



Foam-Height Response in *Saccharomyces cerevisiae* as a Phenotypic Indicator of Acute Metal Toxicity and Its Modulation by Amino Acid–Derived Carbon Nanodots

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Abstract

This study evaluates foam-height response in *Saccharomyces cerevisiae* as a rapid phenotypic indicator of acute toxicological stress induced by selected inorganic salts and its modulation by amino acid–derived carbon nanodots (CNDs). Foam height measured after 20 min, reflecting combined fermentative activity and cell surface properties, was used as an integrative proxy of early cellular responses. Clear dose-dependent inhibitory effects were observed for CuSO₄, NaCl, Na₂SeO₃, and Na₂TeO₃. L-ascorbic acid exhibited a biphasic response. Glycine- and lysine-derived CNDs modulated copper toxicity in a concentration-dependent and compound-specific manner, with GLY-CNDs showing predominantly protective effects, while LYS-CNDs displayed variable outcomes. Although the method does not resolve mechanistic pathways or subtle physiological changes, it reliably captures dominant toxicological trends under acute exposure conditions. The results support the applicability of foam-height response as a simple, rapid, and low-cost complementary screening approach for preliminary toxicity assessment of chemical agents and nanomaterials.

Keywords Yeast · *Saccharomyces cerevisiae* · Toxicology · Rapid test · Carbon-nanodots

1 Introduction

Baker's yeast (*Saccharomyces cerevisiae*) is one of the most intensively investigated eukaryotic microorganisms, widely used in fundamental research, industrial biotechnology, and environmental toxicology. Historically associated with bread-making and brewing [35], it has become a key model organism for studying core eukaryotic processes such as DNA replication, transcription, translation, cell cycle regulation, and apoptosis [10]. Its unicellular nature, rapid growth, ease of cultivation, and well-annotated genome make it highly amenable to experimental manipulation, while the conservation of essential biochemical pathways

with higher organisms underpins its relevance in toxicological studies [22].

Yeast-based bioassays exploit the sensitivity of *S. cerevisiae* to a wide range of environmental stressors, including heavy metals, organic pollutants, and engineered nanomaterials [4]. Common endpoints include growth inhibition, loss of viability, metabolic impairment, and activation of stress-responsive reporter systems [8]. These assays are reproducible, cost-efficient, and ethically favorable alternatives to animal testing, supporting their use in high-throughput screening [1]. Classical toxicological studies have demonstrated that heavy metals such as cadmium and copper disrupt enzyme function, mitochondrial activity, and redox homeostasis, often through the induction of reactive oxygen species (ROS) and oxidative stress pathways [9, 26, 30, 46].

In addition to inorganic toxicants, yeast systems are widely applied in the detection of organic pollutants, including endocrine-disrupting compounds, for example, in the *S. cerevisiae* estrogen screen [25, 38, 42]. The expanding field of nanotechnology has further increased the demand for in vitro models capable of assessing nanoparticle toxicity. Metal-based nanoparticles such as AgNPs, ZnONPs,

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TiO₂NPs, and CuONPs exhibit size- and surface-dependent reactivity, often leading to oxidative stress, membrane damage, and activation of stress signaling pathways in yeast cells ([24, 29, 32, 44]). It should be noted, however, that carbon-based nanomaterials differ fundamentally from metallic nanoparticles: while metal-based NPs frequently exert toxicity via ion release and ROS generation, carbon nanodots are generally considered less inherently toxic and may exhibit protective or modulatory effects depending on their surface chemistry.

Advanced analytical approaches, including transcriptomics and proteomics, have provided detailed insights into yeast stress responses, identifying key pathways related to metal detoxification, oxidative stress, and metabolic adaptation [28, 40]. Techniques such as microplate assays, flow cytometry, and reporter gene systems allow high-resolution and high-throughput characterization of cellular responses [34]. Recent developments further integrate yeast assays into microfluidic and lab-on-a-chip systems, enabling rapid and portable toxicity testing, while computational approaches, including machine learning, are increasingly applied to interpret complex biological response patterns [39]. These advances, together with demonstrated concordance between yeast and higher-organism toxicity data, highlight the importance of *S. cerevisiae* as a versatile platform for toxicological screening [11]. Continued efforts toward standardization and interlaboratory validation are essential for broader regulatory acceptance [20, 36], particularly in the context of safer-by-design nanomaterial development [14].

Parallel to its role in toxicology, *S. cerevisiae* is central to fermentation processes, where metabolic activity leads to CO₂ production and foam formation. Foam generation arises from fermentative gas release and its stabilization by cell surface components, including mannoproteins, and is influenced by cell wall composition and surface hydrophobicity [6, 7, 12, 13, 15, 17, 19, 21, 45]. Genetic and physiological factors play a key role in this process, as demonstrated by studies linking specific cell wall proteins, such as Fpg1p, and surface properties to foam stability [16, 37, 41].

Importantly, cellular stress conditions—including osmotic and oxidative stress and heavy metal exposure—induce rapid changes in metabolic flux and CO₂ production, as well as remodeling of the yeast cell wall ([2, 3, 41]). These changes can be reflected in foam formation patterns. In certain cases, increased foam formation may represent a transient stress response associated with altered metabolism or surface properties rather than enhanced viability, indicating that foam height should be interpreted as a dynamic and context-dependent phenotypic marker rather than a direct measure of cell survival.

Carbon nanodots (CNDs) are nanoscale carbon-based materials, typically below 10 nm in size, characterized by high solubility and tunable surface functionalization. Depending on their composition, they may exhibit antioxidant, metal-chelating, or redox-modulating properties [5]. Amino acid-derived CNDs, such as glycine- and lysine-based nanodots, possess distinct surface chemistries that can influence their interactions with metal ions and biological systems. However, their role in modulating metal-induced stress responses in yeast remains insufficiently understood [18].

