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Mechanisms of cerium-induced stress in plants: A meta-analysis

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Abstract: A comprehensive evaluation of the effects of cerium on plants is lacking even though cerium is extensively applied to the environment. Here, the effects of cerium on plants were meta-analyzed using a newly developed database consisting of approximately 8,500 entries of published data. Cerium affects plants by acting as oxidative stressor causing hormesis, with positive effects at low concentrations and adverse effects at high doses. Production of reactive oxygen species and its linked induction of antioxidant enzymes (e.g. catalase and superoxide dismutase) and non-enzymatic antioxidants (e.g. glutathione) are major mechanisms driving plant response mechanisms. Cerium also affects redox signaling, as indicated by altered GSH/GSSG redox pair, and electrolyte leakage, Ca^{2+}, K^+, and K^+/Na^+, indicating an important role of K^+ and Na^+ homeostasis in cerium-induced stress and altered mineral (ion) balance. The responses of the plants to cerium are further extended to photosynthesis rate (A), stomatal conductance (g_s), photosynthetic efficiency of PSII, electron transport rate, and quantum yield of PSII. However, photosynthesis response is regulated not only by physiological controls (e.g. g_s), but also by biochemical controls, such as via changed Hill reaction and RuBisCO carboxylation. Cerium concentrations <0.1-25 mg L^{-1} commonly enhance chlorophyll *a* and *b*, g_s, A, and plant biomass, whereas concentrations >50 mg L^{-1} suppress such fitness-critical traits at trait-specific concentrations. There was no evidence that cerium enhances yields. Observations were lacking for low concentrations of cerium, whereas concentrations >50 mg Kg^{-1} suppress yields, in line with the response of chlorophyll *a* and *b*. Cerium affects the uptake and tissue concentrations of several micro- and macro-nutrients, including heavy metals. This study enlightens the understanding of some mechanisms underlying plant responses to cerium and provides critical information that can pave the way to reducing the cerium load in the environment and its associated ecological and human health risks.

Keywords: Cerium effects; Environmental Pollution; Nanotechnology; Plant stress mechanisms; Rare earth elements

RESPONSE LETTER

We thank the editor and reviewers for their reviews and comments/suggestions. The comments were helpful to further improve the manuscript. We have considered them and made needed revisions (please see point-by-point responses below).

Below we reply to each comment. Changes are tracked using the Review function of MS Word in the document with changes tracked. The line numbers mentioned below in our responses refer to the document with changes tracked.

Reviewer #1:

An well conducted metanalysis/work which I enjoyed very much! An extensive work is being conducted! I think that the present manuscript could be published prior to some minor revision. It is a well-written manuscript and the authors are analytical and the tables that they are presenting indeed help the author very much. It is conscience and within the scope of the Journal. I would recommend the authors to carefully read again the manuscript and correct some mistakes regarding the articles referenced. Some references are misplaced. Also, some linguistic/grammatical mistakes could be corrected.

Reply: We are thankful to the reviewer for the positive evaluation of our study. As suggested, we carefully went through the paper again and corrected errors and typos regarding references and also minor errors in text. These are shown in track changes in the paper.

Reviewer #2:

This paper is a high-quality meta-analysis of the accumulated data concerning the effects of cerium on plants. The authors, based on a significant number of publications, provide convincing evidence of hormetic effects of cerium and some of their mechanisms. Interestingly, on the one hand, cerium causes the typical effects of strong and mild stressors of any nature (i.e., it acts non-specifically), on the other hand, this element is able to directly participate in redox reactions. The authors discussed the first point exhaustively. However, the second point (redox properties of cerium) is mentioned by the authors only in Introduction. I think it would be useful to briefly describe in the Discussion section which of the identified effects of cerium may be related to its direct participation in redox processes along with the effects of cerium through non-specific stress mechanisms.

Reply: We are grateful to the reviewer for the positive evaluation of our study as well as the many constructive suggestions. Please note that redox properties were mentioned in lines 535-603 of the Discussion. To avoid redundancy, since most mentioned along these lines affect redox biology, this is now clarified at the opening of the respective molecular section (**lines 550-551**). Then, some additional clarifications are made (**lines 564-565 and 575-578**), but we tried to be concise because of the unavoidably large size of the paper (around 9000 words excluding display elements and references).

In addition, some minor revision is required for the manuscript.

1. Graphical Abstract and Highlights. These items are made at a very good level and meet the requirements of the journal.

Reply: Thank you (no change needed).

2. Introduction.

"Rare earth elements (REEs) have been extensively introduced into the environment in the

last decades, due to their wide use in agriculture, technology (e.g. electronics)... "
Please add a comma after e.g. everywhere in the article where you give examples.

Reply: Done throughout the manuscript (changes tracked).

3. "Cerium is, with an average concentration of 62 mg Kg-1, the 25th most abundant element in the Earth's crust, ranking before elements like Cu (60 mg Kg-1) and Pb (13 mg Kg-1) (Migaszewski and Galuszka, 2015; Tao et al., 202) "

Reply: Revised for clarity (**lines 17-18**).

Please replace mg Kg-1 with mg kg-1 everywhere in the paper.

Reply: Changed all over the manuscript (changes tracked).

4. Table S1 N (observation).
Please explain in the note to the table or in the Materials and Methods what this means. Sample size (n) or treatment numbers?

Reply: Clarified (**caption of Table S1**, Supplementary Materials 1).

5. 2.4 Meta-analysis
"An rr=0 suggests that the cerium-treated group does not differ from the control group. An rr>0 suggests a positive effect whereas an rr<0 suggests a negative effect of cerium treatment compared to control conditioning. " However, in some figures (for example, in Fig. S3 for the genus Sorghum, in the figure for the species Brassica napus) logarithm values significantly different from zero are marked as statistically insignificant (ns). In fact, the averages of cerium-treated groups, even in the absence of static significant differences relative to the control, will never completely coincide with the control average because these are sample averages. That is, the logarithms calculated in this study will never be exactly zero. Therefore, the authors should explain whether they took into account this point and statistically significant differences between treatments and the control indicated in the studies from which the data were extracted.

Reply: Please note that the quoted sentence does not refer to statistical significance. A positive or negative effect is not necessarily statistically significant (and lack of statistical significance does not mean lack of effect). The statistical significance depends on the variance (and not the average only). This is now clarified in the methods (**lines 189-191**).

6. Results
1. "Cerium had also a significant positive effect on 17 families and negative effect on 1 family (Supplementary Materials 2, Fig. S2)." The authors in this figure indicated either a positive or a negative effect of cerium for the families (the situation is similar in some other Figures of Supplementary Materials 2). However, some studies have certainly found both stimulating and inhibitory effects of cerium on this family/order and so on. In this case, how did the authors classify these data? Perhaps this point should be explained in Materials and methods or in the captions of the Figures.

Reply: We understand that the reviewer refers to stimulatory and inhibitory effects found within the same study (as different studies have different results, which is the point of meta-analysis). We now clarified this point in the methods (**lines 140-142**).

2. P. 17 L. 369 "Cerium (III) nitrate hexahydrate (Ce(NO3)3☐6H2O) led to similar or higher effects at low doses (≤0.1-1 mg L)... " Please replace Ce(NO3)3☐6H2O with Ce(NO3)3 * 6H2O.

Reply: Changed accordingly (**line 380**).

1. Introduction

Rare earth elements (REEs) have been extensively introduced into the environment in the last decades, due to their wide use in agriculture, technology (e.g., electronics), and medicine (Li et al., 2016; Migaszewski and Galuszka, 2015; Srikant et al., 2021). China, ~~as~~ the major producer of REEs worldwide, mined 140,000 tons in 2020. Another 24,700 tons were produced by Australia (17,000), India (3000), Russia (2700), Brazil (1000), and Vietnam (1000) (Tao et al., 2022). REE contents in the soils of mining and non-mining areas in different countries were reported to range from 18 to 27,550 mg ~~Kg~~kg^{-1} (Mihajlovic et al., 2019; Tao et al., 2022). In sediment samples from different countries, values of relative REE abundance were also reported ~~in the range of~~ to range from 11 to ~~-~~ 3,041 mg ~~Kg~~kg^{-1} (Tao et al., 2022). Hence, the levels of REEs in soils and sediments display a high spatial variability and reach relatively high values. This raises ecotoxicological concerns in recognition of documented effects of REEs on animals and other organisms as well as potential links to human disorders and diseases, especially in areas with ~~potentially~~ elevated REE pollution (González et al., 2015; Pagano et al., 2015; Tao et al., 2022).

Cerium is~~, with an average concentration of 62 mg Kg^{-1},~~ the 25th most abundant element in the Earth's crust (62 mg kg^{-1}), ~~ranking before~~ surpassing elements like Cu (60 mg ~~Kg~~kg^{-1}) and Pb (13 mg ~~Kg~~kg^{-1}) (Migaszewski and Galuszka, 2015; Tao et al., 2022). It belongs to the most extensively applied REEs, leading to its widespread accumulation in the environment (Liang et al., 2005). The long and extensive application of REE microfertilizers in the agricultural practice, in China, considerably enhanced the yields and qualitative value of many crops (Migaszewski and Galuszka, 2015). However, cerium also has a distinct property, that is, its Ce^{3+} form is separated from other trivalent REEs due to its oxidation to Ce^{4+} in aqueous environments with somewhat increased pH or redox potential (Eh) (Migaszewski and Galuszka, 2015).~~;~~ ~~t~~The reverse conversion from Ce^{4+} to Ce^{3+}, due to valence change and electron addition, also occurs in organisms (Farias, 2018). Such chemical transformations suggest the possibility for unpredicted effects of cerium on non-target plants and other organisms. In recent years, nano-forms of cerium have also received increased interest, not only for improving ~~plants~~ plant health (Hu et al., 2020; Rodrigues et al., 2021; Sharifan et al., 2020) but also for medical purposes (e.g., cerium oxide nanoparticles) because of their antimicrobial activity, high oxygen buffering~~,~~ and free radical-scavenging potential, among other properties (Farias, 2018; Jakupec et al., 2005; Li et al., 2016). In many cases the activity of nano-forms of cerium is similar to that of two key antioxidant enzymes, namely, catalase (CAT) and superoxide dismutase (SOD), thus enhancing pro-oxidant activity, although adverse effects, such as on respiratory tract, have also been reported (Li et al., 2016). Because of the relatively high natural abundance of cerium and its ~~the~~ increased anthropogenic emissions ~~of cerium~~ into the environment, there is a need to better comprehend its effects on plants and other organisms.

A literature survey with keywords ‘cerium’, ‘plant’, and ‘review’ (PubMed; 9 July, 2022) revealed ~~no~~ that no comprehensive review focusing on the overall mechanisms underlying cerium effects on plants has been published ~~(e.g. with keywords ‘cerium’, ‘plant’, and ‘review’ in PubMed; 9 July, 2022)~~. Nevertheless, the increasing interest in nano-cerium led to some reviews on the effects of cerium oxide (CeO_2) nanoparticles on plants. These suggested suppression of root biomass but enhancement of shoot biomass in many plants (Lizzi et al., ~~2018~~2017). These reviews also suggest decreased photosynthetic pigments and enhanced gas exchange related to photosynthesis, as well as modified yields and nutritional quality of edible plant products (Lizzi et al., ~~2018~~2017; Prakash et al., 2021). However, the effects varied among studies and plant growth conditions, indicating the degree to which the mechanistic understanding remains incomplete (Lizzi et al., ~~2018~~2017; Prakash et al., 2021).

Some plant species can (hyper)accumulate REEs (Tao et al., 2022).~~;~~ ~~h~~However, hyperaccumulators represent a tiny fraction of 'elite' species, e.g., only approximately 0.2% of the currently known vascular plant species ~~are known to be~~have been identified as hyperaccumulators of metals (Calabrese and Agathokleous, 2021). For 'normal', non-(hyper)accumulator plant species, the REE contents are, generally, considerably low; however, with considerable variation amongst spermatophytes (Tao et al., 2022). For example, REE contents in spermatophytes can range from 0.028 to 386 mg ~~Kg~~kg^{-1} depending on plant species and tissues (Tao et al., 2022). Nevertheless, such REEs still enter the food chain, undergo bioaccumulation/biomagnification, and potentially affect ingesting organisms (Adeel et al., 2019). Importantly, REEs, including lanthanum (La) and cerium (Ce), have also been measured~~,~~ in considerable levels~~,~~ in human blood, hair, and sperm (Li et al., 2013; Marzec-Wróblewska et al., 2015; McDonald et al., 2017). These observations further indicate the widespread presence of REEs, facilitated by trophic transfer, where plants act as a major primary entrance to the trophic chain. Therefore, it is profoundly important to understand cerium effects on plants, not only for revealing the underlying plant mechanisms ~~for plant-soil health continuum~~ but also for understanding how plants may drive risks to the health of herbivores.

Despite the widespread application of REEs in the agriculture over several decades to increase crop productivity, there is lack of systematic assessments on positive versus negative effects of REEs on living organisms, even though some literature reviews highlight the occurrence of hormesis (Agathokleous et al., 2019c; Pagano, 20176; Tommasi et al., 2021, 2022). Such an evaluation can be facilitated by the use of meta-analytic tools that permit summarizing large amounts of data. Meta-analysis is such an important statistical tool that can give answers to questions that cannot be answered by traditional narrative literature reviews. It increases the number of observations, while accounting for study-specific variance, and enhances the statistical power. Meta-analysis also improves the estimated effect size of experimental treatments, and can be utilized to extract quantitative conclusions from an abundant scientific literature. It removes reviewer's bias due to subjective –at least to some degree– review, identifies general trends and patterns, and reduces data processing errors, thus advancing theories and scientific understanding. To date, there has been no meta-analysis on the effect of cerium or other REEs on any organisms (Web of Science; keywords: “cerium” or “rare earth” and meta-analysis (all fields); last update on 28 April 2022), although some regular reviews have examined the effects of REEs on plants and other organisms (Agathokleous et al., 2019c; Cassee et al., 2011; Tao et al., 2022; Tommasi et al., 2021, 2022).

This study aimed at identifying general impacts of cerium on plants (regardless species) after collating a meta-database including approximately 8,500 entries (control-treatment observations). To further partition sources of variance, the effect of cerium was examined for different functional groups, crop types, orders, families, genera, and species of plants, plant ontogenic stages subjected to cerium (seed, vegetative stages, or both), application route (seed, foliage, root, or combinations of them), and growing media (soil or solution). This study also aimed at identifying concentrations that generally produce significant positive effects or toxicities across a spectrum of concentration-response ranges and exposure duration intervals within the context of hormesis~~,~~. This can~~to~~ provide a cost-benefit information platform~~,~~ to reduce the inputs of cerium into the environment and ~~to identify potential toxicities~~optimize the benefits from cerium application. It was of further interest to examine whether the effect of different concentration ranges varies with key plant traits, plant ontogenic stage treated, cerium particle size (nano or bulk), cerium molecular formula, exposure duration, growing medium, and application route. Finally, it was of similar interest to evaluate whether application route, growing medium, cerium form, and treated plant ontogenic stage modify the effect of cerium at different exposure duration intervals. This meta-analysis reveals the integrated mechanisms by which cerium affects plants, advancing the scientific understanding. It also provides a pathway to address the issue of cerium toxicities and risks in the environment, and offers a novel perspective to tackle this issue at a global scale.

2. Materials and methods

2.1 Literature screening

Literature screening was conducted in the Web of Science (http://apps.webofknowledge.com), and covered the entire period with available publications; the last update was conducted on 23 December, 2020. The combination of keywords (method:

Topic) included (cerium) AND (angiosperm OR bryophyte OR cutting OR grass OR gymnosperm OR forest OR hedge OR herb OR herbaceous OR plant OR sapling OR seed OR shrub OR tree OR vegetation OR woody) (Supplementary Materials 1, Fig S1). The search revealed 2,275 publications in English language, and inclusion-exclusion criteria were then applied (Supplementary Materials 1, Fig S2). First, publications were filtered to exclude non-original research (e.g., books, editorials, reviews, and news) based on the type, title, and abstract of publication. Second, articles reporting no application of cerium on plants were excluded based on title and abstract, resulting in 446 publications proceeding to the next stage which was duplicates checking. After excluding duplicates, 233 articles were examined in detail for inclusion eligibility. At this stage, articles and observations were excluded if one or more of the following conditions held true: (1) the experimental organisms were not higher plants, and; (2) measures of dispersion of data around the mean (standard error (SE) or standard deviation (SD)) were not reported, and their estimation was not permitted by the existing information, or; and (3) the experimental treatments were not replicated. This screening resulted in 146 articles that were finally selected for inclusion in the created database (Supporting Information 1, Table S2). The screening of literature, selection of articles, extraction of data, and database preparation were performed in parallel by three independent reviewers under the lead author's supervision, without using workflow-management software.

2.2 Data preparation

The values of means of experimental conditions/groups, the values of given measure of dispersion around the mean (SE or SD), sample size (N), and number of replicates for both the control group (typically zero cerium added) and cerium treatments were gathered in a database. Qualitative information was also collected and recorded in the database in order to study sources of variation (see next section). Data presented in the text or in tables of the reviewed articles were extracted directly. Data that were presented only in graphs were mined with GetData Graph Digitizer v. 2.26 (http://getdata-graph-digitizer.com), with an accuracy of ± 1 % compared to the actual values (Xie et al., 2014). Multiple observations reported in a single article/study were considered to come from independent studies if concerning different genotypes, cultivars, species, cerium concentrations, application techniques, or measurement periods (Feng et al., 2010; Wittig et al., 2009). Therefore, all relevant data from studies reporting both stimulatory and inhibitory effects were included in the database and meta-analysis, regardless of the direction of the effect. Regarding dependent observations in studies reporting traits with multiple treatments data and a common control, the mean values of treatment or control groups were used, according to Lajeunesse (2016). Moreover, if different levels of a stressor were applied to plants in a study, the average value was calculated. The information of plants considered in the meta-analysis is provided in Supplementary Materials 1 (Table S1).

2.3 Sources of variation

To clarify variation in cerium effects and reduce potential confounding of factors other than cerium treatment with uneven distribution across datasets, a plethora of sources of variation were considered. These included functional groups (eudicots or monocots and crops, shrubs, or trees), crop types (cereals, fruit trees, legumes, medicinal, oilseed crops, pasture, vegetable, and wild herbs), orders, families, genera, and species of plants with eligible (see previous section) and sufficient number (see next section) of entries. Furthermore, variation was partitioned into plant traits, plant ontogenic stages subjected to cerium (seed, vegetative stages, or both), cerium concentration ranges and treatment duration, cerium particle size (nano or bulk), cerium molecular form, application route (seed, foliage, root, or combinations of them), and growing medium (soil or solution). In plant ontogenic stages, seed represents cerium application to germinating or non-germinated seeds whereas vegetative stage represents cerium application to plants at any stage after completion of germination.

Regarding the effect of cerium concentration, the majority of studies reported concentrations in mg L^{-1}. Therefore, wherever they could be converted accurately with the reported information, the units were ~~converted~~ changed into mg L^{-1} for harmonization. For a considerable number of entries (about 2700), the concentration unit was mg ~~Kg~~kg^{-1}. Hence, entries of the two units were analyzed separately. To cover the entire continuum of dose-response relationship in order not to preclude the identification of both subtoxic and toxic effects widely occurring in biphasic dose responses, arbitrary concentration ranges were created based on the abundance of entries to provide ranges with logical arrangement of spacing. Given the abundant literature with considerably high number of entries, 17 and 15 segments were created ranging from ≤0.1 mg L^{-1} to 4,000 mg L^{-1} and from >1 mg ~~Kg~~kg^{-1} to 2,000 mg ~~Kg~~kg^{-1}, thus permitting the evaluation of potentially antithetic effects between low and high concentrations. Exogenously applied chemicals exhibit important variation in their effects depending on the treatment period~~Exogenously applied chemicals exhibit important temporal variation in their effects~~ (Agathokleous et al., 2021). Hence, various arbitrary segments of treatment duration were created ~~depending on the data availability~~. Specifically, 11 segments were created, ranging from few hours (<1 day) to 210 days, in order to account for homeostatic controls as well as long-term effects.

2.4 Meta-analysis

Natural log response ratio (rrX) was used to estimate the ~~effect~~ effect size of cerium as

$$rr = ln\left(\frac{X_t}{X_c}\right)$$

where rr is the natural logarithm (ln) of the average of cerium-treaded group (Xt) divided by the average of the control group (Xc) (Feng et al., 2010; Hedges et al., 1999; Wittig et al., 2009). The control group is theoretically cerium-free, e.g., a water-based solution with no added cerium. An rr=0 suggests that the cerium-treated group does not differ from the control group. An rr>0 suggests a positive effect, whereas an rr<0 suggests a negative effect of cerium treatment compared to control condition. The positive or negative rr values are interpreted as biologically positive or negative effects, depending on plant trait under consideration~~However, both negative and positive values may indicate biologically negative or positive effects, depending on plant trait~~ (see results and discussion). Whether an effect is statistically significant or not depends on the variance around the mean, and is determined by the statistical model of meta-analysis.

To pool effect sizes and conduct analyses, a random-effects model was applied, based on the hypothesis that inter-group differences (among studies and groups of comparisons) come from sampling errors as well as from true random variation (Xie et al., 2014). To reduce the uncertainty underlying the estimation, 64,999 bootstrap iterations (maximum number of iterations -permitted by the software) were applied to re-sample data and construct confidence limits around the size of effect and effect size variance (Rosenberg et al., 2000). The estimates of effect size were classified significant when zero (0) was outside the confidence interval (CI) of 95% (Wittig et al., 2009). The total heterogeneity (Q_T) was partitioned to within-group heterogeneity (Q_W) and between-group heterogeneity (Q_B) in order to compare differences between and within categories. ~~Randomized~~ A randomized *p* value <0.05 derived from the resampling technique indicates that ≥2 levels significantly differed between them~~, suggesting no random group variance~~. In order ~~for~~ a categorical level (group) to be included in the meta-analysis, it should be composed of ≥10 observations regardless the number of independent studies or of >5 observations obtained from ≥3 independent studies (Feng et al., 2010; Wittig et al., 2009). The mean effect size and the bootstrapped 95% CIs of each categorical level were calculated for each variable. T~~T~~he meta-analysis was performed with ~~the~~ MetaWin v. 2.1.3.4 (Sinauer Associates, inc., Sunderland, MA, USA) ~~software~~.

3. Results

3.1 Plant taxonomic groups (order, family, genus, species)

The pooled effect of cerium ~~application~~ on different plant taxonomic groups was examined across all studies with random-effects model, independently of other conditions; sources of variance are analyzed in succeeding sections.

Cerium application had a significant positive effect on 17 orders of plants, representing many thousands of species and covering a vast array of food crops as well as plants used for domestic animal feed (Supplementary Materials 2, Fig. S1). The average effect was commonly up to approximately 50% of the control, except for two orders, Apiales (81%) and

Dioscoreales (214%), which also had a greater variance and were composed of a relatively small sample size (Supplementary Materials 2, Fig. S1). This increased effect of cerium on Apiales and Dioscoreales (applied at 63-500 and 100-1000 mg ~~Kg~~kg^{-1}, respectively) was also contributed by the high number of entries regarding Ce in plant tissues (22.2 and 54.5 % of all entries, respectively), of which response is multi-fold greater (see also section 3.3).

