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Coenzyme Q10 and *Terminalia Arjuna* Bark Extract in Cardiovascular Function and Metabolic Homeostasis: Mechanistic Rationale for the COQ10+ Formulation

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Abstract: Cardiovascular disease is the leading cause of death worldwide, claiming 17.9-19.8 million lives annually, with a disproportionately higher burden in low- and middle-income countries. Its pathophysiology involves the interplay between mitochondrial dysfunction, oxidative stress, inflammation, endothelial dysfunction, dyslipidaemia, impaired cardiomyocyte calcium homeostasis, and the metabolic derangements of diabetes mellitus. Coenzyme Q10, a lipophilic component of the mitochondrial electron transport chain, confers cardio protection: the Q-SYMBIO international trial established that adjunctive 300 mg/day CoQ10 for 2 years reduces major adverse cardiovascular events by 50% in patients with NYHA Class III-IV heart failure (hazard ratio: 0.50; 95% CI: 0.32-0.80; p=0.003). Terminalia arjuna, the most extensively investigated cardiovascular herbal medicine in the Ayurvedic tradition, exerts pleiotropic effects via triterpenoid acids, including arjunic, arjunolic, and arjungenin, whose antioxidant properties surpass ascorbic acid; flavonoids such as luteolin and quercetin, which modulate vascular reactivity; and tannins that improve lipid profiles. Notably, Terminalia arjuna is also a natural source of CoQ10, rationalising their combination in a fixed-dose formulation. This review synthesises the preclinical and clinical evidence for the cardio protective effects of Coenzyme Q10 and Terminalia arjuna extract, focusing on COQ10+: a fixed-dose combination of 200 mg CoQ10 and 150 mg standardised Terminalia arjuna extract per tablet. By targeting six key pathways – cardiac mitochondrial bioenergetics, cardiomyocyte calcium homeostasis, endothelial function, dyslipidaemia, oxidative stress, and inflammation – COQ10+ represents a comprehensive therapeutic approach. However, while the efficacy of the individual components is established, the synergy of the combination remains to be elucidated. Consequently, assertions regarding plaque regression, restoration of calcium homeostasis, or reduction in major adverse cardiovascular events should be tempered by recognition that the fixed-dose formulation has yet to undergo clinical evaluation.

keywords: Coenzyme Q10; Terminalia arjuna; Cardiovascular nutraceutical; Mitochondrial function; Heart failure; Atherosclerosis; Endothelial dysfunction; Oxidative stress.

1. Introduction

Cardiovascular disease (CVD) is the leading cause of death worldwide, with 17.9 million deaths per year [1, 11]. As a chronic disease driven by multiple mechanisms, CVD requires comprehensive treatment across

different aspects of pathology [1]. Myocardial mitochondria occupy 30–35% of cardiomyocyte volume and provide more than 90% of cardiac energy as ATP [12, 13]. The phosphocreatine-to-ATP ratio falls by 30–50% during chronic heart failure progression and is significantly linked to disease severity [12, 13]. Mitochondrial dysfunction promotes heart disease through reduced mitochondrial coenzyme Q10, inhibiting electron transport phosphorylation [4, 14]. Excessive mitochondrial ROS production can also oxidise cardiolipin, disorganising respiratory chain supercomplexes, augmenting oxidative stress, and reducing nitric oxide availability via endothelial nitric oxide synthase dysfunction [11, 15]. CoQ10 improves mitochondrial energy metabolism and protects lipid membranes from oxidative damage. Terminalia arjuna extract supports heart muscle contraction, normalises lipid profile, reduces oxidative stress in aqueous conditions, and exerts an endothelium-dependent vasodilating effect through various mechanisms [5, 6, 8, 16-18]. The extract contains CoQ10, which may explain its beneficial effects in combination with CoQ10 supplementation [9, 10].

This review critically assesses the biochemical, pharmacological, and clinical evidence for the cardioprotective effects of Coenzyme Q10 and Terminalia arjuna bark extract, focusing on the combined intervention COQ10+ from Biotex Life Solutions.

2. Product Profile of COQ10+

COQ10+ (Biotex Life Solutions) is a fixed-dose combination nutraceutical combining Coenzyme Q10 (200 mg) and standardised Terminalia arjuna bark extract (150 mg) per serving.

Table 1: Composition of COQ10+ per serving

Component	Amount	Functional role
Coenzyme Q10 (ubiquinone/ubiquinol)	200 mg	Mitochondrial bioenergetics; lipid-phase antioxidant
T. arjuna bark extract	150 mg	Cardiotonic; lipid modulation; antioxidant
Excipients	q.s.	Capsule integrity, stability

The 200 mg CoQ10 dose aligns with the KiSel-10 trial and dose-response data showing >100 mg/day confers substantial mortality benefit in HF meta-analyses [21, 22]. The 150 mg arjuna dose is proportionate to clinical schedules (500 mg extract TID), for once- or twice-daily support [23, 24]. Selection prioritised complementary mechanisms (bioenergetics, redox, calcium handling, lipid metabolism, inflammation), human efficacy, safety, and single-dose compatibility [19, 20, 25]. COQ10+ is for adult use to maintain cardiovascular, metabolic and endothelial function; it is not a drug and should not replace or supplement prescription cardiovascular medications without physician advice.

Fig 1: COQ10+ (Biotex Life Solutions)

Quality Standards:

COQ10+ is manufactured to standards aligned with:

- GMP certification (manufacturing-process hygiene and control)
- FSSAI compliance

- HPLC quantification of marker phytochemicals
- Heavy-metal and microbial testing per pharmacopoeial limits
- Stability testing under ICH accelerated and long-term conditions, including monitoring for CoQ10 oxidation susceptibility [19,20,25]

3. Coenzyme Q10: Biochemistry and Physiological Importance

3.1 Chemical Structure and Redox Forms

CoQ10 has a 1, 4-benzoquinone head with a ten-unit polyisoprenoid tail; the tail confers lipid-solubility, and the head undergoes reversible two-electron redox [26, 27]. In the electron transport chain, it carries electrons from complexes I and II to complex III in the inner mitochondrial membrane [27]. A lipid-soluble antioxidant, it prevents lipid peroxidation by interrupting the free-radical chain [28] and generates energy in the cristae by transferring electrons [4, 29].

In chronic heart failure, decreased myocardial CoQ10 impairs ATP production and depletes energy reserve, reducing output and contractility [3, 30]; supplementation improves prognosis by enhancing mitochondrial function [26, 31]. Endogenous production also declines with age, especially in the heart, contributing to cardiovascular disease [25, 29].

Crystalline CoQ10 is poorly absorbed; self-emulsifying and liposomal formulations improve bioavailability [32, 33], delivering the recommended dose and raising tissue concentrations [32] — useful with impaired gastrointestinal motility or reduced endogenous production in older adults [25,29]. With Terminalia arjuna, CoQ10 gains from arjunic acid's modulation of calcium homeostasis and reduction of oxidative stress-induced plaque formation [34, 35].

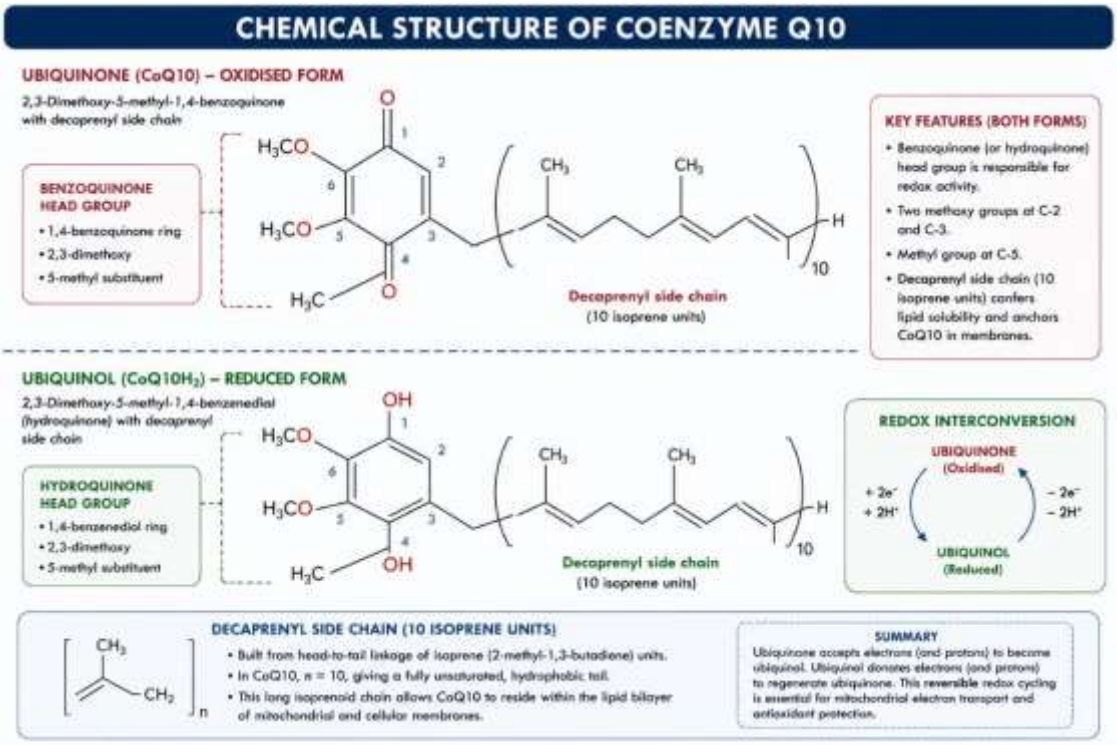

Fig 2: Chemical structure of ubiquinone (oxidised) and ubiquinol (reduced) forms. Shown: 2, 3-dimethoxy-5-methyl-1,4-benzoquinone head group and decaprenyl side chain.

3.2 Ubiquinone and Ubiquinol

CoQ10 exists as oxidised ubiquinone and reduced ubiquinol; ubiquinol predominates (93-95%) as a lipid-soluble antioxidant [27, 36]. Whereas ubiquinone must be converted by complex I to enter the electron transport chain, ubiquinol directly scavenges membrane lipid peroxyl radicals [36, 37] and regenerates α-tocopherol and ascorbate [38]. As a cofactor, CoQ10 shields DNA and proteins from oxidative damage and, at the membrane, regulates redox-sensitive signal transduction molecules [39, 40].

Terminalia arjuna enhances contractility by modulating cardiomyocyte calcium signalling, slows atherosclerosis by reducing LDL oxidation and pro-inflammatory cytokine formation in coronary artery

disease [41], and, with CoQ10, improves endothelial dysfunction in diabetic rats via increased insulin sensitivity and reduced oxidative stress [42]. It counteracts drivers of vascular damage — hyperglycaemia, impaired glucose tolerance, and elevated pro-inflammatory and adhesive molecules [43].

The combination thus benefits diabetes-associated cardiovascular disease by modulating oxidative stress and inflammation while improving vascular function and contractility.

3.3 Endogenous Synthesis

CoQ10 is synthesised via the mevalonate pathway, which statins inhibit, so statin use can cause deficiency [26, 27]; supplementation offsets this and maintains cardiac mitochondrial phosphorylation potential [44]. Other inhibitors include gemfibrozil, some beta-blockers (propranolol, metoprolol), and oral diabetic drugs [45]. Reduced synthesis can leave type 2 diabetes patients with extensive mitochondrial dysfunction and poor response to metabolic stress [46].

Terminalia arjuna extract can prevent further mitochondrial membrane damage in metabolic syndrome [47]. It lowers cardiac oxygen consumption and improves left ventricular performance under ischemic stress from progressive insulin resistance [48]. By reducing lipid peroxidation and enhancing endothelial function, it can ameliorate diabetic patients, who often carry increased lipid load and impaired vascularisation [49]. It also lowers lipid levels and blood viscosity, thereby easing mechanical stress on the heart [50]; by modulating endothelial nitric oxide synthase expression, it can alleviate metabolic syndrome [15].

3.4 Tissue Distribution in Cardiovascular System

Heart tissue holds the highest CoQ10 concentration of any tissue (114 μg/g) [12, 27]; liver and kidneys are also rich. Plasma and tissue levels correlate with ageing and heart failure [4, 26], so supplementation supports mitochondrial function and limits metabolic impact [51, 52]. *Terminalia arjuna* maintains tissue integrity, its triterpenoids and flavonoids combating oxidative stress-induced myocardial damage from metabolic changes [9, 53]. The extract lowers lipid peroxidation and the pro-inflammatory cascade, preventing plaque destabilisation [54, 55]; its triterpenoids enhance contractile function [10]; and in diabetic animals it reduces tissue damage and restores contractility during chronic hyperglycaemia [56]. Both agents affect diabetic dyslipidaemia — CoQ10 lowers total cholesterol and LDL, the extract prevents atherosclerosis [57] — jointly addressing its pathogenesis, including glucotoxicity, and preventing progression [58]. Arjunolic acid and glycosides attenuate cardiac oxidative stress and inflammation [59], valuable since CoQ10 deficiency raises mitochondrial free radicals and impairs antioxidants, damaging membranes [60,61]. Finally, the combination modulates calcium signalling proteins governing excitation-contraction coupling, enhancing contraction [62].