Despite the extensive use of yeast bioassays, most established methods rely on growth inhibition, viability measurements, or molecular reporters. In contrast, the present study introduces foam-height response as a rapid, visually accessible, and integrative phenotypic endpoint that reflects early metabolic and surface-associated changes without requiring specialized instrumentation. This study introduces foam-height response as a non-conventional, rapid phenotypic endpoint that captures integrative metabolic and surface-associated changes, representing a novel and accessible approach for preliminary toxicity screening and nanomaterial interaction analysis.

2 Materials and Methods

2.1 Materials

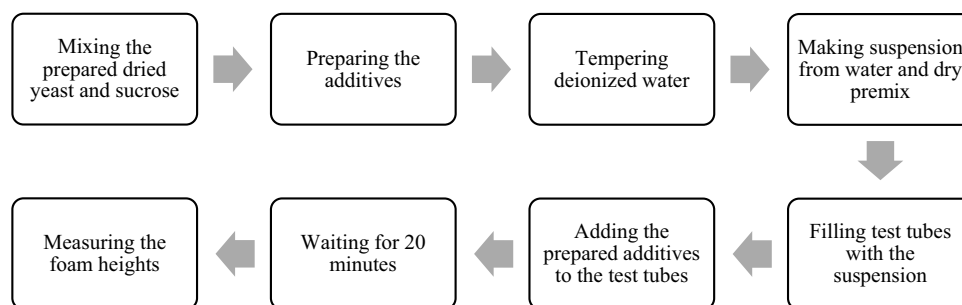
The following materials were used:

- *Saccharomyces cerevisiae* (instant dry yeast; PrJSC "Enzym Company", Lviv, Ukraine),
- sodium chloride (NaCl; Agrobónusz Kft, Hungary),
- L-ascorbic acid (Jubachem Kft, Hungary),
- sucrose (AGRANA Zucker GmbH, Austria),
- copper(II) sulfate (CuSO₄), sodium selenite (Na₂SeO₃), and sodium tellurite (Na₂TeO₃) (Thermo Fisher Scientific, USA),
- deionized water (Debrecen, Hungary).

2.2 Preparation of Yeast Suspensions

A standard yeast suspension was prepared by mixing 25 g of instant dry *Saccharomyces cerevisiae* and 25 g of sucrose with 106 g of deionized water preheated to 30 °C. The mixture was homogenized using an electric mixer for 30 s to obtain a uniform suspension. Aliquots of 20 mL were immediately dispensed into glass test tubes (height: 30 cm; diameter: 2.2 cm) using an automatic pipette. Samples were incubated at room temperature (25 °C) without agitation. The complete sample preparation process is illustrated in Fig. 1.

Fig. 1 Sample preparation process of yeast suspensions



2.3 Experimental Design

Foam height was measured 20 min after sample preparation and used as the primary response variable. Each treatment was performed in three or four independent replicates. For untreated control samples, five replicates were used to assess baseline reproducibility.

2.4 Treatment Conditions

Test compounds were added to the yeast suspension at predefined concentrations, expressed as mg/kg relative to the total mass of the yeast suspension, reflecting the practical preparation of the mixtures. This approach was applied consistently across all treatments to ensure comparability. Dose–response relationships were subsequently investigated using the following reagents and their combinations, applied across concentration ranges of 5–80 000 mg/kg depending on the intensity of the observed effects, as clearly shown in Table 1.

The concentration ranges were defined based on preliminary pilot experiments that evaluated the observable effects of each compound on foam height. These ranges were further supported by previously reported toxicity data in yeast systems [31]. The tested substances included sodium chloride, L-ascorbic acid, copper sulfate, sodium selenite, and sodium tellurite. CNDs derived from glycine (GLY-CNDs) and lysine (LYS-CNDs) were applied at two concentration levels (2.5% and 5%, w/w relative to the yeast suspension). All treatments were applied directly to the freshly prepared yeast suspension prior to incubation. Control samples contained no added compounds.

a Foam Measurements

Foam formation was monitored in static conditions without mechanical agitation or external aeration. Foam height was measured after 20 min as the vertical distance (cm) from the liquid surface to the top of the foam column. Measurements were performed visually using the calibrated scale of the test tubes. Foam height was used as an indirect indicator of fermentative CO₂ production and

Table 1 Summary of reagents and their concentrations added to the yeast suspensions

Yeast suspension treatments		
Reagent	Concentration range (mg/kg)	Additives
L-ascorbic acid	125–80 000	-
NaCl	250–80 000	-
CuSO ₄	5–10 240	-
		2.5%/5% (w/w) LYS-CND
		2.5%/5% (w/w) GLY-CND
Na ₂ SeO ₃	99–26 000	-
		2.5% (w/w) ascorbic acid
Na ₂ TeO ₃	99–26 000	-

associated metabolic activity, influenced by both intracellular processes and cell surface properties.

b Statistical Analysis

Statistical analysis was performed using the R software environment. Differences between groups were evaluated using one-way or two-way analysis of variance (ANOVA), depending on the experimental design. Post hoc comparisons were conducted using Tukey's HSD or Dunnett's test, where appropriate. Statistical significance was accepted at $p < 0.05$. Normality and homogeneity of variance were assessed using the Shapiro–Wilk test and visual inspection of residuals. In cases where assumptions were not fully met, non-parametric tests (Kruskal–Wallis) were applied to confirm the robustness of the results.

