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A Comprehensive Review on Ayurvedic and Pharmacological Aspects of *Picrorhiza kurroa Royle ex Benth*

Varesh Parihar[1*] and Banshidhar Behera[2]
[1]PG Scholar (Ayu), Department of Dravyaguna Vigyan, A and U Tibbia College & Hospital Karol Bagh, New Delhi-110005
[2]Associate Professor (Ayu), Department of Dravyaguna vigyan, A &U Tibbia College and Hospital Karol Bagh, New Delhi-110005

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***Corresponding Author Email:** vareshparihar@gmail.com

Abstract
Picrorhiza kurroa Royal ex Benth, Kutki (P. kurroa) is an important medicinal plant, which has been traditionally recommended and used in Ayurveda for thousands of years with some precautions. The last few decades have witnessed a significant revival of interest in its pharmacology, pharmacognosy and phytochemistry. Kutki is a small perennial herb and rapidly decaying high-value medicinal plant that grows in the north-western Himalayan region of India, Pakistan and hilly parts of Nepal. The leaf, bark and underground parts of the plant, mainly the rhizome, are used in Ayurveda for their medicinal properties. Evidence of its hepatoprotective activity in several experimental and clinical studies has led to the correlation of specific phytochemical components of P. kurroa (e.g., iridoid glycosides, especially picrosides) with precise pharmacological activities, and the efficacy of P. kurroa in many diseases is done. Kutki is mainly used for liver disorders like jaundice as it protects the liver from cell damage caused by free radicals due to its antioxidant and hepatoprotective properties. The present review study is an attempt to provide detailed information about traditional uses, phytochemistry and pharmacological potential of P. kurroa, an important medicinal herb of the western Himalayas.

Keywords
Picrorhiza kurroa, Kutki, Katuka, Pharmacological activities

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1 INTRODUCTION
The word "Picrorhiza" comes from the Greek word "Picros," which means "bitter," and "rhiza," which means "roots." The genus Picrorhiza, which belongs to the Plantaginaceae family, contains two species: *Picrorhiza kurroa Royle ex Benth* and *Picrorhiza scrophulariiflora* Pennell. The majority of species can be found in natural settings like cliffs, mountainside ledges, and crevices. The primary habitat of *Picrorhiza kurroa* Royle ex Benth is at an elevation of 3000 and 5000 m in the northwestern Himalayan region of India Pakistan and the mountainous areas of Nepal [**1**]. This plant grows in the Himalayan region (Garhwal to Bhutan) on moist, organic soils and rocky slopes [**2**]. In Ayurveda, the leaf, bark, and underground parts of the plant, particularly the rhizome, are utilised for their therapeutic properties. *Picrorhiza kurroa* Royle ex Benth (Family: Plantaginaceae, previously classified as *Scrophulareaceae)* is a highly regarded medicinal herb, commonly referred to as "*Kutki,*" "Kurro," or 'Indian gentian. The perennial herb *kutki* has a long history of use in the Indian ayurvedic system to treat respiratory and liver disorders.

The active compounds in *kutki* include kutkoside and iridoid glycosides (IGs), specifically picroside I and II, and they are mainly located in the rhizome and roots. No significant adverse effects have been noted for this plant. The various pharmacological properties of

P.kurroa, an endangered plant of medicinal importance, are noteworthy.

The aim of this review article was to assess the pharmacological effects of *P. kurroa* on various disorders. *P. kurroa* could serve as a natural substitute for conventional treatments aimed at addressing emerging diseases. This study is designed to serve as a reference for upcoming basic and clinical research. It is considered valuable due to its pharmacological effects, which include being hepatoprotective [**3**], anti-inflammatory [**4**], immunomodulatory [**5**], antimicrobial [**6**], antitumor [**7**], anti-carcinogenic [**8**], antioxidant [**9**], anti-neoplastic [**10**], anti-arthritic [**11**], anti-leishmanial [**12**], anti-asthmatic [**13**], anti-diabetic [**14**], anti-fungal [**15**] and cardioprotective [**16**]. It is also helpful for gastrointestinal and urinary disorders, scorpion stings, snake bites, leukoderma and inflammatory conditions.