3.5 Role in the Electron-Transport Chain

Ubiquinone shuttles electrons from complexes I and II (succinate dehydrogenase) to complex III (cytochrome bc1), maintaining the proton-motive force for ATP generation [26, 33]. It preserves mitochondrial energy under ischemic stress [63] and limits oxidative damage to the respiratory chain [64]. CoQ10 thus sustains heart-fibre integrity during ischemia, restoring respiratory chain function and reducing infarct tissue damage in the diabetic heart [64], protecting myocardium from necrosis and shrinking infarct size [65,66]. Where diabetic cardiomyopathy compromises its antioxidant function, combined *Terminalia arjuna* improves mitochondrial thiol-dependent antioxidant systems [67]. Chain integrity also prevents cardiomyocyte remodelling common in diabetes mellitus [68, 69]. Via the Q-cycle, CoQ10 regulates oxidative phosphorylation and the permeability transition pore, preventing programmed death in hypoxic myocytes [70,71], and regulates intracellular calcium homeostasis — deranged in diabetes and vital where calcium governs excitation-contraction coupling, since impaired signalling triggers lethal arrhythmias under metabolic stress [72]. Its antioxidant activity neutralises reactive oxygen species from complexes I and III [73, 74], maintaining the reduced ubiquinone form essential for respiratory function [75, 76]. The combination therefore preserves bioenergetics and chain integrity, and CoQ10 prevents the disrupted fatty acid oxidation of diabetes mellitus [77]. A clinical study showed CoQ10 cut mortality risk by 43% in heart failure patients by raising cardiac energy and reducing dysfunctional contractile signs and symptoms [78]. *Terminalia arjuna* adds cardio protection by modulating extracellular matrix homeostasis, often impaired in the elderly or in diabetes mellitus.

3.6 ATP Production

Each electron pair via CoQ10 lets Complex III pump 4 protons, driving ATP synthase. In HF, myocardial ATP generation falls by 30–50% alongside CoQ10 decline [2, 4, 12]. Replenishing this carrier restores respiratory chain function, narrowing the demand-supply gap [13, 79] and raising left ventricular ejection fraction and global longitudinal strain [14, 80]. Concomitant *Terminalia arjuna* modulates calcium homeostasis, optimising excitation-contraction coupling in the failing myocardium; by sustaining the proton gradient, the combination prevents metabolic-heart-disease exhaustion and the bioenergetic depletion driving cardiomyopathy progression [81, 82]. Arjuna's anti-inflammatory action inhibits plaque progression and destabilisation, addressing vascular damage accompanying impaired myocardial calcium handling [83, 84]. Its synergistic attenuation of C-reactive protein and tumour necrosis factor-alpha suppresses the proinflammatory state worsening endothelial vulnerability, curbing leukocyte adhesion molecule up-regulation and pro-atherogenic cytokine expression in the vascular wall [59,85], which stabilises endothelial nitric oxide synthase (eNOS) activity essential for vasomotor function and preventing vascular disease progression [84,86]. CoQ10 further optimises inner-membrane redox potential, improving Q-cycle efficiency and the proton motive force for ATP synthase activation [70,73], while *Terminalia arjuna* sustains mitochondrial metabolic flexibility, keeping substrate flux into the tricarboxylic acid cycle despite the failing heart's heightened demands [77,83]. By protecting respiratory complexes from oxidative degradation while replenishing CoQ10, the approach mitigates the energy starvation of metabolic cardiomyopathies, bridging myocardial energy consumption and supply [76, 79].

3.7 Antioxidant and Membrane-Protective Activity

Ubiquinol quenches lipid peroxyl radicals, regenerates α-tocopherol from its oxidised radical, and protects inner-membrane cardiolipin — a critical step against permeability transition pore opening [26, 27]. *Terminalia arjuna* reinforces these membranes by modulating lipid peroxidation and preserving myocardial collagen against protease-induced plaque degradation. Its triterpenoids, notably arjunic acid, show free-radical scavenging exceeding ascorbic acid in microsomal lipid peroxidation assays, reducing oxidative membrane susceptibility [5]. The extract also supports the extracellular matrix by reducing matrix-degrading enzyme expression and inhibiting pro-inflammatory cytokines driving plaque destabilisation, crucial for the integrity of myocardium and vascular endothelium [6, 59].

3.8 Factors Associated with CoQ10 Depletion

CoQ10 is reduced in:

- Ageing (post-40) [26];
- Chronic heart failure (~75% of HF patients are deficient) [2,12];
- Type 2 diabetes (altered ubiquinol/ubiquinone ratio reflecting oxidative stress) [36,87];
- Hyperlipidaemia and statin therapy [25,88];
- Chronic oxidative stress [27].

3.9 Bioavailability and Formulation Considerations

CoQ10 is poorly absorbed from conventional powders (<5% bioavailability). Liposomal carriers (81.5% encapsulation efficiency) [33, 89], phospholipid complexes, and the reduced ubiquinol form substantially improve it. Metazome technology showed a 4.3-fold AUC and 3.6-fold Cmax increase versus conventional CoQ10 powder [25, 32].

4. Terminalia Arjun: Botanical and Pharmacological Profile

4.1 Botanical Identity

Terminalia arjuna Wight & Arn. (Indian subcontinent) [90] is a deciduous Ayurvedic cardioprotective tree whose triterpenoids, flavonoids, and glycosides modulate cardiovascular hemodynamics. Bark polyphenols and flavonoids (luteolin, quercetin) protect against vascular oxidative damage and improve myocardial contractility [90], aiding coronary vasodilation, peripheral perfusion, and angina relief [16]. Regular use lowers angina frequency and raises exercise tolerance, notably in severe refractory heart failure [91].

4.2 Traditional Use

Ayurvedic texts term *T. arjuna hridya*, a cardiotonic for palpitations, angina, and post-febrile heart weakness [17,90]. Its bark extract exerts inotropic, vasodilatory, and hypotensive effects, acting as a natural ergogenic aid for cardiopulmonary endurance [16, 91]. The synergistic triterpenoid, flavonoid, and phenolic-

glycoside matrix optimises contractility while attenuating vascular resistance [19, 59, 90]; via metabolic and coronary-flow modulation, it stabilises cardiac function, improves exercise tolerance, and eases chronic-heart-failure symptoms [10, 91].

4.3 Medicinal Part — Bark

The stem bark holds the highest bioactive concentration and is the near-exclusive research focus [16,90]. Rich in triterpenoid acids (arjunic, arjunolic, arjungenin) and saponin glycosides [19, 90], it enhances myocardial inotropy via sarcoplasmic reticulum calcium handling and L-type Ca^{2+} channel activity, correcting heart-failure contractile deficits [18, 91]. It also inhibits matrix metalloproteinases and pro-inflammatory pathways, preventing protease-induced plaque degradation and preserving endothelial extracellular-matrix integrity [59,90], and exerts a prostaglandin E2-like action promoting coronary vasodilation and lowering blood pressure to ease myocardial workload [92].

Fig 3: Stem bark of *Terminalia arjuna*, the principal medicinal part rich in triterpenoids and other cardioprotective phytochemicals.

4.4 Major Phytochemical Constituents

Table 2: Phytochemical Matrix of *T. arjuna* Bark

Compound class	Representative compounds	Pharmacological activities and quantitative notes
Triterpenoid acids	Arjunic acid, arjunolic acid, arjungenin, arjunetin	Cardiotonic; antioxidant > ascorbic acid; anti-inflammatory [5,19,90]
Flavonoids	Luteolin, quercetin, kaempferol, catechin	eNOS activation; endothelial protection [6,7,90]
Tannins	Pyrocatechols, gallic acid, ellagic acid	Lipid-lowering; aqueous-phase antioxidant [8,20,90]
Phytosterols	β-sitosterol, stigmasterol	Membrane stabilisation; anti-inflammatory [90]
Phenolic glycosides	Arjunetin, arjunoside	Cardiotonic activity [20,90]
Intrinsic CoQ10	Ubiquinone	Mitochondrial support in same fraction [9,10]

4.4.1 Arjunolic Acid

Arjunolic acid, a major pentacyclic triterpenoid, provides endothelial protection, membrane stabilisation, and antioxidant activity [9,90], and mitigates diabetic cardiovascular dysfunction by enhancing insulin signalling and inhibiting vascular-wall advanced glycation end-product accumulation [59]. It modulates mitochondrial function and suppresses pro-inflammatory and pro-apoptotic cascades, stabilising rhythm and preventing remodelling in ischemic or hyperglycemic conditions [19,90]; by improving cytokine profile and limiting sodium-induced injury, it preserves myocardial integrity against chronic stress [93]. Endogenous coenzyme Q10 in the matrix acts as a mitochondrial cofactor for ATP production during high myocardial demand [94].

4.4.2 Arjunic Acid

Arjunic acid's free-radical scavenging exceeds ascorbic acid in microsomal lipid-peroxidation, DPPH, and hydrogen-peroxide-haemolysis assays [5], neutralising reactive oxygen species and terminating lipid-peroxidation chains vital to myocardial integrity [5]. By stabilising membranes and limiting oxidative damage from hydrogen peroxide, it preserves homeostasis and guards against ischaemic-reperfusion injury [19,90], countering the oxidative cascades that drive remodelling and bioenergetic decline in heart failure [90]. Synergy of CoQ10 with *T. arjuna* constituents optimises the electron transport chain, correcting the metabolic and mitochondrial dysfunction seen in concomitant cardiovascular and diabetic disease [95].

4.4.3 Arjungenin and Arjunetin

These triterpenoid saponins and glycosides drive inotropic action in isolated myocyte and atria preparations [19,20,90]. As cardiotonics, arjungenin and arjunetin optimise excitation-contraction coupling—sensitising myofibrillar proteins to calcium and enhancing SERCA-mediated calcium sequestration at the sarcolemma and sarcoplasmic reticulum—to correct heart-failure contractile deficits [91,92]. They also stabilise the sarcolemmal membrane against stress injury, preserving structural integrity and pumping efficiency under chronic hemodynamic overload [19,90]. This positions *T. arjuna* as a cardioprotective ergogenic aid bridging Ayurvedic tradition and modern management of cardiovascular endurance and cardiac function [96–98].

4.4.4 Flavonoids

The bark's flavonoid fraction comprises **luteolin, quercetin, kaempferol, apigenin, baicalein, flavone, and arjunone**; total flavonoid content of methanol extracts is 4.8–9.2 mg quercetin equivalents per gram dry bark, varying with geographic origin and harvest season [7,57,99].

These flavonoids supply much of the bark's *in vitro* radical-scavenging activity. **Luteolin** suppresses NF-κB in oxidised-LDL-exposed endothelial cells, cutting VCAM-1 and E-selectin expression and monocyte adhesion in early plaque formation [6,99]. **Quercetin** scavenges peroxyl radicals in lipid bilayers and, like luteolin, modulates endothelial nitric oxide synthase (eNOS) activity via Akt-mediated phosphorylation at serine 1177, raising coronary endothelial NO output [99]. **Kaempferol** inhibits thromboxane A_2 formation, conferring platelet anti-aggregation that supports traditional use in thrombotic cardiovascular syndromes [99]. **Baicalein**, a specific 12/15-lipoxygenase inhibitor, reduces leukotriene-mediated inflammation in vascular smooth muscle [99]. **Arjunone**, a chromone flavonoid unique to *Terminalia*, chelates copper, countering copper-catalysed LDL oxidation in the subendothelial space [7]. The **total flavonoid fraction** thus provides combinatorial antioxidant and anti-inflammatory action complementing the lipid-modulating, inotropic triterpenoids.

4.4.5 Tannins and Polyphenols

Bark polyphenols include **gallic acid, ellagic acid, catechin, epicatechin, and condensed tannins (proanthocyanidins)**, with a total polyphenol content of 110–180 mg GAE/g bark. Tannins largely account for the astringent, vasoconstrictive, and antiviral properties, and condensed proanthocyanidins affect vascular permeability and capillary resistance [6,7,99]; ellagic and gallic acid directly scavenge hydroxyl radicals and copper-induced LDL peroxidation [99].

4.4.6 Intrinsic Coenzyme Q10

The bark also holds measurable ubiquinone-class quinones, which initially suggested its cardioactivity might partly stem from endogenous quinone content [6]. Though small, these motifs in the bark chemotype reinforce the rationale for co-formulating bark extract with pharmacological CoQ10 doses.

4.5 Standardisation

Phytopharmaceutical-grade bark extracts are standardised to these quality markers:

- Total triterpenoids ≥ 5 % w/w (expressed as arjunic acid equivalents)
- Total polyphenols ≥ 5 % w/w (expressed as gallic acid equivalents)
- Heavy-metal limits per pharmacopoeia
- Microbial limits per pharmacopoeia
- HPTLC fingerprint chromatogram matching a reference standard [19,100,101]

4.6 Pharmacokinetics

T. arjuna polyphenols and triterpenoids are absorbed orally within 1–4 hours; triterpenoid plasma half-lives of 4–8 hours support twice-daily dosing. Human data are limited; preclinical studies show hepatic metabolism, biliary excretion, and minimal renal elimination [57,99].

