CHAPTER 3
PLANT PROFILE & REVIEW OF LITERATURE

3.1 PLANT PROFILE

Botanical name: *Smilax china*

3.1.1 Vernacular Names

<table>
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<tr>
<th>Tamil Name</th>
<th>Parangipattai</th>
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<tr>
<td>Hindi Name</td>
<td>Chobchini</td>
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<td>Sanskrit Name</td>
<td>Madusnuhi</td>
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<td>English Name</td>
<td>China root</td>
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3.1.2 Taxonomical Status

<table>
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<th>Plantae</th>
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<td>Division</td>
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<td>Species</td>
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3.1.3 Plant Description

*Smilax china* (Liliaceae) is a deciduous climber with rounded leaves and red berries. The root tubes of which furnish the drug known as china root. It is found in the south Indian states namely Andra Pradesh, Tamilnadu and Karnataka [55]

![Smilax china- Habitat](image)

Figure No.3.1 Smilax china- Habitat

![Root Tuber of Smilax china](image)

Figure No.3.2 Root Tuber of Smilax china

3.1.4 Ethnobotanical Uses

It possesses anti-inflammatory, diuretic, anti-diabetic, anti-psoriatic, digestive properties. It is also Heptoprotective, Nephroprotective and used in cases of Infertility.
3.2 REVIEW OF LITERATURE

3.2.1 LITERATURE REVIEW OF SMILAX CHINA

Cui, M. F. et al., 2001 [56], found that *Smilax china* can be used in chronic pelvic inflammatory diseases.

Liu Yong Ning et al., 2002 [57] reported a study on the pharmacological actions of *Smilax china* Linn on promoting blood circulation.

Jieyun et al., 2003 [58] reported that the aqueous extract from the rhizomes of *Smilax globra* possess immunomodulatory activity in the later phase of adjuvant-induced arthritis in rats.

Zhong Yao Cai., et al., 2003 [59] said that *Smilax china* could significantly inhibit AA mouse’s secondary inflammatory swelling, reduce thymus and spleen weights, decrease CD4/CD8, but had little influence on B Cell. It acts regulating cell-mediated immunity, but has little effect on humoral immunity.

Liu shi-wang et al., 2004 [60] have been reported the inhibition effect of the ethanolic extract of *Smilax china* Linn on micro organisms.

Ruan J, et al., 2005 [61] have isolated dihydrokaempferol-5-O-beta-D-glucoside (I), beta-sitosterol (II), daucosterol (III) from *Smilax china*.

Kuo YH., et al., 2005 [62] has found bioassay-guided fractionation of an ethanol extract of *Smilax china* which led to the isolation of nine phenylpropanoids including six new compounds, smilasides, and three known phenylpropanoids, smiglaside E, heloniosides B, and 2’,6’-diacetyl-3,6-diferuloylsucrose. Structural elucidation of isolates was based on spectroscopic data analysis. These new phenyl propanoids were evaluated against several human tumour cell lines.

Huang si-hang et al., 2006 [63] have studied the effective ingredients of *Smilax china* Linn for treating chronic pelvic inflammation.
Xiao et al., 2006 [64] have reported that the aqueous extract of the tuber of *Smilax china* possess anti-inflammatory and anti-nociceptive activities in rats.

Zhongguo Zhong Yao Za Zhi., 2006 [65]. The ethyl acetate extract of *Smilax china* possesses remarkable anti-inflammatory effects on acute inflammation, and also displays anti-inflammatory effects on the chronic inflammation to a certain extent.

Shao B, et.al., 2007 [66] , Isolated Steroidal saponins were isolated from the BuOH extract of *Smilax china*. Their structures were elucidated on the basis of MS, 1D and 2D NMR spectroscopic analyses and chemical evidence. In the bioassay tests, all compounds showed inhibitory effects on cyclooxygenase-2 enzyme (COX-2) activities at final concentration of 10(-5) M, and only compound 5 showed an inhibitory effect on production of TNFalpha (tumor necrosis factor alpha) in murine peritoneal macrophages at the same concentration.

Yuan-Li Li et.al., 2007, [67] studied the anticancer activity of eight crude extracts of *Smilax china* L. rhizome (SCR) against HeLa cells which was assessed by MTT assay and clonogenic assay, the fraction rich in flavonoids had shown good activity against HeLa cells.

Chen Dong et al., 2007 [68] had studied the effect of *Smilax china* on chronic pelvic inflammation induced by coliform bacteria.

