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Letter to Editor

Comment On "Study on The Carcinogenic Risk of Food Preservatives and Their Related Molecular Targets and Pathway Mechanisms Through Network Toxicology Analysis"

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To Editor

We read with great interest the recent article titled "Study on the carcinogenic risk of food preservatives and their related molecular targets and pathway mechanisms through network toxicology analysis." In this response, we highlight several limitations of the study and offer constructive suggestions for improvement, aiming to support more robust future research. This original study systematically investigated the potential associations between six common food preservatives (sodium benzoate, calcium propionate, potassium sorbate, sorbic acid, sulfur dioxide, and sodium nitrite) and cancer development and progression. Through multi-database mining, we identified 176 cross-targets shared between preservatives and cancer, and further screened 28 core targets (e.g., TP53, PIK3CA, MYC). Molecular docking and dynamics simulations indicated that these preservatives can stably bind to cancer-related proteins such as HRAS and JAK1 and induce conformational changes. Pan-cancer analysis further revealed that the core targets CDK2 and CXCL8 are highly expressed in Kidney Renal Clear Cell Carcinoma (KIRC) and Liver Hepatocellular Carcinoma (LIHC) and are associated with poor prognosis. This study was the first to suggest, from a systems biology perspective, that food preservatives may influence tumor progression by modulating key oncogenes, providing new molecular evidence and risk prediction models for food safety assessment and cancer prevention. Nevertheless, several non-negligible limitations exist, which are detailed below.

Methodological Limitations: The Gap from Computation to Validation

As a purely computational biology study, all conclusions are based on in silico simulations without wet-lab validation – its most significant limitation. First, database heterogeneity and standardization. The study integrated three databases (SuperPRED, STITCH, and CTD) to mine preservative-related targets. However, these databases differ in their underlying principles and evidence weighting: STITCH emphasizes literature mining and experimental chemical-protein interaction data, whereas SuperPRED relies on structure-based predictions. This heterogeneity may introduce systematic bias, and the issue of cross-database data standardization has not been adequately addressed. We suggest that future methodological sections should include the screening thresholds for each database (e.g., score cutoffs, evidence types) and discuss the consistency and discrepancies among targets derived from different sources.

Second, questionable strength of molecular interactions. Our molecular docking results showed binding energies between preservatives and target proteins ranging from -3.9 to -6.2 kcal/mol, which is lower than the typical threshold for strong inhibitors (generally < -7.0 kcal/mol), suggesting that the predicted interactions may be weak. More critically, the exposure concentrations of food preservatives under real human physiological conditions are far lower than the active concentrations of conventional small-molecule drugs [1]. Preservative concentrations in target tissues are typically in the micromolar to millimolar range, and they undergo first-pass metabolism, resulting in very limited bioavailability of the parent compounds [2,3]. For example, sodium benzoate is rapidly conjugated with glycine to form hippuric acid and excreted in urine [4], while nitrite is partially converted to nitric oxide or other reactive nitrogen species in the acidic gastric environment [5]. Therefore, inferring substantial in vivo target modulation by preservatives based solely on docking scores carries a high risk of false positives; the current conclusions should be regarded as computational clues requiring further validation.

Third, risk of information dilution from the combined analysis strategy. Although the study found that six chemically distinct preservatives (including ionic, weak-acid, and gaseous types) co-target well-established cancer drivers such as TP53, PIK3CA, MYC, and AKT1, which suggests a theoretical possibility that different preservatives might interfere with tumor development by affecting key nodes of protein-protein interaction networks, this pooling strategy may mask the unique mechanisms of individual preservatives even as it reveals overall trends. Furthermore, it cannot distinguish causality: whether preservative exposure causes target dysfunction or merely shares downstream pathways with cancer. Future studies should include "preservative-specific pathway analyses" that independently examine the target signatures of each preservative to distinguish true pharmacological effects from computational false positives.

Anomalous Findings and Interpretational Boundaries

A noteworthy finding in this study was the paradoxical prognosis of CDK2 in LIHC: although both mRNA and protein levels were highly expressed, lower expression was paradoxically associated with worse prognosis. This finding contradicts the conventional understanding of CDK2 as a positive regulator of the cell cycle that is typically overexpressed and promotes proliferation in various tumors. To address this anomaly, the robustness of the prognostic analysis should first be rigorously examined, including confirming whether optimal cutoff values (e.g., determined by time-dependent ROC curves) were used and excluding biases due to sample heterogeneity, platform differences, or outlier samples. If the paradoxical association remains stable across multiple grouping strategies, data noise can be preliminarily ruled out, and biological explanations can be sought.

