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Review Article

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Challenges and Perspectives on Plasmid Curing, Medicinal and Pharmacological Traits of Plumbago *Zeylanica* (Chitraka): A Review

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Abstract: From ancient times of vedas, charaksamhita and sushrutsamhita, to modern day developments and research in medicine, the medicinal importance of Chitraka (*Plumbago zeylanica*) as a wonderful Indian remedy has been upheld through the test of time. Chitraka is used in ayurveda for relief from many ailments, especially digestive disorders, bronchitis, diseases of liver, leucoderma, inflammation, piles, itching, laryngitis, rheumatism, diseases of spleen, many skin disorders etc. The root extracts of *P. zeylanica* have been incorporated in various Indian indigenous ayurvedic drug formulations. This paper reviews various aspects of Chitraka like different pharmacological activities, medicinal properties including wound healing, antioxidant, antiulcer, anticancer, leishmanicidal, antifertility, antimalarial, antidiabetic, hypolipidemic, trypanocidal, antibacterial, antifungal, antiviral, anti-inflammatory, antimutagenic, anti-allergic, larvicidal, insecticidal and anxiolytic activities. *P. zeylanica* plant contains naphthoquinones, flavonoids, terpenes, alkaloids, glycosides, steroids, triterpenoids, tannins, phenolic compounds, glucopyranoside, sitosterol saponins, coumarins, carbohydrates, fixed oils, fats and proteins having a wide variety of bioactivities. The important compound responsible for bioactivity is plumbagin which is chemically 5-hydroxy-2-methyl-1,4-naphthoquinone. *Studies of P. zeylanica* roots resulted in identification of plumbagin and lawsone as an active principle exhibiting the plasmid elimination activity. Due to the toxicity of chemical curing agents like acridine orange or ethidium bromide, there is a constant need of developing novel curing agents which are more effective and at the same time their non-toxic nature. Bacterial strains resistant to multiple antibiotics have emerged to which the invention of new antibiotics has failed to match up. The effects of antibiotic resistance are serious with mortality and morbidity constantly on the rise. Therefore *P. zeylanica* root extracts containing lawsone and plumbagin would have great potential as drugs of choice in the treatment of antibiotic resistant bacterial strains. The already ineffective antibiotic therapy can be made effective by converting antibiotic resistant bacteria into sensitive ones. The present review for the first time depicts the use of *P. zeylanica* as antimicrobial and plasmid curing agent in medicinal formulations and it is a novel approach towards the spread of antibiotic resistance especially in the hospital environment.

Keywords: *Plumbago zeylanica*, Plasmid curing, Bioactive compounds, Plumbagin, Lawsone

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1. INTRODUCTION

There is a continuing search for new antimicrobial compounds from other sources including plants as they are known to produce diverse bioactive substances of chemotherapeutic value[1]. The most important of these bioactive compounds are alkaloids, flavonoids, tannins, and phonetic compounds[2]. According to the World Health Organization medicinal plants would be the best source to obtain a variety of drugs[3]. These are not only used for primary health care not just in rural areas in developing countries, but also in developed countries as well where modern medicines are predominantly used[4]. Such plants should be investigated to understand their properties, safety, and efficiency[5]. Microorganisms have developed resistance to many antibiotics which has created immense clinical problems in treatment of infectious diseases. Clinically most important resistance to antibiotics is the result of plasmid encoded genes[6]. Presence of antibiotic resistance genes on bacterial plasmids and transposons has further helped in transmission and spread of drug resistance among pathogenic bacteria like *E. coli, Shigella, Salmonella, Acinetobacter, Staphylococcus, S. pneumoniae* and *M. tuberculosis* [7,8,9]. Secondary metabolites produced by plants constitute a source of bioactive substances and now a day's scientific interest has increased due to search for new drugs from plant origin. Hence, more studies pertaining to the use of plants as therapeutic agents should be emphasized, especially those related to control of antibiotic resistant microbes. This has encouraged research into screening of plants for antimicrobial activities. Chitraka i.e. *Plumbago* is known as "Vanaushadhi plant" (medicinal plant from forest) since ancient times in India and it is interesting to note that its reference is found even in Vedas[10]. Even thereafter we find its reference in ancient "Charaksamhita", as a plant used in various medicinal applications to ensure overall health[11]. It is also referred by "Sushrut"[12]. Chitraka literally means "agni" i.e. fire which has capacity to "burn" the disorders[13]. Charaksamhita gives details of various mixtures and medical preparations in which products of "Chitraka" are used to cure various diseases and disorders[11]. The importance of Chitraka is mentioned in Charaksamhita Adhyaya 15. Charaksamhita explains as to how since ancient times, Chitraka i.e. *Plumbago zeylanica* has been used for ayurvedic treatment, due to its medicinal properties and effects which were experienced since then. It is used in traditional system of Indian medicine against several ailments including diarrhoea, leprosy, digestive disorders, bronchitis, diseases of liver, leucoderma, inflammation, piles, itching, laryngitis, rheumatism, diseases of spleen and many skin disorders[14]. Chitraka stimulates digestive power and helps to accelerate the appetite[15]. Biological activities of crude extracts and active constituents of this plant reported so far include antimicrobial, antimutagenic, antitumor and radio-modifying properties[16]. The pulped roots or aerial parts are abortifacient, while powdered bark, root or leaves are used to treat gonorrhea, syphilis, tuberculosis, rheumatic pain, swellings, wound healing[17] dyspepsia, piles, diarrhoea, skin diseases, leprosy and also reported to possess antibacterial, antifungal properties[18]. Even after the advent of modern branches of science like botany, ethnobotany, microbiology, pharmacognosy, various properties and effects of Chitraka have been studied extensively and it is found to be more and more useful even in modern day medicine. *Plumbago* roots contain naphthoquinones, the chemical compounds having a wide variety of bioactivities[19,20]. With the revitalisation of herbal plants across the world, *P. zeylanica* is widely used for commercial preparation of drugs due to its biological activities[21]. This review is an effort to bring together all the properties and effects of *P. zeylanica* root extracts including plasmid curing and research thereon and expanding horizons thereof in treating patients against various health problems arising out of resistance of bacteria.

