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An Evaluation of Chelation Therapy for Heavy Metal Toxicity and Enhancement of Detoxification Using Natural Alternatives with Special Reference to Developing Countries

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***Abstract*: The objective of this research is to recommend inexpensive and readily available natural detox alternatives that have chelating characteristics for treating heavy metal poisoning, with special reference to Acute Aluminium Phosphide Poisoning (AAIPP), which is prevalent in most developing countries. The catalyst is the use of pesticides and herbicides to increase agricultural production, raising concerns over their effects on the health of farmers. Mercury, Lead, Chromium, Cadmium, and Arsenic are the most common toxic heavy metals that accumulate in the soft tissues of the body. Aluminium Phospide (AIP) is a metallic inorganic compound that mirrors the effects of such heavy metals. The medical treatment for this is chelation therapy, involving the administration of chelating agents to the body to extract heavy metals. Chelating agents are chemical compounds that bind iron, lead, or copper in the blood and are used to treat high concentration levels of these metals. The Molview Simulator is used for reviewing the molecular structure of the natural alternatives to determine their chelating characteristics and to select those that have ring-like structure(s) similar to chelating agents. These proposed alternatives are free from side effects, have no inherent dangers and are a rich source of minerals like magnesium. As an established medical treatment, Magnesium Sulphate is used to alleviate mid-range symptoms of AAIPP.**

***Keywords*: Acute Aluminium Phosphide Poisoning(AAIPP), Agriculture, Anti-inflammatory, Antioxidants, Bioaccumulation, Bonds, Chelates, Chelating, Chelation therapy, Chelators, Detoxification, Developing countries, Heavy metal poisoning, Ligands, Metal toxicity, MolView Simulator, Natural detox alternatives, Sequestering agents.**

1. Introduction

In quite a few developing countries, agriculture is the predominant occupation in the primary sector. With the use of new pesticides and herbicides to increase production in less land per capita, cases of heavy metal poisoning are on the rise, reducing the lifespan and increasing mortality rates of farmers in these countries. Bioaccumulation of these heavy metals leads to a diversity of toxic effects on a variety of body tissues and organs (Mahdi Balali-Mood et al., 2021). The multiple industrial, domestic, agricultural, medical and technological applications have led to their wide distribution in the environment, raising concerns over their potential effects on human health and the environment (Tchounwou et al., 2012).

Many small farm holders do not have affordability and access to medical facilities. Depending on the target group, it is proposed to provide an inexpensive and effective solution, after an in-depth study of the chelation therapy for heavy metal poisoning, with special reference to the treatment of Acute Aluminum Phosphide Poisoning (AAIPP). AAIPP is prevalent throughout the world and specifically in developing countries like India (Agrawal V.K et al.,2015). Acute Aluminum Phosphide (AIP) is an inexpensive, effective and commonly used agricultural pesticide. AAIPP has caused death in 80% of cases recorded since 1992 (Singh D et al., 2003) and although the study was done in the early 2000s, this is nearly based on ten year statistics.

2. Toxic Metals and Chelation Therapy

Mercury, Lead, Chromium, Cadmium, and Arsenic are the most common heavy metals that are toxic and accumulate in the soft tissues of the body (Engwa et al., 2019), causing acute and chronic toxicities in humans. Toxic metals can mimic the action of a key material in the body, causing illness and chronic disposition by interfering with the metabolic process (Jaishankar et al., 2014), especially radioactive heavy metals like uranium or radium, which in the body resembles calcium to the point of being absorbed into human bone, resulting in adverse conditions (IARC Monographs,2001). Aluminium Phospide (AIP) is a metallic inorganic compound that mirrors the effects of heavy metals. Trace elements can also be harmful in excess amounts. However, not every heavy metal is toxic. Some elements like iron are essential.

The basic treatment of heavy metal poisoning is to terminate the exposure to the metal (National Organization for Rare Disorders, NORD, latest 2006). But if it has already been absorbed in the body, chelation is the most powerful and successful way to cure it. The U.S. Food and Drug Administration (FDA) have approved chelation therapy as a remedy for lead poisoning. The therapy is also used for

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excretion of toxic elements from the kidney.