Wantana Reanmongkol et.al., 2007 [69] suggested that the ethanol extract of *smilax corbalaria* rhizomes possess anti-inflammatory activity, and that its actions on the inflammation may be different from those of aspirin.

Guo Yong-Qing et al., 2008 [70] have done a study on the technology of Tissue culture on Smilax china Linn.

Ozsoy et al., 2008 [71] had reported that the leaf extract of *Smilax china* Linn possess antioxidant activity.

Shu Xiao-Shun et al., 2010 [72] have evaluated the in vitro anti microbial activity of *Smilax china* Linn extracts.
Chen Let.al., 2011 [73], found that *Smilax china* L. also exhibits anti-hyperuricemic and nephroprotective activity in hyperuricemic animals.

Venkidesh R., et.al., 2010 [74], evaluated the methanol extract obtained from rhizomes of *Smilax china* L. for hepato protective activity in rats by inducing liver damage by carbontetrachloride. The methanol extract at an oral dose of 200 and 400mg/kg/b.w. exhibited a significant (*P* < 0.05) protective effect by lowering serum levels of SGOT, SGPT, alkaline phosphatase and bilirubin and increasing the levels of total protein levels as compared to silymarin used as a positive control. These biochemical observations were supplemented by histopathological examination of liver sections. The activity may be a result of the presence of flavonoid compounds.

Rajesh Bhati et.al., 2011 [75] found the Pharmacognostical standardization, extraction and antidiabetic activity of *Smilax china* L. rhizome, and among various extracts, the hydroalcoholic and aqueous fractions exhibited anti-diabetic activity in rats with alloxan-induced diabetes.

Vijayalakshmi A et.al., 2011 [76], found the Anticonvulsant and neurotoxic effects of ethanolic extract and ethyl acetate fraction of *Smilax china* which will be useful in controlling petitmal & grandmal seizures.

Anita Murali et.al; 2012 [77], stated the Hepatoprotective properties of the methanol extract of the leaf of *Smilax zeylanica* in paracetamol induced hepatotoxicity in Wistar rats.

C.D.Sarawathi et.al., 2012 [78] investigated the protective effect of *Smilax china* on spermatological parameters subjected to forced swimming stress and Testicular antioxidant activity.

Hye-Kyung Seo, et.al, 2012 [79], documented that *Smilax china* L. possessed antioxidant and antimicrobial substances, and suggested that the ethanol extract can be applied in food and cosmetic industry.
Solomon Raju B.G.et.al., 2012 [80] observed that *Smilax china* is hepatoprotective CCl4 toxicity. Ethanolic extract of *Smilax China* root was evaluated using CCl4 induced hepatotoxicity in albino rats. The degree of protection against liver toxicity was determined by measuring the serum biochemical parameters viz. SGPT (serum alkaline phosphatase), SGOT (serum glutamine oxaloacetate transaminase), SALP (serum alkaline phosphatase), ALP and Bilirubin (Direct and Total). In addition morphological changes of liver like wet liver volume and wet liver weight were recorded. Histopathological findings also showed positive affinity towards the hepatoprotective activity.

Jayaprakasam et.al., 2013 [81], determined the quantitative determination of diosgenin in polyherbal formulation and various extracts from *Smilax china*.

Wein-Xin Wang et.al., 2014 [82], studied the anti-HIV-1 activity of extracts and phenolic compounds from *Smilax China*.

### 3.3 LITERATURE REVIEW OF MERCURIC CHLORIDE

#### 3.3.1 Low dose mercury affects nervous system of foetus and children

Vulnerable periods during the development of the nervous system are sensitive to environmental insults because they are dependent on the temporal and regional emergence of critical developmental processes (i.e. proliferation, migration, differentiation, synaptogenesis, myelination, and apoptosis). Evidence from numerous sources demonstrates that neural development extends from the embryonic period through adolescence. Different behavioural domains (e.g. sensory, motor and various cognitive functions) are observed by different brain areas. Of critical concern is the possibility that developmental exposure to neurotoxicants may result in an acceleration of age-related decline in function. This concern is compounded by the fact that developmental neurotoxicity that results in small effects can have a profound societal impact when amortized across the entire population and across the life span of humans [83].

Maternal consumption during pregnancy of methyl mercury contaminated fish in Japan and of methyl mercury contaminated bread in Iraq caused psychomotor retardation in the offspring. Studies in Iraq suggested adverse foetal effects when maternal hair mercury
concentrations were as low as 20 ppm [84]. Mothers consuming diet containing mercury pass the toxicant to foetus [85].

