A PHYTOPHARMACOLOGICAL REVIEW ON AN ENDANGERED MAGICAL HERB- *Picrorhiza Kurroa*

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ABSTRACT

Plants are the important source of medicine. Herbal medicine occupied a vital position in Indian culture and folklore therapy. Despite of world industrialization and urbanization, the traditional system of medicines is still increasing and provides a remarkable contribution to the pharmaceutical industry. All parts of medicinal plants are effective in the treatment of diseases and help to discover new kinds of drugs. The plant *Picrorhiza kurroa* is a well-known hand medicine that belongs to the genus *Picrorhiza*, a member of the foxglove family, Scrophulariaceae. A bitter extract obtained from the dried rhizomes of 3–4-year-old plants has been widely used in traditional as well as a modern system of medicine as a stomachic, purgative, antiperiodic, cholagogue, cathartic, carminative, anthelminthic, antioxidant, antifungal, anti-inflammatory, cardiotonic, brain tonic. It is also used in dyspepsia, fever, asthma, flatulence, cardiac complaints, and chronic hepatitisThis aim of this is review to elicit the phytochemical and pharmacological properties of the *Picrorhiza kuroa* which has been searched during their detailed study.

Keywords: *Picrorhiza kurroa*, Picroliv, Ethnopharmacology and phytopharmacology

Introduction: It is a well-known fact that human beings depend on nature either directly or indirectly for food and shelter. Among that, the use of medicinal herbs has a very important role in the cultures of civilizations. Throughout the ages, the utility of traditional plants for the huge proportions of the world populations is always a dominant criterion in the healthcare system of developing countries. Despite of world industrialization and urbanization, the traditional system of medicines is still increasing and provides a remarkable contribution to the pharmaceutical industry. All parts of medicinal plants are effective in the treatment of diseases and help to discover new kinds of drugs [1].According to WHO's global report, there is a widespread use of herbal medicine all over the world [2]. It is highly believed that phytomedicine is healthier than synthetic products. Naturally, Plants contain alkaloids, polyphenols, anthocyanins, carotenoids, saponins, glycosides, flavonoids, which have therapeutic properties against many diseases. These exhibit various

pharmacological properties such as antimicrobial, anticancer, anti-inflammatory, anti-diabetic, hepatoprotective, and other therapeutic effects which are proven to be beneficial for mankind. In the present era, use of plant medicine decreased with the rise of modern medicines that produce deleterious effects if used chronically. Recent advancements in the pharmaceutical industries include the combination of plant-derived active ingredients with synthetic drugs. It has been found that about 80% of all established natural products originate from plants. It is reported that phytomedicine-based industries are growing at a rate of 7-15% annually [3].The evaluation of new drugs especially phytochemically obtained materials has again opened a vast area for research and development. As per WHO, about 80% of the population in the world relies on traditional medicine for the treatment of various diseases. Therefore, it is essential to evaluate the rich heritage of traditional medicine [4,5].This review aims to update the biological activities and pharmacological potentials of "Picroliv", the bioactive compound from *Picrorhiza kurroa* which increases the scope of future research. Scientists aim to develop a high specificity drug with reduced side effects that can be explored using these naturally occurring Herbal drugs.

COMMON NAMES

Tamil: Acokarokini, Akutam, Amakkini

Sanskrit: Anjani, Arishta, Katumbhara

Telugu: Katuka-rogani, Katukarogani, Katukkurohini

Hindi: Kardi, Karoi, Karwi

Urdu: Kutki

Nepali: Kurki

Malayalam: Katukhurohani

SCIENTIFIC CLASSIFICATION

Kingdom - Plantae

Division - Dicotyledonae

Class - Asteride

Order - Scrophulariales

Family - Scrophulariaceae

Genus - Picrorrhiza

Species - kurroa

Taxonomy and distribution

The plant *Picrorhiza kurroa* is a well-known medicinal plant that belongs to the *genus Picrorhiza*, a member of the foxglove family, Scrophulariaceae. The new name of Scrophulariaceae is Plantaginaceae, popularly known as 'Indian gentian'.In Greek, "picros" means bitter, and "rhiza" means root. Thus, the plant name is taken from the Punjabi word "Karu", which means bitter as its nature. It is a large plant family, with around 200 genera and 3000 species. The two species *Picrorhiza kurroa* and *Picrorhiza scrophulariiflora* found in the inner ranges of the Himalayas at an altitude of 3000 - 5000m.It is a perennial alpine herb with an elongated rhizome which has a flowering period from June to August[6]. Traditionally well known in the Indian ayurvedic system for the treatment of liver and respiratory disorders [7].