4.7 Quality Control Parameters

- HPLC fingerprint matching against reference standard
- Microbial limit tests per pharmacopoeia
- Heavy-metal testing per FSSAI limits
- Triterpenoid content ≥ 0.5% w/w
- Moisture < 5%
- Ash value within specified range

5. The COQ10+ Formulation and Cardiovascular Pathology

5.1 Impaired Myocardial Energy Metabolism

The myocardium relies almost entirely on mitochondrial oxidative phosphorylation, whose electron-transport chain supplies over 90 % of cardiac ATP. In chronic heart failure, this is progressively lost: Mortensen and colleagues found myocardial CoQ10 falling with declining NYHA functional class, underpinning the "energy-starvation" model [2,12]. The pattern recurs in ischaemic, hypertensive, and diabetic cardiomyopathies, where reduced complex I/III/IV activity tracks impaired left-ventricular ejection fraction [84,102,103]. CoQ10 depletion lowers the ATP/ADP ratio, slowing SERCA2a-mediated calcium reuptake and prolonging relaxation, deepening the diastolic dysfunction that drove the decline — a self-reinforcing bioenergetic-contractile loop [104,105].

5.2 Mitochondrial Reactive Oxygen Species

Normally, 1–2 % of mitochondrial oxygen consumption leaks into superoxide at complexes I and III. CoQ10 depletion increases electron slippage into molecular oxygen, and the superoxide load exceeds manganese superoxide-dismutase and the ubiquinol-peroxiredoxin- thioredoxin cascade. Excess superoxide becomes hydrogen peroxide and, via Fenton chemistry, hydroxyl radicals that peroxidise cardiolipin. Cardiolipin loss destabilises respiratory supercomplex assembly, further cutting electron-transport efficiency and amplifying ROS in a self-perpetuating cycle [15,106,107]. Mitochondrial ROS also signals, but supraphysiological levels oxidise key thiols on RyR2, LTCC, and PLN — direct contributors to the calcium-handling abnormalities explored in Section 7 [104,105].

5.3 Endothelial Dysfunction

The vascular endothelium is highly sensitive to oxidative stress: its key mediator, nitric oxide, is rapidly scavenged by superoxide to peroxynitrite. The resulting loss of NO bioavailability is the earliest clinically measurable endothelial abnormality, seen as reduced brachial-artery flow-mediated dilatation before any structural atherosclerotic change [86,108]. Across chronic heart failure, diabetes, hypertension, dyslipidaemia, and ageing — every condition targeted by COQ10+ — this same oxidative-stress / reduced-NO axis underlies the endothelial phenotype [15,109,110]. Endothelial dysfunction predicts cardiovascular events independently of traditional risk factors, driving a procoagulant, pro-inflammatory, pro-vasoconstrictive state that accelerates disease.

5.4 Reduced Nitric-Oxide Bioavailability

Reduced NO bioavailability spreads from the endothelium into the vessel wall and myocardium. With less NO to activate soluble guanylate cyclase in vascular smooth muscle, systemic vascular resistance rises, coronary perfusion falls, and myocardial oxygen supply drops relative to demand [108,109,111]. Peroxynitrite also oxidises BH4, the essential cofactor of endothelial nitric oxide synthase, converting the enzyme from NO-producing to superoxide-producing — "eNOS uncoupling" that widens the oxidative-stress / NO-deficit gap [15,110]. Strategies raising the ubiquinol pool and activating eNOS via PI3K/Akt signalling (arjuna triterpenoids) can therefore restore NO bioavailability along two converging routes.

5.5 Chronic Vascular Inflammation

Endothelial activation and reduced NO drive NF-κB-mediated expression of vascular cell adhesion molecules (VCAM-1, ICAM-1) and monocyte chemoattractant protein-1, together promoting monocyte rolling, adhesion, and transmigration [15,109]. Persistent low-grade vascular inflammation underlies chronic atherosclerosis and the inflammatory phenotype now recognised in heart failure with preserved ejection fraction — increasingly a nutraceutical-support target [110]. *Terminalia arjuna* bark flavonoid fractions (luteolin, quercetin, kaempferol) suppress NF-κB in oxidised-LDL-stimulated endothelial cells, a mechanistic basis for the documented *in vitro* anti-inflammatory activity [6,7,99].

5.6 Lipid Oxidation and Atherosclerosis

Oxidised LDL (oxLDL) is the central atherogenic ligand, taken up via the monocyte-derived macrophage's scavenger receptor to drive unregulated cholesterol accumulation and foam-cell formation. Ubiquinol-enriched LDL resists copper-catalysed oxidation ex vivo, with prolonged oxidation lag time and fewer immunogenic oxidation epitopes [108,112]. In ApoE-knockout mice, combined vitamin E and CoQ10 supplementation reduced atherosclerotic lesion area by approximately 40 % versus controls, with decreased aortic oxidative stress and fewer intimal-plaque macrophages [113]. *Terminalia arjuna* extracts lower LDL additionally by suppressing HMG-CoA reductase activity, complementing CoQ10's lipid-stabilisation effects [8,114,115].

5.7 Cardiomyocyte Calcium-Handling Abnormalities

The phospholamban/SERCA2a complex governs cardiomyocyte contraction-relaxation: dephosphorylated phospholamban inhibits SERCA2a's ATP-dependent Ca^{2+} pumping, while phosphorylation by PKA at Ser16 or CaMKII at Thr17 relieves it, accelerating SR Ca^{2+} reuptake and relaxation. PLN ablation in transgenic mice yields hypercontractile cardiomyocytes with markedly accelerated relaxation, whereas the human phospholamban-null mutation is lethal in early infancy, causing dilated cardiomyopathy — showing the regulatome's central physiological role [116–119]. In failing hearts, reduced SERCA2a expression and PLN hypophosphorylation prevail, producing prolonged Ca^{2+} transients, impaired lusitropy, and much of the diastolic dysfunction of chronic heart failure [104,105]. COQ10+ addresses this in two ways: CoQ10 replenishes ATP and stabilises mitochondrial Ca^{2+} handling, while prolonged ubiquinol restores SERCA2a protein in animal models of diabetic cardiomyopathy [69].

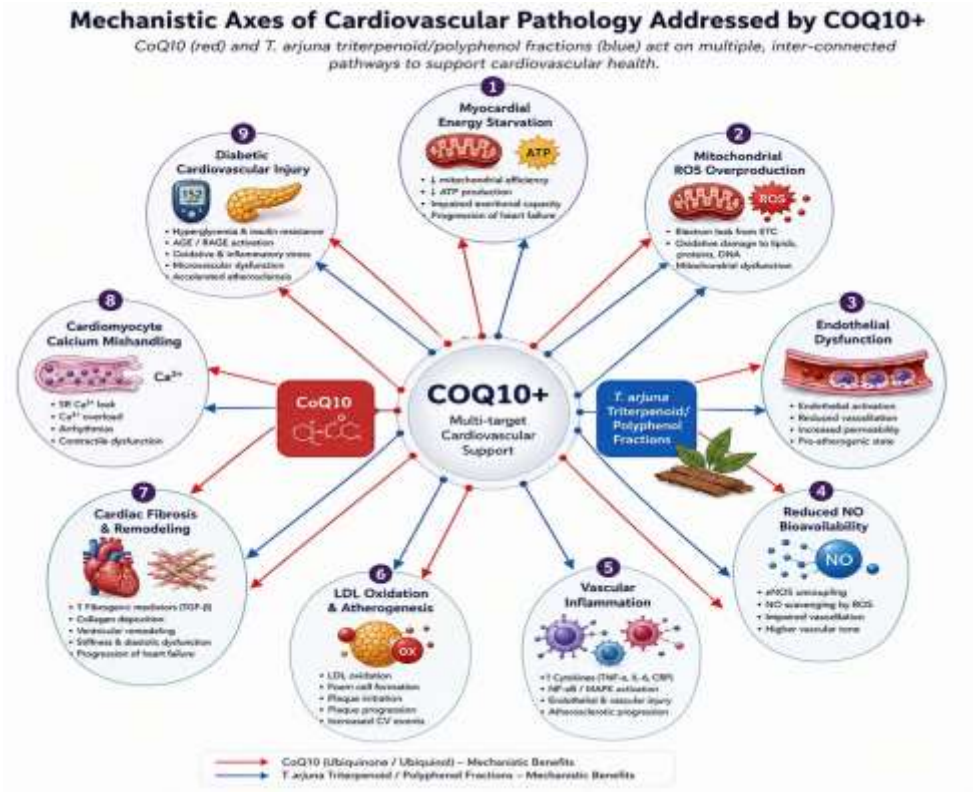

Fig 4: Mechanistic Axes of Cardiovascular Pathology Addressed by COQ10+

A radial schematic depicting nine pathology axes (myocardial energy starvation, mitochondrial ROS, endothelial dysfunction, reduced NO bioavailability, vascular inflammation, LDL oxidation, cardiac fibrosis, cardiomyocyte calcium mishandling, diabetic cardiovascular injury) with two converging arrows from CoQ10 (red) and *T. arjuna* triterpenoid/polyphenol fractions (blue) into each axis. Adapted from [12,15,99,103,104,107,109].

5.8 Cardiac Fibrosis and Ventricular Remodelling

Sustained oxidative stress and angiotensin II drive fibroblast activation, TGF-β1 expression, and interstitial collagen deposition in the failing or ischaemic myocardium. The resulting ventricular stiffness raises filling pressures, worsens diastolic function, and itself stimulates further ROS generation and remodelling — a second self-reinforcing loop [16,17]. *Terminalia arjuna* bark polyphenols attenuate collagen deposition in post-infarction rat myocardium, partly by inhibiting TGF-β1 signalling, complementing CoQ10's direct anti-remodelling and ATP-supportive actions [16,17,99]. Phase-2 human data validating this for either ingredient remain preliminary.

5.9 Diabetes-Related Cardiovascular Injury

Hyperglycaemia drives coordinated mitochondrial, oxidative, glycation, vascular, and contractile injury. Increased glucose flux through the polyol and hexosamine pathways, non-enzymatic glycation of long-lived vascular proteins to advanced glycation end-products, and AGE-RAGE signalling sustain NF-κB activation and ROS production. Oxidative phosphorylation uncouples, cardiomyocyte SERCA2a expression falls, and diabetic cardiomyopathy develops, often independent of overt coronary disease [15,69,103,120]. COQ10+ matches each axis: CoQ10 supports mitochondrial function and restores SERCA2a protein in db/db diabetic mice [69], while *T. arjuna* extract lowers glucose, improves lipid profiles, and protects cardiac tissue against diabetes-induced oxidative stress in animal models [90,99]. The combination thus spans the full cardiometabolic risk profile: hyperglycaemia-induced oxidative stress, lipid abnormalities, endothelial dysfunction, mitochondrial cardiomyocyte impairment, and accelerated atherosclerosis.

Table 3: Mechanisms of Cardiovascular Pathology Addressed by COQ10+, and the Supporting Reference for Each Mechanism

Pathological mechanism	COQ10 mechanism of action	*T. arjuna* mechanism of action	Citation
Myocardial energy starvation	Restores CoQ10 pool required for complex I/III electron shuttling	Increases contractile efficiency through calcium sensitisation	[2,12,99,105]
Mitochondrial ROS overproduction	Pools ubiquinol that quenches lipid radicals and supports superoxide dismutase activity	Polyphenols (luteolin, quercetin, gallic acid) scavenge aqueous-phase radicals.	[7,15,99,106,107]
Endothelial dysfunction	Restores NO bioavailability by reducing superoxide/peroxynitrite	Activates eNOS via PI3K/Akt; reverses impaired FMD in smokers	[15,86,99,108,111]
Reduced NO bioavailability	Indirectly raises NO through reduced oxidative scavenging	Direct PI3K/Akt-mediated eNOS activation	[6,15,99,108]
Vascular inflammation	Suppresses NF-κB; lowers VCAM-1 expression	Flavonoids (luteolin, kaempferol) suppress VCAM-1/ICAM-1/MCP-1	[6,7,44,99]
LDL oxidation	Ubiquinol enrichment of LDL prolongs oxidation lag time	Flavonoid and tannin fractions chelate copper and quench lipid radicals	[99,108,112]
Cardiac fibrosis	CoQ10 indirectly stabilises anti-fibrotic signalling	Polyphenols reduce TGF-β1 expression and collagen deposition	[16,17,99]
Cardiomyocyte calcium mishandling	Restores ATP supply to SERCA2a; protects MPTP	Calcium-sensitising positive inotropy through triterpenoids	[18,69,104,105]
Diabetic cardiovascular injury	Restores SERCA2a in db/db mice; lowers HbA1c	Lowers glucose and lipids in streptozotocin-diabetic rats	[69,86,90,99,120]

6. Effects of Coenzyme Q10 on Cardiovascular Function

6.1 Enhancement of Mitochondrial Energy Production

CoQ10 shuttles electrons from Complex I (NADH: ubiquinone oxidoreductase) and Complex II (succinate: ubiquinone oxidoreductase) via the Q-cycle to Complex III (cytochrome bc1 oxidoreductase); replenishing the ubiquinone pool linearly raises electron transfer and NADH-/$FADH_2$-driven ATP production [26,27,73]. This corrects the chronic-heart-failure bioenergetic deficit, where CoQ10 decline tracked NYHA severity [2,12]; ^{31}P magnetic-resonance spectroscopy shows oral CoQ10 restores phosphocreatine/ATP ratios after 4–8 weeks at 200–300 mg/day [4,27].

