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The rare earth element (REE) lanthanum (La) induces hormesis in plants

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Abstract: Lanthanum is a rare earth element (REE) which has been extensively studied due to its wide application in numerous fields with a potential accumulation in the environment. It has long been known for its potential to stimulate plant growth within a hormetic-biphasic dose response framework. This article provides evidence from a series of high resolution studies published within the last two decades demonstrating a substantial and significant occurrence of lanthanum-induced hormesis in plants. These findings suggest that hormetic responses should be built into the study design of hazard assessment study protocols and included in the risk assessment process. Hormesis also offers the opportunity to substantially improve cost benefit estimates for environmental contaminants, which have the potential to induce beneficial/desirable effects at low doses.

Keywords: dose-response; hormesis; lanthanum; risk assessment; U-shape curve

Capsule: The response of plants to lanthanum is often described by hormetic model

INTRODUCTION

26
27 Lanthanum¹ (La) is the lanthanide with the largest atomic radius. Fifteen lanthanides,
28 scandium (Sc), and yttrium (Y) are chemical elements of the periodic table which have been
29 defined by IUPAC as rare earth elements (REEs). Despite their name, these elements are not
30 particularly rare and can be found in well measurable concentrations in the crust of Earth.
31 REEs do not occur naturally at high concentrations in the environment but may occur at high
32 concentrations due to their utilization by and application within a wide spectrum of fields,
33 including agriculture, industry and medicine (García-Jiménez et al., 2017; Hu et al., 2016;
34 Lin et al., 2017; von Tucher and Schmidhalter, 2005).

35 Dose responses represent the backbone of toxicology and are necessary for assessing
36 the effects of pollutants. Dose response relationships are established for assessing risks and
37 deriving critical levels below which chemicals or pollutants do not pose a threat for adverse
38 effects. Throughout the 20th century, the prevailing belief was that the response of biological
39 organisms to chemical or environmental stressors increases linearly with increasing dose
40 (linear-no-threshold model) or remains neutral up to a certain threshold and then increases
41 linearly with increasing dose (threshold model) (Fig 1).

42 Hormesis is a biphasic dose response characterized by stimulation at low doses and
43 inhibition at high doses (Fig 1). While hormesis has a long history (Calabrese and Baldwin.,
44 1999; Stebbing, 1982), especially in the area of plant biology (Calabrese and Baldwin, 2000;
45 Calabrese and Blain, 2009), it has taken on renewed focus over the past several decades
46 (Abbas et al., 2017; Agathokleous, 2017; Belz and Piepho, 2017; Calabrese and Blain, 2011,
47 2009, Cedergreen et al., 2009, 2007; Agathokleous, 2018; Poschenrieder et al., 2013; Vargas-
48 Hernandez et al., 2017). A recent paper published in *Environmental Pollution* reports the
49 results from an experiment where the effects of La pollution are assessed in soybean
50 seedlings under different acid rain scenarios (Zhang et al., 2017). Although this study focused

¹ From the ancient Greek word λανθάνειν (lanthanein), meaning “stay unnoticed” or “escape attention”

51 on the mechanisms underlying plant response, thanks to its robust experimental design, the
52 results show hormesis induced by the earth lanthanum ion (La^{3+}) and call for re-examination
53 of published literature dealing with the effects of La on plants.

54 ANALYSIS

55 Based on a re-examination of published literature, collective evidence for significant
56 La-induced hormetic responses is shown for 9 species and at least 4 cultivars/varieties in 20
57 studies published in 12 journals over the period 2001-2017; 13 of them (65%) were published
58 in the period 2012-2017.