Cerium also had ~~also~~ a significant positive effect on 17 families and a negative effect on 1 family (Supplementary Materials 2, Fig. S2). The negatively affected Liliaceae was comprised of only 13 observations, 2 studies, and 1 species, and the effects included statistically significant inhibitions of individual-level endpoints based on the original studies too. In these studies either Ce^{3+} (2-50 mg L^{-1}) (Kotelnikova et al., 2019) or nano–cerium oxide (CeO_2; 250-1000 mg L-^{1}) (Andersen et al., 2016) was applied, but with more super-NOAEL (no-observed-adverse-effect-level) concentrations, thus leading to an overall negative pooled effect. Similarly to the effect on orders, the average effect on families was commonly up to approximately 54% of the control, except for two families, Apieaceae (81%) and Dioscoreaceae (214%), with enlarged effect and variance (Supplementary Materials 2, Fig. S2).

Overall, 27 genera were positively affected, 3 genera were negatively affected, and 8 genera were non-significantly affected by cerium application (Supplementary Materials 2, Fig. S3). The average positive effect was commonly up to approximately 75% relative to control, except for *Dioscorea* ~~which~~ that exceeded 200% as aforementioned for its family and order (Supplementary Materials 2, Fig. S3). The negative effect was below 20% (Supplementary Materials 2, Fig. S3). Similarly to the aforementioned studies with negative effects on

Liliaceae family (Andersen et al., 2016; Kotelnikova et al., 2019), the negative effect on *Nicotiana*, *Pisum*, and *Spirodela* genera stems from more decreases in elements and/or more doses ~~≥~~above NOAEL, with even biphasic dose responses observed, and includes significant inhibition of growth too (Skiba et al., 2020; Skiba and Wolf, 2019; Song et al., 2018; Xu et al., 2017). The overall numerically positive effect can also be regarded biologically positive effect for the plants because the vast majority of plant traits covered represent traits of which increase reflects a biologically positive outcome of the plants, such as increased pigments and yields (see section 3.3). That is, the number of observations of traits of which increase can lead to biologically negative effects (e.g., reactive chemical species) is considerably limited in the overall analyses (see section 3.3).

Across all studies, cerium treatment positively affected 30 species, negatively affected 4 species, and had no significant effect on 11 species (Supplementary Materials 2, Fig. S4; see Fig. S5 for an analysis per plant common name). It should also be noted that this represents an overall effect, and the non-significant effect on 11 species does not imply absence of effect on each one of these species. This is because the effect depends upon the traits studied (including also the number of negatively affected versus the number of positively affected) and treatment concentrations as shown in other meta-analyses too (Agathokleous et al., 2021). The negative effect on the 4 species (*Allium cepa*, *Nicotiana tabacum*, *Pisum sativum*, *Spirodela polyrrhiza*) is attributed to the reasons explained ~~earlier~~ previously for families and genera, and was below 20% relative to control except for *Allium cepa* that reached 45% (Supplementary Materials 2, Fig. S4). The degree of average positive effect varied widely with species, but was commonly up to ≈50% except for *Capsicum annuum* (68%), *Coriandrum sativum* (55%), *Cucumis sativus* (78%), *Dioscorea esculenta* (207%), *Lycopersicon esculentum* (184%), and *Medicago sativa* (61%).

3.2 Plant type groups

Across studies, cerium had a significant positive effect on cereals (18%), fruit trees (18%), legumes (22%), medicinal plants (23%), oilseed crops (10%), pastures (17%), vegetables (10%), and wild herds (7%) (Supplementary Materials 2, Fig. S6). The effect of cerium was smaller on vegetables and wild herbs than on cereals, legumes, medicinal plants, and pasture.

A further grouping of plant functional types across studies revealed that cerium positively affected plants regardless the functional group~~s~~ (Supplementary Materials 2, Fig. S7). Specifically, a similar average effect was observed among crops (16%), shrubs (14%), and trees (16%), as well as between eudicots (14%) and monocots (17%) (Supplementary Materials 2, Fig. S7).

3.3 Plant traits (mechanisms)

3.3.1. Trait groups

Cerium significantly enhanced chlorophyll fluorescence (6%), defense system (15%), development (11%), and gas exchange (17%) (Fig. 1; Supplementary Materials 2, Fig. S8). It also positively affected mineral (ion) balance (10%) and increased non-essential elements (305%), which were mainly comprised of cerium and heavy metals (Fig. 1). Conversely, cerium application decreased essential micro- (7%) and macronutrients (4%) as well as photosynthetic pigments (8%), whereas the overall effect on growth, productivity and yields was insignificant (Fig. 1). Hereafter, the results are analyzed for different traits per trait category.

3.3.2. Photosynthesis-related traits

Regarding chlorophyll fluorescence-related traits, cerium increased the actual photosynthetic efficiency of PSII (14%), the coefficient of photochemical quantum yield in dark (2%), the PSII effective quantum yield (4%), the electron transport rate (11%), and the maximal quantum yield (1%) (Fig. 2A; Supplementary Materials 2, Fig. S9).

Gas exchange analysis revealed that photosynthetic rate (22%) and stomatal conductance (13%) were also significantly increased by cerium (Fig. 2B).

Chlorophyll *a* (12%), chlorophyll *b* (13%), and carotenoids (12%) were significantly decreased; however, total chlorophylls (*a*+*b*) and chlorophyll *a* to chlorophyll *b* ratio were not significantly affected (Fig. 2C). It should be clarified that the total chlorophylls (above zero but CI overlapping zero) consisted of nearly twice the number of observations, and ~~was thus~~this trait represented a more robust group compared to the individual chlorophyll pigments.

3.3.3. Biochemical (stress-related) traits

Cerium affected the plant defense system in diverse ways (Fig. 3A). It increased CAT (17%), dehydroascorbate reductase (DHAR; 54%), glutathione (GSH; 12%), reduced GSH to oxidized glutathione ratio (GSH/GSSG; 20%), malondialdehyde (MDA; 33%), reactive oxygen species (ROS; 38%), and SOD (7%) (Fig. 3A; Supplementary Materials 2, Fig. S10). Conversely, it decreased lycopene (7%), membrane permeability (35%), and polyphenol oxidase (28%) (Fig. 3A; Supplementary Materials 2, Fig. S10). Similarly, cerium decreased starch (13%) but increased free thiols (24%), hill reaction (18%), photophosphorylation rate

(17%), and RuBisCO carboxylation (23%) (Fig. 3B; Supplementary Materials 2, Fig. S10).

3.3.4. Elemental/mineral traits

Regarding essential elements, cerium decreased B uptake (13%) and its levels in tissues (10%) and the ratio of carbon to nitrogen (C/N; 8%) (Fig. 4A; Supplementary Materials 2, Fig. S11). It also decreased the levels of Ca (12%), Fe (11%), K (5%), and Mo (31%) in tissues, but increased the uptake of Cu (19%), Fe (58%), Mn (20%), and Ni (76%), although the latter increases are based on a considerably small number of observations (Fig. 4A).

As to non-essential elements, cerium application led to significantly decreased Cd (23%) and Se (13%) levels in tissues and increased Ce (624% and 623%) and Al (67% and 77%) uptake and their levels in tissues (Fig. 4C; Supplementary Materials 2, Fig. S11).

Cerium also altered mineral (ion) balance, with significant increases in Ca^{2+} (9%), electrolyte leakage (15%), K^+ (20%), K^+/Na^+ (19%), and Mg^{2+}-ATP_{ase} (20%) (Fig. 4B; Supplementary Materials 2, Fig. S11).

3.3.5. Growth, productivity, and yields

Cerium significantly increased the total plant biomass (7%), number of root tips (23%), root volume (15%), stem biomass (6%), and stem diameter (11%), and decreased root length (11%) and yields (6%) (Fig. 5; Supplementary Materials 2, Fig. S12). Traits that were overall negatively affected by cerium are further analyzed by concentration ranges (see section 3.4.6).

3.4. Applied cerium concentration

3.4.1. Overall concentration ranges

As explained before, the majority of observations, specifically 5,313 observations, ~~were~~ ~~for~~concerned the concentration unit~~s~~ of mg L^{-1}, representing approximately 62% of the total number of observations in the entire database. An additional 2,648 observations ~~were~~ ~~for~~concerned the concentration unit~~s~~ of mg ~~K~~gkg^{-1}, that is approximately 31% of the total number of observations in the entire database. Therefore, emphasis was ~~given~~ ~~paid~~placed on ~~to~~ the analysis of data given in concentration units of mg L^{-1}.

Across studies, cerium had either a positive or a non-significant effect on plants (Fig. 6). Importantly, the significant positive effect occurred from concentrations as low as ≤0.1 mg L^{-1}, which was kept at similar levels up to 50 mg L^{-1} (%). The concentration of 100 mg L^{-1} also had a positive effect similar to that of concentrations ≤0.1 mg L^{-1} (Fig. 6). For concentrations ≥125-800 mg L^{-1}, only concentrations >210-300 mg L^{-1} and 500 mg L^{-1} had a positive effect. Cerium concentrations of 1000 and ≥1600-2000 mg L^{-1} also led to a positive effect. All these effects were similar to that of concentrations ≤0.1 mg L^{-1} (Fig. 6). Similar results were revealed for the observations with cerium concentrations in mg ~~K~~gkg^{-1}, with significant positive effects of different ranges from as low as >1-5 mg ~~K~~gkg^{-1} ~~through~~ to 1000 mg ~~K~~gkg^{-1} and negative effect at 600 mg ~~K~~gkg^{-1} (Supplementary Materials 2, Fig. S13).

3.4.2. Concentration ranges as a function of application route

The overall effect of cerium, regardless of other factors, showed no clear pattern of variation due to the application route, with only few differences (Supplementary Materials 2, Fig. S14-S15). For instance, root and foliage+root applications had a significant positive effect at concentrations >0.1-1 mg L^{-1}, but ~~not~~ foliage and seed applications had not. This distinction was no longer present at concentrations >1-5 mg L^{-1}, where all application routes led to a significant positive effect on plants. At concentrations >5-10 mg L^{-1}, foliage application did not significantly affect, root and foliage+seed application positively affected, and seed application negatively affected plants. At >10-25 mg L^{-1}, foliage and root application positively affected and seed application negatively affected. The only significant effect at >50-80 mg L^{-1} was a positive influence of seed application. However, at 100 mg L^{-1} the only significant effect was a positive influence of root application (Supplementary Materials 2, Fig. S14-S15). For concentrations ≥125-160 mg L^{-1}, foliage and seed applications but not root application positively affected plants. Regarding concentrations from 200 to 421 mg L^{-1}, no specific application route had positive effects. Then, 1000, ≥1600-2000, and ≥3000-4000 mg L^{-1} significantly positively affected plants when applied to root (Supplementary Materials 2, Fig. S14-S15). For all the significant positive effects, the effects were similar among the different concentration ranges. Since, the unit of mg ~~Kg~~kg^{-1} does not include foliage application, data given in mg ~~Kg~~kg^{-1} were not considered worth of more detailed analysis.

3.4.3. Concentration ranges as a function of cerium particle size

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The effect of cerium (mg L^{-1}) on plants differed between the nano-form and bulk cerium, with half of the concentration ranges showing superiority of nano-cerium (Supplementary Materials 2, Fig. S16). Specifically, nano-cerium had an ~~improved~~ increased effect at concentrations ≤0.1, >1-5, >10-25, >25-50, 100, and >210-300 mg L^{-1} relative to bulk cerium (Supplementary Materials 2, Fig. S16). Less clear was the difference for the analysis of the effect of cerium concentrations in mg ~~Kg~~kg^{-1} (Supplementary Materials 2, Fig. S17). Specifically, nano-cerium had a better effect at >25-50 mg ~~Kg~~kg^{-1} but bulk cerium had a significant positive effect at ≥125-500 mg L^{-1} when nano-cerium had either negative or non-significant effect (Supplementary Materials 2, Fig. S17).

3.4.4. Concentration ranges as a function of cerium molecular formula

Approximately 10 molecular formulas of cerium were analyzed across different concentrations ranges, depending on the availability of observations and sample size (Supplementary Materials 2, Figs. S18-S19). However, the most extensively applied form is cerium dioxide (CeO_2), which widely produced positive effects at various concentrations, e.g.,, at ≤0.1, >0.1-1, >5-10, >10-25, >25-50, and >210-300 mg L^{-1} and at >25-50, >210-300, and 500 mg ~~Kg~~kg^{-1}. The lowest concentrations (≤0.1 mg L^{-1}) produced equal or greater effects than higher concentrations.

Diammonium cerium (IV) nitrate ($Ce(NH_4)_2(NO_3)_6$) had smaller effects at ≤0.1 mg L^{-1} and similar effects at higher concentrations compared to CeO_2. Cerium (III) nitrate hexahydrate ($Ce(NO_3)_3$~~□~~$\times_6H_2O$) led to similar or higher effects at low doses (≤0.1-1 mg L^{-1}), but there were indications toward negative effects at concentrations >5-10 mg L^{-1}. This was also the case for cerium (III) chloride ($CeCl_3$) for similar significant positive effects up to 25 mg L^{-1}, followed by a trend toward negative effects at >25-50 and ≥125-160 mg L^{-1}. Compared to CeO_2, $Ce(NO_3)_3$ had smaller positive effects at concentrations ≤0.1 mg L^{-1}, similar effects at concentrations >0.1-10 mg L^{-1}, and greater positive effects at concentrations >10 mg L^{-1} (Figs. S18-S19). Then, the effect of $Ce(NO_3)_3$ became non-significant or negative at higher concentrations. The observations were insufficient for other molecular formulas for an insightful assessment of the concentration-response spectrum. Furthermore, the number of studies for molecular formulas other than CeO_2 ~~is~~ was extremely small for concentrations in mg ~~Kg~~kg^{-1}, and thus ~~not considered further~~such formulas were not analyzed further.

3.4.5. Concentration ranges as a function of growing medium

The effect of cerium (mg L^{-1}) had little differences between soil and solution growing media (Supplementary Materials 2, Fig. S20). Soil application had no significant effect at >10-25, >25-50, ≥1600-2000, and ≥3000-4000 mg L^{-1}, concentrations at which application to solution positively affected plants. Conversely, application of cerium to solution did not significantly affect plants at 100, ≥125-160, 200, >210-300 mg L^{-1}, while these concentrations had a positive effect in soil medium (Supplementary Materials 2, Fig. S20).

3.4.6. Concentration ranges as a function of ontogenic stage treated

This analysis revealed that at several concentration ranges within which seed treatment had no significant effect (>5-10, >10-25, >210-300, 1000, and ≥1600-2000 mg L^{-1}), treatment at vegetative stages or at both seed and vegetative stages produced significant positive effects (Supplementary Materials 2, Fig. S21). Conversely, at >50-80 and ≥125-160 mg L^{-1} seed treatment, but not treatment at vegetative stages, significantly positively affected plants (Supplementary Materials 2, Fig. S21). For the observations in mg ~~Kg~~kg^{-1}, the effects were more variable and included both negative and positive effects for seed treatment (Supplementary Materials 2, Fig. S22). Overall, seed treatment showed less significant effects; however, the number of observations and studies for seed treatment are limited and -such results should be interpreted with caution.

3.4.7. Concentration ranges as a function of plant trait

The effect of different cerium concentration ranges was analyzed also as a function of selected traits that are key to individual level fitness, namely photosynthetic pigments, photosynthetic rate and stomatal conductance, plant biomass, and yields, some of which were negatively affected in the overall analyses per plant trait (see section 3.3).

Chlorophyll *a* and chlorophyll *b*~~, which were negatively affected in the overall analyses per trait,~~ were significantly increased by concentrations >1-5 mg L^{-1} and decreased by >50-80 and ≥125-160 mg L^{-1} and ~~by~~ ≥320-421 mg ~~K~~kg^{-1}; chlorophyll *b* was also decreased by 100 mg ~~K~~kg^{-1} (Supplementary Materials 2, Fig. S23). Total chlorophylls (*a*+*b*) were significantly increased by concentrations >0.1-1, >10-25, and 100 mg L^{-1} and ~~by~~ >25-50 and >210-300 mg ~~K~~kg^{-1}, with no negative effects occurring at any concentration range. No significant effect was observed for carotenoids at the analyzed concentration ranges (Supplementary Materials 2, Fig. S23).

Photosynthetic rate was enhanced by concentrations >10-25 mg L^{-1} and ~~by~~ >5-10, 100, and 1000 mg ~~K~~kg^{-1}, with no negative effects occurring at the partitioned concentration ranges (Supplementary Materials 2, Fig. S23). Stomatal conductance was significantly affected by >5-10 and 100 mg ~~K~~kg^{-1} only, effects that were positive (Supplementary Materials 2, Fig. S23).

Plant biomass was increased by concentrations ≤0.1, >0.1-1, >1-5, and 100 mg L^{-1} and ~~by~~ 100 mg ~~K~~kg^{-1}, whereas it was decreased by ≥125-160 and 500 mg L^{-1} (Supplementary Materials 2, Fig. S23). However, the only significant effect on yields was suppression by >50-80 and ≥320-421 mg ~~K~~kg^{-1} (Supplementary Materials 2, Fig. S23).

3.4.8. Concentration ranges as a function of exposure duration

A common pattern observed in all the five intervals of low concentrations from ≤0.1 to 10 mg L^{-1} (a 100-fold concentration range) is the common maximization of the positive effect within three days of exposure (Supplementary Materials 2, Figs. S24-S25). This outcome was followed by a decline in response over the course of exposure, but often maintained at significantly positive levels for up to approximately 13 weeks, depending on the concentrations (Supplementary Materials 2, Figs. S24-S25). No clear time-dependent pattern was observed for concentrations >10-100 mg L^{-1}, where significant positive effects were observed at different times depending on the concentration (Supplementary Materials 2, Figs. S24-S25). Lack of a specific time-dependent pattern was also observed for concentrations ≥125 mg L^{-1}, where positive effects occurred early and/or late during the exposure, depending on the cerium concentration (Supplementary Materials 2, Figs. S26-S27). Regarding analysis of meta-data in mg ~~Kg~~kg^{-1} (>5-1000 mg ~~Kg~~kg^{-1}), observations were considerably less abundant and available only for >7-210 days. No specific time-dependent trend was revealed; however, both low and high concentrations induced significant effects early and/or late in the exposure, depending on the concentration range (Supplementary Materials 2, Figs. S28-S29).

3.5. Exposure duration

In accordance with the common time-dependent pattern of low concentrations of cerium (see preceding section), cerium overall effect (regardless other factors) maximized within the first 24 h of exposure, and then declined but remained at significant positive levels up to 60 days, and neutralized >60-210 days after exposure (Fig. 7).

No clear time-dependent pattern among cerium application routes was observed, although treatment of seed had significant overall negative effects at >1-3 and >60 days of exposure (Supplementary Materials 2, Fig. S30).

No clear time-dependent pattern was observed between soil and solution treatment either. (Supplementary Materials 2, Fig. S31). However, treatment of plants grown in solution led to more significant positive effects ~~that~~ than treatment of soil-grown plants. Specifically, cerium application to soil-grown plants had no significant overall effect at >1-3 and >60-90 days.

Regarding the influence of ontogenic stage treated, when analyzed per the different exposure duration intervals, cerium had fewer significant positive effects or more significant negative effects when applied to seed only than when applied to vegetative growth stages (Supplementary Materials 2, Fig. S32). The number of observations for application at both seed and vegetative stages was limited in this analysis.

The time-dependent pattern was generally similar between nano-cerium and bulk cerium (Supplementary Materials 2, Fig. S33).

3.6. Other effects (sources of variation)

Regarding cerium application routes, the overall effect of seed treatment was non-significant, with the majority of values negative (Supplementary Materials 2, Fig. S34). Foliage, root, and seed+foliage application produced a similar positive effect. Moreover, there was no evidence that combined root and foliage application offers an improved effect compared to foliage or root application individually (Supplementary Materials 2, Fig. S34).

As to the plant growing medium, application of cerium into soil substrate produced a significant overall average effect of +12% (Supplementary Materials 2, Fig. S35). However, the effect was significantly higher (19%) when cerium was applied into solution (Supplementary Materials 2, Fig. S35).

Regarding the ontogenic stage treated, ~~seed treatment~~ the average overall effect of seed treatment was non-significant (Supplementary Materials 2, Fig. S36). There was also no significant difference between the significant positive effects of cerium application at vegetative growth stages or at both seed and vegetative growth stages; however, the number of observations for the latter category was considerably small (Supplementary Materials 2, Fig. S36).

4. Discussion

Across all studies, cerium application had an overall positive effect on a plethora of plant orders, representative of over 161,000 species (based on data from www.britannica.com; accessed 11 May 2022), regardless traits and other factors. This is further substantiated by the many families, genera, and species significantly affected by cerium application. The finding that cerium application had an overall positive effect on cereals, fruit trees, legumes, medicinal plants, oilseed crops, pastures, vegetables, and wild herbs shows the potential of cerium to widely affect numerous plants used as main food and dietary supplements of humans and other animals as well as for the production of herbal extracts and pharmaceuticals. Nevertheless, the effect of cerium depends on the type of plants, with a smaller effect on vegetables and wild herbs. These suggest that vegetables and wild herbs may be less responsive to cerium than cereals, fruit trees, and pastures; however, these results should be interpreted with caution due to the considerably small number of studies for cereals, fruit trees, and pastures. The effect of cerium did not differ among crops, shrubs, and trees or between eudicots and monocots, indicating a more homogenous effect of cerium at higher levels of plant functional groups.

Cerium overall enhanced chlorophyll fluorescence and gas exchange. Specifically, the actual photosynthetic efficiency of PSII, the coefficient of photochemical quantum yield in dark, the electron transport rate, the PSII effective quantum yield, and the maximal quantum yield were overall increased, mechanisms that are tightly linked to diverse reaction processes in photosynthesis (Moustakas et al., 2022; Peng et al., 2021). The enhancement of these traits indicates increased efficiency of the PSII electron transfer chain, higher internal efficiency in converting light energy, improved efficiency in capturing primary light energy when PSII is partially closed, and, thus, higher photosynthesis potential of plants under stress (Moustakas et al., 2022; Peng et al., 2021). This is further supported by the overall increased photosynthetic rate and its linked stomatal conductance that this meta-analysis revealed, indicating higher CO_2 uptake by plants and increased photosynthetic rate. Hill reaction reflects the O_2 evolution during the illumination-dependent steps in the process of photosynthesis, which along with the 'Mehler reaction' can contribute to photoprotection in photosynthesizing organisms (Shevela et al., 2012). The effect on Hill reaction activity may also imply analogous effects on CO_2 assimilation, NADP reduction, and phosphorylation inactivation during stress conditions. Cerium also increased the photophosphorylation rate, a stress-indicating status, suggesting the possibility of enhanced needs of ion uptake and management of ion export in stressed cells (Fork and Herbert, 1993). RuBisCO carboxylation capacity is fundamental for improving photosynthesis and yield (Iñiguez et al., 2021).~~, and~~ ~~t~~The overall increased RuBisCO carboxylation by cerium indicates that the enhancement of photosynthesis by cerium is not only due to physiological driving mechanisms (e.g., stomatal conductance) but also due to a biochemical mode of action of cerium. However, this meta-analysis revealed no evidence that the overall enhanced photosynthetic rate is due to increased chlorophylls. Conversely, chlorophyll *a*, chlorophyll *b*, and carotenoids were overall decreased by cerium application, suggesting that cerium causes oxidative stress in plants. As to carotenoids, lycopene in fruit was also decreased by cerium, which further suggests that cerium can affect the nutraceutical value of plant products routinely used for enhancing human health (Imran et al., 2020). Further partitioning the variance into different cerium concentration ranges revealed that total chlorophylls were increased by various concentration ranges from as ~~little~~ small as >0.1-1 mg L^{-1}. Moreover, chlorophyll *a* and chlorophyll *b* were increased by low concentrations (>1-5 mg L^{-1}) but decreased by higher concentrations (>50 mg L^{-1}). These findings suggest that cerium causes a biphasic-hormetic dose response, with low concentrations increasing ~~chlorophylls~~ and higher concentrations decreasing chlorophylls~~them~~. This hormetic pattern of photosynthetic pigments (and photosynthetic rate) was found in numerous photosynthesizing organisms exposed to a wide array of pollutants and other xenobiotics, reflecting an improved defense capacity against environmental challenges (Agathokleous, 2021). Apart from the leaf level, this biphasic-hormetic pattern was also revealed for total plant biomass, which was increased by concentrations ≤0.1-5 and 100 mg L^{-1} (and 100 mg ~~Kg~~kg^{-1}) and decreased by concentrations ≥125 mg L^{-1}. These findings demonstrate the hormetic function of cerium as a xenobiotic inducing oxidative stress, a hypothesis that is further supported by a different perspective. Specifically, the cerium effect was commonly up to 50% relative to control, across all analyses, indicating that it ~~commonly~~ is commonly rather modest. These findings further demonstrate that the positive effect of cerium on plants is not due to a 'fertilizer effect'. Instead, this effect is similar with that induced by xenobiotics within the framework of hormesis, with a maximum low-dose positive effect of typically 30-60%, which is constrained by the biological plasticity bounds (Calabrese et al., 2019; Calabrese and Blain, 2009), even if Ce uptake and its levels in tissues increase by approximately 620% as this meta-analysis revealed.

