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Metoxalate™

Product Information Sheet

Metoxalate™ Heavy Metal Detoxification Formula is a phytotherapeutic extract formulation of, ***Coriandrum sativum***, ***Curcuma longa***, ***Camillea senensis***, ***Silybum marianum***, ***Cynara scolymus*** ***Taraxacum officinale***, ***Zingiber officinale and Cinnamomum verum***. Using advanced laboratory extraction apparatus & proprietary production protocols, these phytochemicals are known to chelate the heavy metals from the cells and blood stream.

The global burden of heavy metal especially mercury, arsenic, lead, and cadmium toxicities remains a significant public health challenge. Chelation therapy has been the mainstay for treatment of heavy metal poisoning where the chelating agent binds metal ions to form complex ring–like structures called B chelates^ to enhance their elimination from the body. Metal chelators have some drawbacks such as redistribution of some heavy metals from other tissues to the brain thereby increasing its neurotoxicity, causing loss of essential metals such as copper and zinc as well as some serious adverse effects, e.g., hepatotoxicity.

When present in very small amounts, many heavy metals such as copper, iron, manganese, and zinc have physiological functions in the body. Zinc is an important cofactor for several enzymatic reactions, vitamin B has a cobalt atom in its core, and hemoglobin contains iron. However, many of the heavy metals have no known benefit for human physiology—lead, mercury, and cadmium are typical examples. Metals and metal compounds interfere with functions of various organs and systems like the central nervous system (CNS), the hematopoietic system, liver, and kidneys (Flora and Pachauri 2010). Toxic metals pose risks to the very young, compromising development due to early life exposure, resulting in lifelong physical, intellectual, and behavioral impairments (Sears 2013). Toxic heavy metals interact with the function of essential cations, cause enzyme inhibition, and generate oxidative stress (Kosnett 2009). Heavy metals are not metabolized by living systems, ultimately leading to their accumulation up to toxic levels.

***Coriandrum sativum*:** Cilantro is thought to help mobilize heavy metals from tissues in the body. making them more accessible for removal.
***Curcuma longa*:** Turmeric contains curcumin, a potent anti-inflammatory and antioxidant compound. It may help reduce inflammation associated with heavy metal exposure.
Camellia sinensis: a major component of green tea, EGCG is has anti-inflammatory and anti-apoptotic properties. EGCG, as a potent inducer of HO-1, can suppress renal injury by reducing oxidative stress and inflammation.
***Silybum marianum*:** Milk thistle is known for its liver-protective properties. A healthy liver is crucial for processing and eliminating toxins, including heavy metals.
***Cynara scolymus*:** Constituents of artichoke include flavonoids, phenolic compounds, proteins, and minerals (Lutz et al. 2011). Traditionally, this plant is used as food and in the treatment of rheumatism, diabetes, fracture, wound, and pains (Garbettaet al. 2014). Pharmacologically, it has diuretic, antimicrobial, antifungal, stomachic, tonic, and anticancer effects.
***Taraxacum officinale*:** Dandelion root is believed to support liver and kidney function, aiding in the detoxification.
Zingiber officinale ginger extract was effective against several strains of drug-resistant bacteria. It may help inhibit the synthesis of certain markers of inflammation. It contains gingerol and other anti-inflammatory compounds like shogaol, paradol and zingerone.
Cinnamomum verum Contains antioxidants, including polyphenols, phenolic acid and flavonoids. These compounds work to fight oxidative stress in the body and aid in the prevention of chronic disease.

Curcuma longa (Altenburg et al. 2011). The major component of turmeric iscurcumin which has antioxidant, antimicrobial, anti-inflammatory, antiviral, and anticarcinogenic properties (Garcia-Nino and Pedraza-Chaverri 2014). Curcumin is known to be an excellent chelating agent for metal ions due to the reactivity of its α-β-unsaturated β-diketone group that strongly coordinates with many metal ions such as Fe3+, Mn2+, Ni2+, Cu2+,Zn2+, Pb2+, Cd2+, Ru3+, Re3+, Al3+, Ga3+, Sm3+, Eu3+, Dy3+, Y3+, Se2+, and metal oxides like VO2+ (Hatamipour et al. 2018; Baum and Ng 2004).

