PLUMBAGINALES: A PHARMACOLOGICAL APPROACH

Selma Ribeiro de Paiva[1,2]
Shirley da Silva Marques[2,3]
Maria Raquel Figueiredo[2]
Maria Auxiliadora Coelho Kaplan[4]

ABSTRACT

Plumbaginales belongs to the superorder Malviflorae and comprises two families, Plumbaginaceae and Limoniaceae. Its representatives are chemically characterized by the presence of naphthoquinones, flavonoids, terpenoids and steroids, many of them being the responsible for biodynamic activities. The extracts of some species of Plumbaginales and also some isolated compounds revealed to be of great importance in the search of new drugs, since they have been described in literature for the treatment of many diseases such as: leishmaniasis, Chagas´ disease, malaria, cancer and others. Plants represent a valuable source of bioactive compounds and should be investigated, as a promise in the development of effective, ready available and lesscostly drugs

Key words: Malviflorae, Plumbaginales, biological activities

INTRODUCTION

The limited available treatment for many diseases and the spread of drug resistance emphasize the need for new therapeutic agents. It is well known that the plant kingdom is a great source of bioactive compounds, but in despite of the large amount of species, only a few of them has been studied in this sense.

Plumbaginales belongs to the superorder Malviflorae and comprises two families, Plumbaginaceae and Limoniaceae, according to Dahlgren (1980). It is represented by herbs and shrubs with a cosmopolitan distribution. Chemically, Plumbaginales is mainly characterized by the presence of naphthoquinones, flavonoids, terpenoids and steroids, the first ones being considered as chemical markers (Paiva, 1999).

Some species of Plumbaginales have been studied on the medicinal point of view and the results demonstrated a wide variety of biological uses, most of them related to the presence of the naphthoquinone plumbagin.

This brief review covers the most important biological properties of Plumbaginales species, demonstrating their great potential.

Chemical and pharmacological search

The search was made in scientific reference works as *Chemical Abstracts* (1907-2003), *Biological Abstracts* (1980-2002), *Web of Science* (1945-2003) and *PubMed* (1960-2003). Abstracts, articles and reviews were the base for the organization of the data bank on chemical composition, biological activities and

[1] Programa de Pós-Graduação em Biotecnologia Vegetal, Universidade Federal do Rio de Janeiro
[2] Laboratório de Química de produtos Naturais, Far-Manguinhos, FIOCRUZ; Rua Sizenando Nabuco, 100, Manguinhos, Rio de Janeiro, Brasil. 21041-250. E-mail: s_Paiva@far.fiocruz.br
[3] Programa de Vocação Cientifica, EPSJV, FIOCRUZ
[4] Núcleo de Pesquisas de Produtos Naturais, Universidade Federal do Rio de Janeiro.

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pharmacological uses of Plumbaginales. The data were divided into several groups according to the following activites: leihsmanicidal, trypanocidal, antimalarial, antiviral, antitumoral, microbiological and inseticide. The other activities not cited before were joined into a separate group, named others.

Leishmanicidal Activity

Leishmaniasis is one of the major public health problem, with two to three million humans affect by the disease annually (Iwu et al., 1994). It is a group of tropical diseases caused by a number of species of protozoan parasites belonging to the genus *Leishmania*. The World Health Organization classify leishmaniasis in four clinical forms: visceral, mucocutaneous, cutaneous diffuse or disseminated cutaneous (Chan-Bacab & Peña-Rodríguez, 2001).

In the case of leishmaniasis, *Plumbago* species have been shown to contain compounds with significant activity. The quinones corresponds to promising antileishmanial substances.

The ethanolic stem extract of *Plumbago scandens* inhibited the growth of *Leishmania amazonensis* promastigotes by 88% at 100ìg/ml. At the same concentration the amastigote growth was inhibited by 61% (Santos et al., 1997). Plumbagin, a naphthoquinone isolated from *Plumbago* species is reported to have an activity (IC_{50}) of 0.42 and 1.1ìg/ml against amastigotes of *Leishmania donovani* and *L. amazonensis* (Chan-Bacab & Peña-Rodríguez, 2001). Plumbagin and its dimers, 3,3'-bisplumbagin and 8,8'-bisplumbagin have been used in the treatment of cutaneous leishmaniasis in Amazonian Bolivia (Sepúlveda-Bozza & Cassels, 1996).