Chelation is the chemical bonding of ions and molecules to metal ions and entails the creation of two or more distinct coordinate bonds between a polydentate ligand (ion or molecule) and a central atom (Flora et al., 2010) shown in Figure 1. Chelates, chelators, chelating or sequestering agents are the names given to these ligands.

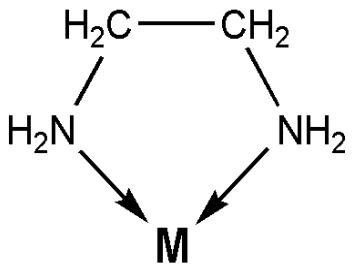


Fig. 1. Chelating structure, where M is the metal; M can be substituted for Lead, Arsenic and other metals

The chelate effect is the attraction of chelating ligands to a metal ion. This can be illustrated using Copper (II) and its affinities for Ethylenediamine, abbreviated as "en" when it is in ligand form and Methylamine, $MeNH_2$.

Ethylenediaminetetraacetic acid injected into the bloodstream, to remove heavy metals from the body (Michigan Medicine, Sep 2020).

$$Cu^{2+} + en \rightleftharpoons [Cu(en)]^{2+}$$
$$Cu^{2+} + 2\ MeNH_2 \rightleftharpoons [Cu(MeNH_2)_2]^{2+}$$

For easier visualization, Figure 2 constructed using the Molview simulation is shown below.

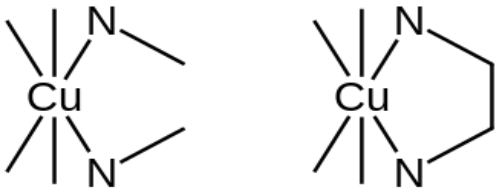


Fig. 2. Cu2+ complexes with non-chelating Methylamine on the left and chelating Ethylenediamine on the right

The copper ion forming a chelate complex with Ethylenediamine results in the creation of a CuC_2N_2 ring with five members. Two monodentate Methylamine ligands with roughly equal donor strength substitute the bidentate ligand, stipulating that the Cu–N bonds are similar in appearance in the two reactions (Lancashire, 2020).

Chelation therapy, part of clinical toxicology, is a medical treatment that involves administering chelating agents to the body in order to extract heavy metals, for which Dimercaptosuccinic acid or DMSA (Figure 3) is used as medication (Aaseth et al.,2016). Table 1 shows the effects of pre and post DMSA administration. Due to the inherent dangers, it must be administered under strict medical supervision; as the chelating agents used may have worse adverse side effects than the toxic metal itself and can have a variety of negative consequences, including death. Copper poisoning, or even Wilson's disease, which is a genetic condition related to buildup of copper in the body, is treated with chelation (Smirnova et al., 2018) using either Penicillamine, or in milder cases, alpha-lipoic acid, ALA for soft tissue treatment (Figure 4).

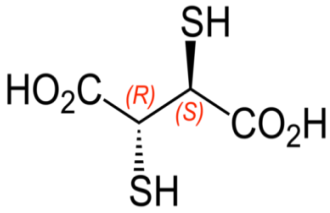


Fig. 3. Structure of DMSA

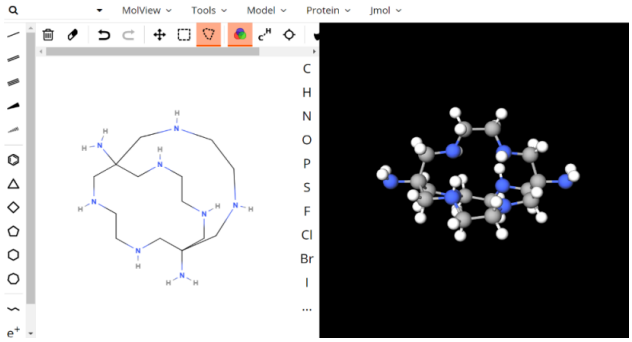


Fig. 4. Diamsar Chelate, commonly used in copper detoxification constructed using MolView simulation

Factors affecting chelation: The most important factor affecting chelation is the size of the molecule formed in the body. Five or six member rings are the most common, however, four-member rings have also been observed (Flora et al., 2010). The lesser number of rings adds more strain on the molecule, making it unstable and potentially dangerous to the human body.