3.3.2. Low dose mercury toxicity affects reproduction

Despite the potential exposure to dietary mercury, most are unfamiliar with their state’s mercury fish consumption advisory. Until source control and environmental remediation efforts can reduce the environmental burden of mercury below levels of concern, combined sport and commercial fish consumption advisories will remain the primary means of reducing human exposure to methyl mercury [86]. If concentration of methyl mercury is very high in mothers they do not conceive, if they do there is low rate of pregnancy and the foetus is aborted or is stillborn. At even lower doses conception and live birth occurred but the child suffered from serious neurological symptoms [87].

Women exposed to mercury vapour not exceeding the time weighted average air concentration of 0.01 mg/m³ declared higher prevalence and incidence rates of menstrual disorders, primary subfecundity, and adverse pregnancy outcome [88]. According to WHO report 0.5 mg/kg Hg contaminated food should not be sold for human consumption. Hg accounts for sub-fertility in Hong Kong males [89]. Organic as well as inorganic mercury decreases the percentage of motile spermatozoa. After 30 min incubation with 20 mol methyl mercuric chloride less than 5% of human spermatozoa only were found motile [90].

Atkinson et al. (2001) [91] investigated the reproductive toxicity of mercuric chloride administered in drinking water to male and female rats from age 30 days through delivery, for two generations. The doses administered were 0, 0.5, 1.0, 1.5 mg/kg-day for males and 0, 0.75, 1.5 and 2.5 mg/kg-day for females of the F0 generation; doses were the same for the F1 generation, except that the highest dose was omitted.

Fertility was affected in a dose related fashion for the treated F0 groups, with reduction by a third from the control population at the lowest dose. However, in the F1 generation no decrease in fertility rates was noted. Live births/litter were reduced in a dose-related fashion for the F1 but not the F2 generation. There was also a dose-related decrease in body weight and the 4th day survival rate in the F1 generation.
In the more recent study, Khan et al. 2004., [92] exposed mice to mercuric chloride for one generation. Male and female mice were given 0, 0.25, 0.5 or 1.0 mg/kg/day of mercuric chloride in their drinking water. All treated groups had a decrease in fertility index of about 60 per cent. There were four live litters for 25 cohabited pairs, compared to 11 for 25 pairs in the control group, which is unusually low. There were significant decrease in live pups/litter and live birth index at the highest dose only. All other measured parameters were within a normal range.

Both of these studies have serious experimental and data reporting deficiencies. In the rat study, the tabulated implant efficiencies are not supported by the data provided, and the offspring sex ratios vary widely without being noted; in both studies, the reported mean live pups/litter are inconsistent with the data provided. At the highest dose in the rat study, the stated number of F1 males is equal to the total number of live offspring, which contradicts the reported sex ratio. OEHHA concludes that these reproductive studies are not suitable for quantitative risk assessment.

Two studies by another group on certain parameters relating to the reproductive process were also found. Ramalingam et al. 2002., [93] orally administered 1 mg/kg/Bw mercuric chloride to male rats for 30 days. Four products related to sperm maturation were evaluated in their spermatozoa at the end of that period: glycercyl phosphoryl choline, sialic acid, carnitine and acetyl carnitine. Another group of rats was exposed and then withdrawn from treatment for thirty days, upon which their spermatozoa were collected and these indices measured. The first group showed significantly decreased levels of all the markers compared to untreated rats. For the second group, the marker levels were not significantly different from untreated animals.

In the second study, Ramalingam et al., 2003 [94] exposed rats for thirty days to mercuric chloride 1.0 and 2.0 mg/kg/day. They measured the circulating hormones testosterone, luteinizing hormone, prolactin, and follicle-stimulating hormone. Testosterone and luteinizing hormone were significantly depressed at both doses, and the other two only at the highest dose.

The studies of Ramalingam et al. (2002, 2003) [93,94] provide evidence that mercuric chloride may be a reproductive toxin, but have limitations for defining a critical
effect for risk assessment. These studies focused only on assessment of the specific parameters without providing any clinical information about the state of the animals, or gross or histological evaluation of the testes or its constituents. Moreover, there is some uncertainty regarding the dosages for the second study. However, if a health-protective concentration in drinking water were derived from these studies, it would be higher than that provided by the NTP (1993) study.