Trypanocidal Activity

Chagas´ disease is a complex clinical problem caused by the flagellate protozoan *Trypanosoma cruzi.* This microorganism is a mostly intracellular parasite, able to infect a broad range of vertebrates. The disease is characterized by an acute illness that is followed in some patients by chronic cardiac and gastrointestinal sequelae (Pereira, 1983).

Plumbagin exhibited high potency (IC_{90}= 1-5 ìg/ml) against six strains of *T. cruzi* epimastigotes, while the dimers 3,3'-bisplumbagin and 8,8'-bisplumbagin were less effective, with IC_{90} in the 25-100 ìg/ml range. In this assay nifurtimox and benznidazole, the only drugs used in the early stages of the disease, also showed IC_{90} values of 25-100 ìg/ml (Sepúlveda-Bozza & Cassels, 1996).

Antimalarial Activity

The treatment and prevention of human malaria reached a lot of difficulties due to the high endemicity of the disease in Amazonia, the new focuses in response to the intense migration and the resistence of *Plasmodium falciparum* to chlorochin as well as to other usual drugs.

Plumbago zeylanica has been used in the traditional medicine against malaria and its ethanolic extract has shown high *in vitro* activity, being of special interest for further investigations (Simonsen et al., 2001)

Plumbagin shows also antimalarial effects. Suraveratum et al. (2000) isolated a *Plasmodium falciparum* enzyme, the succinate dehydrogenase (SDH) from which the activity has been 50% inhibited by the naphthoquinone plumbagin at an inhibitory concentration of 5mM. It also inhibited the *in vitro* growth of the parasite with a 50% inhibitory concentration of 0,27mM.

Antiviral activity

Viruses are constituted basically by proteins and nucleic acids and are reponsible for many diseases from a common cold till more serious diseases as AIDS (Acquired Imuno Deficiency Syndrome), small-pox and poliomyelitis.

Preliminary biological screening indicated that the ethanolic extract of the root of *Limonium sinense* showed potent suppressory effect on herpes simplex virus type-1 (HSV-1) replication. Two constituents, (-)-epigallocatechin 3-O-gallate and samarangenin B, isolated from the *L. sinense* extract demonstrated activity against HSV-1, showing higher inhibitory effects than the positive control acyclovir (Lin et al., 1999). Generally,

quinones are responsible for the plant activity, however in this case, flavonoids were reported as the active molecules.

In the search for novel anti-human immunodeficiency virus type I (anti HIV-1) agents from natural sources, the methanol root extract of *Limonium tetragonum* was screened for its inhibitory effect against RNA-dependent DNA-polymerase (RT). The extract showed significant inhibitory activity on RT activity with 50% inhibitory activity (IC50) of 7,5ìg/ml (Min et al., 2001).

Antitumoral Activity

The tumor is formed by cells with defects in the mithotic cycle. The transformation of a normal cell into a tumor cell is frequently caused by DNA alteration, with the participation of a virus, chemical compounds or physical agents as certain types of radiation (Junqueira & Carneiro, 2000).

Some Plumbaginales species has been described to possess antitumoral activity. Several types of tumors and carcinomas has been used in tests with plant extracts and drugs isolated from them, as it could be seen in table 1.

Table 1. Antitumoral effect of plant extracts and compounds from Plumbaginales.