3 Results

3.1 Baseline Reproducibility Under Controlled Conditions

Foam height of untreated yeast suspensions remained consistent across independent preparations and measurement conditions, indicating good baseline reproducibility of the assay. Mean foam heights showed only minor variation between samples prepared at different time points and locations (Fig. 2). Statistical analysis confirmed the absence of

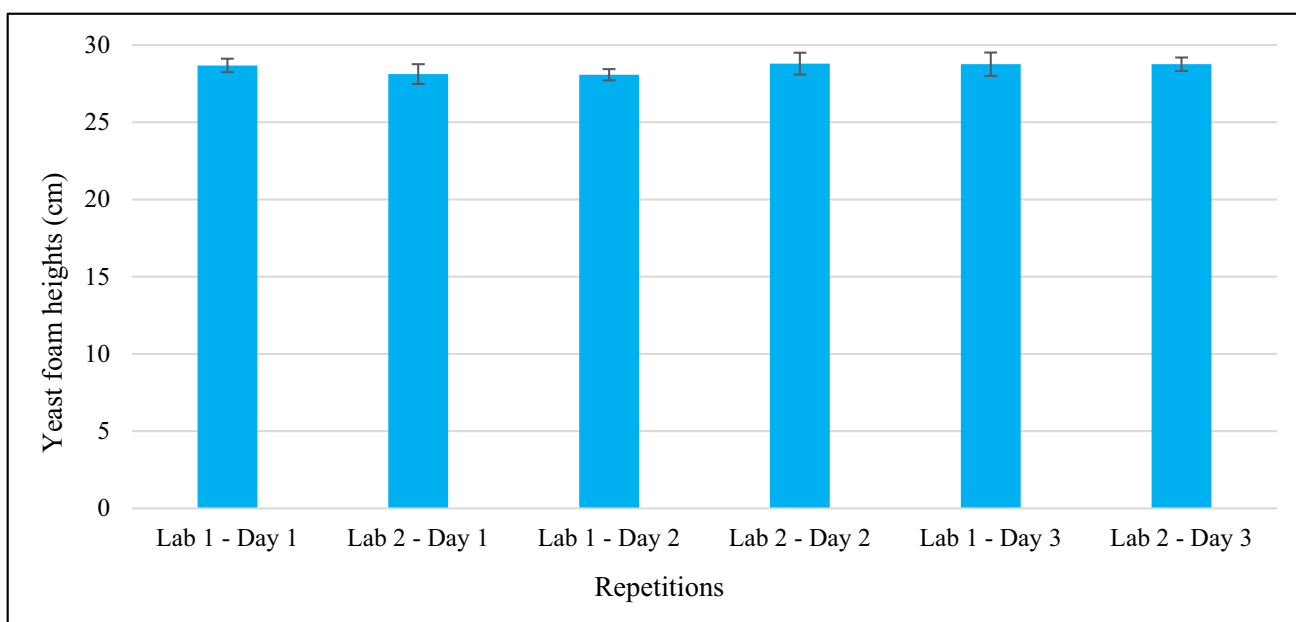


Fig. 2 Foam heights of untreated yeast suspensions at different time points and laboratories

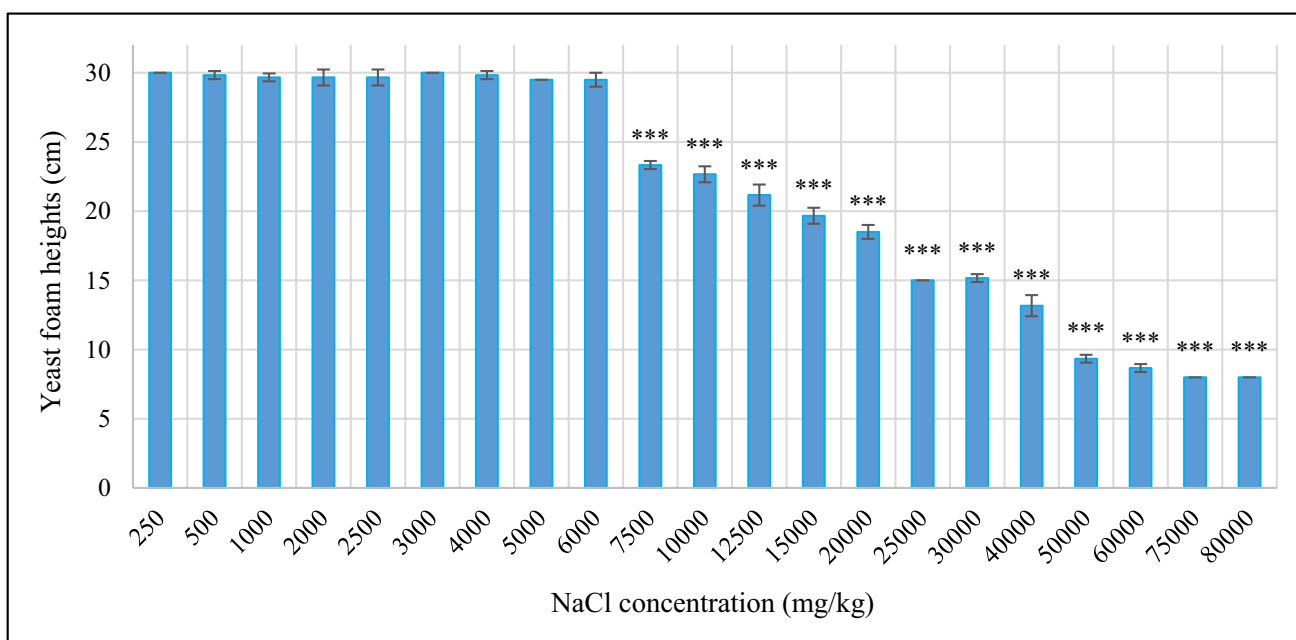


Fig. 3 Yeast suspension foam heights from left to right 7 500, 10 000, 15 000, 30 000, and 60 000 mg/kg concentration NaCl treatments at the 20th minute of the test

significant differences between groups (one-way ANOVA, $F(5,24)=1.71$, $p=0.171$).