2. *CHEMICAL CONSTITUENTS OF PLUMBAGO ROOTS*

Due to the remarkable traditional medicinal properties *P. zeylanica* roots have been extensively screened for their chemical constituents. Major compounds isolated from these plants are naphthoquinones, flavonoids, terpenes, and sterols[22,23,24]. The 1,4-naphthoquinones are important metabolites of *P. zeylanica.* These naphthoquinones are derived mostly by substitution or oligomerisation of monomer, plumbagin. The plant contains a number of naphthoquinone derivatives consisting of monomers, dimers, and trimers[20]. Terpenes include lupeol, lupeol acetate, friedelinol and lupanone. Sterols are β-sitosterol, sitosterone, stigmasterol and stigmasterol acetate. Other chemical constituents include vanillic acid, plumbagic acid, glucose, unidentified tannin, and unidentified glycoside. Free amino acids of *P. zeylanica* include aspartic acid, tryptophane, tyrosine, threonine, histidine, glycine, hydroxyproline, alanine and methionine[25]. Nine compounds were isolated from aerial parts of *P. zeylanica* which includes plumbagin (I), isoshinanolone (II), plumbagic acid (III), beta-sitosterol (IV), 4-hydroxybenzaldehyde (V), trans-cinnamic acid (VI), vanillic acid (VII), 2, 5-dimethyl-7-hydroxychromone (VIII), indole-3-carboxaldehyde (IX)[26,27]. In the research by Patwardhan *et al* Lawsone was isolated for the first time from the roots of *P. zeylanica* [28].

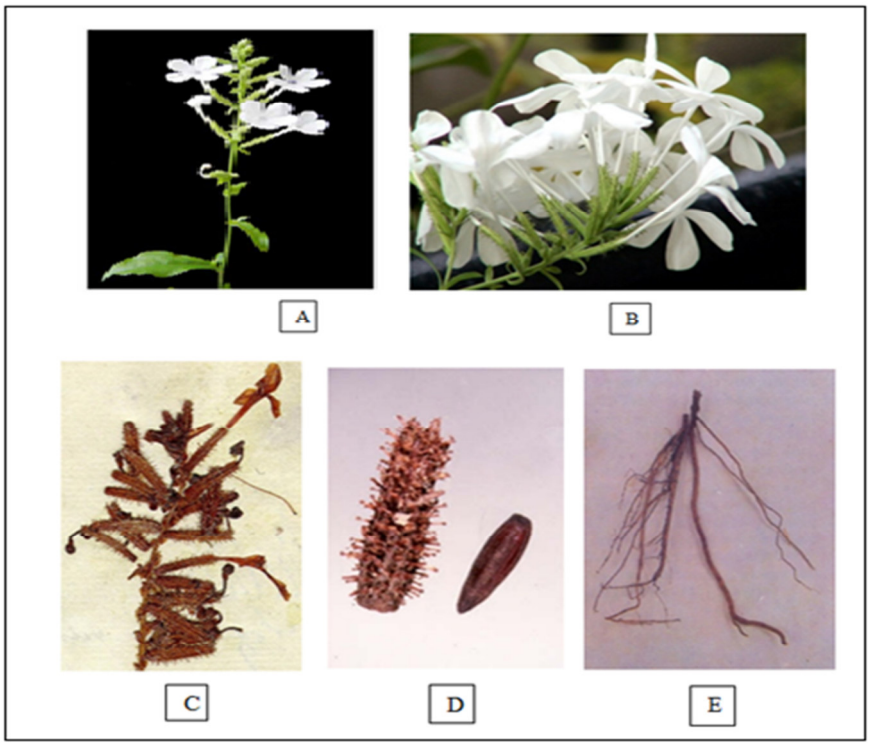

Figure.1 Plumbago zeylanica plant with different parts

Figure Ligand

***A.and B**: Plumbago zeylanica branch with white flowers:*
***C**: P. zeylanica flowers with glandular and elongated spikes.*
***D**: P. zeylanica seed, length 5m*
***E:** Roots of P. zeylanica*

3. *BROAD SPECTRUM MEDICINAL PROPERTIES OF PLUMBAGO ZEYLANICA*

The plant has been used in Indian medicine since the period of Charaka in treatment against inflammations, pile, krimi (worms) and kushtha (various skin diseases)[29,30,31]. *P. zeylanica* and other *Plumbago* species are widely used in several oriental systems of medicine in India, China and Eastern countries like Taiwan, Korea, and Malaysia [23,32]. Roots and root bark are bitter, stomachic, carminative, and astringent to bowels[33,34], antihelminthic, cure intestinal troubles, dysentery, inflammation, piles, bronchitis, itching, and diseases of liver [14]. Root extract is used as a laxative, expectorant, tonic, good appetizer, useful in laryngitis, rheumatism[35], diseases of spleen, ringworm, and scabies [34]. Paste of root with milk, vinegar or salt and water, is applied to open abscesses, leprosy, other skin diseases externally[36]. The renoprotective effect of hydroalcoholic extract *P. zeylanica* was observed in Swiss albino mice[37].Plumbagin from *P. zeylanica* stimulates the central nervous system in small doses. It has well marked antiseptic properties[34]. Plumbagin was found to exhibit fairly good results in early leucoderma and baldness[38]. Plumbagin and its dimmer 3,3'-biplumbagin have been used in treatment of leishmaniasis[39,40]. The important compound responsible for bioactivity is plumbagin, chemically 5-hydroxy-2-methyl-1,4-naphthoquinone. This was studied for its effect on development of antibiotic resistance using antibiotic sensitive strains of *E. coli* and *S. aureus*[41]. Crude extract of *P. zeylanica* containing naphthoquinones was found effective as antimicrobial and plasmid curing agent[42]. *P. zeylanica* root powder displayed estrogenic properties. Three endopeptidases (cathepsin D, renin and chymotrypsin) were studied in the uterus of albino rats after administration of *P. zeylanica* root powder. The changes were compared with effects induced by 17-β-estradiol in the same experimental conditions. Physiological activities of *P. zeylanica* root powder and 17-beta-estradiol mediated and modified in presence of ovaries. Presence of one or both ovaries modified the activities of enzymes. The results confirmed the estrogenic properties of *P. zeylanica* root powder [43,44]. The details of medicinal properties reported includes

3.1 *Wound Healing Activity*

Herbal extract of *P. zeylanica* was used in combination with *Rubia cordifolia, Centella asiatica, Terminalia belerica*, *Withania somnifera* and wound healing activity was evaluated in albino rats. The drug was used in ointment dosage form and then compared with a marketed formulation (Soframycin cream) as reference drug. The herbal drug combination has been observed to promote healing of wounds in animals[45,46]. Wound healing activity of methanolic extract of *P. zeylanica* roots have been reported in wistar albino rats. This study explored the wound healing action of ethanolic root extract of *P. zeylanica* in wistar rats and discovered that the activity is due to to the presence of phytochemicals such as terpenoids, alkaloids, flavonoids, saponins etc. and these compounds are responsible for the wound healing activity of the *P. zeylanica* plant.

