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REVIEW ARTICLE

Medicinal plants and natural products can play a significant role in mitigation of mercury toxicity

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ABSTRACT

Mercury is a heavy metal of considerable toxicity. Scientific literature reveals various plants and plant derived natural products, *i.e.*, phytochemicals, which can alleviate experimentally induced mercury toxicity in animals. The present review attempts to collate those experimental studies on medicinal plants and phytochemicals with ameliorative effects on mercury toxicity. A literature survey was carried out by using Google, Scholar Google, Scopus and Pub-Med. Only the scientific journal articles found in the internet for the last two decades (1998–2018) were considered. Minerals and semi-synthetic or synthetic analogs of natural products were excluded. The literature survey revealed that in pre-clinical studies 27 medicinal plants and 27 natural products exhibited significant mitigation from mercury toxicity in experimental animals. Clinical investigations were not found in the literature. Admissible research in this area could lead to development of a potentially effective agent from the plant kingdom for clinical management of mercury toxicity in humans.

KEY WORDS: mercury; ascorbic acid; natural products; oxidative stress; quercetin

Introduction

The heavy metals are generally characterized as inorganic elements having specific gravity five times of that of water. Almost all the environmental components including biosphere have been consistently threatened by excessive contamination of heavy metals continuously released from various sources. Different heavy metals have been reported to generate adverse effects in diverse ways (Singh *et al.* 2014).

Mercury is a substantially toxic heavy metal which is widely distributed in nature. It exists in the environment in three chemical forms: elemental mercury (poisonous as vapor), organic mercury (methyl mercury and ethyl mercury), and inorganic mercury (mercuric mercury). All these forms have toxic health effects. Mercury and its related compounds are circulated and concentrated in soil and distributed into the air via burning of fossil fuels, industrial furnaces or active volcanos. It then comes back to the soil, water bodies or living organisms. Recycling from atmospheric outflow, deposition in water reservoirs and bioaccumulation or biomagnifications in plants, animals and humans complete the mercury cycle in the environment (Rafati-Rahimzadeh *et al.* 2014).

Subjection to mercury occurs in two ways: through environmental and occupational exposure. Human exposure to mercury specifically takes place via consumption of mercury contaminated food, especially sea fish, water, dental care procedures (using amalgams in endodontics), using mercury based instruments (thermometers and sphygmomanometers), occupational exposure (e.g. mining) and others (using fluorescent light bulbs and batteries, industrial wastes/effluents). Mercury has no known beneficial effects in the human body yet it elicits different ill effects in the body according to its chemical forms. However, several reports point to a beneficial hormetic response promoted by mercury at a low dose in various *in vitro* and *in vivo* models (Helmcke & Aschner , 2010; Heinz *et al.* 2012; Zhang *et al.* 2013; Tan *et al.* 2018).

Exposure to mercury compounds leads to toxic effects on cardiovascular, pulmonary, urinary, gastrointestinal, neurological systems and skin, which might become fatal. Different forms of mercury affect different vital organs of the body, causing damage or failure of these organs

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crucial for the body, which might cause the death of the individual. Mercury toxicity has been a serious environmental public health hazard worldwide provoking several disastrous incidents like Minamata disease in Japan during 1950–1960 (Bernhoft, 2012; Mostafalou & Abdollahi, 2013).

The toxic effects of mercury in the human body and their conventional managements using putative complexing or chelating agents have so far been well studied and reviewed earlier (Bernhoft, 2012; Sabarathinam *et al.,* 2016). But there is no comprehensive account in the studies on alternative options for counteracting mercury toxicity.

The use of medicinal plants and natural products for treatment of ailments is as old as mankind (Kumar *et al.,* 2015). The major merits of traditional or plant based medicine seem to be their perceived efficacy, low incidence of serious adverse reactions and comparatively low cost (Bhattacharya & Haldar, 2012a, b). Literature survey reveals that for the last 12 years only experimental research has been surged in pursuit of medicinal plants and their constituents, i.e. phytochemicals that could mitigate mercury toxicity in experimental animals. Various medicinal plants and natural products afforded significant alleviation from experimentally induced mercury toxicity in animal models. The objective of the present review is to overview and summarize apposite preclinical research findings in this arena.

