their cereal counterparts, the specific clinical evidence required for a health claim extension has not yet been generated [146]. Belobrajdic et al. (2024) provided the first head-to-head in vitro comparison of mushroom and oat β-glucan bile acid binding, finding that while raw oyster mushroom had lower binding capacity than oats despite five-fold greater β-glucan content, the gap narrowed substantially after thermal processing [148]. The ≥30% polysaccharide standardisation of the AURI 25 *P. ostreatus* extract, combined with hot water extraction processing, positions the ingredient in a mechanistic space analogous to—though not yet regulatory-equivalent to—the oat β-glucan paradigm.

Safety profile

Pleurotus ostreatus enjoys an extensive safety record grounded in centuries of culinary consumption across multiple continents. No significant toxicity has been identified in either preclinical or clinical investigations. In the Abrams et al. (2011) trial, 15 g day⁻¹ of freeze-dried material over eight weeks produced no adverse events and no perturbations in hepatic transaminases or creatine kinase [170]. The Jesenak clinical programme, encompassing over 1,500 paediatric subjects across multiple randomised and observational studies, consistently reported favourable tolerability, with the 2022 multicentre study of 1,030 children confirming a beneficial safety profile [162]. The most recent double-blind RCT of pleuran in 249 children documented 98.7% compliance with only mild adverse events and no treatment-related serious adverse events [171].

Regarding the natural lovastatin content, the levels present in hot water extracts at the 660 mg daily dose are expected to fall substantially below the pharmacological threshold associated with statin-related adverse effects (myopathy, hepatotoxicity), which typically emerge at doses of 20–80 mg day⁻¹ of pharmaceutical lovastatin. Rare allergic reactions to *Pleurotus* spores have been reported in occupational settings (mushroom cultivation workers), but these are related to inhalational exposure and are not relevant to oral extract consumption. No clinically significant drug interactions specific to *P. ostreatus* polysaccharide extracts have been documented, though the theoretical possibility of additive statin effects with concomitant pharmaceutical statin use merits mention, particularly given the natural lovastatin content.

Evidence quality assessment and formulation rationale

Applying the evidence evaluation framework established in The evidence framework used in the source publication, the overall evidence supporting *P. ostreatus* for lipid modification is rated as **limited to moderate**. The natural lovastatin component rests on solid mechanistic ground: lovastatin is a proven molecule acting on a proven target (HMG-CoA reductase), and its identity in *P. ostreatus* has been confirmed through multiple validated analytical methods [25,142,144]. However, the variability of lovastatin content across strains and extraction methods, and the lack of specific quantification in the AURI 25 extract, introduces uncertainty regarding the magnitude of the statin contribution. The β-glucan bile acid binding mechanism is similarly well established at the mechanistic level, supported by in vitro data specific to *Pleurotus* species [148,152] and by the strong parallel to EFSA- and FDA-approved claims for oat β-glucans [147], but direct clinical validation for fungal β-glucans at the dose employed in AURI 25 is lacking.

Human clinical evidence exists but remains limited in volume and quality. The Dicks and Ellinger (2020) systematic review identified consistent directional effects across eight trials but rated all at high or unclear risk of bias [164]. More recent, higher-quality studies—particularly the Dicks et al. (2022) double-blind crossover trial—provide mechanistic proof-of-concept (GLP-1 stimulation, NEFA reduction) without yet demonstrating chronic lipid-lowering in a robust design [167]. The clinical evidence for *P. ostreatus* is thus more substantial than that available for *Auricularia auricula-judae* (The Auricularia profile), for which no systematic review exists, but less extensive than the evidence supporting monacolin K at 3 mg day⁻¹ (The monacolin K profile), which benefits from EFSA-authorised health claims.

Notwithstanding these limitations, the **dual-mechanism contribution** of *P. ostreatus* constitutes the strongest argument for its inclusion in the AURI 25 formulation. No other single ingredient in the formulation simultaneously targets both cholesterol synthesis (via HMG-CoA reductase inhibition) and cholesterol reclamation from the gut (via bile acid sequestration). This convergence aligns with the established clinical principle—exemplified by the statin-plus-ezetimibe combination in IMPROVE-IT—that attacking complementary nodes in cholesterol homeostasis yields outcomes superior to single-pathway interventions. The additional contributions of *P. ostreatus* to gut microbiome modulation, SCFA-mediated AMPK activation, NF-κB–dependent anti-inflammatory signalling, and hepatoprotection further enrich the mechanistic portfolio of the formulation, positioning this ingredient as a multifunctional node in the integrated pathway architecture of AURI 25.

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§ 4 MULTI-PATHWAY SYNERGY ANALYSIS

§4.1 An integrated multi-pathway model for multi-target lipid and vascular risk management

The preceding compound-level reviews (the constituent profiles) established the individual pharmacological profiles of policosanol, monacolin K from red yeast rice (RYR), *Auricularia auricula-judae*, and *Pleurotus ostreatus*. Each constituent possesses a distinct primary mechanism of action, supported by evidence that ranges from robust randomised controlled trials to emerging preclinical data. Taken individually, however, none of these compounds addresses the full spectrum of modifiable cardiovascular risk factors. The central proposition of this analysis is that the AURI 25 formulation engages **parallel mechanistically independent biological pathways**—cholesterol biosynthesis inhibition, cholesterol absorption reduction, vascular protection beyond lipid lowering, and gut–liver axis modulation—that collectively offer a breadth of pharmacological coverage exceeding any single-pathway intervention. This multi-pathway framework does not presuppose demonstrated synergism for the specific multi-component combination; rather, it articulates the mechanistic rationale upon which additive or potentially synergistic interactions may be hypothesised and subsequently tested.

Pathway 1 — Cholesterol biosynthesis inhibition at HMG-CoA reductase. Three distinct molecular inputs converge upon the rate-limiting enzyme of the mevalonate pathway. Monacolin K, reviewed in The monacolin K profile, provides direct competitive inhibition of HMG-CoA reductase—the identical mechanism employed by all prescription statins. *Pleurotus ostreatus*, as detailed in The Pleurotus profile, contributes additional naturally occurring lovastatin, thereby supplementing competitive enzyme blockade from a second botanical source. Policosanol (The policosanol profile) is proposed to engage the same enzyme through a fundamentally different pharmacological approach: AMPK-mediated phosphorylation of HMG-CoA reductase at Ser872, which inactivates the enzyme through post-translational modification rather than active-site competition. The convergence of **two mechanistically distinct approaches**—competitive inhibition and allosteric inactivation via kinase-mediated phosphorylation—upon a single molecular target represents a pharmacologically rational design. In principle, competitive inhibition reduces the pool of active enzyme available for catalysis, while phosphorylation-dependent inactivation reduces the total fraction of enzyme in the active dephosphorylated state; these two mechanisms are not mutually exclusive and could operate simultaneously without pharmacodynamic antagonism.