The mechanisms underlying the observed effects caused by cerium are similar to those induced by various biotic and abiotic stressors, from viruses to pollutants (Awasthi, 2020; Carvalho et al., 2020; Moustakas et al., 2022; Poschenrieder et al., 2013). Cerium also had further multiple overall effects on different traits related to the defense system and redox homeostasis. It increased CAT, DHAR, GSH, GSH/GSSG, ROS, and SOD. These effects further support the conclusion that cerium acts as a xenobiotic, with its positive effects attributed to stimulation via adaptive responses activated by low doses of oxidative stress. CAT is an antioxidant enzyme of profound importance in the mitigation of oxidative stress, and its increase indicates an enhanced capacity to eliminate cellular H_2O_2, a ROS, to produce O_2 and H_2O (Nandi et al., 2019). Therefore, an increase ~~of~~ in CAT indicates the existence of oxidative stress. This is also the case of SOD, an enzyme catalyzing the $O_2^{\cdot -}$ into H_2O_2, and providing a first-line defense against ROS-induced damage (Poschenrieder et al., 2013; Zhao et al., 2021). In addition to these enhanced antioxidant enzymes (SOD and CAT), cerium increased also non-enzymatic antioxidants. Specifically, it increased GSH, a thiol molecule playing a central role in stress signaling and antioxidant defense system, which also alters the GSH/GSSG redox state (Hasanuzzaman et al., 2017; Poschenrieder et al., 2013). Free thiols were also enriched, indicating the overall involvement of thiols in enhancing stress tolerance (Tausz et al., 2003; Zagorchev et al., 2013). Thiol-based redox regulation is important for a swift response of chloroplast metabolism to light intensity (Cejudo et al., 2019). Similarly, DHAR is important to couple the GSH and ascorbate pools with the metabolism of H_2O_2, and is involved in plant defense, development, and growth (Ding et al., 2020; Hasanuzzaman et al., 2017). GSH/GSSG ratio reflects homeostasis (redox state) and can serve as an indicator of oxidative stress, which is often increased together with increased CAT, SOD, and GSH (Hasanuzzaman et al., 2017). The GSH/GSSG redox pair plays a major role in controlling redox signaling (Hasanuzzaman et al., 2017; Szalai et al., 2009). As such, increased cellular GSH level and GSH/GSSG ratio are essential for maintaining plant health under oxidative stress (Hasanuzzaman et al., 2017; Szalai et al., 2009). These increases in CAT, DHAR, GSH, GSH/GSSG, ROS, and SOD suggest that the overall increase of ROS by cerium application did not exceed the threshold level for adverse effects. ROS and associated antioxidant molecules act as signaling agents modulating cellular metabolism, in accordance to endogenous and exogenous stimuli, and affect cellular redox homeostasis (De Gara et al., 2010). Polyphenol oxidase is also an antioxidant enzyme driving the conversion of phenols into quinones, and is linked to detoxification and elimination of ROS (Taranto et al., 2017). Their overall significant response to cerium revealed by the meta-analysis (including leaves and roots) indicates their involvement in plant response to cerium-induced stress. A basal level of ROS is beneficial for health and optimal growth, and a mild increase in ROS triggers a hormetic defense response, followed by inhibitory effects at levels above specific thresholds (Jalal et al., 2021; Moustakas et al., 2022; Poschenrieder et al., 2013). Because excessive ROS inhibit chlorophyll synthesis and accumulation (Moustakas et al., 2022; Ruban, 2015), it can be postulated that decreased chlorophylls by higher doses of cerium stems, at least partly, from excessive ROS. Since ETR should also be restricted below some levels to avoid ROS accumulation (Moustakas et al., 2022), it can also be argued that ETR and ROS are involved in the high-dose inhibition of chlorophylls, although the overall effect on non-photochemical quenching was non-significant in the two studies that included it. The stressor mode of action of cerium is further illustrated by the significant alteration of membrane permeability and starch (in leaf and fruit) revealed by the meta-analysis. Starch metabolism plays a key role in the plant response to stress, and its decrease has been shown in numerous plants under various abiotic stresses (Thalmann and Santelia, 2017). Starch reserve remobilization is important to make energy, sugars, and metabolites available to facilitate stress mitigation (Thalmann and Santelia, 2017). Also, decreased membrane permeability, expected at low cerium doses, may protect against increased ion leakage as the stress progresses, whereas high cerium doses would increase it, thus changing the ion balance and promoting ion leakage in damaged tissues (Filek et al., 2012; Mansour, 2013; Niu and Xiang, 2018). The significant stress-related role of cerium is also extended to increased electrolyte leakage, Ca^{2+}, K^+, K^+/Na^+, which indicates that K^+ and Na^+ homeostasis plays a significant role in the response of plants to cerium and that cerium further alters mineral (ion) balance. Increased electrolyte leakage is usually linked to increased ROS, with potentially activated K^+ efflux, and can promote programmed cell death under severe stress (Demidchik et al., 2014). However, under lower doses of stress, K^+ efflux can stimulate catabolic processes and save metabolic energy that is needed for the processes of damage repair and adaptation (Demidchik et al., 2014). Furthermore, higher cytosolic K^+/Na^+ ratio is regarded an important mechanism for higher tolerance to stress (Almeida et al., 2017). Overall, these mechanisms underlying the effects of cerium on plants indicate the presence of oxidative stress and the existence of dual biological responses with positive biological effects up to some stress level followed by adverse effects (Jalal et al., 2021; Moustakas et al., 2022; Poschenrieder et al., 2013). These mechanisms are similar to those found for various air and soil contaminants, such as heavy metals and toxic anions, ground-level ozone, pesticides, nanomaterials, and pharmaceuticals (Agathokleous et al., 2019a, 2019b, 2018; Carvalho et al., 2020; Jalal et al., 2021; Moustakas et al., 2022; Poschenrieder et al., 2013; Shahid et al., 2020).

This meta-analysis also revealed various alterations in essential and non-essential elements as well as in the mineral (ion) balance in plants. The decreased C/N ratio may be partly attributed to the increased allocation of C to C-based metabolites that increase under cerium-induced stress. Coordination of the metabolism of C and N is essential for optimal development and growth, and disrupted signaling driven by C/N balance may have further implications within ecosystems, such as changing the interaction of plants with pests, the quality of plant litter and its decomposition, and altering the ecosystem response to other environmental conditions such as atmospheric CO_2 (Chen et al., 2015; Zheng, 2009). As to essential elements, cerium treatment decreased the uptake of B and increased the uptake of Cu, Fe, Mn, and Ni. It also decreased B, Ca, Fe, K, and Mo levels in tissues. The observation that cerium overall increased the uptake of Fe while decreasing its levels in tissues may suggest its key role in cerium stress as Fe homeostasis must remain under control in stressed plants. Accumulation of Fe within cells can lead to toxicities, and its decreased levels due to cerium treatment may indicate a mechanism to reduce potential Fe-induced toxicity and/or that more Fe is used for photosynthesis and respiration electron-transport chains, to produce electron transport chain components and/or enzyme cofactors (Connolly and Guerinot, 2002; Connorton et al., 2017). The decrease of several essential elements (B, Ca, Fe, K, and Mo) in tissues due to cerium indicates altered elemental homeostasis with unknown implications to plant health in the long term. These alterations extend to non-essential elements too, as cerium treatment decreased Cd and Se in tissues and increased Al uptake and its levels in tissues, although for Al uptake this~~it~~ is weakly supported because it is based on only one ~~independent~~ study (Trujillo-Reyes et al., 2013). Some of these elements typically do not have beneficial effects on plants but widely induce phytotoxicities at high concentrations (Schmitt et al., 2016; Watanabe, 2022). The mechanisms of the increased uptake by plants and their levels in tissues are not understood; however, the possibility of their binding with cerium (e.g., attached on cerium particles) and subsequent release into plant tissues cannot be excluded. The mechanisms of decreasing other non-essential elements in tissues are unknown, warranting further studies.

~~Unlike~~ While Ce uptake and plant tissue levels were~~that~~ increased by approximately 620% due to cerium treatment, the average effect of cerium on other chemical elements ranged from 10% to 77%. However, these effects are significant and raise ecological and human health concerns rising from the arbitrary application of cerium within the agricultural practice. This is because it is now shown that cerium extensively alters the chemical composition of plant tissues decreasing several micronutrients that are important for human health while increasing some heavy metals and decreasing others. Similar to the hormetic effects of cerium on plants at ~~the~~ individual level, cerium changes mineral nutrient concentrations in a dose-dependent fashion too (Ramírez-Olvera et al., 2018). Therefore, the applied concentration of cerium is a key ~~to~~ for minimizing ecological and human health risks.

Besides the physiological and biochemical responses, this meta-analysis revealed an overall negative effect of cerium on root length and yields, which demonstrates that cerium-induced oxidative stress suppressed growth and reproduction traits that are critical to plant fitness. The yield suppression occurred at concentrations >50 mg ~~Kg~~kg^{-1}, in line with the inhibition of chlorophylls *a* and *b* by concentrations >50 mg ~~Kg~~kg^{-1}, as shown by the meta-analysis results. However, total plant biomass was decreased by concentrations >125 mg L^{-1}. Hence, there was no evidence that cerium enhances yields (often decreases them), and yields appear to be more sensitive than plant biomass. These findings indicate that cerium pollution can cause adverse effects to vegetation. Importantly, concentrations that were revealed here to cause various adverse effects on plants widely occur in the environment and specifically in agroecosystems, indicating the potentially hazardous nature of cerium (Moreira et al., 2019; Wiseman et al., 2016). However, numerous factors affect the REE bioavailability to plants including soil physicochemical traits (cation exchange capacity, humic acid, metal oxides, organic and inorganic ligands, pH, redox potential), REE valence, REEs interacting with compounds, Casparian strip in plant root exudates (organic acids), and rhizospheric microbes (Liang et al., 2005; Tao et al., 2022). Thus, the real outcomes can be hardly predicted based on the 'dose' only, and new studies that incorporate such factors in addition to the 'dose' component are needed.

Given that fitness critical traits (photosynthesis rate, photosynthetic pigments, and plant biomass) were enhanced by cerium concentrations as small as ≤0.1-25 mg L^{-1} (or >5-100 mg ~~Kg~~kg^{-1}), depending on the trait, new studies should focus the shift to lower concentrations in the range of ≤0.1-25 mg L^{-1} (or >5-100 mg ~~Kg~~kg^{-1}). This is especially important since the number of observations of yield response was extremely limited at concentrations ≤25 mg L^{-1} (and studies typically lacking a proper 'dose-response' component), which underlines that the

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Making a further step, this meta-analysis provides insightful information regarding the role of cerium molecular formula within a concentration-response spectrum. Based on this information, molecular formulas with lower potency for toxic effects on organisms but with adequate positive effects (e.g., CeO_2) can be selected over more potentially toxic formulas (e.g., $CeCl_3$, $Ce(NO_3)_3 \cdot 6H_2O$, $Ce(NO_3)_3$). However, there is a gap of knowledge about the effect of several molecular formulas of cerium within the full concentration-response continuum.

More research is also needed into combinations of seed treatment and application of cerium at vegetative stages to potentially maximize the positive effect of cerium by appropriately treating seeds under controlled conditions and reducing the load on the field. Besides, the results of meta-analysis call for cost-benefit evaluations to conclude whether cerium should be actively applied ~~within~~ in agriculture, considering the potentially limited positive effects and the large uncertainties about long-term environmental implications of this agricultural practice.

5. Conclusion

This meta-analysis revealed major physiological mechanisms underlying the response of plants to exogenous application of cerium. It is demonstrated that cerium application leads to up to ≈~~approximately~~ 620% increase in Ce uptake and its levels in tissues, on average, offering various positive effects of commonly up to ≈~~approximately~~ 60% relative to control. At concentrations as low as ≤0.1 to 25 mg L^{-1} cerium commonly enhances chlorophylls, g_s, A, and plant biomass; however, at concentrations >50 mg L^{-1} cerium causes various negative effects on plants at trait-specific concentrations. This hormetic pattern is driven by the oxidative stress mode of action of cerium, increasing ROS and their tightly linked antioxidant enzymes and non-enzymatic antioxidants.

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Cerium further alters the redox signaling and mineral (ion) balance, including changes in K^+ and Na^+ homeostasis. Various chlorophyll fluorescence traits can be improved by cerium, enhancing photosynthetic efficiency and quantum yield of PSII, while the increase in A is also linked to biochemical drivers, namely Hill reaction and RuBisCO carboxylation. However, the potential of cerium application to benefit plant yields remains blurred due to lack of data for low concentrations of cerium and negative effects at concentrations >50 mg ~~Kg~~kg^{-1}.

Cerium changes the uptake and level in tissues of several micro- and macro-nutrients, including heavy metals that can pose risks to ingesting organisms. As cerium can decrease the levels of several micronutrients, its arbitrary application in agriculture further suggests that cerium pollution may have further implications for disease risk.

To reduce ecological and human health risks associated to cerium pollution, a shift is needed from very high concentrations of cerium to considerably small concentrations (≤0.1 to

25 mg L^{-1}), often a 1000-fold or higher decrease. ~~Finally, t~~This study also offers further ~~further~~ technical information about the application of cerium that can help to maximize cerium positive effects while minimizing its load in the environment and its associated risks.

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Conflict of Interest E.A. is the Managing Editor of the Virtual Special Issue in which this article is published; however, he was not involved in the peer-review process of this article. The authors declare that they have no conflict of interest.

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Author contributions E.A. conceived the idea, and all authors participated in the study design. E.A. had a leading role and supervised the production of the manuscript. B.Z., C.G., and J.X. surveyed literature, extracted data, and created the data bases with inputs from E.A., C.J.S., and Z.F. B.Z. analyzed data and created display elements with inputs from G.C., J.X., E.A., and Z.F. E.A. drafted the paper, and all coauthors reviewed the draft and contributed intellectual input. All authors approved the final version of manuscript for publication.

Supplementary Materials (for online publication only)

Filename	**Description**

Supplementary Materials 1	Display elements illustrating the keyword combination (Fig. S1), the procedure of literature survey and selection (Fig. S2), description of plants considered in the meta-analysis (Table S1), as well as the complete list of references finally included in the meta-analysis database (Table S2).
Supplementary Materials 2	Figures reporting effect sizes of additional results of further meta-analyses as well as supplementary figures with calculated arithmetic per cent for aiding interpretation by readers (Figs. S1-S36).

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Figures

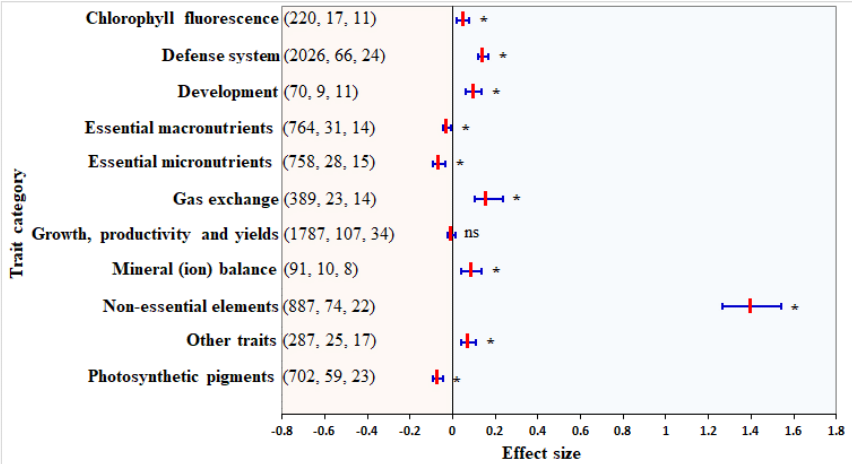

Fig. 1. Effect of cerium on different categories of plant traits. Symbols- (vertical red segments) indicate the mean natural log response ratio (rr) -of cerium application relative to control group (zero cerium dose), while ~~the~~ the horizontal bars around the mean value represent the bootstrapped 95% confidence intervals (CIs). Asterisk (-*) next to CI bars shows a statistically significant cerium effect relative to the control group, whereas “ns” shows a statistically non-significant effect. The three -numbers in parentheses indicate the number of observations ~~-observations number~~ (sample size), studies ~~number,~~ and species ~~number~~ respectively (from left to right). The corresponding plot indicating percent difference from the control is provided in Supplementary Materials 2 (Fig. S8).

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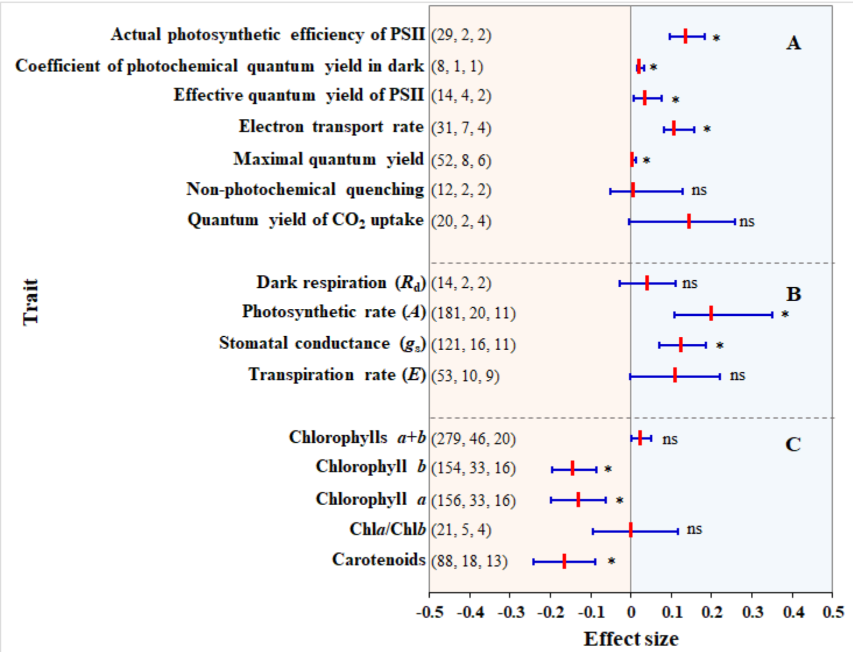


Fig. 2. Effect of cerium on different photosynthesis-related traits. The traits represent chlorophyll fluorescence (A), gas exchange (B), and photosynthetic pigments (C). Symbols indicate the mean natural log response ratio of cerium application relative to control group (zero cerium dose), while the bars around the mean value represent the bootstrapped 95% confidence intervals (CIs). * next to CI bars shows a statistically significant cerium effect relative to the control group, whereas "ns" shows a statistically non-significant effect. The numbers in parentheses indicate the observations number (sample size), studies number, and species number respectively (from left to right). The corresponding plot indicating percent difference from the control is provided in Supplementary Materials 2 (Fig. S9).

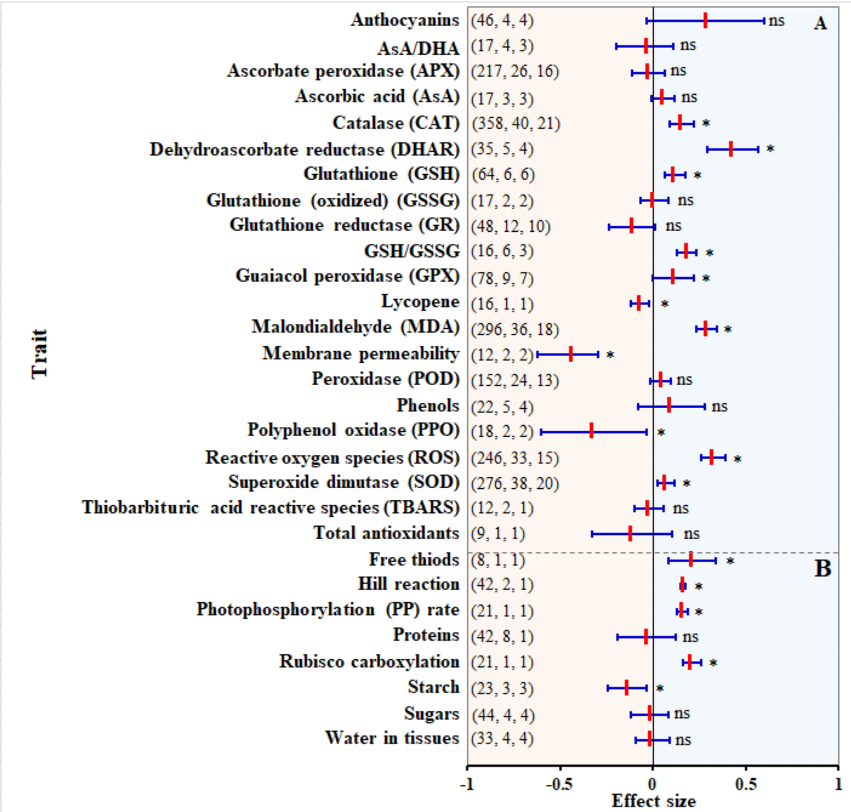


Fig. 3. Effect of cerium on biochemical traits. The traits represent defense system (A) and other stress-related biochemical traits (B). Symbols indicate the mean natural log response ratio of cerium application relative to control group (zero cerium dose), while the bars around the mean value represent the bootstrapped 95% confidence intervals (CIs). * next to CI bars shows a statistically significant cerium effect relative to the control group, whereas "ns" shows a statistically non-significant effect. The numbers in parentheses indicate the observations number (sample size), studies number, and species number respectively (from left to right). The corresponding plot indicating percent difference from the control is provided in Supplementary Materials 2 (Fig. S10).