3.2 Effect of Sodium Chloride on Yeast Activity

Sodium chloride induced a clear concentration-dependent inhibition of yeast activity, as reflected by decreasing foam height (Fig. 3). Foam height remained stable up

to 6 000 mg/kg, indicating tolerance to moderate osmotic stress [27, 43]. A pronounced decline was observed from 7 500 mg/kg onwards, with foam height reduced by more than 25% above 10 000 mg/kg. At the highest concentrations (50 000–80 000 mg/kg), foam formation was minimal. Statistical analysis confirmed a highly significant effect of NaCl concentration (one-way ANOVA, $p<0.001$). Post hoc tests indicated that concentrations $\geq 7\,500$ mg/kg differed

significantly from the control ($p < 0.001$). The progressive decline and plateau at high concentrations are consistent with a transition from adaptive response to reduced metabolic activity at higher concentrations.

3.3 Biphasic Response to L-Ascorbic Acid

L-ascorbic acid induced a non-linear, biphasic response in yeast foam formation (Fig. 4). At low to intermediate concentrations (up to $\sim 3\,000$ mg/kg), foam height decreased, indicating an inhibitory effect. At higher concentrations (approximately $5\,000$ – $15\,000$ mg/kg), foam formation increased, reaching levels comparable to or exceeding the control. Above this range, inhibition became dominant again. Statistical analysis confirmed significant differences between treatment groups (one-way ANOVA, $p < 0.01$). This pattern is consistent with a concentration-dependent shift between inhibitory and transient stimulatory effects.

3.4 Copper Sulfate Toxicity and the Protective Role of GLY-CNDs

Copper sulfate caused strong, concentration-dependent inhibition of yeast activity across the entire tested range (Fig. 5). The addition of GLY-CNDs modified this effect in a concentration-dependent manner (Fig. 6). At

intermediate CuSO_4 concentrations, 2.5% GLY-CND partially alleviated the inhibitory effect, resulting in increased foam height compared to CuSO_4 alone. The 5% GLY-CND treatment showed a more pronounced but non-linear modulation, with substantial recovery of foam height at mid-to-high copper concentrations. At the highest CuSO_4 levels, the differences between treatments diminished, indicating that the protective effect of CNDs was insufficient to counteract severe toxicity. Two-way ANOVA confirmed significant effects of both CuSO_4 concentration and CND treatment, as well as their interaction ($p < 0.0001$).

3.5 Variable Modulation of Copper Toxicity by LYS-CNDs

Lysine-derived carbon nanodots (LYS-CNDs) also modulated copper-induced toxicity, but in a more variable and context-dependent manner than GLY-CNDs (Figs. 7 and 8). At lower and intermediate CuSO_4 concentrations, LYS-CND supplementation partially restored foam height, indicating a protective effect. However, at higher concentrations, this effect was inconsistent, and in some cases, LYS-CNDs further reduced foam formation compared to CuSO_4 alone. These findings indicate that the interaction between LYS-CNDs and copper toxicity is strongly concentration-dependent and may involve both protective and adverse effects.

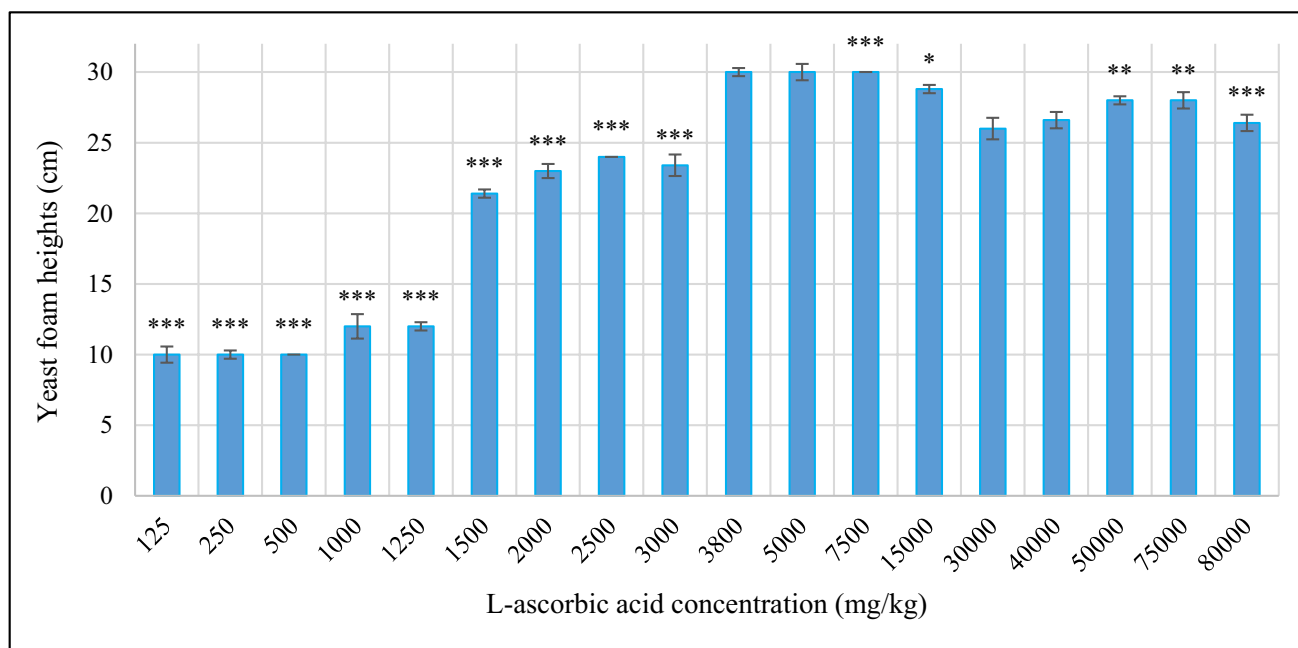


Fig. 4 Yeast suspension foam heights with different L-ascorbic acid concentrations, indicates significant difference compared to the untreated control (*, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.001$)