Pathway 2 — Cholesterol absorption inhibition via bile acid sequestration. Entirely independent of hepatic cholesterol synthesis, this pathway operates within the intestinal lumen. The high-molecular-weight β-glucans (pleuran) of *Pleurotus ostreatus* form viscous gel matrices in the gastrointestinal tract that physically entrap bile acids, reducing their enterohepatic recirculation. *In vitro* studies of cereal β-glucans have demonstrated bile acid binding capacities of **15–27%** relative to the pharmaceutical sequestrant cholestyramine, with binding efficiency modulated by molecular weight and viscosity [172]. The consequent hepatic depletion of the bile acid pool upregulates cholesterol 7α-hydroxylase (CYP7A1), diverting intracellular cholesterol toward *de novo* bile acid synthesis and thereby reducing circulating LDL-cholesterol. The dietary fibre fraction of *Auricularia auricula-judae* polysaccharides contributes additional bile acid interaction capacity within the intestinal lumen, although

direct bile acid binding data for this specific species remain limited (The Auricularia profile). Crucially, this pathway's anatomical and biochemical independence from Pathway 1—operating in the gut rather than the liver, and affecting cholesterol reabsorption rather than synthesis—ensures that any effect is mechanistically additive to hepatic HMG-CoA reductase inhibition.

Pathway 3 — Direct lipid modulation, LDL oxidation prevention, and vascular protection. This pathway encompasses the cholesterol-modulating, antioxidant, anti-inflammatory, and anti-thrombotic activities contributed primarily by *Auricularia auricula-judae* and policosanol. Beyond the antioxidant and anti-inflammatory properties reviewed in The Auricularia profile, *A. auricula-judae* polysaccharides demonstrate direct cholesterol-lowering activity in preclinical models through multiple documented mechanisms: upregulation of ABCA1/ABCG1 transporters that promote cholesterol efflux from macrophages, downregulation of hepatic SREBP-1c lipogenic gene expression that suppresses de novo lipid synthesis, and enhanced lipoprotein lipase activity that accelerates triglyceride-rich lipoprotein clearance (The Auricularia profile). The species additionally improves insulin sensitivity via AKT/AMPK signalling — a metabolically significant pathway, as insulin resistance directly drives hepatic VLDL overproduction and the atherogenic dyslipidaemia pattern. Its polysaccharide and melanin fractions attenuate the oxidative modification of LDL particles, its anti-inflammatory activity through NF-κB pathway modulation suppresses the pro-inflammatory cytokines TNF-α and IL-6 that sustain atherosclerotic plaque progression, and its antithrombin-mediated anticoagulant activity — demonstrated at potency comparable to aspirin — addresses thrombotic risk through a mechanism distinct from the TXA_2-mediated platelet inhibition contributed by policosanol (The policosanol profile). Pathway 3 thus targets cholesterol efflux, hepatic lipogenesis, insulin-driven dyslipidaemia, oxidative stress, vascular inflammation, and platelet hyperactivity — dimensions of cardiovascular risk that persist even when LDL-cholesterol has been pharmacologically optimised.

Pathway 4 — Gut–liver axis modulation through prebiotic mechanisms. Both mushroom species contribute high-molecular-weight polysaccharides that resist human digestive enzymes and reach the colon structurally intact, where they serve as fermentable substrates for commensal bacteria [173,174]. Colonic fermentation yields short-chain fatty acids (SCFAs)—principally acetate, propionate, and butyrate—that exert systemic metabolic effects extending well beyond the gastrointestinal tract. Propionate and butyrate have been demonstrated to activate AMP-activated protein kinase (AMPK) in hepatocytes through a PPARγ→UCP2-mediated reduction in intracellular ATP, establishing a direct signalling conduit from gut microbiota to hepatic lipid metabolism [175]. AMPK activation phosphorylates acetyl-CoA carboxylase (ACC), suppressing *de novo* lipogenesis while simultaneously promoting fatty acid β-oxidation. This pathway further intersects with bile acid metabolism, as microbial remodelling alters the secondary bile acid pool and modulates farnesoid X receptor (FXR) and Takeda G-protein-coupled receptor 5 (TGR5) signalling, influencing hepatic cholesterol handling and glucose homeostasis [176]. Pathway 4 thus represents an indirect but biologically plausible route through which prebiotic polysaccharides from both *Auricularia* and *Pleurotus* influence systemic lipid metabolism—a mechanism increasingly recognised as clinically relevant in the emerging field of cardio-metabolic microbiome research.

Table 6. The multi-pathway synergy model of the AURI 25 formulation.

Pathway	Biological target	Primary compound(s) in AURI 25	Mechanism of action	Evidence level	Pharmaceutical analogue
1. Cholesterol synthesis inhibition	HMG-CoA reductase (hepatic)	Monacolin K (2.9 mg); *Pleurotus* natural lovastatin; Policosanol (AMPK-mediated)	Competitive inhibition (monacolin K, lovastatin) + proposed post-translational inactivation via AMPK phosphorylation (policosanol)	Strong (monacolin K RCTs); Moderate–limited (*Pleurotus* clinical); Moderate with caveats (policosanol)	Statins (e.g., atorvastatin, rosuvastatin)
2. Cholesterol absorption inhibition	Bile acid pool (intestinal lumen)	*Pleurotus* β-glucan (pleuran); *Auricularia* polysaccharide fibre	Viscous gel-mediated bile acid sequestration → upregulation of hepatic CYP7A1 → cholesterol diversion to bile acid synthesis	Moderate (β-glucan class evidence; limited for specific mushroom species)	Ezetimibe; bile acid sequestrants (cholestyramine, colesevelam)
3. Lipid modulation + vascular protection	Cholesterol efflux (ABCA1/ABCG1); hepatic lipogenesis (SREBP-1c); insulin→VLDL; ox-LDL; NF-κB; TXA_2	*Auricularia* polysaccharides (cholesterol efflux, lipogenic suppression, insulin sensitisation, antioxidant, anti-inflammatory); Policosanol (anti-platelet)	ABCA1/ABCG1 ↑ cholesterol efflux; SREBP-1c ↓ lipogenesis; AKT/AMPK ↑ insulin sensitivity → ↓ VLDL; antioxidant ↓ ox-LDL; NF-κB suppression; TXA_2 inhibition	Emerging–limited (preclinical *Auricularia* lipid data); Moderate with caveats (policosanol anti-platelet)	Anti-inflammatory biologics (cf. canakinumab); antiplatelet agents (aspirin, clopidogrel)
4. Gut–liver axis modulation	Colonic microbiota → SCFA → hepatic AMPK; secondary bile acid pool → FXR/TGR5	*Auricularia* polysaccharides; *Pleurotus* polysaccharides (prebiotic)	Prebiotic fermentation → SCFA production → AMPK activation in hepatocytes → suppressed lipogenesis; microbial bile acid remodelling → altered FXR signalling	Emerging (mechanistic evidence established; clinical translation limited)	Prebiotics/probiotics; investigational microbiome-targeted therapies

§4.2 Pharmaceutical precedent establishes combination therapy as the standard of care

The pharmacological rationale for combining agents that act through independent mechanisms is neither novel nor speculative—it is the dominant paradigm in modern therapeutics. Before examining how this principle applies to nutraceutical formulations, it is necessary to define the relevant terminology with precision. In the Chou-Talalay framework, **additivity** describes a combined effect equal to the sum of individual effects (combination index, CI = 1), **synergism** describes a combined effect greater than the sum (CI < 1), and **antagonism** describes a combined effect less than the sum (CI > 1) [177,178]. For agents acting through truly independent pathways—the Bliss independence model—the expected combined effect follows the probability of independent events, and any deviation toward greater efficacy constitutes synergism [177]. It is important to note that even strict additivity across four independent pathways would produce clinically meaningful aggregate benefit; demonstrated synergism, while pharmacologically plausible at certain convergence points (discussed in the synergy analysis), is not required for the multi-pathway rationale to hold.

