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AGRONOMIC, PHYTOTOXICITY AND PHYTOPATHOLOGICAL ASPECTS OF THE EFFECT OF A PARACETAMOL-CONTAINING DRUG, USING WINTER WHEAT (*TRITICUM AESTIVUM*) AND GARDEN CRESS (*LEPIDIUM SATIVUM*) AS BIOINDICATORS, IN THE CONTEXT OF ECOSAFETY

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The aim of the study was to investigate the impact of a paracetamol (PCM)- and additive-containing pharmaceutical (Infulgan) on growth characteristics of the seeds and seedlings of *Triticum aestivum* L. and *Lepidium sativum* L., phytotoxicity for *L. sativum* and on microbial contamination of seeds for *T. aestivum*. **Methods.** Winter soft wheat (*T. aestivum*) variety Bogdana and garden cress (*L. sativum*) variety Afrodita were used as test plants in laboratory conditions (Problematic Research Laboratory of "Ecological Biochemistry, Ichthyology and Biocorrosion" of T.H. Shevchenko National University "Chernihiv Colehium"). Aqueous solutions of Infulgan were used, which contained from 0.1×10^{-5} (10 mg/L) to 0.2% w/v (2,000 mg/L) PCM. In a growth test, the germination energy (%), germination (%) of *T. aestivum* and *L. sativum* seeds (3rd day), and some biometric and morphometric indices of seedlings were evaluated: *T. aestivum*: coleoptile length, number of roots on the 7th day; *L. sativum* — length of roots and shoot on the 5th day, simplified vitality index, relative root growth percentage. Phytotoxic indices were estimated for *L. sativum* only. The seed contamination incidence percentage (CIP) was also estimated. The results were analyzed using mathematical and statistical methods. **Results.** It was established that: 1) germination energy and seed germination rate did not change in all treatments with all concentrations of PCM investigated, when using the pharmaceutical Infulgan; 2) the growth indices of wheat and garden cress were statistically significantly impaired by a solution containing 0.05–0.2% PCM. Moreover, wheat seed was affected considerably by undetermined microbial contamination. A statistically significant decrease (1.2–2.5-fold) in the length of the wheat coleoptile compared to the control was recorded, along with an increase in the number of roots per seed (from 5.9±0.1 to 6.0±0.4 compared to 4.4±0.2 in the control). A significant increase in wheat root formation (5.2±0.2 roots per seed) was also recorded for PCM at 0.025%. PCM concentrations of 0.025%, 0.002%, 0.25×10^{-4}% and 0.1×10^{-5}% did not negatively impact plant growth indices. **Conclusions.** The germination energy and seed germination rate did not change under the influence of PCM as formulated in the pharmaceutical Infulgan at any concentration tested, however, the biometric indices of seedlings changed significantly. A substantial toxicity of Infulgan solutions was observed for *L. sativum*, at concentrations higher than 0.025%. Infulgan at a 0.05–0.2% PCM concentration enhanced root formation with 36%, where not only PCM, but also the excipients of the drug could have played a (so far unexplored) role. In wheat seed with higher PCM concentrations a substantial (so far undefined) microbial contamination of 77–100% was observed. Therefore, the ecotoxicity of PCM and its formulations should be assessed more comprehensively, taking PCM and its excipients (as formulation and as separate compounds) into account. At present known PCM concentrations characteristic of wastewater and environment appear not to pose a risk to the germination and growth of wheat and water cress.

Key words: germination, growth test, Infulgan, microbial infection, acetaminophen, APAP, N-acetyl-*p*-aminophenol.

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INTRODUCTION

Substances, including pharmaceuticals, appear more and more as pollutants in the environment (Zhao et al., 2016; Balakrishna et al., 2017; Tushir et al., 2025). For instance, analgesic-antipyretic drugs, such as paracetamol (PCM, N-acetyl-*p*-aminophenol), are found in soils, and surface and sewage water (Al-Kaf et al., 2017; Doczekalska et al., 2025). Research on uptake and effect on growth indices for crops under the influence of pharmaceuticals started only in the early 2000s (Sleight et al., 2023). According to the European Chemicals Agency (ECHA), https://echa.europa.eu/ro/registration-dossier/-/registered-dossier/12532/6/1, the predicted no-effect concentration for freshwater aquatic ecosystems (PNEC aqua, freshwater) for PCM is 0.134 mg/L. For this compound there is no significant toxic effect at three key trophic levels (fish, invertebrates and algae). The toxicity values for fish, invertebrates and algae are LC50 = 160 mg/L, EC50 = 136 mg/L and EC50 = = 134 mg/L, respectively. PCM is not persistent by nature and is therefore considered biodegradable in the environment. The potential for PCM to bioaccumulate in the tissues of organisms inhabiting aquatic or terrestrial matrices is, according to the ECHA negligible. Noteworthy is the (negative) impact of such substances on wheat, a valuable monocotyledonous crop (An et al., 2009; Türkoğlu et al., 2019, Tercero & Mañas, 2025). The use of dicotyledon plants, known for their sensitivity to ecotoxicants, as test plants helps expand the dataset on the agronomic effects and facilitates their evaluation. Such a test plant is e.g. garden cress (*Lepidium sativum*) (Pflugmacher et al., 2021; Passatore et al., 2022; Bożym & Rybak, 2024; Tkachuk et al., 2024). As far as could be determined there are no publications about the effect of PCM on *L. sativum*, and the research on the ecotoxicity of PCM for other higher plants is limited, apart from the following examples. Nunes et al. (2014) ranged bioindicators belonging to different natural kingdoms in terms of a high to low sensitivity to PCM, as follows: *Daphnia magna — D. longispina — Vibrio fisheri — Cylindrospermopsis raciborskii — Pseudokirchneriella subcapitata — Lemna minor — L. gibba*. They used in their study for the *Lemna* sp. PCM concentrations from 62.5 mg/L to 1,000 mg/L. The authors noted that *L. gibba* demonstrated no sensitivity to PCM at the highest tested concentration of 1,000 mg/L. When *Lens culinaris* (lentil) and *Pisum sativum* (pea) were used as test plants (at PCM concentrations of 1 to 500 mg/L), there was an evident cytotoxic effect in the form of inhibited growth of roots, formation of chromosomal abnormalities and a considerable presence of a micronucleus (Mercado & Galvis, 2023).

