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LEAD TOXICITY ON PHYSIOLOGICAL SYSTEM: A REVIEW WITH HERBAL REMEDIES

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ABSTRACT

Now a days, revelation to noxious heavy metals vestiges an extensive widen professional and ecological tribulations in world. With the increment of urbanization as well as population, human are exposed due to widespread use in industry, agriculture and even as a medicine. In miniature, certain heavy metals are nutritionally important for a healthy life but it becomes toxic when they are not metabolized by the body and accrue in the soft tissues. Especially, currently, lead, cobalt, chromium and arsenic greatly interferes with a number of body functions like hematopoietic system, central nervous system, liver and kidneys. Despite of several efforts, we are still far from an effective treatment of chronic heavy metal, lead poisoning. The study has given overview about the adverse effect of lead in human and also recent strategies like antioxidants, herbal protective agents that took up for a protected, efficient and particular dealing for toxic metals like lead.

KEYWORDS

Metal toxicity, Lead, Oxidative stress, Antioxidant and Herbal agent.

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INTRODUCTION

Day by day civilization as well as industrialization initiates several adverse factors in human health and also environment. Among the adverse factors heavy metals is one. Heavy metals are the chemical substances which bear a specific gravity. Generally the specific gravity has been found at least five times of water's specific gravity. Commonly it is known that the specific gravity is an assessment of density of a certain amount of a solid material,

compared to an equal quantity of water. The specific gravity of water is 1 at 4°C (39°F) where as some known metals with a specific gravity that is higher, such as, arsenic, 5.7; cadmium, 8.65; iron, 7.9; and lead, 11.34 [1]. These heavy metals become toxic when they are not metabolized by the body and are accumulated in the soft tissues. The human body intake the metals during food, water, air. Besides, the integration through the skin happens, when they come in contact with humans in agriculture and in manufacturing, pharmaceutical, industrial, or housing. Industrial exposure accounts for a widespread route of exposure for adults. Intake is the most common route of exposure in children [3]. Children may increase toxic strength from the normal hand-to-mouth activity of small children who get in touch with polluted soil or by in fact eating substance that are not food (dirt or paint chips) [4]. Less ordinary directions of exposure are during a radiological system, from unsuitable dose or screening during intravenous (parenteral) nutrition, from a kaput thermometer, or as of a suicide or slaughter shot [5]. Lead accounts for most of the cases of pediatric heavy metal poisoning [3].

Lead is flexible metal with a bluish, white colour. It is a soft metal and was used in pipes, drains, and soldering materials for long times. The use of lead by humans dates back to thousands of years to the times of Romans, Egyptians and Babylonians. This heavy metal was used extensively in the plumbing systems of ancient Rome. Millions of homes built before 1940, still contain lead (e.g., in painted surfaces), foremost to chronic exposure from weathering, shedding, chalking, and dust. It is reported that industry generates concerning 2.5 million tons of lead throughout the world in a year. The majority of this lead is required for batteries [5]. The rest is used for cable wrapping, plumbing, bullets, and fuel additives. Other uses are as paint pigments and in PVC plastics, x-ray caring, crystal glass production, pencils, and pesticides. Target organs are the brain, blood, bones, kidneys, liver, and thyroid gland [1,2].

The mainly noticeable consequence in children is that of lowered nervous system response, lowered IQ, and gastro-intestinal effects [6, 7]. Lead is a toxicant for almost all organs of the body and has significant incapacitating effects on the nervous, renal, hepatic and hematopoeitic systems. Furthermore, dietary components, such as, sodium citrate, ascorbic acid, amino acids, vitamin D, proteins, fat and lactose can bind to lead and thus enhance the absorption of lead [8]. Lead has the ability to emulate Ca^{2+} ions and can therefore simply pass through membranes. It have a preference to bind to sulfhydryl groups in proteins and enzymes causing errors in their action [9]. The generation of oxidative stress by the production of free radicals and decreasing antioxidant capacity resulting in cell apoptosis has been found after the excessive lead exposure. The foremost scheme of treatment is chelation therapy. However, in recent years, a lot of new research has shown the chelating and antioxidant capacity of natural products.