Review methodology

Internet associated literature survey was carried out by using Google, Scholar Google, Scopus and Pub-Med database search. Only the scientific journal articles published and/or abstracted in internet during the last two decades (1998–2018) were considered here. The experimental preclinical studies on medicinal plants (crude, semi-pure or enriched extracts thereof) and the constituents acquired from plants (including fixed and essential oils) were selected. Combination of phytochemicals was regarded as a separate study. Minerals and semi-synthetic or synthetic analogs of natural products were excluded from the present extent of compilation and review.

Results

Twenty-seven (27) medicinal plants were reported to possess ameliorative effect on mercury toxicity in experimental models of sub-chronic mercury toxicity. The details are summarized in Table 1. A substantial number of the studied plants are indigenous to the Indian subcontinent. These include certain putative medicinal plants recognized in Ayurveda, the traditional system of Indian medicine and worldwide, namely *Zingiber officinalis, Bacopa monnieri, Tribulus terrestris, Allium sativum, Camellia sinensis, Vitis vinifera, Ocimum sanctum* and *Curcuma longa.* The major dietary plants include *Camellia sinensis, Vitis vinifera*, *Zanthoxylum piperitum*, *Triticum aestivum*, *Curcuma longa*, *Zingiber officinalis* and *Allium sativum.* Most of the plants possess both dietary and medicinal values/usages.

The crude extracts of dried plant materials using suitable solvents like ethanol are used for the studies. In case of *Camellia sinensis* (tea leaf), *Rheum palmatum* (rhubarb), *Zanthoxylum piperitum* (Japanese/Korean pepper) and *Vitis vinifera* (grape seed) a specific chemical constituent or active principle enriched extracts were employed and found to have beneficial effects in ameliorating multiple organ toxicities in rodents.

Twenty seven (27) plant derived natural products were found to demonstrate alleviative effects on mercury induced sub-chronic toxicity, mostly in intact rodent models. The details are given in Table 2. Among them two are vitamins, namely ascorbic acid (vitamin C) and α-tocopherol (vitamin E) and one is a pro-vitamin A (β-carotene). Two are fixed oils, viz. pomegranate oil, moringa oil; and two are essential oils namely argan oil and *Selinum vaginatum* oil. Ascorbic acid, α-tocopherol and quercetin are also used as reference compounds in the above mentioned studies on medicinal plant extracts for comparison/validation of experiments. β-carotene and α-tocopherol co-administration showed prominent ameliorative effect by recuperating oxidative stress, indicating the likelihood of this combination for clinical regimen.

Except the cells/cell lines or *in vitro/ex vivo* studies, most common *in vivo* intact models include rodents like mice and rats. Most commonly studied parameters are hematological and antioxidative parameters (biomarkers). Parameters specific for organs include those of liver, kidney, heart, brain, testes, with the liver and brain being the most common. Histopathological studies of these target organs were also performed in some cases. Measurement of mercury contents in concerned tissues was performed in a few cases. Mercury chelating activity *in vitro* was determined in one case. Urinary excretion study of mercury or its metabolites was not performed. Mercuric chloride ($HgCl_2$) was used most routinely as toxicant followed by methyl mercury (CH_3Hg).

Discussion

Mercury toxicity is known and has been reported historically. It results in multi-organ toxicity depending on age, organ and exposure factors. Chelating agents and combinations thereof and certain symptomatic supportive treatments have been conventionally utilized in treatment of mercury toxicity along with advocating avoiding environmental or occupational mercury exposure. Most of the investigators do not appear very confident to advocate any alternative options like supplementation of herbals or antioxidants in management of mercury toxicity; nevertheless, elicitation of oxidative stress by creation of free radicals during the metabolism of mercury in the body is considered to be one of the pertinent mechanisms of mercury toxicity (Rafati-Rahimzadeh *et al.,* 2014; Aflanie, 2015).