3.2 *Antioxidant Activity*

Extracts of *P. zeylanica* and its active ingredient plumbagin have substantial antioxidant capabilities[47]. CapsHT2, a

polyherbal preparation which consist of *P. zeylanica, Comminphora mukul, Allium sativum, Semecarpus anacardium, Hemidesmus indicus, Terminalia arjuna, Tinospora cordifolia, Withania somnifera* and *Ocimum sanctum*, has antioxidant effects[48]. It is known that in almost all cytotoxic effects of naphthoquinones, redox cycling is the most important process involved. In the presence of plumbagin, molecular oxygen can act as a univalent electron acceptor, generating superoxide, a reactive species that can damage various biomolecules. Antioxidant effects of aqueous/alcoholic extracts of *P. zeylanica* roots were studied to understand possible mechanisms of its action[47.] Boiled ethanolic extracts and boiled aqueous extracts were most efficient. These extracts also significantly inhibited lipid peroxidation induced by cumene hydroperoxide, ascorbate-Fe^{2+} and peroxy-nitrite and contained high amounts of polyphenols and flavonoids. Protective effect *of P. zeylanica* was reported[49] against cyclophosphamide-induced genotoxicity and oxidative stress in Swiss albino mice

3.3 *Antiulcer Activity*

The anti-ulcer action of aqueous root extracts of *P. zeylanica* was studied on aspirin and indomethacin induced acute gastric ulceration in albino rats[50]. The extract at doses, 25, 50 and 100 ml/kg observed statistically important ($p < 0.05$) dose dependent inhibition of aspirin induced gastric mucosal damage while in the indomethacin induced ulcer 50 and 100 mg/kg respectively proved statistically significant ($p<0.05$) inhibition. Oral acute toxicity testing showed oral LD_{50} to be greater than 5000 mg/kg which revealed the wide margin of safety of root extracts of *P. zeylanica*[51].

3.4 *Anticancer Activity*

P. zeylanica has been recommended in therapy of cancer in Siddha system of medicine[52]. Earlier work in Indian National Cancer Institute, Bethesda, Maryland, USA, has indicated that naphthoquinones from this plant are associated with anticancer activity[53]. Plumbagin at 1 and 10 µg /ml blocked mitosis in chick embryo fibroblasts in vitro[54]. Plumbagin when administered intra tumour and orally at 2 mg/kg body weight brings about 70% and 60% relapse of tumor (fibrosarcoma) respectively[16]. Plumbagin is active for lymphocytic leukemia at 4 mg/kg body weight. Antitumor activity was also found against Dalton's ascitic lymphoma in mice by enhancing mean survival time and peritoneal cell counts[55]. β-sitosterol from *P. zeylanica* showed cytotoxic activity on the human melanoma cell line (Bowes cells). Plumbagin β-sitosteryl-3β-glucopyranoside-6'-O palmitate showed cytotoxic activity on both human cell lines MCF7 (Breast cancer cells) and bowes melanoma cells[26]. Plumbagin suppressed growth of Raji (erythroleukemia), Calu-1 (human lung carcinoma cell line), Hela (human cervical carcinoma cell line) and Wish (transformed epithelial cell line) tumor cell lines[23]. Cytotoxic activity of b-sitosteryl-3b- glucopyranoside-ad-O-palmitate from *P. zeylanica* was observed against MCF7 and Bowes cancer cell lines. b-Sitosterol inhibited Bowes cell growth and plumbagin was cytotoxic against MCF7 and Bowes cells[26]. Plumbagin was found to be a potential novel agent in the control of hormone-refractory prostate cancer which is the second leading cause of cancer-related deaths in men[56]. Plumbagin inhibits multiple molecular targets including PK Cepsilon, a predictive biomarker of Prostate cancer aggressiveness[57]. Stable plumbagin nanoparticles from *P. zeylanica* root extract were explored as a potential natural drug against prostate cancer. Inhibitory effect of the nanoparticles on the migration properties of prostate cancer cells revealed its therapeutic potentials for prostate cancer[58]. Plumbagin can inhibit cell proliferation, block cell cycle, and induce apoptosis of APL cell line NB4 cells[59]. Plumbagin is a powerful inhibitor of the NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) activation pathway which leads to suppression of NF-κB-regulated gene products, which explains its cell growth modulatory, anticarcinogenic, and radiosensitizing effects[60]. Ethanolic extract of *P. zeylanica* possess substantial anti-cancer action against Ehrlich Ascites Carcinoma in animal models, and it decreases elevated level of lipid per-oxidation having presence of higher terpenoids and flavonoids[61]. Plumbagin repressed the BAX, BCL-2, pro-caspase-3 expression, and cleaved caspase-3 in gastric cancer cells. Plumbagin inhibited the apoptosis in human gastric cancer cells due to its ability to suppress the STAT3 and Akt phosphorylation [62,63].

3.5 *Leishmanicidal Activity*

The quinones in *P. zeylanica* have promising antileishmanial activity against amastigotes of *Leishmania Donovani* and *L. amazonensis*. Plumbagin and its dimers, 3, 3'-bisplumbagin and 8, 8'-bisplumbagin have been used in the treatment of cutaneous leishmaniasis in *Amazonian Bolivia* [64].

