CHAPTER - II
REVIEW OF LITERATURE

2.1. REVIEWS ON PESTICIDES

In the past various studies have been recorded which show that extensive use of pesticide results in the homeostatic disturbance in plants, animals as well as human beings. Insecticides drastically influence carbohydrates, proteins, lipids and other structural components of tissues and blood. Accumulation of insecticides in human body causes many diseases like gastric cancer, cytogenetic damage, kidney infections, etc. (Anna, et al. 1988). Ananya, et al., (2005) reported the oxidative stress and histopathological changes in rat heart following oral lindane administration. Similar reports have been elucidated regarded various pesticides and various harmful side effects. Histochemical studies by Sakr and Okdah, (2004) revealed reduction of polysaccharides as well as total proteins in testes of mice induced by benomyl and with metalaxyl by Sakr, (2011).

2.2. REVIEWS ON CARBAMATE PESTICIDES AND FUNGICIDES

The most common pesticide poisonings reportedly arise from exposure to organophosphates and carbamates (Randy, et al. 1999). Murugesan, et al., (1999) also found that Sarotherodon mossambicus, when exposed to sublethal and lethal concentrations of carbaryl, showed adaptive elevation in the activity levels of Glutamate Oxaloacetate Transaminase (GOT) and Glutamate Pyruvate Transaminase (GPT) enzymes, particularly in liver and muscle. Several works have been conducted with fungicides and its toxicity has been reported. Choudhury, et al., (2003) reported damage of kidney by endosulfan while Zaher, et al., (1997) have sighted similar observations in chickens by carbosulfan. Begum, (2004) found the similar result in liver and muscle tissues of Clarias batrachus during exposed to carbofuran. Calviello, et al., (2006) reported increase in lipid peroxidation and decrease in antioxidant enzymes fungicides in albino rats. Wael M. Al-Amoudi, (2012) demonstrated the haematological and biochemical effects of metalxyl fungicide on albino mice. Significant decrease in RBC count, blood platelets, total protein, albumin and haemoglobin while increase in WBC count, serum triglyceride, serum tansaminases and cholesterol levels was noted by the author suggesting signs of toxicity.
Mancozeb is a widely used fungicide of the carbamate group, probably because of its low acute toxicity in mammals. However, several studies conducted so far have reported its toxicity in various experimental animals as well as in environment. More studies need to be performed to validate its usages and its doses economically. It was found that exposure to a mixture of pesticide, where mancozeb represents more than 50% of that mixture, has the ability to cause DNA damage in small mammals, assessed by comet, micronucleus and sperm abnormality assays. Considering the fact that mancozeb is a widely used pesticide we can say that this pesticide will be the source of the highest levels of manganese found in small mammals and it is the genotoxic agent at issue.

Hence, the present work contributes to alert about hazard effects resulting from pesticide exposure, particularly mancozeb.

2.3. REVIEWS ON MANCOZEB

Several studies showed that mancozeb shows its biological effects through its metabolites like Ethylene Thio Urea and carbon disulphide (Thorn, et al. 1962 and Ivanoa, 1982). Ivano-Chemishanska, (1969) found anorexia and general weakness in animals exposed to maneb, zineb, and mancozeb. Despite its low acute toxicity, mancozeb has been shown to produce adverse effects on reproduction, liver, kidney, central nervous system and chromosomes of bone marrow cells in mice (Sittig and Mane, 1991). Subramaniam, (1991) observed the influence of mancozeb on mitogenetically responsive lipids in rat cerebrum and liver.

Khan and Sinha, (1994) observed decrease in sperm count with increased aberrant head morphology in mice exposed to mancozeb. The gonadal toxicity in female rats after chronic exposure to mancozeb was investigated by Baligar and Kaliwal, (2001) and Bindali, (2002). They observed that the toxic effect probably causes hormonal imbalance and decrease in the levels of protein, glycogen and lipids in the ovary. They also revealed significant increase in the levels of total lipids, phospholipids and neutral lipids in ovary and liver while decrease in uterus. Srivastava, et al., (1999) assessed the toxicological effect during chronic exposure of mancozeb in male rats and also demonstrated its gonadal toxicity. It has been also reported that the exposure of pregnant mice to mancozeb inhibits implantation (Bindali and Kaliwal, 2002).