Pharmacognosy

It is a hairy creeper well grown in moist rock crevices, cliffy and sloppy mountains, and inorganic soils. Kutki, Kurro, kutka, are some of the common names given by local traditional healers. The Plant is self -propagating in nature, but over-harvesting made this plant an endangered species. Leaves are oval-shaped, 2-4 inches long, with a sharp apex or serrated. Flowers are pale purple or white color occurring on a long spike. The fruit is about ½inch long and oval-shaped. The root is a bitter taste and rhizomes have been used in traditional medicine for thousands of years, believed to possess numerous medicinal purposes. A bitter extract obtained from the dried rhizomes of 3–4-year-old plants has been widely used in traditional as well as a modern system of medicine as a stomachic, purgative, antiperiodic, cholagogue, cathartic, carminative, anthelminthic, antioxidant, antifungal, anti-inflammatory, cardiotonic, brain tonic. It is also used in dyspepsia, fever, asthma, flatulence, cardiac complaints, and chronic hepatitis[8,9].

Phytochemistry

The active ingredient isolated to obtain a crystalline compound from the underground parts is "Picroliv" or "Kutkin". It is a standardized mixture of two major C9 – iridoid glycosides, i.e. Picroside I (6-*O*- trans cinnamoylcatalpol) and "Kutkoside" (10-*O*-vanilloylcatalpol) in the ratio of 1:2used in more than 2000 herbal formulations [10].The genus Picrorhiza has 22 irioid glycoside in which *Picrorhiza kurroa* contains 7 iridoid glycosides namely kutkin, kutkoside, picroside V, pikuroside, mussaenosidic acid, bartsioside and boschnaloside[7].Many other active constituents have also been identified, including picrosides II, III, cucurbitacins, apocynin, drosin,veronicoside, pikuroside, cucurbitacins, 4-hydroxy-3-methoxy acetophenone and phenolic compounds and some still unidentified substances[8,11,12].Biosynthesis of Picroside-I occur in shoots and P-II is produced in either stolons or roots [13,14].The Plant propagates vegetatively through stolons, which initially emerged as a young bud, grow into a mature stolon, and then eventually into a rhizome with independent shoots and roots [15,16].It is reported that the pharmacological value is due to kutkin, possess various therapeutic potentials such as hepatoprotective, choleretic, anti-asthmatic and anti-cancerous, antioxidant, anti-

inflammatory, anti-allergic, activity due to the iridoid glycosides present in the plant [17].Cucurbitacins extracted from *Picrorhiza kurroa* involve cucurbitacin B, D and R. Curcubitacins are cytotoxic in nature and exhibits anti-tumorous activities [18]. Apocynin belongs to the catechol group and that able to check neutrophil oxidative burst as well as act against inflammation. Owing to the various pharmacological aspects of this medicinally important endangered herb, researchers developed efficient protocols for various research practices[19,20].

Fig 1 Graphical Presentation of *Picrorhiza kurroa* Royle ex Benth.

Fig 2 Dried rhizome of *Picrorhiza kurroa* Royle ex Benth.

Ethno medical uses : *Picrorhiza kurroa* is used by local peoples of the Himalayan region to treat fever, respiratory disorders, and allergies. kutki used as a hand medicine with mother's milk is advised for newborns to cure stomachache [6]. In Kashmir, it is used for snakebite and scorpion sting in the Indian medicinal system of Ayurveda and Unani, rhizomatous extracts used as the foremost ingredient in Arogyavardhini, a valuable preparation of Ayurveda applied to cure liver and kidney sicknesses. In Nepal, rhizomes are widely used for cough, cold, skin disease, fever, indigestion, liver disease, jaundice, hepatitis, and metabolic disorders [21]. In

Pakistan, kutki used to treat hepatic, nephritic, blood and skin disorders. Chinese herbal medicine uses kutki to treat jaundice, digestive disorders, diarrhea, and dysentery.

Formulation kutkin has various uses in ayurvedic medication. It constitutes as the major ingredient of many such Indian herbal preparations[11]

Table 1 : List of Indian herbal preparations of Picroliv

S.No	Name of the preparation	Manufacturer
1	LIVFIT	Dabur Pharma Limited, India
2	PICROLAX	The Himalaya Drug Company, Bengaluru
3	VIMLIV	Solumiks, Bombay, India
4	LIVOTRIT	Zandu Pharmaceutical Works Ltd. Bombay, India
5	ACILVAN	Acis Lab., Kanpur, India
6	HEPEX	The Anglo-French Drug Co. (Eastern) Ltd. Bombay, India
7	LIVARIN	Patiala Ayurvedic Pharm., Sirhind, India
8	LIVOKIN	Herbomed, Calcutta, India
9	LIERIN	Herbs Era Pharm., Udairajpur, W.B., India
10	LIVOL	Vedic Pharma, Calcutta, India