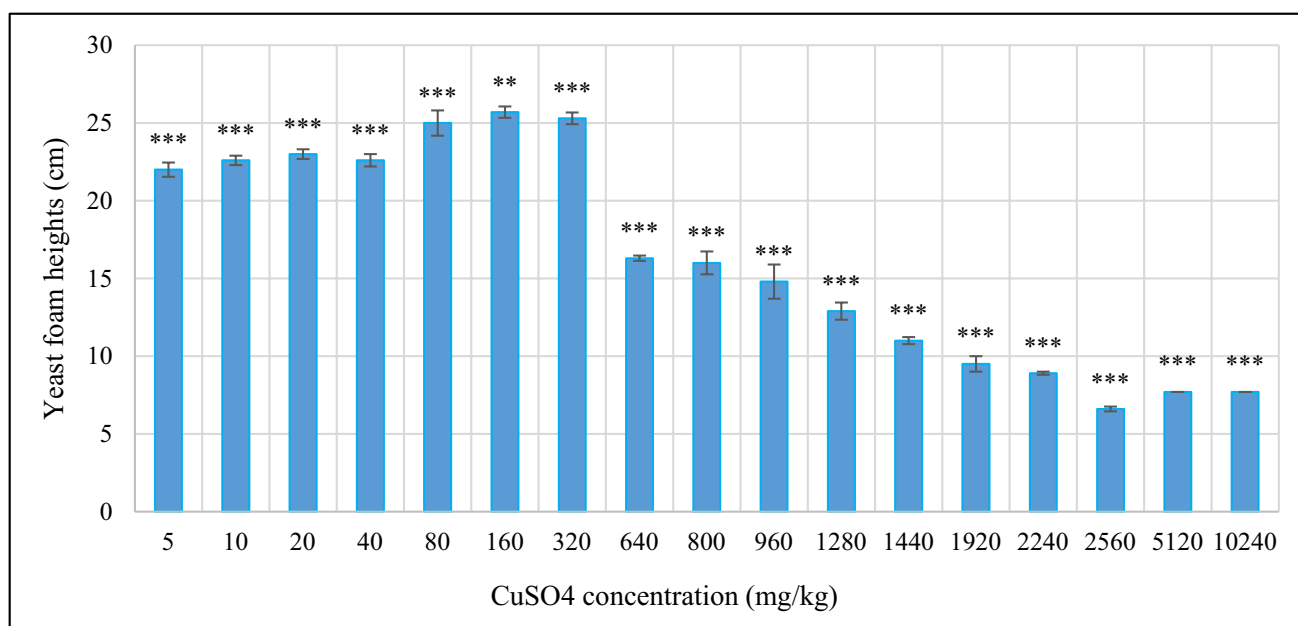


Fig. 5 Yeast suspension foam heights with different CuSO₄ concentrations, indicates significant difference compared to the untreated control (*, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.001$)

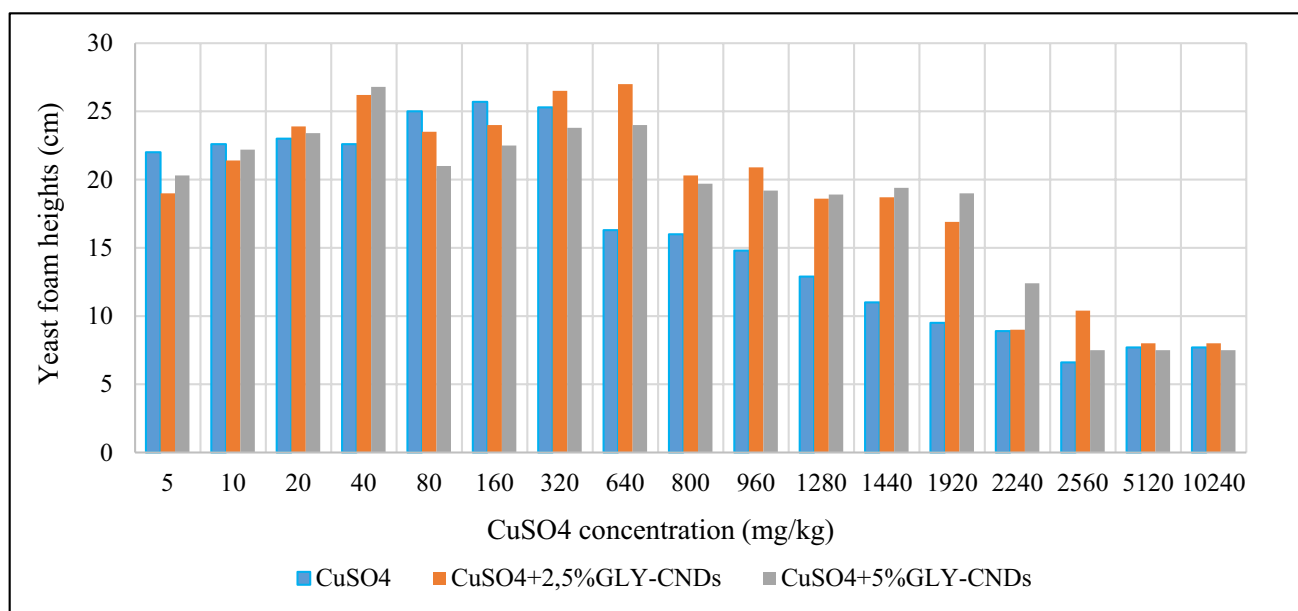


Fig. 6 Yeast suspension foam heights of CuSO₄, CuSO₄+2.5% GLY-CND and CuSO₄+5% GLY-CND with different CuSO₄ concentrations

3.6 Concentration-Dependent Toxicity of Sodium Selenite and Co-Treatment with Ascorbic Acid

Sodium selenite exhibited a threshold-type toxicity response (Fig. 9). Foam height remained largely unaffected at concentrations below ~1 000 mg/kg. Above this range, a gradual decline was observed, followed by a sharp reduction at concentrations $\geq 10\,000$ mg/kg. At the highest concentrations (22 000–26 000 mg/kg), foam formation was nearly

completely suppressed. Statistical analysis confirmed a significant concentration effect (one-way ANOVA, $p < 0.001$). These results indicate a transition from tolerance to rapid metabolic inhibition within a relatively narrow concentration range.