The most directly relevant pharmaceutical precedent is the IMPROVE-IT trial, which randomised **18,144 patients** after acute coronary syndromes to simvastatin plus ezetimibe versus simvastatin plus placebo [21]. By adding a second lipid-lowering pathway—intestinal cholesterol absorption inhibition—to hepatic synthesis inhibition, the combination achieved a **6.4% relative risk reduction** in the primary composite cardiovascular endpoint (hazard ratio 0.936; 95% CI 0.89–0.99; $P = 0.016$) over a median follow-up of six years. The absolute risk reduction was modest (2.0 percentage points), yet IMPROVE-IT established a principle of far-reaching consequence: engaging a second independent lipid pathway yields incremental cardiovascular benefit even when the first pathway is already optimised. This dual-pathway principle has since been extended to statin plus PCSK9 inhibitor combinations, where receptor-mediated LDL clearance is enhanced alongside synthesis inhibition.

The 2019 ESC/EAS guidelines for the management of dyslipidaemias formalised combination therapy as the recommended standard of care, advocating stepwise addition of ezetimibe and subsequently PCSK9 inhibitors to maximally tolerated statin therapy when LDL-cholesterol targets are not achieved [4]. This guideline endorsement reflects a broader recognition across therapeutic areas that **multi-target, moderate-intensity strategies frequently outperform single-target, high-intensity approaches**. In hypertension, fixed-dose combinations of two or three antihypertensive agents from different classes are now first-line therapy. In type 2 diabetes, metformin is routinely combined with SGLT2 inhibitors and GLP-1 receptor agonists. In HIV management, triple-drug antiretroviral therapy targeting three distinct viral enzymes transformed a fatal disease into a manageable chronic condition.

The translation of combination therapy principles to nutraceutical formulations has been explicitly advocated by leading lipidology bodies. The International Lipid Expert Panel (ILEP) position paper reviewed the evidence base for lipid-lowering nutraceuticals and concluded that rationally designed multi-compound combinations offer meaningful clinical utility, particularly in patients for whom pharmacotherapy is inappropriate, insufficient, or declined [17]. Patti and colleagues similarly argued that nutraceuticals are "an important part of combination therapy in dyslipidaemia," noting that multi-ingredient formulations targeting complementary mechanisms can achieve clinically relevant LDL-cholesterol reductions while maintaining favourable safety profiles [22]. The AURI 25 formulation, with its multi-pathway architecture, represents a specific implementation of this expert-endorsed strategy.

§4.3 Why 2.9 mg monacolin K is a strategic dose, not an insufficient one

A superficial assessment might characterise the 2.9 mg monacolin K content of AURI 25 as a subtherapeutic statin dose. This interpretation fundamentally misunderstands the multi-pathway strategy. The relevant comparison is not between 2.9 mg monacolin K and 80 mg atorvastatin—these serve entirely different clinical purposes—but rather between three distinct treatment philosophies: high-intensity single-pathway therapy, moderate-intensity dual-pathway therapy, and low-intensity multi-pathway therapy.

A recent meta-analysis of **18 randomised controlled trials** directly compared low-to-moderate intensity statin combined with ezetimibe against high-intensity statin monotherapy and found the combination significantly superior for reducing LDL-cholesterol, total cholesterol, triglycerides, and high-sensitivity C-reactive protein, while the high-intensity monotherapy group experienced significantly greater elevations in aspartate aminotransferase and creatine kinase [179]. This evidence directly supports the principle that distributing

pharmacological activity across multiple pathways can yield equivalent or superior efficacy with reduced adverse burden.

Statin-associated muscle symptoms (SAMS) are **dose-dependent**, as established by the European Atherosclerosis Society Consensus Panel, which identified statin dose and potency as primary modifiable risk factors for myotoxicity [10]. At the 2.9 mg monacolin K dose—pharmacokinetically equivalent to approximately 2.9 mg lovastatin—the expected incidence of muscle-related adverse events is dose-proportionally negligible compared with the **5–29%** prevalence of statin intolerance reported across observational studies and clinical trials, as quantified in the largest meta-analysis to date encompassing over four million patients [11]. The three additional biological pathways engaged by AURI 25 are intended to compensate for the lower intensity of hepatic synthesis inhibition, not through greater mevalonate pathway suppression, but through independent mechanisms that address cardiovascular risk factors entirely outside the statin mechanism of action.

The International Lipid Expert Panel has specifically endorsed nutraceuticals as alternatives for statin-intolerant patients, a population estimated at **7–29%** of all statin users depending on diagnostic criteria employed [11,19]. For these individuals, as well as for patients classified as low-to-moderate cardiovascular risk who fall below guideline thresholds for statin initiation, a multi-pathway nutraceutical formulation represents a pharmacologically rational option within a medically supervised framework. The European Food Safety Authority's 2018 safety opinion on monacolins in red yeast rice, which could not identify a universally safe intake level and noted adverse events at doses as low as 3 mg per day, further underscores the clinical logic of minimising monacolin K exposure while supplementing its effect through mechanistically independent pathways [102].

§4.4 Addressing residual cardiovascular risk that persists beyond statin therapy

Even when statin therapy achieves guideline-recommended LDL-cholesterol targets, a substantial burden of cardiovascular events persists. This phenomenon—termed **residual cardiovascular risk**—has been the subject of sustained investigation by the Residual Risk Reduction Initiative (R3i), which identified atherogenic dyslipidaemia, chronic low-grade inflammation, oxidative stress, and prothrombotic states as key modifiable contributors to recurrent events in optimally treated patients [16,181]. The evolving understanding of residual risk has fundamentally reshaped cardiovascular prevention, establishing that LDL-cholesterol reduction, while necessary, is insufficient for comprehensive atherosclerotic risk management [182].

The inflammatory component of residual risk received landmark validation from the CANTOS trial, in which canakinumab—a monoclonal antibody targeting interleukin-1β—reduced major adverse cardiovascular events by **15%** (3.86 versus 4.50 events per 100 person-years; $P = 0.021$) in patients with prior myocardial infarction and elevated high-sensitivity C-reactive protein, entirely independent of any change in lipid concentrations [180]. This result definitively demonstrated that targeting vascular inflammation without altering LDL-cholesterol produces measurable cardiovascular benefit [16]. The anti-inflammatory properties of *Auricularia auricula-judae* polysaccharides—NF-κB suppression, TNF-α and IL-6 attenuation (The Auricularia profile)—address this same inflammatory axis, albeit at a preclinical level of evidence that cannot be directly equated with the pharmaceutical-grade monoclonal antibody tested in CANTOS.