PHARMACOKINETICS

Picroliv from *Picrorhiza kurroa* is made of two components Picroside I and Picroside II are irioid glycosides, has poor absorption and oral bioavailability. Following ingestion, picrosides reaches the serum at a low nanomolar concentration with the T_{max} of approximately one hour with the half-life period of picrosides I and picrosides II reach in 50-56m and 15-30m respectively. Predominately, Picroside II (80%) conjugated in the blood as either glucuronide or sulfate, with 20% of circulating picroside II, which is eliminated from the plasma in its free form[22,23].

PHARMACOLOGICAL AND BIOLOGICAL PROFILE OF *P. KURRAO*

Hepatoprotective activity: Various researches show that *Picrorhiza kurroa* is familiar for its hepato-protective activity. In a study, experimental mice pretreated with picroliv, curcumin and ellagic acid for 7 days(50 and 100 mg/kg p.o)in Paracetamol-induced hepatotoxicity (500 mg/kg).The result showed a high level of serum (alanine transaminase, aspartate transaminase, and alkaline phosphatase) and MDA level with

significant decrease in the activity of GSH and catalase levels[24]. Recently, nano formulation of *Picrorhiza kurroa* root and rhizome powder extract is a well-recognized nutraceutical for healthy liver functioning[25].

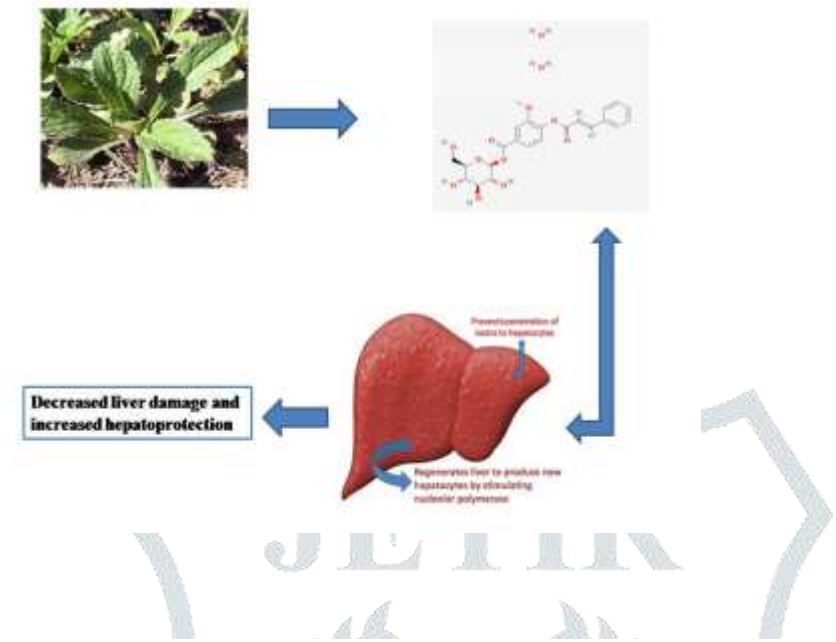

Fig 3 Hepatoprotective action of *Picrorhiza kurroa*

Antioxidant activity: *Picrorhiza kurroa* leaf extract in butanol, ethyl acetate, and ethanol with two different (DPPH and ABTS assays) testing systems shown antioxidant activity. Comparatively ethyl acetate and butanol extract expressed a better radical scavenging activity than ethanol[26]. Comparative study of two species of Picrorhiza such as *Picrorhiza kurroa* and *Picrorhiza scrophulariiflora* evaluated for the antioxidant activity using DPPH at a concentration of 0.1 mg/mL. The scavenging activities of *Picrorhiza kurroa* higher than that of *Picrorhiza scrophulariiflora*[27]. Root extract of *Picrorhiza kurroa* scavenges oxygen‐free radicals, such as superoxide and hydroxyl radicals, and inhibits lipid peroxidation induced by the Fe2+ ascorbate system in rat liver homogenate[28].Ethanol extract of rhizome Accelerates healing of gastric ulcerated stomach wall by free radical scavenging action[29].