6.2 Maintenance of Myocardial ATP Availability

Cardiomyocytes couple ATP demand to work, so the failing heart's 20–40 % fall in ATP versus aerobic myocardium and 50 % drop in ATP/ADP ratio depress SERCA2a-mediated calcium reuptake [104,105]. CoQ10 repletion restores the phosphate pool and normalises calcium cycling; in db/db type 2 diabetic mice, ubiquinol restored SERCA2a protein and improved diastolic function toward non-diabetic values [69].

6.3 Protection Against Oxidative Stress

Superoxide from electron leakage at complexes I and III is dismutated by MnSOD to hydrogen peroxide, then reduced by the glutathione and thioredoxin systems — both dependent on NADPH from the mitochondrial CoQ10/electron-transport chain [106,107]. Ubiquinol also directly quenches lipid peroxyl radicals before they propagate in membranes and LDL [26,73]. In statin-treated CAD patients, 300 mg/day

CoQ10 for 12 weeks lowered plasma malondialdehyde and raised superoxide-dismutase activity versus placebo [44].

6.4 Reduction of Lipid Peroxidation

Ubiquinol, the primary chain-breaking antioxidant of the inner mitochondrial membrane and LDL, halts propagating peroxidation and regenerates tocopherol from the tocopheroxyl radical, linking CoQ10 to vitamin E biology [26,73,113]. In lovastatin-treated subjects, 200 mg/day CoQ10 raised LDL-associated ubiquinol 4.4-fold ($p < 0.0001$) and prolonged LDL oxidation lag time by 19 % ($p < 0.001$) [112].

6.5 Support of Endothelial Function

Endothelial dysfunction, the earliest measurable vascular abnormality, appears as reduced brachial-artery flow-mediated dilatation (FMD). In statin-treated type 2 diabetics with impaired baseline function, 200 mg/day CoQ10 improved FMD by 1.6 % ($p < 0.05$) [86]. In obese MASLD patients with cardiometabolic risk, six months of high-dose CoQ10 reduced augmentation index, improved FMD-derived arterial elasticity, and raised pulse-wave-velocity-corrected vessel compliance versus placebo [121]. A CoQ10 phytosome also improved sublingual microvascular reactivity, single-dose and chronic [122,123].

6.6 Nitric-Oxide Bioavailability

Nitric oxide from endothelial nitric oxide synthase (eNOS) is rapidly scavenged by superoxide to peroxynitrite. Restoring ubiquinol lowers superoxide, prolonging NO half-life and preserving vasodilator capacity [15,86,108]. eNOS also needs tetrahydrobiopterin, which peroxynitrite oxidises and depletes; by cutting peroxynitrite, CoQ10 spares BH4 and keeps eNOS coupled rather than uncoupled and superoxide-producing [15].

6.7 Vascular Tone

By preserving NO bioavailability, CoQ10 lowers resting smooth-muscle tone — the sum of NO-mediated relaxation, endothelin-1-mediated constriction, and sympathetic input — seen as reduced augmentation index, central systolic blood pressure, and pulse-wave-velocity-corrected systemic arterial compliance [108,121,123]. Single-dose CoQ10 phytosome studies show endothelial reactivity gains within hours [122,123].

6.8 Influence on Blood Pressure

Hypertension is the leading single contributor to global cardiovascular mortality. The 2016 Cochrane review of four RCTs in primary hypertension (n = 146) found 100–200 mg/day CoQ10 gave a modest ~−3.0/−2.5 mmHg systolic/diastolic reduction, short of conventional significance [124]; a larger meta-analysis in broader populations showed 4–11 mmHg systolic reductions [125]. In hypertensive metabolic-syndrome patients, 200 mg/day CoQ10 for 12 weeks cut systolic/diastolic BP by 11/7 mmHg with a 12 % fall in serum aldosterone [126]. Umbrella reviews attribute BP heterogeneity to dosing, formulation, and population [127].

6.9 Influence on Cardiac Contractility

Contractility depends on cyclic calcium release, contraction, and reuptake, each aided indirectly by CoQ10-preserved ATP for SERCA2a reuptake and SR reloading [69,104,105]. Q-SYMBIO improved NYHA class in the active arm over 2 years [2,12], and the European sub-cohort (n = 231) confirmed significant LVEF improvement versus placebo [81] — mitochondrial support preventing progressive contractile decline rather than acute positive inotropy.

6.10 Effects on Ventricular Function

Beyond LVEF, CoQ10 reportedly improves stroke volume, septal e′ velocity on tissue Doppler, NT-proBNP, and NYHA class [2,4,121]. In the KiSel-10 RCT of elderly Swedish citizens, selenium plus CoQ10 halved NT-proBNP after 5 years, persisting at 10- and 12-year follow-up [21,128,129] — reflecting lower myocardial wall stress and downstream ventricular benefit.

6.11 Role in Chronic Heart Failure

Chronic heart failure is CoQ10's most-studied indication. Q-SYMBIO (n = 420; 2 years) randomised NYHA II–III patients to 300 mg/day CoQ10 or placebo, with outcomes relative to placebo [2,12]:

- MACE (cardiovascular death, HF hospitalisation, transplant): 14 % vs 25 %, HR 0.50; $p = 0.003$ (intention-to-treat)

- All-cause mortality: 9 % vs 17 %, p = 0.01
- Cardiovascular mortality: significantly reduced, p = 0.02
- HF hospitalisations: significantly reduced, p = 0.05

A European sub-cohort (n = 231) confirmed reproducibility: MACE 9 % vs 27 % (p = 0.001) [81]. A 2017 meta-analysis of 14 RCTs (n = 2149) reported a 31 % relative reduction in all-cause mortality (RR 0.69; 95 % CI 0.50–0.95; p = 0.02) [130]. An independent 2022 meta-analysis of contemporary trials (≥ 100 patients, ≥ 6 months, ≥ 100 mg/day) reported all-cause mortality OR 0.64 (95 % CI 0.48–0.87; p = 0.004) and cardiovascular-mortality OR 0.45 (95 % CI 0.32–0.64; p < 0.00001) [22].

The KiSel-10 trial (n = 443, 5-year intervention, 12-year follow-up) showed:

- 5-year CV mortality: 28.9 % (placebo) vs 12.9 % (selenium + CoQ10) [129]
- 10-year follow-up: CV mortality HR 0.51 (95 % CI 0.36–0.74; p = 0.0003) [128]
- 12-year follow-up: 28.1 % (active) vs 38.7 % (placebo) [21]

Table 4: Summary of CoQ10 Outcome Trials in Chronic Heart Failure

Trial	Year	n	Dose	Duration	Key efficacy finding
Q-SYMBIO	2014	420	300 mg/day	2 years	MACE 14 % vs 25 % (p = 0.003); mortality 9 % vs 17 % (p = 0.01)
Q-SYMBIO EU subgroup	2013	231	300 mg/day	2 years	MACE 9 % vs 27 % (p = 0.001); LVEF and NYHA improved
KiSel-10	2012	443	200 mg/day CoQ10 + 200 µg/day Se	5 years	CV mortality 28.9 % → 12.9 %; NT-proBNP halved
KiSel-10 10-yr follow-up	2015	215	as above	10 years post-intervention	HR 0.51 (95 % CI 0.36–0.74; p = 0.0003)
KiSel-10 12-yr follow-up	2018	184	as above	12 years post-intervention	CV mortality 28.1 % active vs 38.7 % placebo
Li & Liu meta-analysis	2017	2149 (14 RCTs)	varied	varied	Mortality RR 0.69 (95 % CI 0.50–0.95; p = 0.02)
Mareev meta-analysis	2022	14 trials	≥ 100 mg/day	≥ 6 months	All-cause mortality OR 0.64 (p = 0.004); CV mortality OR 0.45

6.12 Relevance in Statin-Treated Individuals

Statins inhibit HMG-CoA reductase, the rate-limiting mevalonate-pathway enzyme also required for ubiquinone biosynthesis, cutting plasma CoQ10 by 25–40 % at therapeutic doses — a depletion proposed to underlie statin-induced myopathy and possibly new-onset diabetes [44,131]. Supplementation restores plasma and possibly tissue CoQ10; heterogeneous trials nonetheless indicate clinically meaningful symptom reduction in affected patients:

Table 5: CoQ10 in Statin-Treated Patients: Key Randomised Trials

Study	n	Dose / Duration	Symptom reduction vs placebo
Taylor et al. 2014	50	400 mg/day, 8 weeks	Pain severity ↓ 40 %, interference ↓ 33 %
Qu et al. 2018 (12-RCT meta-analysis)	575	varied	Pain, weakness, cramps, tiredness all significantly reduced

Fedacko et al. 2012 (with selenium)	60	200 mg/day CoQ10 + 200 µg Se	Pain ↓ 53 %, weakness ↓ 60 %, cramps ↓ 65 %, fatigue ↓ 82 %
Šabović et al. 2014	60	100 mg/day	Muscle pain ↓ 41 % vs 22 % placebo
Lee et al. 2013	51	300 mg/day, 8 weeks	Antioxidant ↑, inflammation ↓, no pain benefit in low-symptom baseline
Dohlmann et al. 2022	43	400 mg/day, 8 weeks (healthy simvastatin users)	Plasma CoQ10 ↑; no muscle-function benefit

Heterogeneous effect sizes fit benefit depending on baseline myopathy severity, plasma CoQ10 achieved with the formulation, and concurrent selenium status [132].

7. COENZYME Q10 AND CARDIOMYOCYTE CALCIUM HANDLING

7.1 Excitation–Contraction Coupling

Depolarisation opens L-type calcium channels; the trigger influx activates sarcoplasmic-reticulum ryanodine receptors, producing calcium-induced calcium release that raises cytosolic [Ca^{2+}] from ~100 nM (diastole) to ~1 µM (systole). Ca^{2+} binds troponin C, relieving troponin I inhibition of actin-myosin for contraction; relaxation follows SERCA2a reuptake and Na^{+}/Ca^{2+}-exchanger extrusion, with mitochondrial Ca^{2+} buffering at high workloads [104,105].

7.2 L-Type Calcium-Channel Activity

L-type calcium channels (LTCC, CaV1.2) supply the trigger calcium for RyR2 activation. Sympathetic PKA/CaMKII phosphorylation of the LTCC β-subunit carboxyl terminus raises open probability and trigger influx, elevating SR calcium load via larger calcium-induced calcium release — the contractility and accelerated relaxation of β-adrenergic stimulation [104,105].

7.3 Ryanodine-Receptor-Mediated Calcium Release

RyR2 releases stored SR calcium on LTCC trigger. In failing hearts, CaMKII hyperphosphorylation and loss of the stabiliser FKBP12.6 cause diastolic SR calcium leak, which depletes SR load (reducing contractile reserve) and raises cytosolic calcium (promoting arrhythmias) — a substrate for sudden cardiac death [104,105].

7.4 SERCA2a-Dependent Ca^{2+} Reuptake

SERCA2a is the sole ATP-dependent pump moving calcium into the SR lumen against a steep gradient, so its expression and post-translational state dominate reuptake kinetics and diastolic lusitropy. Dephosphorylated phospholamban binds and inhibits SERCA2a; PKA (Ser16) or CaMKII (Thr17) phosphorylation relieves this. PLN-knockout cardiomyocytes show approximately 37 % higher SR calcium content and faster calcium decline ($\tau = 112 \pm 6$ ms versus 188 ± 14 ms in wild-type, $p < 0.0001$) [116,118]. The lethal-dilated-cardiomyopathy phenotype of the human phospholamban-null mutation confirms this regulatome as a critical hub in cardiac calcium physiology [117,119].

7.5 Phospholamban Regulation

Phospholamban is a 52-amino-acid integral membrane SR pentamer; monomeric and unphosphorylated, it binds SERCA2a with high affinity, while phosphorylation or dissociation into pentamers relieves inhibition. PKA phosphorylates Ser16 during β-adrenergic drive, and CaMKII Thr17 during high-frequency calcium transients. In failing myocardium, PLN hypophosphorylation and SERCA2a down-regulation slow reuptake, prolonging the calcium transient and diastolic relaxation [104,105].

7.6 Mitochondrial Ca^{2+} Uptake

Mitochondrial calcium uptake via the mitochondrial calcium uniporter is concentration-dependent, saturating at systolic-peak cytosolic [Ca^{2+}]. It stimulates three Krebs-cycle dehydrogenases, matching ATP supply to demand and supporting oxidative phosphorylation; sustained overload, however, opens the mitochondrial permeability transition pore, releasing cytochrome c and triggering apoptotic cardiomyocyte death [102,107].

