Chapter 1

Introduction

1.1 HISTORY

Cadmium (Cd) is a chemical element which is soft, silvery white and ductile with a faint bluish tinge. It was discovered in 1817 by Friedrich Stromeyer and Hermann (Germany) during the same period at different incidents, as an impurity in zinc oxide/carbonate. Cadmium has an atomic number of 48, atomic weight of 112.40, density of 8.65gcm$^{-3}$, melting point of 321°C and a boiling point of 765°C. It belongs to group IIB elements of the periodic table and has stable +2 oxidation state in aqueous solution. There are eight stable isotopes of cadmium - 106Cd, 108Cd, 110Cd, 111Cd, 112Cd, 113Cd, 114Cd, and 116Cd, out of which 112Cd and 114Cd are the most abundant (Nriagu, 1980). Cadmium is a rare element (67th element in order of abundance) and is present in trace amount in the environment. Its average concentration is 0.1-0.2 ppm in the earth’s crust and $\sim$ 1 μg/g in the lithosphere. It is strongly chalcophilic like Zinc (Zn). In several aspects cadmium is similar to zinc as it is present next to zinc in the periodic table. It is almost associated to zinc in mineral deposits and other earth materials. Compared to other metals such as lead and mercury, it does not have a long history of use. Cadmium was not used extensively until the mid-20th century. Yearly, 30,000 tonnes of cadmium is produced mainly for the manufacture of nickel-cadmium (NiCad) batteries, pigments, chemical stabilizers, metal coatings and alloys worldwide (Shimada et al., 2008). Cadmium was discovered in 1817, but was not used commercially until the end of the 19th century. Before the First World War, cadmium was not usually recovered from zinc plants or other nonferrous metal plants, which resulted in an uncontrolled contamination of the environment for decades. This metal was first used in paint pigments and as a substitute for tin in First World War. But, since Second World War, it has been used in batteries, pigments, alloys, electroplating and coating, and stabilizers for plastics (IARC, 1993; Llewellyn, 1994). However, in the late 20th century, the percentage of cadmium used globally in the production of NiCad batteries increased significantly
while the percentages used in other traditional end uses declined dramatically due to environmental and health concerns (Tolcin, 2009).

1.2 PRODUCTION

US Environmental Protection Agency listed cadmium as one of 126 priority pollutants (Waisberg et al., 2003) and according to the Agency for Toxic Substances and Disease Registry (ATSDR) in the United States cadmium is ranked as the 7th priority toxicant (Fay and Mumtaz, 1996). Cadmium has been classified as number 1 category human carcinogen by the International Agency for Research on Cancer of USA (IARC, 1993). Today, about three-fourth of cadmium is used as an electrode component in alkaline batteries, while the remaining being used in pigments, coatings, and platings and as a stabilizer for plastics. The average annual production of cadmium throughout the world increased basically from 20 tonnes in the 1920s, to markedly increased about 12,000 tonnes in the period of 1960-1969, and to about 17,000 tonnes in 1970-1984. Since 1987 it has been fluctuating around 20,000 tonnes (WHO, 2000). In 2005, the annual production of cadmium worldwide was estimated to be 20,000 metric tonnes (Sarkar et al., 2013).

![Figure 1.1 Major producers of cadmium](http://www.mapsofworld.com/minerals/world-cadmium-producers.html)
1.3 ROUTES OF EXPOSURE

In human beings, normally absorption takes place either by ingestion or inhalation. Dermal exposure is negligible. In industries, cadmium can be hazardous both by inhalation and ingestion and can cause acute and chronic intoxications. Cadmium dispersed in the environment can persist in soils and sediments for decades. When consumed by plants from soil, cadmium gets concentrated along with the food chain and ultimately gets accumulated in the body of people eating contaminated foods. Cadmium is also present in tobacco smoke, further contributing to human exposure. The amount of cadmium consumed daily through food in many countries is in the range of 10 to 20 µg per day. Tobacco smoking is an important additional source of exposure for smokers. Since one cigarette contains approximately 1 to 2 µg cadmium, smoking one pack per day results in a daily intake of cadmium that approximates to that derived from food. Absorption through the oral route varies around 5 percentage but can be increased up to 15 percentage in subjects with low iron storage. When exposure is by inhalation, it is estimated that between 10 to 50 percentage of cadmium is absorbed, depending on the particle size and the solubility of cadmium compounds. In the case of cadmium in tobacco smoke (mainly in the form of cadmium oxide), an average of 10 percent of cadmium is absorbed (Bernard, 2008).