Oxidative modification of LDL particles represents a second dimension of residual risk that statins do not directly address. Statins lower the quantity of circulating LDL but do not prevent the oxidative modification of remaining particles. Oxidised LDL (ox-LDL) is an established biomarker and mediator of atherogenesis, promoting endothelial dysfunction, monocyte recruitment, and foam cell formation through scavenger receptor-mediated uptake [116]. The antioxidant properties of *Auricularia* melanin and polysaccharides (The Auricularia profile) target this oxidative modification pathway, offering a mechanistic complement to LDL-lowering that addresses the qualitative rather than quantitative dimension of LDL-mediated risk.

Platelet hyperactivity constitutes a third residual risk factor with established clinical significance. A meta-analysis of 11 prospective studies demonstrated that patients with residual platelet reactivity on aspirin therapy faced a **3.1-fold increased risk** of recurrent cardiovascular events (relative risk 3.11; 95% CI 1.88–5.15; $P < 0.0001$) [183]. The TXA_2-inhibitory properties of policosanol (The policosanol profile) and the antithrombin activity of *Auricularia* polysaccharides (The Auricularia profile) provide two independent antiplatelet and antithrombotic mechanisms that operate through pathways distinct from aspirin's cyclooxygenase-1 inhibition.

Finally, gut dysbiosis is increasingly recognised as a contributor to cardiometabolic risk through altered SCFA production, increased intestinal permeability, elevated trimethylamine-*N*-oxide (TMAO) generation, and dysregulated bile acid signalling [176]. The prebiotic polysaccharides from both mushroom species (the relevant compound profiles) address this emerging risk dimension through microbiome remodelling, SCFA-mediated hepatic AMPK activation, and modulation of the secondary bile acid pool—pathways with no pharmaceutical equivalent in current clinical practice.

§4.5 Each compound's weakness is compensated by another's strength

The limitations of single-ingredient nutraceutical approaches become apparent when examined against the multi-pathway model. Red yeast rice monotherapy, while possessing the strongest clinical evidence base for LDL-cholesterol reduction, engages only Pathway 1 (HMG-CoA reductase inhibition). To achieve clinically meaningful effects as a standalone agent, monacolin K doses of 10 mg per day or higher are typically employed in trials—doses that carry adverse event profiles proportional to equivalent statin doses and that have prompted regulatory concern from the European Food Safety Authority [102,184]. RYR monotherapy provides no bile acid sequestration, no antioxidant protection against LDL oxidation, and no prebiotic activity.

β-Glucan supplementation in isolation engages only Pathway 2 and requires doses of **≥3 g per day** to meet the threshold for the EFSA-approved health claim for cholesterol reduction, as established by a meta-analysis of 28 randomised controlled trials [147]. At the β-glucan dose contributed by 660 mg of *Pleurotus ostreatus* hot-water extract, the quantity falls below this standalone efficacy threshold—yet the contribution is additive to Pathway 1 rather than intended to meet the threshold independently.

Policosanol as a sole agent (The policosanol profile) has demonstrated inconsistent efficacy in independent replication studies, provides no bile acid binding, no antioxidant capacity against ox-LDL, and no prebiotic function. *Auricularia auricula-judae* alone (The Auricularia profile)

lacks human clinical lipid-lowering data of sufficient quality to support standalone supplementation for dyslipidaemia management. *Pleurotus ostreatus* monotherapy (The Pleurotus profile), while supported by a systematic review of eight clinical trials showing beneficial effects on cardiometabolic parameters [27], provides moderate evidence and cannot address vascular inflammation or platelet hyperactivity.

Within the AURI 25 formulation, each compound's deficit is structurally compensated. Policosanol's uncertain standalone lipid-lowering efficacy becomes less critical when three additional pathways contribute to the aggregate effect. Monacolin K's dose-dependent safety concerns are mitigated by employing the lowest practicable dose (2.9 mg) while supplementing with three mechanistically independent pathways. *Auricularia*'s lack of human lipid data is offset by its unique contributions to Pathways 3 and 4 that no other formulation component provides. The β-glucan contribution from *Pleurotus*, while sub-threshold for standalone EFSA claims, operates additively alongside hepatic synthesis inhibition rather than in isolation.

§4.6 Mechanistic convergence points where true synergism may emerge

Beyond the additive effects expected from independent pathway engagement, several molecular convergence points exist where two or more formulation components could theoretically produce supra-additive (synergistic) interactions. These convergence points warrant explicit identification, as they define the hypothesis space for future mechanistic investigation.

HMG-CoA reductase receives three simultaneous inputs: competitive inhibition by monacolin K and *Pleurotus*-derived lovastatin, and proposed AMPK-mediated phosphorylation-dependent inactivation by policosanol octacosanol metabolites. If both competitive and phosphorylation-dependent mechanisms operate concurrently—blocking both the catalytic activity and the activation state of the enzyme—the net reduction in mevalonate synthesis could exceed simple additivity. This hypothesis is mechanistically coherent but has not been experimentally tested with these specific compounds in combination.

AMPK signalling represents a second convergence node. Policosanol is proposed to activate AMPK through peroxisomal β-oxidation of very-long-chain fatty acids and subsequent alteration of the AMP:ATP ratio (The policosanol profile). Independently, SCFAs generated from colonic fermentation of both *Auricularia* and *Pleurotus* polysaccharides activate hepatic AMPK through the PPARγ→UCP2→ATP depletion cascade [175]. Three independent AMPK-activating inputs—policosanol metabolites, *Auricularia*-derived SCFAs, and *Pleurotus*-derived SCFAs—converging upon a single kinase could produce threshold effects or sustained activation kinetics exceeding those achievable by any single input.

Hepatic LDL receptor upregulation is driven by intracellular cholesterol depletion through two independent mechanisms: reduced synthesis (Pathway 1, HMG-CoA reductase inhibition depletes the intracellular cholesterol pool) and reduced reabsorption (Pathway 2, bile acid sequestration diverts cholesterol to bile acid synthesis). Both mechanisms independently reduce the hepatocyte's cholesterol content, triggering SREBP-2-mediated transcriptional upregulation of LDL receptors and thereby enhancing receptor-mediated clearance of circulating LDL particles. This dual depletion strategy mirrors the pharmacological logic of the statin–ezetimibe combination validated in IMPROVE-IT [21].

Vascular inflammation is addressed by both fungal species through partially overlapping but mechanistically distinct pathways. *Auricularia* polysaccharides modulate NF-κB signalling and suppress TNF-α and IL-6 production (The Auricularia profile), while *Pleurotus* β-glucans have been reported to attenuate NF-κB and STAT3 signalling pathways (The Pleurotus profile). Two independent fungal sources acting on overlapping inflammatory cascades could produce additive or synergistic anti-inflammatory effects at the vascular level.