59 Hormesis in a variety of species

60 *Taxus yunnanensis* cell cultures exposed to La^{3+} ($\leq 46.2 \mu\text{M}$, 28 d) displayed a
61 hormetic response (MAX at $5.8 \mu\text{M}$) in average cell growth rate (Fig 2A) and taxol
62 production (Wu et al., 2001). Desert broomrape cell cultures (*Cistanche deserticola* Ma)
63 exposed to La^{3+} ($\leq 0.1 \text{ mmol L}^{-1}$, 30 d) showed hormetic response (MAX at 0.01 mmol L^{-1})
64 in dry weight (Fig 2B) and phenylethanoid glycosides content and production (Ouyang et al.,
65 2003). Similarly, bush bean (*Phaseolus vulgaris* L.) treated with $\text{LaCl}_3 \leq 72 \mu\text{mol Kg}^{-1}$ and
66 spinach (*Spinacea oleracea* L.) treated with $\text{LaCl}_3 \leq 360 \mu\text{mol Kg}^{-1}$ for more than a month
67 showed MAX at $3.6 \mu\text{mol Kg}^{-1}$ (bean 110%, spinach 135%), however non-significant for
68 bean (von Tucher and Schmidhalter, 2005). Durum wheat (*Triticum durum* Desf.) treated
69 with La^{3+} ($\leq 10 \text{ mM}$, 9 d) showed hormesis in root length with MAX at 0.01 mM (Fig 2C),
70 although the stimulation at 0.01 and 0.1 mM did not appear at 6 and 12 days (d'Aquino et al.,
71 2009). Horseradish (*Armoracia rusticana* G.Gaertn.) had greater (114%) and lower (69%)
72 average cell size of fourth true leaf 6 days after treatment (DAT) with 30 or $80 \mu\text{M}$ LaCl_3
73 compared with $0 \mu\text{M}$ LaCl_3 (Wang et al., 2014a). When horseradish was exposed to 13 doses
74 ranging between 0 and 200 LaCl_3 in a field experiment conducted annually for five years,
75 hormetic dose-response relationship appeared in yield (Fig 2D), net photosynthetic rate (P_N),
76 chlorophyll content and peroxidase activity, with MAX at $35 \mu\text{M}$ (Wang et al., 2014a);

77 Supporting Information, Table S1). Rangpur lime plants (*Citrus limonia* Osbeck) also
78 showed significant stimulation in wet weight by 50 mg La chloride heptahydrate (LaCl_3
79 $7\text{H}_2\text{O}$) in contrast to significant inhibition by 100, 200 and 400 mg $\text{LaCl}_3 \cdot 7\text{H}_2\text{O}$, three weeks
80 after the treatments application (Turra et al., 2015).

81 **Hormesis in rice**

82 Hormesis was found multiple times in rice (*Oryza sativa* L.). Seedlings grown in red
83 soil and exposed to LaCl_3 (≤ 1200 mg Kg^{-1}) displayed hormesis with MAX at 30 mg Kg^{-1} in
84 plant height and tillers (Fig 2E) at 30 DAT, but not at 80 DAT, however MAX was non-
85 significant for tillers (Zeng et al., 2006). In other studies, hormesis was found in fresh root
86 weight (Fig 2F), length of total nodal root, number of nodal roots and number of total lateral
87 roots of nodal roots (Liu et al., 2013), and in soluble protein content and activity of
88 peroxidase (Fig 2G) and catalase in the roots (Liu et al., 2016) of seedlings exposed to La^{3+}
89 (≤ 1.5 mM, 13 d) with MAX at 0.05 or 0.1 mmol L^{-1} . When exposed to 0, 81.6, 1224.5 and
90 2449 μM LaCl_3 , rice displayed hormesis in P_N , stomatal conductance, Hill reaction rate,
91 apparent quantum yield (AQY) and carboxylation efficiency (CE) at different growth stages
92 and at different pH; stimulation occurred only at 81.6 μM (Wang et al., 2014b). Hormesis
93 appeared in the content of Mg, P, K, Ca, Mn, Fe and Ni, transcription of several chloroplast
94 ATPase subunit genes, activity of Mg^{2+} -ATPase, P_n , dry and fresh weight of leaves, leaf
95 area and relative growth rate in rice exposed to 0, 0.08, 1.2, and 2.4 mM La ($\text{LaCl}_3 \cdot 6\text{H}_2\text{O}$) for
96 15 d; MAX commonly occurred at 0.08 mM (Hu et al., 2016).