Sources of Lead Exposure

Lead painting is a prime source of lead contact and the key source of lead toxicity in children. "The U.S. Department of Housing and Urban Development estimated that 38 million homes in the United States contain lead paint. Of those, 24 million are considered to contain significant lead-based paint hazards, including deteriorating paint and/or contaminated dust or soil outside the home. As lead paint deteriorates and airborne lead settles, it contaminates dust and soil." [10] Contact to soil that restrains particulate lead has been shown to be significantly hazardous for children, who are more generally open to the elements by ingestion of house dust or soil. Lead exposure can also occur during remodeling of a home built prior to 1978,

when lead-based paints were still in commerce. Blood lead levels are more intimately related to interior dust exposure than to outdoor soil exposure [11].

In a population-based study, children who lived in a home that had undergone through renovation, repair, or remodeling work in the prior year were at 1.3 times greater risk of having an elevated blood lead level than children not exposed to such activities. The risk was even higher among children living in homes where practices, such as the removal of paint with heat guns, had been used [12]. Drinking water is also a major source of lead exposure, predictable to be accountable for around 20 percent of the total daily exposure experienced by the majority of the U.S. population [13, 14].

Lead pollution of civic water supply may be an under-reported trouble. The metal is also found in lead-glazed ceramics or lead-containing glaze may contain significant amounts. One study linked the storing of food in lead-glazed containers with high blood lead levels. Children's toys, vinyl lunchboxes, contaminated candy imported from Mexico, and children's jewelry produced outside the United States have all been shown to contain significant amounts of lead. Construction workers are known to have a high risk for coming into the inorganic element's exposure.[14] Herbal remedies from India, China, and other parts of Asia may be potential sources of lead exposure.[10,15]

Effect of Lead on Hematological System

Lead toxicity usually apparents itself as anemia due to damage of red blood cells and reduced the production [16]. Lead inhibits certain enzymes necessary for heme production like delta-aminolevulenic acid (δ-ALA), coproporphyrinogen and ferrochelotase. The inhibitory effect is most significant in δ-ALA. In the presence of Pb (II), strong binding interaction is seen preferentially. δ-ALA catalyses the asymmetric addition of 2 molecules of ALA to form porphobilinogen, which is the second step in heme synthesis [16]. Lead has the facility to displace zinc at the metal binding location ensuing in an increase in the ALA levels in blood and plasma [17]. A variety of studies have recommended that chronic exposure to lead leads to a decrease in erythrocyte membrane permeability which is due to a decrease in membrane transfer protein [18,19]. As lead relocates zinc from its position, an increase in the amount of zinc protoporphyrin in blood is also a biological marker for lead poisoning [20].

Effect of Lead on the Renal System

Chronic exposure to lead can cause severe renal problems. The lead toxicity in chronic stage is responsible to decline glomerular filtration rate, hypertension, hyperurecemia, gout and renal failure. Short term exposure is typically seen with lead-induced nuclear inclusion bodies in the proximal tubular lining cells whereas prolonged exposure to lead can show diffuse interstitial or peritubular fibrosis. In acute lead toxicity, proximal tubular damage and manifestation as glycosuria and aminoaciduria is found. Proximal tubule cell mitochondria are significant targets for lead. Lead impairs renal function and decreases activities involved with heme synthesis as many of the enzymes involved are present in the mitochondria [21].

Effect of Lead on the Hepatic System

Lead combines to shape a dogged complex with mitochondria in the liver. It is reported that, liver is the highest repository (33%) of lead in soft tissues followed by kidney. In chronic ingestion, lead leads to decrease the liver reduced glutathione (GSH) levels. Other studies have indicated that an increase in reactive oxygen species (ROS) in the liver. ROS play a vital role to persuade apoptosis under physiological and pathological circumstances and

goes ahead to a significant increase in DNA damage and apoptosis. Experimental studies on animal have shown a decrease in CYP450 levels. The CYP450 is requisite for catalysis of macrobiotic substrates, as well as estradiol-17 beta enzyme levels. The estradiol beta enzyme is important hormone involved in female reproduction ad sexual development of organs. A single dose of lead nitrate can cause a significant proliferation of liver cells of Wistar rat by propagation the number of cells inflowing mitosis[21, 22]. This adds to the theory of lead being a potent toxic agent.