Hore Maitis, et al., (1997) studied the long term exposure of mancozeb on clinical–haemato-biochemical and pathological changes in rats. Oral administration of maneb was
found to inhibit protein synthesis in testes and liver of rats by Ivanonva and Izmirova, (1997). Further significant increase in body weight ratio and thyroid inactivity and toxicity induced by mancozeb was reported by Kackar, et al., (1997 b) in mancozeb exposed rat. Srivastava, et al., (1999) investigated the effects of mancozeb and its metabolite ethylenethiourea on biochemicals and enzymatic parameters in Clarius batrachus. Several workers studied the biochemical effects of mancozeb and dithiocarbamates in various experimental animals.

Similar studies were reported with mancozeb in testis, thyroid and adrenal of rat (Nicolau, 1982). Parimala, et al., (2005) found significant gonadal toxicity in mancozeb exposed rats. Mancozeb though possesses low acute toxicity however produce adverse effects in fertilization, damage to liver, kidney, central nervous system and chromosomes of bone marrow cells in mice. Similar toxicity was also reported in testis of male rats by Joshi, (2005).

Several data suggests Ethylene Bis Dithio Carbamates may have immunomodulatory effects. Several reports indicated pesticide immunotoxicity as well as generation of oxygen free radicals (Banerjee, et al. 1996 and 1998, Seth, et al. 2002) in rats and mice. Emanuela, et al., (2005) reported the same based on whole blood assay. However, the influence of mancozeb on immune system has not been well understood.

Bhavan, et al., (2001) suggested that the increase in free amino acids level was the result of breakdown of protein for energy requirements and impaired incorporation of amino acids in protein synthesis and decline in nucleic acids level. Decrease in protein content under toxicity stress was reported by Khare, et al.,(2002) while the decrease in total protein level and increase in free amino acids level in both tissue and liver suggest the high protein hydrolytic activity due to elevation of protease activity (Muley, 2007).

Sakr, (2007) also reported the increase of serum transaminases enzymes on mancozeb induced toxicity in albino rats and studied the ameliorating effects using ginger. Kechrid, (2007) found that administration of mancozeb significantly increased the activity of the above enzymes as well as alkaline phosphatases which are associated with pathomorphological changes in liver. Srivastava, et al., (2013) found that the level of serum transaminases was enhanced by mancozeb and Ethylene thiourea in Clarius batrachus.

Mancozeb and treatments have found to alter levels of protein, glycogen and total lipids in liver, uterus and ovary in rats and mice (Mahadevaswami, et al. 2000). Raghavendra, et al., (2010) studied the effect of mancozeb on thyroid, testis, accessory reproductive organs
and biochemical constituents in albino mice and found significant results. Decrease in the
glycogen level and total lipids in kidney while increase of total lipids in liver, anti-
spermatogenic and anti-androgenic activity was observed by them. Ksheerasagar, et al.,
(2011) suggested carbosulfan had adverse effects on kidney functions leading to
physiological impairment.

O’Hara and DiDonto, (1985) reported that mancozeb induced histopathological
changes in the liver and adrenal gland of mice. Nebbia and Ferrero, (1991) observed
significant decrease in the levels of blood glucose and globulin, due to low thyroxin level
demonstrated that mancozeb causes normocytic types of anaemia, significant decrease in
blood glucose and globulin levels as well as significant pathological changes in liver, kidney,
spleen, heart and also brain. Similar observations were also made by Kackar, et al., (1999 a).
Significant work on the thyroid gland and gonads were done by many workers in mancozeb
induced rats were toxicity was observed (Lu and Kennedy, 1986; Tsuda, et al. 1973; Taurog,

2.4. REVIEWS ON MEDICINAL PLANTS

Plants play a strategic role in maintaining human health and improving the quality of
human life. Medicinal plants play an important role in pharmacology and medicine. Nearly
80% of the world population depends on botanical preparations as medicine to meet their
health needs (Ogbera, et al. 2010). Traditional knowledge of medicinal plants in India has
been in use since very ancient times and its description is even mentioned in Rigveda and
Atharvaveda. The health hazards of human and other ecologically important animals by
pesticides needs to be minimized by biocides or herbicides as well as medicinal plants to cure
such ill-effects with minimum side effects. Studies on the therapeutic effects of various plants
are being conducted on different models induced with various toxic compounds and
significant positive results have been obtained.