7.7 ATP-Dependent Ca^{2+} Transport

SERCA2a hydrolyses one ATP per calcium ion transported, so its activity is limited by cytosolic ATP from mitochondrial oxidative phosphorylation. Myocardial CoQ10 loss in chronic heart failure lowers the ATP/ADP ratio, limiting SERCA2a activity and slowing reuptake; CoQ10 repletion therefore acts indirectly but pharmacologically meaningfully on calcium handling [12,104,105].

7.8 Calcium Overload and Mitochondrial Injury

Sustained cytosolic calcium overload during ischaemia–reperfusion drives mitochondrial calcium overload and MPTP opening; released cytochrome c and other pro-apoptotic factors initiate apoptotic cardiomyocyte death, compounding infarct-related cell loss. CoQ10 pretreatment attenuates MPTP opening and reduces infarct size in experimental ischaemia-reperfusion models via antioxidant and membrane-stabilisation actions [102,103,107].

7.9 CoQ10-Mediated Protection of Calcium Homeostasis

CoQ10 contributes to cardiomyocyte calcium homeostasis through three complementary mechanisms:

- **Mitochondrial preservation**: CoQ10 stabilises mitochondrial membrane potential and prevents MPTP opening, attenuating mitochondrial calcium overload and the resulting apoptotic cascade [102,107].
- **ATP support for SERCA2a**: Restoration of CoQ10 raises the ATP/ADP ratio and re-energises SERCA2a-mediated reuptake, accelerating calcium decline and improving lusitropy [12,104,105].
- **Direct SERCA2a protein restoration**: In the db/db diabetic mouse, ubiquinol restored SERCA2a protein expression toward non-diabetic values, paralleling the improvement in diastolic function [69].

The earliest demonstration that exogenous CoQ10 attenuates calcium-handling failure under oxidative stress was Nakamura and colleagues' 1984 "tension prolongation phenomenon" study [133], since recapitulated by phospholamban-knockout studies, the SERCA2a gene-therapy literature, and the diabetic ubiquinol study above.

8. CARDIOVASCULAR EFFECTS OF *TERMINALIA ARJUNA*

8.1 Antioxidant Activity

Terminalia arjuna bark is among the most antioxidant-rich Ayurvedic tissues. Aqueous, ethanolic and methanolic extracts show concentration-dependent DPPH, ABTS, superoxide and hydroxyl-radical scavenging in vitro, with IC_{50} comparable to ascorbic acid [99,134,135], reflecting triterpenoids, flavonoids (luteolin, quercetin, kaempferol), tannins (gallic acid, ellagic acid, catechin) and condensed proanthocyanidins [7,99]. In hyperlipidaemic rats, it also raises SOD, catalase and glutathione-peroxidase activity [16,136].

8.2 Anti-inflammatory Effects

Extracts suppress NF-κB in LPS-stimulated macrophages and inhibit COX-2, iNOS and TNF-α transcription [99]. In a rat CCl_4 cardiac oxidative-stress model, extract lowered myocardial TNF-α, IL-6 and lipid peroxidation and partially reversed cardiotoxicity (myocyte vacuolation, interstitial inflammation) [135]. Flavonoids luteolin, kaempferol and quercetin down-regulate NF-κB in oxLDL-exposed endothelial cells [6,99].

8.3 Myocardial Protective Activity

T. arjuna is directly myocardial-protective. In rat ischaemia-reperfusion models, pre-treatment recovered left-ventricular developed pressure toward pre-ischaemic values, reduced CK-MB release and decreased infarct size [16,17,99]. Partial L-NAME and propranolol blockade indicates combined NO-dependent and β-adrenergic components.

8.4 Anti-ischaemic Effects

Standardised extract reduces ligation-induced ST-segment elevation, improves time to ST depression on treadmill testing and prolongs exercise duration in stable angina [23,137]. Coronary vasodilation, positive inotropy and reduced myocardial oxygen demand provide the mechanistic framework [17,99].

8.5 Effects on Myocardial Contractility

Bark extract is positively inotropic across preparations:

- **Isolated rat atria**: aqueous extract raised force concentration-dependently, partly blocked by propranolol (β_1-adrenoceptor) [138,139].
- **Adult rat ventricular myocytes**: aqueous extract raised cell shortening 131 ± 24 % ($p < 0.001$) without changing calcium transient amplitude — calcium sensitisation, not raised cytosolic calcium [18].
- **Guinea pig Langendorff hearts**: ethanolic extract raised force concentration-dependently via cAMP-dependent and -independent pathways [140].
- **F10 fraction**: the aqueous eluate carried the highest inotropic activity in adult rat myocytes [141].

Unlike cardiac glycosides (Na^+/K^+-ATPase inhibition) or catecholamines (raised cytosolic calcium), *T. arjuna* triterpenoids act mainly via β-adrenergic engagement plus calcium sensitisation [17,99].

8.6 Support of Coronary Circulation

Polyphenol-rich fractions activate eNOS via PI3K/Akt in endothelial cells, raising NO and coronary vasodilation [99,111]. Chronic smokers given 500 mg bd for 2 weeks showed complete reversal of impaired brachial-artery FMD (3.05 ± 0.75 % to 9.84 ± 0.59 %, $p < 0.001$), matching non-smokers [111].

8.7 Effects on Endothelial Function

Bark extract is endothelial-protective: aqueous extract reduces ICAM-1 and VCAM-1 in oxLDL-stimulated HUVEC and improves endothelium-dependent relaxation in phenylephrine-precontracted rat aortic rings, the arjunic acid fraction half-maximally relaxing them at micromolar concentrations, L-NAME-sensitively [6,99].

8.8 Nitric-Oxide-Mediated Vasodilation

This dual NO pathway is unique among cardiovascular botanicals: polyphenols raise NO via eNOS/PI3K/Akt while triterpenoids prolong NO half-life by lowering oxidative stress, supporting acute vasodilation and chronic vascular protection [6,99,111].

8.9 Effects on Blood Pressure

Bark extract is modestly antihypertensive experimentally, mainly via NO-dependent vasodilation and modest triterpenoid-glycoside diuresis. Human data are limited: pilot studies suggest small systolic reductions of 4–8 mmHg over 8–12 weeks of 500–750 mg/day in stable angina [99,137]. With CoQ10 in COQ10+, larger reductions may result given CoQ10's aldosterone-reducing and NO-restoring actions [15,126].

8.10 Lipid-Modulating Effects

Terminalia arjuna produces reproducible hypolipidaemic effects across experimental models:

Table 6: Lipid-Modulating Activity of *T. arjuna* in Animals

Study (first author, year)	Model	Dose, duration	Outcome vs control
Khanna 1996	Triton- and cholesterol-fed rats	100 mg/kg, 15 days	↑ LCAT, ↓ HMG-CoA reductase, normalised LDL/HDL
Shaila 1997	Hyperlipidaemic rabbits	100 mg/kg, 12 weeks	↑ HDL-C, ↓ LDL-C, ↓ aortic lipid deposits
Subramaniam 2010	Hypercholesterolaemic rabbits	100 mg/kg ethanolic fraction	TC 235→211 mg/dL; LDL 134→122 mg/dL; ↓ lesion area
Patil 2011	Hyperlipidaemic rats	100 mg/kg, 4 weeks	TC ↓ 31 %, TG ↓ 28 %, ↑ HDL

Mojarradgandoukmolla 2021	Hyperlipidaemic rats	50 mg/kg, 4 weeks	TC ↓ 26 %, MDA ↓ 38 %, SOD ↑ 44 %

The mechanism involves HMG-CoA reductase suppression (the statin target), raised plasma LCAT and antioxidant protection of circulating lipoproteins [8,114,115,136,142].

8.11 Antifibrotic and Antiremodelling Effects

Polyphenol and triterpenoid fractions reduce interstitial collagen and TGF-β1 in post-infarction rat myocardium, attenuating maladaptive remodelling; arjunolic acid mediates much of this by inhibiting activated fibroblast proliferation [16,17,99]. Human validation is awaited.

8.12 Protection Against Ischaemia–Reperfusion Injury

In ex vivo rat heart ischaemia-reperfusion models, pretreatment reduces infarct size, membrane lipid peroxidation and CK-MB release; L-NAME blockade indicates NO-dependent salvage [16,17,99].

8.13 Influence on Platelet and Thrombotic Pathways

In ex vivo studies, *T. arjuna* kaempferol and arjunetin inhibit thromboxane A_2 formation and modestly inhibit ADP-induced platelet aggregation [99], suggesting adjunctive thrombotic-risk reduction, though dedicated platelet-function trials are lacking.

9. ARJUNA BARK AND CALCIUM-DEPENDENT CARDIOVASCULAR FUNCTION

9.1 Calcium-Dependent Myocardial Contraction

Cardiomyocyte contraction begins with cytosolic calcium binding to troponin C; force per beat depends on transient amplitude, myofilament calcium sensitivity and calcium-decline kinetics. *T. arjuna* triterpenoids raise myofilament calcium sensitivity without affecting SR calcium release, giving inotropy distinct from agents that raise cytosolic calcium [18].

9.2 Potential Modulation of Calcium Entry

In atrial preparations, low extract concentrations raise contractile force without altering action-potential duration, indicating activity downstream of L-type calcium entry [138,139]; its β-adrenoceptor component involves PKA phosphorylation of LTCC and RyR2, coupling to calcium influx at higher doses [138,140].

9.3 Vascular Smooth-Muscle Calcium Signalling

Vascular smooth-muscle contraction depends on calcium entry through voltage-dependent L-type and receptor-operated channels plus IP3-mediated SR release. Tannin and triterpenoid fractions suppress voltage-dependent calcium entry in rat aortic smooth-muscle cells, a basis for the bark's vasodilator activity [99].

9.4 Effects on Cardiac Contractile Strength

The inotropic effect on rat isolated atria is dose-dependent and partially reversed by β-blockade [18,138,139]. In guinea pig Langendorff preparations, ethanol extracts raised contractile force concentration-dependently and improved post-ischaemic recovery [140].

9.5 Protection Against Calcium-Overload Injuries

Antioxidant polyphenols attenuate calcium overload from oxidative damage to membrane ion channels and calcium-handling proteins, complementing the COQ10+ combination's coverage of the calcium-mitochondrial interface.

9.6 Current Limitations of the Evidence

Direct human data on arjuna-mediated calcium modulation are lacking. The LVEF improvement in published CAD trials [143] reflects combined inotropy and afterload reduction rather than isolated calcium modulation, and extrapolations from animal data remain preliminary.

10. POTENTIAL MODULATION OF ATHEROSCLEROTIC PLAQUE FORMATION, PROGRESSION AND STABILITY

Atherosclerosis develops over decades through endothelial activation, LDL infiltration and oxidation, monocyte adhesion and transmigration, foam-cell formation, smooth-muscle migration and proliferation, and fibrous-cap formation. Rupture exposes thrombogenic core material, causing acute coronary syndromes, while stable plaques occlude the lumen, causing angina, claudication or stroke [15,109]. Endothelial dysfunction, lipid oxidation, inflammation and VSMC proliferation together set plaque growth and stability.

Cu^{2+}- and 12/15-lipoxygenase-mediated LDL oxidation is the rate-limiting initiating step. Ubiquinol enrichment prolongs the oxidation lag and makes LDL far more resistant to copper oxidation ex vivo [108,112]; vitamin E plus CoQ10 inhibit lesion initiation and progression in ApoE-knockout mice beyond either alone [113]. Disturbed flow, oxidised LDL and advanced glycation end-products activate endothelial NF-κB, raising VCAM-1, ICAM-1 and E-selectin, whose suppression reduces monocyte recruitment and lesion initiation [15]; *T. arjuna* flavonoids (luteolin, kaempferol, ellagic acid) are NF-κB-suppressive here [6,7,99]. VCAM-1/ICAM-1 drive monocyte adhesion and MCP-1 the transmigration gradient [109], while aqueous extract cuts VCAM-1 ~40 % in oxLDL-stimulated HUVEC [6,99]. Intimal macrophages take up oxLDL via CD36 and SR-A to form foam cells; CoQ10 lowers oxLDL availability [108,112] and *T. arjuna* flavonoids and tannins down-regulate CD36 [6,99]. VSMC migration and proliferation into fibrous lesions are driven by PDGF-BB and TGF-β; triterpenoid fractions inhibit PDGF-BB-stimulated VSMC proliferation at sub-toxic concentrations [16,99].

Intraplaque macrophage activation drives MMP-2/MMP-9 release that thins the fibrous cap toward rupture. Q-SYMBIO and KiSel-10 reduced inflammatory biomarkers in supplemented populations [2,129], and *T. arjuna* extracts additionally cut intraplaque macrophage IL-6 and TNF-α [99,135]. Combined suppression across these axes slows progression: ApoE-knockout mice on vitamin E plus CoQ10 had 40 % smaller aortic lesions than controls after 6 months, with less oxidative stress and fewer intimal inflammatory macrophages [113]. Cap stabilisation guards against rupture (cause of most acute coronary syndromes): *T. arjuna* triterpenoid and polyphenol fractions cut intraplaque-macrophage MMP-9 and raise collagen [6,99]. CoQ10 remains untested in dedicated plaque-stability trials.