Table 1. Medicinal plants with mercury toxicity ameliorative potential.

Sl. No.	Botanical name	Plant Part/ Extracts used	Toxicant used	Experimental model	Organ(s)/system/ cell line involved	Reference(s)
1	*Zingiber officinale*	Rhizome	$HgCl_2$	Rats	Liver, kidney	Joshi *et al.*, 2017a
2	*Paullinia cupana*	Fruit	CH_3Hg	Round worm (*Caenorhabditis elegans*)	Whole organism	Arantes *et al.*, 2016
3	*Annona coriacea*	Leaf	$HgCl_2$	*Staphylococcus aureus*, *Escherichia coli*, and *Pseudomonas aeruginosa*	Whole organism (cells)	Júnior *et al.*, 2016
4	*Lygodium venustum*	Aerial parts	$HgCl_2$	*Escherichia coli*	Whole organism (cells)	Figueredo *et al.*, 2016
5	*Rheum palmatum*	Total anthraquinone extract of root	$HgCl_2$	Rats	Kidney	Gao *et al.*, 2016
6	*Triticum aestivum*	Aerial parts	$HgCl_2$	Rats	Liver, Haematological	Lakshmi *et al.*, 2014
7	*Dendropanax morbifera*	Leaf	$(CH_3)_2Hg$	Rats	Brain	Kim *et al.*, 2015
8	*Zanthoxylum piperitum*	Glycoprotein (ZPDC)	$HgCl_2$	Mice	Liver, murine hepatocytes	Lee *et al.*, 2014
9	*Solanum sessiliflorum*	Fruit	CH_3Hg	Rats	Testes	Frenedoso *et al.*, 2014
9	*Acacia arabica*	Gum	$HgCl_2$	Rats	Kidney	Gado & Aldahmash, 2013
10	*Bacopa monnieri*	Aerial parts	CH_3Hg	Rats	Brain	Sumathi *et al.*, 2012; Ayyathan *et al.*, 2015
11	*Camellia sinensis*	Leaf polyphenol extract	$HgCl_2$	Rats	Kidney	Liu *et al.*, 2011
12	*Allium sativum*	Bulb	CH_3Hg	Human	Peripheral leukocytes	Abdalla *et al.*, 2010
13	*Allium sativum*	Bulb	CH_3Hg	Rats	Brain	Bellé *et al.*, 2009
14	*Tribulus terrestris*	Fruit	$HgCl_2$	Mice	Kidney, Liver	Kavitha *et al.*, 2006; Jagadeesan *et al.*, 2005; Jagadeesan & Kavitha, 2006
15	*Ginkgo biloba*	Leaf	$HgCl_2$	Rats	Brain, lung, liver, and kidney	Sener *et al.*, 2007
16	*Eruca sativa*	Seeds	$HgCl_2$	Rats	Kidney	Alam *et al.*, 2007
17	*Ocimum sanctum*	Leaf	$HgCl_2$	Onion (*Allium cepa*)	Root tip cells (meristems)	Babu & Uma Maheswari, 2006
18	*Ocimum sanctum*	Leaf	$HgCl_2$	Mice	Hematological, Liver	Sharma *et al.*, 2002
19	*Halimeda incrassata*	Whole plant	CH_3Hg	Rats, Mice	Hematological, GT1-7 mouse hypothalamic cells	Linares *et al.*,, 2004
19	*Juglans sinensis*	Leaf	$HgCl_2$	Rabbits	Kidney	Ahn *et al.*, 2002
20	*Vitis vinifera*	Seed proanthocyanidin extract	CH_3Hg	Rats	Brain	Yang *et al.*, 2012
21	*Curcuma longa*	Rhizome	$HgCl_2$	Rats	Liver	Joshi *et al.*, 2017b
22	*Artemisia absinthium*	Aerial parts	$HgCl_2$	Rats	Brain	Hallal *et al.*, 2016
23	*Hygrophila auriculata*	Whole plant	$HgCl_2$	Rat	Liver	Sridhar *et al.*, 2013
24	*Eugenia jambolana*	Leaf	$HgCl_2$	*Escherichia coli*, lettuce (*Lactuca sativa*) seeds	–	Sobral-Souza *et al.*, 2014
25	*Eugenia uniflora*	Leaf	$HgCl_2$	*Escherichia coli*, lettuce (*Lactuca sativa*) seeds	–	Cunha *et al.*, 2016
26	*Psidium guajava var. pomifera*	Leaf	$HgCl_2$	Yeast (*Saccharomyces cerevisiae*)	–	Pinho *et al.*, 2017
27	*Launaea taraxacifolia*	Leaf	$HgCl_2$	Rats	Brain	Owoeye & Arinola . 2017

