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A Practical Approach to Elevated Lipoprotein(a): Is There a Role for Nutraceuticals in Clinical Practice?

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ABSTRACT

Lipoprotein(a) [Lp(a)] is a lipoprotein particle predominantly determined by genetic factors and independently associated with atherosclerotic cardiovascular disease and calcific aortic valve stenosis. Although its recognition as a risk modifier has increased, few widely available interventions substantially lower its concentrations. Statins and ezetimibe do not meaningfully reduce Lp(a), whereas PCSK9 inhibitors produce moderate reductions, and therapies directed at apolipoprotein(a) remain under development or cardiovascular outcome evaluation. In this setting, nutraceuticals have been proposed as accessible alternatives or adjuncts. This practical review summarizes the available clinical evidence for L-carnitine, coenzyme Q10, flaxseed, curcumin, berberine, pectin, Ginkgo biloba, Xuezhikang, N-acetylcysteine, phytosterols, omega-3 fatty acids, and other natural products. The most consistent evidence for Lp(a) lowering comes from meta-analyses of randomized trials of L-carnitine, coenzyme Q10, and flaxseed, although absolute effects are generally modest. Pectin, Ginkgo biloba, and Xuezhikang produced larger reductions in individual studies, but with low certainty and limited replication. No evidence demonstrates that nutraceutical-mediated Lp(a) lowering reduces cardiovascular events. We propose a pragmatic approach centered on global cardiovascular risk stratification, intensive control of LDL-C and other modifiable risk factors, and, only after shared decision-making, an individualized trial of one nutraceutical followed by laboratory reassessment after 8-12 weeks. Nutraceuticals should neither replace proven therapies nor be used as an isolated strategy in individuals at high or very high risk.

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1. INTRODUCTION

Lipoprotein(a) [Lp(a)] consists of a low-density lipoprotein-like particle containing apolipoprotein B-100 covalently bound to apolipoprotein(a). This structure combines atherogenic, proinflammatory, and potentially thrombogenic properties. Epidemiological, genetic, and Mendelian randomization studies support a causal association between elevated Lp(a), atherosclerotic cardiovascular disease, and calcific aortic valve stenosis [1-3].

Lp(a) concentrations are determined mainly by the *LPA* gene, remain relatively stable throughout adult life, and are only modestly influenced by diet, exercise, or weight loss. Contemporary consensus statements therefore recommend measuring Lp(a) at least once in adult life, with repeat testing in selected circumstances, such as kidney or liver disease, major inflammatory states, pregnancy, or uncertainty regarding the reliability of the initial measurement [1,2]. Values of >=50 mg/dL or >=125 nmol/L are frequently used to indicate increased risk, but risk is continuous, and no exact universal conversion between mg/dL and nmol/L exists because apolipoprotein(a) isoform size varies [1,2].

Clinical interest in Lp(a) contrasts with the scarcity of available specific treatments. Unlike LDL-C, Lp(a) responds poorly to conventional lipid-lowering interventions. In an individual-patient-data meta-analysis of 5,256 participants from six randomized trials, atorvastatin, pravastatin, and rosuvastatin did not lower Lp(a); compared with placebo, statins increased the geometric mean by approximately 11%, although the magnitude varied according to the drug and baseline concentration [4]. A second systematic review of randomized trials found an overall neutral result, reinforcing that there is no evidence of a clinically meaningful Lp(a)-lowering effect [5]. Therefore, elevated Lp(a), or a small increase after statin initiation, is not a reason to discontinue treatment: the reductions in LDL-C and cardiovascular events achieved with statins substantially outweigh this laboratory change.

Ezetimibe should likewise not be prescribed specifically to lower Lp(a). A meta-analysis of randomized monotherapy trials showed a nonsignificant change of -7.06% (95% CI -20.25 to +6.13); sensitivity analyses and comparisons of ezetimibe added to statin therapy did not confirm a consistent reduction [6]. Another meta-analysis similarly concluded that ezetimibe, either alone or added to a statin, has no relevant effect on Lp(a) [7]. Its indication remains based on lowering LDL-C and atherosclerotic risk, not on directly treating elevated Lp(a). PCSK9 monoclonal antibodies and inclisiran reduce Lp(a) by approximately 15-30%, together with a much greater reduction in LDL-C [8]. Niacin may lower Lp(a) by 20-40%, but it has not demonstrated additional cardiovascular benefit when added to contemporary therapy and has limited tolerability; therefore, it is not recommended specifically to treat elevated Lp(a) [8,9]. Lipoprotein apheresis remains reserved for exceptional situations and depends on local eligibility criteria.

Lifestyle interventions should be strongly recommended to reduce global cardiovascular risk, but their direct effect on Lp(a) is small and inconsistent. Cross-sectional studies and interventions involving aerobic exercise or moderate training have generally shown no significant change; athletes exposed to very high training volumes represent an inconsistent exception without clear therapeutic applicability [10,11]. Similarly, diet-induced weight loss does not predictably lower Lp(a), and some studies have reported stability or even a transient increase. Bariatric surgery may lower Lp(a) in selected cohorts and meta-analyses, but this effect is not explained by weight loss alone and is heterogeneous across procedures [11,12]. Exercise, diet, and weight reduction therefore remain essential for blood pressure, insulin resistance, triglycerides, physical fitness, and overall cardiovascular risk, but should not be presented as specific treatments for Lp(a).