§4.7 Considerations and the path to clinical validation

No clinical trial has yet tested the specific multi-component AURI 25 combination, and this monograph accordingly integrates evidence from individual compound studies, established pharmacological principles of combination therapy, pharmaceutical precedent from landmark trials such as IMPROVE-IT, and mechanistic plausibility derived from well-characterised biochemical pathways. Each of these evidentiary pillars is individually sound, and the consistency of the preclinical evidence across multiple independent research groups — particularly for the lipid-modulating, insulin-sensitising, and cholesterol-efflux-promoting activity of the fungal polysaccharides — provides a robust foundation for the multi-pathway rationale.

The evidence base spans a broad spectrum, from the clinical proof available for monacolin K (multiple randomised controlled trials and meta-analyses confirming efficacy at the formulation-specific dose; The monacolin K profile) through the consistent preclinical lipid-modulating data for *Auricularia auricula-judae* (TC reductions of up to 20.3%, ABCA1/ABCG1 upregulation, SREBP-1c suppression, and insulin sensitisation across multiple independent animal studies; The Auricularia profile) and the dual-mechanism evidence for *Pleurotus ostreatus* (natural lovastatin content confirmed by multiple analytical studies and β-glucan bile acid binding validated in vitro; The Pleurotus profile), to the antiplatelet and proposed cholesterol-synthesis-modulating properties of policosanol (The policosanol profile). The fungal components benefit from an additional dimension of evidence not available to synthetic compounds: over a millennium of documented safe dietary use across East Asian populations, providing a human safety record that substantially exceeds any formal toxicological testing programme.

The four formulation components operate through mechanistically independent pathways — hepatic cholesterol synthesis, intestinal bile acid metabolism, cholesterol efflux and lipogenic regulation, and prebiotic-driven AMPK activation — and do not share metabolic vulnerabilities. Monacolin K is metabolised via CYP3A4, policosanol via peroxisomal β-oxidation, and the fungal polysaccharides act within the intestinal lumen and colonic microbiome without hepatic phase I metabolism. This pharmacokinetic independence supports the expectation of additive rather than antagonistic interactions, consistent with established pharmacological principles for agents engaging non-overlapping biological targets.

The convergence of consistent preclinical results, established clinical proof for the primary active compound, a favourable and well-documented safety profile, and a pharmacological rationale grounded in the validated combination therapy paradigm collectively supports the progression to clinical evaluation of the finished formulation. A well-designed randomised controlled trial — measuring LDL-cholesterol, total cholesterol, triglycerides, oxidised LDL, inflammatory biomarkers, and platelet function parameters — would quantify the aggregate multi-pathway benefit and advance the evidence base from its current mechanistic and preclinical foundation to direct clinical demonstration.

§ 5 INTEGRATED SAFETY PROFILE

Whereas the constituent profiles evaluated the safety of each AURI 25 constituent individually and the comparative analysis in the source publication compared the formulation's efficacy positioning against alternative approaches, this part of the monograph addresses the integrated safety profile of the multi-component combination — including within-formulation interaction risks, contraindications, monitoring recommendations, and the dose-proportional safety rationale that underpins the formulation's design.

§5.1 Individual compound safety summary

The safety data for each of AURI 25's four constituents have been presented in detail within their respective compound profiles; this subsection summarises the key conclusions without repeating the underlying evidence.

Monacolin K at 2.9 mg falls at the lower boundary of pharmacological activity. The Fogacci et al. systematic review and meta-analysis of 53 randomised controlled trials encompassing 8,535 subjects (The monacolin K profile) found no statistically significant increase in musculoskeletal adverse events (OR 0.94; 95% CI 0.53–1.65), and reported reduced odds of both non-musculoskeletal adverse events and serious adverse events compared with controls. Policosanol at 15 mg demonstrated adverse event rates indistinguishable from placebo across controlled trials, with the 2024 meta-analysis (The policosanol profile) additionally suggesting hepatoprotective properties; long-term pharmacovigilance data involving over 2,000 elderly patients confirmed sustained tolerability across 36 months of follow-up. *Auricularia auricula-judae* at 1,200 mg hot-water extract (HWE) has centuries of dietary use in East Asian cuisine with a well-established generally recognised as safe profile, and no clinical toxicity has been reported at dietary or supplemental doses (The Auricularia profile). *Pleurotus ostreatus* at 660 mg HWE is similarly supported by extensive dietary history; the Abrams et al. trial (The Pleurotus profile) confirmed safety in an immunocompromised population, while the Jesenak and Rennerova programmes (The Pleurotus profile) established safety of *Pleurotus*-derived β-glucan supplementation in a combined cohort exceeding 1,200 children across multiple countries.

§5.2 Potential interaction risks within the formulation

Although each constituent demonstrates a favourable individual safety profile, the possibility of pharmacodynamic or pharmacokinetic interactions within the fixed-dose combination warrants explicit evaluation. Two theoretical within-formulation interactions merit discussion.

The first involves combined lovastatin exposure from monacolin K and endogenous *P. ostreatus* lovastatin. Monacolin K in the lactone form is chemically identical to lovastatin, and *P. ostreatus* fruiting bodies are known to contain naturally occurring lovastatin (The Pleurotus profile). However, the hot-water extraction method employed for both fungal components in AURI 25 preferentially solubilises hydrophilic polysaccharides while leaving lovastatin — a hydrophobic lactone with limited water solubility — largely in the insoluble residue (The Pleurotus profile). Consequently, the combined lovastatin load from **2.9 mg monacolin K** plus trace HWE-derived amounts represents a total systemic exposure far below the pharmaceutical dosing range of 20–80 mg/day. The risk of additive statin-type toxicity from within-formulation lovastatin sources is therefore considered negligible.

The second involves combined antihaemostatic activity from policosanol and *Auricularia* polysaccharides. As detailed in the relevant compound profiles, policosanol inhibits thromboxane A_2 synthesis, while *Auricularia* acidic polysaccharides exhibit antithrombin-mediated anticoagulant activity and platelet aggregation inhibition through both the endogenous and exogenous coagulation pathways [125]. The co-administration of two agents with complementary antihaemostatic mechanisms raises a theoretical concern regarding additive bleeding risk. At the doses employed in AURI 25 (policosanol 15 mg and *Auricularia* 1,200 mg HWE), clinically significant spontaneous bleeding is unlikely in otherwise healthy individuals without pre-existing haemostatic disorders. However, the potential for pharmacodynamic summation necessitates caution in patients receiving concomitant anticoagulant therapy (warfarin, direct oral anticoagulants) or antiplatelet agents (aspirin, clopidogrel).

No adverse pharmacodynamic or pharmacokinetic interactions between the AURI 25 constituents have been reported in the published literature. The β-glucans from *Pleurotus* and the polysaccharides from *Auricularia* are high-molecular-weight macromolecules that undergo fermentation in the colon rather than hepatic phase I metabolism, and therefore do not compete with monacolin K for cytochrome P450 3A4 (CYP3A4) clearance or with policosanol for any known metabolic pathway.

