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.
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 (Bernhof, 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 (Bernhof, 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 Selinium 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 (HgCl₂) was used most routinely as toxicant followed by methyl mercury (CH₃Hg).  

### 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 herbs 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; Afnian, 2015).
| Sl. No. | Botanical name         | Plant Part/Extractions used | Toxicant used | Experimental model | Organ(s)/system/cell line involved | Reference(s) |
|---------|------------------------|-----------------------------|---------------|--------------------|-----------------------------------|--------------|
| 1       | Zingiber officinale    | Rhizome                     | HgCl₂         | Rats               | Liver, kidney                     | Joshi et al., 2017a |
| 2       | Paullinia cupana       | Fruit                       | CH₃Hg         | Round worm (Caenorhabditis elegans) | Whole organism                  | Arantes et al., 2016 |
| 3       | Annona coriacea       | Leaf                        | HgCl₂         | Staphylococcus aureus, Escherichia coli, and Pseudomonas aeruginosa | Whole organism (cells)            | Júnior et al., 2016 |
| 4       | Lygodium venustum     | Aerial parts                | HgCl₂         | Escherichia coli   | Whole organism (cells)             | Figueredo et al., 2016 |
| 5       | Rheum palmatum        | Total anthraquinone extract of root | HgCl₂ | Rats               | Kidney                            | Gao et al., 2016 |
| 6       | Triticum aestivum     | Aerial parts                | HgCl₂         | Rats               | Liver, Haematological             | Lakshmi et al., 2014 |
| 7       | Dendropanax morbifera | Leaf                        | (CH₃)₂Hg      | Rats               | Brain                             | Kim et al., 2015  |
| 8       | Zanthoxylum piperitum | Glycoprotein (2PDC)         | HgCl₂         | Mice               | Liver, murine hepatocytes         | Lee et al., 2014  |
| 9       | Solanum sessiliflorum | Fruit                       | CH₃Hg         | Rats               | Testes                            | Frenedoso et al., 2014 |
| 10      | Acacia arabica        | Gum                         | HgCl₂         | Rats               | Kidney                            | Gado & Aldahmash, 2013 |
| 11      | Bacopa monnieri       | Aerial parts                | CH₃Hg         | Rats               | Brain                             | Sumathi et al., 2012; Ayyathan et al., 2015 |
| 12      | Camellia sinensis     | Leaf polyphenol extract     | HgCl₂         | Rats               | Kidney                            | Liu et al., 2011  |
| 13      | Allium sativum        | Bulb                        | CH₃Hg         | Human              | Peripheral leukocytes             | Abdalla et al., 2010 |
| 14      | Allium sativum        | Bulb                        | CH₃Hg         | Rats               | Brain                             | Bellé et al., 2009 |
| 15      | Tribulus terrestris   | Fruit                       | HgCl₂         | Mice               | Kidney, Liver                     | Kavitha et al., 2006; Jaga-deesan et al., 2005; Jaga-deesan & Kavitha, 2006 |
| 16      | Ginkgo biloba         | Leaf                        | HgCl₂         | Rats               | Brain, lung, liver, and kidney    | Sener et al., 2007 |
| 17      | Eruca sativa          | Seeds                       | HgCl₂         | Rats               | Kidney                            | Alam et al., 2007  |
| 18      | Ocimum sanctum        | Leaf                        | HgCl₂         | Onion (Allium cepa) | Root tip cells (meristems)        | Babu & Lima Maheswari, 2006 |
| 19      | Ocimum sanctum        | Leaf                        | HgCl₂         | Mice               | Hematological, Liver              | Sharma et al., 2002 |
| 20      | Halimeda incrassata   | Whole plant                 | CH₃Hg         | Rats, Mice         | Hematological, GT1-7 mouse        | Linares et al., 2004 |
| 21      | Juglans sinensis      | Leaf                        | HgCl₂         | Rabbits            | Kidney                            | Ahn et al., 2002  |
| 22      | Vitis vinifera        | Seed proanthocyanidin extract | CH₃Hg | Rats               | Brain                             | Yang et al., 2012  |
| 23      | Cucuma longa          | Rhizome                     | HgCl₂         | Rats               | Liver                             | Joshi et al., 2017b |
| 24      | Artemisia absinthium  | Aerial parts                | HgCl₂         | Rats               | Brain                             | Hallal et al., 2016 |
| 25      | Hygrophila auriculata | Whole plant                 | HgCl₂         | Rat                | Liver                             | Sridhar et al., 2013 |
| 26      | Eugenia jambolana     | Leaf                        | HgCl₂         | Escherichia coli, lettuce (Lactuca sativa) seeds | – | Sobral-Souza et al., 2014 |
| 27      | Eugenia uniflora      | Leaf                        | HgCl₂         | Escherichia coli, lettuce (Lactuca sativa) seeds | – | Cunha et al., 2016 |
| 28      | Psidium guajava var. pomifera | Leaf | HgCl₂ | Yeast (Saccharomyces cerevisiae) | – | Pinho et al., 2017 |
| 29      | Launaea taraxacifolia | Leaf                        | HgCl₂         | Rats               | Brain                             | Owowe & Arinola, 2017 |