While therapies targeting the synthesis or assembly of apolipoprotein(a) are being investigated, patients and clinicians frequently seek accessible interventions. Several nutraceuticals have been studied, but the literature is heterogeneous, includes small populations, and uses different units and formulations. This review critically summarizes these data and proposes a practical approach without attributing to nutraceuticals a cardiovascular outcome benefit that has not been demonstrated.

2. METHODS

We conducted a narrative review oriented toward clinical practice. We prioritized systematic reviews, meta-analyses of randomized clinical trials, consensus statements, and recent therapeutic reviews that directly assessed Lp(a). Individual clinical studies were used when no quantitative synthesis was available, particularly for pectin, Ginkgo biloba, and Xuezhikang. We considered study design, number of participants, dose, duration, absolute or relative change in Lp(a), statistical significance, concomitant effects on LDL-C, and safety limitations. Results reported in mg/dL, percentages, and standardized mean differences were retained in their original units because these measures are not directly interchangeable. Products assessed only for LDL-C, without demonstrable Lp(a) measurement, were identified separately and were not considered evidence-based options for lowering Lp(a).

3. WHY DOES A LABORATORY REDUCTION NOT AUTOMATICALLY INDICATE CLINICAL BENEFIT?

An Lp(a) reduction may represent a biologically interesting signal, but it does not establish reductions in myocardial infarction, stroke, mortality, or progression of aortic stenosis. This issue is particularly important for nutraceuticals: most studies were short, included only a few dozen participants, and used Lp(a) concentration as a surrogate outcome. Analytical variability and the skewed distribution of Lp(a) may also amplify findings in small samples.

Magnitude of effect and certainty of evidence must also be distinguished. Ginkgo biloba, pectin, and Xuezhikang produced relative reductions of approximately 23-27% in individual studies, but these findings are less reliable than a smaller absolute reduction reproduced across multiple trials and summarized in a meta-analysis. Clinical selection should therefore not be based solely on the largest published percentage.

4. NONGENETIC CONDITIONS ASSOCIATED WITH CHANGES IN LP(A)

Although 70-90% of Lp(a) variability is genetically determined, several acquired conditions may raise or lower its concentration. This is relevant when a result is unexpectedly high, varies across serial measurements, or was obtained during acute illness. Identifying an associated condition does not eliminate the genetic component and, in most cases, should not delay cardiovascular risk stratification (Table 1).

5. CLINICAL EVIDENCE FOR THE MAIN NUTRACEUTICALS

Doses, treatment durations, effect magnitudes, and practical interpretations are summarized in Table 2.

5.1 L-Carnitine

L-carnitine has one of the most consistent quantitative evidence bases. A meta-analysis of seven trials, eight treatment arms, and 375 participants found a mean reduction of 8.82 mg/dL (95% CI -10.09 to -7.55), with an estimate of approximately -9.00 mg/dL when oral administration was analyzed separately [16]. Doses ranged from approximately 1 to 4 g/day, and treatment duration was heterogeneous. Despite the magnitude of the estimate, the trials included distinct clinical populations, including patients undergoing hemodialysis, which limits extrapolation to asymptomatic individuals with elevated Lp(a). Gastrointestinal adverse effects may occur; high doses require caution in patients with epilepsy and advanced kidney disease.

5.2 Coenzyme Q10

A meta-analysis of seven randomized trials involving 409 participants found a mean reduction of 3.54 mg/dL (95% CI -5.50 to -1.58; $p<0.001$), with a stronger signal of benefit in individuals with baseline Lp(a) >=30 mg/dL [17]. Doses generally ranged from 120 to 300 mg/day for 4-12 weeks. CoQ10 is usually well tolerated but may cause gastrointestinal symptoms and may interfere with coumarin anticoagulants. Its effect on Lp(a) is modest and should not be interpreted as a substitute for indicated lipid-lowering therapies.

5.3 Flaxseed

A meta-analysis of seven trials involving 629 participants found a mean reduction of 2.06 mg/dL (95% CI -3.85 to -0.27; $p=0.024$), with no relevant heterogeneity and a signal of greater effect in longer interventions [18]. Another synthesis found a small standardized reduction [19]. Seeds, flour, lignans, and oils were used at different doses and in different formulations, preventing definition of an optimal preparation. Flaxseed may also contribute to a modest LDL-C reduction and increased fiber intake, but it should be introduced progressively because of abdominal bloating, diarrhea, and possible interference with drug absorption when taken simultaneously.

5.4 Curcumin

Highly bioavailable curcumin formulations reduced Lp(a) in a recent meta-analysis, reported as a standardized mean difference of -0.96 (95% CI -1.82 to -0.11; I2=90.6%) [20]. Trials used approximately 80-1,000 mg/day for 6-12 weeks; regimens included nanocurcumin 80 mg/day for three months and curcuminoids 1,000 mg/day combined with piperine 10 mg/day for 8-12 weeks. This metric cannot be compared numerically with mg/dL, and the high heterogeneity reduces precision. Differences in formulation and bioavailability mean that 1,000 mg of conventional curcumin cannot be considered equivalent to 80 mg of nanocurcumin. Curcumin may cause gastrointestinal discomfort and requires caution in patients with gallstones or biliary obstruction and in those taking anticoagulants or antiplatelet agents.

