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Human and veterinary antibiotics induce hormesis in plants: Scientific and regulatory issues and an environmental perspective

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ABSTRACT

Veterinary and human pharmaceuticals have been widely used in the developed world, thus increasing their accumulation in the environment and thereby posing ecological risks. Earlier studies report that active pharmaceutical ingredients induce hormesis in plants, i.e. at low doses may enhance plant health whereas at high doses may suppress plant vigor. There is hitherto no study critically reviewing the effects of antibiotics on plants within a hormetic context despite effects of low doses on plants can have implications to animals, including humans, and to ecological processes. This study critically reviews for first time antibiotic-induced hormesis in plants, both quantitatively and qualitatively. Hormesis was induced by several antibiotics in a variety of species and endpoints. The maximum stimulatory response (MAX) was commonly < 1.5-fold the control response and the distance from MAX to no-observed-adverse-effect level (NOAEL) was commonly up to 10–fold. Further quantitative and qualitative evaluations are provided and discussed in relation to scientific and regulatory aspects. Low doses of antibiotics are equally important as high doses as they can negatively affect plants, depending on plant tissues and the time tissues are subject to exposure. Antibiotic-induced hormesis in plants provides a significant environmental perspective and should be incorporated into the hazard and risk assessment process.

Capsule: Common antibiotics released in the environment induce hormesis in plants, urging for re-examination of the risk assessment practices by worldwide regulatory agencies.

1. Introduction

Common veterinary and human antibiotics have been widely used in the developed world. Projections for the global economy for the period 2017–2050 suggest that the global increases in healthcare costs may be 0.33 trillion USD to nearly 1.2 trillion USD per year by 2050 due to resistance of microbes to antimicrobials (World Bank Group, 2017).

Overuse of medical services is now widely recognized, especially in high income countries (Brownlee et al., 2017). It is also noted that unsupervised misuse and overuse of common pharmaceuticals such as antimicrobials, antidepressants, and combination-analgesics often occurs in the developed world (Adams, 2011; Hanlon et al., 2011; Jureidini and Tonkin, 2006; Kluonaitis et al., 2017; World Bank Group, 2017). Misuse and overuse of pharmaceuticals by humans for personal healthcare but also for veterinary purposes, especially in the developed world with high meat demands too, increase the likelihood of accumulation in environmental wastes (Ashfaq et al., 2017; Bártíková et al., 2016; Kümmerer, 2009a, 2009b; Rastogi et al., 2018). Hence, such pharmaceuticals pose an environmental contamination issue (Awad et al., 2014; Küster and Adler, 2014; Li et al., 2015; Rehman et al., 2015; Watkinson et al., 2009).

Ecological risks from pharmaceuticals were identified in the later decades of the 20th century (Larsson, 2014). However, potential ecological risks of pharmaceutical waste accumulation in the environment remain underexplored and not well understood (Ashfaq et al., 2017; Christou et al., 2018; Kümmerer, 2009a, 2009b). Due to concerns of potential ecological hazards, some institutes have considered them

Abbreviations: EPA, Environmental Protection Agency; MAX, maximum stimulatory response in the low-dose zone of a dose-response relationship; NOAEL, no-observed-adverse-effect level derived from a complete dose-response relationship

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within an ecological risk assessment context (e.g. Korea Environment Institute, Park et al., 2007). Likewise, some regulatory authorities have created guidelines for ecological risk assessment of human-used pharmaceuticals as in the case of the European Medicines Agency (Ågerstrand et al., 2015). Due to methodological difficulties, e.g. large number of present active pharmaceutical ingredients in use, and uncertainties related to lack of spatiotemporal variability (Kostich and Lazorchak, 2008; Kostich et al., 2010, 2014), leading regulatory authorities, such as the US Environmental Protection Agency (EPA), have not incorporated the potential effects of pharmaceuticals by the means of a complete dose-response continuum into the process of ecological risk assessment.

Dose responses are studied for scientific and regulatory purposes, i.e. for guiding science-based risk assessment. The nature of the dose response in the low dose region has been debated for several decades. Although it was previously thought that there was a neutral response or a decreasing response with increasing dose in the low dose region, it is now extensively documented that low doses of stressors typically upregulate biological/physiological adaptive functions, resulting in nonlinear dose response relationships with potential positive (i.e., beneficial) responses in the low dose region and negative responses at higher doses (Calabrese, 2017; Calabrese, 2015; Calabrese, 2013; Calabrese and Blain, 2005, 2011; Calabrese and Blain, 2009; Calabrese and Mattson, 2017; Cedergreen et al., 2007; Hashmi et al., 2014). This phenomenon (Fig. 1) is called hormesis (Agathokleous et al., 2018a; Calabrese et al., 2007). Hormetic studies for plants are now accumulating, showing that chemicals and physical stressors induce hormesis in numerous plant species and endpoints, including yields and photosynthesis (Belz et al., 2018; Belz et al., 2008; Belz and Duke, 2017; Calabrese and Blain, 2009; Cedergreen, 2008; Cedergreen and Olesen, 2010; Cedergreen et al., 2007; Poschenrieder et al., 2013; Vargas-Hernandez et al., 2017). More recently, it was shown that environmental factors, including gaseous air pollutants and rare earth elements, can induce hormesis in plants (Agathokleous, 2018; Agathokleous et al., 2018b, 2018c).

Pharmaceuticals from wastes can be absorbed by plants, accumulate in the tissues (Bassil et al., 2013; Herklotz et al., 2010), and eventually enter the food web (Fig. 2). This can have severe consequences to humans and other animals. What is more fascinating is the potential of common veterinary and human pharmaceuticals to affect plants. Would anyone have imagined in the 1950s that paracetamol, used by humans, against e.g. headaches and pain, could significantly affect plant biology? It is now known that this is the case (An et al., 2009).

