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Reconsidering the Metabolic Effects of TBHQ: An Overlooked Interaction between Dietary Antioxidants, Lipid Metabolism, and Inflammatory Pathways

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Dear Editor

In recent years, there has been increasing attention on the role of dietary antioxidants in the prevention and modulation of metabolic disorders, particularly metabolic syndrome (MetS). While natural antioxidants have consistently demonstrated beneficial metabolic effects, not much is known about the long-term metabolic consequences of synthetic antioxidants used in food processing. Among these, tertiary butylhydroquinone (TBHQ) is widely incorporated into edible oils to prevent lipid oxidation and prolong shelf life. Despite its technological advantages, the biological relevance of TBHQ exposure to metabolic health remains poorly characterized.

Beyond its established technological role as a synthetic antioxidant added to edible oils to prevent oxidative deterioration, TBHQ has been shown to exert biological activity at the cellular level. Experimental evidence indicates that TBHQ activates the nuclear factor erythroid 2–related factor 2 (Nrf2) signaling pathway, thereby influencing redox balance and phase II detoxification processes (Liu *et al.*, 2023, Ma *et al.*, 2025). Although Nrf2 activation is generally cytoprotective, emerging evidence suggests that sustained or excessive activation may disrupt metabolic homeostasis, particularly in organs central to lipid and glucose regulation. This dual and context-dependent nature of Nrf2 signaling cytoprotective under physiological conditions which is potentially disruptive when chronically activated, raises important questions regarding the long-term metabolic implications of sustained TBHQ exposure (Gumeni *et al.*, 2023, Singh and

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Chadha, 2024). Indeed, while TBHQ can induce phase II detoxification enzymes through Nrf2-dependent mechanisms, chronic exposure has also been associated with pro-oxidant effects and potential carcinogenicity, partly through the formation of reactive metabolites and GSH conjugates (Gharavi *et al.*, 2007, Xu *et al.*, 2021). Furthermore, TBHQ has been reported to modulate additional signaling pathways, including NF-κB, PI3K/AKT, Wnt, and Hedgehog pathways, underscoring its pleiotropic and context-dependent biological actions (Whisel and Rice, 2025, Zhao *et al.*, 2020, Zhu *et al.*, 2021).

These mechanistic considerations are particularly relevant in the context of MetS, a condition characterized by dyslipidemia, insulin resistance, and chronic low-grade inflammation. Experimental studies suggest that TBHQ may influence key regulators of lipid metabolism, including peroxisome proliferator-activated receptors (PPARs) and sterol regulatory element-binding proteins (SREBPs) (Mika *et al.*, 2023). Alterations in these pathways could plausibly affect circulating lipid parameters such as triglycerides and low-density lipoprotein cholesterol. However, direct evidence from long-term human clinical studies is scarce, and existing data are largely extrapolated from short-term experimental models or heterogeneous dietary contexts (Esazadeh *et al.*, 2024, Shintyapina *et al.*, 2017). To date, no well-controlled, long-term human clinical trials have systematically evaluated the metabolic effects of habitual dietary TBHQ exposure. This gap underscores the need for carefully designed human studies that account for dose, duration, metabolic status, genetic background, and overall dietary composition.

In addition to lipid regulation, TBHQ may influence inflammatory pathways that are central to MetS pathophysiology. Pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) contribute to insulin resistance and atherosclerotic progression. Moreover, redox-sensitive signaling mechanisms provide a plausible link between TBHQ exposure and inflammatory modulation (Awali *et al.*, 2026). Notably, reported effects vary depending on dose, duration of exposure, and metabolic context. For example, tBHQ has been shown to activate MAPK pathways including JNK, ERK, and p38in a time and dose-dependent manner, with oxidative stress contributing to ERK activation (Yu *et al.*, 1997). Such mechanistic complexity, involving both Nrf2-dependent and Nrf2-independent pathways, may explain the divergent findings reported across experimental systems.

An additional and largely underexplored dimension is inter-individual variability in response to TBHQ. Genetic polymorphisms in genes involved in lipid metabolism (e.g., APOA5, LDLR), inflammatory regulation (e.g., IL6), and adipokine signaling (e.g., ADIPOQ) may significantly modify metabolic responses to dietary exposures. Also, gene diet interactions are increasingly recognized as determinants of cardiometabolic risk (Curti *et al.*, 2012, Duarte *et al.*, 2025); however, their potential role in modulating susceptibility to TBHQ exposure has not been adequately investigated. For instance, the well-characterized rs662799 polymorphism in the *APOA5* gene influences triglyceride responses to dietary fat intake, providing a biologically plausible framework for differential metabolic responses to TBHQ-containing oils (de Luis *et al.*, 2021).

Moreover, the metabolic effects of TBHQ-containing oils should be interpreted in comparison with those of oils naturally rich in bioactive compounds, such as polyphenols and tocopherols. Natural oil matrices may exert synergistic antioxidant and anti-inflammatory effects that differ fundamentally from those of isolated synthetic additives. Distinguishing the intrinsic properties of the oil from the effects of added TBHQ is therefore essential for accurately evaluating metabolic outcomes.

Given the widespread consumption of TBHQ-containing oils, particularly through processed foods, the current lack of robust human data represents a notable gap in nutritional and metabolic research. Future studies should prioritize well-designed clinical trials with sufficient

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duration, standardized dietary interventions, and comprehensive metabolic and inflammatory profiling. Integrating genetic analyses may further clarify the mechanisms underlying inter-individual differences in response to TBHQ.

In conclusion, although TBHQ remains an effective food preservative, its broader metabolic implications warrant more systematic and translational investigation. A comprehensive framework integrating redox biology, lipid metabolism, inflammatory signaling, and gene–diet interactions is essential not only to clarify the role of TBHQ in metabolic syndrome, but also to refine current paradigms of dietary risk assessment in the context of chronic exposure. Incorporating inter-individual genetic variability into such evaluations may further align future research with emerging principles of precision nutrition, particularly in populations at elevated cardiometabolic risk.

Authors' contributions

All authors contributed to the conceptualization and writing of the manuscript.

Conflicts of interest

The authors declared no conflicts of interest.

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