

ORIGINAL ARTICLE

Probiotics against alleviation of lead toxicity: recent advances

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ITX120219A04 • Received: 19 September 2019 • Accepted: 03 October 2019

ABSTRACT

Lead is a toxic heavy metal and there is no specific, safe and efficacious therapeutic management of lead toxicity. Scientific literature reported that some probiotic microorganisms alleviated experimentally induced lead toxicity. The present review attempts to collate the experimental studies on probiotics with ameliorative effects. Literature survey revealed that four (4) types of probiotic microorganisms exhibited significant protection from lead toxicity in experimental pre-clinical studies. No clinical study with significant outcome was found in the literature. From the outcomes of the preclinical studies it appears that probiotics are prospective for alleviation and treatment of lead toxicity.

KEY WORDS: probiotics; lead; lactobacilli; oxidative stress

Introduction

Lead (Pb) is a non-essential heavy metal of considerable toxicity with deleterious effect on most organ systems of humans and animals resulting in multisystem disease. It is considered as a potential worldwide threat to the environment. It undergoes biomagnification in the food chain. Environmental or occupational lead exposure in humans can produce chronic ill-health effects including hematological, hepatic, renal, pulmonary, nervous, cardiovascular, musculoskeletal and reproductive dysfunctions. Lead is also recognized as human carcinogen by the International Agency for Research on Cancer (IARC). Lead toxicity and its alleviation is a highly researched and recurrently published issue; nevertheless, complete control and prevention of lead exposure still appear far from being attained (Flora *et al.* 2012; Assi *et al.* 2016).

The most commonly used therapeutic strategy for heavy metal poisoning is chelation therapy to promote metal excretion. However, chelators for Pb toxicity are themselves reported to have a number of different safety and efficacy concerns. Chelating agents such as CaNa₂EDTA and meso-2,3-dimercaptosuccinic acid

(DMSA) have been reported to have protective effects against Pb toxicity. However, CaNa₂EDTA can cause renal toxicity, especially during repeated high-dose treatment and in patients with renal diseases (Porru & Alessio, 1996). Because of its relative lack of selectivity, other essential metals such as zinc, iron and manganese are also reported to be simultaneously excreted and depleted following CaNa₂EDTA therapy (Aposhian *et al.* 1995). DMSA also has side effects such as appetite loss, nausea and diarrhea (Liebelt & Shannon, 1994). Furthermore, most of the chelating agents are administered subcutaneously or intraperitoneally, which might precipitate severe adverse effects. Hence, chelating agents are not suitable for high dose and long term treatment for chronic lead toxicity. Therefore, alternative options for counteracting lead toxicity appear necessary. Medicinal plants and constituents thereof (phytochemicals) have been reported to possess lead and other heavy metal toxicity ameliorative effects in pre-clinical studies (Kim *et al.* 2015; Bhattacharya, 2017; 2018a, b). There is a necessity to find safe and efficient dietary interventions against lead toxicity. Dietary strategies appear advantageous, as nutritional ingredients they can easily and affordably be incorporated into the regular diet and thus overcome the adverse effects of the chelation therapy.

Probiotics are living non-pathogenic microorganisms. When taken, they improve the intestinal microbial balance by preventing the growth of pathogens and thus they confer a health benefit to the host. Probiotics include species of *Bifidobacterium*, *Lactobacilli* as well as the yeast

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Saccharomyces (Foligné *et al.* 2013). The dairy products like curd, sour milk, yogurts and other fermented milk products contain these probiotics. Probiotic formulations containing these microorganisms are also available commercially as nutraceutical or functional food and are often prescribed for patients undergoing antimicrobial therapy. There is good number of studies and reviews indicating the benefits of probiotics in relation to antibiotic associated diarrhoea/constipation, allergy, lactose intolerance, reduction of cholesterol as well as development of the immune system and protection against gut pathogens (Jankovic *et al.* 2010; Rijkers *et al.* 2010; Feng *et al.* 2019). A literature survey reveals that it was from the last decade only that experimental pharmacological research has been started to assess probiotics against lead toxicity. So far there is no comprehensive account on studies on probiotics against lead toxicity. The objective of the present short review is to explore and summarize preclinical research findings in this sphere.

Review method

Internet assisted literature study was carried out by using Google, Scholar Google, Scopus, Web of Science, EMBASE and PubMed database search. Only the scientific journal articles published and/or abstracted in internet during the last decade (2009–2019) were considered. The experimental pre-clinical studies on probiotic microorganisms were selected. Clinical studies were also searched but no appreciable result was obtained. Combination of two or more natural microorganisms was regarded as a separate study.

Results

Four (4) types of probiotic microorganisms – three bacteria namely *Lactobacillus sp.*, *Pediococcus pentosaceus*, *Bacillus sp.*, and one yeast – *Saccharomyces cerevisiae* were reported to possess pre-clinical lead toxicity ameliorative potential. Except the first one, the rest three were used as a mixture with the first one. The details are summarized in Table 1. Two relevant clinical studies have been reported but their outcome was found to be indeterminate.

There is 1 (one) study *in vitro* in cell line. Out of the total of the 5 (five) *in vivo* studies in intact models, 3 (three) utilized mice, 1 (one) used broiler chicken and 1 (one) study used common carp fish (*Cyprinus caprio*). Most commonly studied parameters are hematological and tissue (liver, kidney, etc.) antioxidative parameters (biomarkers). Histopathological studies of these target vital organs and measurement of lead contents in concerned tissues were also performed in all *in vivo* studies. Urinary excretion study of lead or its metabolites was not performed. Fecal excretion study of lead was reported in 1 (one) case. Lead acetate was used as toxicant in most of the studies.

