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# Human supplementation with *Pediococcus acidilactici* GR-1 decreases heavy metals levels through modifying the gut microbiota and metabolome

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Exposure to heavy metals (HMs) is a threat to human health. Although probiotics can detoxify HMs in animals, their effectiveness and mechanism of action in humans have not been studied well. Therefore, we conducted this randomized, double-blind, controlled trial on 152 occupational workers from the metal industry, an at-risk human population, to explore the effectiveness of probiotic yogurt in reducing HM levels. Participants were randomly assigned to two groups: one consumed probiotic yogurt containing the HM-resistant strain *Pediococcus acidilactici* GR-1 and the other consumed conventional yogurt for 12 weeks. Analysis of metal contents in the blood revealed that the consumption of probiotic yogurt resulted in a higher and faster decrease in copper (34.45%) and nickel (38.34%) levels in the blood than the consumption of conventional yogurt (16.41% and 27.57%, respectively). Metagenomic and metabolomic studies identified a close correlation between gut microbiota (GM) and host metabolism. Significantly enriched members of *Blautia* and *Bifidobacterium* correlated positively with the antioxidant capacities of GM and host. Further murine experiments confirmed the essential role of GM and protective effect of GR-1 on the antioxidative role of the intestine against copper. Thus, the use of probiotic yogurt may be an effective and affordable approach for combating toxic metal exposure through the protection of indigenous GM in humans.

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## INTRODUCTION

Heavy metal (HM) contamination is a major environmental concern that poses considerable health risks to humans<sup>1</sup>. More than 20 million hm<sup>2</sup> of cultivated land has been polluted by HMs worldwide<sup>2</sup>. Furthermore, millions of workers in China, Pakistan, and Europe are exposed to toxic metals in their work environment<sup>3–5</sup>. Approximately 1.8 million people work in brick kiln factories in Pakistan, where substantial levels of HMs such as cadmium (Cd), zinc (Zn), chromium (Cr), and nickel (Ni) are released<sup>4</sup>. The chemical industry accounts for 1.1% of the gross domestic production, with 115,700 employees being exposed to HMs in the European Union<sup>5</sup>. The consumption of HM-contaminated food is another major route for toxic metal accumulation in the body<sup>6</sup>. Excessive levels of HMs in the body induce oxidative stress (OS), resulting in various tissue lesions and elevated risks of cancer and other diseases in the long term<sup>7</sup>. Therefore, in addition to occupational exposure, dietary exposure to HMs may also be a long-term hidden threat to human health, affecting several people<sup>2</sup>. An effective treatment for HM toxicity is still lacking. Although chelation therapy is used to treat acute metal intoxication, it is associated with undesirable side effects<sup>8</sup>. A few dietary supplements (e.g., essential metals, vitamins, and

phytochemicals) can alleviate HM-induced OS and tissue damage, although modestly<sup>9,10</sup>. Therefore, there is an urgent need for safe and effective methods to protect humans from the risk of HM exposure.

Probiotics are defined as living microorganisms that confer a health benefit on the host when administered in adequate amounts<sup>11</sup>. They exert beneficial effects on the gastrointestinal tract and immune system and also have other benefits such as the prevention of diabetes<sup>12</sup>, osteoporosis, depression, and anxiety and also the reduction of blood pressure<sup>13–16</sup>. The most attractive benefit of probiotics is that they reduce the accumulation of hazardous substances such as toxic metals, antibiotics, and pesticides in the host<sup>17</sup>. Most studies on the use of probiotics to detoxify toxic metals have been conducted in small animal models such as rats<sup>18</sup>, fruit flies<sup>19,20</sup>, honeybees<sup>21</sup>, the Nile tilapia<sup>22</sup>, and zebrafish<sup>23</sup>, whereas very few studies have been conducted in humans<sup>24,25</sup>. The first human trial using the probiotic strain *Lactobacillus rhamnosus* as an intervention agent to prevent HM accumulation indicated the efficacy of probiotics in preventing increases in toxic metal levels in the blood of human adults rather than children<sup>26</sup>. Similarly, another human trial demonstrated that an 8-week-long consumption of *L. plantarum* CCFM8610 markedly reduced blood Cd levels of the people belonging to towns near

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