REVIEW OF LITERATURE
2. REVIEW OF LITERATURE

An attempt is made in this chapter to review briefly the data available on the physical, chemical and biological properties of plumbagin.

2.1 Plumbagin

2.1.1 Structure and Chemical properties

Investigations of the active principle responsible for the various medicinal qualities attributed to roots of the plants *Plumbago europaea*, *Plumbago zeylanica* and *Plumbago rosea* date from Dulongs isolation of the substance Plumbagin in a fairly pure form in 1828. Roy and Dutt in 1928 recognized the quinone like character of the yellow pigment established the presence of an acidic hydroxyl group and obtained naphthalene and B-methyl naphthalene on distillation of the substance over zinc dust.

The correct formula \( \text{C}_{11} \text{H}_8\text{O}_3 \) was established by Madinaveitia and Gallego (1928) and they suggested that plumbagin is a methyl derivative of juglone (5-hydroxy 1,4-naphthoquinone). Fisher and Dunn (1936) synthesized
PLUMBAGIN

(2-methyl-5-hydroxy-1,4-naphthoquinone)

Fig. 1
plumbagin in laboratory and confirmed it to be 2-methyl 5-
hydroxy 1,4-naphthoquinone (Fig.1).

2.1.2 Occurrence

The various species of the plant plumbago from
which plumbagin is extracted belongs to the family
plumbaginacea. In India, the plants are found in the
plains of Bengal, U.P. and South India as perennial herbs
(Nadkarni and Nadkarni, 1954). Plumbago zeylanica is
widely distributed in tropical and subtropical regions of
Asia, Australia and Africa (Vander Vijver and Lotter, 1971).

2.1.3 Structure activity relationship

Quinones are known to participate in oxidation
reaction in mitochondria, chromatophore
fragments, chloroplast, and some bacteria (Gruber et al.,
1963). The O-quinone methides have the ability to alkylate
DNA (Chmielewska, 1960). Among the simple benzoquinone
derivatives 2,5-diazaidinyl compounds exhibit significant
antineoplastic activity. Linn et al (1973) hypothesized
that benzoquinones may act as a potential bioreductive
alkylating agent. Quinones undergo isomerization possibly
assisted internally by the phenolic hydroxyl to O-quinone methide. The methide may alkylate DNA.

2.1.4 Physical properties

The natural plumbagin as received is dull orange in color and melted at 75-78°C, the sample apparently having deteriorated on storage. Plumbagin is freely soluble in petroleum ether, methanol and ethanol. It is moderately soluble in hot water and is almost insoluble in cold water and acids, but is soluble in dilute alkalies.

1.5 Biological properties

Plumbago zeylanica and Plumbago rosea are essentially used in the extraction of plumbagin. P. zeylanica and P. rosea are differentiated as red and white varieties. P. rosea is used as rubefacient, vesicant, local eczolic and sudorific. It has been reported to cure leprosy. An oil prepared using this as an
ingredient is externally used in rheumatic and paralytic infections. The root bark is a skin irritant. Both P. zeylanica and P. rosea administered to albino rats in large doses acts as an acronarcotic poison. It is used by the native people as it induces abortion. Reports also describe its use in a compound formulation in the treatment of cancer, syphilis and leprosy (Mudaliar, 1969; Kirtikar and Basu, 1975).

Antifertility activity of plumbagin has been reported by Saksena et al., (1970) and Gupta et al., (1971). It is also known to possess anti-cancer, anti-fungal and anti-bacterial activity (Mohana and Purushothaman, 1980). Plumbagin has been reported to influence spermatogenesis and accessory sex organs in adult rats (Shantakumari et al., 1980). It has been screened by the National Cancer Institute, Bethesda, Maryland, USA (1980) and has been indicated that certain naphthoquinones like lapachol and plumbagin are associated with tremendous biological activity viz. anti-cancer and anti-malarial.

2.1.5.1 Anti-cancer activity

Plumbagin when given either intratumour or orally at 42 mg/kg body wt. to wistar rats, brings about 70% and
60% regression of fibrosarcoma (respectively). ED_{50} of plumbagin is found to be almost 16 mg/kg body wt. orally and ip in mice.

Results obtained from National Cancer Institute, Bethesda (1980) shows that plumbagin is active against P_{388} Lymphocytic Leukaemia at 4 mg/kg body wt. It showed no activity against L1210 - lymphoid leukaemia.

