Evolutionary clues unlock CoQ10 biofortification

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Spotlight

Evolutionary clues unlock CoQ_{10} biofortification

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Coenzyme Q (CoQ) is vital for human health, but structural differences limit its supplementation from crops. In a recent study, Xu *et al.* traced its diversification across plant lineages and identified distinct targets for precise engineering. Their work highlights how utilising evolutionary signatures can enable crop biofortification and guide future strategies to enhance nutritional value.

CoQ, also known as ubiquinone, is a lipid-soluble antioxidant and a vital component of the mitochondrial electron transport chain. In eukaryotic cells, it transfers electrons between complexes I and II to complex III, enabling ATP production through the oxidative phosphorylation. Beyond its role in energy metabolism, CoQ functions as a membrane-associated antioxidant and takes part in various redox-regulated cellular processes [1]. Deficiencies in CoQ, whether caused by genetic mutations or age-related decline, have been linked to cardiovascular disease, neurodegeneration, and metabolic disorders [2–4]. Consequently, CoQ, particularly CoQ_{10}, the primary form in humans, has garnered increasing interest as a dietary supplement and therapeutic agent, with an anticipated global annual market value expected to reach nearly US$2 billion by 2032[i].

Although CoQ has an essential role in mitochondrial respiration and is widely conserved across different forms of life, it shows structural variation among various taxa, mainly in the length of its isoprenoid side chain. Humans synthesise CoQ_{10} (which contains ten isoprenoid units), whereas baker's yeast (*Saccharomyces cerevisiae*) produces CoQ_6. The composition of CoQ varies even more among land plants; most flowering plants, including key crops, such as rice and wheat, produce CoQ_9. This variation in chain length influences how well plant-derived CoQ can be used by humans, because CoQ_9 is less efficiently incorporated into human mitochondrial membranes. Consequently, many herbaceous crops, including all cereal food crops, are regarded as unsuitable sources of CoQ_{10} supplements.

In their recent study, Xu *et al.* uncovered the evolutionary origins of CoQ structural diversity in flowering plants and identified specific molecular targets for bioengineering crops with improved nutritional value [4]. By analysing liquid chromatography–tandem mass spectrometry (LC-MS/MS) data from 134 land plant species, the authors showed that CoQ_{10}, the same isoform found in human mitochondria, represents the ancestral state in angiosperms. By contrast, CoQ with shorter isoprenoid tails, particularly CoQ_9, appears to have evolved independently on multiple occasions through convergent evolution. This transition is especially clear in vegetable, fruit, and oil crops, such as cucumbers, pumpkins, sunflowers, and lettuce, as well as in cereals, including rice, wheat, maize, and barley.

Using a phylogenomic approach to *Coq1*, the gene encoding the polyprenyl transferase that initiates CoQ side-chain synthesis, the authors uncovered a striking pattern: a single amino acid change at position 240, where either isoleucine or methionine replaces leucine, is strongly associated with the switch from CoQ_{10} to CoQ_9 production. This residue change appears to have evolved multiple times to reduce the length of the quinone side chain.

To test whether this single site was functionally causal, Xu *et al.* introduced targeted mutations into Coq1 enzymes expressed in *Escherichia coli*, demonstrating that changing residue 240 was enough to switch production from CoQ_9 to CoQ_{10}. Structural modelling further showed how the ancestral leucine at site 240 creates a steric pocket that favours longer isoprenyl chains, providing a mechanistic explanation for its evolutionary retention in CoQ_{10}-producing species.

However, when applying this strategy to crops, the authors found that editing site 240 alone was not always sufficient. In both rice and wheat, they used prime editing to introduce not only the key leucine residue, but also additional substitutions in Coq1, guided by sequence comparisons with natural CoQ_{10}-producing plant homologues. This combined editing approach enabled effective *in planta* chain-length conversion.

The study by Xu *et al.* highlights an emerging approach in plant synthetic biology: using evolutionary signatures or natural variability to guide rational metabolic reprogramming. Instead of designing pathways from scratch, researchers can follow naturally occurring mutations that influence metabolite profiles and then replicate these changes in target crops or for recombinant bioproduction (Figure 1). This approach is supported by previous examples. For instance, the structural characterisation of chalcone synthase enzymes was used to optimise enzymes for flavonoid biosynthesis [5], and ancestral sequence reconstruction, coupled with biochemical characterisation, guided the engineering of plant terpene synthases with specific product profiles [6,7]. In the case of CoQ biosynthesis, recognising the same residue change across different lineages offers both functional insights and a guide for precise editing.