Effect of Lead on the Nervous System

The central nervous system (CNS) particularly the developing nervous system is also targeted by lead poisoning. Children are more vulnerable to intellectual, psychological and neurological effects due to lead poisoning. As per previous discussion, lead has the ability to cross the blood brain barrier without difficulty. Its orientation in calcium mediated cellular processes grounds various incapacitating possessions on the development and function of the brain. Not only in children, but chronic exposure to lead initiates neurological functioning problems in adults. Blood lead concentrations, even those below 10 g/dl, have been shown to have an inversely proportional relationship with IQ levels. The neurotoxic effect of lead in workers appears to be initiated at a level lower than 18 g/dl whereas this threshold is much lower for children at 5g/dl. The induction of oxidative stress is the major effect of lead on the brain. The oxidative induction occurs, where the neurotransmitter glutamate is the main effectors. Excess levels of glutamate and aspartate can lead to neuronal damage and death. NMDA or N-methyl-D-aspartate is most sensitive to excitatory amino acids. The activation of NMDA leads to an augment in lipid peroxidation in the hippocampus region [23]. Recent studies on Alzheimer s Disease have publicized that the delayed over expression of Amyloid Precursor Protein (APP) in old age, long after Pb exposure has ceased, imply that developmental exposure to Pb had reprogrammed the responsiveness of the *APP* gene [21, 24].

Effect of Lead on the cardiovascular system

It is well known that lead has toxic effect in the cardiovascular system. Lead intensity is related with protracted heart rate corrected QT and QRS intervals in terms of the cardiac electrical cycle. Increased risk of intraventricular defect and prolonged QT and QRS intervals were seen more commonly in men below the age of 65 whereas AV conduction defect was seen for older men after lead exposure. Studies done on hypertensive patients revealed a positive relation between associated blood levels and blood pressure [21].

Effect of Lead on Reproductive System

Lead poisoning has also adverse effect on reproductive system also. The lead exposure brings the reduction of fertility in both men and women. In a study on male battery workers it was found to cause testicular atrophy, lowered testosterone levels and hypospermia. Exposure to inorganic lead at levels more than 40 g/dl, causes impaired male reproductive activity. Generally, in humans, protamines protect sperm DNA where zinc is requisite for sperm chromatin stability and binds to protamine P2. As lead can put back zinc, it diminishes the HP2-DNA interaction leading to alterations in sperm chromatin condensation thus reducing fertility. In women the effect of lead also noticeable as irregular estrus, decreased gestational period and abnormalities in the offspring [25, 26]. In some cases, spontaneous abortion has been accounted. Animal studies on female specimens have shown that postnatal exposure to lead through the critical hypothalamic development stage and adjusts the development and function of reproductive system [27].

Lead and Oxidative Stress

Free radicals are generated from endogenous (mitochondria, cytP450 mechanism, peroxisomes) as well as exogenous sources (xenobiotics, chemical reactions). Free radical generation causes oxidative stress which is an originator of damage to the organs of the body. One of the most significant effects of lead poisoning is the induction of this oxidative stress via the production of free radicals and lowering of antioxidant system. Although reactive oxygen species (ROS) are imperative in signaling processes, extreme production leads to cellular and tissue damage. ROS attack lipid membranes, proteins and nucleic acids. Mitochondria utilize O_2 to produce H_2O_2, however, at the same time it produces radicals such as superoxide (O_2^-), H_2O_2 and hydroxyl (OH) radicals. The enzymatic reaction of nitric oxide synthase leads to the formation of super- oxide radicals. Nitrous oxide synthase (NOS) also produces NO which exits as nitrosonium (NO^+) or even peroxynitrite (ONOO) by reaction with superoxide radical. Lead exists as a divalent cation and has electron sharing abilities resulting in covalent attachments with sulhydryl groups of proteins. Lead has the ability to bind to enzymes such as superoxide dismutase (SOD), glutathione peroxidase (GPx), catalase (CAT), and glucose-6-phosphate dehydrogenase (G6PD). GPx, SOD and CAT are especially susceptible to lead toxicity as their function is dependent on the presence of trace metals, particularly zinc, copper and selenium. An excess of superoxide radical inhibits action of NO leading to significant effects on cardiac function [28-30]. ROS have also been cited in several neurodegenerative disorders such as Alzheimer s and Parkinson s disease [21].