The other important factor is the effect of the metal ion, in this case a heavy, toxic metal. The order of stability of chelates using different ligands: Pd>Cu >Ni>Co >Zn> Cd> Fe>Mn>Mg

Table 1
Spontaneous urine excretions of toxic metals prior to chelation therapy (pre) and after several rounds of DMSA chelation for five subjects

	Pbμg/L)		Mg (μg/L)		As (μg/L)		Al (μg/L)	
Subject	**Pre**	**Max**	**Pre**	**Max**	**Pre**	**Max**	**Pre**	**Max**
I	1.1	1.9	0.060	0.062	1.1	1.1	11.6	24.4
II	0.12	1.7	0.11	0.21	0.12	1.1	2.4	7.3
III	0.14	0.28	0.53	0.76	0.14	0.94	8.0	13.5
IV	0.15	1.3	0.056	0.056	0.16	2.8	7.2	17.0
V	0.13	1.7	0.044	0.046	0.13	1,4	0.33	6.5

Source: Mikirova et al., 2011

was presented by Mellor and Maley (1948). The same was proven by Irving and William's (1948) study on the stability of chelates during extraction: Zn < Cu > Ni> Co > Fe >Mn. The stability of complexes is greatly increased by chelation, as demonstrated by the two studies mentioned. The enhanced stability conferred on a complex is what the chelate effect is and this stops the spreading of heavy metal poisoning and metallic inorganic compounds in the body.

There are multitude of other factors like ligand substitution, which directly influences the chances of chelation; number of rings derived from the chelate effect, contributing to its stability; and of course, the strength of the chelating agents themselves (Lancashire, 2020), which again is dependent on the heavy metal and metallic inorganic compound being dealt with.

3. Prevalence of Heavy Metal Poisoning in Developing Countries

As stated in the introduction, in developing countries like India, acute Aluminium Phosphide poisoning (AAIPP), is a prevalent, but an under-reported problem. According to a study in the Indian Journal of Anesthesia, Jul-Aug, 2010, the mortality from AAIPP was 59.3% of admissions of patients with AAlPP. Aluminium Phosphide, or AIP, a metallic inorganic compound is a highly toxic fumigant for stored cereals and other grains that is sold under a variety of brand names, including QuickPhos and Celphos. The lethal dose of AIP is between 0.15 and 0.5 gram (Singhai et al., 2014). The phosphine content of AIP is responsible for its intense toxicity, which is unrelated to Aluminium.

4. Research Methodology

Uniqueness of Research: The distinctiveness of this research is that it seeks to find the most readily available solutions like Natural alternatives that have chelating characteristics, by reviewing their chemical compounds and structure, for people in need**.**

Simulation tool: The MolView Simulator is used for simulating the results and is considered a virtual laboratory in the absence of actual laboratory facilities during the Pandemic. MolView is one of the top modeling software in chemistry and is an online web-application and used in research on metal complex studies (Muriel et al., 2020). The software was used to upload major molecular compounds in natural alternatives for determining chelating effects and to determine the similarity of their chemical bonding structures with those of the medication. Natural alternatives with mainly non-enzymatic antioxidants properties were selected and filtered based on the above property.

Rice is a main staple in developing countries as well as seafood. Keeping this in mind, a search was made for natural chelating alternatives that have a ring like portion that allows for bonds to be formed between the ligands and metal ions, by viewing the molecular structure of staple food and many natural chelating alternatives on MolView Simulator and selecting those that have a ring like structure similar to chelating agents. A few staple food like rice, tuna and swordfish, some high protein food like soybeans, eggs and fruits like banana were rejected and are recommended to be consumed in lesser quantities, because they lacked a ring like molecular structure to be really viable as a chelating agent (Figure 5 and 6). Examples are seen below.