Plant	Plant Organ/ Extract/ Compound	Type of tumors	Results	Reference
Plumbago rosea (syn. *P. indica*)	Roots ethanolic extract	S-180 solid tumor and Ehrlich ascites carcinoma	The extract have only a weak tumor effect, it may be a good candidate for use with radiation to enhance the tumor killing effect	(Devi et al., 1994)
Limonium axillare	Geraniin		The tannin showed a slightly higher activity than the extract	(Ahmed et al., 1999)
Limonium axillare	Leaves alcoholic extract	Ehrlich ascites carcinoma	Active with ED_{50}=19.5±1.50 (*in vitro*) In vivo, the mean survival time of the treated mice was 23 days while that of control was 10 days only	(Kandil et al., 2000)
Limonium axillare	Myricetin-3-O-β-D-sorboside	Ehrlich ascites carcinoma	Active with ED_{50}=17.8±1.20 (*in vitro*) In vivo, the mean survival time of the treated mice was 24 days while that of control was 10 days	(Kandil et al., 2000)
*Plumbago*sp.	Plumbagin	Dalton´s ascitic lymphoma	After 14 days, plumbagin-treated groups were able to reverse the changes in hematological parameters and proteins, consequent to tumor inoculation	(Kavimani et a., 1996)

The leaf alcoholic extract of *Limonium axillare* and a flavonol glycoside (myricetin-3-O-â-D-sorboside) were used in cytotoxic assays. Many types of cells lines were used, corresponding to many types of leukemia and cancer such as: non-small cell lung cancer, colon cancer, CNS cancer, melanoma, ovarian cancer, prostate cancer, renal cancer and breast cancer. The results indicated

that the isolated compound was more active than the alcoholic extract. The best results were observed against CNS and breast cancers (Kandil et al., 2000).

The naphthoquinone plumbagin is responsible for many of the biological activities described in literature. However this molecule, depending on its concentration, has a high level of toxicity and can cause the death of the animal. In order to reduce the toxicity and increase the activity, many studies have been made, with protection carriers, as it could be seen in table 2. These studies evaluated the efficiency of plumbagin on tumor cells.

Table 2. Use of carriers in order to reduce toxicity and enhance the activity of plumbagin.

Carriers	Results	Reference
Niosomes	Not to active	(Kini et al., 1997)
Albumin microspheres	Promising results. Plumbagin given at a dose of 5mg/kg, the albumin microsphere showed an antitumor and antifertility activity	(Kini et al., 1997)
Poly (D, L-lactide)- co-glycolide microspheres	The microspheres had a higher activity than the plain drug in sarcoma 180 tumor	(Singh et al., 1996)
Poly (lactic-co-glycolic) biodegradable injectable implant	The toxicity was reduced, suggesting that the gel implant could be an effective drug delivery system for reducing toxicity and enhancing the therapeuticaly efficacy as antitumoral of plumbagin	(Singh et al., 1997)
Beta-cyclodextrin inclusion complex	Reduced the toxicity and enhanced the antitumor efficacy against Erhlich ascites carcinoma	(Singh & Udupa, 1997)

Microbiological Activity

Infectious diseases account for a high proportion of the health problems in developing countries. Claims of effective therapy for the treatment of these diseases have prompted the interest in scientific investigation.

Extracts from roots of *Plumbago zeylanica* showed microbiological properties. The aqueous extract and its partition (petroleum ether, dichloromethane, methanol, aqueous residue) were effective against *Salmonella gallinarum*, *Escherichia coli*, *Proteus vulgaris* and *Klebsiella pneumoniae* (Desta, 1993).

Aqueous and alcoholic extracts from roots of *Plumbago zeylanica* exhibited activity against *Bacillus subtilis*, *Escherichia coli*, *Proteus vulgaris*, *Salmonella typhimurium*, *Pseudomonas aeruginosa* and *Staphyloccocus aureus*. Among various extracts from different plants, alcoholic extract from *Plumbago zeylanica* was one that shown potential activity. It was also analysed for cellular toxicity, being negative for this test (Ahmad et al., 1998).

The alcoholic extract from roots of *Plumbago zeylanica* was tested against multi-drug resistant of clinical origin (*Salmonella paratyphi*, *Staphyloccocus aureus*, *Escherichia coli* and *Shigella dysenteriae*). The extract exhibited strong antibacterial activity against all tested bacteria. Chemical analysis of the crude extracted revealed the presence of flavonoids, saponins and

naphthoquinone (Beg & Ahmad, 2000).