The microbial removal of PCM from the environment appears to be an effective remediation technique (Wu et al., 2012). Bacterial strains isolated from spinach shoots and roots, and identified as *Burkholderia*, *Sphingomonas*, *Pseudomonas*, *Staphylococcus*, *Stenotrophomonas*, and *Kocuria*, showed potential to biodegrade PCM and other organic micropollutants (Badar et al., 2022). However, microbial degradation of PCM produces a critical metabolite, 1,4-benzoquinone, which is a more stable and more toxic compound than PCM itself (De Gusseme et al., 2011; Zhang et al., 2013; Li et al., 2014). The 1,4-benzoquinone may form so-called Michael adducts and alkylate DNA and crucial cellular proteins, damaging cells. Moreover, quinone may generate reactive oxygen species (ROS), resulting in oxidative stress and further cell damage (Bolton et al., 2000; Wang et al., 2006). In most described cases, PCM conversion in microbes was proposed to proceed via 4-aminophenol to hydroquinone, which is the major route in biodegradation. Identified intermediates during the hydroquinone-degrading pathway of paracetamol are hydroquinone, malonic acid, succinic acid, 4-aminophenol, 2-hexenoic acid, oxalic acid, formic acid, nitrate, nitrite (Wu et al., 2012). Lara-Moreno et al. (2024) identified 4-aminophenol, hydroquinone and trans-2-hexenoic acid during microbial degradation of PCM that quickly disappeared, but residual toxicity remained, indicating the presence of other, non-detected intermediates. A number of specific PCM-degrading bacterial strains are known, for example: *Delftia tsuruhatensis*, *Pseudomonas aeruginosa* HJ1012, *Burkholderia* sp. AK-4, *Rhodococcus ruber* IEGM77, *Stenotrophomonas* sp. f1, *Pseudomonas* sp. f2, *Pseudomonas* sp. fg-2, *Cupriavidus necator* F1, *Pseudomonas moorei* KB4, *Pseudomonas extremaustralis* CSW01, *Stutzerimonas stutzeri* CSW02,

Amycolatopsis sp. Poz14 (De Gusseme et al., 2011; Wei et al., 2011; Wu et al., 2012; Zhang et al., 2013; Hu et al., 2013; Marchlewicz et al., 2015; Żur et al., 2018; Rios-Miguel et al., 2022; Lara-Moreno et al., 2024; Jan-Roblero et al., 2025).

In addition to the main active substance, pharmaceuticals often contain supplementary substances (excipients), including natural additives, with bioactive properties in their formulations (Gupta et al., 2019). These additives can be natural in origin, but industrially obtained, for example, sorbitol (Kocaman, 2024) and citric acid (Mallhi et al., 2019; Tahjib-Ul-Arif et al., 2021). In general, previous studies have focused on studying the effects of pure PCM and have not considered its agronomic and phytotoxic effects in the presence of excipients (An et al., 2009; Sharma et al., 2018; Türkoğlu et al., 2019; Kudrna et al., 2020; Badar et al., 2022; Omotola et al., 2023; Ali et al., 2024). This study was aimed at investigating the impact of a PCM- and excipients-containing pharmaceutical on growth characteristics of the seeds and seedlings of *Triticum aestivum* L. and *Lepidium sativum* L., phytotoxicity and on microbial contamination of seeds. It was hypothesized that by using simple and accessible test indicators (seed germination energy, seed germination, number of roots or length of roots and shoots and phytotoxicity), would accurately indicate the influence of the pharmaceutical (PCM plus additives) on the test plants.

MATERIALS AND METHODS

Materials. Seeds of winter soft wheat (*T. aestivum*) variety Bogdana and garden cress (*L. sativum*) variety Afrodita were used in the study. The sample size in one replicate was 10 seeds; the experiment was conducted in three independent replicates ($n = 3$).

We investigated the phytotoxic activity of the pharmaceutical Infulgan (used in intravenous infusion in human medicine) which contains 10,000 mg/L PCM in a sterile (according to the information on the packaging) aqueous solution containing also the following additives in the formulation the percentage content of which is not indicated on the packaging: citric acid monohydrate, sodium citrate, sorbitol (E420) and anhydrous sodium sulfite (E221). This pharmaceutical was used to produce aqueous solutions with a PCM content from 0.1×10^{-5}% (10 mg/L) to 0.2% (2,000 mg/L) w/v: variant $P_{0.2}$ — 0.2%, variant $P_{0.1}$ — 0.1%, variant $P_{0.05}$ — 0.05%, variant $P_{0.025}$ — 0.025%, variant $P_{0.002}$ — 0.002%, variant $P_{0.000025}$ — 0.25×10^{-4}%, variant $P_{0.000001}$ — 0.1×10^{-5}%. Distilled water was used as a control (variant P0).