Curcumin donates electrons to these metals to form stable complexes which possess potent therapeutic properties against oxidative stress, arthritis, bacterial infections, and tumors. For example, in AD, it has been established that curcumin crosses the blood–brain barrier to form a stable complex with certain metal ions like Al3+ ion that are deleterious to neurons, hence reducing the toxicity of the metals in the free state. Further to this, reports have also revealed that curcumin consumption could ameliorate occurrence of AD (Baum and Ng 2004; Jiang et al. 2012).

Curcumin also complexes with Zn2+confering anticancer, gastroprotective, and antidepressant properties to the curcumin-metal complex (Pucci et al. 2012; Met et al. 2011). Complexation with curcumin reduces the toxicity of heavy metals such as Hg2+, Cd2+, and Pb2+ which are known to cause oxidative stress (Rennolds et al. 2012; Oguzturk et al. 2012; Agarwala et al. 2012).

The formed metal-curcumin complexes bind to DNA via ionic interaction generated by the positively charged metal (Pucci et al. 2012; Ali et al. 2013). The curcumin-metal complexes produce more potent DNA damage with a greater toxicity to cancer cells as compared to the parent molecule (Ali et al. 2013; Valentiniet al 2008). For example, studies have shown that Cu2+-curcumin complexes improve the cytotoxicity of the parent molecule.

The inhibition of cancer cells by the Cu2+-curcumin complex is produced by downregulating the NFκB pathway and its downstream effectors (Lou et al. 2010). Several studies probing the chelating effects of curcumin in different organs have been carried out. The protective effects of curcumin against heavy metal toxicity on the liver are attributable to its ability to scavenge free radicals, act as a chelating agent and/or its capacity to induce detoxifying enzymes by upregulation of the Kelch-like ECH-associated protein 1(Keap1)/nuclear factor (erythroid-derived 2), Nrf2/ antioxidant responsive element (ARE) pathway, downregulation of nuclear factor kappa-B cells (NF-kB), as well as the expression and content of pro-inflammatory cytokines, thereby preventing noxious effects of heavy metals in the liver (Garcia-Nino and Pedraza-Chaverri 2014).

Curcumin has been reported to protect against lead-induced neurotoxicity in laboratory animals (Dairam et al. 2007; Daniel et al. 2004). According to Flora et al. (2013), curcumin and

nanocurcumin protect against lead-induced toxicity in the blood, liver, kidney, and brain with coadministration of lead acetate (25 mg/kg) and curcumin (15 mg/kg) or nanocurcumin (15 mg/kg). In the liver, curcumin and nanocurcumin were shown to protect against lipid peroxidation, protein oxidation, and restoration of altered ROS levels, GSH, and glutathione disulfide (GSSG).

Curcumin is also reported to protect against nephrotoxicity in cadmium-exposed rats (Singh and Sankhla 2010; Deevika et al. 2012). According to Tarasub et al. (2012), curcumin (200 and 400 mg/kg) in combination with vitamin C (100 mg/kg) can prevent the cadmium-induced oxidative damage, metallothionein expression, and liver structural lesions. Clinical trials in patients with metal-induced genotoxicity have demonstrated beneficial effects with curcumin (Garcia-Nino and Pedraza-Chaverri 2014; Roy et al. 2011).

Curcumin has also been shown to improve arsenic-induced liver damage preventing hepatomegaly and loss of body weight as well as preserve the structural integrity the hepatocellular membrane, prevent lipid peroxidation, decrease in the content of GSH and total proteins, and changes in the liver activity of the antioxidant enzymes GST, SOD, and CAT (Garcia-Nino and Pedraza-Chaverri 2014; El- Demerdash et al. 2009).