Co-treatment with L-ascorbic acid did not significantly alter the effect of sodium selenite. Neither the main effect of ascorbic acid nor its interaction with concentration was statistically significant (two-way ANOVA, $p > 0.05$).

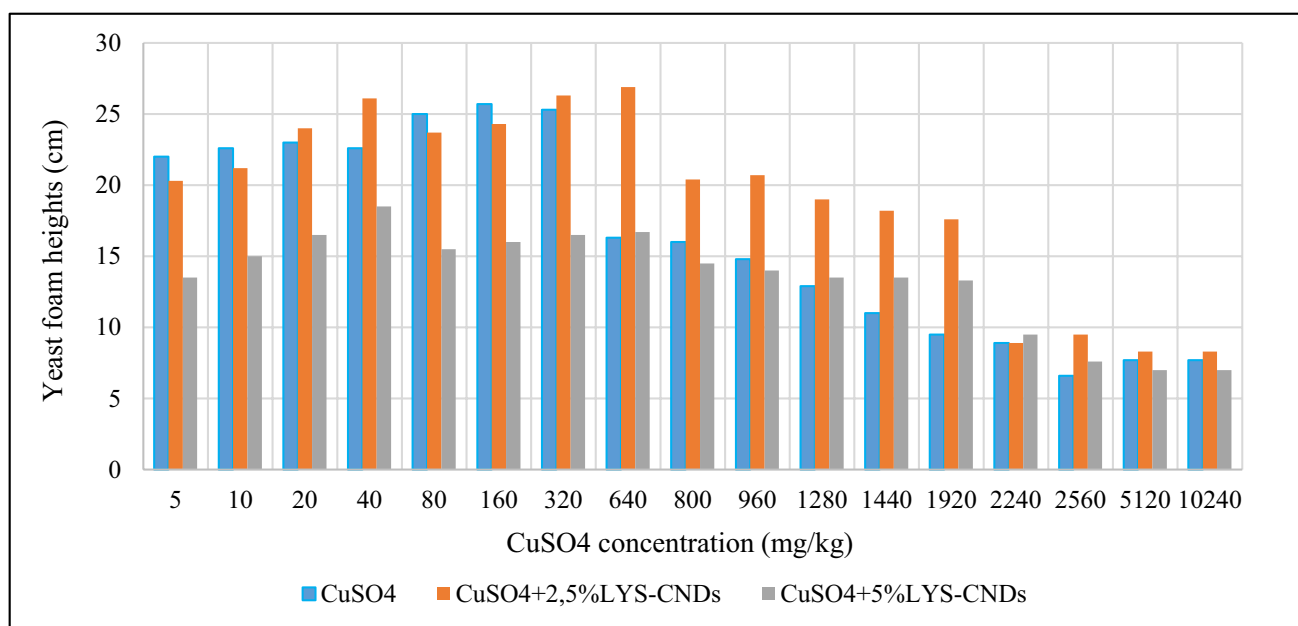
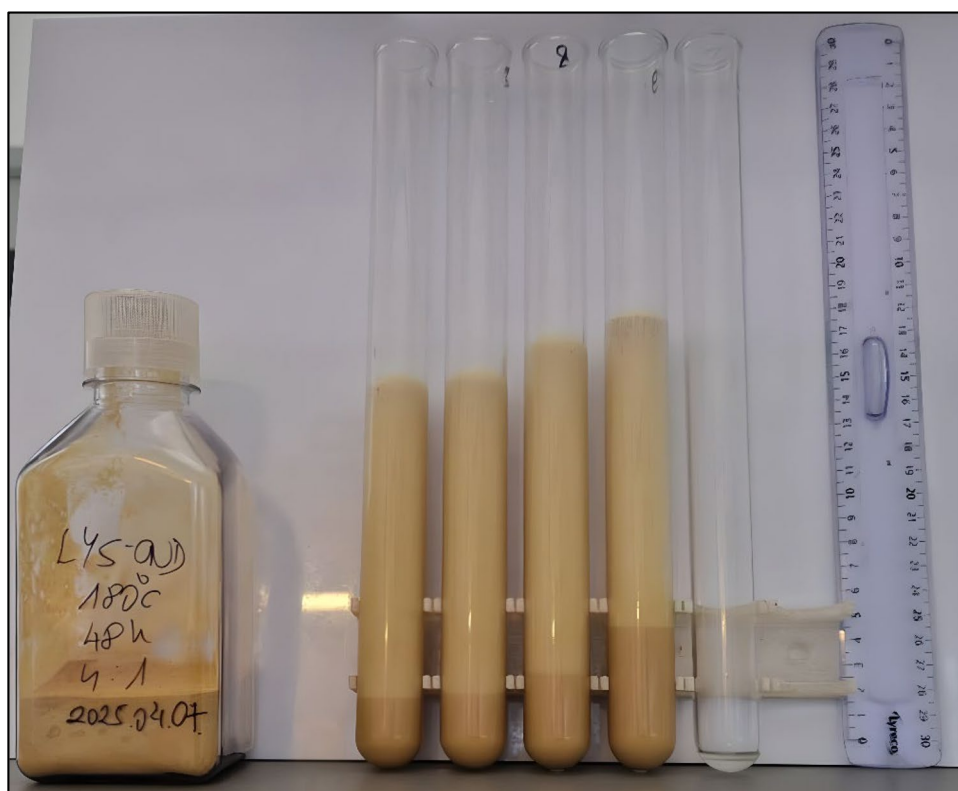