5.5 Berberine

Pooled data from two placebo-controlled trials, one including 100 women and the other 84 men, evaluated oral berberine 500 mg twice daily (1,000 mg/day), with assessments at 8 and 12 weeks [21]. In women, Lp(a) decreased by 0.71 standard deviations, accompanied by reductions in LDL-C and apolipoprotein B; an equivalent pattern was not demonstrated in men. This recent finding requires replication and consistent reporting in absolute units. Berberine may cause drug interactions, gastrointestinal symptoms, and hypoglycemia and should be avoided during pregnancy and lactation.

5.6 Pectin, Ginkgo biloba, and Xuezhikang

Pectin 15 g/day for four weeks reduced Lp(a) by approximately 27% in a small randomized placebo-controlled trial [8,22]. Ginkgo biloba 120 mg twice daily for two months was associated with an approximate 23% reduction in an isolated clinical study [8,22]. Although attractive, these results have not been adequately replicated. Ginkgo requires particular caution in patients at risk of bleeding, those with epilepsy, and those taking anticoagulants or antiplatelet agents.

Xuezhikang is a red yeast rice extract containing monacolins, among other constituents, with pharmacological activity similar to lovastatin. In a randomized trial, 1.2 g/day for six weeks lowered Lp(a) by approximately 23% [8,22]. It should not be regarded as an inert supplement: it may cause myopathy, elevated transaminases, and interactions similar to those of statins. Commercial standardization varies, and red yeast rice products may contain citrinin. In patients already receiving statins, this combination should not be used indiscriminately.

5.7 N-Acetylcysteine and Phytosterols

A small study of 12 individuals with elevated Lp(a), whose median baseline concentration was 87.0 mg/dL, reported a 7% reduction after N-acetylcysteine 1.2 g/day for six weeks ($p=0.02$) [23]. Applied to the baseline median, this percentage corresponds arithmetically to approximately 6.1 mg/dL, but the study did not report an absolute mean difference; this value should therefore be regarded as an estimate rather than a directly observed effect. In the same study, seven participants with lower baseline Lp(a) did not respond to 1.2 g/day for four weeks or 2.4 g/day for an additional two weeks. A later trial in 40 patients with type 2 diabetes and proteinuria, using 600 mg twice daily for two months, likewise found no significant reduction [24]. Taken together, these data do not support clinically relevant Lp(a) lowering with NAC. Phytosterols/stanols showed a statistically significant but extremely

small effect in a meta-analysis. The published effect unit should be verified in the full text before final submission. In practice, phytosterols may be useful for LDL-C lowering but should not be selected specifically to reduce Lp(a).

5.8 Omega-3 Fatty Acids

A meta-analysis of 12 randomized trials and 9,722 participants found no significant reduction: mean difference -0.54 mg/dL (95% CI -1.52 to +0.44; *p*=0.28) [25]. In the subgroup with baseline Lp(a) >=30 mg/dL, the estimate was -5.03 mg/dL but remained nonsignificant (*p*=0.24). Omega-3 fatty acids should therefore not be prescribed specifically to lower Lp(a), although particular formulations may have separate indications related to hypertriglyceridemia or cardiovascular risk.

5.9 Products Without Demonstrated Benefit or With Insufficient Evidence

Soy isoflavones did not significantly reduce Lp(a). A meta-analysis of garlic found a nonsignificant overall effect and a possible increase in Lp(a) in longer studies. Vitamin C, vitamin E/tocotrienols, policosanol, and a combination of red yeast rice, a probiotic, niacin, and CoQ10 did not demonstrate consistent lowering. Resveratrol, bergamot, alpha-lipoic acid, psyllium, green tea, spirulina, chlorella, silymarin, and artichoke have been studied for LDL-C or other metabolic parameters, but the clinical evidence is insufficient to recommend them specifically for lowering Lp(a).

6. A STEPWISE NUTRACEUTICAL APPROACH FOR PATIENTS WITH ELEVATED LP(a)

Persistently elevated Lp(a) after statin or ezetimibe therapy should not be interpreted as failure of these drugs, because they are prescribed primarily to reduce LDL-C and cardiovascular risk rather than to lower Lp(a) directly. Before considering a nutraceutical, the clinician should confirm that LDL-C and apolipoprotein B are adequately controlled, other modifiable risk factors have been addressed, and no secondary condition potentially accounting for the increase is present.

Two clinical scenarios may be considered. In a patient at low or intermediate risk without established cardiovascular disease, a nutraceutical trial may be discussed after shared decision-making, particularly in the presence of persistently elevated Lp(a), a family history of premature cardiovascular disease, or a strong desire for additional intervention. In patients at high or very high risk, with established atherosclerotic disease, familial hypercholesterolemia, or recurrent events, a nutraceutical should be considered only as an adjunct and never as a substitute for statins, ezetimibe, PCSK9 inhibitors, or other indicated therapies.

Selecting the First Nutraceutical

Initial selection should prioritize consistency of evidence, safety, availability, and potential additional metabolic benefits. Although Ginkgo biloba, pectin, and Xuezhikang produced substantial percentage reductions in individual studies, L-carnitine and CoQ10 have more consistent quantitative support from meta-analyses of randomized trials. L-carnitine lowered Lp(a) by approximately 8.82 mg/dL, whereas CoQ10 produced a mean reduction of 3.54 mg/dL. Flaxseed had a smaller effect but may be useful when increased fiber intake and modest LDL-C lowering are also desired.

A pragmatic sequence may be proposed:

1. First option: L-carnitine

Start with 1-2 g/day divided into one or two administrations. If well tolerated, the dose may be increased to 3-4 g/day, within the range evaluated in trials. Monitor for nausea, abdominal discomfort, diarrhea, body odor, and, in susceptible patients, a possible reduction in seizure threshold.