1.4 CADMIUM – INDUSTRIAL USES

About 30,000 tonnes of cadmium is produced annually worldwide, mainly for NiCad batteries, pigments, chemical stabilizers, metal coating and alloys (Flora, 2009). Cadmium is found in various forms and they are used for various purposes listed below (Huff et al., 2007).

Cadmium chloride – Preparation of cadmium sulphide, dyeing and calico printing, electroplating, pigment manufacture, vacuum tubes and fungicide (previously used)

Cadmium hydroxide – alkaline batteries

Cadmium nitrate – glass and porcelain colorant and photographic emulsions
Cadmium oxide – silver zinc storage batteries, heat stabilizers for plastics and alloys

Cadmium sulphate – electroplating

Cadmium stearate – lubricant and plastic stabilizer

Cadmium sulphide – pigment

1.5 SOURCES OF CADMIUM EXPOSURE

Human beings are exposed to cadmium from all environmental media including air, drinking water, cigarette smoke and food. Cigarette smoke and food are the major sources of cadmium exposure, while, air and drinking water contribute to a lesser extent. The natural source of cadmium is volcanic emissions, weathering, erosion, and river transport. The major routes of occupational exposure are inhalation of dust and fumes and incidental ingestion of dust from contaminated hands, cigarettes or food (Hallenbeck, 1984).

World Health Organization (WHO) cadmium guidelines

Provisional tolerable monthly intake (PTMI) of cadmium:
- **Food** - The Joint Food and Agriculture Organization of the United Nations (FAO)/WHO Expert Committee on Food Additives (JECFA) recently in 2010 established a provisional tolerable monthly intake for cadmium of 25 µg/kg body weight.
- **Drinking water** - 3µg/l
- **Air** - 5ng/m³ (annual average)

1.5.1 SMOKING

The tobacco plant naturally accumulates relatively high concentrations of cadmium into leaves. Thus, smoking tobacco is an important source of exposure, and the daily intake may exceed from that of food for heavy smokers. Cigarette smoking can cause significant increase in the concentration of cadmium in kidneys, the main target organ for cadmium toxicity. World Health Organization (WHO) estimates that smoking

1.5.2 SOIL

Absorption of cadmium by soil depends strongly on the pH, with its mobility decreasing with increasing alkalinity (Alloway, 1995; Holm et al., 2003). Soil organic matter is also an important factor (Holm et al., 2003; Kabata-Pendias and Mukherjee, 2007). Sauve et al (2000) found that the variability in soil-water partition coefficients for cadmium collected from 70 different studies and above was largely explained by differences in soil pH, soil organic matter content and total cadmium concentration. Strobel et al (2005) observed that anthropogenic cadmium may be more readily released from soil than pedogenic cadmium associated with soil minerals such as apatite (a group of phosphate minerals).

Soil Guideline Values (SGV)

Soil Guideline Values (SGVs) for cadmium are presented according to land use. The SGVs apply only to cadmium and its inorganic compounds (Environment agency, 2009).

- Residential - 10 (mg kg\(^{-1}\) DW)
- Allotment - 1.8 (mg kg\(^{-1}\) DW)
- Commercial - 230 (mg kg\(^{-1}\) DW)

(DW – dry weight)

1.5.3 AIR

Higher concentration of cadmium in air are associated with heavily industrialized cities, mainly due to refinery and smelting activities, (Hiatt and Huff, 1975) where the levels may be several hundred times higher than those found in non-contaminated areas (Friberg et al., 1974). The concentration of cadmium in air in non-industrial areas is about 0.000001 mg/m\(^3\) (Lewis et al., 1972). Air pollution mainly occurs due to the highest potential exposure of cadmium by production and refining, NiCad battery production, cadmium pigment manufacturing and formulation, cadmium alloy
production, mechanical plating, zinc smelting, soldering and polyvinyl chloride compounding (Huff et al., 2007). Mainly cadmium present in the air is associated with particulate matter in the respirable range (diameter 0.1-1.0µm). Cadmium is released into the atmosphere predominantly as elemental cadmium and cadmium oxide and from some sources as cadmium sulphide by coal combustion and nonferrous metal production. Cadmium residence time in air is relatively short (days to weeks) but is sufficient enough to allow long-range transport in the atmosphere.