Fig. 7 Yeast suspension foam heights of CuSO₄, CuSO₄+2.5% LYS-CND and CuSO₄+5% LYS-CND with different CuSO₄ concentrations

Fig. 8 Yeast suspension foam heights from left to right 5, 10, 20, and 40 mg/kg concentration CuSO₄ treatments at the 20th minute of the test with 5% LYS-CND additive



3.7 Yeast Toxicity Profile of Sodium Tellurite

Sodium tellurite induced a strong concentration-dependent inhibition of yeast activity (Fig. 10). Foam height decreased progressively across the tested concentration range,

with substantial suppression observed at intermediate concentrations and near-complete inhibition at the highest levels. Statistical analysis confirmed a highly significant concentration effect (two-way ANOVA, $p < 0.001$). Under the tested conditions, the overall toxicity profile of tellurite

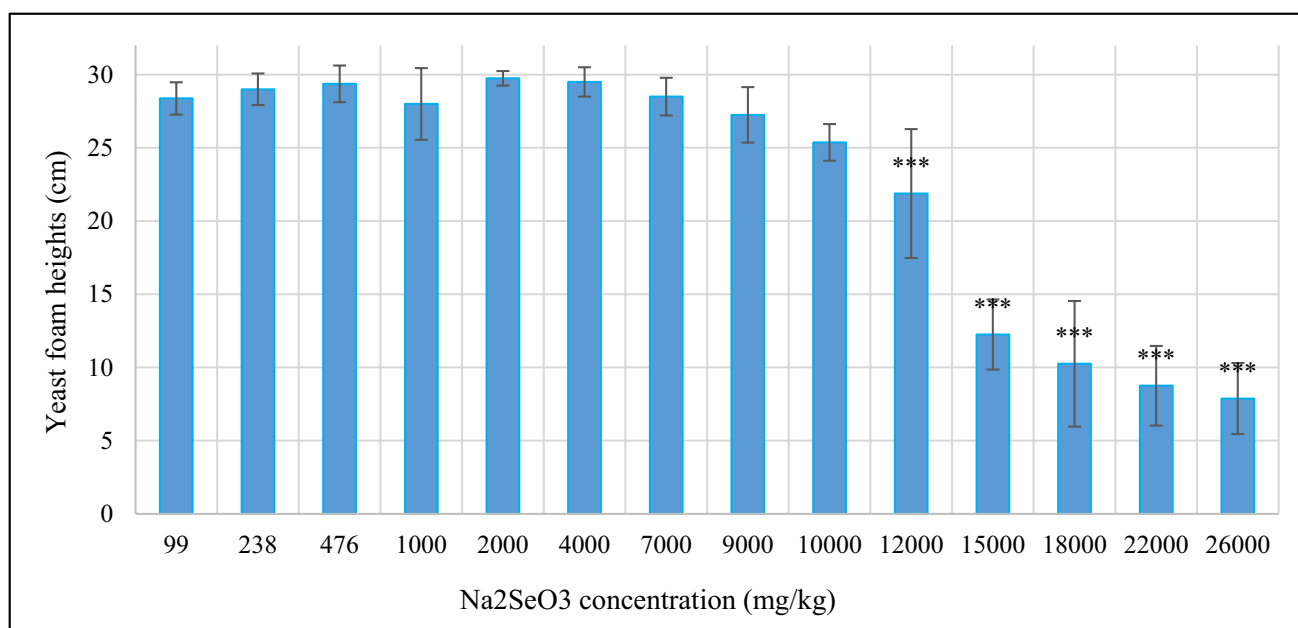


Fig. 9 Yeast suspension foam heights with different Na₂SeO₃ concentrations, indicates significant difference compared to the untreated control (*, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.001$)