Indices of test plants studied. Agronomic, phytotoxic and phytopathological indices of plants were estimated in a growth test under non-sterile laboratory conditions. To assess the effect Infulgan on the susceptibility of seeds to microbial contamination under conditions close to natural ones, all experiments were performed in non-sterile systems (Magaña Ugarte et al., 2024; Johnston-Monje, Martínez, 2025). A sterile filter paper disk in a sterile Petri dish was moistened with the appropriate sterile serial dilution of the pharmaceutical or sterile distilled water (control), and 10 non-sterile seeds of the appropriate test plant species were placed per dish. The dishes were then kept in the dark in a thermostat at 23±2°C.

The timing for measuring test indicators was based on the current seed quality assessment standard for Ukraine (Natsionalnyi standart Ukrainy, 2004) and methods used by Matějovič et al., 2024, Ranucci et al., 2024 and Amantayev et al., 2025, to optimally facilitate the detection of physiological and pathological changes in seedlings. The germination energy (%) and germination (%) of the seeds of *T. aestivum* and *L. sativum* (on the 3rd day), and the following biometric and morphometric indices of seedlings were evaluated: *T. aestivum* (on the 7th day from the start of the experiment): coleoptile length, number of roots (as an indicator that is simply and quickly measured, and convenient for a large number of samples) — on the 7th day from the start of the experiment; *L. sativum*: length of roots and shoot on the 5th day, simplified vitality index (SVI) and relative root growth percentage (RRG, %). The following formulas were used (Bosker et al., 2019; Wu et al., 2024):

$$\textit{Germination energy} = \frac{\text{Number of seeds that germinated on the 3rd day}}{\text{Number of tested seeds}} \times 100\%;$$

$$\textit{Germination} = \frac{\text{Number of seeds that germinated on the 5th (\textit{L. sativum}) or on the 7th (\textit{T. aestivum}) day}}{\text{Number of tested seeds}} \times 100\%;$$

$$SVI = \text{Germination} \times \text{Average length of seedlings at the end of germination (mm)};$$

$$RRG = \frac{\text{Average length of the roots in a test solution}}{\text{Average length of the roots in the control}} \times 100\%;$$

To detect external microbial contamination of seeds, a biological method (seed analysis in a humid chamber) was used, which is based on stimulating the growth and development of microorganisms present in/on the material. The softening and sliminess of seed tissues, the appearance of spots, deformations, deformities, mycelium bloom, and the death of parts of seedlings were visually assessed. Based on the visual determination of the presence of affected seeds, the contamination incidence percentage — CIP, was calculated using the formula (following Ghimire et al., 2023):

$$CIP = \frac{\text{Number of contaminated seeds}}{\text{Total number of seeds}} \times 100\%.$$

Phytotoxic indices were only estimated for *L. sativum*: seed germination index (SGI) and root length index (RLI) (Bagur-González et al., 2011; Tkachuk et al., 2022), using the formulas:

$$SGI = \frac{\text{Number of germinated seeds in the experiment} - \text{Number of germinated seeds in control}}{\text{Number of germinated seeds in control}};$$

$$RLI = \frac{\text{Average root length in the experiment} - \text{Average root length in control}}{\text{Average root length in control}}.$$

The obtained data were compared with the toxicity scale according to Bagur-González et al. (2011):

SGI and/or RLI ≥ 0 — no toxicity; –0.25 ≤ SGI and/or RLI < 0 — low toxicity; –0.5 ≤ SGI and/or RLI < –0.25 — moderate toxicity, –0.75 ≤ SGI and/or RLI < –0.5 — high toxicity, –1 ≤ SGI and/or RLI < –0.75 — extremely high toxicity.

Statistics. The dilution series of the pharmaceutical was performed in three repeats. A Student's t-test was conducted to determine the statistical significance of the differences between dilutions of the pharmaceutical. Software package Past 4.03 (Hammer et al., 2001) was used for statistical processing of the data. A 95% confidence interval was used ($p \leq 0.05$).

RESULTS

The effect of pharmaceutical Infulgan dilutions on T. aestivum. The effect of Infulgan dilutions is presented in **Fig. 1** and **Table 1**.

Infulgan with 0.2% (2,000 mg/L), 0.1% (1,000 mg/L) and 0.05% (500 mg/L) PCM showed a statistically significant negative effect on seed survival, coleoptile length and number of roots formed after seed emergence (**Fig. 1**, **Table 1**). The seeds were considerably affected by microbial contamination and subsequent