Chelation Therapy and Its Side Effects

Chelation therapy is classically followed to treat lead poisoning. Commonly used lead chelators include succimer (meso-DMSA), DMSA, $CaNa_2EDTA$, Dimercaprol (BAL), Unithiol (DMPS) and D- penicillamine (DPA) (85-87). However, synthetic chelators also show some side effects.

The most common adverse effects were nausea, vomiting, diarrhea, appetite loss, and loose stools; reported in clinical trials of succimer in children and adults. A significant number of individuals treated with BAL experience repulsive side effects, including nausea, vomiting, sweating, high fever, hypertension, and tachycardia. The acute and chronic use of DMSA causes gastrointestinal side effects with dermatologic reactions such as papular rash, pruritis and mucocutaneous reactions during clinical trials [31]. Common adverse reactions that have occurred in patients treated for heavy metal poisoning include nausea, vomiting, headache, fatigue, rash, and pruritis. Cardiac arrest has been reported in one report which describes three deaths associated with chelation-therapy-related hypocalcemia. In a study, treatment with penicillamine showed an adverse reaction on patients and included transient leucopenia, transient thrombocytopenia, rash, enuresis, and abdominal pain [32]. In animal studies, it has been found that provocative chelation therapy can lead to mobilization of lead towards the nervous system [21, 33]. Repeated chelation therapy could result in renal impairment as the kidney is the eliminatory route of the mobilized lead.

Current expansion towards phytomedicine

Impact of *Coriandum sativum* to treat Lead Toxicity

Coriandum sativum is commonly known as coriander or cilantro. It is a spice crop. It is clearly identified by its specific fragrance. Variety of remedial assets with carminative and a diuretic role has been found in coriander. Antioxidant coriander contains compounds that are free radical scavengers

[34]. Like caffeic acid, chlorogenic acid, vanillic acid, pcoumaric acid, ferulic acid, coriander restrains the dynamic phenolic acid compounds (cis and trans form) [34, 35]. Quercetin, the flavonoids in coriander leaves have been identified as an important free radical scavenger. Besides, kaempferol and acacetin has been found as free radical scavenger [34, 35]. Supplementation of coriander in lead affected animals (experimental) resulted in lowered blood lead levels and improved parameters of lead toxicity as well as ameliorated the unfavorable effects of lead toxicity on different organs. The ethanolic extract improved the reduced RBC, WBC count and heamoglobin concentration. Moreover, treatment with *Coriandrum sativum* extract showed to restore stress levels [36]. Coriander's extract supplementation has shown to increase SOD, CAT and GPx levels in tissues (liver and kidney). Treatment of lead affected group also has shown lowered lipid peroxidation in the tissues [36, 37]. Studies on the exact active compound responsible for this ameliorating effect and the mechanism are being researched upon presently.

Impact of *Curcuma longa* to treat lead toxicity

Turmeric is basic material as a spice and food coloring agent in every kitchen in India, China and South East Asia. Curcumin {1,7-bis (4-hydroxy-3-methoxyphenyl)-1, 6-heptadiene-3, 5-dione} (diferuloyl methane), a yellow colored, bioactive agent found from the turmeric or *Curcuma longa* [38]. Curcumin has pharmaceutical relevance. It shows powerful antioxidant and anti-inflammatory properties [38]. Apart from phenolic or beta-diketo group, it has several functional groups including carbon-carbon double bonds and phenyl rings containing different amounts of hydroxyl and methoxy substituents [38]. Topical research studies have also found that curcumin can be used in cancer treatment as a chemopreventive in conjunction with chemotherapy. Keeping these specifics in mind, the prospect of curcumin has being used to care for heavy metal toxicity. In laboratory experiments on animal suggested that curcumin is able to reduce lead induced neurotoxicity, hepatoxicity and cardiotoxicity. It has role to increase the antioxidants enzymes like, SOD, GSH and CAT levels and has reduced the level of lipid peoxidation. Lead induced genotoxicity, due to its interaction with DNA and proteins causing single and double strand breaks and DNA-protein cross-linking, is reduced with management with curcumin. Apart from curcumin being a free radical scavenger; it has been previously proposed that turmeric is a potent inhibitor of lipid peroxidation via the inhibition of the lipoxygenase and cyclooxygenase pathways of archidonate metabolism. Another mode of mechanism that has been proposed recently is that of curcumin being a natural chelator for heavy metals. Hence curcumin, used so plentifully in many countries, could be a strong heavy metal chelator with little or no side effects[21].