Preliminary studies with plumbagin from Plumbago zeylanica were reported to have antitumour activity on rat fibrosarcoma (Chandrasekaran and Nagarajan unpublished observations; Krishnaswamy and Purushothaman, 1980).

2.1.5.2 Antibacterial and Antifungal activity

Plumbagin inhibits growth of both gram positive and gram negative bacteria. It shows antibacterial activity against Staphylococcus aureus, Staphylococcus citreus, Staphylococcus albus, Salmonella paratyphi, S. dubulin at 20 ug/ml. Plumbagin shows antifungal activity at 10 ug/ml viz., Rh. nigricans, E. floccosum, M. nana, P. notatum and P. canadense (Purushothaman, 1980).

Reports on the antimicrobial activity of 557 spp of vascular plants towards Saccharomyces vini and
Lactobacillus plantarum have led to the identification of several substances. Two of these substances are plumbagin and juglone used commercially as preservative for non-alcoholic drinks and wines (Shcherbanovskii, 1982).

2.1.5.3 Effect of plumbagin on cell growth and mitosis

Plumbagin isolated from the root of Plumbago rosea was found to possess significant activity on cell growth and mitosis of chick embryo fibroblast (Santhakumari et al., 1980). Plumbagin in lower concentration stimulates colchicine in acting as a spindle poison. At higher concentrations it exhibits radiomimetic, nucleotoxic and cytotoxic effects by inducing cytoplasmic vacuolization, karyopyknosis and nuclear polymorphism.

2.1.5.4 Histopathology

Dutta and Chatterjee (1976) showed that when albino mice fed orally with crude extract of the roots of P. zeylanica resulted in thinning of the layer of the stomach and intestine.

Histological observations on vital organs viz., liver, spleen, heart and lung of the animals exposed to various doses of plumbagin in wistar rats do not show any
significant deviation from the normal picture (Purushothaman, 1980).

Plumbagin injected at 4 mg/kg body wt. in rats did not produce any microscopically recognisable lesion (Purushothaman, 1983).

2.1.5.5 Metabolism of plumbagin

Plumbagin in rats given at 1.6 mg/0.2 ml could not be detected in blood up to 24 h. Except for the first 2 h urine, all other samples showed plumbagin. The major proportion being excreted at 24 h with traces at 48 h of urine sample. Considerable amount of plumbagin was also excreted in the faeces (Chandrasekaran and Nagarajan, 1981).

2.1.5.6 Abortifacient effect

Plumbagin has been found to be a powerful irritant to smooth muscle and uterus (Bhatia and Lal, 1933). It serves as an abortifacient when applied to os uteri (Kirtikar and Basu, 1973).
2.1.5.7 Mutagenic effect

Among the 16 naphthoquinones tested, plumbagin and few other naphthoquinones were found to be mutagenic in strain TA 2637 of Salmonella typhimurium (Tikkanen et al., 1983).

2.1.5.8 Plumbagin as a plasmid curing agent

Plumbagin was reported to show high efficiency in the range of 80-95% in eliminating plasmid borne nod and nif genes in strains Rhizobium meliloti-4013 and Rhizobium leguminosarum-2001 (Bharathi et al., 1988). Plumbagin was also reported to exclusively eliminate only stringent plasmids (Polasa et al., 1988).

2.1.5.9 Induction of a specific DNA repair response in E. coli

Spencer et al (1985) have shown that E. coli cells which were actively growing were mutagenised when exposed to plumbagin which is a redox cycling quinone that increases the flux of oxygen radicals in the cell. The toxicity of plumbagin was not found to be mediated by membrane damage. Plumbagin pretreatment given to the cells of partially reactivated lambda phage damaged by exposure
to riboflavin plus light, a treatment that produces oxygen species. The result suggested the induction of a DNA-repair response.

2.1.5.10 Clastogenic Effect of Plumbagin

Plumbagin was found to induce acentric fragments in mouse and syrian hamster bone marrow cells (Santhiya, 1983). Plumbagin was found to have mild clastogenic effects in root meristem of Allium cepa. It was also found to induce sister chromatid exchanges (SCEs) in mouse bone marrow and cultured human lymphocytes (Santhiya, 1983).

Cytogenetic damage induced by plumbagin was assessed by employing micronucleus test in mouse bone marrow, (Ramani, 1989). Here significant induction of micronuclei by plumbagin was observed at all concentrations studied (3.75 mg, 7.50 mg, 15.00 mg/kg body weight). It is not strictly dose-dependent. It was toxic to proliferating bone marrow cells by decreasing the proportion of young erythrocytes.