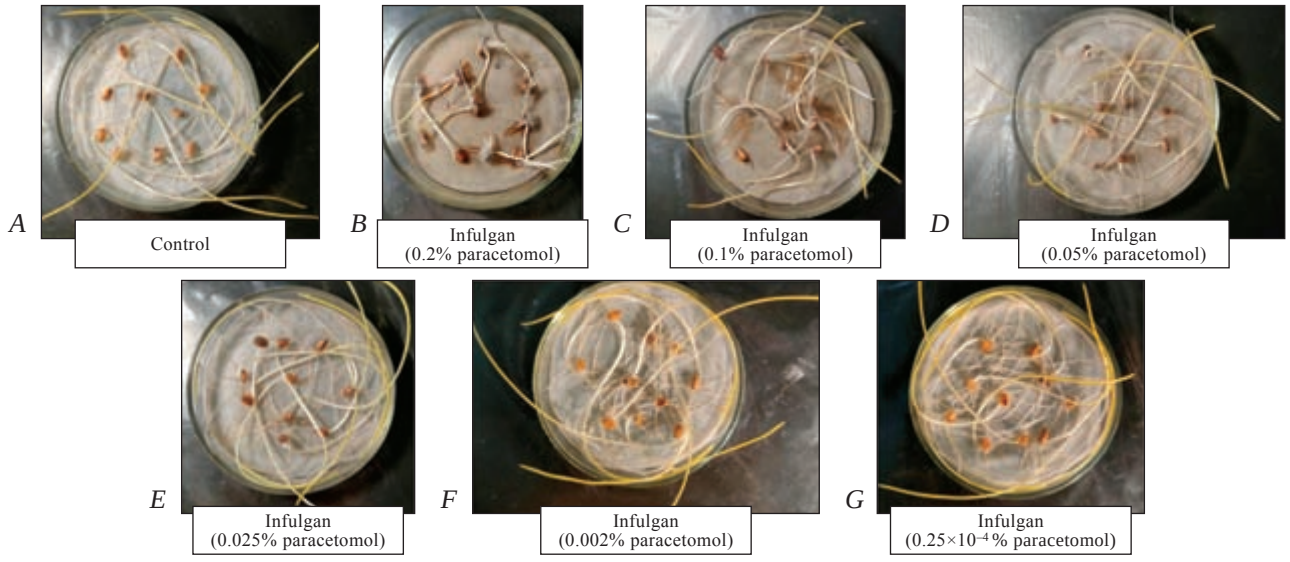

Fig. 1. Winter wheat seedlings of the variety Bogdana 7 days after treatment of seeds with different Infulgan dilutions: *A* — variant P_0; *B* — variant $P_{0.2}$; *C* — variant $P_{0.1}$; *D* — variant $P_{0.05}$; *E* — variant $P_{0.025}$; *F* — variant $P_{0.002}$; *G* — variant $P_{0.000025}$

Table 1. Effect of different dilutions of the pharmaceutical Infulgan in a seed germination test, using winter wheat variety Bogdana

Experiment variant	Germination energy, %	Germination, %	Coleoptile length, mm	Number of roots / one seed	CIP, %
P_0	97±3	97±3	109.9±5.0	4.4±0.2	6.7±6.7
$P_{0.2}$	90±6	90±6	44.2±1.6*	6.0±0.4*	83.3±3.3*
$P_{0.1}$	90±3	90±3	69.9±2.7*	5.9±0.2*	100±0*
$P_{0.05}$	100±0	100±0	93.0±3.5*	5.9±0.1*	80.0±0*
$P_{0.025}$	100±0	100±0	109.1±3.9	5.2±0.2*	3.3±3.3*
$P_{0.002}$	100±0	100±0	112.9±3.5	4.2±0.1	6.7±3.3
$P_{0.000025}$	100±0	100±0	107.2±4.3	4.2±0.1	6.7±3.3

Note: * — The difference compared to the control is significant at $p \leq 0.05$. CIP = contamination incidence percentage.

degradation, the CIP was from 80% to 100%, compared to 6.7% in the control. A 2.5 fold (0.2% PCM), 1.6-fold (0.1% PCM), 1.2-fold (0.05% PCM) decrease in the length of the coleoptile compared to the control was recorded, along with an (unexpected) increase in the number of roots per one seed, viz. 6.0±0.4, 5.9±0.2 and 5.9±0.1 respectively, compared to 4.4±0.2 in the control (**Table 1**). An increase in root formation was also recorded for the variant with a PCM concentration of 0.025%, namely 5.2±0.2 roots per one seed.

Decrease in compound(s) concentration in the solutions led to a decrease in the negative impact on the growth indices of wheat (**Fig. 1**, **Table 1**). For PCM concentrations of 0.025%, 0.002% and 0.25×10^{-4} % on wheat, no statistically significant difference in the coleoptile length was found compared to the control and this was true for number of roots when using dilutions of 0.002% and 0.25×10^{-4} %. The CIP in these variants was at the control level, viz.3.3 to 6.7% (**Table 1**).

Test indices of Lepidium sativum under the impact of the pharmaceutical Infulgan solution with different concentrations of PCM. The results of the effect of Infulgan on the germination, growth indices and phytotoxicity on *L. sativum* are presented in **Fig. 2** and in **Tables 2** and **3**.