Cardioprotective activity : Pre-treatment with picroliv (80 mg kg_1 day_1 for 15 days) through oral route significantly prevents the adverse changes to the myocardium and maintains normal physiological functions of the heart in rats. The cardioprotective effect of *Picrorhiza kurroa* is probably due to its free radical scavenging ability against Isoproterenol induced lipid peroxidation, which is mainly responsible for, the irreversible necrosis of the myocardial membrane or its ability to inhibit the lipid accumulation in the myocardium by its hypolipidemic property[30] In isoproterenol-induced cardiotoxicity rats, *Picrorhiza kurroa* pretreatment (200mg/kg) significantly reduces the adverse effect exhibited such as hemodynamic changes, oxidative stress, and various other myocardial damage. Thus, it is highly appreciated for its antioxidant, antiperoxidative, and cardioprotective activity [31]. It is reported that the protective effect of Plantainoside D

from the leaves of *Picrorhiza scrophulariiflora* against adriamycin-induced apoptosis in H9c2 cardiac muscle cells exhibits potent scavenging activity against reactive oxygen species and prevents NF-kappaB activation [32].

Hypolipidemic activity The antihyperlipidemic activity of *Picrorhiza kurroa* using alcoholic,chloroform and aqueous root extracts studied in Triton wr- 1339 induced albino rats. It is compared with different dose such as low (50mg/kg), high (200mg/kg) and standard reference Atorlip-20(4mg/kg bw). The results showed a significant decrease in triglyceride and cholesterol level[33].

Hydroalcoholic extract (200mg/kg and 400 mg/kg b.i.d) of *Picrorhiza kurroa* in high-fat diet mouse assessed for Hypolipidemic property. On treatment with picroliv, the therapeutic content of *Picrorhiza kurroa* root, showed a drastic change in liver infiltration and reverse to normal condition. Also concluded that at the dose of 400mg/kg, as compared to Silymarin , kutki showed more improvement in decrease of liver lipids[34].

Analgesic &Anti-inflammatory property

Antiarthritic activity of *Picrorhiza kurroa* rhizome extract showed the potential activity against inflammatory mediators such as interleukins, tumor necrosis factor and matrix metalloproteinases[35].

Analgesic activity of *Picrorhiza kurroa* proved by research in ethanolic root extract (250 mg/kg, 500 mg/kg) using hot plate and acetic acid compared with pentazocin. 500mg/kg dose of *Picrorhiza kurroa* roots is effective as an analgesic and as having a similar effect to the standard drug pentazocine[36].

Nephroprotective activity : The nephroprotective property of glucosidal extract of *Picrorhiza kurroa(250mg/kg and 500mg/kg for 14 days)*in Nimuslide induced nephrotoxicity. Histopathological and biochemical parameters confirm to prevent the free radicals and toxic effects of the Nimuslide and thus validate its ethnomedicinal use[37].

Protective effect of picroliv (600 mg/kg b.w.p.o) in the kidney by comparing the Arogyawardhini, containing *Picrorhiza kurroa* as a major ingredient and ethanolic extract of the rhizome .The proposed result of serum creatinine and blood urea showed the antioxidant and oxidative radical scavenging activities and also concluded that formulation was found to have better activity as compared to the rhizome[38].

Antimicrobial activity

Picrorhiza kurroa root extract for the antifungal activity against *Candida tropicalis*, C.*albicans*, *Penicillium marneffei and Trichophyton rubrum*. Alcoholic solvent of the root extract at 10% was effective in the inhibition of these clinical fungal isolates[39].

The antibacterial and antifungal activity of *Picrorhiza kurroa* dried stolon extract by agar well diffusion method. Crude methanol and acetone extract was used against pathogens such as Bacillus subtilis,Ecoli,Erwinia

chrysanthemi, Fusarium oxysporum,Gloeocercosporasorghi,Rhizoctonia solani, Sporisoriums citamineum. Results showed a wider spectrum of antimicrobial activity[40].

Hypoglycemic activity

In streptozocin-induced diabetic rats, Hydro Alcoholic extract of rhizome (100 and 200 mg/kg body weight) treated to study the antihyperglycemic potential of *Picrorhiza kurroa.* It is reported that β-cell regeneration with enhanced insulin secretion & production, improves hepatic and renal functions against Oxidative damage[41].Standardized aqueous extract of *Picrorhiza kurroa* (100 and 200 mg/kg/day p.o) administered to streptozotocin induced diabetic rats to explore the mechanism of antidiabetic activity. Histopathological and molecular investigations had shown the evidence of regeneration of β-cells and, increased GLUT-4 expression, which in turn facilitated glucose uptake by skeletal muscles in diabetic rats[42].