Schliebs, et al., (1997) pointed out that systemic administration of defined extracts
from Withania somnifera and Shilajit differentially affect the cholinergic but not the


In the current study undertaken the ameliorating action of herbal drugs in mancozeb induced toxicity in albino mice is being assessed. Since time immemorial medicinal plants have occupied a prime place in treatment of various diseases and ailments. Being cost effective with minimal side effects and easy availability they are nowadays gaining popularity in the treatment regimen. Saha, *et al.*, (1961) noted ecobolic properties of Indian medicinal plants. Two plants, *Aloe barbadensis* and *O. sanctum* have been selected for the present study to observe the therapeutic role of their respective leaf extracts in mancozeb induced toxicity in albino mice. Several works have been conducted to observe their therapeutic roles in different models.

### 2.4.1. Review on *Aloe vera*

*Aloe* is one of the oldest healing plants known to mankind. There are more than 300 species of *Aloe* plants of which *Aloe barbadensis* is being referred to as *Aloe vera*. It has number of healing properties and has been in use since millennia throughout the world. It contains numerous constituents which demonstrate its healing properties. The chemical constituents and biological activity of *Aloe* was reviewed by Joshi, (1998). Shelton, (1990) also studied the chemical and therapeutic properties of *Aloe vera*.
The effect of toxins on kidney can be supplemented by antioxidants which are present in Aloe extract like alanine. Alanine, an amino acid which displays antioxidant activity is available in A. vera (Duke, 1985). Vazquez, (1996) reported anti-inflammatory activity of extracts from A. vera gel changes were observed in the kidney of mancozeb exposed albino mice. Likewise Bolkent, et al., (2004) demonstrated kidney protection by A. vera from diabetes induced damage. Bhaya and Saini, (2008) studied the antioxidative property of A. vera leaf extract against radiation induced oxidative stress by measuring level of Lipooxygenase and Glutathione contents in irradiated alone and Aloe treated irradiated mice liver and suggested that aloe can be one of the best approaches to control Reactive Oxygen Species-mediated pathogenesis and possible anticancer activities due to its antioxidative properties.


Joshi and Dixit, (1986) noticed hypolipidemic effect of Aloe barbadensis in cholesterol fed albino rats. Ajabnoor, (1990) studied effect of Aloes on blood glucose levels in normal and alloxan diabetic mice. The hypoglycaemic action of A. vera was established by many workers in mice, rabbits as well as humans (Ghannam, et al. 1986, Ajabnoor, 1990 and Afolabi, et al. 2007). The cholesterol lowering activity was reported by Tizard, et al., (1989). Naveena, et al., (2011) reported that treatment with A. vera restored the serum biochemical parameters towards normal levels and decreased the levels of lipid peroxidation and increased the levels of reduced glutathione and other antioxidant enzymes. Polysaccharides, particularly acemannan has reached proprietary status. In a small trial with monkeys it was found that orally administered aloe gel lowered total cholesterol by 61% and also that proportion in the high density lipoprotein (High Density Lipid) increased (Dixit and Joshi, 1983).

In another study, Saoo, et al., (1996) reported antiviral activity of aloe extracts against cytomegalovirus. The immune enhancing property of Aloe was also demonstrated by many workers (Winters, et al. 1981, Pittman, 1992 and Zhang and Tizard, 1996). Davis, (1991) found some immunomodulatory properties of the aloe gel due to its specific polysaccharide content. Research on immune stimulation has indicated that acemannan, a polysaccharide within Aloe ferox, stimulated macrophage cytokine production and killer T cells (Zhang, et
al. 2006). Ghanem, (2005) demonstrated mancozeb induced anticancer activity by Aloe. Similar studies were also conducted by Bhaya and Saini, (2008).