2. Alternative first-line option: CoQ10

Use 120-200 mg/day, preferably with a fat-containing meal. In the absence of response and with good tolerability, 300 mg/day may be considered. The main adverse effects are gastrointestinal discomfort, headache, and insomnia. A possible reduction in warfarin effect should be monitored.

3. Food-based option: flaxseed

Use approximately 30-40 g/day of ground flaxseed, starting with a lower dose and increasing gradually. It should be taken with adequate fluids and separated by several hours from drugs for which absorption is critical. Flatulence, abdominal distention, diarrhea, or constipation may limit use.

4. Fiber-rich option: pectin

The studied dose was 15 g/day for four weeks. Pectin may be considered when concomitant LDL-C lowering is desired, but its Lp(a)-specific effect was demonstrated in only one small trial. It should be introduced gradually because of bloating, gas, and changes in bowel habits.

Assessing Response

Lp(a) and the lipid profile should be repeated after 8-12 weeks, preferably in the same laboratory and without simultaneous introduction of other interventions. This strategy helps distinguish a possible true response from laboratory variability.

For pragmatic purposes, the following operational categories may be used:

- No response: change below approximately 10% or within assay variability.
- Partial response: reduction of approximately 10-20%.
- More substantial response: reduction greater than 20%, confirmed by a second measurement.

These thresholds are operational and have not been validated as therapeutic targets. Even a reduction greater than 20% does not establish a proportional reduction in cardiovascular risk.

What Should Be Done When the First Nutraceutical Does Not Work?

If there is no response, the first product should be discontinued. A sequential trial of another agent may then be undertaken rather than immediately adding several supplements. For example: L-carnitine -> CoQ10 -> flaxseed or pectin.

This sequential approach makes it possible to identify which product was responsible for a response or adverse event. Curcumin or berberine may be considered later in selected patients, but their formulations are more heterogeneous and their interaction potential is greater.

Ginkgo biloba and Xuezhikang would not be initial options. Ginkgo produced a marked reduction in one isolated study but may increase bleeding risk and interact with anticoagulants and antiplatelet agents. Xuezhikang contains monacolins with lovastatin-like activity and may cause myopathy and hepatotoxicity, especially when combined with a statin.

Is There a Role for Combinations?

Evidence is insufficient to routinely recommend nutraceutical combinations for lowering Lp(a). A study in hemodialysis patients evaluated L-carnitine and CoQ10 alone and in combination, but its results do not establish superiority of the combination or permit generalization to the broader population. Any combination should therefore be presented as an experimental, individualized strategy rather than a guideline-based recommendation.

A combination may be considered when the patient has had a partial response and tolerated the first product; LDL-C and other risk factors are already adequately treated; no clinically relevant interactions exist; the patient understands the uncertainty of the evidence; and clinical and laboratory monitoring is feasible.

When a combination is selected, it is preferable to maintain the first agent at the lowest effective dose and add the second at a low starting dose. Pragmatically acceptable possibilities include L-carnitine 1-2 g/day plus CoQ10 120-200 mg/day, or CoQ10 120-200 mg/day plus ground flaxseed 20-30 g/day. Doses may be adjusted after 8-12 weeks according to response and tolerability. The two products should not be introduced simultaneously at the outset because doing so prevents identification of which one produced benefit or an adverse event.

Combinations that should be avoided or used with caution are summarized in Table 3.

Monitoring During Treatment

In addition to Lp(a) and the lipid profile, monitoring should be individualized. Transaminases and creatine kinase may be considered with Xuezhikang or red yeast rice, particularly when combined with statins. Blood glucose should be monitored when berberine is used in patients receiving diabetes treatment. INR should be monitored in warfarin users who start or discontinue CoQ10. Muscular, gastrointestinal, hemorrhagic, or neurological symptoms should prompt immediate reassessment.

6.1 Step-by-Step Clinical Algorithm

Step 1 - Confirm the Measurement Context

The first decision is not which supplement to choose, but how to interpret the result correctly. The unit, laboratory method, and presence of conditions that may transiently alter the concentration should be reviewed, including nephrotic syndrome, advanced kidney disease, liver abnormalities, major inflammatory states, and pregnancy. Converting mg/dL to nmol/L using a fixed factor is not recommended.

Step 2 - Estimate Global Cardiovascular Risk

Lp(a) should act as a risk amplifier rather than an isolated parameter. A history of atherosclerotic disease, aortic stenosis, familial hypercholesterolemia, premature events in the family, diabetes, hypertension, smoking, kidney disease, LDL-C, non-HDL cholesterol, and apolipoprotein B determines the intensity of intervention. In selected primary prevention patients, coronary artery calcium scoring may assist when therapeutic decisions remain uncertain.

Step 3 - Aggressively Reduce Modifiable Risk

The foundation of management is achieving the LDL-C target appropriate to risk with therapies of proven efficacy. Statins should not be discontinued because Lp(a) remained high or increased slightly. Ezetimibe, bempedoic acid, and PCSK9 inhibitors may be added according to risk, LDL-C, access, and tolerability. Blood pressure, glycemia, smoking, weight, physical activity, sleep, and diet should be addressed comprehensively. Lifestyle has little direct effect on Lp(a), but it reduces the absolute risk upon which Lp(a) acts.