97 **Hormesis in soybean**

98 Hormesis was also frequently found in soybean (*Glycine max* L.). Seedlings treated
99 with La^{3+} (≤ 1.2 mM, 7 d) and simulated acid rain with pH 7.0, 4.5 or 3.5 showed hormesis in
100 chlorophyll content and main root length at all pH levels; in plant height, leaf area,
101 photochemical yield of photosystem II (Φ_{PSII}) and Hill reaction rate (Fig 2H) only at pH 7.0;
102 in initial fluorescence (F_0), dry weight of leaves and stem and dry weight of root at pH 7.0

103 and 4.5; and in P_n at pH 7.0 and 3.5 (Wen et al., 2011). In the same experimental design,
104 hormesis was found in Mg at pH 4.5; in nitrate reductase transcriptional level at pH 7.0 (Fig
105 2D); in K and Fe content at pH 7.0 and 4.5; and in nitrate reductase activity at all pH levels
106 (Xia et al., 2017). Under the same conditions, hormesis was found in multiple root endpoints:
107 amino acid content at pH 7.0; glutamine synthetase activity at pH 7.0 and 4.5; NO^{-3} content at
108 pH 7.0 and 3.5; glutamate dehydrogenase (DGH) activity at pH 4.5 and 3.5; nitrate reductase
109 activity and NH^{+4} content; and glutamine-oxoglutarate amino transferase (GOGAT) activity
110 (Fig 2J) and soluble protein content at all pH levels (Zhang et al., 2017). In the latter three
111 studies stimulation occurred at 0.08 mM. Hormesis was also found in P_N (Fig 2K), content of
112 Cu in roots, and content of Cu, Fe and Zn in shoots of seedlings treated with $\text{La}(\text{NO}_3)_3 \cdot 6\text{H}_2\text{O}$
113 (160 μM , 28 d), with significant stimulation at 5 and/or 10 μM (de Oliveira et al., 2015).

114 **Hormesis in broad bean**

115 Finally, several hormetic dose responses were found in and claimed for broad bean
116 (*Vicia faba* L.) too. Clear U-shape dose-responses were found in guaiacol peroxidase (GPX)
117 activity, heat shock protein 70 (HSP 70) level and endoprotease isozymes (Fig 2L) in roots of
118 seedlings exposed to $\text{La}(\text{NO}_3)_3$ (0-12 mg/L = 10.2-433 μg La/g root dry weight, 15 d) with
119 MAX at 0.5 or 1 mg/L (=74.9 or 108 $\mu\text{g/g}$), although with high variance (Wang et al., 2011).
120 In a further study, seedlings hydroponically cultured under 6 μmol cadmium chloride (CdCl_2)
121 L^{-1} and a range of $\text{La}(\text{NO}_3)_3$ levels (0-480 mg/L, 15 d) showed hormesis in Cd content,
122 superoxide dismutase (SOD) activity, GPX activity, catalase activity, ascorbate peroxidase
123 (APX) isozyme activity and HSP 70 production (Fig 2M) in the roots; stimulation occurred
124 between 2 and 120 for all endpoints and was significant for all endpoints except APX activity
125 (Wang et al., 2012a). Under the same experimental conditions, leaf K and Mo content and
126 APX activity (Fig 2N) showed clear hormetic responses with significant effects in the low
127 dose region being observed in the range 8-120 mg/L; catalase activity also showed U-shaped
128 dose response but with no any significant effects (Wang et al., 2012c). Root HSP 70