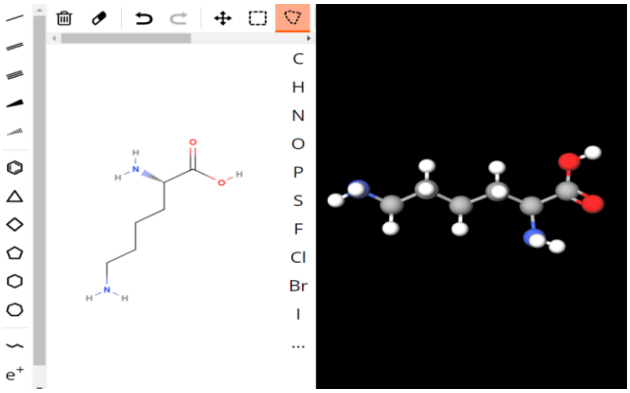


Fig. 5. Lysine, commonly found in soybeans and bananas, has no ring-like structure

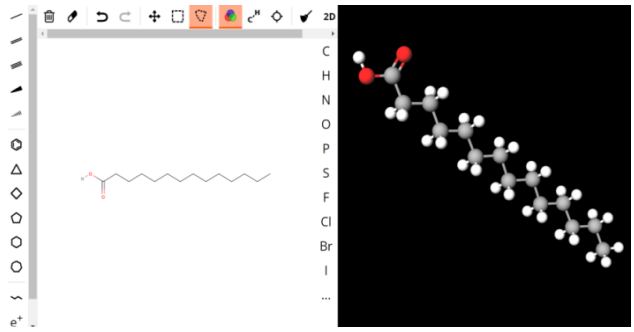


Fig. 6. Myristic Acid, commonly found in fish like Tuna, has no ring-like structure

5. Research Outcome: Alternative Natural Detox Treatments for Heavy Metal Poisoning

An attempt has thus been made to identify native natural alternatives that by nature of their inherent compounds, binds itself to the heavy metal molecules, specifically Aluminium Phosphide and removes them through the digestive process. These can be grown by farmers alongside their major crops and can also be part of the daily dietary habit in countries where AAIPP is prevalent and easily and inexpensively available. As the body is already accustomed to certain amounts of chlorophyll, it doesn't trigger an immune response, significantly reducing chances of side effects. In addition, eating foods high in vitamins and minerals can have protective effects for those exposed to heavy metals.

Due to lack of lab facilities during the Pandemic, finding a common component of common chelating agents that would then enable its identification in other compounds with chelating properties was carried out using simulation studies. Using the MolView simulator (Figure 7, 8), it is seen that they have a ring or ring-like portion that allows for bonds to be formed between the ligands and metal ions. The results are presented below.

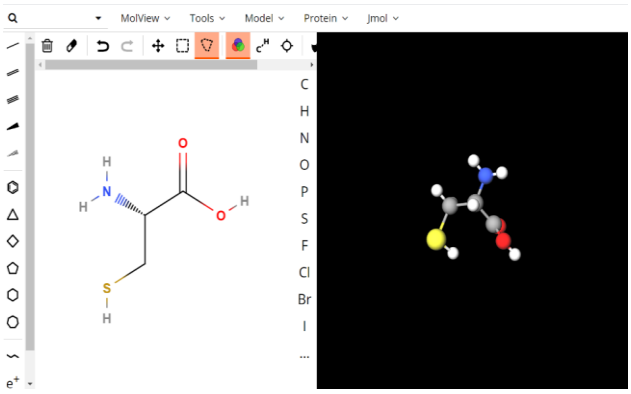


Fig. 7. L-Cysteine found in Yoghurt and Oatmeal has a ring like structure facilitating chelation