Step 4 - Determine Whether a Nutraceutical Trial Is Appropriate

A trial may be discussed with an informed patient, particularly in the setting of persistently elevated Lp(a), residual risk, a desire for an additional intervention, and no contraindications. It should not delay proven treatment or be presented as event prevention. To facilitate interpretation, only one product should initially be selected, preferably a standardized formulation with quality control. Based on consistency of the available evidence, L-carnitine or CoQ10 would be the most defensible options for an individual trial. Flaxseed may be attractive when increased fiber intake and modest lipid improvement are also desired. Pectin is a plausible food-based alternative, but its specific effect on Lp(a) comes from a single study. Curcumin and berberine should be considered more

cautiously because of formulation heterogeneity and interactions. Despite their published effect magnitude, Ginkgo biloba and Xuezhikang should not be first-line options: the former because of bleeding risk and interactions, and the latter because it functions in practice as a statin-containing product with variable dose and purity.

Step 5 - Reassess Objectively

Lp(a), the lipid profile, and tolerability may be reassessed after 8-12 weeks, ideally in the same laboratory and without other simultaneous changes. A laboratory response should be interpreted together with biological and analytical variation. If there is no clinically perceptible reduction, the product should be discontinued, avoiding indefinite use based only on expectation. Even when a response occurs, a proportional reduction in cardiovascular events cannot be assumed.

Step 6 - Refer More Complex Situations

Patients with progressive cardiovascular disease despite optimized treatment, very high Lp(a), familial hypercholesterolemia, recurrent premature events, or aortic stenosis should be evaluated in a specialized center. Advanced LDL-C-lowering therapy, apheresis according to local criteria, or eligibility for clinical trials of Lp(a)-targeted therapies may be appropriate.

The proposed pragmatic algorithm for clinical use is shown in Figure 1.

7. SAFETY, QUALITY, AND INTERACTIONS

The term “natural” does not mean risk-free. Supplement composition may vary across manufacturers and countries, and the labeled dose does not always correspond to the amount actually present. Combination products make it difficult to attribute efficacy and adverse effects to a specific component.

Before prescribing, clinicians should review kidney and liver function, bleeding risk, pregnancy, lactation, epilepsy, and the use of anticoagulants, antiplatelet agents, glucose-lowering drugs, antihypertensive drugs, and statins. Xuezhikang and other red yeast rice products require attention to muscular symptoms and hepatotoxicity. Ginkgo and curcumin may increase bleeding risk in susceptible settings. Berberine has multiple interactions and should not be used during pregnancy. Fibers such as flaxseed and pectin should be separated in time from drugs for which absorption is critical.

8. LIMITATIONS OF THE EVIDENCE

The main limitations are small sample sizes, short follow-up, clinical heterogeneity, different baseline Lp(a) concentrations, nonstandardized formulations, and the use of different units. Some meta-analyses combine populations with kidney disease, diabetes, dyslipidemia, or established cardiovascular disease, and their effects may not be generalizable. Selective publication is possible because small positive studies may be more likely to be published. Finally, none of the nutraceuticals discussed has an outcome trial demonstrating that its Lp(a)-lowering effect reduces cardiovascular events.

This is a narrative rather than a systematic review. Its purpose is to organize the available evidence for prudent clinical use, not to issue formal or graded recommendations.

9. FUTURE PERSPECTIVES

The treatment of elevated Lp(a) is evolving rapidly. Antisense oligonucleotides, small interfering RNAs, and oral inhibitors of particle assembly have produced marked reductions in early- and intermediate-phase studies [26-29]. However, laboratory lowering and event reduction are not equivalent, and cardiovascular outcome trials must determine the clinical role of these strategies. Until a specific treatment with proven clinical benefit becomes widely accessible, the most robust approach remains recognition of the risk conferred by Lp(a) and intensive reduction of the modifiable atherogenic burden.

10. CONCLUSION

L-carnitine, CoQ10, and flaxseed have pooled evidence of small-to-moderate reductions in Lp(a). Pectin, Ginkgo biloba, and Xuezhikang produced apparently larger effects, but these are supported by isolated studies with low certainty. Curcumin and berberine are promising but remain heterogeneous and insufficiently standardized. Omega-3 fatty acids, vitamins C and E, policosanol, soy isoflavones, and garlic have not shown consistent benefit for this purpose.

In practice, nutraceuticals may occupy, at most, an individualized adjunctive role. Management should remain centered on cardiovascular risk stratification, intensive LDL-C/apoB lowering, control of modifiable factors, and access to proven therapies. When a nutraceutical is tested, one agent should be used at a time, interactions and formulation quality should be assessed, Lp(a) should be repeated after 8-12 weeks, and the intervention should be stopped if there is no objective response. This strategy provides a pragmatic option without extending beyond the available evidence.

Declarations

Ethics Approval and Consent to Participate

Not applicable. This article is a narrative review of previously published studies and did not involve the recruitment of human participants, collection of new patient data, or use of identifiable personal information. Therefore, institutional ethics committee approval and informed consent were not required.

Consent for Publication

Not applicable. The manuscript does not contain identifiable individual patient data, images, or case information requiring consent for publication.

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Competing Interests

The authors declare that they have no competing interests relevant to the content of this article.

Author Contributions

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Data Availability

No new datasets were generated or analyzed for this narrative review. All information discussed in the manuscript was obtained from previously published sources cited in the reference list.