3.3.3 Low dose mercury affects nervous system of adults

Low concentrations of some metals, including mercury can directly induce synuclein fibril formation which are the major constituent of intracellular protein inclusions (Lewy bodies and Lewy neurites) in dopaminergic neurons of the substantia nigra leading to Parkinson's [95]. Moreover, low concentrations of cobalt and mercury are able to induce oxidative stress, cell cytotoxicity which may lead to neuro degenerative diseases, such as Alzheimer's and Parkinson's diseases [96]. Mercury binds to sulphhydryl groups of proteins and disulfide groups in amino acids resulting in inactivation of sulfur and blocks related enzymes, cofactors and hormones [97].

3.3.4 Low dose mercury toxicity affects renal system

Kidneys accumulate highest levels of mercury compared to brain and liver [98]. Renal toxicity of mercuric chloride is well documented in literature. Nuclear factor B (NF- B) is a thiol dependent transcriptional factor that promotes cell survival and protects cells from apoptotic stimuli. Mercuric ion Hg (2+) is one of the strongest thiol-binding agents known. It impairs NF- B activation and DNA binding at low M concentrations in kidney epithelial cells leading to apoptosis [99]. Renal function and immunologic markers among chloralkali workers with long-term low exposure to mercury vapour when examined indicated an effect of exposure on the kidney proximal tubule cells [100].

Renal dysfunction increases plasma Creatinine level upon methyl mercury intoxication for 5 ppm mercury for 2 years [101]. Decrease in protein (brain and liver) acid and alkaline phosphatase and glutathione S transferase was observed upon 0.5 mol/ml mercury for five consecutive days, while thiobarbituric acid reactive substances (TBARS)
were found to be significantly increased in brain and liver indicating free radical stress [102].

3.3.5 Mercury affects Endocrine Function

Tiwari and Bhattacharya, 2004 [103] evaluated the effect of mercuric chloride on thyroid function by measuring thyroid peroxidase and thyroxine, in a study of the protective effects of phospholipids on mercury toxicity. Groups of mice were given approximately 10 mg/kg/day of mercuric chloride for 7, 14, or 21 days. The thyroxine and peroxidase levels were depressed by nearly one half compared to that of controls. Daily co-administration of an “essential phospholipid” preparation antagonized these effects of mercury. These data suggest mercuric chloride impacts thyroid function; however, the dose used is rather high compared to other critical effect doses.

3.3.6 Low dose mercury toxicity affects immune system

The immune system plays an important regulatory role in the host defense mechanisms. Persons with certain autoimmune and allergic diseases, such as systemic lupus, multiple sclerosis, autoimmune thyroiditis or atopic eczema, often show increased lymphocyte stimulation by low doses of inorganic mercury [104]. It has been repeatedly shown that the heavy metal mercury can induce or exacerbate lupus like autoimmunity in susceptible strains of rats and mice. A hallmark of such autoimmune induction is the accompaniment of an immune shift, in which there is usually an initial skewing toward a Th2-like immune environment [105].

Exposure to methyl mercury significantly enhanced lymphocyte responsiveness in most of the exposed groups at the low concentration of 5 g/l, with the highest proliferative response (four-fold increase) in the methyl mercury chloride group [106]. Prolonged exposure to low doses of inorganic mercury, suggested an in vivo functional defect of the monocyte-macrophage system [107]. The exposure to very low levels of metallic mercury led to subtle impairment of circulating monocyte and NK cells (as percentages) in a particular group of workers, even though they remained clinically asymptomatic [108].
Recent research on inorganic mercury associated immunotoxicity is less intense than it was during the 1990s, but work continues along several promising mechanistic lines using sensitive strains of rats, mice and other animals. In particular, specific strains of mice have been developed which show mercury induced autoimmunity, in which the onset of autoimmunity seems to be linked with the MHC (major histocompatibility complex) H-2 genes. Thus the strains of mice with specific H-2 haplotypes s and q are the most likely to manifest mercury induced autoimmunity, in which antibodies are produced against the nucleolar protein fibrillarin (Nielsen and Hultman, 2002.)[109].

In a study comparing eight different strains of autoimmune-susceptible strains of mice, (Nielsen and Hultman, 2002,) [109] exposed groups of male and female mice to radioactively-labelled mercuric chloride in their drinking water at doses from 0.5 to 1.0 mg/kg/day for ten weeks before sacrifice. Mercury containing antibodies were monitored. In addition, serum IgE was monitored to demonstrate the onset of autoimmunity. The authors found an increase in antibody titre associated with mercury dose and exposure duration, which reached a steady state over time. Female mice tend to respond to mercury with larger, earlier increasing, antibody titres than males.