1.5.4 DRINKING WATER

About 98% of the ingested cadmium comes from terrestrial foods while 1% comes from aquatic foods and another 1% from drinking water (Van-Assche, 1998). Cadmium in water gets accumulated more rapidly in the sediments than in living organisms. Twenty percentage of cadmium in water was found in suspended particles. Ground water contamination from electroplating operations has been reported to cause concentrations up to 3.2 mg/l cadmium (National Research Council, 1977).

Reported background levels of cadmium in uncontaminated compartments extend over several orders of magnitude (all values in µg/L)

- Freshwater 0.05 to 0.2
- Coastal seawater up to 0.05
- Open ocean seawater 0.01 to 0.1
- Riverine and lake sediments up to 5000
- Marine sediments 30 to 1000
- Soils of non-volcanic origin 10 to 1000.
- Typical Ocean Concentrations of Cadmium: EPA 1981: 0.00011 mg/l (0.11 µg/L).
1.6 CADMIUM – PROPERTIES

1.6.1 PHYSICAL PROPERTIES

CADMIUM METAL (Cd)

It is a silvery-white, odorless and lustrous blue-tinged malleable metal. Its molecular weight is 112.41, and its oxidation state is +2. Melting point of cadmium is 320.9°C, density is 8.642 (g/cm$^3$). It is insoluble in water and soluble in ammonium nitrate, dilute nitric acid and hot sulphuric acid. It is usually not present in the environment in its pure form, but is present as a mineral compound with other elements such as oxygen (cadmium oxide), chlorine (cadmium chloride), or sulphur (cadmium sulphate, cadmium sulphide) (ATSDR, 1998). Cadmium closely resembles zinc; they mainly differ in their boiling points, 907 and 767°C respectively. Both form divalent cations with a complete shell of electrons (Valle, 1995).

CADMIUM CHLORIDE (CdCl$_2$)

It is a colourless, white crystalline compound of cadmium. It is a hydroscopic, rhombohedral or hexagonal crystal. Its molecular weight is 183.32, melting point is 568° and density is 4.047 (g/cm$^3$). It is completely soluble in water (140 g/L) and acetone, slightly soluble in methanol and ethanol, and insoluble in diethyl ether.

1.6.2 CHEMICAL PROPERTIES

Cadmium is located in group IIB (group 12) of the periodic table along with zinc and mercury. It is a rare element not found in nature in its pure state, but occurs mainly as sulphide forms in zinc deposits. Almost all cadmium compounds have an oxidation state +2. Cadmium when heated gets oxidized and forms cadmium oxide fumes. Cadmium and its compounds are not combustible, but they may decompose in fires and result in the release of corrosive and toxic fumes (Llewellyn, 1994).
1.7 MECHANISM OF CADMIUM TOXICITY

1.7.1 ABSORPTION

The absorption of cadmium through food in the digestive tract is 3-5% and 10-40% through inhaled cadmium, but may be higher (about double) in individuals with iron deficiency. Other dietary factors and physiological factors such as high fat or protein content in the diet or zinc deficiency may also influence oral absorption of cadmium. Dermal absorption of cadmium is generally very low and is about 0.2-0.8% (Hallenbeck, 1984). The intestinal absorption of cadmium increases when the body iron stores are depleted. There is a common pathway for cadmium and iron absorption through the divalent metal transporter-1 (DMT-1) which accounts for high accumulation of cadmium during iron deficiency (Park et al., 2002; Waalkes, 2003).

1.7.2 DISTRIBUTION

After ingestion or inhalation through food, drinking water or smoke, cadmium is transported to liver via high molecular weight proteins in the blood such as erythrocyte membranes and plasma albumin and then to the tissues (Nordberg et al., 1971).