3.6 *Antifertility Activity*

Extracts of *Plumbago* roots, when applied to ostium uteri, caused abortion[65,66]. In albino rats plumbagin showed anti-implantation and abortifacient activities when given orally (1-2 mg/100gm body wt) without showing teratogenic effect. Application of plumbagin in doses 0.005-5µg, prevented oocyte development and affected fecundity and fertility in housefly *Musca domestica*[67]. Plumbagin demonstrated strong anti-progestational activity [68]. Its root powder was 100% abortificient and showed 75% anti-implantation effects in rats. The antiimplantation effects depend on doses as well as initiation of treatment on specific days of pregnancy. Dose dependent anti-implantation response was 40-45% and 75%. The abortifacient response was 100% and dependent on mode of treatment in relation to the days of pregnancy[69]. The plumbagin-free alcohol extract of root of *P. zeylanica* possesses antifertility activity in rats and is free from adverse actions[70,65]. *P. zeylanica* therapy during the first 7 days of pregnancy abolished uterine proteins of 13,000, 19,000 and 26,000 and 75,000 Dalton molecular weights resulting in pre-implantationary loss. Proteins having molecular weights 55,000 and 65,000 Dalton were absent in aborted rats that were given *P. zeylanica* root powder from day 6 to day 17 of pregnancy[71]. Anti-implantation and abortifacient activity were reported in albino rats without any teratogenic effect of plumbagin in the doses of 1mg/100g[72].

3.7 *Antimalarial Activity*

Plumbagin from *P. zeylanica* was reported to show potent antimalarial activity against *Plasmodium falciparum* both in mice and *in vitro* by regulating lipid peroxidation

mechanism[73,74]. The activity of *Plasmodium falciparum* enzyme, succinate dehydrogenase has been 50% inhibited by plumbagin at an inhibitory concentration of 5mM. It also prevented the *in vitro* growth of the parasite with a 50% inhibitory concentration of 0.27mM.

3.8 *Antidiabetic Activity*

Methanol extracts of *P. zeylanica* (root), had displayed mixed inhibition to alpha-glucosidase enzyme activity with 100% inhibition with the IC50 value of 3.46 µg/ml [75.] Plumbagin (15 and 30 mg/ kg b wt) was orally administered to streptozotocin-induced diabetic rats for 28 days. An oral glucose tolerance test was performed on21st day. Plumbagin drastically lowered the blood glucose and substantially improved all other biochemical parameters to near normal. Plumbagin improved the activity of hexokinase and reduced the activities of glucose-6- phosphatase and fructose-1,6-bisphosphatase considerably in treated diabetic rats. Enhanced GLUT4 mRNA and protein expression were observed in diabetic rats after treatment with plumbagin[76].

3.9 *Hypolipidaemic Activity*

Ethanolic extract (50% v/v) of roots of *P. zeylanica* alone and combined with vitamin E, an antioxidant, in hyperlipidaemic rabbits, showed significant decrease in serum total cholesterol, LDL cholesterol and triglyceride levels. Plumbagin lowered serum cholesterol and LDL-cholesterol, by 53-86% and 61-91% respectively. It lowered cholesterol / phospholipid ratio by 45.8% and elevated the decreased HDL-cholesterol significantly[77]. Marked reduction was seen with formulation of *P. zeylanica* and vitamin E. The total cholesterol/HDL and LDL/HDL cholesterol ratios were found significantly lowered. These results indicate that *P. zeylanica* extract contain hypolipidaemic and antioxidant substances and its use as a therapeutic tool in hyperlipidaemic subjects will be of benefit and promote further investigation in this field.

3.10 *Trypanocidal Activity*

Plumbagin from *P. zeylanica* exhibited high potency (IC 90= 1-5µg/ml) against six strains of *Trypanosoma cruzi epimastigotes*, while the dimer 3, 3'-bisplumbagin and 8, 8'-bisplumbagin were less effective, with IC 90 in the 25-100 µg/ml range[64].

3.11 *Anti-inflammatory activity*

P. zeylanica has various medicinal properties and is used in formulations of several ayurvedic compounds to treat inflammatory disorders such as rheumatoid arthritis and laryngitis[78]. The phosphate buffered saline extract of roots of *P. zeylanica* was investigated for anti-inflammatory activity. The extract stabilized red blood cells subjected to heat. The extract exhibited a biphasic response. Enzymatic activities of both alkaline and acid phosphatases were reduced, while adenosine triphosphatase activity was stimulated in liver homogenates of formaldehyde induced arthritic rats[79]. Analgesic and anti-inflammatory activity of hydroalcoholic extract of *P. zeylanica* leaf was reported[80,81]. According to Chen and his co-workers extracts of *P. zeylanica* containing suberosin inhibited proliferation of human peripheral blood mononuclear cells through the modulation of the transcription factors NF-AT and NF-kappaB[82] which provides an explanation for the anti-inflammatory activity of *P. zeylanica*.

3.12 *Anti Allergic Activity*

The antiallergic properties of the 70% ethanol extract of *P. zeylanica* stems were studied. It inhibited systemic anaphylactic shock in mice, reduced homologous passive cutaneous anaphylaxis and skin reactions induced by histamine or serotonin in rats. Ethanol extract of *P. zeylanica* stems (50 µg/ml) markedly increased intracellular cAMP content of rat mast cells. This extract inhibited mast cell-dependent immediate allergic reactions, mediated by reducing the release of mediators such as histamine from mast cells via elevating intracellular cAMP level and weakening the inflammatory action of mediators[83].

3.13 *Anxiolytic Activity*

The *in-vitro* anti-anxiety or anxiolytic activity of *P. zeylanica* in mice was associated with the anxiolytic drug diazepam. Activity of *P. zeylanica* leaf extracts was observed to be effective in mice. Male swiss albino mice between 8 - 10 weeks old weighing 20 - 25 gm were used in the research. A good response was observed in open field test[84].