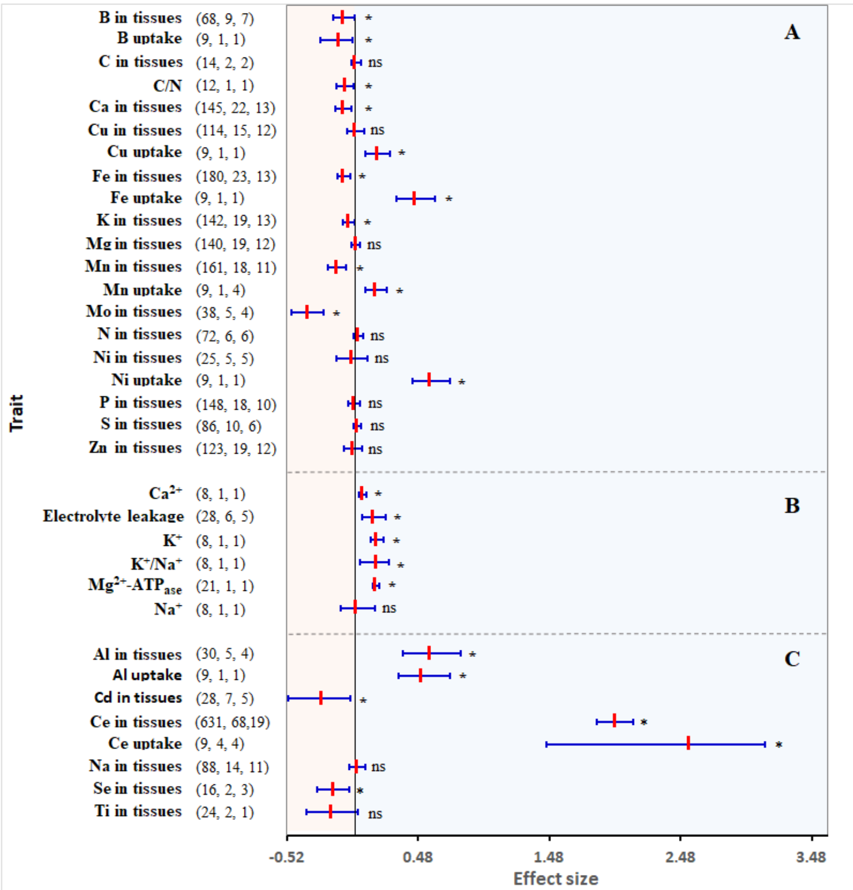


Fig. 4. Effect of cerium on elemental traits. The traits represent micro- and macro-nutrients essential for plant growth (A), mineral (ion) balance (B), and non-essential elements (C). Symbols indicate the mean natural log response ratio of cerium application relative to the control group (zero cerium dose), while the bars around the mean value represent the bootstrapped 95% confidence intervals (CIs). * next to CI bars shows a statistically significant cerium effect relative to control group, whereas "ns" shows a statistically non-significant effect. The numbers in parentheses indicate the observations number (sample size), studies number, and species number respectively (from left to right). The corresponding plot indicating percent difference from the control is provided in Supplementary Materials 2 (Fig. S11).

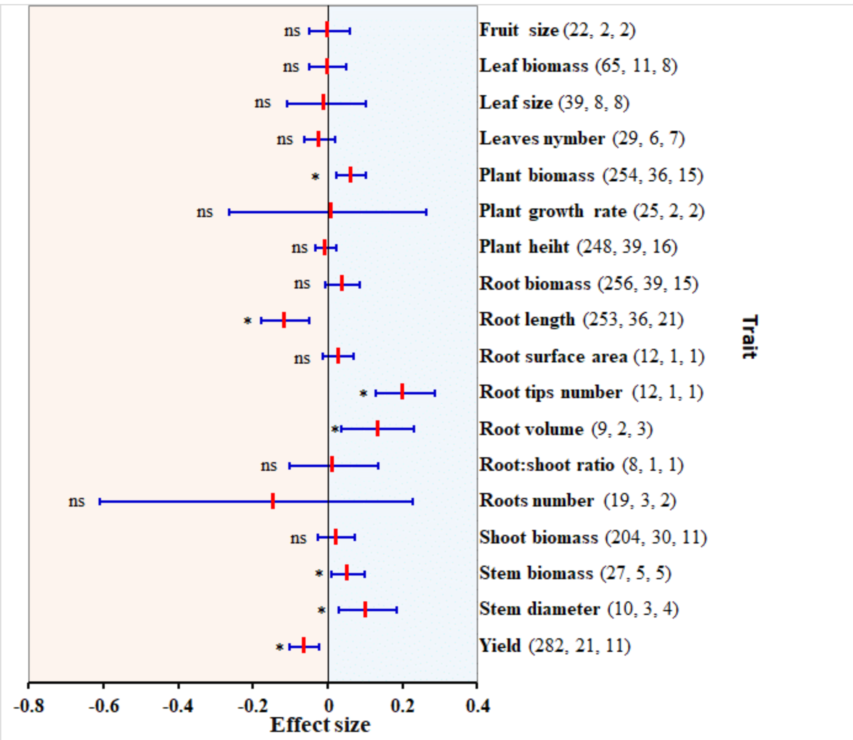


Fig. 5. Effect of cerium on different traits related to growth, productivity, and yields. Symbols indicate the mean natural log response ratio of cerium application relative to control group (zero cerium dose), while the bars around the mean value represent the bootstrapped 95% confidence intervals (CIs). * next to CI bars shows a statistically significant cerium effect relative to the control group, whereas "ns" shows a statistically non- significant effect. The numbers in parentheses indicate the observations number (sample size), studies number, and species number respectively (from left to right). The corresponding plot indicating percent difference from the control is provided in Supplementary Materials 2 (Fig. S12).

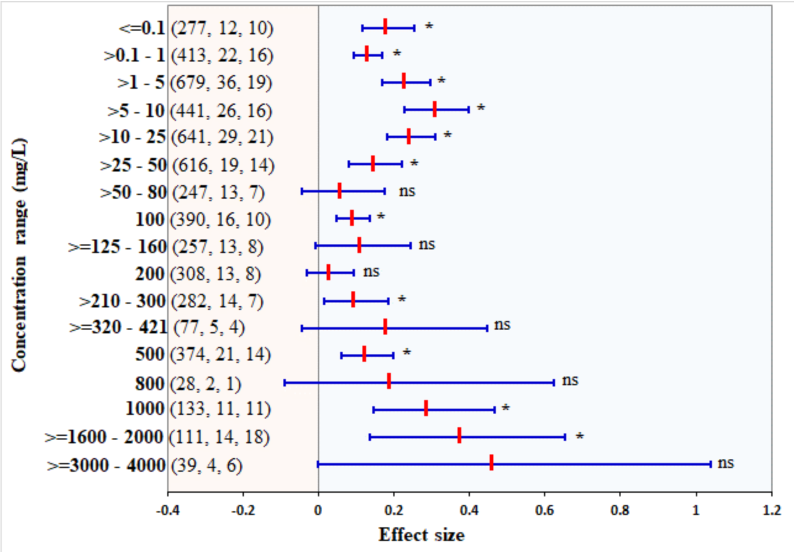


Fig. 6. Overall effect of cerium on plants (all traits pooled) as a function of different concentration ranges. Symbols indicate the mean natural log response ratio of cerium application relative to the control group (zero cerium dose), while the bars around the mean value represent the bootstrapped 95% confidence intervals (CIs). * next to CI bars shows a statistically significant cerium effect relative to control group, whereas "ns" shows a statistically non-significant effect. The numbers in parentheses indicate the observations number (sample size), studies number, and species number respectively (from left to right). The corresponding plot indicating percent difference from the control is provided in Supplementary Materials 2 (Fig. S13). The effect of different concentrations is further partitioned to different sources of variation (see sections 3.4.2-3.4.8).

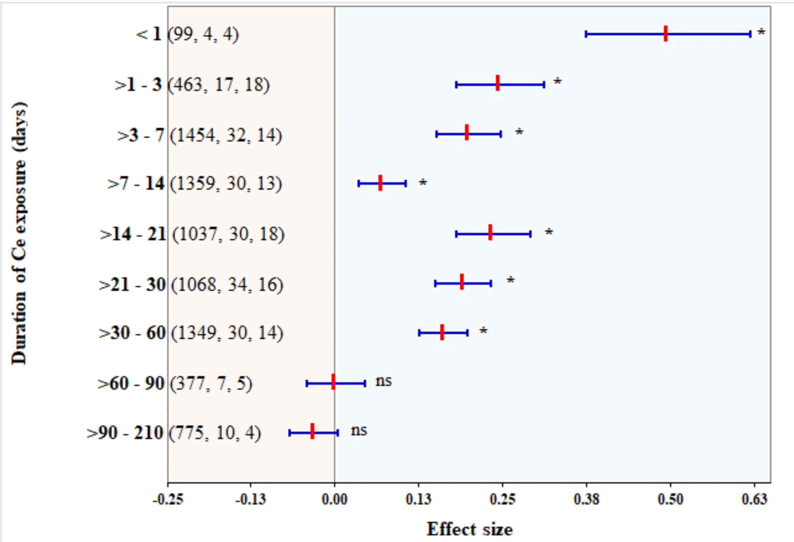
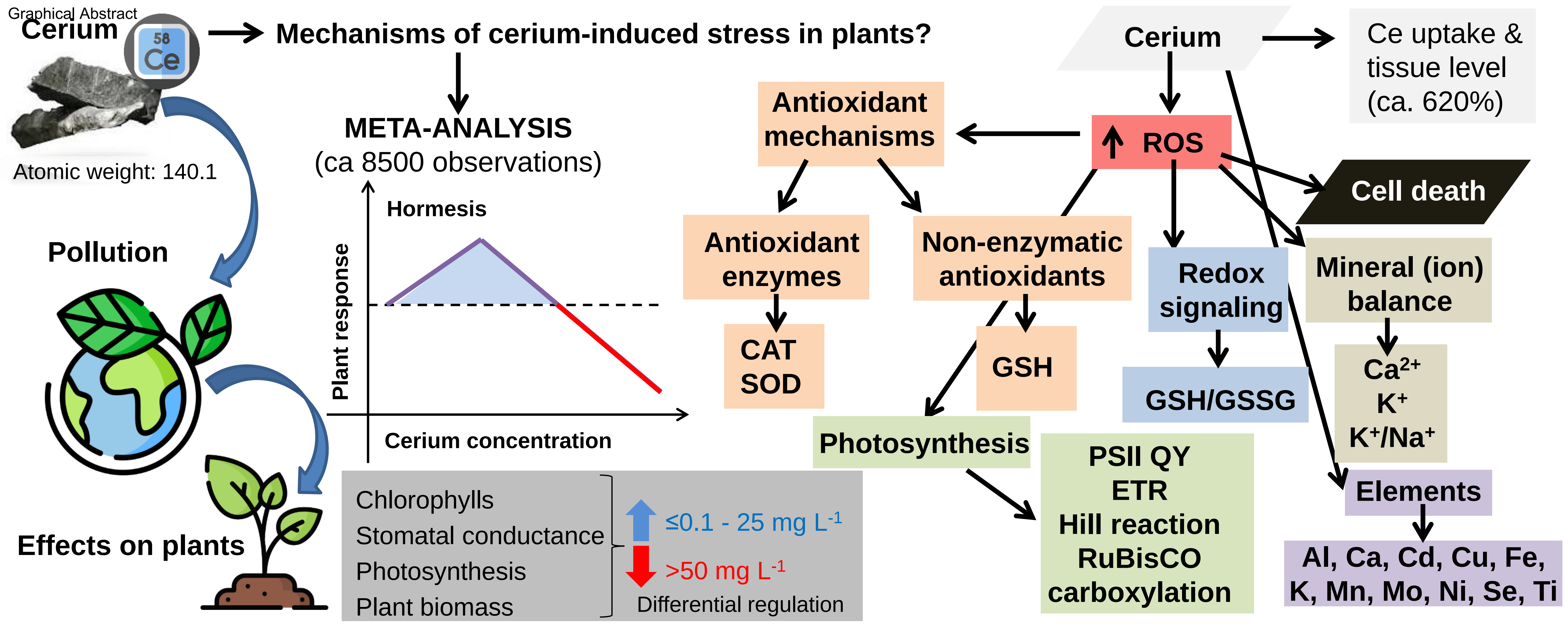


Fig. 7. Overall effect of cerium on plants (all traits pooled) as a function of exposure duration. Symbols indicate the mean natural log response ratio of cerium application relative to the control group (zero cerium dose), while the bars around the mean value represent the bootstrapped 95% confidence intervals (CIs). * next to CI bars shows a statistically significant cerium effect relative to control group, whereas "ns" shows a statistically non-significant effect. The numbers in parentheses indicate the observations number (sample size), studies number, and species number respectively (from left to right). The effect of different exposure durations is further partitioned to different sources of variation (see section 3.5).

Graphical Abstract



Highlights

- Effects of cerium exposure on plants were identified through meta-analysis
- Cerium induces ROS and causes stress with benefits or toxicities depending on dose
- Both antioxidant enzymes and non-enzymatic antioxidants are induced by cerium
- Cerium alters redox signaling, ion homeostasis, and plant nutrient dynamics
- Chlorophylls, photosynthesis, and biomass decrease or increase depending on dose

1. Introduction

Rare earth elements (REEs) have been extensively introduced into the environment in the last decades, due to their wide use in agriculture, technology (e.g., electronics), and medicine (Li et al., 2016; Migaszewski and Galuszka, 2015; Srikant et al., 2021). China, the major producer of REEs worldwide, mined 140,000 tons in 2020. Another 24,700 tons were produced by Australia (17,000), India (3000), Russia (2700), Brazil (1000), and Vietnam (1000) (Tao et al., 2022). REE contents in the soils of mining and non-mining areas in different countries were reported to range from 18 to 27,550 mg kg^{-1} (Mihajlovic et al., 2019; Tao et al., 2022). In sediment samples from different countries, values of relative REE abundance were also reported to range from 11 to 3,041 mg kg^{-1} (Tao et al., 2022). Hence, the levels of REEs in soils and sediments display a high spatial variability and reach relatively high values. This raises ecotoxicological concerns in recognition of documented effects of REEs on animals and other organisms as well as potential links to human disorders and diseases, especially in areas with elevated REE pollution (González et al., 2015; Pagano et al., 2015; Tao et al., 2022).

Cerium is the 25th most abundant element in the Earth's crust (62 mg kg^{-1}), surpassing elements like Cu (60 mg kg^{-1}) and Pb (13 mg kg^{-1}) (Migaszewski and Galuszka, 2015; Tao et al., 2022). It belongs to the most extensively applied REEs, leading to its widespread accumulation in the environment (Liang et al., 2005). The long and extensive application of REE microfertilizers in the agricultural practice, in China, considerably enhanced the yields and qualitative value of many crops (Migaszewski and Galuszka, 2015). However, cerium also has a distinct property, that is, its Ce^{3+} form is separated from other trivalent REEs due to its oxidation to Ce^{4+} in aqueous environments with somewhat increased pH or redox potential (Eh) (Migaszewski and Galuszka, 2015). The reverse conversion from Ce^{4+} to Ce^{3+}, due to valence change and electron addition, also occurs in organisms (Farias, 2018). Such chemical transformations suggest the possibility for unpredicted effects of cerium on non-target plants and other organisms. In recent years, nano-forms of cerium have also received increased interest, not only for improving plant health (Hu et al., 2020; Rodrigues et al., 2021; Sharifan et al., 2020) but also for medical purposes (e.g., cerium oxide nanoparticles) because of their antimicrobial activity, high oxygen buffering and free radical-scavenging potential, among other properties (Farias, 2018; Jakupec et al., 2005; Li et al., 2016). In many cases the activity of nano-forms of cerium is similar to that of two key antioxidant enzymes, namely, catalase (CAT) and superoxide dismutase (SOD), thus enhancing pro-oxidant activity, although adverse effects, such as on respiratory tract, have also been reported (Li et al., 2016). Because of the relatively high natural abundance of cerium and its increased anthropogenic emissions into the environment, there is a need to better comprehend its effects on plants and other organisms.

A literature survey with keywords ‘cerium’, ‘plant’, and ‘review’ (PubMed; 9 July, 2022) revealed that no comprehensive review focusing on the overall mechanisms underlying cerium effects on plants has been published. Nevertheless, the increasing interest in nano-cerium led to some reviews on the effects of cerium oxide (CeO_2) nanoparticles on plants. These suggested suppression of root biomass but enhancement of shoot biomass in many plants (Lizzi et al., 2017). These reviews also suggest decreased photosynthetic pigments and enhanced gas exchange related to photosynthesis, as well as modified yields and nutritional quality of edible plant products (Lizzi et al., 2017; Prakash et al., 2021). However, the effects varied among studies and plant growth conditions, indicating the degree to which the mechanistic understanding remains incomplete (Lizzi et al., 2017; Prakash et al., 2021).

Some plant species can (hyper)accumulate REEs (Tao et al., 2022). However, hyperaccumulators represent a tiny fraction of 'elite' species, e.g., only approximately 0.2% of the currently known vascular plant species have been identified as hyperaccumulators of metals (Calabrese and Agathokleous, 2021). For 'normal', non-(hyper)accumulator plant species, the REE contents are, generally, considerably low; however, with considerable variation amongst spermatophytes (Tao et al., 2022). For example, REE contents in spermatophytes can range from 0.028 to 386 mg kg^{-1} depending on plant species and tissues (Tao et al., 2022). Nevertheless, such REEs still enter the food chain, undergo bioaccumulation/biomagnification, and potentially affect ingesting organisms (Adeel et al., 2019). Importantly, REEs, including lanthanum (La) and cerium (Ce), have also been measured in considerable levels in human blood, hair, and sperm (Li et al., 2013; Marzec-Wróblewska et al., 2015; McDonald et al., 2017). These observations further indicate the widespread presence of REEs, facilitated by trophic transfer, where plants act as a major primary entrance to the trophic chain. Therefore, it is profoundly important to understand cerium effects on plants, not only for revealing the underlying plant mechanisms but also for understanding how plants may drive risks to the health of herbivores.

Despite the widespread application of REEs in agriculture to increase crop productivity, there is lack of systematic assessments on positive versus negative effects of REEs on living organisms, even though some literature reviews highlight the occurrence of hormesis

(Agathokleous et al., 2019c; Pagano, 2016; Tommasi et al., 2021, 2022). Such an evaluation can be facilitated by the use of meta-analytic tools that permit summarizing large amounts of data. Meta-analysis is an important statistical tool that can give answers to questions that cannot be answered by traditional narrative literature reviews. It increases the number of observations, while accounting for study-specific variance, and enhances the statistical power. Meta-analysis also improves the estimated effect size of experimental treatments, and can be utilized to extract quantitative conclusions from an abundant scientific literature. It removes reviewer bias due to subjective –at least to some degree– review, identifies general trends and patterns, and reduces data processing errors, thus advancing theories and scientific understanding. To date, there has been no meta-analysis on the effect of cerium or other REEs on any organisms (Web of Science; keywords: "cerium" or "rare earth" and meta-analysis (all fields); last update on 28 April 2022), although some regular reviews have examined the effects of REEs on plants and other organisms (Agathokleous et al., 2019c; Cassee et al., 2011; Tao et al., 2022; Tommasi et al., 2021, 2022).

This study aimed at identifying general impacts of cerium on plants (regardless species) after collating a meta-database including approximately 8,500 entries (control-treatment observations). To further partition sources of variance, the effect of cerium was examined for different functional groups, crop types, orders, families, genera, and species of plants, plant ontogenic stages subjected to cerium (seed, vegetative stages, or both), application route (seed, foliage, root, or combinations of them), and growing media (soil or solution). This study also aimed at identifying concentrations that generally produce significant positive effects or toxicities across a spectrum of concentration-response ranges and exposure duration intervals within the context of hormesis. This can provide a cost-benefit information platform to reduce the inputs of cerium into the environment and optimize the benefits from cerium application. It was of further interest to examine whether the effect of different concentration ranges varies with key plant traits, plant ontogenic stage treated, cerium particle size (nano or bulk), cerium molecular formula, exposure duration, growing medium, and application route. Finally, it was of similar interest to evaluate whether application route, growing medium, cerium form, and treated plant ontogenic stage modify the effect of cerium at different exposure duration intervals. This meta-analysis reveals the integrated mechanisms by which cerium affects plants, advancing the scientific understanding. It also provides a pathway to address the issue of cerium toxicities and risks in the environment, and offers a novel perspective to tackle this issue at a global scale.

2. Materials and methods

2.1 Literature screening

Literature screening was conducted in the Web of Science (http://apps.webofknowledge.com), and covered the entire period with available publications; the last update was conducted on 23 December, 2020. The combination of keywords (method: Topic) included (cerium) AND (angiosperm OR bryophyte OR cutting OR grass OR gymnosperm OR forest OR hedge OR herb OR herbaceous OR plant OR sapling OR seed OR shrub OR tree OR vegetation OR woody) (Supplementary Materials 1, Fig S1). The search revealed 2,275 publications in English language, and inclusion-exclusion criteria were then applied (Supplementary Materials 1, Fig S2). First, publications were filtered to exclude non-original research (e.g., books, editorials, reviews, and news) based on the type, title, and abstract of publication. Second, articles reporting no application of cerium on plants were excluded based on title and abstract, resulting in 446 publications proceeding to the next stage which was duplicates checking. After excluding duplicates, 233 articles were examined in detail for inclusion eligibility. At this stage, articles and observations were excluded if one or more of the following conditions held true: (1) the experimental organisms were not higher plants; (2) measures of dispersion of data around the mean (standard error (SE) or standard deviation (SD)) were not reported, and their estimation was not permitted by the existing information; and (3) the experimental treatments were not replicated. This screening resulted in 146 articles that were finally selected for inclusion in the created database (Supporting Information 1, Table S2). The screening of literature, selection of articles, extraction of data, and database preparation were performed in parallel by three independent reviewers under the lead author's supervision, without using workflow-management software.

2.2 Data preparation

The values of means of experimental conditions/groups, the values of given measure of dispersion around the mean (SE or SD), sample size (N), and number of replicates for both the control group (typically zero cerium added) and cerium treatments were gathered in a database. Qualitative information was also collected and recorded in the database in order to study sources of variation (see next section). Data presented in the text or in tables of the reviewed articles were extracted directly. Data that were presented only in graphs were mined with GetData Graph Digitizer v. 2.26 (http://getdata-graph-digitizer.com), with an accuracy of ± 1 % compared to the actual values (Xie et al., 2014). Multiple observations reported in a single article/study were considered to come from independent studies if concerning different genotypes, cultivars, species, cerium concentrations, application techniques, or measurement periods (Feng et al., 2010; Wittig et al., 2009). Therefore, all relevant data from studies reporting both stimulatory and inhibitory effects were included in the database and meta-analysis, regardless of the direction of the effect. Regarding dependent observations in studies reporting traits with multiple treatment data and a common control, the mean values of treatment or control groups were used, according to Lajeunesse (2016). Moreover, if different levels of a stressor were applied to plants in a study, the average value was calculated. The information of plants considered in the meta-analysis is provided in Supplementary Materials 1 (Table S1).