1.7.3 METABOLISM

After cadmium is transported to the liver, it stimulates the synthesis of metallothionein, a low molecular weight protein (7000 Da), which has been extensively studied in mammals and is also known to exist in a number of non-mammalian species (Nordberg and Kojima, 1979). In all the tissues, cadmium stimulates the production of metallothionein, this formed metallothionein binds to cadmium (forms Cd-MT complex), and this complex is released from the liver and moves via blood to the kidneys (Dunnick and Fowler, 1987). In the kidneys, the cadmium-metallothionein complex is filtered by the glomerulus and is reabsorbed by the proximal tubular cells. Elemental cadmium is released at low pH in the lysosomes during proteolysis of the reabsorbed metallothionein. This free cadmium induces the production of renal metallothionein which subsequently binds to the metal cadmium, forming cadmium-metallothionein complex again (Dorian et al., 1992). There is no evidence that cadmium undergoes any direct metabolism such as oxidation or reduction in biological systems. However, the positively-charged Cd\(^{2+}\) ion
gets bound to negatively charged groups in macromolecules, such as sulphhydril groups in proteins (Dunnick and Fowler, 1987). The intracellular release of cadmium is responsible for the generation of reactive oxygen species, depletion of glutathione, lipid peroxidation, DNA damage and culminating ultimately in oxidant-induced cell death and renal toxicity.

1.7.4 ELIMINATION

After absorption cadmium is eliminated slowly through the urine and faeces. Small amounts of cadmium get conjugated with glutathione, cysteine or metallothionein and are excreted through the faeces. During elimination, the faeces generally contain much higher levels of cadmium than in the urine because most ingested cadmium is never absorbed (Lucis et al., 1972). Because of its long biological half-life of 15 to 30 years, the rate of cadmium excretion is very low; therefore, cadmium gets accumulated in the blood, kidney, liver and many other organs, making it a very toxic metal (Henson and Chendrese, 2004).

![Fig 1.2 Mechanism of Cadmium toxicity](image)
1.8 EFFECT OF CADMIUM ON VARIOUS ORGANS

Cadmium affects various organs of the body during acute and chronic toxicity conditions.

1.8.1 EFFECT OF CADMIUM ON SKIN

Wound healing in the skin depends on the availability of appropriate trace metals as enzyme cofactors and structural components in tissue repair. Cadmium is implicated in the induction of metallothionein at wound sites leading to a marginal reduction in zinc during the period of inflammatory or granulation tissue formation and epidermal cell proliferation. However this was followed by a rise in zinc concentration and decrease in calcium concentration, thus cadmium delayed the wound healing process (Lansdown et al., 2001).

1.8.2 EFFECT OF CADMIUM ON LIVER AND KIDNEY

Kidney (mainly renal cortex) and liver are considered to be the main target organs in the case of exposure to cadmium by oral and inhalation routes (Yamano et al., 1999; Yiin et al., 1999). Liver is the major organ susceptible to the toxic effects of cadmium due to accumulation after both acute and chronic poisoning. During long-term chronic occupational exposure to cadmium, the kidneys are typically the most critically affected organs. In the year 1980, WHO recommended that the cadmium concentration in urine should not be allowed to reach 10 μg Cd/g creatinine, since concentration above this limit leads to the risk of renal dysfunction (WHO, 1980). It is commonly known that cadmium is mainly accumulated in the kidneys and liver tissues of animals and leads to organ damage (Massanyi et al., 1995b; Toman and Massanyi, 1996).

1.8.3 EFFECT OF CADMIUM ON THE BRAIN

Cadmium enters into the brain parenchyma and neurons through blood brain barrier (Nishimura et al., 2006) and results in neurological alterations in humans (Rose et al., 1992) and animal models (Lukawski et al., 2005) leading to lower attention, olfactory dysfunction and memory deficits. In addition to that, cadmium exposure can cause cerebral damages, such as inhibition of acetylcholine esterase activity in rats. The brain is
highly susceptible to lipid peroxidation because of its increased rate of oxygen utilization, an abundant supply of polyunsaturated fatty acids, a deficient antioxidant defense system and higher concentration of some transition metals such as copper and iron in several regions. The higher susceptibility of membrane to lipid peroxidation can lead to membrane damage which results in loss of adenosine triphosphatases activity and changes in cell functions (Pari and Murugavel, 2007).

1.8.4 EFFECT OF CADMIUM ON LUNGS

The respiratory system is affected severely by the inhalation of cadmium-contaminated air. Exposure to cadmium results in shortness of breath, lung edema, destruction of mucous membranes, pneumonitis, pulmonary emphysema, interstitial fibrosis and cancer (Amanuma and Suzuki, 1987; IARC, 1993; Seidal et al., 1993).