4. ANTIMICROBIAL PROPERTIES OF *PLUMBAGO ZEYLANICA*

4.1 *Antibacterial Activity*

Extracts from roots of *P. zeylanica* showed antimicrobial properties. Aqueous extract and its partition (petroleum ether, dichloromethane, methanol, and aqueous residue) were effective against *S. gallinarum*, *E. coli*, *P. vulgaris* and *K. pneumoniae*[85]. Aqueous and alcoholic extracts from roots of *P. zeylanica* demonstrated activity against *B. subtilis*, *E. coli*, *P. vulgaris*, *S. typhimurium*, *P. aeruginosa* and *S. aureus*. Among various medicinal plant extracts, alcoholic extract of *P. zeylanica* was found to show potentially interesting activity against pathogenic and opportunistic microorganisms[86]. Alcoholic extract of *P. zeylanica* plant roots was tested against multidrug-resistant clinical isolates of bacteria, *S. paratyphi*, *S. aureus*, *S. albus*, *E. coli*, *S. dysenteriae*, *K. pneumoniae* and *B. subtilis*[87]. The extract displayed strong antibacterial activity against all test bacteria irrespective of their antibiotic resistance behaviour. Phytochemical analysis of crude extract revealed the presence of flavonoids, saponins and naphthoquinones. Plumbagin along with some related naphthoquinones was found effective against *E. coli, C. jejuni, Bacillus sp., Staphylococcus sp., Mycobacterium sp., C. diptheriae*[88](Table 1). It has shown antibacterial activity against *Acineobacter*[89] Antibacterial activity of *Plumbago* root extracts reported against *S. marcescence* and *P. mirabilis* was reported for first time[42]. Anti-*Helicobacter pylori* activity of *P. zeylanica* was detected by [90]. Methanolic extract of *P. zeylanica* roots showed anti-bacterial effect against *Bacillus subtilis* [91]. Ethyl acetate extract exhibited lowest minimum inhibitory concentrations against five *H. pylori* strains, of which ranged from 0.32 to 1.28 mg ml/l. Ethanolic extract of *P. zeylanica* showed anti-microbial activity against *Salmonella typhi, Pseudomonas aeruginosa, Bacillus subtilis* and *Staphylococcus aureus* [92].

4.2 *Antifungal Activity*

Broad spectrum antifungal activity of *Plumbago* root extracts was reported. Antifungal activity of *P. zeylanica* against *F. oxysporium* and *C. humicolus,* was reported for the first time[42]. *P. zeylanica* also showed antifungal activity against *P. notatum*, *P. canadense*, *R. nigricans*, and *E. floccosum* at concentration 10µg/ml[16]. High potency was observed in the extracts of *P. zeylanica* (4mg/ml) against *Candida* which indicates that the plant has a potential source for anticandidal drugs[93]. *P. zeylanica* naphthoquinones were effective against *A. flavus*, a fungus that contaminates commercial products walnuts[94]. The quinines delayed germination of fungus, its growth and aflatoxigenesis. A very dilute solution (i.e. a concentration of 1:50,000) of plumbagin was lethal to a wide spectrum of bacteria and pathogenic fungi, i.e. *Coccidioides imminites*, *Histoplasma capsulatum*, *Trichophyton* spp., *C. albicans*, *A. niger* and *A. flavus*[95].

4.3 *Antiviral Activity*

80% methanolic extracts of *P. zeylanica* exhibited antiviral activities against coxsackievirus B3 (CVB3), influenza A virus and herpes simplex virus type1 Kupka (HSV-1) using cytopathic effect (CPE) inhibitory assays in HeLa, MDCK, and GMK cells, respectively. It was confirmed with plaque reduction assays[96].

Table 1. Antimicrobial activity of plumbagin

Organism	MIC of Plumbagin from *P. zeylanica* (µg/ml)
Gram positive bacteria [16,97,98]	
Bacillus subtilis	0.2
Staphylococcus aureus	20
S. citreus	20
S. albus	20
Gram negative bacteria [16, 97,99]	
Salmonella dublin	20
Salmonella. paratyphi	20
Klebsiella Pneumonia	20
Pseudomonas aeruginosa	12.5
Escherichia coli	50
Rhinotricum nigricans	10
Penicillium canadense	10
Penicillium notatum	10
Penicillium lilacinum	10
Metarhizium *nana*	10
Candida albicans	0.78
Protozoa [46]	
Leishmania donovani	10 – 20
Leishmania mexicana	10 – 20

MIC: Minimum inhibitory concentration

5. *INSECTICIDAL AND LARVICIDAL ACTIVITY*

Insects can act as vectors of various diseases. The control of insects is of great importance; mainly in developing countries where they are commonly endemic, most of them are transmitted zoonotically. Plumbagin affects insect growth, metamorphosis, lowers the ability of mating in males and has larvicidal activity (Table 2). Hexane and chloroform and hexane crude extracts of *P. zeylanica* showed highest larvicidal activity against *A. gambiae* i.e. LC50 6.4 and 6.7 µg/ml respectively [100]. *P. zeylanica* extract possesses larvicidal activity against second, third, and fourth instar larvae of *Aedes aegypti*. LC (50) values of all the extracts in different solvents of *P. zeylanica* were less than 50 ppm against all tested larval[101].

Table 2. Effect of plumbagin on different insects

Sr. No.	Insect	Activity
1	*Musca domestica* (Diptera -Muscidae)	Affect insect growth and Metamorphosis[102]
2	*Dysdercus koenigii* (Heteroptera - Pyrrhocoridae)	Lower growth rate and rise the time taken for molting. Reduce ability of mating in males and affect fecundity of females in freshly moulted adults[103]
3	*Dactylotum corallinum* (Orthoptera -	Insect feeding deterrent[104]

	Acrididae)	
4	*Helicoverpa armigera* (Lepidoptera - Noctuidae)	Insect growth regulator. Affect number of major protein bands in protein profiles of cuticle of treated larvae. It also affects neurosecretory cells [105]
5	*Dysdercus koenigii* (Heteroptera - Pyrrhocoridae)	Growth regulator[106]
6	*Arachnis aulaea* (Lepidoptera - Arctiinae)	Responsible for selectivity feeding Behavior [104]
7	*Culex fatigans* (Diptera - Culicidae)	Larvicidal activity[107]
8	*Phoetaliotes nebrascencis* (Orthoptera - Acrididae)	Insect feeding deterrent [104]
9	*Sphenarium purpurascens* (Orthoptera - Acrididae)	Insect feeding deterrent [104]
10	*Culex quinquefasciatus* (Diptera - Culicidae)	Larvicidal activity [108]

6. ANTIMUTAGENIC ACTIVITY

Antimutagenic activity of plumbagin from *P. zeylanica* was tested against known chemical mutagens in a standard mutagenicity test system of Ames using *S. typhimurium* strains[109]. Plumbagin did not show any mutagenic effect, whereas it reduced significantly mutagenic effect of 4-nitrophenylene diamine, phenyl hydrazine and sodium azide in test strains of *S. typhimurium,* suggesting that plumbagin possessed antimutagenic activity. Actively growing *E. coli* cells when exposed to plumbagin, a redox cycling quinone which increases flux of O_2 radicals in the cell, were mutagenized by this treatment[110]. *E. coli* showed an inducible DNA repair response specific for the type of oxidative damage generated during incubation with plumbagin. Methanolic extracts of *P. zeylanica* roots exhibited varying levels of antimutagenicity [111].