The extracts of *Limonium californicum* was effective in the inhibition of the verotoxin production by enterohemorrhagic *Escherichia coli*. Sakagami et al. (2001) suggests that the administration of this plant extract might prevent the production of verotoxin in the human intestines.

In a study, Mahoney et al. (2000) showed the use of several naphthoquinones effective against *Aspergillus flavus*, a fungus that contaminates the commercial products walnuts. The quinones delayed germination of the fungus, its growth and the aflatoxigenesis.

Insecticide Activity

Insects can act as vectors of various diseases. The control of them is of great interest, mainly in developing countries where there are commonly endemic, most of them are transmitted zoonotically.

Plumbagin has many effects against insects, as it could be seen in table 3.

Table 3. Effect of plumbagin in different insects.

Insect	Activity	Reference
Helicoverpa armigera (Lepidoptera – Nortuidae)	Insect growth regulator Affect the number of the major protein bands in the protein profiles of the cuticle of treated larvae. Affect also the neurosecretory cells.	(Krishnayya & Rao, 1995)
Dysdercus koenigii (Heteroptera - Pyrrhocoridae)	Toxic to the fifth instar nymphs Reduce the growth rate and increase the time taken for molting Reduce the ability of mating in males and affect the fecundity of females in freshly-moulted adults.	(Satyanarayana et al., 1999)
Dysdercus koenigii (Heteroptera - Pyrrhocoridae)	Growth regulator	(Banerjee et al., 2001)
Arachnis aulaea (Lepidoptera - Arctiinae)	Responsible for the selectivity feeding behaviour	(Villavicencio & Perez-Escandon, 1994)
Culex fatigans (Diptera - Culicidae)	Larvicidal activity	(Ghosh et al., 1994)
Culex quinquefasciatus (Diptera - Culicidae)	Larvicidal activity	(Chockaligan et al., 1990)
Dactylotum coralllinum (Orthoptera – Acrididae)	Insect feeding deterrent	(Villavicencio & Perez-Escandon, 1992)
Phoetaliotes nebrascencis (Orthoptera – Acrididae)	Insect feeding deterrent	(Villavicencio & Perez-Escandon, 1992)
Sphenarium purpurascens (Orthoptera – Acrididae)	Insect feeding deterrent	(Villavicencio & Perez-Escandon, 1992)
Musca domestica (Diptera – Muscidae)	Affect the insect growth and the metamorphosis	(Rao et al., 1996)

Other activities

An enzymatic screening made with the root extracts of *Plumbago indica* (sin. *P. rosea*), *P. zeylanica*, *P. auriculata* (sin. *P. capensis*) and *P. europaea* (sin. *P. albus*) has shown effect as gastro-intestinal flora normalizer. The investigations were directed into the possibilities of the presence of some powerful enzymes in the root of *Plumbago* species. The *P. zeylanica* flowers showed greater effect on digestive stimulus activity than the other *Plumbago* species (Poul et al., 1999).

Plumbago indica showed a macrofilaricidal property against *Setaria digitata*, a filarial parasite of cattle. Complete inhibition of motility was observed for concentrations ranging from 0,02 to 0,05mg/ml. The fractionation of the crude extract resulted in the isolation of the active molecule plumbagin (Mathew et al., 2002).

The effects of a 50% ethanol extract of the root of *Plumbago zeylanica* were investigated on central nervous system in rats. The extract showed enhancement of the spontaneous ambulatory activity without inducing sterotypic behaviour. The neurochemical estimations revelaed elevated levels of dopamine and homovanillic acid in striatum compared with the control rats. The results indicated stimulatory properties of the extract, which may be mediated by dopaminergic mechanisms in the rat brain (Bopaiah & Pradham, 2001).

The phosphate buffered saline extracts of the roots of *Plumbago zeylanica* was investigated and a possible anti-inflammatory action was speculated (Oyedapo, 1996).

CONCLUSION

Plumbaginales species showed a wide range of biological activities, suggesting a great pharmacological and biotechnological potential. Medicinal plants hold promise as sources of chemical leads for the development of new drugs.

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