CoQ10 addresses the pathway mainly through its lipid-phase antioxidant mechanism: 200 mg/day during lovastatin therapy raised LDL-associated ubiquinol 4.4-fold and prolonged LDL oxidation lag time 19 % [112], and 300 mg/day over 12 weeks reduced circulating inflammatory markers in CAD patients [44]. *T. arjuna* adds non-overlapping mechanisms — HMG-CoA reductase-mediated lipid lowering [8,115], LDL copper chelation and peroxyl-radical quenching [99], VCAM-1 reduction with eNOS activation [6,99], CD36 down-regulation [99] and PDGF-BB–VSMC inhibition [16,99] — supporting a more complete atheroprotective effect than either agent alone.

Intensive statin lipid-lowering yields modest regression within 12–24 months on high-resolution MRI [110]. Preclinical CoQ10-with-vitamin-E and CoQ10 + *T. arjuna* studies suggest combined nutraceutical intervention could produce modest regression over prolonged administration, untested in humans with the COQ10+ combination.

Table 7: Summary of Plaque-Biology Intervention Points of CoQ10 and *T. arjuna*

Plaque biology step	**CoQ10 action**	***T. arjuna* action**	**Citations**
Endothelial activation	Reduced NF-κB activation; ↓ VCAM-1	Flavonoid NF-κB suppression; luteolin, kaempferol	[6,44,99]
LDL oxidation	Ubiquinol enrichment; lag-time prolongation	Tannin copper chelation; peroxyl radical scavenging	[99,108,112]
Monocyte recruitment	↓ Inflammatory cytokines	↓ VCAM-1, ↓ MCP-1	[6,44,99]
Foam-cell formation	↓ oxLDL availability	↓ CD36 expression	[99,108]
VSMC proliferation	Indirect (lower inflammation)	PDGF-BB–stimulated VSMC inhibition	[16,99,113]

Intraplaque inflammation	↓ MMP-9 release	↓ IL-6, ↓ TNF-α; ↓ MMP-9	[44,99,135]
Fibrous cap stability	Indirect	↑ Collagen content; ↓ MMP-9	[2,6,99]

11. DIABETES-RELATED CARDIOVASCULAR COMPLICATIONS

11.1 Effects of CoQ10 in Diabetes

CoQ10 trials and meta-analyses in T2DM include:

- **Suksomboon 2015 meta-analysis (24 RCTs, n = 1012)**: CoQ10 significantly lowered fasting glucose ~0.4 mmol/L, HbA1c ~0.3 %, triglycerides 0.4 mmol/L, and systolic BP 3.7 mmHg versus placebo [120].
- **McRae 2020 umbrella review (6 meta-analyses)**: confirmed HbA1c and FMD gains; BP and lipid evidence low-quality [127].
- **Hamilton 2009**: 200 mg/day CoQ10 improved brachial FMD by 1.6 % in statin-treated T2DM [86].
- **Chew 2008**: fenofibrate + CoQ10 improved hemodynamics and diastolic function in T2DM with LV diastolic dysfunction [144].
- **Huynh 2012**: reversed SERCA2a loss and diastolic dysfunction in db/db mice [69].
- **Lee 2013**: 300 mg/day CoQ10 over 12 weeks reduced oxidative damage and inflammation in CAD patients on statins [44].

Table 8: Clinical Trials of CoQ10 in Type 2 Diabetes

Study	n	Dose/duration	Population	Outcome	Citation
Hamilton 2009 RCT	23	200 mg/day, 12 weeks	Statin-treated T2DM	FMD ↑ 1.6 % vs placebo	[86]
Chew 2008 RCT	83	200 mg/day, 12 weeks	T2DM with LV diastolic dysfunction	Hemodynamic benefit	[144]
Lee 2013 RCT	51	300 mg/day, 8 weeks	CAD on statins	↓ MDA, ↑ SOD, ↓ inflammatory markers	[44]
Suksomboon 2015 (meta-analysis)	1012 (24 RCTs)	varied	T2DM	FBG ↓ 0.4 mmol/L; HbA1c ↓ 0.3 %; SBP ↓ 3.7 mmHg	[120]
McRae 2020 (umbrella)	6 meta-analyses	varied	cardiometabolic	HbA1c ↓, FMD ↑; BP/lipids equivocal	[127]
Huynh 2012 (animal)	db/db mice	ubiquinol-equivalent	Type 2 diabetic model	SERCA2a restored, diastolic function ↑	[69]

11.2 Effects of *T. arjuna* in Experimental Diabetes

Terminalia arjuna bark extract protects streptozotocin- and high-fat-diet diabetic rat models [90,99], with in vivo evidence in three domains:

- **Glucose-lowering**: 100–500 mg/kg lowers fasting glucose in STZ-diabetic rats, parallel to metformin in some comparisons.
- **Antioxidant restoration**: bark polyphenols raise SOD, catalase, and glutathione in cardiac and hepatic tissue of diabetic rats [99].

- **Myocardial protection**: reduces histological markers of diabetic cardiomyopathy, including myocyte vacuolation and interstitial fibrosis [90,99].

11.3 Scientific Relevance of COQ10+ in Cardiometabolic Support

Table 9: COQ10+ aligns mechanistically with each component of the diabetic cardiovascular risk profile:

Pathological axis	**CoQ10 mechanism**	***T. arjuna* mechanism**	**Citation**
Hyperglycaemia-induced oxidative stress	Restores ubiquinol pool	Flavonoid/polyphenol ROS scavenging	[15,99,103,106]
AGE-RAGE activation	Lowers ROS upstream	NF-κB suppression, eNOS activation	[15,99]
Diabetic endothelial dysfunction	Raises NO bioavailability	Reverses FMD in smokers	[86,99,111]
Diabetic dyslipidaemia	Protects LDL against oxidation	HMG-CoA reductase suppression	[8,112,115]
Diabetic cardiomyopathy	Restores SERCA2a	Positive inotropy / anti-fibrotic	[16,69,99]
Accelerated atherosclerosis	LDL oxidation suppression	Foam-cell suppression	[6,99,113]

The combination thus covers the full cardiometabolic risk profile [69,99,120,127].

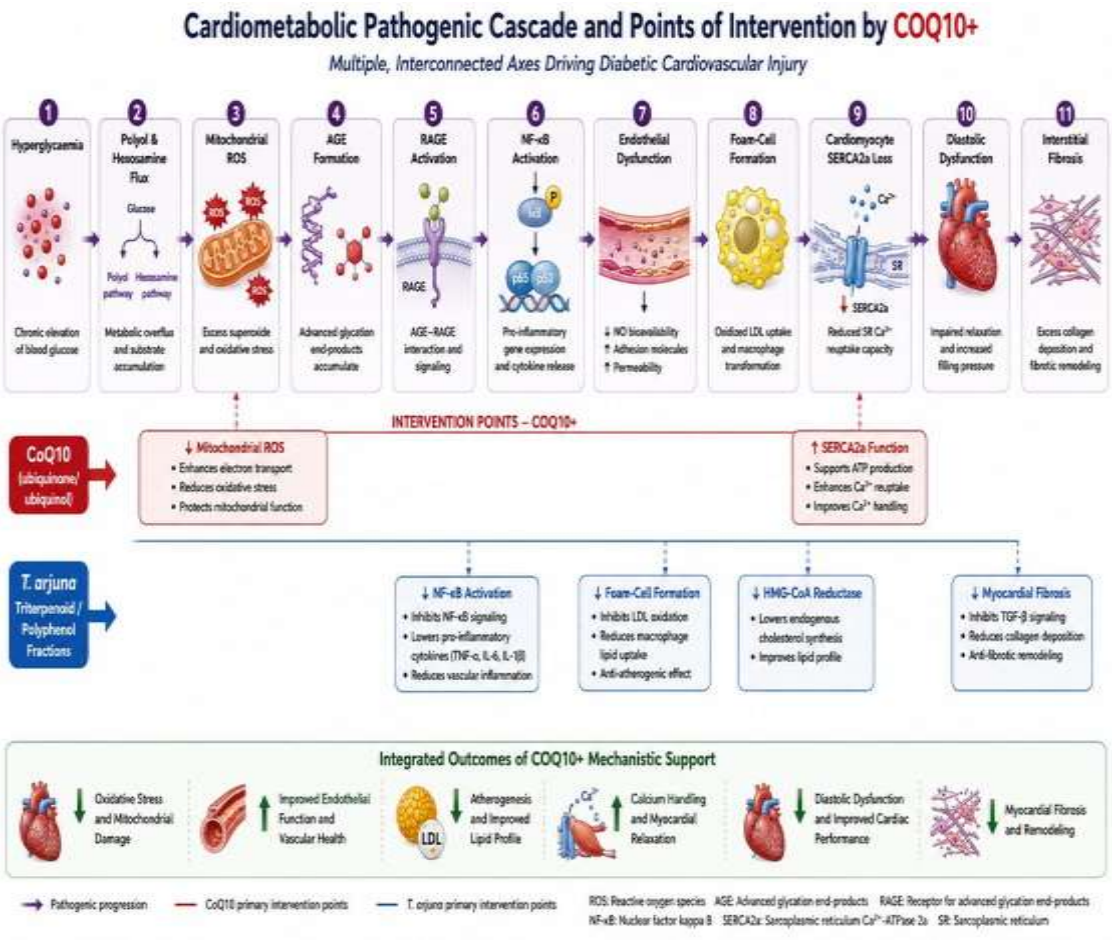

Fig 5: Mechanisms of COQ10+ in Diabetic Cardiovascular Injury

Hyperglycaemia → polyol/hexosamine flux → mitochondrial ROS → AGE formation → RAGE activation → NF-κB drive → endothelial dysfunction → foam-cell formation → cardiomyocyte SERCA2a loss → diastolic dysfunction → interstitial fibrosis. CoQ10 acts on mitochondrial ROS and SERCA2a; *T. arjuna* acts at NF-κB, HMG-CoA reductase, foam-cell formation, and myocardial fibrosis. Adapted from [15,69,99,103,120].

12. MECHANISTIC COMPLEMENTARITY OF THE COQ10+ FORMULATION

CoQ10 is the obligate electron carrier between respiratory complexes I/II and III in the inner mitochondrial membrane [26,73]. Repletion raises electron-transport efficiency and ATP output, cuts mitochondrial ROS leakage, and stabilises the membrane potential for calcium uptake [2,73], improving diastolic function, lowering inflammatory signalling, and reducing myocardial wall stress — contributing to reduced cardiovascular mortality in Q-SYMBIO [2,12] and KiSel-10 [21,128,129].

Standardised *T. arjuna* bark extract delivers oleanane-type triterpenoids (arjunic acid, arjunolic acid, arjungenin) and polyphenols (luteolin, quercetin, kaempferol, gallic acid, ellagic acid) driving calcium-sensitising positive inotropy, NO-mediated vasodilation, lipid modulation, anti-atherogenesis, and anti-fibrosis [18,99,139] — unlike any licensed cardiovascular medicine.

CoQ10 is the principal lipid-phase antioxidant in membranes and circulating LDL; *T. arjuna* polyphenols act in lipid and aqueous phases and chelate the transition metals driving Fenton chemistry [44,99,113]. Together they broaden antioxidant coverage, with synergy shown in vitamin E + CoQ10 ApoE-knockout mouse studies [113]; each may also shield the other from oxidative degradation during intestinal transit [7,44,99].

Both suppress NF-κB activation in immune cells: CoQ10 reduces inflammatory cytokines in statin-treated CAD patients [44]; *T. arjuna* flavonoids (luteolin, kaempferol, quercetin) modulate COX-2 and 12/15-lipoxygenase pathways, reduce ICAM-1/VCAM-1/MCP-1 expression, and lower IL-6/TNF-α release [99].

CoQ10 raises bioavailable NO by curbing superoxide-mediated NO scavenging [15,86,108]; arjuna triterpenoids and flavonoids activate eNOS directly via PI3K/Akt signalling [99,111], converging on acute and chronic NO-mediated vasodilation. Outcomes include FMD improvement of 1.6 % (CoQ10 in statin-treated T2DM) [86] and complete FMD reversal in chronic smokers (arjuna 500 mg bd × 2 weeks) [111].

Terminalia arjuna triterpenoids provide calcium-sensitising positive inotropy, raising contractile force per unit cytosolic calcium [18,139]; CoQ10 aids lusitropy by restoring ATP to SERCA2a and stabilising mitochondrial calcium handling [69,105] — covering systolic (arjuna) and diastolic (CoQ10) function.

CoQ10 also supports mitochondrial Ca^{2+} buffering and SERCA2a ATP supply [69]; arjuna triterpenoids modulate myofilament Ca^{2+} sensitivity and reduce vascular smooth-muscle Ca^{2+} entry [18,99] — covering cardiac (SR lumen/ATP) and vascular (myofilament/SMC) Ca^{2+} handling.