7. *FORMULATIONS AND PHARMACOLOGICAL ACTIVITIES OF PLUMBAGO ZEYLANICA:*

The root extracts of *Plumbago* species have also been incorporated in various Indian indigenous ayurvedic drug formulations, namely Chitrakadi vati, Chitraka-haritaki, Dashamoolarishta, Yakritaplihari lauha, Drakshasava, Lauhasava, Ashwagandharishtha, Chitrakadi lauha, Chitrakadi ghrita, Chitrakadi taila, Chitrakadi Lepa as well as Asokarishtam, Livosprin, Livomyn, Livokin etc [112] (Table 3). Importance of *P. zeylanica* and its possible pharmaceutical activity for the development of new herbal formulations had been evaluated[113]. *P. zeylanica* showed antipyretic, antibacterial, antifungal, antifertility, anticancer, anticoagulant, antitumor, hepatoprotective and cytotoxic activities[114]. Plumbagin given orally at 2 mg/kg, decreased tumor growth by 70%. Tropical application of plumbagin has been found to be useful in patients with common wart. Plumbagin[115] has various pharmacological activities like antimalarial, cardiotonic etc[116]. It has been described in literature and is shown to possess a wide variety of bioactivities[16]. It shows activity against several gram-positive bacteria, gram-negative bacteria as well as *Candida* species.

Table 3. Formulations with a root powder of Chitraka manufactured in India

Name of formulation	Ingredients	% of *P. zeylanica (Chitraka)*	Use	Manufacturer	Reference
Chitrakadi vati	Chitraka, pimpali mool, Lavanani, Ajamodra, Hingu, Vyosham, Doxari, Chavya	12.5	Increases digestive capacity	Bharadwaj Pharmaceuticals, Baidyanath, Ayurved Rasashala, Unjha Pharmaceuticals, Kahdiwale Vaidya.	112
Chitraka-haritaki	Chitraka, Dashamoolakvath, Awala swaras, Guduchi swaras, Haritaki, Vyosh, Trijat,	20	Tuberculosis, cough, cold, worms, tumer, breathlessness	AVP (Kerala), as per demand	117

	Yavakshara, Shahad				
Dashamoolarishta	Dashamool, Danti, Chitraka mool, Haritaki	20	Piles, colitis, anemia, to increase digestive capacity	Arkashala, Sandu Brothers, Bharadwaj Pharmaceuticals, Baidyanath, Ayurved Rasashala, Unjha Pharmaceuticals, Kahdiwale Vaidya.	112
Yakritaplihari lauha	Hinguloth parad, Gandhak, Loha, Abrhakam, Tamra bhasma, Manashila, Rajani choorna, Jaipal, Takan, Sheelajatu, Danti, Chitraka, Nirgundi, Adrak, Brungaraj ras.	2 - 5	All types of ascitis. Increases digestive capacity.	As per demand	117
Drakshasava	Draksha, Madha, Khadisakhar, Dhataki, Kankol, Lavang, Jaiphal, Mire, Pimpli, Chitraka, Chavya, Pimpal mool, Renuka	5	Worms, skin diseases, tonic, wounds, eye infections etc.	Arkashala, Sandu Brothers, Bharadwaj Pharmaceuticals, Baidyanath, Ayurved Rasashala, Unjha Pharmaceuticals, Kahdiwale Vaidya.	112
Lauhasava	Lohachurna, Trikatu, Triphala, Yavani, Widang, Mustaka, Chitraka, Dhatki Phool, Shahad, Gud, Shudhajal	1	Ascitis, splenic disorders, itching, cardiac disorders	Arkashala, Sandu Brothers, Bharadwaj Pharmaceuticals, Baidyanath, Ayurved Rasashala, Unjha Pharmaceuticals, Kahdiwale Vaidya.	111
Ashwagandharishtha	Ashwagandha, Shwetamusali, Manjishtha, Harithaki, Rajani, Daru halad, Madhuk, Rasna, Vidari, Arjun, Trivruta, Chandana shwet, Chandana rakta, Wacha, Chitraka, Ananta, Nishottar, Dhatki, Madha, Trikatu, Trijat, Nagkeshar	1	Coma, epilepsy, weakness	Arkashala, Sandu Brothers, Bharadwaj Pharmaceuticals, Baidyanath, Ayurved Rasashala, Unjha Pharmaceuticals, Kahdiwale Vaidya.	112
Chitrakadi lauha	Chitraka, Nagar, Vasa, Shalparni, Talpushpa, Apamarg, Manak, Loha bhasma, Abhraka Bhasma, Pimpli Choorna, Tamra Bhasma, Javakahara, Sendhav, Sarvalavana, Gomutra	20	Splenomegaly, hepatic disorders, fever, jaundice, edema, dysentery	As per demand	112
Chitrakadi ghrita	Chitraka, Takra, Kshira	30	Dysentery, digestive disorders	AVP (Kerala), Baidyanath	112
Chitrakadi taila	Chitraka arka, Trivruta, Patha, Bakuchi, Ashwamar, Sudha, Wacha, Kalihari, Saptaparni, Sajjikshar, Jyotishmati	9	Fistula, wound healing, skin disorders	AVP (Kerala)	112
Chitrakadi Lepa	Chitraka, Ela, Bimbi, Wasa, Arka, Suntha	16	Rash type skin diseases	As per demand	112

8. ACTION OF PLUMBAGIN

Charak has described Chitraka as Deepan-pachan dravya (useful in digestion)[117]. In fact, practitioners of Indian system of medicine have been using drugs in the form of a decoction or powder for centuries. A chemical substance 'Plumbagin' was first isolated in 1829 by[118] Dulong D Astafort form *P. zeylanica* and first synthesized by Fieser and

