Scientific evidence linking long-term exposure to heavy metals with a growing number of adverse health effects has been reported in peer-reviewed literature with increasing frequency. Heavy metals, defined as those metallic elements with a specific gravity at least five times that of water, are common in nature and exposure may come from either occupational or residential sources.

In trace amounts, certain metals, including manganese, iron, copper, nickel, cobalt, zinc, cadmium, magnesium, and calcium are necessary for normal physiological function. However, chronic exposure to some of these same elements at higher levels can affect nearly all organ systems and result in significant illnesses and reduced quality of life.

The heavy metals lead and cadmium are among the top seven hazardous substances included on the U.S. Department of Health and Human Services 2007 CERCLA Priority List of Hazardous Substances. Lead toxicity can affect nearly every organ and body system, but especially the central nervous system. Chronic lead exposure has been linked with weakness in fingers, wrists and ankles; high blood pressure, anemia, brain, kidney, and reproductive damage. In the United States, the removal of lead from gasoline and most paints, ceramics, and pipes has led to a sharp decline in blood lead levels in the general population. However, lead poisoning remains a significant threat for certain subpopulations, including individuals who live in older homes or who may be exposed to occupational sources of lead, and young children, who are more vulnerable to the effects of lead poisoning.

Cadmium. Chronic exposure to high levels of cadmium has been linked with central nervous system damage, intestinal damage, kidney disease, and fragile bones. The effects in human children are similar to those of adults. However, in a recent study, the offspring of animals exposed to high levels of cadmium displayed changes in behavior and learning ability. Predominant sources of cadmium include cigarette smoke, batteries, paint, plastics, workplace air (in facilities where cadmium is used), and contaminated air and water.

The prevailing therapeutic option for heavy metal decontamination is chelation therapy (CT). CT involves the injection or ingestion of a chelating agent which binds with heavy metals, rendering them less chemically active. Once bonded, the metal enters the bloodstream, where it is eventually excreted in the urine. Common chelating agents include ethylene diamine tetracetic acid (EDTA), dimercaprol (also called British Anti-Lewisite or BAL), succimer, and dimercaptosuccinic acid (DMSA). CT is also used as a treatment for cardiovascular disease and is currently under evaluation by the U.S. National Institutes of Health as a treatment for post-myocardial infarction patients.

Disadvantages of CT. Although effective for treating arsenic, lead, iron, mercury, and aluminum poisoning, CT is not effective for treatment of cadmium poisoning. Additionally, these therapies are not without predictable side effects. For instance, the nature of the lipophilic compounds used in CT may enhance the removal of vitamins and minerals that are essential for health. Also, while they may decrease intracellular levels of heavy metal, they may also redistribute toxic metals to other organ systems.

CT can be time-consuming and expensive, and unsatisfactory compliance with CT has been reported. For example, iron CT may require 8-12 hour infusions 5-7 times a week and may cost as much as $35,000 (USD) annually.

Metallothionein: A Natural Chelating Agent

Increasing awareness of the effects of heavy metal toxicity combined with limited therapeutic options has created a market need for a safe and effective method to detoxify heavy metals without significant contraindications or side effects.

The cellular protein metallothionein (MT) plays a crucial role in the chain of activities leading to the excretion of toxic metals. It also serves to transport zinc and copper. The body’s natural chelating agent, MT efficiently binds to several toxic metals, especially cadmium and mercury, for delivery to the liver or kidneys for conjugation and excretion.

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serves to prevent the reaction of toxic metals with other biomolecules, thereby attenuating their toxicity. Established literature indicates upregulation of MT with zinc supplementation.

Regulation and Mechanism of Metallothionein. Downregulation of Protein Kinase C (PKC) results in increased phosphorylation of Metal Transcription Factor 1 (MTF-1), leading to increased expression of MT in mRNA. MTF-1 induced MT binds to metal within the cell. Once metal is mobilized by MT, it is transported through the cell membrane and to the liver. In the liver, the metal undergoes conjugation with glutathione (phase II detoxification) and is transformed into a mercapturate. The metal mercapturate is then ready to be excreted.

RECENT STUDY RESULTS

A clinical study measured the efficacy of a novel formulation consisting of zinc and andrographis, turmeric, and hops botanicals. The formulation was found to modulate the regulation of genes associated with biotransformation and detoxification; specifically the genes associated with metallothionein production.

The 14-day study was conducted at the Functional Medicine Research Center—the clinical research arm of Metagenics—and included 9 adult subjects. Within the study design, no dietary or lifestyle modifications were required other than avoidance of ethanol alcohol.

Methodology. Each subject received a proprietary formulation consisting of zinc citrate (1.67 mg), Andrographis paniculata extract (50 mg), curcuminoids from Curcuma longa (50 mg), and a proprietary blend of polyphenolic-rich hops (Humulus lupulus) and Luduxin® (887 mg). Dosing was 3 tablets twice daily with food for a total of 10 days. Subjects were evaluated at baseline, Day 3, Day 6, Day 8, Day 10 (end of dosing), and Day 14 (washout).

Efficacy evaluation. Formula efficacy was measured by changes from baseline in the gene expression (mRNA levels) of MT using quantitative polymerase chain reaction (qPCR) technology. Clinical efficacy was evaluated by measuring heavy metal excretion through urine.

Safety evaluation. Formula safety was evaluated by monitoring tests, including comprehensive metabolic profile (CMP); cell blood count (CBC); gamma glutamyl transferase (GGT); and a review of vital signs, symptom surveys, and adverse event reports. No changes in basic labs including hematology, electrolytes, and liver and kidney function were demonstrated through the study. However, 2 subjects reported minor symptoms, including headache and mild gastric upset.

Result highlights. MT mRNA levels increased an average of 37-fold, significantly higher than the results reported by an earlier study of zinc alone. (See Figure 1.) Significant increases in urinary excretion of cobalt, tin, lead, cadmium, barium, and arsenic were observed. (See Figure 2.) Excretion of other minerals (sulfur, magnesium, calcium, zinc, selenium, potassium, iron, and copper) did not increase appreciably during the study, but an upregulation in the excretion of manganese was observed. A 9-fold increase in the excretion of mercury was seen in 2 of the 9 study patients.
CONCLUSIONS

A novel formulation consisting of zinc and key botanicals involved in the regulation of gene expression associated with biotransformation and detoxification has been shown to increase the expression of metallothionein mRNA and excretion of clinically relevant toxic metals, with minimal effect on nutrient compounds. Based on in vitro and clinical study results, this formulation naturally, and without significant side effects, upregulates production of metallothionein proteins in the body supporting the clearance of certain heavy metals.

REFERENCES


*Luduxin consists of a mixture of rho iso-alpha acids (from Humulus lupulus) and magnesium salt produced via proprietary process.