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Declaration of Generative Artificial Intelligence and AI-Assisted Technologies in the Writing Process

The manuscript was originally written by the authors in Portuguese and subsequently translated into English with the assistance of a generative artificial intelligence tool. Artificial intelligence was also used to improve grammar, clarity, readability, and language consistency. The authors critically reviewed, corrected, and edited the entire translated manuscript, verified its scientific content and references, and take full responsibility for the accuracy, integrity, and final content of the article. No artificial intelligence tool was listed as an author or used to replace the authors' scientific judgment.

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Tables and Figure

Table 1. Nongenetic conditions associated with changes in Lp(a) concentrations

Condition	Change in Lp(a)	Context or possible mechanism	Practical implication
Nephrotic syndrome/severe proteinuria	Increase, sometimes 3- to 5-fold	Compensatory increase in hepatic lipoprotein synthesis due to urinary protein loss	Treat kidney disease and repeat Lp(a) after proteinuria is controlled
Chronic kidney disease	Usually less than a 2-fold increase; more evident as GFR declines	Reduced catabolism, proteinuria, and inflammation	Interpret together with GFR and albuminuria
Dialysis, particularly peritoneal dialysis	May increase approximately 2-fold	Protein losses, inflammation, and altered clearance	When available, consider the value obtained before advanced kidney disease
Systemic lupus erythematosus	Higher values in some cohorts, particularly with proteinuria, nephritis, lower GFR, and inflammatory activity	Association with inflammation, lupus nephritis, nephrotic syndrome, and kidney dysfunction	Assess disease activity, nephritis, and proteinuria; SLE alone should not be considered a proven direct cause
Other active autoimmune or inflammatory diseases	Variable and inconsistent increase	Lp(a) may behave as an acute-phase reactant	During intense inflammation, consider repeating the measurement after disease control
Hypothyroidism	Variable increase; reductions of up to approximately 20% after hormone replacement have been reported	Reduced lipoprotein catabolism and changes in hepatic synthesis	Assess TSH and treat hypothyroidism according to its own indication
Hyperthyroidism	Usually reduced; Lp(a) may increase after thyroid function normalizes	Increased clearance and changes in lipoprotein metabolism	Repeat testing after euthyroidism is achieved when necessary
Pregnancy	May increase approximately 2-fold	Hormonal changes and increased hepatic lipoprotein synthesis	Avoid defining baseline status from an isolated measurement during pregnancy; repeat postpartum

Condition	Change in Lp(a)	Context or possible mechanism	Practical implication
Menopause	Increase of up to approximately 30%	Reduced estrogenic activity	Interpret in the context of global cardiovascular risk
Estrogen hormone therapy	May reduce approximately 20-30%	Hormonal modulation of hepatic apo(a) synthesis	Do not prescribe hormone therapy solely to lower Lp(a)
Tamoxifen and selective estrogen receptor modulators	Reductions reported in some studies	Modulation of hepatic apo(a) synthesis	Do not use specifically to treat elevated Lp(a)
Growth hormone use	May increase, occasionally approaching 2-fold	Stimulation of hepatic apo(a) synthesis	Interpret in the context of the endocrinological indication
Advanced chronic liver disease	Usually reduced	Reduced hepatic capacity for apo(a) synthesis	Low Lp(a) may reflect liver dysfunction rather than low lifetime cardiovascular risk
Severe acute inflammation	Transient change, usually a mild or moderate increase	Acute-phase response	Repeat after the inflammatory process resolves if the result is unexpected
Major acute infection	Transient variation	Systemic inflammatory response	Avoid interpreting a single measurement during severe infection
Major surgery or trauma	Transient change	Acute metabolic and inflammatory response	Consider repeat testing after clinical recovery
Diabetes mellitus with nephropathy or proteinuria	May increase	The increase appears more closely related to kidney injury and proteinuria than to diabetes alone	Assess kidney function and albuminuria
Mild liver disease or steatotic liver disease	Variable findings	Depends on synthetic function, insulin resistance, and disease severity	Do not automatically attribute Lp(a) changes to steatosis
African ancestry	Baseline concentrations are generally higher	Genetic determination and a distinct distribution of apo(a) isoforms	Not a secondary cause, but relevant to clinical interpretation
Age and sex	Usually a small influence; a possible increase after menopause	Hormonal and metabolic factors	Do not independently explain markedly elevated values

Abbreviations: apo(a), apolipoprotein(a); GFR, glomerular filtration rate; Lp(a), lipoprotein(a); SLE, systemic lupus erythematosus; TSH, thyroid-stimulating hormone.