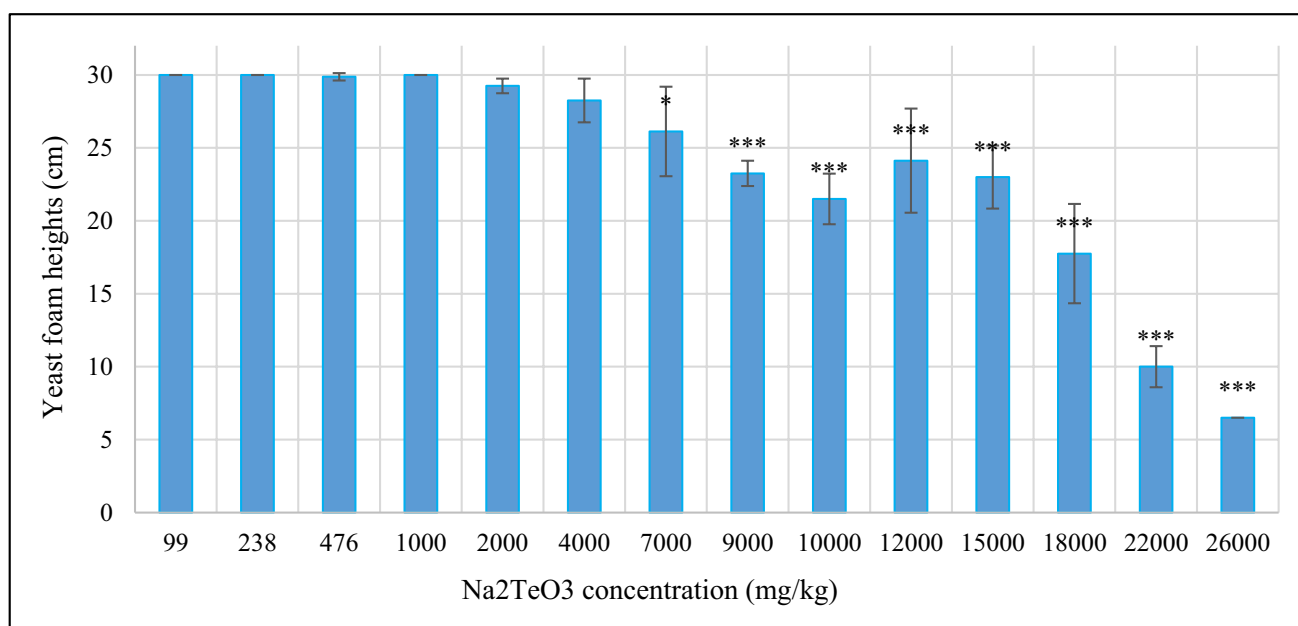


Fig. 10 Yeast suspension foam heights with increasing Na₂TeO₃ concentrations, indicates significant difference compared to the untreated control (*, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.001$)

was comparable to that of selenite, although differences in response dynamics were observed.

Pearson correlation analysis revealed strong negative correlations between concentration and foam height for all tested toxicants at higher concentration ranges, supporting the suitability of foam height as a consistent quantitative response parameter across treatments.

4 Discussion

4.1 Foam Height as a Phenotypic Indicator

The present study demonstrates that foam-height response in *Saccharomyces cerevisiae* can serve as a rapid and integrative phenotypic indicator of acute toxicological stress.

Changes in foam height reflected clear dose-dependent effects across all tested compounds, indicating that this simple readout captures dominant alterations in yeast activity under stress conditions. Foam formation is directly linked to fermentative CO₂ production and is influenced by both metabolic activity and cell surface properties. Therefore, changes in foam height likely represent a combined effect of intracellular metabolic processes and extracellular structural factors, rather than a single specific biochemical pathway.

4.2 Comparison with Established Markers

The observed inhibitory effects of copper, selenite, and tellurite are consistent with previously reported mechanisms of toxicity in yeast, including oxidative stress, mitochondrial dysfunction, and enzyme inhibition [9, 23, 30, 46]. These processes are known to reduce cellular metabolic activity, which is in agreement with the decreased foam formation observed in the present study. Although classical endpoints such as growth inhibition, viability, and ROS production were not directly measured, foam height is inherently linked to fermentative metabolism and can therefore act as a proxy for major functional changes in cellular activity. The strong dose–response relationships observed here support this interpretation. Future studies integrating foam-height measurements with established markers such as cell viability, growth kinetics, and ROS production would be valuable to further validate and mechanistically interpret the observed responses.

4.3 Mechanistic Interpretation

The modulation of copper toxicity by amino acid–derived carbon nanodots suggests that these nanomaterials interact with the toxicant and/or the biological system in a concentration-dependent manner. Several potential mechanisms may explain these effects.

First, carbon nanodots may reduce the bioavailability of metal ions through surface interactions or chelation-like processes. Second, their reported antioxidant properties may contribute to the attenuation of oxidative stress. Third, interactions with the yeast cell surface could influence membrane properties or gas–liquid interface behavior, thereby indirectly affecting foam formation. The distinct responses observed between GLY-CNDs and LYS-CNDs likely reflect differences in surface functionalization and charge characteristics, which can alter their interaction with both metal ions and cellular structures [33]. These mechanisms are not mutually exclusive and may act simultaneously depending on concentration and environmental conditions. These interpretations remain hypothetical, as no direct mechanistic measurements were performed in the present study.

4.4 Limitations

Several limitations of the present approach should be acknowledged. Foam height is an indirect and integrative parameter that does not provide information on specific intracellular mechanisms. Established markers such as ROS production, cell viability, or mitochondrial activity were not measured and would be required to confirm the underlying biological processes. In addition, foam formation may be influenced by physicochemical properties of the medium, including surface tension and colloidal interactions, which were not independently controlled in this study. The use of mass-based concentration units (mg/kg) reflects the experimental setup but may limit direct comparison with studies using volumetric exposure systems. Furthermore, the effect of CNDs alone on foam formation was not investigated, which would be necessary to distinguish intrinsic nanomaterial effects from interaction-based modulation. Accordingly, foam height should be considered a complementary screening parameter rather than a substitute for established toxicological endpoints.

5 Conclusion

Foam-height response in *Saccharomyces cerevisiae* provides a simple and rapid phenotypic readout capable of capturing dominant toxicological trends under acute exposure conditions. The method reliably reflects concentration-dependent effects of various toxicants and reveals modulatory interactions with carbon nanodots. While the approach does not replace established mechanistic assays, it offers a low-cost and accessible complementary tool for preliminary toxicity screening and for identifying interaction patterns between chemical agents and nanomaterials.

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Author Contributions Conceptualization, D.S. (Dávid Semsey) and J.P.; methodology, D.S. (Dávid Semsey) and D.S. (Daniella Sári); formal analysis D.S. (Dávid Semsey); investigation, D.S. (Dávid Semsey) and D.S. (Daniella Sári); resources, D.S. (Dávid Semsey) and J.P.; data curation D.S. (Dávid Semsey); writing—original draft preparation, D.S. (Dávid Semsey); writing—review and editing D.S. (Dávid Semsey) and G.T., D.S. (Daniella Sári) and G.T.; visualization D.S. (Dávid Semsey); supervision, J.P.; project administration, J.P.; funding acquisition, J.P. All authors have read and agreed to the published version of the manuscript.

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Data Availability No datasets were generated or analysed during the current study.

Declarations

Ethical Approval This study does not involve any human participants or vertebrate animals. All experimental procedures were conducted using microbial model organisms (*Saccharomyces cerevisiae*) and complied with relevant institutional and national guidelines.

Informed Consent None.

Research Involving Humans and Animals Statement None.

Conflicts of interest The authors declare no competing interests.

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