1.8.5 EFFECT OF CADMIUM ON REPRODUCTIVE SYSTEM

Cadmium affects the reproductive functions adversely. The testis is extremely sensitive to cadmium toxicity. Exposure to cadmium toxicity primarily impairs testicular function. Since 1950, in vivo studies have shown that acute exposure to cadmium causes blood testis barrier (BTB) disruption, germ cell loss, testicular edema, hemorrhage, necrosis, and sterility in several mammalian species (e.g. rodents, rabbit, dog, calf and stallion). Moreover, in vitro studies have also illustrated cadmium-induced damage to testicular cells (Li and Heindel, 1998). Recent studies have reported that men exposed to cadmium and/or other environmental toxicants are associated with reduced male fertility such as reduced sperm count and poor semen quality (Benoff et al., 2000; Benoff et al., 2009). Mechanisms of toxic effects of cadmium in the testis include damage to the vascular endothelium of leydig and sertoli cells, the induction of oxidative stress and impaired antioxidant defense mechanisms, which results in their morphological and functional changes like inhibition of testosterone synthesis and spermatogenesis impairment. Cadmium also interferes with prostate function, which alters its hormonal activity, secretion and impairs fertility in men (Goyer et al., 2004).
Reactive oxygen species (ROS) have an important role in the normal functioning of reproductive system and in the pathogenesis of infertility in females (Ashok et al., 2004). Lower concentration of ROS is essential for normal reproductive process in the female reproductive tract but higher production of ROS is known to cause detrimental effects (Mankovska and Serebrovska, 1998). Concordance with these reports, Roopha et al (2011) reported that the increase in ovarian lipid peroxidation might be due to the concomitant increase in the production of free radicals like hydrogen peroxide and superoxide radicals in the ovary of cadmium exposed rats.

1.8.6 EFFECT OF CADMIUM ON CARDIOVASCULAR SYSTEM

Cadmium induces cardiac damage (Kopp et al., 1980) and leads to hypertension (Glauser et al., 1976). Cadmium increases the oxidative stress in myocardial tissue by lipid peroxidation, which results in the increased production of ROS. This formed ROS further stimulate myocytes hypertrophy, re-expression of fetal gene programs and apoptosis in cardiac myocytes in culture. The production of ROS increased due to systemically and in the myocardium of patients with ischemic-reperfused heart and heart failure induced-oxidative stress (Mollaoglu et al., 2006).

1.8.7 EFFECT OF CADMIUM ON THE BONE

Cadmium has been recently identified as a risk factor for osteoporosis. Jarup et al (1998) reported that long-term high level exposure to cadmium leads to bone changes and were considered to be associated with kidney disease. But low cadmium exposure (occupationally as well as environmentally exposed people) leads to a decrease in bone mineralization (Alfven et al., 2002), and also induced experimentally at low doses in rats (Ohta et al., 2000). Cadmium-induced renal damage associated with severe osteoporosis and osteomalacia with multiple fractures among persons with Itai-Itai disease in Japan (during the period of 1912-1945) was due to both direct effects of cadmium on bone and indirect effects via the kidney (Bhattacharyya, 2009).
1.8.8 EFFECT OF CADMIUM ON THE PANCREAS

Cadmium can cause pancreatic beta-cell damage which results in suppression of insulin secretion, increased glucose intolerance, and have diabetogenic effects. Due to sub or chronic exposure a marked disturbance in glucose homeostasis, the destruction of pancreatic islets insulin secretion and increase in gluconeogenic enzymes were observed in rats. Increase in blood glucose level and decrease in plasma insulin secretion were observed in long-term cadmium exposure. Pancreatic beta-cells are highly susceptible to oxidative stress damage, which is generated by chronic exposure causing pancreatic beta-cell dysfunction and apoptosis (Chang et al., 2013).

1.9 TREATMENT FOR CADMIUM TOXICITY

Cadmium toxicity can be reduced by using antidotes which act as chelating agents. Chelation is the formation of a metal ion complex in which the metal ion is associated with a charged or uncharged electron donor referred to as ligand.

1.9.1 ETHYLENEDIAMINETETRAACETIC ACID (EDTA)

EDTA is used as an antidote for metal toxicity. It is mainly used for the treatment of childhood lead poisoning and also can be used for the treatment of cadmium. Calcium disodium ethylenediaminetetraacetic acid, a derivative of EDTA (CaNa₂EDTA) is the most commonly used chelating agent. The mechanism of the cadmium reduction/removal with Ca-EDTA is the replacement of the calcium ion in the EDTA by cadmium and the excretion of the chelate through the kidney (Hilmy et al., 1986).
Ca-EDTA is toxic to the renal system causes the tubular necrosis, severe degeneration of proximal tubular cells, alterations in urine such as hematuria, proteinuria and elevated blood urea nitrogen. Side effects include renal failure, hypocalcaemia, hypotension, bone marrow depression, prolonged bleeding time, convulsions, fatigue, headache, fever, lacrimation, glycosuria, myalgia, hepatotoxicity, increased urinary frequency, abnormal changes in ECG and gastrointestinal problems. (Flora and Pachauri, 2010).