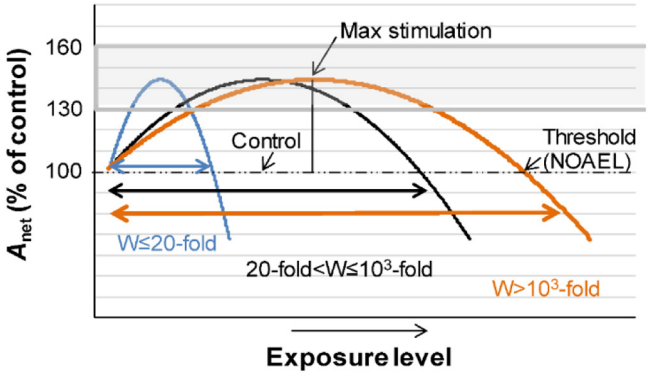

Fig. 1. Hypothetical examples of typical hormetic responses in dose-response relationship studies. Net photosynthetic rate (A_{net}) is used as reference integrative endpoint. Three curves show the relative distribution of hormetic zones. The upper limit of the hormetic dose zone (W) is the "classical" toxic threshold which is called no-observed-adverse-effect level (NOAEL). The maximum stimulation is usually lower than 200% of control and within the range of 130–160% of control (grey rectangle), and W is usually about 10- to 20-fold with some exceptions where it exceeds 1000-fold (Calabrese, 2015; Calabrese, 2013; Calabrese and Blain, 2005, 2011; Calabrese and Blain, 2009; Cedergreen et al., 2007).

Phytotoxic effects (high exposures and adverse effects) of antibiotics and other pharmaceuticals have been reviewed in particular detail (Bártíková et al., 2016; Christou et al., 2018; Pan and Chu, 2017). However, while low exposures and hormesis have been considered (Bártíková et al., 2016; Christou et al., 2018; Pan and Chu, 2017), there is hitherto no detailed or integrated evaluation. Given that data regarding hormesis are available, a critical examination of hormesis induced by pharmaceuticals in plants is needed due to novel developments in the field of dose response with significant implications for scientific and policy practices.

For first time, this study aims to critically review, document, qualify, and quantify hormetic dose responses induced by antibiotics in plants, and provides an important integration of data and theory to identify and characterize critical aspects of the source-exposure-health outcome continuum.

2. Hormesis induced by antibiotics in plants

Hormetic responses of plants to human/veterinary antibiotics were first reported nearly two decades ago (Migliore et al., 2000). In particular, the aquatic weed *Lythrum salicaria* L. displayed hormetic responses of growth endpoints in a 35-day exposure to flumequine (Fig. 3A), a Quinolone antibiotic (Migliore et al., 2000). This was the case for growth endpoints of cucumber, Cucumis sativus L. (Fig. 3B), lettuce, *Lactuca sativa* L., and radish, *Raphanus sativus* L., plants which showed hormetic-like response to enrofloxacin, a fluoroquinolone antibiotic, after 10, 20, or 30 days of exposure, in a subsequent experiment (Migliore et al., 2003). These were the first studies showing hormesis induced by common human/veterinary antibiotics, providing an important perspective upon which to develop subsequent studies.

Subsequent studies published within the last ten years provide significant evidence supporting the initial findings. Overall, hormesis was induced by common human/veterinary antibiotics (e.g. amoxicillin, ampicillin, penicillin, sulfadiazine, sulfadimethoxine, tetracyclines) in several species (*Brassica napus* L., *Capsella bursa-pastoris* (L.) Medik., *L. salicaria* L., *Triticum aestivum* L., *Zea mays* L.), for a series of biochemical, growth, production, and physiology-related endpoints (Fig. 3; Electronic Supplementary materials) (Jin et al., 2009; Liu et al., 2013; Migliore et al., 2000, 2003, 2010a, 2010b; Minden et al., 2017; Opriş et al., 2013; Pan and Chu, 2016; Xie et al., 2010, 2011a, 2011b; Zhang et al., 2017).

To assess antibiotic-induced hormesis, data were extracted from tables or figures (Adobe Photoshop CS4 Extended v.11, Adobe Systems Incorporated, CA, USA) of 13 retrieved peer reviewed research articles suggestive of antibiotic-induced hormesis, which often incorporated multi-factorial experimental designs (Jin et al., 2009; Liu et al., 2013; Migliore et al., 2000, 2003, 2010a, 2010b; Minden et al., 2017; Opriş et al., 2013; Pan and Chu, 2016; Xie et al., 2010, 2011a, 2011b; Zhang et al., 2017). The response to antibiotic treatment (% of control response) was calculated as $Response = \mu_C/\mu_T \times 100$, where μ_c is the mean value of μ of the control and μ_T is the mean value of μ at an antibiotic dose/concentration level T. Wherever possible, dose-response relationships were developed, and the no-observed-adverse-effect level (NOAEL) was estimated.

Following the protocol of the Hormesis Database (Calabrese and Blain, 2011), a database with 240 hormetic-like entries was created (Electronic Supplementary materials). These entries reflect 14 plant species and > 15 antibiotics. Approximately 40 unique endpoints are included, while 65% of the entries are growth and production endpoints. The geometric mean of the maximum stimulatory response (MAX) was 124% (Table 1). The NOAEL could be estimated for 138 dose-response relationships. The geometric mean of the MAX to NOAEL distance was 5.6. Only one dose-response relationship (0.7%) had MAX to NOAEL distance > 100, and only one (0.4%) had MAX > 200%. The

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