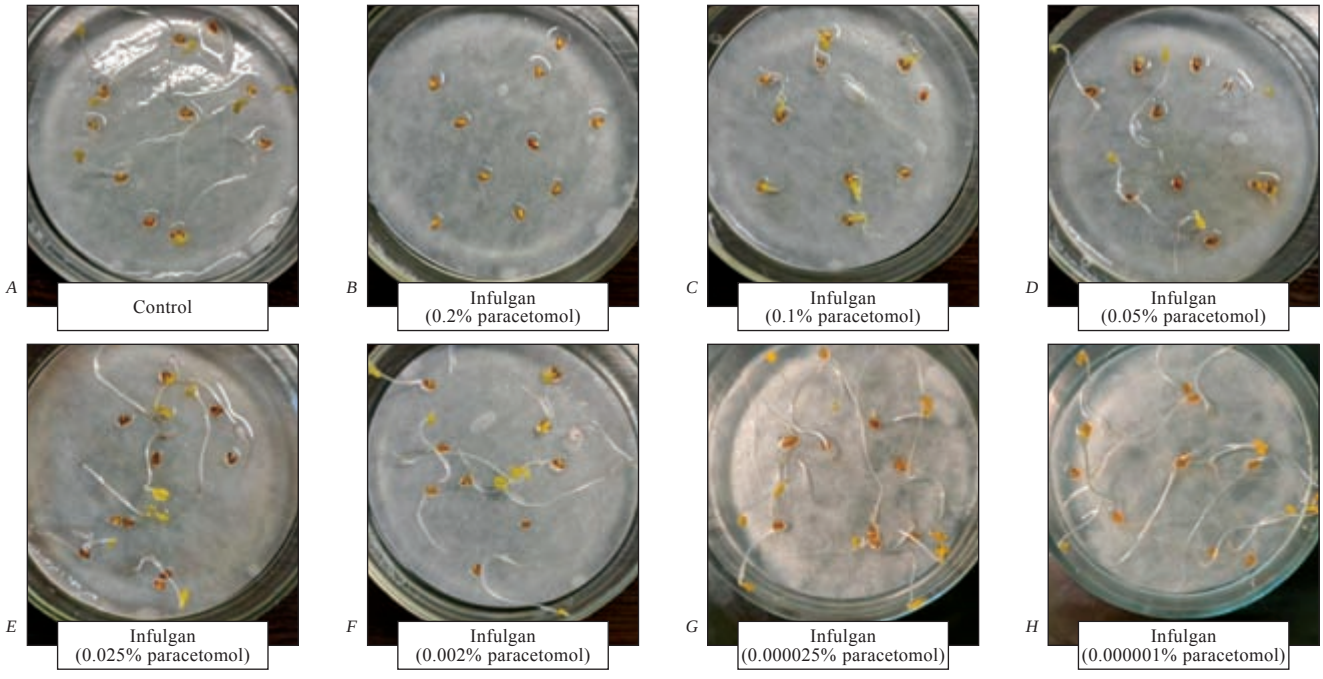

Fig. 2. Effect (germination and root length) of aqueous solutions of Infulgan on seedlings of *L. sativum* (5th day of the experiment): *A* — variant P_0; *B* — variant $P_{0.2}$; *C* — variant $P_{0.1}$; *D* — variant $P_{0.05}$; *E* — variant $P_{0.025}$; *F* — variant $P_{0.002}$; *G* — variant $P_{0.000025}$; *H* — variant $P_{0.000001}$

Table 2. Effects on garden cress (*Lepidium sativum*) when using aqueous solutions of Infulgan with different concentrations of PCM, as compared to the control (100%)

Experiment variant	Germination energy, %	Germination, %	Root length, %	Shoot length, %	SVI, %	RRG, %
P_0	100	100	100	100	100	—
$P_{0.2}$	92.3±11.5	96.1±13.8	3.2±0.0*	0.0*	1.7±0.0*	3.2
$P_{0.1}$	96.1±3.8	96.1±3.8	8.0±1.3*	33.1±3.4*	18.1±1.7*	8.0
$P_{0.05}$	100	100	38.3±5.4*	84.1±10.9	58.1±7.6*	38.3
$P_{0.025}$	80.0±10.0	80.0±10.0	64.2±6.7*	119.3±10.5	81.2±7.2	64.2
$P_{0.002}$	84.5±10.2	84.5±10.2	68.7±15.0	92.9±17.6	66.9±13.3	68.7
$P_{0.000025}$	107.2±0.0	107.2±0.0	102.8±5.9	98.9±3.9	109.1±5.5	102.8
$P_{0.000001}$	107.2±0.0	107.2±0.0	110.7±4.0	103.4±3.1	116.6±3.4	110.7

Note: * — The difference compared to the control is significant at $p \leq 0.05$. SVI = simplified vitality index; RRG = relative root growth.

Table 3. Phytotoxic effects on garden cress (*Lepidium sativum*) of different aqueous solutions of Infulgan

Experiment variant*	RLI	Interpretation of phytotoxicity test results	Growth inhibition
P_0	0.00	No toxicity	Nil
$P_{0.2\ (2000\ mg/liter)}$	–0.97	Extreme toxicity	> 90%
$P_{0.1}$	–0.92	Extreme toxicity	> 90%
$P_{0.05}$	–0.62	High toxicity	> 60%
$P_{0.025}$	–0.36	Moderate toxicity	> 30%

Note: * — Concentration of PCM; RLI = root length index.

Changes in germination energy and germination percentage of *L. sativum* seeds were statistically insignificant for all concentrations of PCM used (**Table 2**). However, the biometric and morphometric indices were significantly impaired at PCM concentrations of 0.05% to 0.2% (**Fig. 2**, **Table 2**). At 0.2% PCM, there was only germination of primary roots, which were c. 30 times smaller than those of the control. At more diluted PCM concentrations of 0.1%, 0.05% and 0.025%, toxicity decreased, resulting in longer root and shoot length. Still root and shoot length were smaller than those of the control plants: variant $P_{0.1}$ — 12.5 times (roots) and 3.0 times (shoots); variant $P_{0.05}$ — 2.6 times (roots); variant $P_{0.025}$ — 1.6 times (roots). Moreover, the SVI index was significantly lower than in control (**Table 2**). With further dilution of PCM there was no toxic impact on the investigated growth indices of *L. sativum* seedlings (**Table 2** and **3**). Summarizing: a 100-fold decrease in PCM concentration (from 0.2% to 0.002%) resulted in a 21.5-fold decrease in the toxic impact on the root length. Differences between PCM concentrations of 0.002%, 0.25×10^{-4} % and 0.1×10^{-5} % and the control were insignificant (**Table 2**). Generally, shoot length was less impaired by the different toxic concentrations of PCM than the root length (up to c. 24 times, **Table 2**). No signs of microbial infection were observed for *L. sativum* seeds in all study variants — CIP was 0%.

DISCUSSION

The occurrence of pollutants, such as analgesic-antipyretic drugs, including PCM, in the environment requires agronomic and phytopathological studies of their impact on plants. For that reason, wheat as a valuable crop, and garden cress, as a sensitive bioindicator, were chosen as test plants in this study.