Following the successful transition from CoQ_9 to CoQ_{10} in grains and leaves, over

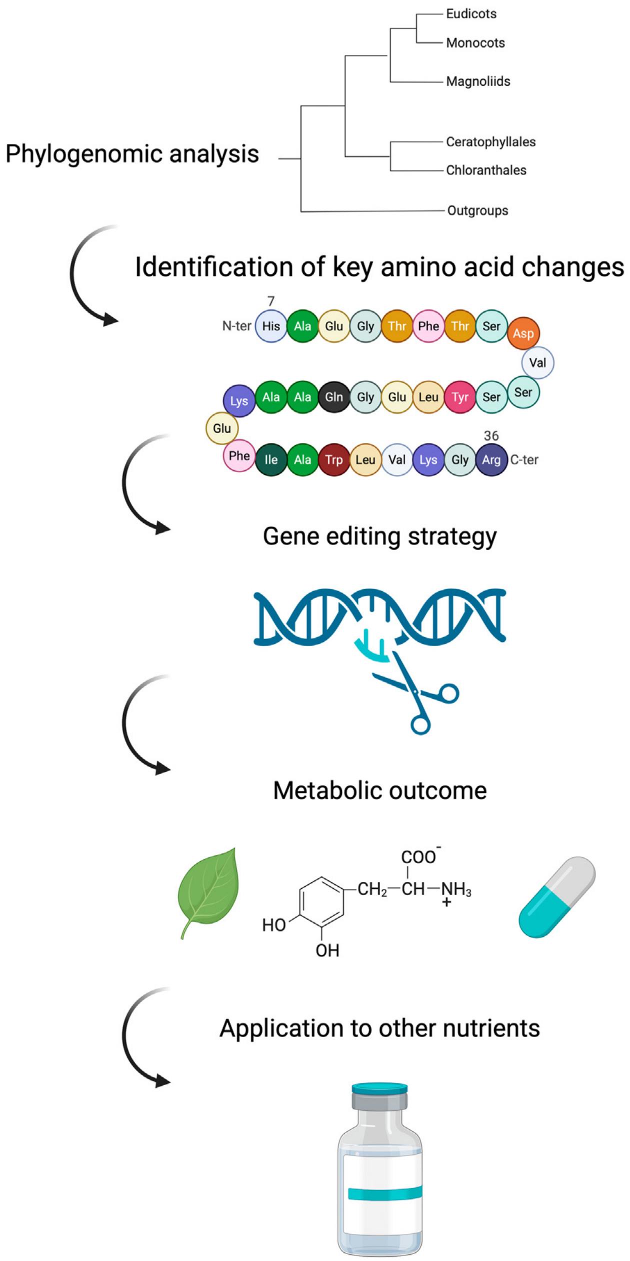

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Figure 1. Generalisable strategy for metabolic reprogramming using synthetic biology. By using phylogenomic analysis, key amino acids can be identified. Gene editing with CRISPR-Cas technology enables precise modifications, resulting in altered metabolic outcomes. Extracts can be utilised and combined with other nutrients. Figure created using BioRender (biorender.com).

75% of the total CoQ content in engineered rice plants comprised the CoQ_{10} isoform, a significant nutritional shift. Notably, neither the overall metabolite profiles nor the agronomic performance differed significantly from those of wild-type controls, indicating a minimal physiological cost. In wheat, where Coq1 is encoded by six alleles across three subgenomes, the process was more complex. However, through homozygous substitutions in two subgenomes, the authors still achieved markedly increased CoQ_{10} levels.

The successful engineering of CoQ_{10}-producing crop plants marks a significant advance in developing functional foods that support human nutrition and help prevent micronutrient-related diseases, especially in areas with limited access to synthetic supplements. Directly increasing CoQ_{10} levels in widely consumed staple crops aligns with consumer preferences for naturally sourced health products and offers a practical solution for dietary enrichment without major changes to eating habits.

Crucially, Xu *et al.*'s framework is highly adaptable. Their integration of phylogenomic insight with precise gene editing offers a roadmap for customised manipulation of crop metabolic output by mimicking naturally evolved traits. Similar approaches could be used to enhance levels of other nutritionally beneficial compounds, such as omega-3 fatty acids, flavonoids, or vitamins. As gene editing technologies continue to improve in efficiency and multiplexing capacity, the potential for reprogramming complex metabolic networks is expected to grow in the foreseeable future.

As the approach depends on transgene-free base editing, it may face fewer regulatory hurdles in some jurisdictions and could achieve wider public acceptance compared with other genetically modified organisms. However, the intersection of biotechnological advances in nutrition and public trust remains a highly contentious issue, emphasising the importance of proactive engagement with consumers, policymakers, and stakeholders.

Xu *et al.*'s study illustrates how evolutionary biology can directly inform targeted nutritional innovation. It provides a strong example of combining basic plant science with applied genetic engineering to produce sustainable, health-promoting crops. This approach could greatly influence the future of food security and human health.

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Declaration of interests

The authors declare no competing interests.

Resources

[i] www.gminsights.com/industry-analysis/coenzyme-q10-coq10-market

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