Table 2. Nutraceuticals and natural products studied for Lp(a) lowering

Nutraceutical or product	Studies/participants	Studied dose	Duration	Effect on Lp(a)	Significance	Practical interpretation
Ginkgo biloba	Small clinical study	120 mg twice daily	2 months	Approximately -10.4 mg/dL (-23%)	Significant	Marked effect from a single study; consider bleeding risk and interactions
L-carnitine	7 RCTs; 8 arms; n=375	1-4 g/day	1-24 weeks	-8.82 mg/dL (95% CI -10.09 to -7.55); oral: approximately -9.00 mg/dL	p<0.001	Best balance between effect magnitude and pooled evidence
Xuezhikang	n=60	1.2 g/day	6 weeks	Approximately -6.78 mg/dL (-23%)	p<0.05	Single-study result; contains monacolins and requires statin-like precautions
Coenzyme Q10	7 RCTs; n=409	120-300 mg/day	4-12 weeks	-3.54 mg/dL (95% CI -5.50 to -1.58)	p<0.001	Pooled evidence, although the absolute effect is modest
Flaxseed	7 RCTs; n=629	Different formulations; generally 30-40 g/day	Approximately 4-12 weeks	-2.06 mg/dL (95% CI -3.85 to -0.27)	p=0.024	Small effect; may also improve LDL-C and fiber intake
Highly bioavailable curcumin	Multiple RCTs	80-1,000 mg/day; nanocurcumin 80 mg/day or curcuminoids 1,000 mg/day plus piperine 10 mg/day	6-12 weeks	SMD -0.96 (95% CI -1.82 to -0.11)	p<0.05	Potential benefit with high heterogeneity; SMD is not directly comparable with mg/dL
Berberine	2 RCTs; approximately n=184	500 mg twice daily; total 1,000 mg/day	8-12 weeks	Women: -0.71 SD (95% CI -1.12 to -0.31)	Significant in women	Sex-dependent result; absolute data in mg/dL are unavailable
Pectin	Small randomized study	15 g/day	4 weeks	Approximately -27%	Significant	Marked relative effect from one short study
N-acetylcysteine	n=12 with elevated Lp(a)	600 mg twice daily; total 1.2 g/day	6 weeks	-7%; approximately -6.1 mg/dL when applied to a baseline median of 87 mg/dL	p=0.02	The 6.1 mg/dL reduction is estimated, not directly reported; another trial was negative

Nutraceutical or product	Studies/participants	Studied dose	Duration	Effect on Lp(a)	Significance	Practical interpretation
Phytosterols/stanols	7 articles; 12 comparisons	Generally 1.5-2.0 g/day; exact range in Lp(a) studies requires confirmation	Weeks to months	Statistically significant but extremely small effect; the published unit requires confirmation	p=0.017	May lower LDL-C but should not be chosen specifically to treat Lp(a)
Omega-3 - overall population	12 RCTs; n=9,722	Various EPA/DHA doses	Variable	-0.54 mg/dL (95% CI -1.52 to +0.44)	p=0.28	No significant Lp(a) reduction
Omega-3 - baseline Lp(a) >=30 mg/dL	Meta-analysis subgroup	Various EPA/DHA doses	Variable	-5.03 mg/dL (95% CI -13.42 to +3.37)	p=0.24	Nonsignificant signal of benefit
Soy isoflavones	10 studies; 11 arms; n=973	Various doses and formulations	Variable	SMD +0.08 (95% CI -0.05 to +0.20)	p=0.228	No demonstrated benefit
Garlic - overall result	6 RCTs	Various preparations	Variable	+16.86% (95% CI -4.59 to +38.31)	p=0.124	No reduction; numerical trend toward an increase
Garlic - studies >12 weeks	RCT subgroup	Various preparations	>12 weeks	+54.59% (95% CI +30.47 to +78.71)	p<0.001	Possible Lp(a) increase; do not recommend for this purpose
Vitamin C	RCTs with n=44 and n=101	1-4.5 g/day	12 weeks-8 months	No significant reduction	NS	Not recommended for Lp(a) lowering; high doses have specific risks
Vitamin E/tocotrienols	n=40	Tocotrienols 140 mg/day plus alpha-tocopherol 80 mg/day	6 weeks	No significant reduction	NS	No demonstrated benefit
Policosanol	n=143	10-80 mg/day	12 weeks	No significant reduction	NS	No demonstrated benefit
Red yeast rice + probiotic + niacin + CoQ10	n=33	Combination product; doses depend on formulation	12 weeks	Lp(a) unchanged	NS	LDL-C decreased, but Lp(a) did not
Resveratrol	Small clinical studies	Generally 100-500 mg/day	Approximately 4-12 weeks	Inconsistent or nonquantifiable data	-	Not recommended specifically for Lp(a)
Bergamot	Small dyslipidemia studies	Approximately 500-1,500 mg/day	4-12 weeks	No consistent Lp(a) result	-	May lower LDL-C, but Lp(a) evidence is undefined

Nutraceutical or product	Studies/participants	Studied dose	Duration	Effect on Lp(a)	Significance	Practical interpretation
Alpha-lipoic acid	Metabolic RCTs	Generally 300-600 mg/day	4-24 weeks	No defined effect on Lp(a)	-	Evidence primarily concerns LDL-C and glucose metabolism
Psyllium/soluble fiber	Multiple RCTs	Approximately 5-15 g/day	4-24 weeks	No defined effect on Lp(a)	-	May lower LDL-C but should not be used specifically for Lp(a)
Green tea/catechins	RCTs and lipid meta-analyses	Generally 300-800 mg/day of catechins	Weeks to months	Insufficient Lp(a) data	-	Possible modest LDL-C reduction
Spirulina	Metabolic studies; meta-analysis of 20 studies, n=1,076	Approximately 1-8 g/day	4-24 weeks	No established Lp(a)-specific effect	-	Available evidence concerns the general lipid profile
Chlorella	Small RCTs	Approximately 1-10 g/day	Weeks to months	Insufficient Lp(a) data	-	Not recommended specifically for Lp(a)
Silymarin	Metabolic RCTs	Approximately 200-1,400 mg/day	Weeks to months	Insufficient Lp(a) data	-	Occasional LDL-C effects reported, but not Lp(a) effects
Artichoke	RCTs and lipid meta-analyses	Approximately 500-1,800 mg/day of extract	6-12 weeks	Insufficient Lp(a) data	-	May lower LDL-C but has no Lp(a)-specific indication

Abbreviations: CoQ10, coenzyme Q10; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); NS, not significant; RCT, randomized controlled trial; SD, standard deviation; SMD, standardized mean difference.