The decrease in growth, noted in this study, appears related to the presence of elevated concentrations of PCM. It has been demonstrated before that PCM at concentrations of 1–500 mg/L caused inhibition of growth and chromosomal and micronuclei anomalies in plant cells (Mercado & Galvis, 2023). A decrease in the length of wheat roots and stems was shown for 99% pure PCM at a concentration of 668.8 mg/L (which has not been observed in practical conditions in the environment). However, with chronic exposure to lower concentrations (1.4–22.4 mg/L), wheat

growth was still inhibited. On the 7th day, the activity of peroxidase and superoxide dismutase in the leaves increased, but after 14 days of exposure, the activity of peroxidase significantly decreased, indicating damage to the antioxidant system of wheat by PCM (An et al., 2009). The effect of PCM on three wheat varieties, viz. Ahmetağa, Cemre and Michelangelo (root and stem development on day 5 at 25, 50 and 100 μg PCM/mL and antioxidant enzyme activities for superoxide dismutase, peroxidase and catalase on day 15 at 50, 100 and 250 mg PCM per 650 g soil) retarded the root and stem development, and increased the electrolyte leakage and antioxidant enzyme activities in plants (Türkoğlu et al., 2019). These results indicate that agricultural land and irrigation water when contaminated with high doses of PCM can cause deleterious effects on plants.

Lettuce plants (*Lactuca sativa* L.) germinated in an experimental greenhouse with semi-controlled conditions under the influence of 5 μM, 50 μM, 500 μM, and 5 mM PCM for 14 days in an acute and chronic variant, greater sensitivity to chronic exposure was observed. At the highest concentration photosynthesis and fluorescence were decreased with 31 and 18% respectively. In a study using onion (*Allium cepa* L.) as a test plant, a phytotoxic effect on root tip germination of PCM at 0.1 mg/L, but not 0.01 mg/L, was shown (Omotola et al., 2023). A DNA fragmentation analysis demonstrated induction of apoptosis at 0.1 mg/L of PCM, but not at 0.01 mg/L (Omotola et al., 2023). A single application of PCM (250 mg/L), with or without addition of amino acids, showed toxic effects (reduced chlorophyll and antioxidants content and yield traits) on seedling growth and other physiological and biochemical aspects of *Brassica napus* germinated from sterilized seeds in a pot experiment under drought conditions (Ali et al., 2024). PCM (98% purity) at concentrations of 50–200 mg/L, in 20% Hoagland's solution to applied to spinach (*Spinacia oleracea*) in a hydroponic system lead to a pronounced phytotoxic effect during the eight-day test period, with a significant decrease in plant morphological parameters and a negative effect on the photosynthetic apparatus of plants. Spinach organs demonstrated significant absorption and translocation of the drug from the roots to the above-ground part on the fourth day. Remarkably drug degradation was observed after eight days (Badar et al., 2022).

Our results are consistent with the results obtained by other researchers on the phytotoxic effect of PCM on test plants as described above, in particular, wheat. It should be noted that our study did not use pure PCM, as in previous studies on this topic, but the pharmaceutical PCM-containing drug Infulgan that contained auxiliary medicinal substances. Sorbitol, one of the additives in Infulgan, could also have played a negative, plant growth influencing role in our experiments, it was found to impair overall plant growth and photosynthetic pigments at concentrations of 0.2–1.0 M, apart from some increase in dry weight and nitrate reductase (Jain et al., 2010). The influence of these additives therefore needs further (separate) investigations. As far as could be traced we used garden cress (*L. sativum*) for the first time to determine the toxicity of a PCM-containing drug. We could not establish whether the microbial contaminations which we observed were due to weakening of test plants by PCM and/or its additives or that they were just present in/on some seeds of the tested seed lot. A strong microbial contamination was found in the 0.05–0.2% PCM treatment. Further research should investigate this phenomenon in more detail, where more controls and more seeds will be included and the causal agents will be identified. Degradation of PCM could occur in seeds contaminated with microorganisms, since a number of microorganisms, including bacteria, but also microscopic fungi, are capable of biodegrading this compound (De Gusseme et al., 2011; Wei et al., 2011; Wu et al., 2012; Hu et al., 2013; Zhang et al., 2013; Li et al., 2014; Marchlewicz et al., 2015; Żur et al., 2018; Badar et al., 2022; Rios-Miguel et al., 2022; Lara-Moreno et al., 2024; Jan-Roblero et al., 2025). Fungi such as *Fusarium* spp. can cause decrease in coleoptile length of wheat (Hadjout et al., 2024). Increased development of pathogenic fungi is conditioned by a low pH (4–6) and this low pH was a characteristic of our pharmaceutical dilution solutions (Rousk et al., 2009; Ali et al., 2017). Sorbitol may stimulate growth of microorganisms, including fungi (Patriarca et al., 2011), but the influence of the other additives of Infulgan, viz citric acid and sodium sulphite, that are generally hampering microbial growth (Holmquist et al., 1983; Shokri, 2011) remains to be investigated. The noted induced root formation in wheat cannot be explained merely by the impact of PCM, since no considerable changes in the number of wheat roots at a PCM concentration of 0.5 to 1 g/L were noted in an earlier study, although germination was severely reduced in wheat, as we also observed, from 84.5 to 69.75% at 1 g/L (Khalaf et al., 2019). Probably, the induction of root forma-

tion was also promoted by metabolites of beneficial microbes (Verbon and Liberman, 2016).

The observed absence of microbial contamination in garden cress seeds may be related to its antimicrobial properties, although no antimicrobial activity of *L. sativum* against phytopathogenic microorganisms has been found till now. But oil extracts from the leaves and seeds of *L. sativum* at concentrations from 1 to 3 μg/ml (agar diffusion method) exhibited antibacterial and antifungal activity against *Escherichia coli* and *Staphylococcus aureus*, and *Aspergillus niger* and *Candida albicans*, respectively (Adera et al., 2022). This aspect deserves further investigation.