2.3 Sources of variation

To clarify variation in cerium effects and reduce potential confounding of factors other than cerium treatment with uneven distribution across datasets, a plethora of sources of variation were considered. These included functional groups (eudicots or monocots and crops, shrubs, or trees), crop types (cereals, fruit trees, legumes, medicinal, oilseed crops, pasture, vegetable, and wild herbs), orders, families, genera, and species of plants with eligible (see previous section) and sufficient number (see next section) of entries. Furthermore, variation was partitioned into plant traits, plant ontogenic stages subjected to cerium (seed, vegetative stages, or both), cerium concentration ranges and treatment duration, cerium particle size (nano or bulk), cerium molecular form, application route (seed, foliage, root, or combinations of them), and growing medium (soil or solution). In plant ontogenic stages, seed represents cerium application to germinating or non-germinated seeds whereas vegetative stage represents cerium application to plants at any stage after completion of germination. Regarding the effect of cerium concentration, the majority of studies reported concentrations in mg L^{-1}. Therefore, wherever they could be converted accurately with the reported information, the units were changed into mg L^{-1} for harmonization. For a considerable number of entries (about 2700), the concentration unit was mg kg^{-1}. Hence, entries of the two units were analyzed separately. To cover the entire continuum of dose-response relationship in order not to preclude the identification of both subtoxic and toxic effects widely occurring in biphasic dose responses, arbitrary concentration ranges were created based on the abundance of entries to provide ranges with logical arrangement of spacing. Given the abundant literature with considerably high number of entries, 17 and 15 segments were created ranging from ≤0.1 mg L^{-1} to 4,000 mg L^{-1} and from >1 mg kg^{-1} to 2,000 mg kg^{-1}, thus permitting the evaluation of potentially antithetic effects between low and high concentrations. Exogenously applied chemicals exhibit important variation in their effects depending on the treatment period (Agathokleous et al., 2021). Hence, various arbitrary segments of treatment duration were created. Specifically, 11 segments were created, ranging from few hours (<1 day) to 210 days, in order to account for homeostatic controls as well as long-term effects.

2.4 Meta-analysis

Natural log response ratio (rrX) was used to estimate the effect size of cerium as

$$rr = ln\left(\frac{X_t}{X_c}\right)$$

where rr is the natural logarithm (ln) of the average of cerium-treaded group (Xt) divided by the average of the control group (Xc) (Feng et al., 2010; Hedges et al., 1999; Wittig et al., 2009). The control group is theoretically cerium-free, e.g., a water-based solution with no added cerium. An rr=0 suggests that the cerium-treated group does not differ from the control group. An rr>0 suggests a positive effect, whereas an rr<0 suggests a negative effect of cerium treatment compared to control condition. The positive or negative rr values are interpreted as biologically positive or negative effects, depending on plant trait under consideration (see results and discussion). Whether an effect is statistically significant or not depends on the variance around the mean, and is determined by the statistical model of meta-analysis.

To pool effect sizes and conduct analyses, a random-effects model was applied, based on the hypothesis that inter-group differences (among studies and groups of comparisons) come from sampling errors as well as from true random variation (Xie et al., 2014). To reduce the uncertainty underlying the estimation, 64,999 bootstrap iterations (maximum number of iterations permitted by the software) were applied to re-sample data and construct confidence limits around the size of effect and effect size variance (Rosenberg et al., 2000). The estimates of effect size were classified significant when zero (0) was outside the confidence interval (CI) of 95% (Wittig et al., 2009). The total heterogeneity (Q_T) was partitioned to within-group heterogeneity (Q_W) and between-group heterogeneity (Q_B) in order to compare differences between and within categories. A randomized *p* value <0.05 derived from the resampling technique indicates that ≥2 levels significantly differed between them. In order a categorical level (group) to be included in the meta-analysis, it should be composed of ≥10 observations regardless the number of independent studies or of >5 observations obtained from ≥3 independent studies (Feng et al., 2010; Wittig et al., 2009). The mean effect size and the bootstrapped 95% CIs of each categorical level were calculated for each variable. The meta-analysis was performed with MetaWin v. 2.1.3.4 (Sinauer Associates, inc., Sunderland, MA, USA).

3. Results

3.1 Plant taxonomic groups (order, family, genus, species)

The pooled effect of cerium on different plant taxonomic groups was examined across all studies with random-effects model, independently of other conditions; sources of variance are analyzed in succeeding sections.

Cerium application had a significant positive effect on 17 orders of plants, representing many thousands of species and covering a vast array of food crops as well as plants used for domestic animal feed (Supplementary Materials 2, Fig. S1). The average effect was commonly up to approximately 50% of the control, except for two orders, Apiales (81%) and Dioscoreales (214%), which also had a greater variance and were composed of a relatively small sample size (Supplementary Materials 2, Fig. S1). This increased effect of cerium on Apiales and Dioscoreales (applied at 63-500 and 100-1000 mg kg^{-1}, respectively) was also contributed by the high number of entries regarding Ce in plant tissues (22.2 and 54.5 % of all entries, respectively), of which response is multi-fold greater (see also section 3.3).

Cerium also had a significant positive effect on 17 families and a negative effect on 1 family (Supplementary Materials 2, Fig. S2). The negatively affected Liliaceae was comprised of only 13 observations, 2 studies, and 1 species, and the effects included statistically significant inhibitions of individual-level endpoints based on the original studies too. In these studies either Ce^{3+} (2-50 mg L^{-1}) (Kotelnikova et al., 2019) or nano–cerium oxide (CeO_2; 250-1000 mg L^{-1}) (Andersen et al., 2016) was applied, but with more super-NOAEL (no-observed-adverse-effect-level) concentrations, thus leading to an overall negative pooled effect. Similarly to the effect on orders, the average effect on families was commonly up to approximately 54% of the control, except for two families, Apieaceae (81%) and Dioscoreaceae (214%), with enlarged effect and variance (Supplementary Materials 2, Fig. S2).

Overall, 27 genera were positively affected, 3 genera were negatively affected, and 8 genera were non-significantly affected by cerium application (Supplementary Materials 2, Fig. S3). The average positive effect was commonly up to approximately 75% relative to control, except for *Dioscorea* that exceeded 200% as aforementioned for its family and order (Supplementary Materials 2, Fig. S3). The negative effect was below 20% (Supplementary Materials 2, Fig. S3). Similarly to the aforementioned studies with negative effects on Liliaceae family (Andersen et al., 2016; Kotelnikova et al., 2019), the negative effect on *Nicotiana*, *Pisum*, and *Spirodela* genera stems from more decreases in elements and/or more doses above NOAEL, with even biphasic dose responses observed, and includes significant inhibition of growth too (Skiba et al., 2020; Skiba and Wolf, 2019; Song et al., 2018; Xu et al., 2017). The overall numerically positive effect can also be regarded biologically positive effect for the plants because the vast majority of plant traits covered represent traits of which increase reflects a biologically positive outcome of the plants, such as increased pigments and yields (see section 3.3). That is, the number of observations of traits of which increase can lead to biologically negative effects (e.g., reactive chemical species) is considerably limited in the overall analyses (see section 3.3).

Across all studies, cerium treatment positively affected 30 species, negatively affected 4 species, and had no significant effect on 11 species (Supplementary Materials 2, Fig. S4; see Fig. S5 for an analysis per plant common name). It should also be noted that this represents an overall effect, and the non-significant effect on 11 species does not imply absence of effect on each one of these species. This is because the effect depends upon the traits studied (including also the number of negatively affected versus the number of positively affected) and treatment concentrations as shown in other meta-analyses too (Agathokleous et al., 2021). The negative effect on the 4 species (*Allium cepa*, *Nicotiana tabacum*, *Pisum sativum*, *Spirodela polyrrhiza*) is attributed to the reasons explained previously for families and genera, and was below 20% relative to control except for *Allium cepa* that reached 45% (Supplementary Materials 2, Fig. S4). The degree of average positive effect varied widely with species, but was commonly up to ≈50% except for *Capsicum annuum* (68%), *Coriandrum sativum* (55%), *Cucumis sativus* (78%), *Dioscorea esculenta* (207%), *Lycopersicon esculentum* (184%), and *Medicago sativa* (61%).

3.2 Plant type groups

Across studies, cerium had a significant positive effect on cereals (18%), fruit trees (18%), legumes (22%), medicinal plants (23%), oilseed crops (10%), pastures (17%), vegetables (10%), and wild herds (7%) (Supplementary Materials 2, Fig. S6). The effect of cerium was smaller on vegetables and wild herbs than on cereals, legumes, medicinal plants, and pasture.

A further grouping of plant functional types across studies revealed that cerium positively affected plants regardless the functional group (Supplementary Materials 2, Fig. S7). Specifically, a similar average effect was observed among crops (16%), shrubs (14%), and trees (16%), as well as between eudicots (14%) and monocots (17%) (Supplementary Materials 2, Fig. S7).

3.3 Plant traits (mechanisms)

3.3.1. Trait groups

Cerium significantly enhanced chlorophyll fluorescence (6%), defense system (15%), development (11%), and gas exchange (17%) (Fig. 1; Supplementary Materials 2, Fig. S8). It also positively affected mineral (ion) balance (10%) and increased non-essential elements (305%), which were mainly comprised of cerium and heavy metals (Fig. 1). Conversely, cerium application decreased essential micro- (7%) and macronutrients (4%) as well as photosynthetic pigments (8%), whereas the overall effect on growth, productivity and yields was insignificant (Fig. 1). Hereafter, the results are analyzed for different traits per trait category.

3.3.2. Photosynthesis-related traits

Regarding chlorophyll fluorescence-related traits, cerium increased the actual photosynthetic efficiency of PSII (14%), the coefficient of photochemical quantum yield in dark (2%), the PSII effective quantum yield (4%), the electron transport rate (11%), and the maximal quantum yield (1%) (Fig. 2A; Supplementary Materials 2, Fig. S9).

Gas exchange analysis revealed that photosynthetic rate (22%) and stomatal conductance

(13%) were also significantly increased by cerium (Fig. 2B).

Chlorophyll *a* (12%), chlorophyll *b* (13%), and carotenoids (12%) were significantly decreased; however, total chlorophylls (*a*+*b*) and chlorophyll *a* to chlorophyll *b* ratio were not significantly affected (Fig. 2C). It should be clarified that the total chlorophylls (above zero but CI overlapping zero) consisted of nearly twice the number of observations, and this trait represented a more robust group compared to the individual chlorophyll pigments.

3.3.3. Biochemical (stress-related) traits

Cerium affected the plant defense system in diverse ways (Fig. 3A). It increased CAT (17%), dehydroascorbate reductase (DHAR; 54%), glutathione (GSH; 12%), reduced GSH to oxidized glutathione ratio (GSH/GSSG; 20%), malondialdehyde (MDA; 33%), reactive oxygen species (ROS; 38%), and SOD (7%) (Fig. 3A; Supplementary Materials 2, Fig. S10). Conversely, it decreased lycopene (7%), membrane permeability (35%), and polyphenol oxidase (28%) (Fig. 3A; Supplementary Materials 2, Fig. S10). Similarly, cerium decreased starch (13%) but increased free thiols (24%), hill reaction (18%), photophosphorylation rate (17%), and RuBisCO carboxylation (23%) (Fig. 3B; Supplementary Materials 2, Fig. S10).

3.3.4. Elemental/mineral traits

Regarding essential elements, cerium decreased B uptake (13%) and its levels in tissues (10%) and the ratio of carbon to nitrogen (C/N; 8%) (Fig. 4A; Supplementary Materials 2, Fig. S11). It also decreased the levels of Ca (12%), Fe (11%), K (5%), and Mo (31%) in tissues, but increased the uptake of Cu (19%), Fe (58%), Mn (20%), and Ni (76%), although the latter increases are based on a considerably small number of observations (Fig. 4A).

As to non-essential elements, cerium application led to significantly decreased Cd (23%)

and Se (13%) levels in tissues and increased Ce (624% and 623%) and Al (67% and 77%) uptake and their levels in tissues (Fig. 4C; Supplementary Materials 2, Fig. S11).

Cerium also altered mineral (ion) balance, with significant increases in Ca^{2+} (9%), electrolyte leakage (15%), K^+ (20%), K^+/Na^+ (19%), and Mg^{2+}-ATP_{ase} (20%) (Fig. 4B; Supplementary Materials 2, Fig. S11).

3.3.5. Growth, productivity, and yields

Cerium significantly increased the total plant biomass (7%), number of root tips (23%), root volume (15%), stem biomass (6%), and stem diameter (11%), and decreased root length (11%) and yields (6%) (Fig. 5; Supplementary Materials 2, Fig. S12). Traits that were overall negatively affected by cerium are further analyzed by concentration ranges (see section 3.4.6).

3.4. Applied cerium concentration

3.4.1. Overall concentration ranges

As explained before, the majority of observations, specifically 5,313 observations, concerned the concentration unit of mg L^{-1}, representing approximately 62% of the total number of observations in the entire database. An additional 2,648 observations concerned the concentration unit of mg kg^{-1}, that is approximately 31% of the total number of observations in the entire database. Therefore, emphasis was placed on the analysis of data given in concentration units of mg L^{-1}.

Across studies, cerium had either a positive or a non-significant effect on plants (Fig. 6). Importantly, the significant positive effect occurred from concentrations as low as ≤0.1 mg L^{-1}, which was kept at similar levels up to 50 mg L^{-1} (%). The concentration of 100 mg L^{-1} also had a positive effect similar to that of concentrations ≤0.1 mg L^{-1} (Fig. 6). For concentrations

≥125-800 mg L^{-1}, only concentrations >210-300 mg L^{-1} and 500 mg L^{-1} had a positive effect. Cerium concentrations of 1000 and ≥1600-2000 mg L^{-1} also led to a positive effect. All these effects were similar to that of concentrations ≤0.1 mg L^{-1} (Fig. 6). Similar results were revealed for the observations with cerium concentrations in mg kg^{-1}, with significant positive effects of different ranges from as low as >1-5 mg kg^{-1} to 1000 mg kg^{-1} and negative effect at 600 mg kg^{-1} (Supplementary Materials 2, Fig. S13).

3.4.2. Concentration ranges as a function of application route

The overall effect of cerium, regardless of other factors, showed no clear pattern of variation due to the application route, with only few differences (Supplementary Materials 2, Fig. S14-S15). For instance, root and foliage+root applications had a significant positive effect at concentrations >0.1-1 mg L^{-1}, but foliage and seed applications had not. This distinction was no longer present at concentrations >1-5 mg L^{-1}, where all application routes led to a significant positive effect on plants. At concentrations >5-10 mg L^{-1}, foliage application did not significantly affect, root and foliage+seed application positively affected, and seed application negatively affected plants. At >10-25 mg L^{-1}, foliage and root application positively affected and seed application negatively affected. The only significant effect at >50-80 mg L^{-1} was a positive influence of seed application. However, at 100 mg L^{-1} the only significant effect was a positive influence of root application (Supplementary Materials 2, Fig. S14-S15). For concentrations ≥125-160 mg L^{-1}, foliage and seed applications but not root application positively affected plants. Regarding concentrations from 200 to 421 mg L^{-1}, no specific application route had positive effects. Then, 1000, ≥1600-2000, and ≥3000-4000 mg L^{-1} significantly positively affected plants when applied to root (Supplementary Materials

2, Fig. S14-S15). For all the significant positive effects, the effects were similar among the different concentration ranges. Since, the unit of mg kg^{-1} does not include foliage application, data given in mg kg^{-1} were not considered worth of more detailed analysis.

3.4.3. Concentration ranges as a function of cerium particle size

The effect of cerium (mg L^{-1}) on plants differed between the nano-form and bulk cerium, with half of the concentration ranges showing superiority of nano-cerium (Supplementary Materials 2, Fig. S16). Specifically, nano-cerium had an increased effect at concentrations ≤0.1, >1-5, >10-25, >25-50, 100, and >210-300 mg L^{-1} relative to bulk cerium (Supplementary Materials 2, Fig. S16). Less clear was the difference for the analysis of the effect of cerium concentrations in mg kg^{-1} (Supplementary Materials 2, Fig. S17). Specifically, nano-cerium had a better effect at >25-50 mg kg^{-1} but bulk cerium had a significant positive effect at ≥125-500 mg L^{-1} when nano-cerium had either negative or non-significant effect (Supplementary Materials 2, Fig. S17).

3.4.4. Concentration ranges as a function of cerium molecular formula

Approximately 10 molecular formulas of cerium were analyzed across different concentrations ranges, depending on the availability of observations and sample size (Supplementary Materials 2, Figs. S18-S19). However, the most extensively applied form is cerium dioxide (CeO_2), which widely produced positive effects at various concentrations, e.g., at ≤0.1, >0.1-1, >5-10, >10-25, >25-50, and >210-300 mg L^{-1} and at >25-50, >210-300, and 500 mg kg^{-1}. The lowest concentrations (≤0.1 mg L^{-1}) produced equal or greater effects than higher concentrations.

Diammonium cerium (IV) nitrate ($Ce(NH_4)_2(NO_3)_6$) had smaller effects at ≤0.1 mg L^{-1}

and similar effects at higher concentrations compared to CeO_2. Cerium (III) nitrate hexahydrate ($Ce(NO_3)_3 \times _6H_2O$) led to similar or higher effects at low doses (≤0.1-1 mg L^{-1}), but there were indications toward negative effects at concentrations >5-10 mg L^{-1}. This was also the case for cerium (III) chloride ($CeCl_3$) for similar significant positive effects up to 25 mg L^{-1}, followed by a trend toward negative effects at >25-50 and ≥125-160 mg L^{-1}. Compared to CeO_2, $Ce(NO_3)_3$ had smaller positive effects at concentrations ≤0.1 mg L^{-1}, similar effects at concentrations >0.1-10 mg L^{-1}, and greater positive effects at concentrations >10 mg L^{-1} (Figs. S18-S19). Then, the effect of $Ce(NO_3)_3$ became non-significant or negative at higher concentrations. The observations were insufficient for other molecular formulas for an insightful assessment of the concentration-response spectrum. Furthermore, the number of studies for molecular formulas other than CeO_2 was extremely small for concentrations in mg kg^{-1}, and thus such formulas were not analyzed further.

3.4.5. Concentration ranges as a function of growing medium

The effect of cerium (mg L^{-1}) had little differences between soil and solution growing media (Supplementary Materials 2, Fig. S20). Soil application had no significant effect at >10-25, >25-50, ≥1600-2000, and ≥3000-4000 mg L^{-1}, concentrations at which application to solution positively affected plants. Conversely, application of cerium to solution did not significantly affect plants at 100, ≥125-160, 200, >210-300 mg L^{-1}, while these concentrations had a positive effect in soil medium (Supplementary Materials 2, Fig. S20).

3.4.6. Concentration ranges as a function of ontogenic stage treated

This analysis revealed that at several concentration ranges within which seed treatment had no significant effect (>5-10, >10-25, >210-300, 1000, and ≥1600-2000 mg L^{-1}), treatment at vegetative stages or at both seed and vegetative stages produced significant positive effects (Supplementary Materials 2, Fig. S21). Conversely, at >50-80 and ≥125-160 mg L^{-1} seed treatment, but not treatment at vegetative stages, significantly positively affected plants (Supplementary Materials 2, Fig. S21). For the observations in mg kg^{-1}, the effects were more variable and included both negative and positive effects for seed treatment (Supplementary Materials 2, Fig. S22). Overall, seed treatment showed less significant effects; however, the number of observations and studies for seed treatment are limited and such results should be interpreted with caution.

3.4.7. Concentration ranges as a function of plant trait

The effect of different cerium concentration ranges was analyzed also as a function of selected traits that are key to individual level fitness, namely photosynthetic pigments, photosynthetic rate and stomatal conductance, plant biomass, and yields, some of which were negatively affected in the overall analyses per plant trait (see section 3.3).

Chlorophyll *a* and chlorophyll *b* were significantly increased by concentrations >1-5 mg L^{-1} and decreased by >50-80 and ≥125-160 mg L^{-1} and ≥320-421 mg kg^{-1}; chlorophyll *b* was also decreased by 100 mg kg^{-1} (Supplementary Materials 2, Fig. S23). Total chlorophylls (*a*+*b*) were significantly increased by concentrations >0.1-1, >10-25, and 100 mg L^{-1} and >25-50 and >210-300 mg kg^{-1}, with no negative effects occurring at any concentration range. No significant effect was observed for carotenoids at the analyzed concentration ranges (Supplementary Materials 2, Fig. S23).

Photosynthetic rate was enhanced by concentrations >10-25 mg L^{-1} and >5-10, 100, and 1000 mg kg^{-1}, with no negative effects occurring at the partitioned concentration ranges

(Supplementary Materials 2, Fig. S23). Stomatal conductance was significantly affected by >5-10 and 100 mg kg^{-1} only, effects that were positive (Supplementary Materials 2, Fig. S23).

Plant biomass was increased by concentrations ≤0.1, >0.1-1, >1-5, and 100 mg L^{-1} and 100 mg kg^{-1}, whereas it was decreased by ≥125-160 and 500 mg L^{-1} (Supplementary Materials 2, Fig. S23). However, the only significant effect on yields was suppression by >50-80 and ≥320-421 mg kg^{-1} (Supplementary Materials 2, Fig. S23).

3.4.8. Concentration ranges as a function of exposure duration

A common pattern observed in all the five intervals of low concentrations from ≤0.1 to 10 mg L^{-1} (a 100-fold concentration range) is the common maximization of the positive effect within three days of exposure (Supplementary Materials 2, Figs. S24-S25). This outcome was followed by a decline in response over the course of exposure, but often maintained at significantly positive levels for up to approximately 13 weeks, depending on the concentrations (Supplementary Materials 2, Figs. S24-S25). No clear time-dependent pattern was observed for concentrations >10-100 mg L^{-1}, where significant positive effects were observed at different times depending on the concentration (Supplementary Materials 2, Figs. S24-S25). Lack of a specific time-dependent pattern was also observed for concentrations ≥125 mg L^{-1}, where positive effects occurred early and/or late during the exposure, depending on the cerium concentration (Supplementary Materials 2, Figs. S26-S27). Regarding analysis of meta-data in mg kg^{-1} (>5-1000 mg kg^{-1}), observations were considerably less abundant and available only for >7-210 days. No specific time-dependent trend was revealed; however, both low and high concentrations induced significant effects early and/or late in the exposure, depending on the concentration range (Supplementary Materials 2, Figs. S28-S29).

3.5. Exposure duration

In accordance with the common time-dependent pattern of low concentrations of cerium (see preceding section), cerium overall effect (regardless other factors) maximized within the first 24 h of exposure, and then declined but remained at significant positive levels up to 60 days, and neutralized >60-210 days after exposure (Fig. 7).

No clear time-dependent pattern among cerium application routes was observed, although treatment of seed had significant overall negative effects at >1-3 and >60 days of exposure (Supplementary Materials 2, Fig. S30).

No clear time-dependent pattern was observed between soil and solution treatment either. (Supplementary Materials 2, Fig. S31). However, treatment of plants grown in solution led to more significant positive effects than treatment of soil-grown plants. Specifically, cerium application to soil-grown plants had no significant overall effect at >1-3 and >60-90 days.

Regarding the influence of ontogenic stage treated, when analyzed per the different exposure duration intervals, cerium had fewer significant positive effects or more significant negative effects when applied to seed only than when applied to vegetative growth stages (Supplementary Materials 2, Fig. S32). The number of observations for application at both seed and vegetative stages was limited in this analysis.

The time-dependent pattern was generally similar between nano-cerium and bulk cerium (Supplementary Materials 2, Fig. S33).

3.6. Other effects (sources of variation)

Regarding cerium application routes, the overall effect of seed treatment was non-significant, with the majority of values negative (Supplementary Materials 2, Fig. S34). Foliage, root, and seed+foliage application produced a similar positive effect. Moreover, there was no evidence that combined root and foliage application offers an improved effect compared to foliage or root application individually (Supplementary Materials 2, Fig. S34).

As to the plant growing medium, application of cerium into soil substrate produced a significant overall average effect of +12% (Supplementary Materials 2, Fig. S35). However, the effect was significantly higher (19%) when cerium was applied into solution (Supplementary Materials 2, Fig. S35).

Regarding the ontogenic stage treated, the average overall effect of seed treatment was non-significant (Supplementary Materials 2, Fig. S36). There was also no significant difference between the significant positive effects of cerium application at vegetative growth stages or at both seed and vegetative growth stages; however, the number of observations for the latter category was considerably small (Supplementary Materials 2, Fig. S36).