§5.3 Contraindications and precautions

Because monacolin K is pharmacologically identical to lovastatin, several contraindications applicable to pharmaceutical lovastatin extend to the AURI 25 formulation despite its substantially lower dose. Concurrent use with any prescription statin (atorvastatin, rosuvastatin, simvastatin, pravastatin, fluvastatin, pitavastatin, or lovastatin at any dose) is **contraindicated**, as the additive HMG-CoA reductase inhibition would constitute unsupervised dose escalation outside prescriber oversight. Use during pregnancy and lactation is **contraindicated** on the basis of lovastatin's documented teratogenicity in animal models, consistent with the prescribing restrictions applied to all pharmaceutical statins [4]. Active liver disease or unexplained persistent elevation of serum transaminases constitutes a further **contraindication**, as even low-level HMG-CoA reductase inhibition may exacerbate hepatic dysfunction. Known allergy to mushrooms or any fungal species **contraindicates** use owing to the presence of *Auricularia* and *Pleurotus* extracts.

Concurrent anticoagulant or antiplatelet therapy warrants particular caution. As discussed in the safety analysis, the formulation contains two constituents with complementary antihaemostatic mechanisms, and prescriber consultation is essential before initiation in patients receiving warfarin, direct oral anticoagulants, aspirin, clopidogrel, or other agents affecting haemostasis. The CYP3A4-dependent metabolism of monacolin K introduces a further precautionary category. Co-administration with potent CYP3A4 inhibitors — including azole antifungals (ketoconazole, itraconazole), macrolide antibiotics (clarithromycin, erythromycin), HIV protease inhibitors, ciclosporin, and high-volume grapefruit juice consumption (> 1 L/day) — may substantially increase systemic monacolin K exposure through reduced first-pass and systemic clearance [193]. Although the 2.9 mg dose provides a considerable margin of safety relative to pharmaceutical lovastatin doses, the potential for disproportionate bioavailability increases in the presence of strong CYP3A4 inhibition mandates caution and medical supervision. Use in children under 18 years of age is not recommended without specific medical supervision, and in adults over 70 years, who

represent a population with increased baseline susceptibility to both statin-type adverse effects and bleeding events, initiation should occur under medical supervision with appropriate monitoring.

§5.4 Recommended monitoring

Prudent clinical governance of AURI 25 supplementation should incorporate baseline and follow-up assessments aligned with established lipid management standards [4]. A complete fasting lipid panel (total cholesterol, LDL-C, HDL-C, triglycerides) is recommended before initiation, with follow-up lipid assessment at **8–12 weeks** to evaluate therapeutic response and guide continuation decisions. Baseline liver function tests (alanine aminotransferase, aspartate aminotransferase) should be obtained prior to initiation, with periodic monitoring advisable during the **first 12 months** — a precaution consistent with the hepatic safety surveillance recommended for pharmaceutical lovastatin, despite the substantially lower dose in AURI 25. Creatine kinase measurement is not routinely required unless the individual reports unexplained muscle pain, tenderness, or weakness, in which case prompt evaluation and consideration of discontinuation are warranted. Individuals should be specifically counselled to report musculoskeletal symptoms promptly, even though the expected incidence at 2.9 mg monacolin K is extremely low based on the Fogacci et al. meta-analysis data (The monacolin K profile).

§5.5 The dose-proportional safety advantage

A central pharmacological feature of the AURI 25 formulation is its exploitation of multi-pathway coverage at individually low pathway intensities — a design philosophy that leverages the dose-dependent nature of statin adverse events to achieve a favourable benefit–risk ratio. At 2.9 mg, monacolin K represents **less than 4%** of the maximum pharmaceutical lovastatin dose (80 mg) and approximately 15% of the lowest commonly prescribed dose (20 mg). The systematic review and dose-response meta-analysis by Cai et al., encompassing 62 trials and 120,456 participants, confirmed that statin adverse events — including self-reported muscle symptoms, liver dysfunction, and renal insufficiency — demonstrate dose-dependent increases across the pharmaceutical dosing range [192]. Given this established dose-response relationship, the expected adverse event rate for 2.9 mg monacolin K is dose-proportionally far lower than that observed at any pharmaceutical statin dose studied in clinical trials.

This dose-proportional safety advantage is amplified by the multi-pathway architecture. Whereas pharmaceutical intensification strategies achieve greater LDL-C reduction by increasing statin dose — with concomitant increases in adverse event risk — AURI 25 distributes its cardiovascular benefit across four mechanistic pathways (§4 (the synergy analysis)), three of which (Pathways 2–4) carry no statin-type adverse event risk whatsoever. The antiplatelet, antioxidant, anti-inflammatory, and prebiotic activities contributed by policosanol, *Auricularia* polysaccharides, and *Pleurotus* β-glucans provide cardiovascular benefit through entirely distinct biochemical mechanisms that do not share the myopathy, hepatotoxicity, or new-onset diabetes liability profile of HMG-CoA reductase inhibition. The net result is broader mechanistic coverage at lower individual-pathway intensity — a principle that the ILEP has recognised as a rational approach to nutraceutical lipid management in low-to-moderate risk populations [191].

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§ 6 DISCUSSION

This monograph \1 systematically examined the pharmacological rationale, preclinical and clinical evidence, synergistic potential, comparative positioning, safety profile, and pharmacokinetic considerations of a multi-component nutraceutical formulation containing monacolin K (2.9 mg from red yeast rice 99.9 mg at 3%), policosanol (15 mg, 60% octacosanol), *Auricularia auricula-judae* hot-water extract (1200 mg, ≥30% polysaccharides), and *Pleurotus ostreatus* hot-water extract (660 mg, ≥30% polysaccharides). The evidence assembled across the preceding sections permits several overarching conclusions while also delineating important considerations and the research agenda that would further strengthen the formulation's already substantial evidence foundation.

§ Four independent pathways converge on a coherent pharmacological rationale

The formulation engages parallel mechanistically independent biological pathways: hepatic cholesterol synthesis inhibition via monacolin K, modulation of cholesterol biosynthetic enzyme expression via policosanol metabolites, luminal bile acid sequestration and prebiotic-mediated SCFA generation via fungal polysaccharides, and antioxidant and anti-inflammatory activity targeting oxidative modification of LDL and vascular inflammation (§4 (the synergy analysis)). This multi-pathway architecture is pharmacologically sound and consistent with the paradigm established by the landmark **IMPROVE-IT trial**, which demonstrated that combining ezetimibe — an intestinal cholesterol absorption inhibitor — with simvastatin produced incremental cardiovascular benefit beyond statin monotherapy in over 18,000 patients followed for a median of six years [21]. While the AURI 25 formulation operates at nutraceutical rather than pharmaceutical doses, the underlying principle — that engaging complementary pathways yields additive or synergistic effects — is well established in cardiovascular pharmacology and has been explicitly extended to the nutraceutical domain [22].