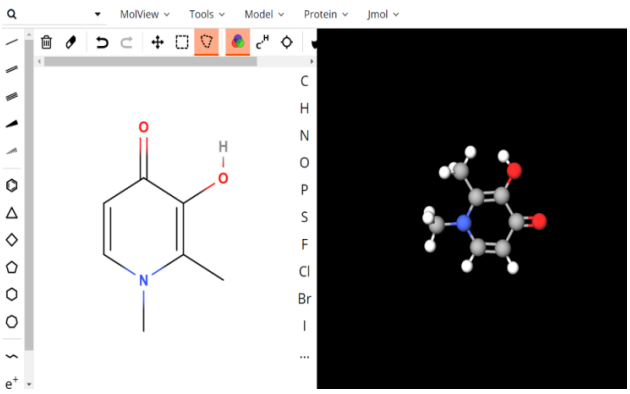
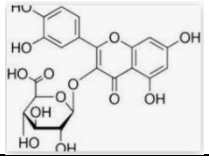
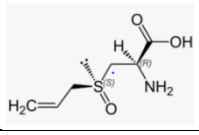
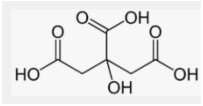
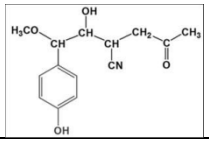
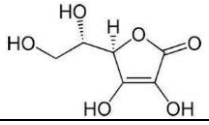
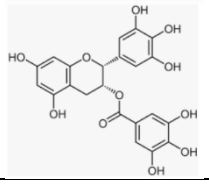
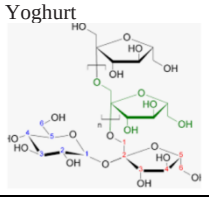


Fig. 8. CP20, a bidentatehydroxypyridinonefound in Chickpeas used to chelate iron

Table 2
Recommended natural chelating alternatives

S. No.	Recommended detox food	Chemical compounds	General compound class	Few main properties
1	Cilantro 	Linalool, decanal, decenal, decanol, undecenal, dodecenal, tetradecenal and pentadecanol	Amino Acid and long chain fatty alcohol	Anti-inflammatory, antifungal, antimicrobial and significant chelating properties
2	Garlic 	N-acetylcysteine, S-allyl-cysteine (SAC), S-allyl-mercapto cysteine (SAMC)	Organosulfur compounds	SAC has antioxidant, anti-inflammation, regulated redox, pro energetic, anti-apoptotic, and signaling capacities while SAMC shows an anticancer activity
3	Lemon 	Limonene, sabinene, citronellal, linalool, nera l, geranial, (E)-β-ocimene, myrcene, citronellol, β-caryophyllene, terpne-4-ol, geraniol and α-pinene	Terpenoid compounds (essential oil in citrus fruits)	Antimicrobial, antifungal, anti-inflammatory, anti-cancer, depurative, antiscorbutic
4	Chlorella 	Protein, carbohydrates minerals, crude fiber, lipids, ash and twenty phenolic acids	Phenolic Acid	Antioxidant anti-inflammatory, and brain-protective properties, effective metal toxin binding agent
5	Tomato 	Phenolics, lycopene, anthocyanin, ascorbic acid, glycoalkaloids, tomatine and carotenoids	Carotenoids Polyphenols	Antioxidant, anti-inflammatory
6	Green Tea 	Proteins, amino acids such as theanine or 5-N-ethylglutamine, glutamic acid, tryptophan, glycine, serine, aspartic acid, tyrosine, valine, leucine, threonine and arginine	Amino acids	Antioxidant, anti-inflammatory, antifungal, antibiotic, antiandrogen
7	Probiotics/ Yoghurt 	Acetic acid, Formic acid, Lactic acid and Hydrochloric acid.	Organic acid.	Antibacterial and antifungal properties anti-inflammatory

Source: Chemical compound, class and properties from multiple online sources

Table 3
Test results of a compounded potent strain of chlorella used in trials over three years

Heavy Metals Tested	Mean % increase after provocation	Mean % increase of Placebo	Number in Sample	Results on Statistical Test	Degrees of Freedom	Level of Significance
ARSENIC -U	7409	11.16	84	-	-	p<0.0005
ARSENIC -F	59.83	61.13	84	-	-	p<0.05
LEAD- U	466.47	-16.95	84	-	-	p<0.005
LEAD- F	142.16	-6.01	84	-	-	p<0.05
CADMIUM - U	67	27.91	84	-	-	p<0.05
CADMIUM - F	43.13	22.62	84	-	-	p<0.05
ANTIMONY - U	59.16	14.91	84	-	-	p<0.05
ANTIMONY - F	50	6.61	84	-	-	p<0.05
NICKEL -U	80	5.52	77	t=1.425	76	p<0.158
BISMUTH –U	564	7.95	19	t=2.109	18	p<0.04
URANIUM -U	707	18.23	76	t=1.015	75	p<0.03
MERCURY -U	448	0.80	56	t=5.395	55	p<0.0005

Source: Georgiou, 2018

The table 2, includes structures of a few natural alternatives with ring or ring like formations, replicating the chelating component of common chelating agents.