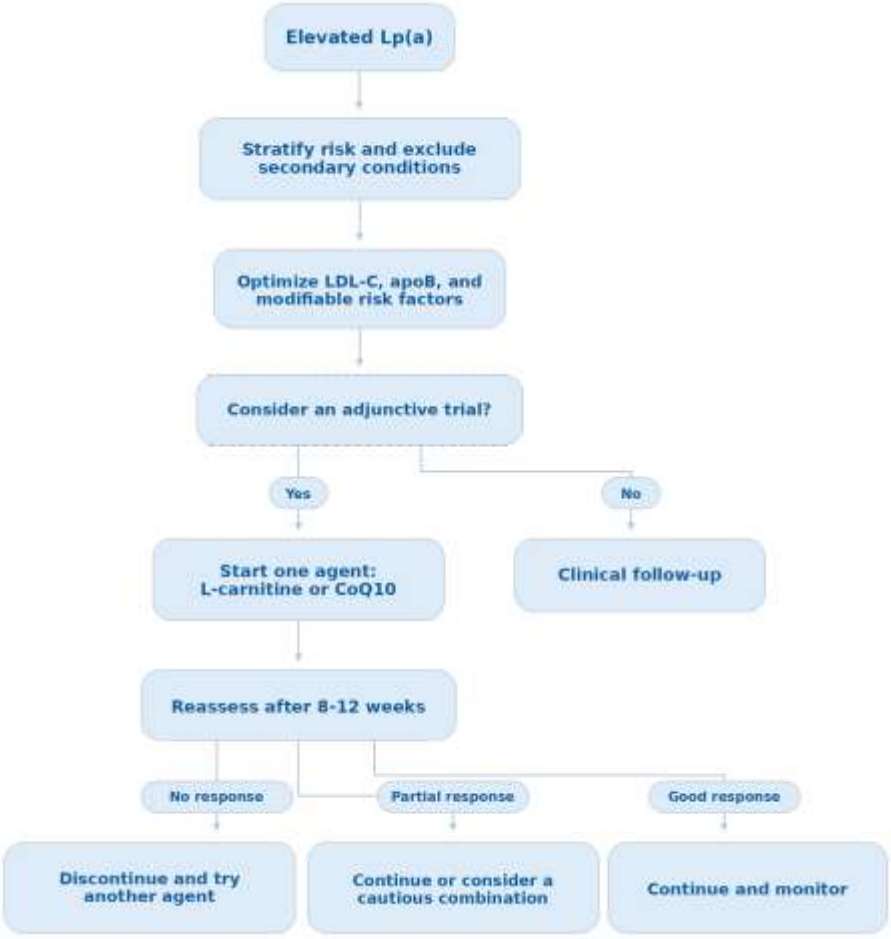
Table 3. Nutraceutical-drug combinations and clinical situations requiring caution

Combination or situation	Main concern	Practical approach
Statin + Xuezhikang/red yeast rice	Duplicate pharmacological effect, myopathy, and hepatotoxicity	Avoid; if exceptionally used, monitor muscular symptoms, transaminases, and creatine kinase as clinically appropriate
Anticoagulant or antiplatelet agent + Ginkgo biloba	Possible increase in bleeding risk	Avoid or use only after individualized bleeding-risk assessment
Anticoagulant or antiplatelet agent + high-dose curcumin	Possible increase in bleeding risk	Use cautiously and review bleeding signs and other interactions
Ginkgo biloba + curcumin	Possible additive bleeding risk	Avoid empirical combination

Combination or situation	Main concern	Practical approach
Warfarin + CoQ10	Possible reduction in anticoagulant effect and INR changes	Monitor INR when starting, adjusting, or discontinuing CoQ10
Berberine + glucose-lowering agents	Hypoglycemia	Monitor glucose and consider adjustment of antidiabetic treatment
Berberine + cyclosporine or relevant CYP/P-gp substrates	Potential increase in drug concentrations	Review interactions before use and avoid when monitoring is not feasible
Flaxseed or pectin taken with other medications	Reduced or delayed absorption	Separate administrations by several hours, particularly for drugs with critical absorption
L-carnitine in a patient with epilepsy	Possible increased susceptibility to seizures	Assess individually and avoid in uncontrolled epilepsy
Multiple products started simultaneously	More adverse events and inability to identify efficacy or causality	Start one agent at a time and reassess after 8-12 weeks

Abbreviations: CoQ10, coenzyme Q10; CYP, cytochrome P450; INR, international normalized ratio; P-gp, P-glycoprotein.

Figure 1. Pragmatic algorithm for the adjunctive management of elevated Lp(a)



Legend: After confirming elevated Lp(a), stratify cardiovascular risk, exclude secondary conditions, and optimize LDL-C, apoB, and other modifiable factors. If an adjunctive nutraceutical trial is selected after shared decision-making, start one agent, reassess after 8-12 weeks, and continue, switch, or consider a cautious combination according to response and tolerability. Nutraceuticals do not replace therapies with proven cardiovascular benefit.
Abbreviations: apoB, apolipoprotein B; CoQ10, coenzyme Q10; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a).