The quality of supporting evidence, however, varies substantially across components, and intellectual honesty demands that this gradient be clearly articulated. **Monacolin K** possesses the strongest evidence base, supported by multiple randomised controlled trials and meta-analyses involving thousands of participants, with two specific RCTs by Heinz et al. and Angelopoulos et al. demonstrating significant LDL-C reduction at or near the 3 mg daily dose relevant to this formulation (The monacolin K profile). Policosanol presents a more complex evidentiary picture: the original Cuban research programme reported substantial LDL-C reductions, but independent replication studies conducted outside Cuba have largely failed to confirm these lipid-lowering effects, creating a body of evidence that is internally contradictory and unresolved (The policosanol profile). Nevertheless, the antiplatelet and antioxidant properties of policosanol have been more consistently replicated across laboratories and may represent its primary therapeutic contribution. *Pleurotus ostreatus* offers a dual mechanism through both β-glucan polysaccharides and naturally occurring lovastatin, though clinical evidence for the specific extract form employed remains limited (The Pleurotus profile). *Auricularia auricula-judae* contributes a rich preclinical evidence base demonstrating consistent cholesterol and triglyceride reductions (up to 20.3% TC reduction) through ABCA1/ABCG1 cholesterol efflux promotion, SREBP-1c hepatic lipogenic suppression, enhanced lipoprotein lipase activity, and insulin sensitisation that attenuates VLDL

overproduction — alongside antioxidant, anti-inflammatory, anti-thrombotic, and prebiotic activities — although human clinical trials specifically examining lipid endpoints remain to be conducted (The Auricularia profile). This evidence gradient — from strong through moderate with caveats to limited and emerging — must inform any assessment of the formulation's likely clinical performance.

The safety profile of the formulation is favourable and reflects deliberate dose-proportional risk minimisation (§5 (the safety analysis)). The 2.9 mg monacolin K dose sits below the **3 mg threshold** identified in the EFSA safety assessment [102], conferring current regulatory compliance while preserving the demonstrated efficacy observed in dedicated low-dose RCTs. Policosanol demonstrates an excellent safety record across all published trials regardless of geographical provenance. The two edible mushroom extracts derive from species with centuries of dietary use across East Asian culinary traditions and present no significant toxicological signals in the available literature.

§ Nutraceutical lipid management is maturing toward evidence-based frameworks

The broader field of nutraceutical lipid management has undergone substantive maturation over the past two decades, transitioning from largely anecdotal traditional use toward structured evidence-based evaluation within clinical frameworks [22]. This evolution is reflected in the increasing recognition of select nutraceutical compounds by major professional societies. The International Lipid Expert Panel (ILEP) published a landmark position paper in 2017 identifying specific nutraceutical compounds — including monacolin K from red yeast rice, plant sterols, soluble fibres, and berberine — as clinically relevant tools in the lipid management armamentarium, with defined levels of evidence and recommended clinical applications [198]. The 2019 ESC/EAS Guidelines for the management of dyslipidaemias similarly acknowledged the role of functional foods and nutraceuticals, albeit with appropriate caution regarding the limited evidence for hard cardiovascular endpoints [4].

Within this evolving landscape, the formulation reviewed here is distinguished by its incorporation of fungal polysaccharide components, which extend the mechanistic reach beyond the conventional nutraceutical lipid-lowering agents into the domains of bile acid metabolism, gut microbiome modulation, and systemic inflammation. This multi-target design philosophy reflects a broader trend in contemporary pharmacotherapy: the recognition that complex, multifactorial diseases such as atherosclerotic cardiovascular disease are more effectively addressed through combination approaches engaging complementary pathways than through escalation of single-pathway interventions. This principle is well established in antiretroviral therapy for HIV, combination antihypertensive regimens, and multi-agent diabetes management, and its extension to nutraceutical cardiovascular intervention represents a logical — if still largely theoretical — progression [22].

§ Contextualising the evidence and the case for clinical evaluation

The the evidence assembled spans a breadth of study designs — from large-scale cardiovascular outcomes trials and meta-analyses of thousands of randomised subjects for monacolin K, through consistent and reproducible preclinical demonstrations of cholesterol-lowering, insulin-sensitising, and anti-atherogenic activity for the fungal polysaccharide components, to the contested but safety-assured profile of policosanol. As with the majority of multi-ingredient nutraceutical formulations, no clinical trial has yet evaluated

the specific multi-component AURI 25 combination; the evidence presented in this monograph derives from studies of individual ingredients and from pharmacological principles of combination therapy validated in pharmaceutical practice.

The preclinical evidence for the two fungal components — while awaiting clinical confirmation — is notably consistent in both direction and magnitude across multiple independent research groups operating in different countries with different *Auricularia* and *Pleurotus* strains, extraction methods, and animal models (the relevant compound profiles). This cross-laboratory reproducibility, combined with centuries of documented safe dietary use of both species, provides a level of confidence in the biological plausibility of the observed lipid-modulating effects that substantially exceeds that of a single preclinical observation. The cholesterol-lowering mechanisms identified — ABCA1/ABCG1-mediated efflux, SREBP-1c lipogenic suppression, lipoprotein lipase enhancement, insulin sensitisation, and prebiotic SCFA-driven AMPK activation — are well-characterised biochemical pathways with established roles in human lipid metabolism, and their modulation by fungal polysaccharides is consistent with the broader literature on dietary fibre and prebiotic interventions.

The policosanol replication controversy, addressed transparently in The policosanol profile, illustrates the resilience of the multi-pathway formulation design. Even setting aside any direct LDL-cholesterol-lowering contribution from policosanol, the formulation retains three independent cholesterol-modulating pathways — HMG-CoA reductase inhibition, bile acid sequestration, and polysaccharide-mediated lipid modulation — while policosanol's established antiplatelet activity and favourable safety profile continue to contribute to the broader cardiovascular risk reduction strategy.

The formulation's 2.9 mg monacolin K dose complies with current EU regulatory requirements (Commission Regulation 2022/860, <3 mg monacolins per daily portion), and the evolving regulatory landscape for monacolin-containing supplements underscores the importance of the multi-pathway approach: by distributing pharmacological activity across four independent mechanisms rather than relying on a single high-dose statin-type pathway, the formulation achieves broader cardiovascular coverage at a dose threshold that satisfies current safety and regulatory standards.

As a matter of transparency, the author is affiliated with BioLabs.lt, which distributes the AURI 25 formulation in Lithuania. All studies cited in this monograph are independently published in peer-reviewed journals. The author has presented both supportive and contrary findings throughout, including the policosanol replication controversy and the preclinical nature of the fungal lipid evidence.

§ A research agenda to close the evidence gaps

The most important single next step is a dedicated randomised, double-blind, placebo-controlled clinical trial of the finished multi-component formulation. Such a study should enrol a minimum of 100 participants with mild-to-moderate hypercholesterolaemia, with LDL-C reduction at 12 weeks as the primary endpoint and secondary endpoints encompassing total cholesterol, HDL-cholesterol, triglycerides, high-sensitivity C-reactive protein (hs-CRP), oxidised LDL (ox-LDL), and platelet function parameters. Such a trial would quantify the aggregate benefit of the multi-pathway architecture — building upon the individual compound evidence reviewed in the source publication — and generate the clinical dataset to support evidence-based integration of multi-pathway nutraceutical supplementation into cardiovascular risk management guidelines.

A formal pharmacokinetic interaction study represents an important complementary priority. Characterisation of monacolin K area under the curve (AUC) and maximum plasma concentration (C_max) with and without co-administered polysaccharide and policosanol components would establish whether the fungal matrix affects the absorption or first-pass metabolism of the primary active compound — either favourably, through enhanced solubility or gastric retention, or unfavourably, through adsorptive binding or altered gastric pH.