1.9.2 2, 3-DIMERCAPROL (BRITISH ANTI LEWISITE) (BAL)

2, 3-Dimercaprol is a chelating agent, produced by British biochemists at Oxford University during the period of World War II. It has a 3-carbon backbone with two sulphhydryl (–SH) groups and a hydroxyl group. Since 1949 it has been clinically used for the treatment of arsenic, cadmium and mercury poisoning (Flora and Pachauri, 2010). The mechanism of cadmium intoxication by 2, 3-Dimercaprol might be due to the chelation of cadmium ions with the sulphhydryl groups of 2, 3-Dimercaprol.

![2, 3-Dimercaprol](image)

Fig 1.4 2, 3-Dimercaprol

Because of its oily nature, the drug is not well absorbed orally and for greater absorption administration of BAL needs deep intra-muscular injection that is painful and allergic. Side effects include fever, conjunctivitis, lacrimation, headache, paresthesias (tingling sensation), tremor, nausea, liver damage, high blood pressure, heart rate and hemolysis (Janakiraman et al., 1978).
1.9.3 MESO-2, 3-DIMERCAPTO Succinic Acid (DMSA)

Dimercaptosuccinic acid (DMSA) is a chemical derivative of dimercaprol. It is a dithiol (two sulphhydryl groups) compound. DMSA is used as an effective antidote for heavy metal poisoning (Flora et al., 2008). It is 95 % plasma protein bound, mainly one of its sulphhydryl groups binds with cysteine residue present in the albumin, leaving the other sulphhydryl group available to chelate metals (Miller, 1998). Adverse side effects include gastrointestinal discomfort, neutropenia and increased liver enzymes.

![Fig 1.5 Meso-2, 3-Dimercaptosuccinic Acid](image)

1.10 DIETARY COMPOUNDS AS DRUGS

The consumption of natural products is as ancient as human civilization with their therapeutic properties. The main sources of drugs used were minerals, plant and animal products (De Pasquale, 1984). The reasons for this were ease availability of pure compounds which were structurally modified easily to produce potentially more active and safer drugs which could be easily performed. Furthermore, the use of natural products had different points of view regarding the concepts of health and disease. Natural products which are secondary metabolites have been used as traditional medicine and these are the most successful source of potential drug (Rates, 2001).

Nowadays, there is an increasing interest on dietary polyphenols (secondary metabolites) because of its potent antioxidant property. Higher intake of vegetables, fruits and whole grains that are rich in polyphenolic content, has been linked to lower the risk of many diseases like cancer, cardiac diseases, chronic inflammation, diabetes and many
degenerative diseases. It has been well established that polyphenols suppress the production of free radicals, thus reducing the rate of oxidation by inhibiting the formation or deactivating the reactive active species and precursors of free radicals. In addition to radical scavenging activity, polyphenols are also known as metal chelators (Tsao, 2010). Furthermore, polyphenols, which constitute the active principles present in many medicinal plants, change the activity of various enzymes and cell receptors and not all polyphenols are absorbed with equal efficacy. They are extensively metabolized by intestinal and hepatic enzymes and by the intestinal micro flora (Middleton et al., 2000).

1.10.1 CLASSIFICATION OF POLYPHENOLS

Dietary polyphenols are the abundant antioxidants in human diet. Polyphenols are mainly classified into two types by their source of origin, biological function, and chemical structure.