Mercado and Galvis (2023), in a study on the sensitivity of *Lens culinaris* and *Pisum sativum* plants to PCM, also determined inhibition of root growth for these plants, although at a concentration down to 0.0001% (1 mg/L), which is 20 times lower than the lowest concentration used by us for wheat and garden cress. It appears therefore that *L. culinaris* and *P. sativum* are more sensitive bioindicators for PCM than wheat and garden cress, although garden cress and wheat are more sensitive than *Lemna gibba*, which is not sensitive even at concentrations of 1 g/L (Nunes et al., 2014). However, it is essential to compare the results of studies on the effect of the toxic substance with those having the same treatment period. The experimental duration in our present study and that of Mercado & Galvis (2023) differed: 5 days and 3 days, respectively. It could have caused the difference in the results.

Studies of the uptake and translocation by common vegetables Great Lakes lettuce (*Lactuca sativa* L.), spinach (*Spinacia oleracea* L.), pickling cucumber (*Cucumis sativus* L.), and chili pepper (*Capsicum annuum* L.) of pharmaceutical products, including PCM, showed that this compound was not detected in any of the leaves and stems (Wu et al., 2013). Therefore, PCM would pose a negligible risk to humans through consumption of these vegetables. The authors explain the non-detectable uptake of PCM by plant roots by its low octanol–water partition coefficient (log Dow) — 0.46 (Wu et al., 2013). However, a linear increase in PCM in grain and roots and a significant decrease in grain yield (up to 50%) was recorded in an experiment with PCM-tolerant corn hybrid ICI 339 and PCM-sensitive corn hybrid Syngenta 7720 when applied in two doses of aqueous solutions containing 0.31, 0.62, 0.93 and 1.24 g of PCM per litre (Hammad et al., 2018). Huber et al. (2009), using an *Armoracia rusticana* cell culture as model system, investigated the fate and metabolism of PCM in plant tissues. Six hours after incubation with 1 mM PCM, the distribution of PCM and related metabolites in cells was as follows: up to 18% PCM, 64% PCM-glucoside, 17% PCM-glutathione and 1% of the corresponding cysteine conjugate. The authors noted significant similarities between the detoxification systems of plants and mammals, discussed the formation of a highly reactive intermediate N-acetyl-*p*-benzoquinone imine in plants, due to the presence of P450 enzymes, and noted the great potential of using plants for wastewater treatment in artificial wetlands (Huber et al., 2009). In the biotransformation of PCM in cucumber, common bean, alfalfa, tomato and wheat, its conjugation with glutathione (GSH) plays an important role, minimizing the phytotoxicity of PCM and other pharmaceutical and personal care products in plants (Sun et al., 2019).

The PCM concentration in sewage waters was found to range from 0.7×10^{-8} % to 0.246×10^{-4} % (0.07–246 μg/L), in drinking water 0.002–0.298 μg/L, in groundwater 0.015–1.89 μg/L (Al-Kaf et al., 2017) or in aquatic environments in the range of 0.01–0.3 mg/L (Hammad et al., 2018). In surface waters, the highest recorded concentration was 0.065 mg/L (Nunes et al., 2014). PCM is sometimes found in raw, untreated wastewater at high concentrations (in mg per Liter), especially in hospital wastewater. Its removal in wastewater treatment plants, however, ensures a significant reduction of its concentration in wastewater treatment plant discharges and surface waters to nanograms per Liter (Wu et al., 2012). Based on the obtained experimental data, one may predict that the pharmaceutical Infulgan will not have a considerable impact on the environment, including growth parameters of plants, if it enters the agroecosystem along with the sewage water, since the concentrations, noted for these waters, do not reach the thresholds of biological activity. For Ukraine, PCM is a compound found in wastewater and bottom sediments, but its amount is either not indicated by the authors or is less than the permissible values associated with effective treatment of wastewater from pharmaceutical production. Thus, among a number of pharmaceuticals, PCM was found at the sites located upstream Municipal Sewage Works (the city of Kharkiv, Ukraine), but its amount is not indicated by the authors (Vystavna et al., 2009). The absence of PCM in wastewater associated with pharmaceutical enterprises in the Zhy-

tomyr region, which indicates the high efficiency of wastewater treatment at the enterprises, was noted by Kozhukhova et al. (2023). High sorption properties of K_2TiO_3 for the removal of PCM from an aqueous solution were shown (the degree of extraction was up to 88% of PCM during the first 30 minutes), which can be used as an alternative sorbent for PCM from wastewater of pharmaceutical enterprises (Kozhukhova et al., 2023). Effective removal of PCM and other pharmaceuticals by constructed wetland processing hospital wastewaters in East Ukraine has been shown. In this case, the intensification of the process was determined by an increase in the residence time in water and an increase in macrophyte cover (Vystavna et al., 2017). Eco-friendly "green" approaches to environmental remediation from pollutants are gaining importance today (Biswas and Sarkar, 2024). In particular, effective removal of PCM from aqueous solutions has been shown for carbon adsorbents obtained from agricultural waste, namely walnut, hazelnut and pistachio shells (Doczekalska et al., 2025). However, it is essential to determine the accumulation of harmful substances in water bodies or soils, which may lead to an increase in the concentration of chemical components and thus a negative impact on living organisms (Correia and Rasteiro, 2025; Varatharajan et al., 2025). Moreover, the actual content of PCM in pharmaceutical preparations may exceed the levels declared by the manufacturer (Jain et al., 2023). In addition, complex mixtures and combinations with other xenobiotics can significantly enhance the effects of pharmaceutical drugs on nature and human health, which requires further research (do Amaral et al., 2019; Ferreira et al., 2023).

