

Whole Foods Versus Isolated Compounds: Why Nutrition Trials Keep Asking the Wrong Question

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Dear Editor,

Large randomized trials of isolated antioxidant compounds have repeatedly returned null or adverse results, even as whole-food dietary patterns rich in the same compounds remain associated with better health. I write to suggest that this is not a paradox but a predictable consequence of a recurring design choice: testing single high-dose nutrients in isolation.

According to PubMed, many dietary phytochemicals do not act primarily as direct radical scavengers but as mild stressors that, at the low doses found in food, activate adaptive cellular pathways such as Nrf2, thereby inducing the cell's own antioxidant enzymes and protective proteins. The *in vivo* benefit, in other words, is hormetic and depends on a low dose delivered in a food matrix.

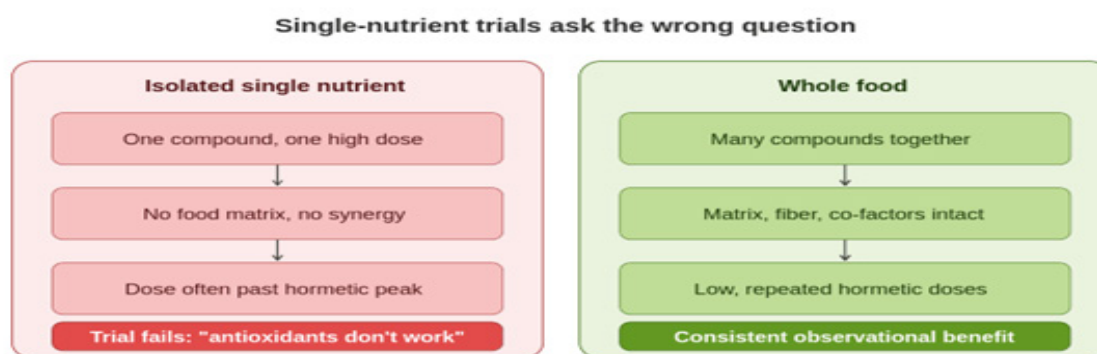
According to PubMed, several plant antioxidants act as low-dose stressors that prepare cells to resist more severe stress, activating signaling at low doses while becoming cytotoxic at high doses, and their *in vivo* benefits are unlikely to be explained by direct antioxidant capacity alone. A trial that isolates one such

compound and administers it at a high, sustained dose removes the food matrix and may land beyond the hormetic peak—testing almost the opposite of the mechanism thought to underlie the food's benefit. This matters because null trials of isolated nutrients are frequently interpreted as evidence that “antioxidants don't work,” when a more careful reading is that isolated high-dose antioxidants don't work—which is a different and more defensible claim. The whole-food evidence is not thereby refuted; it is simply addressing a different intervention.

I would encourage investigators and editors to treat single-compound supplement trials and whole-food pattern studies as answering distinct questions, and to be cautious about generalizing from the former to the latter. Where the hypothesized mechanism is hormetic and matrix-dependent, trial designs that preserve dose realism and food context will be far more informative than another high-dose monotherapy.

Sincerely,

Mueen Ahmed KK



The mechanism is the food pattern, not the isolated molecule the trial tested

Isolated single- nutrient trials strip away the food matrix and often overshoot the hormetic dose, testing nearly the opposite of the mechanism that makes whole foods beneficial.



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