On atherogenesis, CoQ10 reduces lipid-phase LDL oxidation [108,112,113]; arjuna acts via lipid lowering, foam-cell and MCP-1 suppression, and antiproliferative activity in VSMCs [8,16,99,114]. Combination studies remain unpublished, though the additive appeal is strong.

Both have published efficacy in cardiometabolic T2DM complications: CoQ10 lowers HbA1c (~0.3 %) and FBG (~0.4 mmol/L) and improves FMD [120,127]; arjuna bark extract lowers lipids and myocardial oxidative stress in experimental diabetes [8,99,115]. In COQ10+, they thus address hyperglycaemia-induced oxidative stress, AGE-RAGE activation, dyslipidaemia, endothelial dysfunction, cardiomyocyte impairment, and accelerated atherosclerosis [69,86,99,103,120].

Published evidence supports additive, mechanistically complementary effects. Pharmacological synergy — an effect exceeding the sum of parts — can only be claimed through formal pharmacodynamic and clinical-trial pharmacokinetic interaction studies, recommended in future COQ10+ development plans [110].

13. EVIDENCE IN SPECIFIC CARDIOVASCULAR CONDITIONS

Both have published chronic heart-failure evidence; CoQ10's the larger: Q-SYMBIO (n = 420) and KiSel-10 (n = 443) documented significant reductions in cardiovascular mortality, all-cause mortality, HF hospitalisations, and cardiovascular biomarkers [2,21,128,129] (Sections 14 and 6.11). *T. arjuna* has smaller but meaningful pilot RCT evidence in NYHA II–III heart failure, improving LVEF (42 → 53 %), LV mass, and quality of life [24,137,143].

Terminalia arjuna is the most extensively studied COQ10+ ingredient for stable angina. In a double-blind RCT of 45 patients, standardised bark extract improved exercise duration, time to ST-segment depression, and anginal frequency equivalent to isosorbide mononitrate, with better gastrointestinal tolerability [23]. A meta-analysis in chronic stable angina identified 11 RCTs (n = 595) but judged methodological quality variable and effect estimates not yet robust [145]. CoQ10's role is more modest, improving endothelial function and reducing angina-equivalents in selected subpopulations, with less-documented direct anti-anginal activity [44,108].

In post-MI CAD patients with LV dysfunction, 500 mg/8 h *T. arjuna* bark powder improved LVEF from 42.25 ± 9.96 % to 52.67 ± 12.32 % ($p < 0.05$) and reduced LV mass index from 159.18 ± 51.11 to 127.47 ± 52.40 g/m² ($p < 0.05$) over 3 months [143]. In parallel work, the same investigator found a 50 % reduction in anginal episodes ($p < 0.01$), delayed ST-segment depression on treadmill testing, and prolonged time to onset of angina [137]. In statin-treated CAD patients, CoQ10 reduces oxidative stress and inflammatory biomarkers at 300 mg/day [44] and lowers lipid peroxidation markers over weeks [108,112].

Both have modest antihypertensive activity. The 2016 Cochrane review found small BP reductions for CoQ10 in primary hypertension [124], while broader meta-analyses show larger effects (4–11 mmHg systolic) across heterogeneous populations [125]. The strongest evidence is a randomised crossover double-blind RCT in hypertensive metabolic-syndrome patients: 200 mg/day CoQ10 cut systolic and diastolic BP by 11 mmHg and 7 mmHg, with a 12 % reduction in serum aldosterone [126]. *T. arjuna* shows modest antihypertensive activity in experimental hypertension, with limited human BP-specific trials [17,99].

Both independently improve brachial-artery FMD and sublingual microvascular reactivity. CoQ10 improves FMD by approximately 1.6 % in statin-treated T2DM patients [86] and further in MASLD [121], dyslipidaemic subjects [108], and healthy volunteers on phytosome formulation [122,123]. Arjuna completely reverses impaired FMD in chronic smokers within 2 weeks (3.05 → 9.84 %, $p < 0.001$) [111]. Combined, they raise NO bioavailability via antioxidant and direct eNOS-activation (Arjuna) pathways.

Terminalia arjuna bark extract has reproducible lipid-lowering activity in five animal studies and limited human pilots [8,114,115,136,142]. CoQ10 alone has limited or no effect on LDL-C but supports HDL resistance to oxidation, distinct from quantitative lipid lowering [120,127]. The combination delivers

quantitative lipid reduction (arjuna via HMG-CoA reductase suppression) and qualitative improvement (CoQ10 via LDL-oxidation suppression).

CoQ10 and *T. arjuna* have complementary atheroprotective mechanisms: vitamin E + CoQ10 inhibited ApoE-knockout mouse atherosclerosis by 40 % [113], and *T. arjuna* bark extract reduces atherosclerotic lesion area in hypercholesterolaemic rabbits [114]. Combined trials are lacking, but the mechanistic complementarity described above supports joint evaluation.

In the db/db mouse model, ubiquinol reverses SERCA2a protein loss and improves diastolic dysfunction in type 2 diabetes [69]. Pilot MASLD evidence with cardiometabolic risk supports vascular and myocardial benefits from 6 months of high-dose CoQ10 [121], and *T. arjuna* shows myocardial protection in experimental diabetes [90,99] — supporting a COQ10+ rationale in diabetic cardiomyopathy, which requires formal clinical evaluation.

Both address statin-associated CoQ10 depletion via distinct routes: CoQ10 directly repletes the depleted cofactor, while *T. arjuna* bark extract, a botanical antioxidant, spares vitamin E and indirectly supports the ubiquinol pool through lipid antioxidant protection [44,99,131]. Randomised evidence in statin-treated patients appears in Section 6.12.

Both improve submaximal exercise tolerance, time to ST-segment depression on treadmill testing, and NYHA functional class. Q-SYMBIO documented NYHA-class improvement in chronic HF over 2 years [2]; *T. arjuna* improved exercise duration and reduced anginal frequency in stable-angina RCTs [23,137]. COQ10+ combines CoQ10's mitochondrial ATP-restoring activity with arjuna's vasodilatory, positive inotropic, and lipid-modulating activity.

14. CLINICAL EVIDENCE FOR COENZYME Q10

Table 10: CoQ10 has been evaluated in RCTs across heart failure, hypertension, diabetes, MASLD, statin myopathy, and endothelial dysfunction. Major RCTs (chronological):

Trial	Year	n	Population	Dose/duration	Primary endpoint	Key result
Q-SYMBIO	2014	420	NYHA II–III HF	300 mg/day / 2 years	MACE	14 % vs 25 %, p = 0.003
KiSel-10	2012	443	Elderly Swedish	200 mg/day + 200 µg Se / 5 years	CV mortality	12.9 % vs 28.9 %
Hamilton (T2DM)	2009	23	Statin-treated T2DM	200 mg/day / 12 weeks	FMD	↑ 1.6 % vs placebo
Chew (T2DM-HF)	2008	83	T2DM with LV diastolic dysfunction	200 mg/day / 12 weeks	Hemodynamics	Improved diastolic function
Sabbatinelli (dyslipidaemia)	2020	70	Mild–moderate dyslipidaemia	Ubiquinol 100–200 mg/day / 24 weeks	FMD, LDL-oxidation lag	FMD ↑, lag time ↑
Vrentzos	2024	70	MASLD cardiometabolic	6 months high-dose	Vascular, myocardial function	Improved PWV, FMD, LS
Lee	2013	51	CAD on statins	300 mg/day / 8 weeks	MDA, SOD	Antioxidant ↑, inflammation ↓
Young (metabolic syndrome HTN)	2011	60	HTN with metabolic syndrome	200 mg/day / 12 weeks	BP	SBP ↓ 11 mmHg; DBP ↓ 7 mmHg
Taylor (statin myopathy)	2014	50	Statin myopathy	400 mg/day / 8 weeks	Pain	Pain severity ↓ 40 %
Cicero (phyto endothelial)	2022	30	Healthy volunteers	Single phytosome dose	PWV	Acute endothelial reactivity ↑
Šabović (statin myopathy)	2014	60	Mild–moderate statin myopathy	100 mg/day	Pain	Pain ↓ 41 % vs 22 %

These major trials draw on references [2,12,44,86,108,121–123,126,128,129,131,144,146].

Endothelial-function evidence supports CoQ10 use in:

- Statin-treated T2DM patients: FMD ↑ 1.6 % [86]
- MASLD with cardiometabolic risk: PWV-derived arterial elasticity ↑, FMD ↑, augmentation index ↓ [121]
- Mild–moderate dyslipidaemia: ubiquinol enrichment of LDL, FMD ↑ [108]
- Healthy volunteers on phytosome formulation: acute endothelial reactivity ↑ after single dose [122,123]

Table 11: Meta-Analyses of CoQ10 Across Indications

First author (year)	Indication	# trials / n	Endpoint	Effect	Citation
Li & Liu 2017	Heart failure	14 / 2149	All-cause mortality	RR 0.69 (95 % CI 0.50–0.95), p = 0.02	[130]
Mareev 2022	HFrEF (LVEF < 50 %)	14 / varied	CV mortality	OR 0.45 (p < 0.00001)	[22]
Qu 2018	Statin-induced myopathy	12 / 575	Muscle symptoms	Pain, weakness, cramps, fatigue all ↓	[147]
Suksomboon 2015	T2DM	24 / 1012	FBG, HbA1c, BP, TG	HbA1c ↓, FBG ↓, TG ↓, SBP ↓ (all significant)	[120]
McRae 2020 (umbrella)	Cardiometabolic	6 meta-analyses	Multiple	HbA1c ↓, FMD ↑; BP/lipids equivocal	[127]
Ho 2016	Primary hypertension	4 / 146	SBP / DBP	Small, non-clinically significant	[124]
Karimi 2025	Adults BP & HR	varied	SBP / DBP / HR	Pooled reduction 4–11 mmHg	[125]

An updated 2024 systematic review and meta-analysis of prospective cohort studies (1990–2024) of CoQ10 in CVD found supplementation protective against incident CV events in adequate dose/formulation-response populations, though overall evidence was low-to-moderate quality [14].

Limitations of Clinical Evidence:

- Heterogeneous CoQ10 formulations and doses across studies (Section 3.9)
- Few long-term outcome trials beyond Q-SYMBIO and KiSel-10
- Few trials in diverse ethnic populations
- Limited evaluation of dose-response and pharmacokinetic interactions
- Few large combination studies with arjuna or other botanicals

15. CLINICAL EVIDENCE FOR *TERMINALIA ARJUNA*

In a double-blind RCT of 45 patients, Bharani showed standardised *T. arjuna* bark extract improved exercise duration, time to ST-segment depression, and anginal frequency equivalent to isosorbide mononitrate, with better GI tolerability [23]. A chronic stable angina meta-analysis identified 11 RCTs (n = 595) but rated methodology variable and effect estimates not yet robust [145].

In post-MI CAD patients with LV dysfunction, 500 mg/8 h bark powder raised LVEF from 42.25 ± 9.96 % to 52.67 ± 12.32 % (p < 0.05) and lowered LV mass index from 159.18 ± 51.11 to 127.47 ± 52.40 g/m² (p < 0.05) over 3 months [143]. The same investigator found a 50 % reduction in anginal episodes (p < 0.01), delayed ST-segment depression on treadmill testing, and prolonged time to angina onset [137]; QoL improved in both.

A pilot RCT of standardised *T. arjuna* stem-bark water extract in NYHA II HF patients at 750 mg bd over 12 weeks reported symptom and QoL improvement (preliminary) [24]. Dwivedi's validated LVEF improvement in CAD patients indirectly supports use in HF with reduced LVEF, though larger multicenter trials remain unpublished [137,143].

The Bharani 2004 study of 30 chronic smokers showed complete reversal of impaired brachial-artery FMD by 500 mg bd bark extract over 2 weeks: FMD rose from 3.05 ± 0.75 % to 9.84 ± 0.59 % (p < 0.001), matching healthy non-smokers [111]. In vitro, aqueous bark extract and isolated triterpenoid fractions confirm eNOS activation, ICAM-1/VCAM-1 suppression, and NO-mediated vasodilation [6,99].

Human BP data on *T. arjuna* are limited. Experimental studies documented mild antihypertensive activity in hypertensive rats, partly via NO-dependent vasodilation and mild diuretic effects of triterpenoid glycosides [99]. Pilot studies suggest 4–8 mmHg systolic reductions over 8–12 weeks [99]. Dedicated BP-specific randomised trials are absent.

Terminalia arjuna bark extract has well-documented hypolipidaemic effects in five animal models [8,114,115,136,142]. The Khanna 1996 study showed a 64% reduction of total cholesterol and an 80% reduction of LDL-C with 100 mg/kg bark extract in cholesterol-fed rats [8]. Human data are limited to a small pilot showing modest TC and LDL reductions; large multicenter lipid-specific trials are lacking.