4. Discussion

Across all studies, cerium application had an overall positive effect on a plethora of plant orders, representative of over 161,000 species (based on data from www.britannica.com; accessed 11 May 2022), regardless traits and other factors. This is further substantiated by the many families, genera, and species significantly affected by cerium application. The finding that cerium application had an overall positive effect on cereals, fruit trees, legumes, medicinal plants, oilseed crops, pastures, vegetables, and wild herbs shows the potential of cerium to widely affect numerous plants used as main food and dietary supplements of humans and other animals as well as for the production of herbal extracts and pharmaceuticals. Nevertheless, the effect of cerium depends on the type of plants, with a smaller effect on vegetables and wild herbs. These suggest that vegetables and wild herbs may be less responsive to cerium than cereals, fruit trees, and pastures; however, these results should be interpreted with caution due to the considerably small number of studies for cereals, fruit trees, and pastures. The effect of cerium did not differ among crops, shrubs, and trees or between eudicots and monocots, indicating a more homogenous effect of cerium at higher levels of plant functional groups.

Cerium overall enhanced chlorophyll fluorescence and gas exchange. Specifically, the actual photosynthetic efficiency of PSII, the coefficient of photochemical quantum yield in dark, the electron transport rate, the PSII effective quantum yield, and the maximal quantum yield were overall increased, mechanisms that are tightly linked to diverse reaction processes in photosynthesis (Moustakas et al., 2022; Peng et al., 2021). The enhancement of these traits indicates increased efficiency of the PSII electron transfer chain, higher internal efficiency in converting light energy, improved efficiency in capturing primary light energy when PSII is partially closed, and, thus, higher photosynthesis potential of plants under stress (Moustakas et al., 2022; Peng et al., 2021). This is further supported by the overall increased photosynthetic rate and its linked stomatal conductance that this meta-analysis revealed, indicating higher CO_2 uptake by plants and increased photosynthetic rate. Hill reaction reflects the O_2 evolution during the illumination-dependent steps in the process of photosynthesis, which along with the ‘Mehler reaction’ can contribute to photoprotection in photosynthesizing organisms (Shevela et al., 2012). The effect on Hill reaction activity may also imply analogous effects on CO_2 assimilation, NADP reduction, and phosphorylation inactivation during stress conditions. Cerium also increased the photophosphorylation rate, a stress-indicating status, suggesting the possibility of enhanced needs of ion uptake and management of ion export in stressed cells (Fork and Herbert, 1993). RuBisCO carboxylation capacity is fundamental for improving photosynthesis and yield (Iñiguez et al., 2021). The overall increased RuBisCO carboxylation by cerium indicates that the enhancement of photosynthesis by cerium is not only due to physiological driving mechanisms (e.g., stomatal conductance) but also due to a biochemical mode of action of cerium. However, this meta-analysis revealed no evidence that the overall enhanced photosynthetic rate is due to increased chlorophylls. Conversely, chlorophyll *a*, chlorophyll *b*, and carotenoids were overall decreased by cerium application, suggesting that cerium causes oxidative stress in plants. As to carotenoids, lycopene in fruit was also decreased by cerium, which further suggests that cerium can affect the nutraceutical value of plant products routinely used for enhancing human health (Imran et al., 2020). Further partitioning the variance into different cerium concentration ranges revealed that total chlorophylls were increased by various concentration ranges from as small as >0.1-1 mg L^{-1}. Moreover, chlorophyll *a* and chlorophyll *b* were increased by low concentrations (>1-5 mg L^{-1}) but decreased by higher concentrations (>50 mg L^{-1}). These findings suggest that cerium causes a biphasic-hormetic dose response, with low concentrations increasing and higher concentrations decreasing chlorophylls. This hormetic pattern of photosynthetic pigments (and photosynthetic rate) was found in numerous photosynthesizing organisms exposed to a wide array of pollutants and other xenobiotics, reflecting an improved defense capacity against environmental challenges (Agathokleous, 2021). Apart from the leaf level, this biphasic-hormetic pattern was also revealed for total plant biomass, which was increased by concentrations ≤0.1-5 and 100 mg L^{-1} (and 100 mg kg^{-1}) and decreased by concentrations ≥125 mg L^{-1}. These findings demonstrate the hormetic function of cerium as a xenobiotic inducing oxidative stress, a hypothesis that is further supported by a different perspective. Specifically, the cerium effect was commonly up to 50% relative to control, across all analyses, indicating that it is commonly rather modest. These findings further demonstrate that the positive effect of cerium on plants is not due to a 'fertilizer effect'. Instead, this effect is similar with that induced by xenobiotics within the framework of hormesis, with a maximum low-dose positive effect of typically 30-60%, which is constrained by the biological plasticity bounds (Calabrese et al., 2019; Calabrese and Blain, 2009), even if Ce uptake and its levels in tissues increase by approximately 620% as this meta-analysis revealed.

The mechanisms underlying the observed effects caused by cerium are similar to those induced by various biotic and abiotic stressors, from viruses to pollutants (Awasthi, 2020; Carvalho et al., 2020; Moustakas et al., 2022; Poschenrieder et al., 2013). Cerium also had further multiple overall effects on different traits related to the defense system and redox homeostasis. It increased CAT, DHAR, GSH, GSH/GSSG, ROS, and SOD. These effects further support the conclusion that cerium acts as a xenobiotic, with its positive effects attributed to stimulation via adaptive responses activated by low doses of oxidative stress. CAT is an antioxidant enzyme of profound importance in the mitigation of oxidative stress, and its increase indicates an enhanced capacity to eliminate cellular H_2O_2, a ROS, to produce O_2 and H_2O (Nandi et al., 2019). Therefore, an increase in CAT indicates the existence of oxidative stress. This is also the case of SOD, an enzyme catalyzing the $O_2^{\cdot -}$ into H_2O_2, and providing a first-line defense against ROS-induced damage (Poschenrieder et al., 2013; Zhao et al., 2021). In addition to these enhanced antioxidant enzymes (SOD and CAT), cerium increased also non-enzymatic antioxidants. Specifically, it increased GSH, a thiol molecule playing a central role in stress signaling and antioxidant defense system, which also alters the GSH/GSSG redox state (Hasanuzzaman et al., 2017; Poschenrieder et al., 2013). Free thiols were also enriched, indicating the overall involvement of thiols in enhancing stress tolerance (Tausz et al., 2003; Zagorchev et al., 2013). Thiol-based redox regulation is important for a swift response of chloroplast metabolism to light intensity (Cejudo et al., 2019). Similarly, DHAR is important to couple the GSH and ascorbate pools with the metabolism of H_2O_2, and is involved in plant defense, development, and growth (Ding et al., 2020; Hasanuzzaman et al., 2017). GSH/GSSG ratio reflects homeostasis (redox state) and can serve as an indicator of oxidative stress, which is often increased together with increased CAT, SOD, and GSH (Hasanuzzaman et al., 2017). The GSH/GSSG redox pair plays a major role in controlling redox signaling (Hasanuzzaman et al., 2017; Szalai et al., 2009). As such, increased cellular GSH level and GSH/GSSG ratio are essential for maintaining plant health under oxidative stress (Hasanuzzaman et al., 2017; Szalai et al., 2009). These increases in CAT, DHAR, GSH, GSH/GSSG, ROS, and SOD suggest that the overall increase of ROS by cerium application did not exceed the threshold level for adverse effects. ROS and associated antioxidant molecules act as signaling agents modulating cellular metabolism, in accordance to endogenous and exogenous stimuli, and affect cellular redox homeostasis (De Gara et al., 2010). Polyphenol oxidase is also an antioxidant enzyme driving the conversion of phenols into quinones, and is linked to detoxification and elimination of ROS (Taranto et al., 2017). Their overall significant response to cerium revealed by the meta-analysis (including leaves and roots) indicates their involvement in plant response to cerium-induced stress. A basal level of ROS is beneficial for health and optimal growth, and a mild increase in ROS triggers a hormetic defense response, followed by inhibitory effects at levels above specific thresholds (Jalal et al., 2021; Moustakas et al., 2022; Poschenrieder et al., 2013). Because excessive ROS inhibit chlorophyll synthesis and accumulation (Moustakas et al., 2022; Ruban, 2015), it can be postulated that decreased chlorophylls by higher doses of cerium stems, at least partly, from excessive ROS. Since ETR should also be restricted below some levels to avoid ROS accumulation (Moustakas et al., 2022), it can also be argued that ETR and ROS are involved in the high-dose inhibition of chlorophylls, although the overall effect on non-photochemical quenching was non-significant in the two studies that included it. The stressor mode of action of cerium is further illustrated by the significant alteration of membrane permeability and starch (in leaf and fruit) revealed by the meta-analysis. Starch metabolism plays a key role in the plant response to stress, and its decrease has been shown in numerous plants under various abiotic stresses (Thalmann and Santelia, 2017). Starch reserve remobilization is important to make energy, sugars, and metabolites available to facilitate stress mitigation (Thalmann and Santelia, 2017). Also, decreased membrane permeability, expected at low cerium doses, may protect against increased ion leakage as the stress progresses, whereas high cerium doses would increase it, thus changing the ion balance and promoting ion leakage in damaged tissues (Filek et al., 2012; Mansour, 2013; Niu and Xiang, 2018). The significant stress-related role of cerium is also extended to increased electrolyte leakage, Ca^{2+}, K^+, K^+/Na^+, which indicates that K^+ and Na^+ homeostasis plays a significant role in the response of plants to cerium and that cerium further alters mineral (ion) balance. Increased electrolyte leakage is usually linked to increased ROS, with potentially activated K^+ efflux, and can promote programmed cell death under severe stress (Demidchik et al., 2014). However, under lower doses of stress, K^+ efflux can stimulate catabolic processes and save metabolic energy that is needed for the processes of damage repair and adaptation (Demidchik et al., 2014). Furthermore, higher cytosolic K^+/Na^+ ratio is regarded an important mechanism for higher tolerance to stress (Almeida et al., 2017). Overall, these mechanisms underlying the effects of cerium on plants indicate the presence of oxidative stress and the existence of dual biological responses with positive biological effects up to some stress level followed by adverse effects (Jalal et al., 2021; Moustakas et al., 2022; Poschenrieder et al., 2013). These mechanisms are similar to those found for various air and soil contaminants, such as heavy metals and toxic anions, ground-level ozone, pesticides, nanomaterials, and pharmaceuticals (Agathokleous et al., 2019a, 2019b, 2018; Carvalho et al., 2020; Jalal et al., 2021; Moustakas et al., 2022; Poschenrieder et al., 2013; Shahid et al., 2020).

This meta-analysis also revealed various alterations in essential and non-essential elements as well as in the mineral (ion) balance in plants. The decreased C/N ratio may be partly attributed to the increased allocation of C to C-based metabolites that increase under cerium-induced stress. Coordination of the metabolism of C and N is essential for optimal development and growth, and disrupted signaling driven by C/N balance may have further implications within ecosystems, such as changing the interaction of plants with pests, the quality of plant litter and its decomposition, and altering the ecosystem response to other environmental conditions such as atmospheric CO_2 (Chen et al., 2015; Zheng, 2009). As to essential elements, cerium treatment decreased the uptake of B and increased the uptake of Cu, Fe, Mn, and Ni. It also decreased B, Ca, Fe, K, and Mo levels in tissues. The observation that cerium overall increased the uptake of Fe while decreasing its levels in tissues may suggest its key role in cerium stress as Fe homeostasis must remain under control in stressed plants. Accumulation of Fe within cells can lead to toxicities, and its decreased levels due to cerium treatment may indicate a mechanism to reduce potential Fe-induced toxicity and/or that more Fe is used for photosynthesis and respiration electron-transport chains, to produce electron transport chain components and/or enzyme cofactors (Connolly and Guerinot, 2002; Connorton et al., 2017). The decrease of several essential elements (B, Ca, Fe, K, and Mo) in tissues due to cerium indicates altered elemental homeostasis with unknown implications to plant health in the long term. These alterations extend to non-essential elements too, as cerium treatment decreased Cd and Se in tissues and increased Al uptake and its levels in tissues, although for Al uptake this is weakly supported because it is based on only one study (Trujillo-Reyes et al., 2013). Some of these elements typically do not have beneficial effects on plants but widely induce phytotoxicities at high concentrations (Schmitt et al., 2016; Watanabe, 2022). The mechanisms of the increased uptake by plants and their levels in tissues are not understood; however, the possibility of their binding with cerium (e.g., attached on cerium particles) and subsequent release into plant tissues cannot be excluded. The mechanisms of decreasing other non-essential elements in tissues are unknown, warranting further studies.

While Ce uptake and plant tissue levels were increased by approximately 620% due to cerium treatment, the average effect of cerium on other chemical elements ranged from 10% to 77%. However, these effects are significant and raise ecological and human health concerns rising from the arbitrary application of cerium within the agricultural practice. This is because it is now shown that cerium extensively alters the chemical composition of plant tissues decreasing several micronutrients that are important for human health while increasing some heavy metals and decreasing others. Similar to the hormetic effects of cerium on plants at individual level, cerium changes mineral nutrient concentrations in a dose-dependent fashion too (Ramírez-Olvera et al., 2018). Therefore, the applied concentration of cerium is a key for minimizing ecological and human health risks.

Besides the physiological and biochemical responses, this meta-analysis revealed an overall negative effect of cerium on root length and yields, which demonstrates that cerium-induced oxidative stress suppressed growth and reproduction traits that are critical to plant fitness. The yield suppression occurred at concentrations >50 mg kg^{-1}, in line with the inhibition of chlorophylls *a* and *b* by concentrations >50 mg kg^{-1}, as shown by the meta-analysis results. However, total plant biomass was decreased by concentrations >125 mg L^{-1}. Hence, there was no evidence that cerium enhances yields (often decreases them), and yields appear to be more sensitive than plant biomass. These findings indicate that cerium pollution can cause adverse effects to vegetation. Importantly, concentrations that were revealed here to cause various adverse effects on plants widely occur in the environment and specifically in agroecosystems, indicating the potentially hazardous nature of cerium (Moreira et al., 2019;

Wiseman et al., 2016). However, numerous factors affect the REE bioavailability to plants including soil physicochemical traits (cation exchange capacity, humic acid, metal oxides, organic and inorganic ligands, pH, redox potential), REE valence, REEs interacting with compounds, Casparian strip in plant root exudates (organic acids), and rhizospheric microbes (Liang et al., 2005; Tao et al., 2022). Thus, the real outcomes can be hardly predicted based on the 'dose' only, and new studies that incorporate such factors in addition to the 'dose' component are needed.

Given that fitness critical traits (photosynthesis rate, photosynthetic pigments, and plant biomass) were enhanced by cerium concentrations as small as ≤0.1-25 mg L^{-1} (or >5-100 mg kg^{-1}), depending on the trait, new studies should focus the shift to lower concentrations in the range of ≤0.1-25 mg L^{-1} (or >5-100 mg kg^{-1}). This is especially important since the number of observations of yield response was extremely limited at concentrations ≤25 mg L^{-1} (and studies typically lacking a proper 'dose-response' component), which underlines that the notion that the higher dose is always the best for enhancing yields is invalid. These results can provide the basis to highly reduce the load of cerium into the environment, which can be further promoted by turning into nano-cerium as this meta-analysis showed it is equally or even more effective than its bulk counterpart. Cerium-carrying nanoparticles can have positive effects on humans too (Li et al., 2016), and thus nano-cerium effects deserve more attention.

Making a further step, this meta-analysis provides insightful information regarding the role of cerium molecular formula within a concentration-response spectrum. Based on this information, molecular formulas with lower potency for toxic effects on organisms but with adequate positive effects (e.g., CeO_2) can be selected over more potentially toxic formulas (e.g., $CeCl_3$, $Ce(NO_3)_3 \cdot 6H_2O$, $Ce(NO_3)_3$). However, there is a gap of knowledge about the effect of several molecular formulas of cerium within the full concentration-response continuum.

More research is also needed into combinations of seed treatment and application of cerium at vegetative stages to potentially maximize the positive effect of cerium by appropriately treating seeds under controlled conditions and reducing the load on the field. Besides, the results of meta-analysis call for cost-benefit evaluations to conclude whether cerium should be actively applied in agriculture, considering the potentially limited positive effects and the large uncertainties about long-term environmental implications of this agricultural practice.

5. Conclusion

This meta-analysis revealed major physiological mechanisms underlying the response of plants to exogenous application of cerium. It is demonstrated that cerium application leads to up to ≈620% increase in Ce uptake and its levels in tissues, on average, offering various positive effects of commonly up to ≈60% relative to control. At concentrations as low as ≤0.1 to 25 mg L^{-1} cerium commonly enhances chlorophylls, g_s, A, and plant biomass; however, at concentrations >50 mg L^{-1} cerium causes various negative effects on plants at trait-specific concentrations. This hormetic pattern is driven by the oxidative stress mode of action of cerium, increasing ROS and their tightly linked antioxidant enzymes and non-enzymatic antioxidants.

Cerium further alters the redox signaling and mineral (ion) balance, including changes in K^+ and Na^+ homeostasis. Various chlorophyll fluorescence traits can be improved by cerium, enhancing photosynthetic efficiency and quantum yield of PSII, while the increase in *A* is also linked to biochemical drivers, namely Hill reaction and RuBisCO carboxylation. However, the potential of cerium application to benefit plant yields remains blurred due to lack of data for low concentrations of cerium and negative effects at concentrations >50 mg kg^{-1}.

Cerium changes the uptake and level in tissues of several micro- and macro-nutrients, including heavy metals that can pose risks to ingesting organisms. As cerium can decrease the levels of several micronutrients, its arbitrary application in agriculture further suggests that cerium pollution may have further implications for disease risk.

To reduce ecological and human health risks associated to cerium pollution, a shift is needed from very high concentrations of cerium to considerably small concentrations (≤0.1 to 25 mg L^{-1}), often a 1000-fold or higher decrease. This study also offers further technical information about the application of cerium that can help to maximize cerium positive effects while minimizing its load in the environment and its associated risks.

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Author contributions E.A. conceived the idea, and all authors participated in the study design. E.A. had a leading role and supervised the production of the manuscript. B.Z., C.G., and J.X. surveyed literature, extracted data, and created the data bases with inputs from E.A., C.J.S., and Z.F. B.Z. analyzed data and created display elements with inputs from G.C., J.X., E.A., and Z.F. E.A. drafted the paper, and all coauthors reviewed the draft and contributed intellectual input. All authors approved the final version of manuscript for publication.

Supplementary Materials (for online publication only)

Filename	Description
Supplementary Materials 1	Display elements illustrating the keyword combination (Fig. S1), the procedure of literature survey and selection (Fig. S2), description of plants considered in the meta-analysis (Table S1), as well as the complete list of references finally included in the meta-analysis database (Table S2).
Supplementary Materials 2	Figures reporting effect sizes of additional results of further meta-analyses as well as supplementary figures with calculated arithmetic per cent for aiding interpretation by readers (Figs. S1-S36).

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Figures

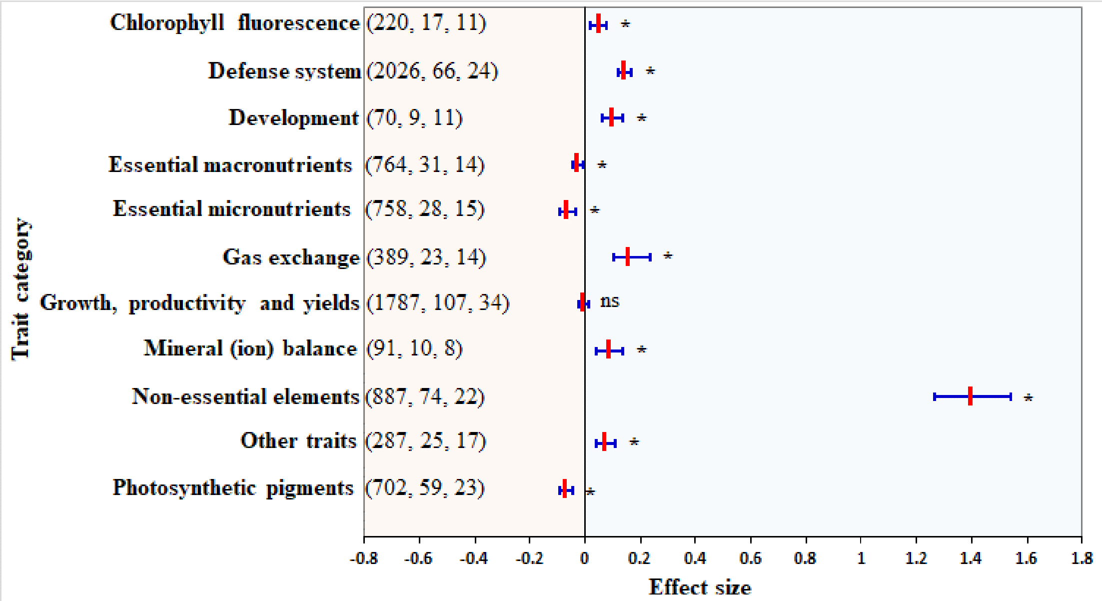


Fig. 1. Effect of cerium on different categories of plant traits. Symbols (vertical red segments) indicate the mean natural log response ratio (rr) of cerium application relative to control group (zero cerium dose), while the horizontal bars around the mean value represent the bootstrapped 95% confidence intervals (CIs). Asterisk (*) next to CI bars shows a statistically significant cerium effect relative to the control group, whereas "ns" shows a statistically non-significant effect. The three numbers in parentheses indicate the number of observations (sample size), studies and species respectively (from left to right). The corresponding plot indicating percent difference from the control is provided in Supplementary Materials 2 (Fig. S8).