Table 2. Natural products with mercury toxicity ameliorative potential.

Sl. No.	Name	Toxicant used	Experimental Model	Organ(s)/System/ Cell line involved	Reference(s)
1	6-gingerol	$HgCl_2$	Rats	Liver, Kidney	Joshi *et al.*, 2017a
2	*Moringa oleifera* oil	$HgCl_2$	Rats	Testes	Abarikwu *et al.*, 2017
3	Schisandrin B	$HgCl_2$	Rats	Kidney	Liu *et al.*, 2011
4	*Bixin*	CH_3Hg	Rats	Liver, Hematological	Barcelos *et al.*, 2012
5	Norbixin	CH_3Hg	Rats	Liver, Hematological	Barcelos *et al.*, 2012
6	β-carotene	$HgCl_2$	Nile tilapia (*Oreochromis niloticus*)	Hematological	Elseady *et al.*, 2013
7	β-carotene + α-Tocopherol	CH_3HgCl	Mice	Liver, Brain, Kidney	Andersen & Andersen, 1993
8	α-Tocopherol	$HgCl_2$	Mice	Testes	Rao & Sharma, 2001
9	α-Tocopherol	$HgCl_2$	Rats	Liver, Kidney, Brain	Agarwal *et al.*, 2010a
10	α-Tocopherol	CH_3Hg	Rats	Fetus	Abd El-Aziz *et al.*, 2012
11	Ascorbic acid	$HgCl_2$	Human	Leucocytes	Rao *et al.*, 2001
12	Ascorbic acid	$HgCl_2$	Olive flounder (*Paralichthys olivaceus*)	Kidney	Lee *et al.*, 2016
13	Ascorbic acid	$HgCl_2$	Rats	Spleen, Hematological	Ibegbu *et al.*, 2014
14	Astaxanthin	$HgCl_2$	Rats	Kidney	Augusti *et al.*, 2008
15	Quercetin	$HgCl_2$	Rats	Kidney	Shin *et al.*, 2015
16	Quercetin	CH_3Hg	Rats	Hepatocytes, Leucocytes	Barcelos *et al.*, 2011a
17	Quercetin	$HgCl_2$	Human	Leucocytes	Barcelos *et al.*, 2011b
18	Lycopene	$HgCl_2$	Rats	Kidney, Liver	Augusti *et al.*, 2007; Yang *et al.*, 2011; Deng *et al.*, 2012
19	Lycopene	$HgCl_2$	Mice	Hematological	Cavusoglu *et al.*, 2009
20	Curcumin	$HgCl_2$	Rats	Liver, Kidney, Brain, Testes	Agarwal *et al.*, 2010b; Tamer & Saad, 2013; García-Niño & Pedraza-Chaverrí, 2014; Joshi *et al.*, 2017b, Liu *et al.*, 2017
21	Coumarin	$HgCl_2$	Human	Peripheral lymphocytes	Patel & Rao, 2015
22	Andrographolide	$HgCl_2$	Human	Peripheral lymphocytes	Patel & Rao, 2015
23	Fisetin	CH_3Hg	Rats	Fetus brain	Jacob & Thangarajan, 2017
24	Naringin	$HgCl_2$	Human	Leucocytes	Harisa *et al.*, 2014
25	Luteolin	$HgCl_2$ and $C_9H_9HgNaO_2S$*	Human	Mast cells	Asadi *et al.*, 2010
26	Luteolin	$HgCl_2$	Mice	Liver	Yang *et al.*, 2016
27	Luteolin	$HgCl_2$	Rats	Liver	Zhang *et al.*, 2017
28	Myricetin	CH_3Hg	Mice	Brain	Franco *et al.*, 2010
29	Thymol	$HgCl_2$	Human	Hepatocarcinoma (HepG2) cell line	Shettigar *et al.*, 2015
30	Vitamin K	CH_3Hg	Rats	Brain	Sakaue *et al.*, 2011
31	Berberine	$HgCl_2$	Rats	Brain, Liver, Kidney	Othman *et al.*, 2014; Moneim, 2015
32	Diallylsulphide	$HgCl_2$	Rats	Brain	Ansar, 2015
33	Pomegranate oil	$HgCl_2$	Rats	Kidney	Boroushaki *et al.*, 2014
34	Hydroxytyrosol	$HgCl_2$	Human	Erythrocytes and neuroblastoma	Officioso *et al.*, 2016
35	Glucan	$C_9H_9HgNaO_2S$*, $Hg(O_2CCH_3)_2$¶	Mice	Immunological	Vetvicka & Vetvickova 2009
36	*Selinum vaginatum* oil	CH_3Hg	Rats	Brain	Thiagarajan *et al.*, 2018
37	Argan oil	$HgCl_2$	Rats	Liver	Necib *et al.*, 2013