Dunn after a century in 1936[119]. Its active principle content is an alkaloid "Plumbagin" which stimulates secretion of sweat, urine and bile and has stimulant action on the nervous system. Plumbagin is quinine and is capable of abstracting electrons from electron transfer components and diverts the electron flow to molecular dioxygen to form superoxide radicals[120]. 0_2^- Gives rise to OH radicals and H_2O_2 by enzymatic and non-enzymatic reactions responsible for damage to micromolecules including DNA in microorganisms. Non-DNA damaging concentrations of plumbagin diminished the DNA damage induced by catechol, which provides support for the idea that plumbagin may act as an antioxidative agent at low concentrations[121].Plumbagin induced mammalian topoisomerase II-mediated DNA cleavage in vitro[93]. Treatment of a reaction mixture containing this naphthoquinone and topoisomerase II at an elevated temperature of 65 ^{0}C resulted in a great reduction in DNA cleavage. Plumbagin has anticancer, antileishmanial, antibacterial, antifungal properties as well as a contraceptive effect. It has a potential as a chemotherapeutic agent[56]. It also has cardiotonic action[116], insecticidal activity[122], hypolipidemic and anti-atherosclerotic effect by reducing the level of cholesterol and LDL cholesterol in rabbit[123]. Plumbagin augments macrophage bactericidal activity by potentiating oxyradical release at low concentration whereas at higher concentration it has inhibitory activity[124]. Plumbagin when administered orally, at a dosage of 4 mg/kg body weight induces tumor regression in 3-methyl-4-dimethyl amino azobenzene (3MeDAB) induced hepatoma in Wistar male rats[56]. Certain gluconeogenic enzymes, namely, glucose-6-phosphatase and fructose -1,6-diphosphatase decreased in tumor hosts, whereas plumbagin administration increased gluconeogenic enzyme levels in treated animals. These investigations indicate the molecular basis of different biological behavior of 3MeDAB induced hepatoma and anti-carcinogenic property of plumbagin against hepatoma studied in rats. When tested against the resistant strain of *M. tuberculosis* H37Rv, plumbagin exhibited inhibitory activity at <12.5 microg/mL[125]. The major effects of plumbagin on chick embryo fibroblast cultures were arrest of cell growth and proliferation decrease in mitotic index with accumulation of cells in metaphase at 1 µg concentration. There was indication of chromosomal aberrations like clumping of chromosomes, with degeneration as shown by nuclear and cytoplasmic vacuolization and nuclear polymorphism. Plumbagin at lower concentration behaves like a spindle poison by preventing entry of cells into mitosis like colchicines but at higher concentrations it exhibits nucleotoxic and cytotoxic effects. Plumbagin effects on reproductive function of rat. It causes selective testicular lesions in dogs. The wet weight of testes and epididymides decreases. Plumbagin inhibits spermatogenesis. It results in significant decrease in protein and RNA contents of testes and epididymides associated with loss in weight of these organs[54].

9. PLASMID CURING BY P. ZEYLANICA ROOT EXTRACT, PLUMBAGIN AND LAWSONE

Development and spread of antibiotic resistance are problems with prolonged chemotherapy against bacterial infections. Elimination of plasmid mediated drug resistance in pathogenic strains of bacteria is of great importance both, in treatment of bacterial infection and in microbial genetics. The already ineffective therapy can be made effective by converting resistant cells into sensitive ones[126]. Reversal of drug resistance by plumbagin has been recorded in microorganisms[127]. DNA strand session and plasmid curing activity of an Indian folk medicine constituent Chitrak has been previously reported[128]. *P. zeylanica* extract cured plasmid from 14% *E. coli* (pUK 651) treated cells, confirmed by determining the loss of resistance markers in cured derivative culture [87]. The root extracts cured plasmid encoded antibiotic resistances from the clinical isolates and reference strains at curing efficiencies of 4 to 100%. Petroleum ether root extract of *P. zeylanica* demonstrated higher plasmid curing activity and was higher than known plasmid curing agents like ethidium bromide or acridine orange[129]. Plumbagin was effective in selectively eliminating stringent, conjugative, multidrug-resistant plasmids from *E. coli* strains. Simultaneous loss of resistance to antibiotics in plumbagin-treated cell indicated loss of plasmid[99]. Plumbagin at 50µg/ml cured silver resistance from *Acinetobacter baumannii* BL88 at a frequency of 69%. Along with Ag^r other markers i.e Cd^r, Sb^r, Ap^r and Sm^r were also cured at varying frequencies[130]. Plumbagin was found to be effective in curing the plasmids pUPI 102(Tc ^{r}, Cm ^{r}, Hg ^{r}) and pUPI 103(Pn ^{r}, Cb ^{r}, Km ^{r}) from antibiotic and metal resistant strains of *Acinetobacter baumannii* [131]. Plumbagin at subinhibitory concentration 62.5 µg/ml eliminated the plasmid pUPI200(Sm ^{r}, Km ^{r}, Gm ^{r}) from *E. coli* K12 J53.2 with 21% curing efficiency[132]. *A. baumannii* C11, a soil isolate exhibited high level of resistance to multiple antibiotics and heavy metals. Plumbagin eliminated resistances at following efficiencies: Gm^r (100%), Nm (100%), Cn^r (80%), Ct^r (100%), Cm^r (74%), Tp^r (100%), Pn^r (18%), Ag^r (100%), Hg^r (100%), Cd^r (100%)[133]. Plasmid pUPI102 (Gm^r, Nm^r, Tc^r, Hg^r) from *A. junii* ACN4 was cured by plumbagin[134]. Plumbagin was found to be far more effective as a plasmid curing and antibacterial agent than its metal complexes. It caused DNA strand scission[128]. Plumbagin has been used in plasmid elimination from antibiotic resistant clinical strains of *Acinetobacter* [135]. Plasmids pUPI275 (Sm^r, Sd^r) and pUPI276 (Ag^r, Ap^r, Cb^r, Tc^r, Cm^r,) from *A. baumannii* BL54 were cured by treatment with plumbagin[136,137]. Plumbagin intercalates into DNA molecule and induces topoisomerase-II mediated DNA cleavage in vitro[97]. Curing ability of plant extract is due to plumbagin as it intercalates with DNA molecule and inhibits plasmid replication selectively at sub-MIC concentration. It is dependent on ability of plumbagin to undergo redox cycling to produce superoxide that can damage various macromolecules (Table 4). In a research investigation,[28] Patwardhan and her coworkers purified a compound Lawsone from *P. zeylanica* roots able to eliminate antibiotic resistance and cure plasmids from pathogenic strains resistant to multiple antibiotics without any ill effect on mammalian cells. The synergistic effect of lawsone with the antibiotic exhibited its tremendous potential in modern day therapeutics. The non-toxic, non-mutagenic, plasmid curing and plasmid transfer inhibiting role of lawsone made it a potential drug of choice in the treatment of antibiotic resistant bacterial strains, demonstrating a new dimension in antibiotic therapy.