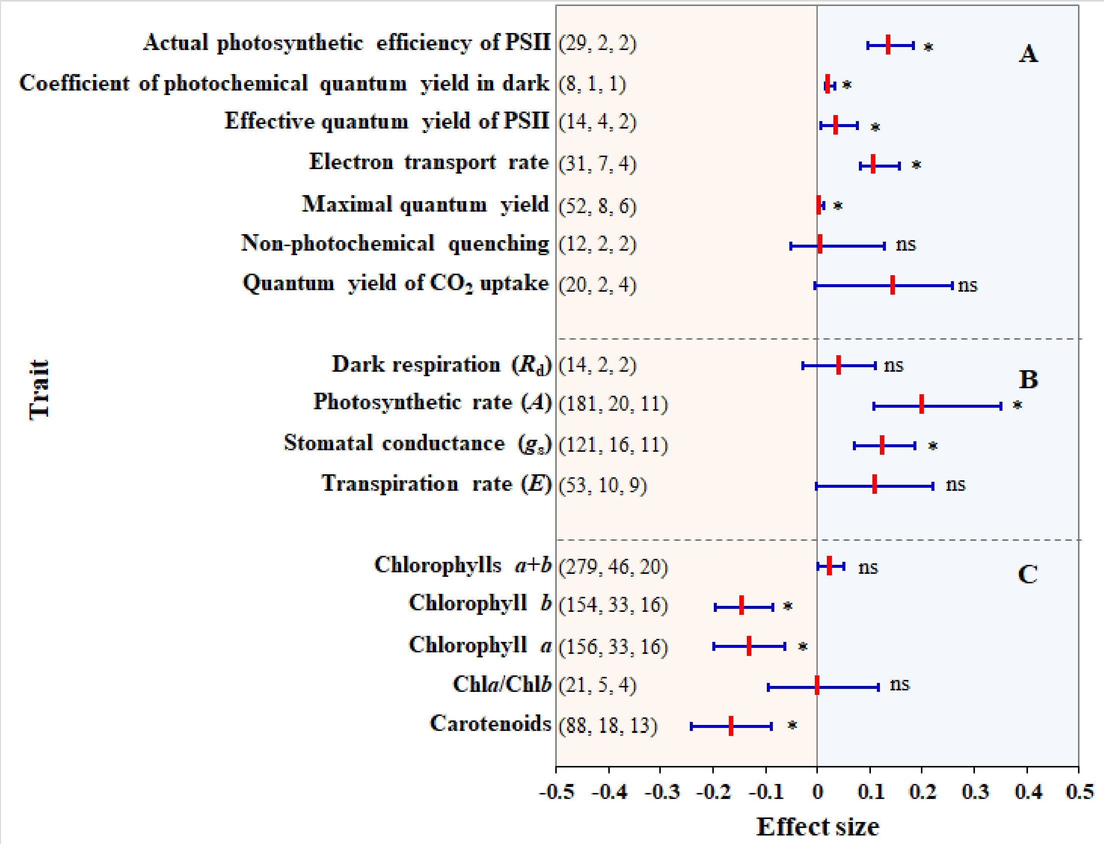


Fig. 2. Effect of cerium on different photosynthesis-related traits. The traits represent chlorophyll fluorescence (A), gas exchange (B), and photosynthetic pigments (C). Symbols indicate the mean natural log response ratio of cerium application relative to control group (zero cerium dose), while the bars around the mean value represent the bootstrapped 95% confidence intervals (CIs). * next to CI bars shows a statistically significant cerium effect relative to the control group, whereas “ns” shows a statistically non-significant effect. The numbers in parentheses indicate the observations number (sample size), studies number, and species number respectively (from left to right). The corresponding plot indicating percent difference from the control is provided in Supplementary Materials 2 (Fig. S9).

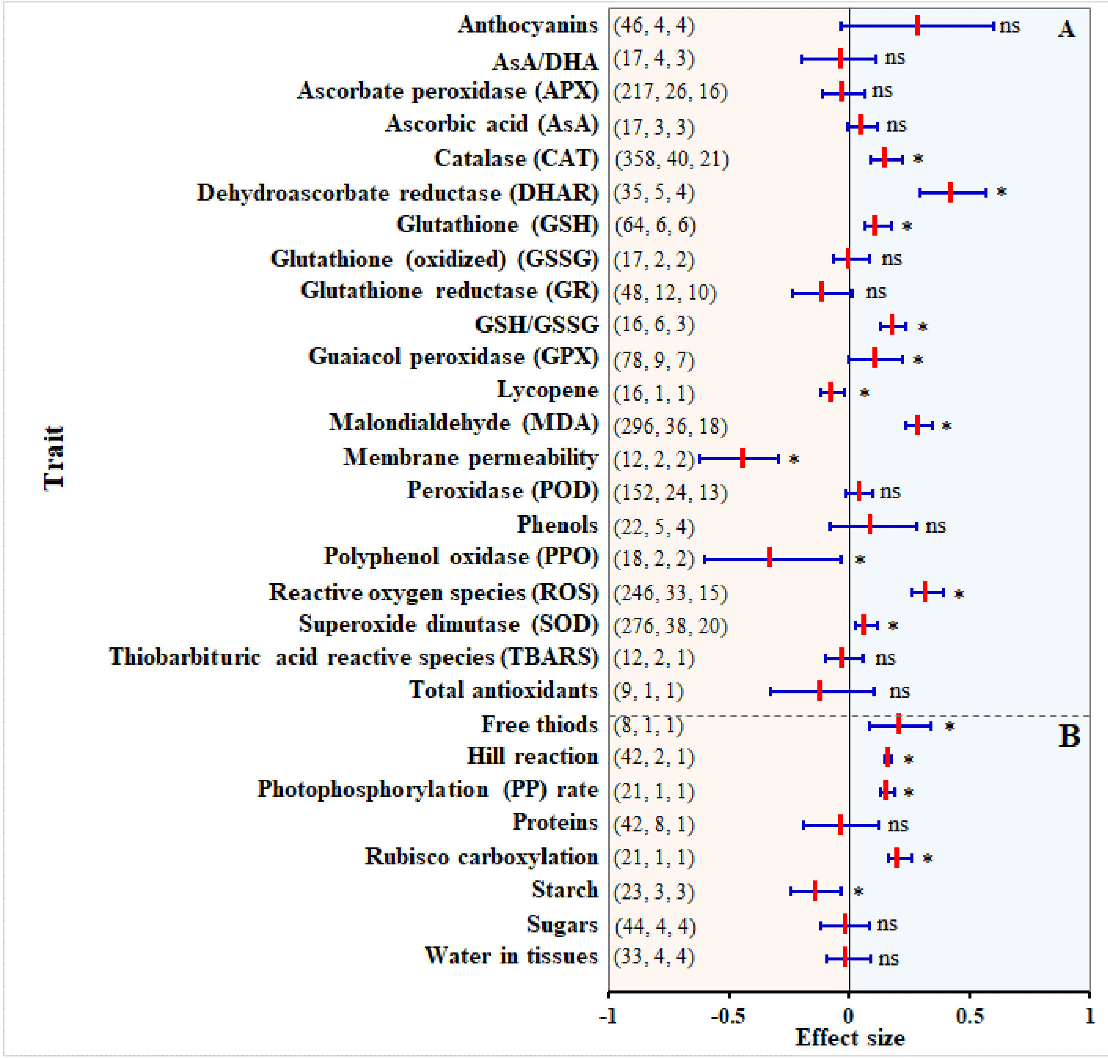


Fig. 3. Effect of cerium on biochemical traits. The traits represent defense system (A) and other stress-related biochemical traits (B). Symbols indicate the mean natural log response ratio of cerium application relative to control group (zero cerium dose), while the bars around the mean value represent the bootstrapped 95% confidence intervals (CIs). * next to CI bars shows a statistically significant cerium effect relative to the control group, whereas "ns" shows a statistically non-significant effect. The numbers in parentheses indicate the observations number (sample size), studies number, and species number respectively (from left to right). The corresponding plot indicating percent difference from the control is provided in Supplementary Materials 2 (Fig. S10).

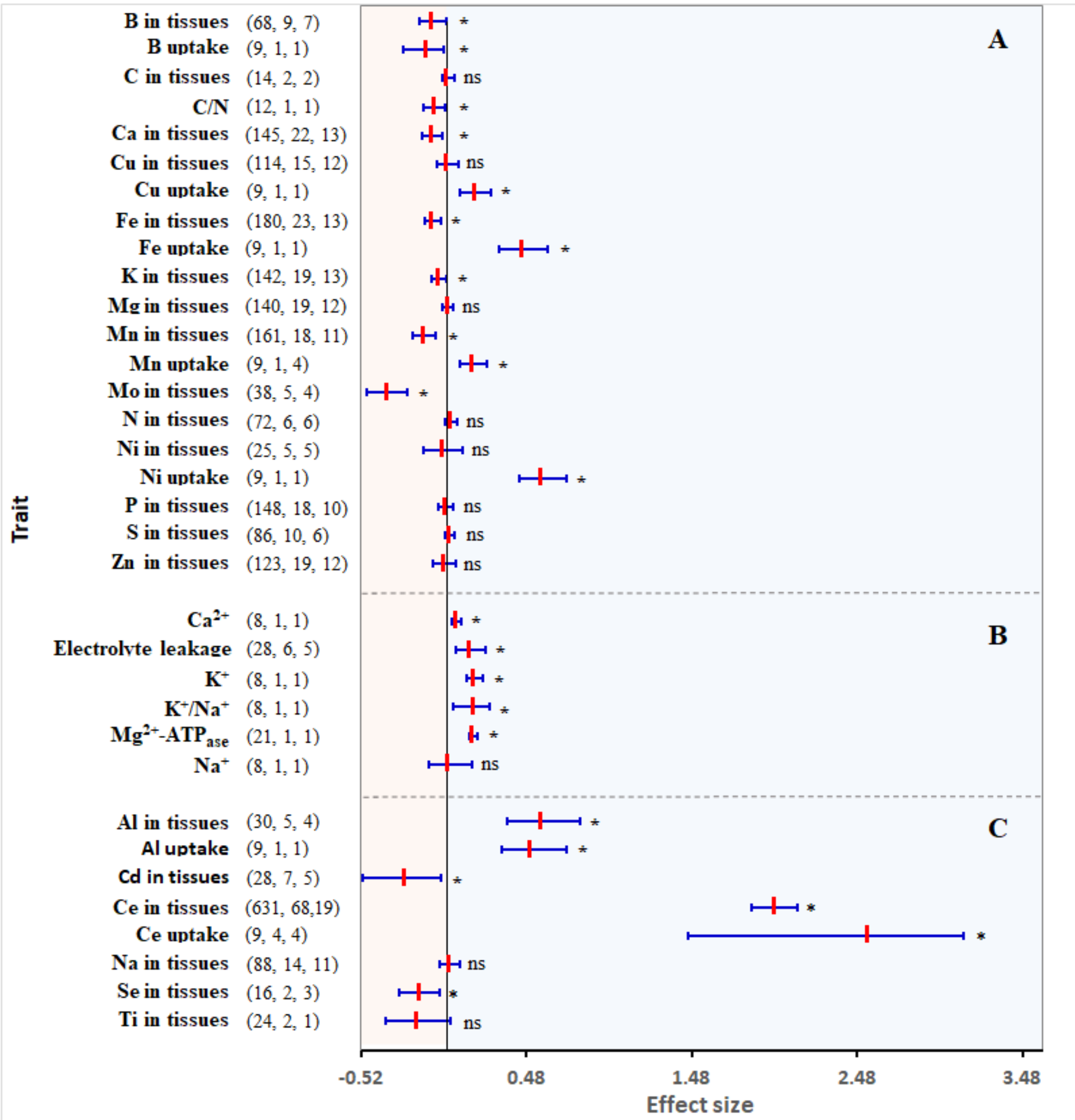


Fig. 4. Effect of cerium on elemental traits. The traits represent micro- and macro-nutrients essential for plant growth (A), mineral (ion) balance (B), and non-essential elements (C). Symbols indicate the mean natural log response ratio of cerium application relative to the control group (zero cerium dose), while the bars around the mean value represent the bootstrapped 95% confidence intervals (CIs). * next to CI bars shows a statistically significant cerium effect relative to control group, whereas "ns" shows a statistically non-significant effect. The numbers in parentheses indicate the observations number (sample size), studies number, and species number respectively (from left to right). The corresponding plot indicating percent difference from the control is provided in Supplementary Materials 2 (Fig. S11).

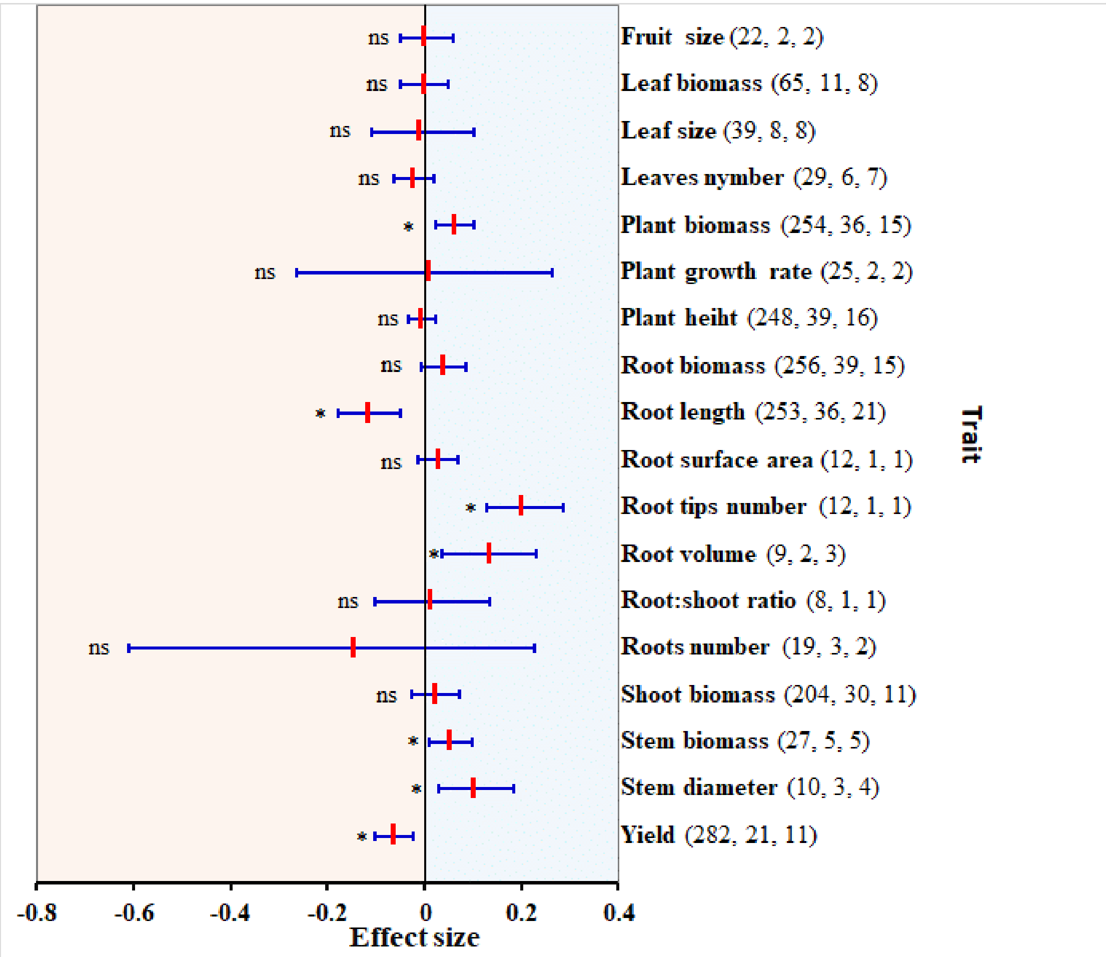


Fig. 5. Effect of cerium on different traits related to growth, productivity, and yields. Symbols indicate the mean natural log response ratio of cerium application relative to control group (zero cerium dose), while the bars around the mean value represent the bootstrapped 95% confidence intervals (CIs). * next to CI bars shows a statistically significant cerium effect relative to the control group, whereas “ns” shows a statistically non- significant effect. The numbers in parentheses indicate the observations number (sample size), studies number, and species number respectively (from left to right). The corresponding plot indicating percent difference from the control is provided in Supplementary Materials 2 (Fig. S12).

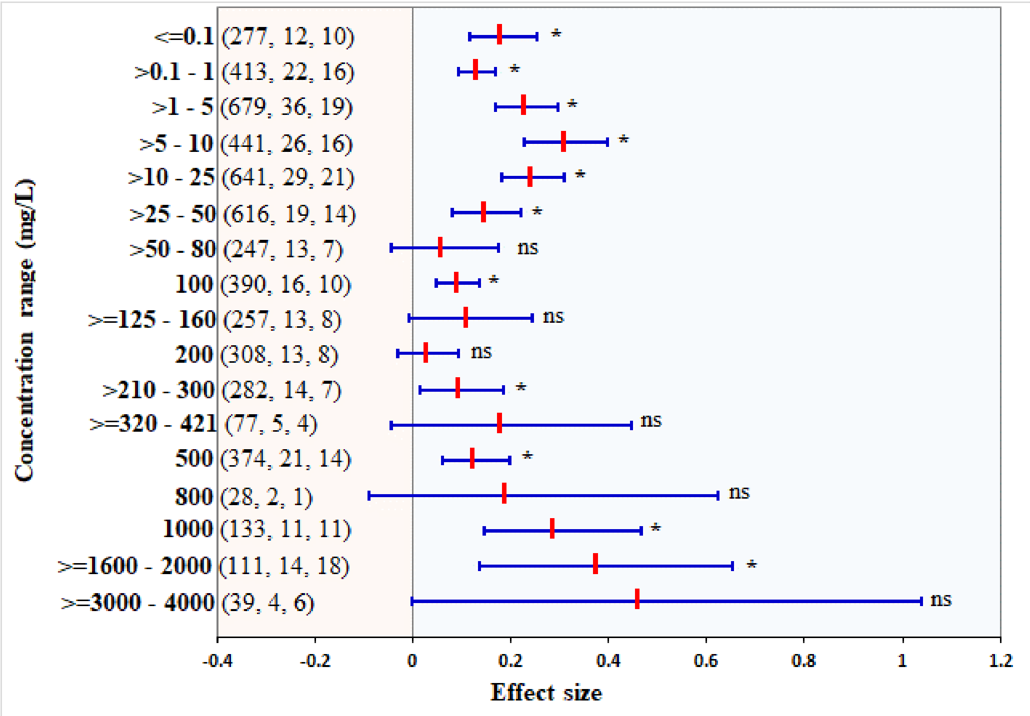


Fig. 6. Overall effect of cerium on plants (all traits pooled) as a function of different concentration ranges. Symbols indicate the mean natural log response ratio of cerium application relative to the control group (zero cerium dose), while the bars around the mean value represent the bootstrapped 95% confidence intervals (CIs). * next to CI bars shows a statistically significant cerium effect relative to control group, whereas “ns” shows a statistically non-significant effect. The numbers in parentheses indicate the observations number (sample size), studies number, and species number respectively (from left to right). The corresponding plot indicating percent difference from the control is provided in Supplementary Materials 2 (Fig. S13). The effect of different concentrations is further partitioned to different sources of variation (see sections 3.4.2-3.4.8).

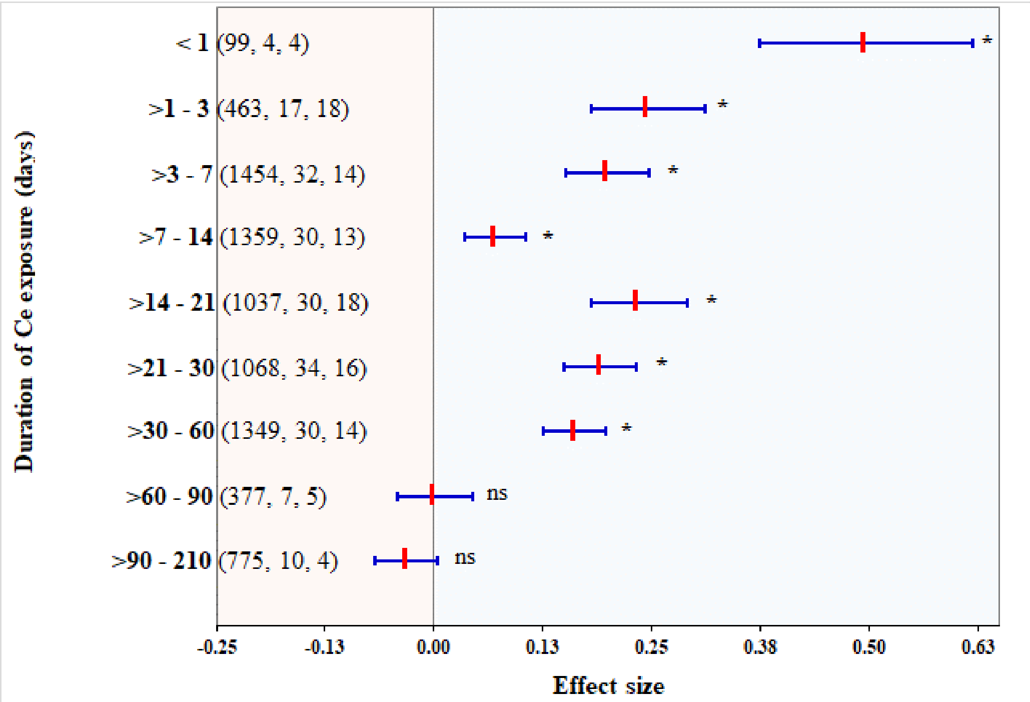


Fig. 7. Overall effect of cerium on plants (all traits pooled) as a function of exposure duration. Symbols indicate the mean natural log response ratio of cerium application relative to the control group (zero cerium dose), while the bars around the mean value represent the bootstrapped 95% confidence intervals (CIs). * next to CI bars shows a statistically significant cerium effect relative to control group, whereas “ns” shows a statistically non-significant effect. The numbers in parentheses indicate the observations number (sample size), studies number, and species number respectively (from left to right). The effect of different exposure durations is further partitioned to different sources of variation (see section 3.5).