Anticarcinogenic effect

Several studies indicate that antioxidant and anti-inflammatory rich plant-derived compounds and their extracts have high chemopreventive properties by targeting the signal transduction pathways of carcinogenesis[43]. Hydroalcoholic extract of *Picrorhiza kurroa* investigated for the anticancer property. In vitro and in vivo screening of the extract using cell lines explored significant reduction in the tumor regression parameters and viable tumor cell count. The study concludes that the anticarcinogenic potential is due to the presence of apocyanin,cucurbitacins B and E; betulinic acid; picrosides 1 and 2.

Study on Methanolic and aqueous extracts of *Picrorhiza kurroa* rhizome using XTT assay in human breast, liver, prostate cancer cell lines reported loss of cell viability and better antiproliferation activity[44].

Immunomodulatory property

Ethanolic and aqueous extract of the *Picrorrhiza kurroa* rhizomes evaluated for the immunomodulatory effects induced by cyclophosphamide. Study results concluded that the test extracts possessed promising immunostimulant activity by producing more antibodies against cell-mediated immune response in their serum. But the alcoholic extract is more potent than aqueous extract in producing delayed-type hypersensitivity response[45].

Antiulcerogenic activity

Picrorhiza kurroa rhizome extract used to heal the indomethacin-induced acute stomach ulcers by altering the prostaglandins, EGF, and oxidative stress level. Methanol extract of *P. kurroa* rhizomes (20 mg/kg, p. o) compared with omeprazole (3 mg/kg, p. o).Biochemical parameter Results showed that the *Picrorhiza kurroa* heals the ulcers by reducing oxidative stress, and promoting mucin secretion, prostaglandin synthesis, and augmenting expressions of cyclooxygenase enzymes and growth factors[46].

Anticonvulsant effect

ethanolic root extract investigated for the anticonvulsant property on experimental mice with maximal electroshock-induced seizures and pentylenetetrazole, picrotoxin-induced seizures. On observation, *Picrorhiza kurroa* (100 mg/kg) showed a significant decrease in convulsions and mortality rate. Thus study concludes that test extract possesses anticonvulsant activity against electrically and chemically induced seizures in mice[47].

Antiasthmatic activity

In histamine stimulated broncho-constriction, ethanolic root extract exhibits good antiasthmatic activity. extract showed a significant result (52.16%)compared with beta 2 agonists salbutamol (65.83%). The influence of the plant extract on isolated guineapig ileum analyzed to recognize the pathway by which the extract exhibited muscle relaxant activity. The analysis showed that the extract is effective at a concentration of 100 mg/ml against acetylcholine and histamine-induced contraction. The result revealed antiasthmatic activity of the extract due to the presence of saponins and flavonoids[48].

Clastogenic effect

Clastogenic potential of *Picrorhiza kurroa* rhizome extract examined on cultured human peripheral blood lymphocytes .Two independent phases were used for the study such as Initial Chromosome Aberration Assay (Phase I) and Confirmatory Chromosome Aberration Assay (Phase II). On testing up to the highest concentration 2500 µg/mL and compared with Mitomycin and cyclophosphamide which shows the significant number of structural chromosome aberrations. Whereas *Picrorhiza kurroa* does not induce chromosome aberrations at concentrations tested. Thus, the study concludes that *Picrorhiza kurroa* rhizome extract is completely safe to be used as a medicine since it manifests its healing effects without causing genotoxicity[49].

Choleretic and Anticholestatic Effect

Cholestatic liver diseases are important causes of liver cirrhosis and liver transplantation with limited treatment. Aqueous solutions of Picroliv at different doses administered to conscious and anaesthetized experimental rats. The result showed the dose-dependent increase in bile flow, cholic and deoxycholic acid content. Anticholestatic effects were tested against paracetamol- and ethynylestradiol (EE)-induced cholestasis. Paracetamol reduced the volume of bile and the amount of bile salts. Treatment with Picroliv (6 and 12 mg/kg)results in a complete reversal of the decrease in bile flow[50].

Antimalarial activity

In a study conducted, Ethanolic extract of roots and leaves of *Picrorhiza kurroa administered* to Experimental mice to determine the antimalarial activity against the parasite *Plasmodium berghei.* Results showed the group of animals treated with the root and leaf extract of *Picrorhiza kurroa* was effective in treating malaria parasites. The root extract produced good inhibition effect than leaves [51].

Conclusion & Future Perspectives

In conclusion, this review is an attempt to update and emphasize the versatile utility of the *Picrorhiza kurroa*. It is well known for its various pharmacological roles and one of the important constituents in many herbal preparations. Herbal drugs provide a very feasible alternative to Indian medicine which plays an essential role in traditional system of medicine. *Picrorhiza kurroa* is familiar for its rich ethnomedical significance. Furthermore, extensive research work should be carried out to explore the bioactive compounds and its mechanism of action at the molecular level to treat various ailments.

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