Limitations of Existing Studies:

- Small sample sizes: most clinical reports have n < 50
- Variable sources and standardisation of bark extract
- Short treatment durations (3–12 weeks)
- Limited blinding and randomisation in early studies
- Absence of large multicenter trials
- Lack of long-term outcome data
- Heterogeneity of phytochemical constituents across geographic sources

16. EVIDENCE SPECIFIC TO THE COQ10+ PRODUCT

COQ10+ integrates two ingredients with independently published clinical evidence. Its fixed-dose rationale rests on convergent mechanisms rather than product-specific trial data: Q-SYMBIO and KiSel-10 for CoQ10 [2,21], the stable angina and CAD RCTs for *T. arjuna* [23,137,143], and umbrella mechanistic evidence for combined antioxidant, anti-inflammatory, endothelial-protective, calcium-handling, and lipid-modulating activity [6,27,110].

Each unit dose of COQ10+ contains:

- **Coenzyme Q10**: 200 mg of bioavailable CoQ10 (phytosome formulation or solubilised ubiquinol), with identity, purity, potency, and stability verified to pharmaceutical-grade parameters.
- **Terminalia arjuna bark extract**: 500 mg of standardised bark extract (≥ 5 % total triterpenoids as arjunic acid equivalents; ≥ 5 % total polyphenols as gallic acid equivalents) [19,101].

Both doses fall in the upper half of clinically tested ranges. The CoQ10 dose is supported by PK and efficacy data showing maximal effect at 200–300 mg/day with water-soluble or ubiquinol formulations [108,121,123,148]. The arjuna dose falls within the 400–1000 mg/day range used in published trials of stable angina, HF, and endothelial dysfunction [23,111,137,143].

Stability is documented to end of shelf-life at controlled room temperature (25 °C / 60 % RH), tested under ICH accelerated (40 °C / 75 % RH for 6 months) and long-term (25 °C / 60 % RH for 24 months) conditions. The product is assigned a shelf-life of ≥ 24 months in the marketed packaging.

To establish the combination's efficacy and safety, the following randomised controlled programme is recommended:

- **Phase 1: PK interaction**: Single-dose, crossover, randomised open-label study in healthy volunteers, primary endpoint of plasma CoQ10 and bark polyphenol pharmacokinetics with and without co-administration.
- **Phase 2: Endothelial function pilot**: 12-week, double-blind, placebo-controlled RCT in prehypertensive and early-metabolic syndrome subjects, primary endpoint FMD.
- **Phase 3: HF RCT**: 2-year, double-blind RCT in NYHA II–III HFrEF patients on optimal pharmacotherapy, primary endpoints NT-proBNP and LVEF.
- **Phase 4: CAD-AS composite**: 1-year, double-blind RCT in stable CAD patients, composite endpoint of MACE, FMD, hs-CRP, NT-proBNP.

17. SAFETY AND TOLERABILITY

CoQ10's safety record is extensive: up to 1,200 mg/day for 12 months without serious adverse events [21,124]. The Cochrane Hypertension review found no adverse-event difference versus placebo [124]; 12-year KiSel-10 follow-up showed no excess mortality [21].

T. arjuna bark extract, 400–1000 mg/day for up to 6 months, is well tolerated with no attributed serious adverse events [23,111,137,143]; Bharani 2002 noted better GI tolerability than isosorbide mononitrate [23]. Data beyond 6 months are limited.

Mild GI upset (nausea, abdominal discomfort, soft stool) affects roughly 3–7 % on high-dose pharmaceutical-grade CoQ10 and 2–5 % on bark extract, eased by food.

CoQ10 modestly lowers BP, especially in hypertensive and metabolic-syndrome populations [124,126]; bark extract adds mild diuretic and vasodilator activity [99]. In COQ10+, these may potentiate ACE inhibitors, ARBs, CCBs, and diuretics — monitor BP at initiation and cut antihypertensive doses if SBP falls below target.

CoQ10 modestly lowers fasting glucose (~0.4 mmol/L) and HbA1c (~0.3 %) in T2DM [120]; bark extract lowers glucose in diabetic animal models [99]. Additive hypoglycaemic risk with sulfonylureas, insulin, and metformin is small but possible [120,127].

Hypersensitivity to any COQ10+ component (CoQ10, bark extract, excipients, capsule shell) is a contraindication.

Pregnancy and lactation involve heightened pharmacological sensitivity; lacking human data on either ingredient, COQ10+ is not recommended.

No dose adjustment is needed in older adults, in whom CoQ10 may be particularly indicated given reduced endogenous synthesis with age and higher statin use, polypharmacy, cardiovascular comorbidity, and greater orthostatic-hypotension risk [124,126].

Both ingredients carry ≥ 12 months of published safety data with no endocrine, hepatic, renal, or haematological signals, though pharmacovigilance is limited beyond 6 months for *T. arjuna* bark extract and 12 months for CoQ10. Selenium co-supplementation (as in KiSel-10) is not in COQ10+ and has its own high-dose risks (skin and nail changes; GI symptoms; very rarely cardiotoxicity).

18. DRUG–SUPPLEMENT INTERACTION CONSIDERATIONS

CoQ10, related to vitamin K, shows rare INR shifts; with high-dose warfarin it may modestly attenuate INR, and *T. arjuna* polyphenols may add minor vitamin-K-like effects [110]. Arjuna flavonoids (kaempferol, arjunetin) modestly reduce platelet function.

Aspirin, clopidogrel, ticagrelor and prasugrel act on platelets, weakly augmented by arjuna flavonoids; bleeding risk is low but warrants monitoring in dual antiplatelet therapy or thrombocytopenia [99].

CoQ10 and arjuna triterpenoids/polyphenols both modestly lower BP; consider additive hypotension with ACE inhibitors, ARBs, CCBs, and diuretics [99,124,126].

CoQ10 lowers glucose modestly, especially in T2DM [120], as does *T. arjuna* bark extract in diabetic animal models [99]; the additive effect with sulfonylureas, insulin, or metformin is small [120,127].

Statins deplete CoQ10 by inhibiting the mevalonate pathway; adding CoQ10 addresses this and may reduce statin-induced muscle symptom incidence and severity (Section 6.12). With bark extract adding lipid-lowering activity, statin-treated patients may gain co-formulation benefit [44,131,132,146,147].

Nitrates and arjuna may cause additive NO-mediated vasodilation, making symptomatic hypotension possible though rare. COQ10+ with isosorbide mononitrate produced antianginal effects equal to ISMN alone with better tolerability, arjuna being the principal botanical [23].

CoQ10 + *T. arjuna* suit adjunctive use with ACE inhibitors, beta-blockers, SGLT2 inhibitors, MRAs, and ARNIs; trial evidence supports compatibility rather than clinically meaningful interactions [2,129].

Both act on myocardial electrophysiology: CoQ10 may reduce arrhythmia susceptibility via improved cellular energetics, *T. arjuna* via antioxidant polyphenols. Additive QT effects with amiodarone or sotalol are unlikely [2,99].

Both may modulate platelet function and bleeding risk, so stopping 1–2 weeks before elective surgery is reasonable, though rare significant bleeding supports continuation in most cases — including urgent cardiovascular indications (e.g., transplant wait-listing) under physician supervision [99,110].

19. STRENGTHS OF THE COQ10+ FORMULATION

COQ10+ combines bioenergetic and phytochemical (arjuna) mechanisms in one fixed-dose formulation, addressing the mitochondrial, vascular, contractile, lipid, and inflammatory axes of cardiovascular pathophysiology.

CoQ10 addresses HF energy starvation by replenishing myocardial ubiquinone and supporting ATP for SERCA2a in chronic HF [2,12,69].

CoQ10 acts in the lipid phase and arjuna polyphenols in both aqueous and lipid phases, giving broader antioxidant coverage than either alone; arjuna polyphenol copper chelation extends this to the Fenton-chemistry axis [7,44,99,113].

Both independently improve endothelial function in randomised trials [86,111]; combined, they add antioxidant and direct eNOS-activating (arjuna) mechanisms, supporting stronger NO bioavailability than either alone [99,108].

COQ10+ spans the cardiometabolic continuum — dyslipidaemia, T2DM, metabolic syndrome, MASLD, diabetic cardiomyopathy, and statin-induced CoQ10 depletion — matching the prevalence of cardiometabolic comorbidity in contemporary medicine [110,120,121,127].

COQ10+ addresses statin-induced CoQ10 depletion via its CoQ10 component, bark extract, adding lipid-phase antioxidant protection. RCT data support CoQ10 in statin myopathy and metabolic-syndrome dyslipidaemia [44,131,132,146,147].

COQ10+ addresses seven mechanistic axes at once — mitochondrial bioenergetic support, ROS neutralisation, anti-inflammatory pathways, endothelial NO preservation, calcium homeostasis, lipid modulation, and anti-atherogenesis — a multi-target architecture beyond single-target approaches [110].

20. LIMITATIONS OF THE CURRENT EVIDENCE

The principal limitation is the absence of large randomised controlled trials of the fixed-dose combination as a finished product; mechanistic complementarity supports use, but product-specific clinical data are lacking. Heterogeneity of CoQ10 formulations undermines comparability — conventional powder-in-capsule ubiquinone reaches ~1–2 µg/mL at standard doses, whereas water-soluble solubilised, ubiquinol soft-gel, and phytosome formulations reach 2–5 µg/mL [123,148–150]. Bark extracts vary in triterpenoid and polyphenol content by geographic source (50+ accessions tested), harvest season, extraction, and standardisation [7,19,100,101]; COQ10+ uses a bark extract with HPTLC-fingerprint identity and total triterpenoid/polyphenol assays, under defined phytochemical acceptance criteria. Direct human evidence linking either ingredient to specific calcium-handling readouts is limited [104,105], and animal extrapolations — notably db/db mouse studies where ubiquinol restores SERCA2a [69] — need human validation. Neither ingredient has been tested for plaque regression in adequately powered human trials [99,113]. Most trials run 8–24 weeks; long-term (≥ 5 years) outcome data exist only for KiSel-10 (12-year follow-up) [21,128,129]. Many *T. arjuna* reports have n < 50 [23,137,143,145]. Hard cardiovascular outcomes for the combination are absent; Phase 3 trials with adequate power, ≥ 2-year follow-up, and endpoints of NT-proBNP, LVEF, FMD and MACE are required.

21. FUTURE RESEARCH DIRECTIONS

Pharmacokinetic studies should establish whether *Terminalia arjuna* polyphenols compromise CoQ10 absorption or CoQ10 alters Arjuna-component metabolism, measuring plasma CoQ10 levels, exposure (AUC), and polyphenol metabolites after single doses of the combination and each component alone.

Dose-ranging studies should define independent dose–response relationships for CoQ10 and Arjuna bark extract before combination testing; a factorial 2 × 2 trial would then determine whether COQ10+ is additive or synergistic versus placebo.

An initial 12-week double-blind placebo-controlled Phase 2 trial in prehypertension or metabolic syndrome should use flow-mediated dilatation as surrogate endpoint. Subsequent trials should target heart failure and diabetic diastolic dysfunction endpoints: NT-proBNP, LVEF, six-minute walk test, tissue-Doppler e′ velocity, HbA1c, microvascular perfusion and quality of life.

Mechanistic substudies might assess SERCA2a, phospholamban and RyR2-related biomarkers alongside vascular pulse-wave velocity, capillaroscopy and laser-Doppler perfusion, with longer-term coronary CT angiography or carotid plaque analyses also considered.

Finally, pharmacovigilance studies should assess long-term tolerability — gastrointestinal intolerance, hypotension, hypoglycaemia, dermatological reactions and bleeding risk — particularly in patients on anticoagulant or antiplatelet therapy.

22. Conclusion

Cardiovascular disease remains the leading cause of global mortality despite optimal lipid-lowering, antihypertensive, antiplatelet, and heart-failure therapy, and this residual risk motivates mechanistically complementary nutraceutical strategies. COQ10+ combines two ingredients acting on non-overlapping cardiovascular axes. **Coenzyme Q10**, the sole endogenous lipid-soluble mitochondrial electron carrier and principal lipophilic LDL antioxidant, and standardised ***Terminalia arjuna*** **bark extract** deliver a

polychemical triterpenoid–polyphenol matrix. Together, CoQ10 restores mitochondrial electron-transport efficiency, ATP supply to SERCA2a, and NO bioavailability, while *T. arjuna* adds inotropy, vasodilation, and hypolipidaemic, anti-atherogenic, and anti-fibrotic activity — jointly covering the mitochondrial, vascular, contractile, lipid, anti-inflammatory, and calcium-handling axes that drive residual risk in optimally managed patients. Both components have well-characterised safety profiles (CoQ10 up to 1,200 mg/day [21,124]; arjuna 400–1,000 mg/day [23,111,137,143]). The principal limitation is the absence of large randomised trials of the finished combination; Phase 1 pharmacokinetic, Phase 2 pilot, and Phase 3 endpoint studies are recommended to bridge mechanism to direct clinical evidence. COQ10+ therefore represents a mechanism-based, multi-target nutraceutical and a scientifically rational adjunct to contemporary cardiovascular pharmacotherapy in patients with persistent residual risk.

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