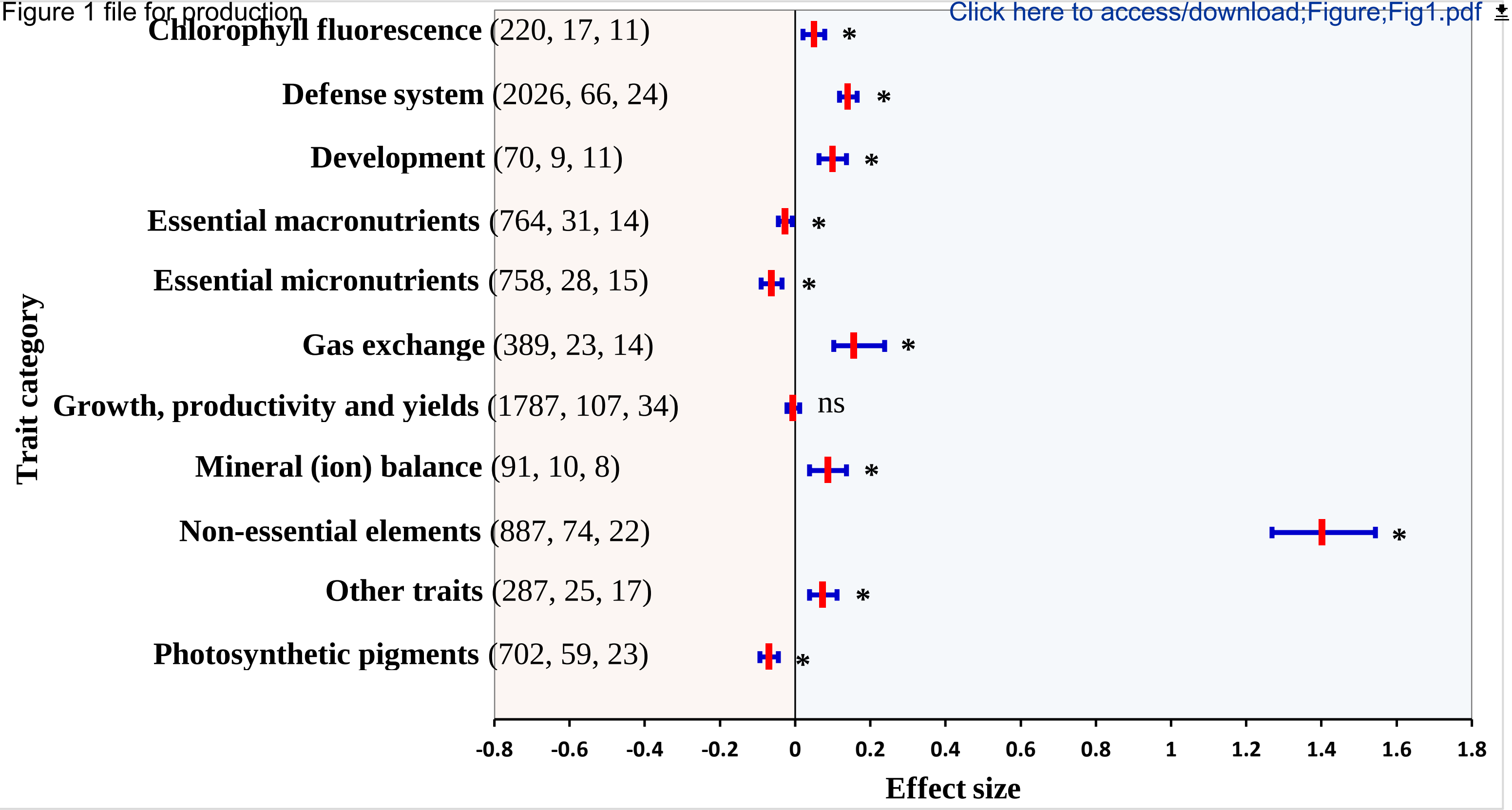

Chlorophyll fluorescence (220, 17, 11)
*
Defense system (2026, 66, 24)
*
Development (70, 9, 11)
*
Essential macronutrients (764, 31, 14)
*
Essential micronutrients (758, 28, 15)
*
Gas exchange (389, 23, 14)
*
Growth, productivity and yields (1787, 107, 34)
ns
Mineral (ion) balance (91, 10, 8)
*
Non-essential elements (887, 74, 22)
*
Other traits (287, 25, 17)
*
Photosynthetic pigments (702, 59, 23)
*
Trait category
-0.8
-0.6
-0.4
-0.2
0
0.2
0.4
0.6
0.8
1
1.2
1.4
1.6
1.8
Effect size

Figure 2 file for production

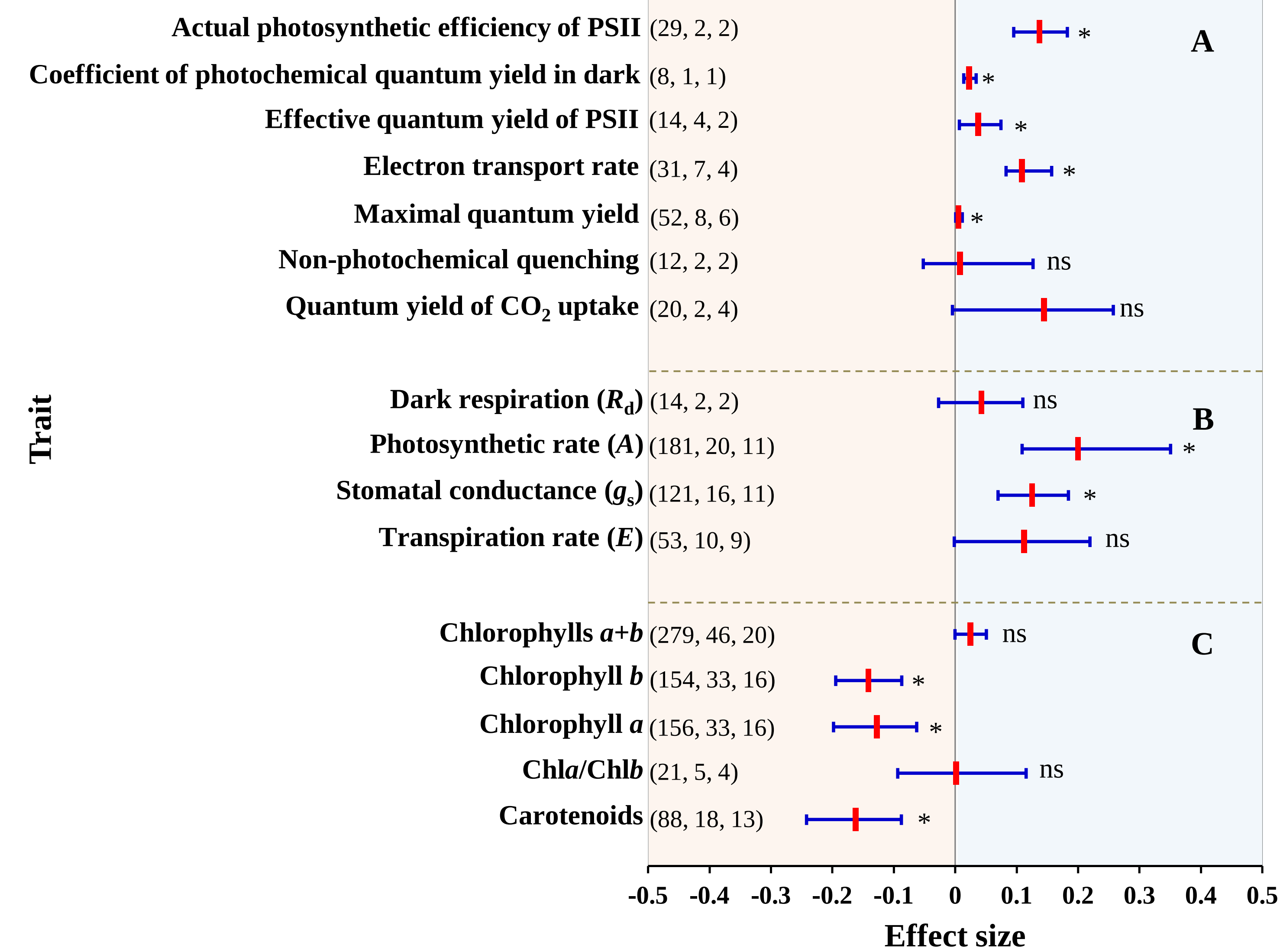
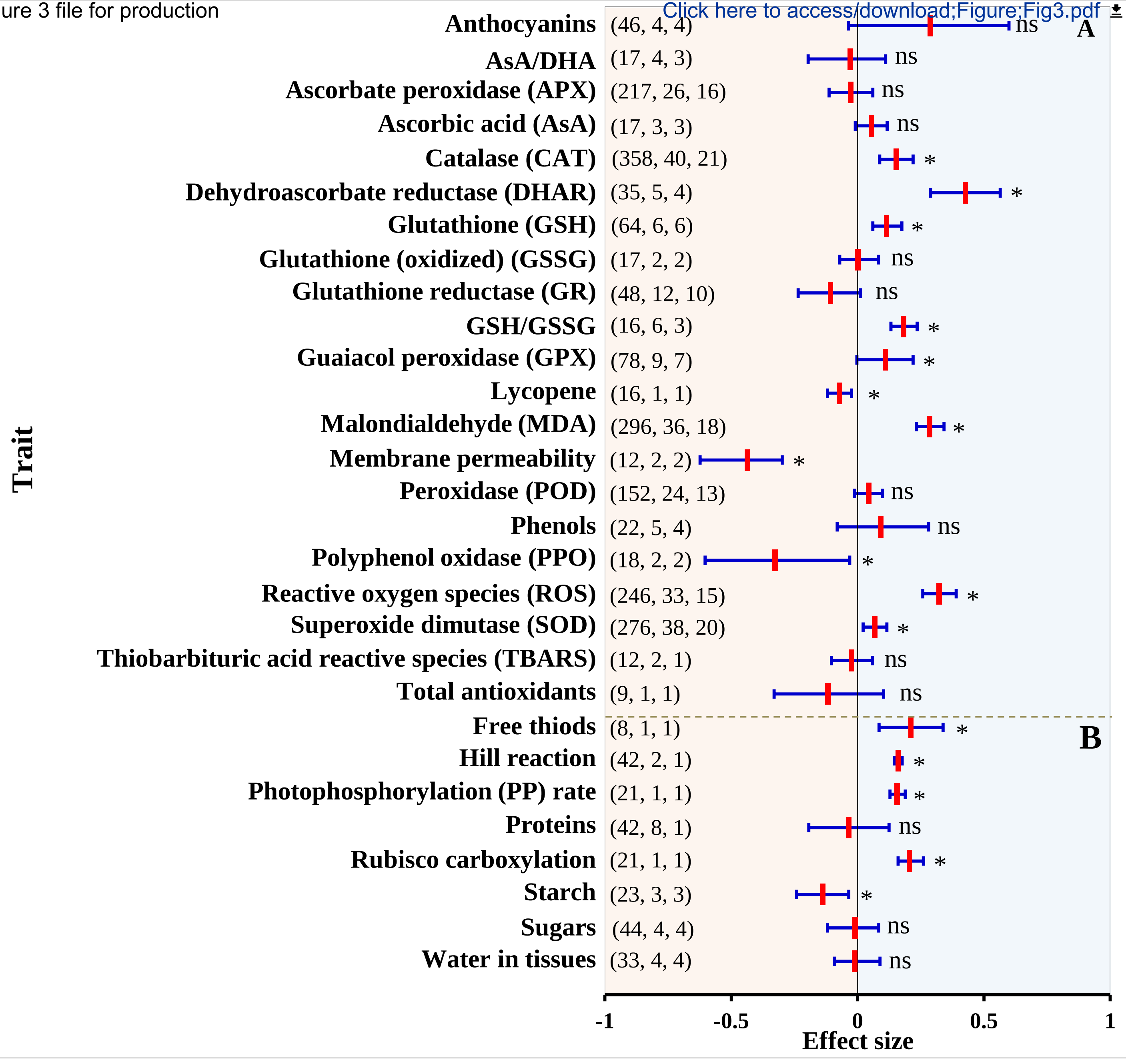
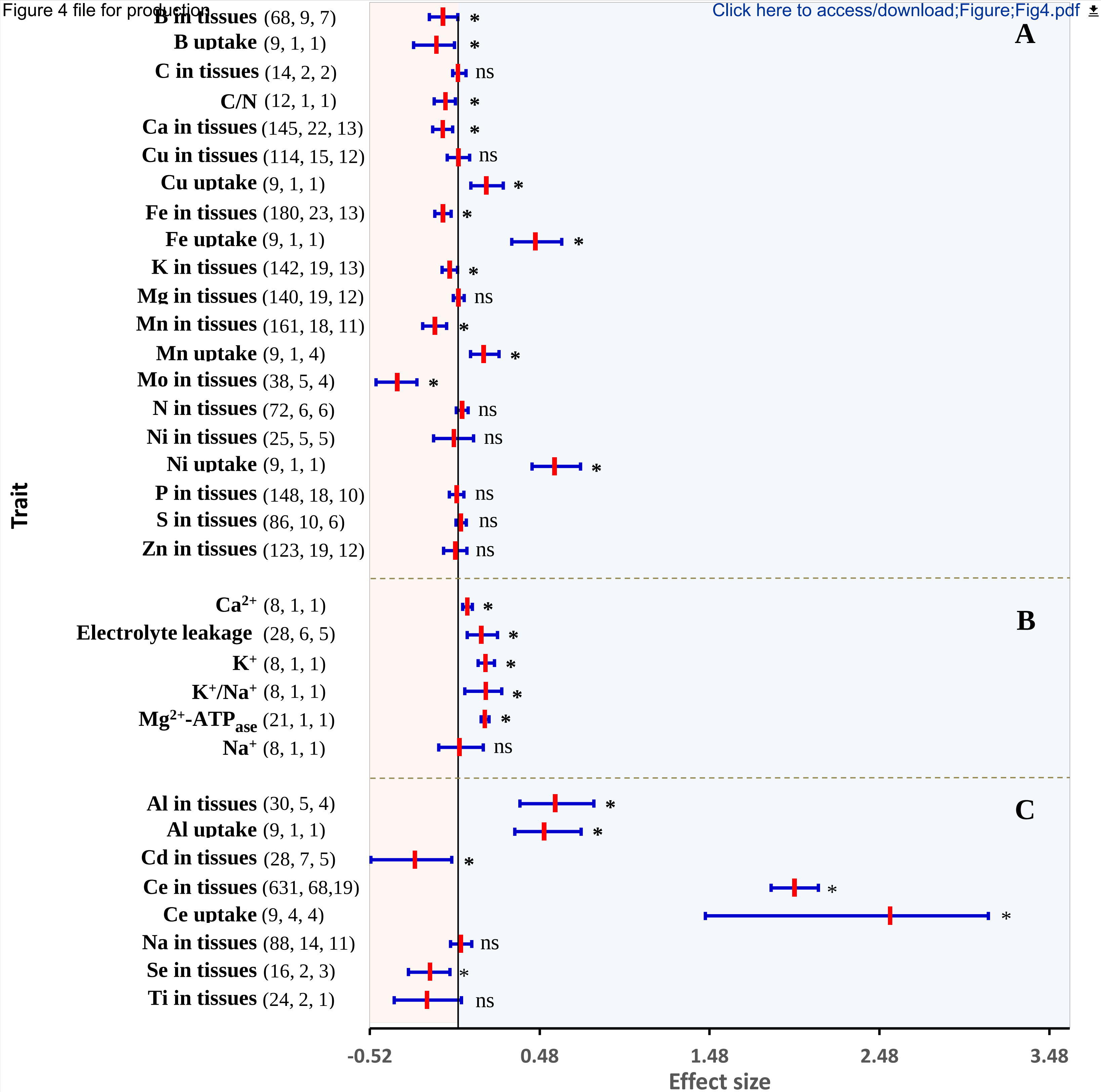
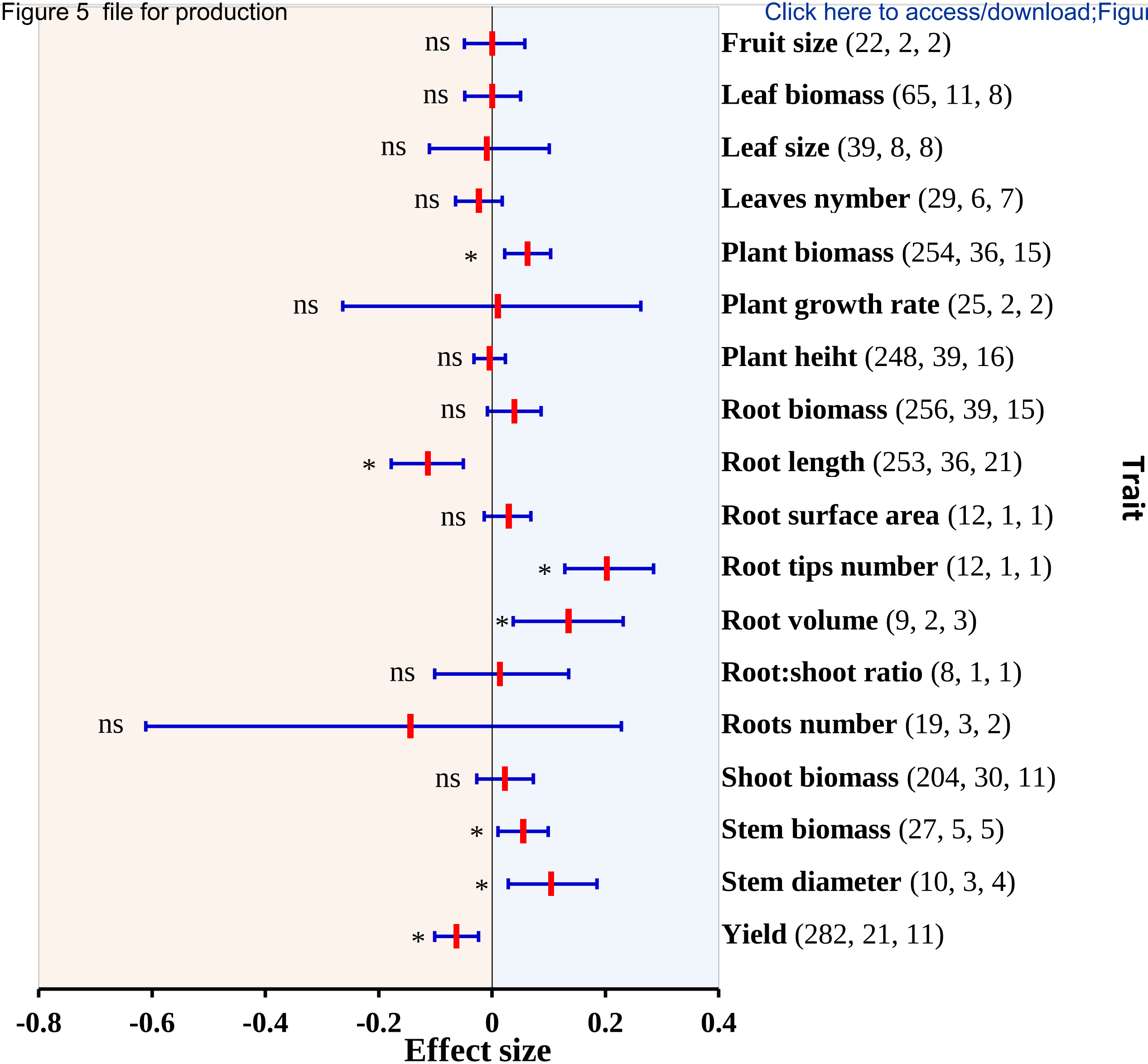
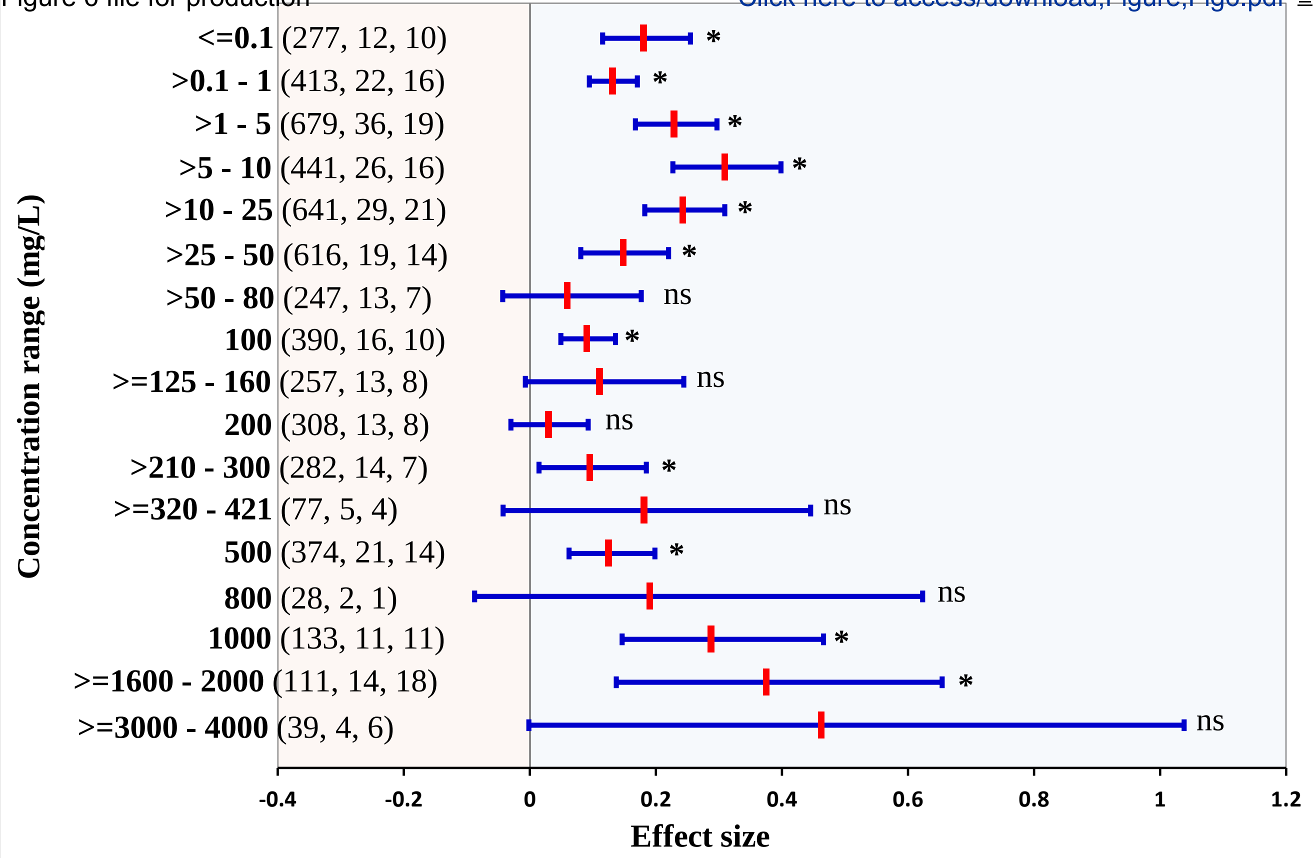


Figure 3 file for production




A
B in tissues (68, 9, 7) *
B uptake (9, 1, 1) *
C in tissues (14, 2, 2) ns
C/N (12, 1, 1) *
Ca in tissues (145, 22, 13) *
Cu in tissues (114, 15, 12) ns
Cu uptake (9, 1, 1) *
Fe in tissues (180, 23, 13) *
Fe uptake (9, 1, 1) *
K in tissues (142, 19, 13) *
Mg in tissues (140, 19, 12) ns
Mn in tissues (161, 18, 11) *
Mn uptake (9, 1, 4) *
Mo in tissues (38, 5, 4) *
N in tissues (72, 6, 6) ns
Ni in tissues (25, 5, 5) ns
Ni uptake (9, 1, 1) *
P in tissues (148, 18, 10) ns
S in tissues (86, 10, 6) ns
Zn in tissues (123, 19, 12) ns
B
Ca^{2+} (8, 1, 1) *
Electrolyte leakage (28, 6, 5) *
K^+ (8, 1, 1) *
K^+/Na^+ (8, 1, 1) *
Mg^{2+}-ATP_{ase} (21, 1, 1) *
Na^+ (8, 1, 1) ns
C
Al in tissues (30, 5, 4) *
Al uptake (9, 1, 1) *
Cd in tissues (28, 7, 5) *
Ce in tissues (631, 68,19) *
Ce uptake (9, 4, 4) *
Na in tissues (88, 14, 11) ns
Se in tissues (16, 2, 3) *
Ti in tissues (24, 2, 1) ns
Trait
-0.52
0.48
1.48
2.48
3.48
Effect size


ns
Fruit size (22, 2, 2)
ns
Leaf biomass (65, 11, 8)
ns
Leaf size (39, 8, 8)
ns
Leaves nymber (29, 6, 7)
*
Plant biomass (254, 36, 15)
ns
Plant growth rate (25, 2, 2)
ns
Plant heiht (248, 39, 16)
ns
Root biomass (256, 39, 15)
*
Root length (253, 36, 21)
ns
Root surface area (12, 1, 1)
*
Root tips number (12, 1, 1)
*
Root volume (9, 2, 3)
ns
Root:shoot ratio (8, 1, 1)
ns
Roots number (19, 3, 2)
ns
Shoot biomass (204, 30, 11)
*
Stem biomass (27, 5, 5)
*
Stem diameter (10, 3, 4)
*
Yield (282, 21, 11)
Trait
-0.8
-0.6
-0.4
-0.2
0
0.2
0.4
Effect size



<=0.1 (277, 12, 10) *
>0.1 - 1 (413, 22, 16) *
>1 - 5 (679, 36, 19) *
>5 - 10 (441, 26, 16) *
>10 - 25 (641, 29, 21) *
>25 - 50 (616, 19, 14) *
>50 - 80 (247, 13, 7) ns
100 (390, 16, 10) *
>=125 - 160 (257, 13, 8) ns
200 (308, 13, 8) ns
>210 - 300 (282, 14, 7) *
>=320 - 421 (77, 5, 4) ns
500 (374, 21, 14) *
800 (28, 2, 1) ns
1000 (133, 11, 11) *
>=1600 - 2000 (111, 14, 18) *
>=3000 - 4000 (39, 4, 6) ns
Concentration range (mg/L)
-0.4
-0.2
0
0.2
0.4
0.6
0.8
1
1.2
Effect size

Figure 7 file for production

Click here to access/download;Figure;Fig7.pdf