2.4.2. Review on *Ocimum sanctum*

*O. sanctum* known as Tulsi is commonly used in Ayurveda for its numerous healing properties. Several studies have been conducted so far to establish the healing properties of tulsi scientifically.

The membrane stabilizing property of *O. sanctum* has also been shown to be responsible for hepatoprotective action (Sen, *et al.* 1988). Ubaid, *et al.*, (2003) studied the effect of *O. sanctum* on the unpredictable hepatotoxicity induced by antitubercular drugs in rats and found significant prevention of histological alterations, decrease of hepatic lipid peroxidase and increase in the level of superoxide dismutase and catalase. Sharma, *et al.*, (2002) showed that *O. sanctum* aqueous leaf extract significantly decreased Serum Glutamate Oxaloacetate Transaminases (SGOT) and Serum Glutamate Pyruvate Transaminases (SGPT) level in mercury induced toxicity in Swiss albino mice. Razvi, *et al.*, (2003) observed the effect of *O. sanctum* on the unpredictable hepatotoxicity induced by antitubercular drugs in rats. Chaturvedi, *et al.*, (2007) demonstrated the protective and preventive role of *O. sanctum* in ethanol induced liver toxicity in rats. Oboh, *et al.*, (2009) reported that oil from leaves contain eugenol which have antibacterial, anti-yeast and insecticidal action while the extracts have hepatoprotective effect by reducing the damage caused by radiation exposure, environmental pollution or toxicants. Soha Mohamed, (2011) studied the curative effect of basil on liver injury in rats.

Tulsi was shown to be effective in reducing blood glucose and cholesterol levels (Rai, *et al.* 1997a) probably due to its antioxidant properties (Sethi, *et al.* 2004). The antioxidant property of *O. sanctum* contributed by its flavonoids content was reported by Uma Devi and Ganasoundari, (1999). Sharma, (2002) worked on *O. sanctum* and found its protective role against mercury induced toxicity in Swiss albino mice.

Geetha and Vasudevan, (2004) noted the inhibition effect of *O. sanctum* on lipid peroxidation. Probably urosolic acid was responsible for inhibition of lipid peroxidation (Balanehru and Nagarajan, 1991 and Liu, 1995). Sarkar, *et al.*, (1994) demonstrated lowering of Low Density Lipid cholesterol and increase of High Density Lipid cholesterol along with in vivo lipid peroxidation in rabbits was inhibited by aqueous extract of *O. sanctum*.

*O. sanctum* reduced fasting blood sugar, uronic acid, total amino acids, total cholesterol, triglyceride, phospholipids and total lipids in diabetic rats showing hypoglycemic
and hypolipidemic effect (Rai, et al. 1997a). Geetha and Vasudevan, (2004) reported significant modulation of superoxide dismutase, catalase, glutathione-S- transferase, non-enzymatic antioxidants and lipid peroxidation end product malondialdehyde levels by O. sanctum oil treatment. O. sanctum was found to lower cholesterol, lactate dehydrogenase and alkaline phosphatase levels without affecting blood glucose and urea levels in rats (Vats, et al. 2004).


Tulsi was found to enhance cell-mediated immunity in human induce increased cellular and immune mediated action (Shah and Qadry, 1989). Medirrata, (1988, 2002) and Gupta, et al. (2006) also evaluated the immunomodulatory potential of antioxidant effects O. sanctum. Mediratta, et al., (2008) suggested that O. sanctum seed oil can attenuate the immunotoxicity and oxidative stress produced by lindane as well as the Delayed Type Hypersensitivity response was also significantly antagonized suggesting that O. sanctum seed oil significantly attenuated the lindane suppressed humoral as well as cell- mediated immune response.

So far no substantial significant work with regard to comparative curative study of A. vera and O. sanctum in mancozeb induced mice has yet been done. Further, little reports were available on the role of aqueous extract of A. vera and O. sanctum on mancozeb induced damage with respect to immunomodulatory potential in albino mice. **Hence the present investigation is planned to carry out a comprehensive study on the protective response of the selected herbal extracts against mancozeb induced toxicity in haematological, biochemical as well as immunomodulatory potential in Swiss albino mice.**