Based on this, we propose two plausible biological hypotheses. First, tissue-specific functional switching: CDK2 may participate in cellular stress regulation. For instance, the compound Mollugin exerts anti-HCC effects accompanied by changes in CDK2 expression by inducing excessive Reactive Oxygen Species (ROS) leading to DNA damage and cell cycle arrest, suggesting that CDK2 may act as a cell cycle checkpoint responder in DNA damage response pathways [6]. Additionally, CCNE1 (a key regulatory subunit of CDK2) and CDK2 have been co-identified as crucial drivers of HCC development, and loss of their function significantly suppresses hepatocarcinogenesis, inversely suggesting that under specific genetic or microenvironmental contexts (e.g., DNA repair pathway activation status), modulation of CDK2 activity may influence tumor cell sensitivity to damage [7]. Second, compensatory signaling rewiring: when CDK2 activity is reduced, CDK1, CDK4, and others may be compensatorily upregulated through transcriptional or protein stability mechanisms to maintain Rb-E2F pathway activity. Such compensation might activate more aggressive signaling programs, such as promoting Epithelial-Mesenchymal Transition (EMT) or immune microenvironment remodeling [8,9]. Notably, the limited efficacy of CDK inhibitors is partly attributable to tumor cells activating compensatory kinase signals through "pathway rewiring", indirectly supporting the compensatory signaling rewiring hypothesis [10]. Moreover, CDK2 showed a protective trend in LIHC prognosis but acted as a risk factor in KIRC. This further illustrates that the function of the same gene is highly dependent on cancer-specific microenvironments and cannot be simply classified as uniformly "oncogenic" or "tumor suppressive". Similar functional plasticity is observed for classic molecules like TGF-β, whose direction of action is finely regulated by tissue origin, mutational background, and immune microenvironment [11].

External Validation and Clinical Translation Bottlenecks of the Prognostic Model

In this study, these risk score-based prognostic models were constructed for KIRC, LIHC, Glioblastoma (GBM), and Pancreatic Adenocarcinoma (PAAD), identifying CDK2 and CXCL8 as key risk genes shared across multiple cancer types. In each model, patients in the high-risk group had significantly worse overall survival than those in the low-risk group, and the Area Under the Curve (AUC) for predicting one-year survival reached above 0.85 in some models, indicating good goodness-of-fit and short-term predictive potential. However, the model has two major limitations regarding clinical translation. First, lack of independent external validation. Current model performance evaluation relies entirely on the TCGA training set, without validation using external cohorts such as GEO, posing a risk of overfitting. Additionally, the study did not employ calibration curves to assess agreement between predicted probabilities and actual survival, nor did it use Decision Curve Analysis (DCA) to quantify the net clinical benefit of the model across different threshold probabilities. These omissions leave the model's generalizability uncertain, its applicability to diverse

populations, platforms, or conditions unverified, and its clinical decision-making value therefore unreliable.

Second, the model did not associate risk scores with key clinicopathological parameters. Although risk scores can reflect patient survival stratification to some extent, clinical variables such as tumor stage, pathological grade, and treatment response (e.g., chemoradiotherapy sensitivity) also significantly impact prognosis. Without elucidating the independent or synergistic relationships between the risk score and these variables, it is difficult to determine whether the model provides incremental predictive value beyond traditional clinical indicators, limiting its potential utility in guiding individualized treatment.

Future Research Directions

1) Wet-lab validation: Use Surface Plasmon Resonance (SPR) or Isothermal Titration Calorimetry (ITC) to determine the dissociation constant (KD) of representative preservatives with key targets (e.g., sodium benzoate-HRAS); detect HRAS GTPase activity and MAPK8 phosphorylation levels in cellular models following preservative treatment.

2) Independent cohort validation: Validate the generalizability of the prognostic model in multi-center datasets such as GEO and ICGC, and supplement with calibration curves and DCA.

3) CDK2 functional validation: Combine clinicopathological stratification analyses with CRISPR-Cas9 or siRNA-mediated knockdown technologies to knock out or knock down CDK2 in LIHC (e.g., Huh7) and KIRC (e.g., 786-O) cell lines, respectively, to validate phenotypic differences and causality across cancer types.

4) Preservative-specific pathway analysis: Independently examine the target signatures of each preservative to avoid dilution of key mechanistic signals due to pooled analysis.

Conclusion

In summary, this study provides a novel systems biology perspective and testable computational hypotheses regarding the potential associations between food preservatives and cancer. Although the current conclusions are primarily based on computer simulations and have certain limitations that await further validation by experimental and clinical data, these findings may still offer valuable references for food safety assessment and cancer prevention research, and may open up new directions for future investigation.

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Author contributions

Fuling Zeng, Fuyan Lai, and Jiaxin Zeng conceived and designed the commentary. Fuyan Lai and Jiaxin Zeng performed the literature review and drafted the manuscript. Fuling Zeng critically revised the manuscript for important intellectual content. All authors read and approved the final version.

Declaration of Interest Statement

The authors declare no competing interests.

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Data availability

No new data were generated or analyzed in support of this commentary.

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