* Thiomersal, ¶ Mercury (II) acetate.

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Higher plants, whether dietary or medicinal, and their constituents traditionally possessed an overriding impact in drug discovery and served as the basis of premature medicines (Das *et al.,* 2013; Bhattacharya & Haldar, 2011). There is ample literature currently being available on usefulness of medicinal plants and constituents thereof against experimental mercury and other heavy metal/metalloid poisonings (Bhattacharya, 2017; 2018). Such reports of mercury are comparatively few as compared to those of lead, arsenic and cadmium. From the present literature survey it appears that medicinal plants have played a significant role in mitigation of experimentally induced mercury toxicity in animals. The crude or semi-pure plant extracts in general, exhibit antioxidant activities and thus show toxicity abrogative potential in reducing mercury induced oxidative insult. Besides, modulation of apoptosis is another less reported way of amelioration of mercury-induced organ toxicity by medicinal plant extracts. Mercury chelating property of plant extract *in vitro* is the least reported possible mechanism of protective effect operative along with antioxidant activity. Most of the literature neither discuss their possible clinical utility or ability in decreasing body mercury burden nor execute any endeavor to identify, isolate or characterize the active constituent(s). This is the major limitation of most of these works.

The present literature probe revealed that nearly all of the medicinal plants and natural products possessing preclinical mercury toxicity alleviative effects simultaneously revealed considerable innate antioxidant property by repression of mercury-induced oxidative stress by multimodal elevation of endogenous enzymatic and non-enzymatic fortification systems that resulted in mitigation of mercury-induced toxicity in animals. The 27 natural products tested are entrenched nutraceuticals or dietary supplements and these are all well described as natural antioxidants. This indicates the beneficial role of antioxidant supplementation and strongly corroborates the exhortation of antioxidant therapy to humans. At the experimental stage, a segment of researchers opines this respect (Patrick, 2002; Gupta *et al.,* 2015; Officioso *et al.,* 2016). Notwithstanding, the benefits of these compounds at organic and cellular level require validation in human subjects with mercury toxicity. So far no clinical study was found in the scientific literature where medicinal plants or phytochemicals suppressed any kind of mercury toxicity in humans. The inherent toxicity of mercury may be the limiting factor here.