- Phenolic acids (non-flavonoid polyphenolic compounds)
- Flavonoids

- Phenolic acids

  Phenolic compounds are further divided into two types
  - Benzoic acids – based on C1 – C6 backbones
    Examples - Protocatechuic acid, Vanilinic acid, Gallic acid, syringic acid
  - Cinnamic acids – based on C3 – C6 backbones
    Examples – p-coumaric acid, ferulic acid, sinapic acid

- Flavonoids

  Flavonoids have the C6–C3–C6 structural backbone in which the two C6 units (Ring A and Ring B) are of phenolic nature.
  Examples - quercetin and kaempferol, Naringenin, Hesperetin, etc. (Tsao, 2010).
1.10.2 *p*-COUMARIC ACID (*p*-CA)

*p*-coumaric acid (3-(4-hydroxyphenyl)-2-propenoic acid), a dietary polyphenol is a derivative of cinnamic acid and possesses a hydroxyl group. It is mainly present in plants and forms a part of human diet (King and Young, 1999). It is a secondary metabolite of the plant phenylpropanoid pathway (Nishiyama *et al*., 2010) (Fig 1.7).

Fig 1.6 Structure of *p*-coumaric acid

*p*-coumaric acid can be available in two forms in plants. Soluble form of *p*-coumaric acid is mainly present in fruits, vegetables and cereals. Insoluble form of *p*-coumaric acid is mainly found in lignocelluloses (esterified with lignin) (Ou *et al*., 2012). It is present in fruits like blueberry, cranberry, pear, cherry, apple, orange, grapefruit, cherry juice, apple, lemon, peach, vegetables like potato, lettuce, spinach and beverages such as coffee, tea (Han *et al*., 2007). The absorption, bioavailability and elimination of *p*-coumaric acid are very high when compared to the other compounds. The intestinal absorption efficiency of *p*-coumaric acid is 100 times greater than that of gallic acid and the relative bioavailability of *p*-coumaric acid is found to be 70 times greater than that of gallic acid in humans (Konishi *et al*., 2004).

*p*-coumaric acid was well studied to prove its antioxidant property (Zang *et al*., 2000), anti-HIV activity (Shimizu *et al*., 1993), anti-fungal properties (Bandara *et al*., 1988), anti-melanogenic activity (An *et al*., 2010), anti-mutagenic properties (Ferguson *et al*., 2003), anti-inflammatory effect (Pragasam and Rasool, 2013) and immunomodulatory effect (Pragasam *et al*., 2013). In addition it was also proved to
inhibit platelet aggregation (Luceri et al., 2007), reduce stomach cancer (Ferguson et al., 2005), reduce formation of carcinogenic nitrosamines (Kikugawa et al., 1983) and inhibit neuronal injury (Vauzour et al., 2010), inhibit the growth of human breast and colon cancer cells (Hudson et al., 2000), downregulates the mRNA expression levels of the key angiogenic factors vascular endothelial growth factor and basic fibroblast growth factor (Kong et al., 2013).

Recent studies have reported that p-coumaric acid possesses cardio-protective effect against doxorubicin (Abdel-Wahab et al., 2003), isoproterenol (Jyoti and Prince, 2013) and sodium arsenite-induced cardio-toxicity (Prasanna et al., 2012). p-coumaric acid induces the phase II antioxidants and detoxifying enzymes (Yeh and Yen, 2006). The mechanism of antioxidant properties of phenolic compounds constitute binding of metal ions, scavenging of reactive oxygen and nitrogen species, upregulation of endogenous antioxidants as well as the repair of oxidative damage to biomolecules (Ursini et al, 1999).
Fig 1.7 Phenylpropanoid pathway in plants
Table 1.1 Concentration of $p$-coumaric acid in red fruits determined by HPLC (Jakobek et al., 2007)

<table>
<thead>
<tr>
<th>Fruits</th>
<th>$p$-coumaric acid content (mg/kg of fresh weight)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blueberry</td>
<td>54.90</td>
</tr>
<tr>
<td>Blackberry</td>
<td>5.94</td>
</tr>
<tr>
<td>Strawberry</td>
<td>16.86</td>
</tr>
<tr>
<td>Red raspberry</td>
<td>4.24</td>
</tr>
<tr>
<td>Sweet cherry</td>
<td>5.40</td>
</tr>
<tr>
<td>Sour cherry</td>
<td>19.12</td>
</tr>
<tr>
<td>Elderberry</td>
<td>10.80</td>
</tr>
<tr>
<td>Black currant</td>
<td>31.60</td>
</tr>
<tr>
<td>Red currant</td>
<td>8.26</td>
</tr>
</tbody>
</table>
Table 1.2 Concentration of \( p \)-coumaric acid in herbs determined by HPLC (Wojdylo et al., 2007)