In another study, Via et al. (2003) [110] studied whether low doses of inorganic mercury promoted autoimmunity in a mouse lupus model (splenocyte induced graft versus host disease). Groups of five BDF1 mice of a non-autoimmune susceptible strain were injected with 0, 20 or 200 μg/kg mercuric chloride every other day for 15 days; five days thereafter they received mouse splenocytes intravenously to produce a mild graft vs. host disease. Surviving mice were terminated at four months, based on morbidity of the animals. The mercury pre-treatment apparently resulted in increased mortality, glomerular nephritis, and proteinuria, with greater effects at 20 than at 200 μg/kg mercuric chloride. At sacrifice, there was only one mouse remained in the low-dose group and three in the high-dose group, while all five survived in the control group. The authors conclude that the mercury pre-treatment increased the susceptibility of the mice to graft vs. host disease, and hypothesized that “the two doses of mercuric chloride may have different effects on autoimmunity.” The authors acknowledge that neither mercury dose alone results in immunotoxicity in this strain. Considering the small number of mice per group, lack of a
dose-response, the non-oral route of administration, and lack of effects of mercury alone, the results do not appear usable for quantitative risk assessment of inorganic mercury.

Mellergard et al. (2004) [111] studied the systemic autoimmune response in H-2 mice, a condition with antinucleolar antibodies targeting the nucleolar protein fibrillarin, transient polyclonal B-cell activation, hyperimmunoglobulinemia, and systemic immunoglobulin deposits. Mice were given 6 mg/kg/day of mercuric chloride in drinking water for 22 weeks. Pre-treatment with several immune response inhibiting agents suppressed the formation of antinucleolar antibodies with mercuric chloride. Mercuric chloride induced a strong systemic autoimmune response, including renal IgG deposits in tight skin mice. However, inorganic mercury did not cause dermal fibrosis, the precursor to skin thickening (Hansson and Abedi-Valugerdi., 2004, [112]. The tight skin mouse was developed to have a propensity toward skin thickening, to experimentally mimic human scleroderma.

It was reported that mercuric chloride inhibits nitric oxide production in cultured murine macrophages, while modulating p38 cytokine expression by mitogen active protein kinase (Kim et al., 2002) [113]. In a more recent study, Kim and Sharma(2003) [114] explored the effect of mercuric chloride on murine T and B lymphoma cell lines and found an increase in reactive oxygen generation with an increase in necrosis and apoptosis.

In earlier studies, mercuric chloride administration to the Brown Norway rat had been shown to result in Th2-dominated autoimmunity with increased immunoglobulin E concentrations and gut vasculitis, with the involvement of mast cells in the early phase. Viven et al. (2004) [115] investigated the development of caecum vasculitis upon injection of mercuric chloride into Brown Norway rats, and found that mast cells do play a key role. In this case the autoimmunity induced by mercuric chloride apparently resolved itself after two weeks, and then provided resistance to further challenges by mercuric chloride. This resistance seemed to be due at least in part to decreased numbers of mast cells in the gastric mucosa.

None of the above mentioned studies is suitable for derivation of a critical dose for risk assessment; they either used higher doses than those used to derive the PHG, or involved mercuric chloride directly injected into the animals, which is an inappropriate
administration route for drinking water risk assessment. However, it is important to note that these studies indicate that critical doses for inorganic mercury effects on sensitive strains of experimental animals are about 1 mg/kg/Bw, and thus support the critical dose selection for the existing PHG. As shown below, the critical effects used for the existing PHG development were decrease in rat body weight gain and increase in relative and absolute kidney weights observed in the subchronic (6 month) study at doses of 0.46 mg/kg/day and greater, with a NOAEL of 0.23 mg/kg-day.

3.3.7 Low dose mercury toxicity affects genome

The reports for mercury genotoxicity have been coming since 1980. First report showing clear cytotoxic effects of 20 years exposure to methyl mercury on human population with a wide range of mercury exposure, based on a well known biological marker, hair mercury a clear relation between methyl mercury contamination and cytogenetic damage in lymphocytes at levels well below 50 mg/g was found. Although their results strongly suggest that, under the conditions examined, methyl mercury is both a spindle poison and a clastogen, the biological significance of these observations are as yet unknown [118]. A long-term follow up of these subjects should be under taken. Theoretically, methyl mercury induced chromosome damage in germline cells could give rise to abnormal offspring. Mercuric chloride exposure in short term blood cultures lead to high sister chromosome exchanges and induced C-anaphases (abnormal mitosis) [119]. The chromosomal genotoxicity of mercury has been attributed to its interaction with microtubule assembly Mercury inhibits microtubule assembly at concentrations above 1 M, and inhibition is complete at about 10 M [118].