129 production showed also a *U*-shaped dose-response (Fig 2O) when seedlings were exposed to
130 9 doses of $\text{La}(\text{NO}_3)_3$ (0-16 mg L^{-1} , 10 d), with MAX at 0.5 mg L^{-1} albeit non-statistically
131 significant (Wang et al., 2012b). In a different study, seedlings exposed to 5 low doses of
132 $\text{La}(\text{NO}_3)_3$ (0-8 mg L^{-1} , 20 d), showed significant effects, only at 2 or 4 mg L^{-1} , that would
133 contrast the expected effects by high doses in root Cu content, tail length of root tips (Fig 2P)
134 and apical leaves nuclei, and tail moment of root tips and apical leaves nuclei (Wang et al.,
135 2012d).

136 CONCLUSIONS

137 This study provides evidence from a series of recent papers showing that hormesis
138 commonly occurs in a variety of plants in response to La. These findings build upon a strong
139 historical research foundation demonstrating La-induced hormesis in plants during the last
140 three decades of the 20th century (Hu et al., 2004).

141 The effects at low La doses may be driven by micro-interference to the molecular
142 structure of vitronectin-like protein (VN), whereas the effects of high La doses may be upon
143 binding to VN with a formation of stable La-VN complexes that leads to damage in the VN
144 molecular structure (Wang et al., 2017).

145 The collective evidence presented here challenges the research community to assess
146 the nature of the dose response over the full dose-response continuum and with appropriate
147 dose spacing especially in the low dose zone. It also suggests the need to investigate whether
148 a prior exposure to low doses of La, which induce biological stimulation, can protect against
149 a subsequent exposure to higher doses of La, so called preconditioning (Calabrese, 2016a,
150 2016b).

151 La-induced hormesis in plants, as well as the broader hormetic literature, indicate that
152 hormesis should be incorporated within the hazard and risk assessment process for deriving
153 environmental quality standards. REEs, including La, can be utilized in agricultural practice

154 (Ozaki et al., 2000; Tommasi and D'Aquino, 2017; Xu et al., 2002; Zhang et al., 2015), and,
155 thus, hormesis should be incorporated into the agricultural practice as well for the optimum
156 beneficial effects within an optimized cost benefit framework.

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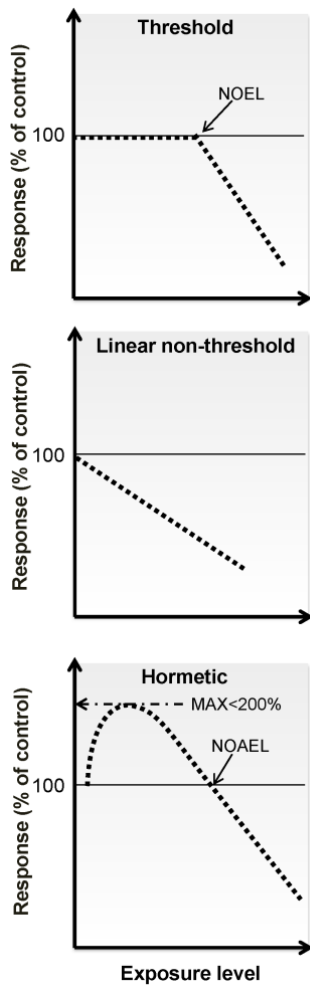
303 **Captions**

304 **Fig 1.** Hypothetical threshold, linear non-threshold (LNT), and hormetic dose-response
305 models. The maximum stimulatory response (MAX) in the hormetic model is commonly
306 below 200%. The toxicological thresholds above which adverse effects appear in the
307 threshold and hormetic models are indicated by no-observed-effects-level (NOEL) and no-
308 observed-adverse-effects-level (NOAEL).

309
310 **Fig 2.** Typical examples of hormetic dose responses from published literature. When needed,
311 response data were estimated from figures of reviewed articles using image analysis software
312 (Adobe Photoshop CS4 Extended v.11, Adobe Systems Incorporated, CA, USA).

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330 **Fig 1.**



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