<table>
<thead>
<tr>
<th>Herbs</th>
<th>( p )-coumaric acid content (mg/100 gm dry weight)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Salvia officinalis</em> (Garden sage)</td>
<td>10.3</td>
</tr>
<tr>
<td><em>Marrubium vulgare</em> (White horehound)</td>
<td>31.6</td>
</tr>
<tr>
<td><em>Silybum marianum</em> (Milk thistle)</td>
<td>53.6</td>
</tr>
<tr>
<td><em>Taraxacum officinale</em> (Dandelion)</td>
<td>2.1</td>
</tr>
<tr>
<td><em>Petroselinum sativum</em> (Parsley)</td>
<td>11.2</td>
</tr>
<tr>
<td><em>Echinacea purpurea</em></td>
<td>19.5</td>
</tr>
<tr>
<td><em>Acorus calamus</em> (Vasambu)</td>
<td>4.31</td>
</tr>
<tr>
<td><em>Humulus lupulus</em> (Hop)</td>
<td>22.8</td>
</tr>
<tr>
<td><em>Herniara glebra</em> (Rupturewort)</td>
<td>23.3</td>
</tr>
<tr>
<td><em>Glycyrrhiza glabra</em> (Liquorice)</td>
<td>11.0</td>
</tr>
<tr>
<td><em>Hypericum perforatum</em> (Vettai pakku)</td>
<td>32.3</td>
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<tr>
<td><em>Juglans regia</em> (Walnut)</td>
<td>125.0</td>
</tr>
<tr>
<td><em>Cynamomum zeynalicum</em> (Lavangapattai)</td>
<td>10.3</td>
</tr>
<tr>
<td><em>Trigonella foenum graecum L</em> (Fenugreek)</td>
<td>29.4</td>
</tr>
<tr>
<td><em>Epilobium hirsutum</em></td>
<td>38.3</td>
</tr>
<tr>
<td><em>Polygonum aviculare</em></td>
<td>14.8</td>
</tr>
<tr>
<td><em>Valeriana officinalis</em></td>
<td>6.2</td>
</tr>
<tr>
<td><em>Chelidonium majus</em></td>
<td>71.70</td>
</tr>
<tr>
<td><em>Curcuma longa</em> (Turmeric)</td>
<td>5.96</td>
</tr>
</tbody>
</table>
Table 1.3 Concentration of $p$-coumaric acid in various foods of plant origin determined by HPLC (Neveu et al., 2010).

<table>
<thead>
<tr>
<th>Various foods</th>
<th>$p$-coumaric acid content (mg/100 gm fresh weight)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vegetables (raw)</strong></td>
<td></td>
</tr>
<tr>
<td>Tomato</td>
<td>0.13</td>
</tr>
<tr>
<td>Olive (green)</td>
<td>5.90</td>
</tr>
<tr>
<td>Olive (black)</td>
<td>1.43</td>
</tr>
<tr>
<td><strong>Fruit juices (Pure)</strong></td>
<td></td>
</tr>
<tr>
<td>Apple</td>
<td>0.93</td>
</tr>
<tr>
<td>Pomegranate</td>
<td>5.38</td>
</tr>
<tr>
<td>Kiwi</td>
<td>9.00</td>
</tr>
<tr>
<td><strong>Nuts</strong></td>
<td></td>
</tr>
<tr>
<td>Peanuts, dehulled</td>
<td>2.53</td>
</tr>
<tr>
<td>Peanuts, dehulled and roasted</td>
<td>6.46</td>
</tr>
</tbody>
</table>

Table 1.4 Concentration of $p$-coumaric acid in beverages determined by HPLC

<table>
<thead>
<tr>
<th>Beverages</th>
<th>$p$-coumaric acid content</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coffee</td>
<td>4.7mg/200ml (Natella et al., 2007)</td>
</tr>
<tr>
<td>Wine</td>
<td>8mg/l (Goldberg et al., 1998)</td>
</tr>
</tbody>
</table>
1.11 AIM AND OBJECTIVES OF THE STUDY

The present study has been designed to investigate the protective efficacy of $p$-coumaric acid, a dietary polyphenol against cadmium chloride-induced toxicity in rats.

- To investigate the protective role of $p$-coumaric acid against cadmium chloride-induced hepato-renal toxicity in rats

- To investigate the protective effect of $p$-coumaric acid on pro-inflammatory cytokines levels in the serum of cadmium chloride-induced toxicity in rats