Mercury chelating activity of plant extract *in vitro,* reported in a recent study (Pinho *et al.,* 2017) appears to be a novel protective mechanism which requires further studies involving concurrence *in vivo*. Few plant extracts showing mercury toxicity protective effects in bacterial and plant models exhibited *in vitro* iron chelating effects along with antioxidant properties (Sobral-Souza *et al.,* 2014; Cunha *et al.,* 2016). Such plants should be further investigated for possible mercury chelating potential in pre-clinical set up.

Recent reviews suggest that people, who are at risk of arsenic, lead and cadmium exposure, should consume vitamin and antioxidant rich food on a regular basis for prevention of possible toxicity (Zhai *et al.,* 2015; Bhattacharya, 2017; 2018). So far there is no work on the effect of dietary supplementation of edible or medicinal plants and/or their bioactive constituents in animals or humans with long-term and environmentally-relevant low levels of mercury exposure. Research work should be formulated in this facet.

The most studied natural products like ascorbic acid, α-tocopherol, quercetin, β carotene (Figures 1–4) in rodents require further comprehensive clinical

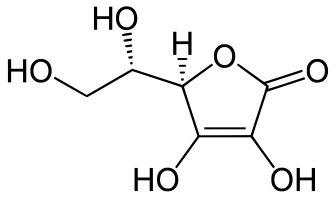

Figure 1. Vitamin C (ascorbic acid).

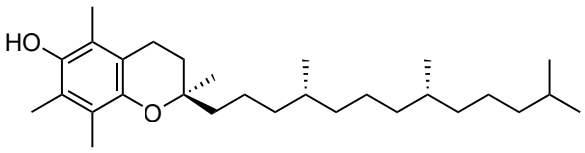

Figure 2. Vitamin E (α tocopherol).

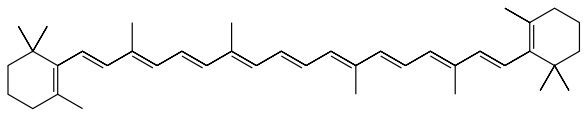

Figure 3. Beta carotene.

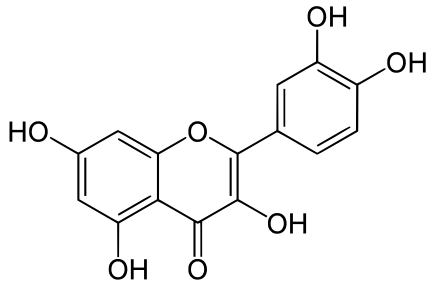

Figure 4. Quercetin.

exploitation. More of such pre-clinically worthy phytochemicals could be introduced for clinical studies. These agents could be used alone, in combination, or concomitantly with mainstream or newer chelating agents. These agents thus may aid in disease reversal or may serve as auxiliary, complementary or disease modifying agents and hence could help in palliative therapy by reducing the patient's agonies.

It is therefore hypothesized that the present facts and findings, although demonstrated principally in lower animal models, will have sustainable ameliorative potential against mercury toxicity and possible preventive mitigation to those subjects potentially susceptible to environmental mercury exposure. These apparently introductory studies could serve as pivot for further investigation which may lead to discovery of any potentially useful agent in clinical management of mercury toxicity in humans in due course, which may act by a distinct mode other than synthetic chelation, like modulation of oxidative stress, gene regulation or apoptosis. The material explored and presented in the current concise review appears to be quite motivating for further mechanistic pre-clinical and definitively designed clinical studies on dietary and medicinal plants and natural products in particular, for management of mercury toxicity hazard in humans.

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