Discussion and conclusions

Chronic lead toxicity is considered a serious concern to biosphere. Apart from advising avoiding environmental or occupational lead exposure, relevant awareness; and certain acute and symptomatic treatments, there is no evidence based definitive treatment regimen prevailing to combat sub-chronic or chronic lead toxicity in humans. Notwithstanding, supplementation of antioxidants may be recommended (Kim *et al.* 2015; Lamidi & Akefe, 2017). Several mechanisms have been explained so far as mode of lead toxicity, including disruption of endogenous oxidant-antioxidant balance. Elicitation of oxidative stress by overproduction of oxidative and nitrosative free radicals during the metabolism of lead in the body is considered to be pertinent event in exertion of lead toxicity (Patra *et al.* 2011; Lopes *et al.* 2016).

It is believed that, the beneficial properties of probiotic bacteria are related to their capacity to act by different mechanisms apart from modulation of gut microbiome, thus resulting in improved intestinal microbial balance and other benefits to the host (Monachese *et al.* 2012).

Present pre-clinical research work has demonstrated that probiotic microorganisms are able to protect animals/fish/cell line from lead toxicity principally by antioxidant effects. Intestinal lead sequestration *in vitro* is a less reported mode. Oral administration of these agents effectively reduced lead accumulation in tissue, alleviated tissue oxidative stress; reversed hepatic, renal and DNA damage and ameliorated the corresponding histopathological changes of lead-exposed tissues. The organisms of *Lactobacilli* are reported to be effective. The commercial formulation containing a mixture of different probiotic microorganisms also exhibited a similar outcome.

Previous researchers have noted a potential antioxidative property of probiotics *in vitro* and *in vivo*, including human subjects (Kullisaar *et al.* 2003; Ejtahed *et al.* 2012; Wang *et al.* 2017), presenting the mode of action of probiotics for lead toxicity amelioration *in vivo*. The cardinal mechanism is abrogation of lead-induced oxidative stress by probiotics, operative in systemic circulation (blood) followed by the organs of detoxification (liver), excretion (kidney) and other vital organs, thus alleviating tissue toxicity (Table 1). Further biochemical and mechanistic studies are necessary in this direction.

Two clinical studies have been reported so far. One randomized pilot study investigated the potential of *L. rhamnosus* GR-1 supplemented yogurt to lower lead levels in at-risk populations of pregnant women and in children in Tanzania. However, the strain *L. rhamnosus* GR-1 could not significantly reduce blood levels of Pb in pregnant women or children (Bisanz *et al.* 2014). Another recent randomized double blind study used long term oral supplementation of commercial formulation containing mixture of *Sreptococcus thermophilus* and strains of *Lactobacilli* and *Bifidobacteria* to pregnant woman in Italy to assess lead exposure in infants *via* breast milk but could not confirm whether prophylactic use of probiotics could reduce the absorption of lead (Astolfi *et al.* 2019).

Table 1. Protective effects of probiotics against lead toxicity.

Sl. No.	Probiotic microorganism(s)	Experimental model/cell line	Observed effects with proposed mechanisms	Reference(s)
1	<i>Lactobacillus plantarum</i> CCFM8661	Mice	Normalization of δ -aminolevulinic acid dehydratase (ALAD) and other antioxidative parameters and decreasing the lead levels in blood and tissues	Tian <i>et al.</i> , 2012
2	Mixture of <i>Lactobacillus acidophilus</i> , <i>Lactobacillus plantarum</i> , <i>Bacillus subtilis</i> , <i>Bacillus licheniformis</i> , <i>Pediococcus pentosaceus</i> , and <i>Saccharomyces cerevisiae</i>	Broiler chicken (<i>Gallus domesticus</i>)	Decreased lead accumulation in tissues with normalized antioxidant parameters	Ghenioa <i>et al.</i> , 2015
3	<i>Lactobacillus delbrueckii</i> subsp. <i>bulgaricus</i> KLD51.0207	Mice	Alleviation of lead-induced hepatic and renal toxicity by excreting Pb in feces	Li <i>et al.</i> , 2017
4	<i>Lactobacillus plantarum</i> CCFM8661	Mice	Alleviation of Pb toxicity by decreasing blood and tissue Pb concentration through abrogation of oxidative stress	Zhai <i>et al.</i> , 2018
5	<i>Lactobacillus reuteri</i> P16	Common carp (<i>Cyprinus carpio</i>)	Improvement of growth and hematological parameters, modulation of oxidative stress and gene expression	Giri <i>et al.</i> , 2018
6	<i>Lactobacillus rhamnosus</i> GR-1 (LGR-1)	Human intestinal epithelial cell line (Caco-2)	Pb absorption and immobilization reducing its translocation across the intestinal epithelium <i>in vitro</i>	Daisley <i>et al.</i> , 2019

From the handful of demonstrated protective outcomes of the preclinical studies it appears that probiotics or probiotic mixtures have the prospect for alleviation and treatment of lead toxicity in humans. Nevertheless, this preclinical research appears to be in a quite initial stage. Definitive clinical studies are needed for due corroboration. The pre-clinically proven probiotics could be clinically tested alone or along with putative or newer chelating agents. Based on the outcome, probiotics may produce synergy, aid in disease reversal or may serve as auxiliary, complementary or disease modifying agents and thus could help in reducing the patient's adversities as palliative therapy.

Probiotics have long and widely been used as dietary supplement worldwide and are generally regarded as safe and well tolerated. Probiotic supplementation may be considered a new dietary therapeutic strategy against lead toxicity, concomitantly with conventional chelation, antioxidant, anti-inflammatory and other supportive therapy. Admissible research in this field could lead to development of a potentially useful functional food or therapeutic agent in management of lead toxicity in humans.

Declaration of interest: *The author reports no conflict of interest. The author alone is responsible for the content and writing of this paper.*

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