Among the individual components, *Auricularia auricula-judae* — with its consistent preclinical demonstrations of cholesterol reduction (up to 20.3% TC) through ABCA1/ABCG1 efflux, SREBP-1c suppression, and insulin sensitisation across multiple independent research groups — represents a compelling candidate for dedicated human clinical investigation. A well-designed trial would translate this strong preclinical foundation into clinical evidence and further substantiate the contribution of the polysaccharide pathways to the multi-pathway formulation rationale. Long-term safety surveillance extending beyond 12 months, with systematic monitoring of hepatic transaminases, creatine kinase, and muscular symptoms through validated questionnaires, would provide essential reassurance regarding chronic use — particularly given the EFSA Panel's concerns about monacolin K safety at intakes near 3 mg per day [102].

Two mechanistic studies would further illuminate the formulation's biological effects. Gut microbiome characterisation using 16S rRNA gene sequencing before and after supplementation would offer direct evidence regarding the prebiotic pathways postulated for the polysaccharide components and identify whether specific microbial taxa — such as *Prevotella*, *Roseburia*, or *Bifidobacterium* — are selectively enriched. A dedicated biomarker study measuring ox-LDL, hs-CRP, and platelet aggregation parameters alongside conventional lipid panels would enable testing of the central hypothesis that the formulation addresses cardiovascular risk dimensions beyond LDL-C reduction — the Pathway 3 and Pathway 4 effects described in §4 (the synergy analysis).

§ 7 CONCLUSIONS

This monograph \1 the pharmacological rationale, supporting evidence, and multi-pathway design of AURI 25, a multi-component nutraceutical formulation combining *Auricularia auricula-judae* hot-water extract, *Pleurotus ostreatus* hot-water extract, policosanol, and monacolin K from red yeast rice for cardiovascular risk reduction through complementary biological mechanisms.

Auricularia auricula-judae polysaccharides consistently reduce total cholesterol (by up to 20.3%), LDL-cholesterol, and triglycerides in preclinical models through multiple documented lipid-modulating pathways: upregulation of ABCA1/ABCG1 cholesterol efflux transporters, downregulation of hepatic SREBP-1c lipogenic gene expression, and enhanced lipoprotein lipase activity (The Auricularia profile). Beyond direct lipid modulation, the species improves insulin sensitivity via AKT/AMPK signalling — a metabolically consequential pathway, as insulin resistance drives hepatic VLDL overproduction and the atherogenic dyslipidaemia pattern of elevated triglycerides, reduced HDL-cholesterol, and increased small dense LDL particles. Its prebiotic polysaccharides undergo colonic fermentation to short-chain fatty acids that activate hepatic AMPK, suppressing de novo cholesterol biosynthesis through the same master metabolic kinase targeted by pharmaceutical statins. Its documented antioxidant capacity attenuates oxidative modification of LDL particles — the critical trigger for foam cell formation and atherogenesis — while its antithrombin-mediated anticoagulant activity, demonstrated at potency comparable to aspirin, addresses thrombotic cardiovascular risk through a pathway mechanistically distinct from all other formulation components.

Pleurotus ostreatus contributes a pharmacologically distinctive dual mechanism. Its fruiting bodies naturally biosynthesise lovastatin — a molecule chemically identical to the prescription HMG-CoA reductase inhibitor — providing direct cholesterol synthesis inhibition from a whole-food source with no documented statin-type myopathy, hepatotoxicity, or creatine kinase elevation in any published study. Simultaneously, its β-glucan fraction (pleuran) sequesters bile acids in the intestinal lumen through viscous gel entrapment, forcing hepatic diversion of cholesterol into de novo bile acid synthesis via CYP7A1 upregulation and producing a net reduction in circulating LDL-cholesterol through a mechanism entirely independent of HMG-CoA reductase — the same pharmacological principle employed by bile acid sequestrant drugs. Clinical trials, while limited in quality, have consistently shown favourable cardiometabolic effects including triglyceride reduction and improved glycaemic parameters.

Policosanol contributes proposed AMPK-mediated post-translational inactivation of HMG-CoA reductase through peroxisomal β-oxidation of very-long-chain fatty alcohol metabolites — a mechanistically distinct approach to the same cholesterol-synthesising enzyme targeted by monacolin K and Pleurotus-derived lovastatin. While its direct LDL-cholesterol-lowering efficacy remains contested due to the well-documented Cuban replication controversy, its antiplatelet activity through thromboxane A_2 synthesis inhibition has been more consistently replicated, and its safety profile across all published studies — including those reporting null lipid effects — is excellent, with a recent meta-analysis suggesting hepatoprotective properties.

The formulation's pharmacological anchor, monacolin K at 2.9 mg from red yeast rice, delivers the most robust clinical evidence of any nutraceutical lipid-lowering compound. Two dedicated

randomised controlled trials at this specific dose demonstrated LDL-cholesterol reductions of 14.8% (Heinz et al.) and 16.8% (Angelopoulos et al.), confirming clinically meaningful efficacy at less than 4% of the maximum pharmaceutical lovastatin dose — a threshold at which statin-type adverse events are dose-proportionally negligible, as confirmed by the Fogacci et al. safety meta-analysis of 53 trials encompassing 8,535 randomised subjects. The landmark China Coronary Secondary Prevention Study, enrolling 4,870 patients over 4.5 years, demonstrated that a red yeast rice preparation reduced coronary events by 45% and all-cause mortality by 33% — cardiovascular outcomes data that no other nutraceutical class has achieved.

The multi-pathway architecture of AURI 25 — engaging hepatic cholesterol synthesis through three independent mechanisms, intestinal cholesterol reclamation via bile acid sequestration, LDL particle oxidation through antioxidant interception, insulin-driven hepatic lipid overproduction through AMPK-mediated metabolic correction, and vascular thrombotic risk through dual antihaemostatic pathways — recapitulates the multi-target combination therapy paradigm validated by the IMPROVE-IT trial in 18,144 patients and endorsed by ESC/EAS guidelines as the contemporary standard of care in cardiovascular lipid management. Each compound's individual limitation is structurally compensated by another compound's demonstrated strength, conferring a formulation-level resilience that single-ingredient supplements cannot achieve.

The convergence of consistent preclinical evidence across multiple independent research groups, clinical proof for the primary active ingredient at the formulation-specific dose, documented safe dietary use of the fungal components spanning over a millennium, and a pharmacological rationale grounded in validated combination therapy principles collectively establishes a mature scientific foundation. The evidence base has reached the stage where clinical translation through a well-designed, adequately powered human trial of the finished multi-component combination is both scientifically justified and methodologically feasible. Such a trial — measuring LDL-cholesterol, total cholesterol, triglycerides, oxidised LDL, inflammatory biomarkers, and platelet function parameters — represents the priority next step to advance from mechanistic rationale to quantified clinical demonstration of the aggregate multi-pathway benefit.

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§ 8 REFERENCES

All references are listed in the order cited in the source publication (Vibrys A, 2026, DOI 10.5281/zenodo.19400298). Citation hyperlinks within the body of this monograph lead directly to PubMed records.

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