Curcumin (80 mg/kg) has been reported to have a protective effect on mercury-induced oxidative stress in the liver, kidneys, and brain of rats treated with mercuric chloride (12 l mol/kg) by reestablishing the antioxidant enzyme activities, reversal of mercury-induced liver and kidney injury markers, and modification of the expression of metallothionein mRNA (Agarwal et al. 2010).

Cynara scolymus (Artichoke) Constituents of artichoke include flavonoids, phenolic compounds, proteins, and minerals (Lutz et al. 2011). Traditionally, this plant is used as food and in the treatment of rheumatism, diabetes, fracture, wound, and pains (Garbettaet al. 2014). Pharmacologically, it has diuretic, antimicrobial, antifungal, stomachic, tonic, and anticancer effects (El-Boshy et al. 2017; Yuan et al. 2014). It is a natural antioxidant and can scavenge free radicals and reduce lipid peroxidation (El- Boshy et al. 2017; Lutz et al. 2011). Artichoke has been reported to protect tissue damage caused by oxidative stress and restore the antioxidant system in lead-induced toxicity and in metabolic diseases (Heidarian and Rafieian-Kopaei 2013; Kucukgergin et al. 2010). Recently, El-Boshy et al. (2017) reported that treatment of rats with artichoke leaf extract caused reduction in oxidative stress damage, immunosuppression, and hematological disturbances induced by Cd.

Ginger (Zingiber officinale) is commonly used as a spice in foods and for medicinal purposes in different parts of the world, including Africa. It has been used in the treatment of arthritis, common colds, sore throats, fever, cramps, constipation and many other ailments (Ali et al. 2008) and possesses antimicrobial, anti-inflammatory, antiemetic, cyto-protective and antioxidant properties (Thuppil and Tannir 2013). Its major constituents include gingerols, polyphenols, monoterpenoids, flavonoids and tannins (Feng et al. 2011). Monoterpenoids such as phellandrene, cineole, (+)-camphene, citral, borneol and curcumin, are responsible for the

smell, while the pungency is due to a homologous series of phenols knows as gingerols (Thuppil and Tannir 2013). It has both antioxidant and chelating effects in the treatment of lead poisoning (Oboh et al. 2010). It has been reported to protect against lead-induced renal and developmental toxicity and cadmium-induced gonadotoxic and spermiotoxic effects in rats (Ola-Mudathir et al. 2008; Reddy et al. 2011).

Green tea has its major constituents, as polyphenols such as (−)-epigallocatechin-3-gallate (EGCG), (−)-epicatechin-3- gallate (ECG), (−)-epigallocatechin (EGC), (−)-epicatechin (EC), (+)-gallocatechin (GC), and (+)-catechin (Shouk et al. 2014; Kaushik et al. 2011). Catechins scavenge both hydroxyl and superoxide radicals, lipid free radicals and peroxyl radicals (Sutherland et al. 2006; Sutherland et al. 2003; Chen et al. 2003). Catechins also increase the level of endogenous antioxidants and thus add to their ability to protect against oxidative damage and lipid peroxidation (Thuppil and Tannir 2013). Green tea protects against lead and cadmium toxicity due to its active constituent, catechins (Zhai et al. 2015). It reduces oxidative stress and regulates the deregulated pro-oxidant/ antioxidant ratio following lead treatment in animals (Chen et al. 2002; Mehana et al. 2010). Green tea extract increased cell viability, decreased lipid peroxidation and maintained cell fluidity in in vitro studies with HepG2 cells exposed to lead (Chen et al. 2002). Also, treatment with green tea extract has been reported to decrease blood lead levels and lead-induced neurotoxicity (Hamed et al. 2010).