Impact of Tea on Lead toxicity

Tea has been notorious for long years to restrain compounds that are favor for health and have antioxidant behavior [40-43]. Tea is one of the most popular beverages around the world. Various varieties of tea, in particular green, black and Oolong are used and consumed in considerable quantities. The major green tea polyphenols are epigallocatechin-3-gallate (EGCG), epicatechin-3-gallate (ECG), epigallocatechin (EGC), epicatechin (EC), gallocatechin (GC), and catechin [40, 43]. Catechins are free radical scavengers and can scavenge both hydroxyl and superoxide radicals as well as lipid free radicals and peroxyl radicals [43]. Catechins also have the aptitude to chelate metals such as Cu^{2+} and Fe^{2+} due to their catechol configuration, and shape inactive complexes [43, 44]. Catechins also increase the level of endogenous

antioxidants adding to their skill to protect against oxidative damage and lipid peroxidation which accounts for some of their cytoprotective action. EGCG has the highest antioxidant action due to the presence of gallate moiety on the C ring and has been confirmed to have potent neuroprotective abilities against Parkinson s disease, in animal studies [42, 43].

Polyphenols in black tea, the falvins and the rubins also have antioxidant properties [41]. Tea extracts have ameliorating effects on lead induced toxicity. Recent animal studies and in vitro and in vivo studies have shown that management with lead resulted in oxidative stress induced necrosis of hepatocytes as well as biliary hyperplasia, edema and mild fibrosis. Treatment with green tea extract reduced oxidative stress and regulating the deregulated prooxidant/antioxidant ratio [47]. In vitro studies with HepG2 cells decreased cell viability and stimulated lipid peroxidation by exposure to Pb. Electron Spin Resonance (ESR) studies showed that lead could decrease the fluidity in polar surfaces of cells. Supplementation with green tea extract increased cell viability, decreased lipid peroxidation and maintained cell fluidity [44]. Mitochondrial dysfunction is improved and rapid elevation of Ca^{2+} on exposure to lead has been revealed to lessen when treated with catechins [45]. Lead induced toxicity in blood and brain (due to small amount of SOD and GST and elevated lipid peroxidation) has been reduced on treatment with green tea extract and blood lead levels have been shown to decrease [48]. Along with its free radical scavenging ability and regulation of pro-oxidant/antioxidant status, tea compounds having the chance of metal chelation show great secure for dealing of lead toxicity.

Impact of *Allium sativum* on Lead toxicity

Allium sativum is the scientific name of garlic. Conventionally garlic has been known as a remedy for dog bites, intestinal confusion, flatulence, skin diseases and wounds. It is a pungent plant bulb closely associated to onions, shallots and leeks. Garlic's medicinal properties have been accredited to its organosulfur compounds. Garlic contains three glutamyl peptides, that is, L-glutamyl-S-(2-propenyl)-L-cysteine (GSAC), L-glutamyl-S-(trans-1-propenyl)-L-cysteine (GSPC), and L-glutamyl-S-methyl-L-cysteine (GSMC); their corresponding sulfoxide derivatives, that is, (+)-S-(2- propenyl)-L-cysteine sulfoxide (alliin), (+)-S-(trans-1-propenyl)-L-cysteine sulfoxide (isoalliin), and (+)-S-methyl-L-cysteine sulfoxide (methiin), respectively; and (1S,3R,5S)-5-methyl-1,4-thiazane-3-carboxylic acid 1-oxide (cycloalliin). Allicin and other sulfur compounds are responsible for the characteristic odor of garlic. In addition, garlic is one of the vegetables that contain prominent levels of selenium which plays a key task in maintaining the body's antioxidant defense system as well as prevention of cancers [21, 49, 50]. It has been recognized to prevent and cure cardiovascular diseases as well as other metabolic diseases such as thrombosis and atherosclerosis and shows also a lipid lowering effect inhibits platelet aggregation and lowers blood pressure. Garlic also boosts immunity and along with its other health benefits, it has been used for centuries to retard or slow down aging. Elderly garlic extract (AGE) contains phytochemicals water and lipid soluble organosulfur compounds and flavonoids (allicin and selenium) that have antioxidant properties. Garlic has higher radical scavenging ability than onion as well as reducing capacity and hydrogen peroxide scavenging ability [51]. The strong antioxidant potential and the natural chelating ability of allicin and sulfhydryl groups, make it a strong candidate for the therapeutic treatment of lead toxicity, especially chronic lead poisoning [51]. Animal studies have shown garlic and its main bioactive component, allicin, to be effective in lowering lead