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### 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                  | HgCl₂         | Rats               | Liver, Kidney                      | Joshi et al., 2017a |
| 2      | *Moringa oleifera* oil      | HgCl₂         | Rats               | Testes                            | Abarkwut et al., 2017 |
| 3      | Schisandrin B               | HgCl₂         | Rats               | Kidney                            | Liu et al., 2011 |
| 4      | *Bixin*                     | CH₃Hg         | Rats               | Liver, Hematological              | Barcelos et al., 2012 |
| 5      | Norbixin                    | CH₃Hg         | Rats               | Liver, Hematological              | Barcelos et al., 2012 |
| 6      | β-carotene                  | HgCl₂         | Nile tilapia (*Oreochromis niloticus*) | Hematological | Elseady et al., 2013 |
| 7      | β-carotene + α-Tocopherol   | CH₃HgCl       | Mice               | Liver, Brain, Kidney              | Andersen & Andersen, 1993 |
| 8      | α-Tocopherol                | HgCl₂         | Mice               | Testes                            | Rao & Sharma, 2001 |
| 9      | α-Tocopherol                | HgCl₂         | Rats               | Liver, Kidney, Brain              | Agarwal et al., 2010a |
| 10     | α-Tocopherol                | CH₃Hg         | Rats               | Fetus                             | Abd El-Aziz et al., 2012 |
| 11     | Ascorbic acid               | HgCl₂         | Human              | Leucocytes                        | Rao et al., 2001 |
| 12     | Ascorbic acid               | HgCl₂         | Olive flounder (*Paralichthys olivaceus*) | Kidney | Lee et al., 2016 |
| 13     | Ascorbic acid               | HgCl₂         | Rats               | Spleen, Hematological            | Ibegbu et al., 2014 |
| 14     | Astaxanthin                 | HgCl₂         | Rats               | Kidney                            | Augusti et al., 2008 |
| 15     | Quercetin                   | CH₃Hg         | Rats               | Kidney                            | Shin et al., 2015 |
| 16     | Quercetin                   | CH₃Hg         | Rats               | Hepatocytes, Leucocytes           | Barcelos et al., 2011a |
| 17     | Quercetin                   | HgCl₂         | Human              | Leucocytes                        | Barcelos et al., 2011b |
| 18     | Lycopene                    | HgCl₂         | Rats               | Kidney, Liver                     | Augusti et al., 2007; Yang et al., 2011; Deng et al., 2012 |
| 19     | Lycopene                    | HgCl₂         | Mice               | Hematological                     | Cavusoglu et al., 2009 |
| 20     | Curcumin                    | HgCl₂         | Rats               | Liver, Kidney, Brain, Testes      | Agarwal et al., 2010b; Tamer & Saad, 2013; Garcia-Nino & Pedraza-Chaverro, 2014; Joshi et al., 2017b, Liu et al., 2017 |
| 21     | Coumarin                    | HgCl₂         | Human              | Peripheral lymphocytes            | Patel & Rao, 2015 |
| 22     | Andrographolide             | HgCl₂         | Human              | Peripheral lymphocytes            | Patel & Rao, 2015 |
| 23     | Fisetin                     | CH₃Hg         | Rats               | Fetus brain                       | Jacob & Thangarajan, 2017 |
| 24     | Naringin                    | HgCl₂         | Human              | Leucocytes                        | Harisa et al., 2014 |
| 25     | Luteolin                    | HgCl₂ and CH₃HgNaO₄S^* | Human | Mast cells                        | Asadi et al., 2010 |
| 26     | Luteolin                    | HgCl₂         | Mice               | Liver                             | Yang et al., 2016 |
| 27     | Luteolin                    | HgCl₂         | Rats               | Liver                             | Zhang et al., 2017 |
| 28     | Myricetin                   | CH₃Hg         | Mice               | Brain                             | Franco et al., 2010 |
| 29     | Thymol                      | HgCl₂         | Human              | Hepatocarcinoma (HepG2) cell line | Shettigar et al., 2015 |
| 30     | Vitamin K                   | CH₃Hg         | Rats               | Brain                             | Sakaue et al., 2011 |
| 31     | Berberine                   | HgCl₂         | Rats               | Brain, Liver, Kidney              | Othman et al., 2014; Moneim, 2015 |
| 32     | Diallylsulphide             | HgCl₂         | Rats               | Brain                             | Ansar, 2015 |
| 33     | Pomegranate oil             | HgCl₂         | Rats               | Kidney                            | Borouchaki et al., 2014 |
| 34     | Hydroxytyrosol              | HgCl₂         | Human              | Erythrocytes and neuroblastoma    | Officiozo et al., 2016 |
| 35     | Glucan                      | C₆H₅HgNaO₄S^* and Hg(O₂CCH₃)_₂ | Mice | Immunological | Vetvicka & Vetvickova 2009 |
| 36     | Selinium vaginatum oil      | CH₃Hg         | Rats               | Brain                             | Thiagarajan et al., 2018 |
| 37     | Argan oil                   | HgCl₂         | Rats               | Brain                             | Necib et al., 2013 |

*Thiomersal, ¶Mercury (II) acetate.
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
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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