3.3.8 Human Population Studies on Mercuric Chloride

Silva et al., (2004) [119] investigated the potential association of mercury exposure with indicators of autoimmune disease in persons exposed to mercury in the Brazilian Amazon area. One group (n = 98) was exposed to mercury (probably metallic) via gold mining, and another group (n = 140) was exposed primarily by eating fish contaminated by methyl mercury); controls (n = 98) were presumed to have low exposures to mercury, although the median of their hair mercury levels was similar to the second group. The gold miners had a substantially higher rate of elevated antibodies to nuclear and nucleolar
protein than the other two groups, and also a much higher prevalence of active malaria. The population presumed to have higher exposure to methyl mercury had higher antibody levels than the control population.

3.3.9 Molecular mechanisms of low dose mercury toxicity

It is difficult to classify the molecular basis of low dose mercury toxicity to tissues and organ systems initially due to lack of data, finally because it is a complex cascade of interrelated events that may directly or indirectly translate into pathological state of a particular organ system. Its neurotoxicity to cerebellum at higher doses has been related to impairment of motor function [120] and its genotoxicity to neuronal cells in foetal state may result in abnormal off springs or foetal deaths but its exact mode of activity at low doses, particularly at environmentally relevant concentrations which lead to subtle delays in neurodevelopment remain unexplored. Basically it blocks essential functional groups in biomolecules and also displaces essential metal ions from them. Mercuric ion is known as one of the strongest thiol binding agents.

Intracellular mercury therefore attaches itself to thiol residues of proteins particularly glutathione and cysteine resulting in inactivation of sulfur and blocks related enzymes, cofactors and hormones [97]. Its molecular interactions with sulphydryl groups in molecules of albumin, metallothionein, glutathione, and cysteine have been implicated in mechanisms involved in renal [121] and neuronal toxicity [122,123]. The other functional groups besides SH for which mercury has high affinity include, CONH2, NH2, COOH and PO4[124]. It also blocks immune function of Mn and Zn leading to deficiency of principal antioxidant enzyme, superoxide dismutase, CuZn-SOD and Mn-SOD [125] which has a role in various diseases, including Alzheimer's disease, Parkinson's disease, Cancer, Downs syndrome, Dengue, etc. [126]. Moreover, in cerebellar granule cells in culture, low concentration of mercury causes a rise in [Ca2+] which may trigger a cascade of events leading to impairment of mitochondrial energy metabolism and generation of reactive oxygen species [123]. Mercury by inhibiting glutamic acid uptake further sensitises neurones to excitotoxic injury [123].

The combination of these mercury triggered events enhances free radical stress that has been cited widely in literature [98,127].
Free radical stress has been frequently reported as key player in disease progression of as many as 50 diseases [128,129], aging and degenerative disorders [130]. Mercury obstructs neurotransmission by acting as a strong competitive inhibitor of muscarinic cholinergic receptors and this aspect awaits further study. The renal changes in workers with chronic low level exposure to mercury indicated increased tubular antigens and enzymes, altered levels of biochemical enzymes, such as decreased urinary output of eicosanoids and glycosaminoglycans, and a more acidic pH. However since urinary function was normal, the clinical significance of these findings is yet to be determined [131].

The observed reduced lymphocyte proliferation associated with low levels of mercury [107,108] may translate into reduced resistance to disease. Low level, nontoxic inorganic mercury pre-exposure may interact with other risk factors, genetic or acquired, to promote subsequent autoimmune disease development [132]. Though molecular basis of immunotoxicity of mercury is relatively less studied, recent researches show that low dose mercury suppresses immune response by reducing nitric oxide (NO) synthesis by inhibition of the nuclear factor B (NF- B) pathway and modulating cytokine expression by p38 mitogen-activated protein kinase (p38 MAPK) activation as observed in J774A.1, murine macrophage cell line [133]. Mercury salts cause allergy by inducing IgE synthesis and promoting Th2 - cytokine profile [134].

Recently in a major break through, rise in apolipoprotein-E 4 genotype has been proposed as a biomarker for low-dose mercury toxicity [135] and rise in apolipoprotein-E due to mercury has been advocated as a pathogenic factor for Alzheimer disease [135,136].