levels in soft tissues and blood [52]. Allicin and its antioxidant properties have ameliorated the oxidative stress induced damage to various organs such as the liver, kidneys, brain and reproductive organs by lowering lipid peroxidation, scavenging free radicals and renewing the levels of endogenous antioxidant enzymes. Treatment with aqueous and methanolic extracts of garlic has helped stabilize the enzyme levels and has lowered the abnormally high levels of aminotransferases and lipid peroxidation [53].

Impact of *Zingiberofficinale* (Ginger) to reduce lead toxicity

Ginger is a common household spice used widely in India, China and South East Asia as an ingredient in the cooking as well as for its therapeutic value. In history, to treat arthritis, common colds, sore throats, fever, cramps constipation and other unrelated problems, ginger is used. From several studies, it has been found that ginger has antimicrobial, anti-inflammatory, anitemetic, cytoprotective and antioxidant properties. The most potent and important chemical constituents include monoterpenoids, gingerols, polyphenols, falovonoids and tannins. Monoterpenoids such as phellandrene, cineole, (+)-camphene, citral, borneol and curcumene, are responsible for the smell. The pungency is due to a homologous series of phenols knows as gingerols. Among the series of gingerols, the most potent is Gingerol-(6). The antioxidant activity is connected to the phenolic and flavonoid composition. The potent antioxidant activities exhibited by both fresh and dry ginger have been used to study its ability to treat lead toxicity. In addition, few recent studies have indicated a possible chelating property in ginger. Animal studies here shown that effects of lead on the liver lead to apoptosis, increased malondialdehyde (MDA) levels, lowered SOD levels and lessening in liver weight. Treatment with ginger has shown to increase the plasma SOD levels and lower lipid peroxidation and cell apoptosis [54]. Another study has shown ginger extracts ability to augment renal levels of SOD, CAT and GPx in lead treated male rats. The ameliorating effects of ginger on lead poisoning have been studied in developmental toxicity. Supplementation with ginger has been shown to lower the number of fetal deaths, growth retardation and fetal length and increase the fetal weight [55]. Although a relatively recent consideration, ginger has the potential to be a serious treatment or preventive source in lead poisoning[21].

Other sources recently being studied

The above discussed plant sources are not only restricted against lead poisoning, there are several other natural sources gifted by nature to being explored for their therapeutic effects against lead poisoning. These include *Tinosporia cordifilia* (Guduchi), *Thurnbergia laurofolia* (Laurel clock vine or Blue trumpet vine), *Artemisia absinthium* (Green Ginger or Grand wormwood), *Azadirachta indica* (Neem), *Lycopersicon* sps (tomato, love apple) and several others [21, 56, 57]. The extraction, isolation and identification of the active compounds are presently being studied as these could lead to novel lead compounds for the treatment.

CONCLUSION

Over the last many years, lead has been noticeable as not only an environmental contaminant but also serious health susceptibility. Due to its cost effectiveness and stability, lead is used generously in various industries. Unfortunately, lead is readily taken up by living beings and directly interacts with, and hence disturbs, the normal functioning of the body. From the above discussion, it may focus in the readers mind that natural source can be use as substitute of synthetic chelators and beneficial as use of these natural sources have nearly no side

effects or nominal at best. Another key feature in this is the easy availability and cost effectiveness of these plants. Moreover, in case of lead poisoning, where the symptoms are not as obvious and many times go undiagnosed, then routinely intake of the plant source may maintain the organ in safe. While the risk of lead poisoning is still rampant in these countries, knowledge and awareness of such natural sources as a alternate for chelating agents will establish to be helpful for the various populations facing this problem and will be affordable.

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CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

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