CONCLUSIONS

The germination energy and seed germination rate did not change under the influence of PCM as formulated in the pharmaceutical Infulgan at any concentration tested, however, the biometric indices of seedlings changed significantly. The toxicity for *L. sativum* of Infulgan solutions, containing different amounts of PCM, was found along with the species-specific reaction of plants. Infulgan with a 0.05–0.2% PCM concentration likely enhanced microbial infection of wheat grain with 77% and enhanced root formation with 36%, where not only PCM, but also the excipients of the drug could have played a (so far undetermined) role. Therefore, the ecotoxicity of PCM and its formulations should be assessed more comprehensively, taking into account the full composition of the drug under investigation. When taking published PCM concentrations characteristic of wastewater into account, they appear not to pose a risk to the germination and growth of wheat and garden cress at present. One should consider, however, the possibility of accumulation of harmful substances in the environment and the increase in the concentration, which defines further perspective of the studies of their impact on plants.

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АГРОНОМІЧНІ, ФІТОТОКСИЧНІ ТА ФІТОПАТОЛОГІЧНІ АСПЕКТИ ДІЇ ПРЕПАРАТУ, ЩО МІСТИТЬ ПАРАЦЕТАМОЛ, З ВИКОРИСТАННЯМ ОЗИМОЇ ПШЕНИЦІ (*TRITICUM AESTIVUM*) ТА КРЕС-САЛАТУ (*LEPIDIUM SATIVUM*) ЯК БІОІНДИКАТОРІВ, У КОНТЕКСТІ ЕКОЛОГІЧНОЇ БЕЗПЕКИ

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Мета дослідження полягала в оцінці впливу фармацевтичного препарату «Інфулган», що містить парацетамол (РСМ) та допоміжні речовини, на характеристики росту насіння та проростків озимої пшениці (*Triticum aestivum* L.) та крес-салату (*Lepidium sativum* L.), фітотоксичність для *L. sativum* та на мікробне забруднення насіння для *T. aestivum*. **Методи.** Як тестові рослини використовували озиму м'яку пшеницю (*T. aestivum*) сорту Богдана та крес-салат (*L. sativum*) сорту Афродіта у лабораторних умовах (Проблемна науково-дослідна лабораторія «Екологічної біохімії, іхтіології та біокорозії» Національного університету «Чернігівський колегіум» імені Т.Г. Шевченка). Використовували водні розчини «Інфулгану», які містили РСМ у концентраціях від $0{,}1\cdot10^{-5}$ % (10 мг/л) до 0,2% (2000 мг/л) (*w*/*v*). У тесті на ріст оцінювали енергію проростання (%), схожість (%) насіння *T. aestivum* та *L. sativum* (3-й день), а також деякі біометричні та морфометричні показники проростків: для *T. aestivum* — довжина колеоптиля, кількість коренів на 7-й день; для *L. sativum* — довжина коренів та пагона на 5-й день, спрощений індекс життєздатності, відносний відсоток росту коренів. Фітотоксичні індекси оцінювали лише для *L. sativum*. Також оцінювали відсоток забруднення насіння (CIP). Результати аналізували за допомогою математичних та статистичних методів. **Результати.** Встановлено, що: 1) енергія проростання та схожість насіння не змінювалися у всіх варіантах обробки з усіма досліджуваними концентраціями РСМ при використанні фармацевтичного препарату «Інфулган»; 2) показники росту пшениці та крес-салату були статистично значуще погіршені розчином, що містив 0,05–0,2% РСМ. Крім того, насіння пшениці значно зазнало впливу невизначеного мікробного забруднення. Було зафіксовано статистично значуще зменшення (у 1,2–2,5 раза) довжини колеоптиля пшениці порівняно з контролем, а також збільшення кількості коренів на насінину (від 5,9±0,1 до 6,0±0,4 порівняно з 4,4±0,2 у контролі) що може бути пов'язано з впливом мікробної інфекції. Також було зафіксовано значне збільшення коренеутворення пшениці (5,2±0,2 коренів на насінину) для РСМ у концентрації 0,025%. Концентрації РСМ 0,025%, 0,002%, $0{,}25\cdot10^{-4}$ % та $0{,}1\cdot10^{-6}$ % не вплинули негативно на показники росту рослин. **Висновки.** Енергія проростання та схожість насіння не змінювалися під впливом РСМ, що міститься у фармацевтичному препараті «Інфулган», у жодній із протестованих концентрацій, проте біометричні показники проростків суттєво змінилися. Значна токсичність розчинів «Інфулгану» спостерігалася для *L. sativum* при концентраціях, вищих за 0,025%. «Інфулган» у концентрації РСМ 0,05–0,2% посилював коренеутворення на 36%, де не тільки РСМ, але й допоміжні речовини препарату могли відігравати (поки що невивчену) роль. У насінні пшениці з вищими концентраціями РСМ спостерігалося суттєве (поки що невизначене) мікробне забруднення на рівні 77–100%. Отже, екотоксичність РСМ та його рецептур слід оцінювати більш комплексно, враховуючи РСМ та його допоміжні речовини (як рецептуру, так і окремі сполуки). Наразі відомі концентрації РСМ, характерні для стічних вод та навколишнього середовища, не становлять ризику для проростання та росту пшениці та крес-салату.

Ключові слова: проростання, ростовий тест, «Інфулган», мікробна інфекція, ацетамінофен, APAP, N-ацетил-*p*-амінофенол.