Table 4. Plasmid curing by P. zeylanica root extract, Plumbagin and Lawsone in Acinetobacter and E. coli

Strain	Plasmid	Resistance markers cured	Reference
A. baumannii C11	pUPI 101	Cd^r	89
A. junii ACN4	pUPI 102	Gm^r, Nm^r, Tc^r, Hg^r	89

A. baumannii CA114	pUPI 104	Ap^r, Km^r	89
A. baumannii APH5	pUPI 105	Cd^r	89
A. baumannii APH5	pUPI 106	Pn^r	89
A. baumannii APH5	pUPI 107	Cb^r	89
A. baumannii B32	pUPI 108	Pn^r, Ap^r, Cb^r, Am^r, Cp^r, Cm^r, Km^r	89
A. baumannii B32	pUPI 109	Tc^r, Sm^r, Hg^r,	89
A. baumannii B32	pUPI 110	Cu^r,	89
A. baumannii C11	pUPI 111	Pn^r, Cb^r, Km^r	89
A. baumannii C11	pUPI 112	Cp^r, Nm^r, Hg^r	89
A. baumannii BL110	pUPI 200	Sm^r, Km^r, Gm^r, Cp^r	89
A. baumannii CA114	R751	Tp^r, Su^r	89
A. baumannii BL88	pUPI 199	Ag^r, Cd^r, Sb^r, Ap^r, Sm^r	136
A. baumannii BL54	pUPI 275	Sm^r, Cd^r	136
A. baumannii BL54	pUPI 276	Ap^r, Tc^r, Cm^r, Ag^r	136
A. baumannii A24	pUPI281	St^r, Ap^r, Gm^r, Ak^r	28
E. coli 46R641	Tp181	Ap^r, Cm^r, Km^r, Sm^r, Su^r, Tc^r	99
E. coli 48R371	R162	Ap^r, Cm^r, Sm^r, Su^r, Tc^r	99
E. coli 44R266	R6K	Ap^r, Sm^r,	99
E. coli 42R873	TP154	Ap^r, Km^r, Tc^r	99
E. coli HB101	pBR322	Ap^r, Tc^r	99
E. coli HB101	pBR329	Ap^r, Cm^r, Tc^r	99
E. coli 391	RP4	Ap^r, Km^r, Tc^r	138
E. coli 393	pKT231	Km^r, Sm^r	138
E. coli 398	pRK2013	Ap^r, Km^r,	138
E. coli	PUK651	Ap^r, Km^r, Co^r	87
E. coli	pRK2013	Ap^r, Km^r	28

Ap-Ampicillin; Tc-Tetracycline; Km-Kanamycin; Sm-Streptomycin; Cb-Carbenicillin; Pn-Penicillin; Su-Sulphonamide; Cm-Chloramphenicol; Nm-neomycin; Tp-Trimethoprim; Cp-Ciprofloxacin; Gm-Gentamycin; Co-Cobalt; Hg: Mercury

10. DISCUSSION

From primordial times of Vedas, Charaksamhita and Sushrutsamhita, to present day advances and research in medicine, the therapeutic importance of Chitraka i.e., *Plumbago zeylanica* as an excellent Indian remedy, have been upheld through test of time. Therefore, now it is very much essential to make further efforts to explore about nature and utilize *P. zeylanica* plant for betterment of mankind in today's age of infections and pollutions. In fact, today there is a need to combine branches of allopathic medicine with ayurvedic science for benefit of mankind. Formulations and preparations of *P. zeylanica* roots, their effects and pharmacological activities were studied. One of the ways to overcome antibiotic resistance problem is to eliminate genes encoding antibiotic resistance in bacteria. Because of toxicity of other curing agents like acridine orange and ethidium bromide, there is a constant need of developing novel curing agents which are more effective and at the same time nontoxic. Lawsone and plumbagin could eliminate antibiotic resistance and cure plasmids from pathogenic strains that are resistant to multiple antibiotics without any ill effect on mammalian cells at lower concentration. Goal of this review was to explore the significance of *P. zeylanica* and its potential medicinal and plasmid curing activity for the development of new herbal formulations. The findings and outcomes of this research would be useful in using plumbagin and lawsone from *P. zeylanica* roots as potential drugs of choice in the treatment of antibiotic resistant bacterial strains. These findings are of particular significance as plasmid encoded antibiotic resistance is a major challenge for physicians to treat. Already ineffective antibiotics could become effective if plasmid encoded antibiotic resistance is eliminated from the population. *P. zeylanica* root extracts can eliminate the plasmid encoded antibiotic resistance and render the cell sensitive to the antibiotics. The ineffective or outdated antibiotics could be rejuvenated if used in combination with such curing agents like plumbagin and lawsone. This would be a novel approach towards controlling multidrug resistant bacterial infections especially in hospital environment. Clarification of exact mechanism by which lawsone triggered plasmid curing in bacterial cells is not known at present and requires further extensive investigation.

11. CONCLUSION

P. zeylanica is used from centuries in Ayurvedic medicine. It is a valuable medicinal plant universally used in herbal formulations. It is chemically rich with its diverse contents including many active secondary metabolites like plumbagin and lawsone. The pharmacological attributes of *P. zeylanica* have been revalidated in modern-day sciences through several in vivo and in vitro studies. The present investigation elaborates broad spectrum medicinal properties of *Plumbago zeylanica* including antioxidant, antiulcer, anticancer, leishmanicidal, antifertility, antimalarial, antidiabetic, hypolipidaemic, trypanocidal, antibacterial, antifungal, antiviral, anti-inflammatory, antimutagenic, anti-allergic, larvicidal, insecticidal, wound healing and anxiolytic activities. This plant has immense potential as a plasmid curing agent. The present study reveals applications of root extracts of *P. zeylanica* as plasmid curing agents to contain the infections and the spread of antibiotic resistance especially in hospital environment. Plasmid elimination

activity of *P. zeylanica* root extracts, plumbagin and lawsone has been documented for the first time in the present review.

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13. CONFLICT OF INTEREST

Conflict of interest declared none.

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