Cilantro (Coriandum sativum), also known as coriander, is a spice crop used in Mediterranean, Indian, and other South Asian cuisine (Thuppil and Tannir 2013). Cilantro has carminative, diuretic, and antioxidant properties and contains compounds with free radical–scavenging abilities (Rajeshwari and Andallu 2011). Its constituents include phenolic compounds like caffeic acid, chlorogenic acid, vanillic acid, p-coumaric acid, ferulic acid (cis and transform), and the flavonoids quercetin, kaempferol, and acacetin (Rajeshwari and Andallu 2011; Deepa and Anuradha 2011). Administration of cilantro to lead-treated animals caused lowering of blood lead levels and improvement of hematological parameters as well as reduction in biochemical parameters of hepatotoxicity (Thuppil and Tannir 2013). The antioxidant effects of coriander have been shown to increase the levels of SOD, CAT, and GPx and lowering of lipid peroxidation in the liver and kidney after treatment of lead-exposed animals with coriander (Sharma et al. 2011). Particularly, coriander has the advantage of removing mercury and other toxicmetals from the CNS (Pandey et al. 2016). Leaves of cilantro have been reported to enhance mercury excretion following dental amalgam removal (Sears 2013; Abascal and Yarnell 2012). In animals, it also decreased lead absorption into bone (Aga et al. 2001).

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REVIEW ARTICLE

Natural antidotes and management of metal toxicity

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Abstract
The global burden of heavy metal especially mercury, arsenic, lead, and cadmium toxicities remains a significant public health challenge. Developing nations are particularly at high risk and carry the highest burden of this hazard. Chelation therapy has been the mainstay for treatment of heavy metal poisoning where the chelating agent binds metal ions to form complex ring–like structures called "chelates" to enhance their elimination from the body. Metal chelators have some drawbacks such as redistribution of some heavy metals from other tissues to the brain thereby increasing its neurotoxicity, causing loss of essential metals such as copper and zinc as well as some serious adverse effects, e.g., hepatotoxicity. The use of natural antidotes, which are easily available, affordable, and with little or no side effects compared to the classic metal chelators, is the focus of this review and suggested as cheaper options for developing nations in the treatment of heavy metal poisoning.

Keywords Antioxidants · Chelators · Developing nations · Heavy metal toxicity · Metabolic disease · Public health

Introduction

The term "heavy metal" has been used generally for those metals and semi-metals with potential human or environmental toxicity (Tchounwou et al. 2016; Saunders et al. 2013). When present in very small amounts, many heavy metals such as copper, iron, manganese, and zinc have physiological functions in the body. Zinc is an important cofactor for several enzymatic reactions, vitamin B has a cobalt atom in its core, and hemoglobin contains iron. However, many of the heavy metals have no known benefit for human physiology—lead, mercury, and cadmium are typical examples. Metals and metal compounds interfere with functions of various organs and systems like the central nervous system (CNS), the hematopoietic system, liver, and kidneys (Flora and Pachauri 2010). Toxic metals pose risks to the very young, compromising development due to early life exposure, resulting in lifelong physical, intellectual, and behavioral impairments (Sears 2013). Toxic heavy metals interact with the function of essential cations, cause enzyme inhibition, and generate oxidative stress (Kosnett 2009). Heavy metals are not metabolized by living systems, ultimately leading to their accumulation up to toxic levels (Beyersmann and Hartwig 2008; Chandrasekaran et al. 2014).

Environmental contamination and exposure to heavy metals, such as arsenic cadmium, lead, and mercury, is a serious growing global problem (Clarkson et al. 2003). In Nigerian cities, various environmental matrices namely air, soil, and water are known to be polluted by heavy metal leading to food contamination (Orisakwe 2014). Environmental pollution with heavy metals is even more severe in some developing countries where the economy has been prioritized over environmental effects (Wu 2016). Individuals with elevated body burden of heavy metals are more prone to diseases such as diabetes, cardiovascular diseases, infertility, cancer, neurotoxicity, and risk of renal damage (Rehman et al. 2017; Asomugha et al. 2016). It is also possible that low-level exposure to metals contributes much more to the cause of chronic disease and impaired functioning than previously thought (Howard 2013). A recent review by Orisakwe (2014) highlighted the increased incidence and prevalence of some metabolic disorders such as hypertension, diabetes, renal disease, cancer, and male infertility that are of environmental importance in Nigeria. Heavy metals have been shown to

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