6. Evaluation and Conclusion

As an established medical treatment, Magnesium Sulphate will alleviate most of the mid-range symptoms of AAIPP (Gurjar et al., 2011). Other therapies like Dopamine infusion have also been used in the past to treat dizziness, cramps and nauseousness successfully. However, these medical treatments and organic detoxification programs and therapies may not be accessible or affordable to people most affected by it, the small farmers. So, based on literature research, simulation research as well as informal discussions with competent experts in the field, the best remedy recommended is a suite of natural compounds, as they have no inherent dangers or side effect, need not be administered in medical centers under supervision, have significant chelating characteristics, are easily absorbed in the body, inexpensive, easily accessible and just need dietary changes. The bonding structures of the simulated (sample) natural alternatives are consistent with those of chelating agents. These are food that are rich in amino and organic acids, Sulphur compounds, essential oils, phenolic acids, food carotenoids and long chain fatty alcohol.

Test results of chlorella consumption is shown in Table 3. As shown in Figure 9, research indicates that the consumption of chlorella and cilantro together can eliminate an average of 87% Lead, 74% of Aluminum and 91% Mercury in about a month and a half (Felty, 2016). Natural Alternatives have the advantage of being primarily excreted through urine, thus reducing chances of re-absorption through the bowels (Georgiou, 2018). The natural alternatives recommended above have magnesium amongst other compounds, thus a veritable solution for AAIP.A synergistic approach of chelation therapy coupled with natural alternatives can be explored to boost immunity and induce oxidative stress, the most effective way of eliminating or decreasing the severity of AAIPP.

Limitations: This list of natural alternatives needs to be evaluated in extensive laboratory and field trials. This was limited because of the COVID-19 scenario. Hence, the accuracy of conclusions may not be totally perfect, even if the theory holds true. Suffice to say, that even if partially effective, these natural compounds will strengthen the immunity, provide antioxidants, add vitamins and minerals and contribute to the general well-being. Administration of natural and synthetic antioxidants like, quercetin, catechin, taurine, captopril, gallic acid, melatonin, N-acetyl cysteine, α- lipoic acid has been recognized in the recovery against heavy metal intoxication (Flora 2013).

The Future: In areas where it is rampant, clinical studies based on stratified systematic sampling, considering the type of metal poisoning, the demographics of the affected population, intensity of toxicity, mortality rate and attendant factors are recommended be carried out for a period of 3-4 months. Two sample groups should be considered, one under administration of natural alternatives and another, a combined/synergistic therapy.

Ethics and Environmental considerations: For the recommended procedures, the natural alternatives and the synergistic therapy, no adverse side effects are expected, as one is completely organic with no environmental impact and the other a well-established therapy. All trials in future will be conducted with the subjects' informed consent.

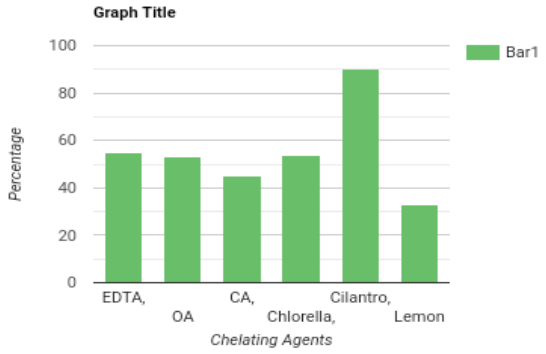


Fig. 9. Efficacy of chelating agents (Georgio, 2018) constructed using rapidtables.com

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