2 Vernacular Name

Hindi : Kutki
English : Hellebore
Sanskrit : *Kandaruha, Matsyashakala, Katurohini, Chakrangi, Rohini, Tikta, Katumbhara*
Gujrati : Kadu, Katu
Marathi : Kutki, Kalikutki
Punjabi : Karru, kaur
Assamese : Katki, Kutki
Oriya: Katuki
Tamil: Katuka rohini, Katuku rohini, Kadugurohini
Telugu: Karukarohini
Urdu: Kutki

'Kutki is used by various synonyms in classical literature, such as in *Bhavprakash Nighantu*. These synonyms describe biological activity or typical traits, i.e *Kandaruha* (The plant can grow from stem cuttings), *Chakrangi* (When cut, the stem appears like a wheel), *Matsyashakala* (Rhizome resembles fish scales), *Ashoka* (Relieves grief), *Rohini* (Protects organs with regenerative ability), *Katurohini* (Has regenerative action), *Krushnabheda* (Can cause black stools), *Tikta* (Has a very bitter taste) *Katumbhara* (Full of bitter principles) *Matsyapitta* (Bitter taste like fish bile and similar action).To demonstrate some biological effects and clinical uses associated with *Kutki* that pertain to this review are *Bhedaneeya* (promoting excretion / downwords expelled of solid or liquid *purisha*), *Deepaniya* (facilitate appetite), *Rechani* (laxative action), *Aruchihara* (improving appetite), *Yakrutdalyodar-nashak* (liver enlargement), Shotha-*nashak* (anti-inflammatory), *Kamala-nashak* (alleviating jaundice), *Jalodarnashan* (useful in ascites), *Pramehaghna* (useful in pre-diabetic and diabetic states), and *Hrudya* (favourable for the heart) [**17**].

3 BOTANICAL AND MORPHOLOGICAL DESCRIPTION [**18**].

Feature	Description
Plant Type	Small perennial herb
Height	10-20 cm
Stem	Small, leafy, weak, creeping; erect at flowering
Roots	6-10 inches long, hard, wrinkled, greyish to brown
Rhizomes	2.5–12.0 cm long, 0.3–1.0 cm thick, cylindrical, irregularly curved, jointed nodes with branching and rooting
Rhizome Appearance	Externally greyish-brown
Aerenchyma Presence	Found in leaves, aerial stem, and rhizome
Leaves	Basal, alternate, 5-15 cm long, oval, acuminate, serrate, stalked, winged, oblanceolate/narrowly spathulate, coarsely toothed
Leaf Hairs	Two types of glandular hairs present
Flowers	White or pale purple, bisexual, on long terminal spikes
Calyx	5 equal parts
Corolla	4-5 lobed, actinomorphic
Stamens	4, slightly didynamous, inserted on corolla tube
Stigma	Capitate
Fruits/Capsules	Acute, ovoid, swollen, 6-10 mm, tapered at the top, splits into 4 valves
Seeds	Numerous, pale brown, 1 x 0.8 mm, ellipsoid, thick transparent seed coat

Kutki Plant | Flowers | Inflorescence | Dried Rhizome

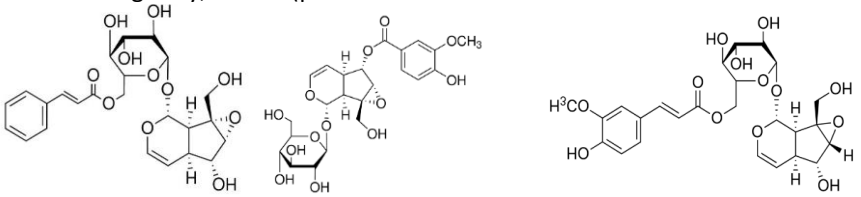
5 TAXONOMY OF *PICRORHIZA KURROA* (Table no. 1)

Table No. 1

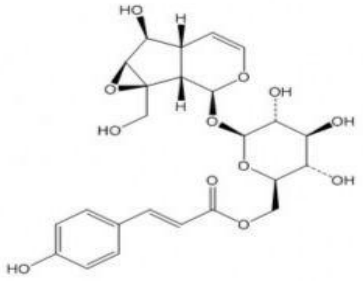
Kingdom	Plantae
Subkingdom	Tracheobionta
Super-division	Spermatophyta
Division	Magnoliophyta
Class	Mannoliopsida
Subclass	Asteridae
Order	Lamiales
Old Family	Scrophulariaceae
New Family	Plantaginaceae
Genus	Picrorhiza
Species	P. kurroa

6 Phytochemistry of *P. kurroa*

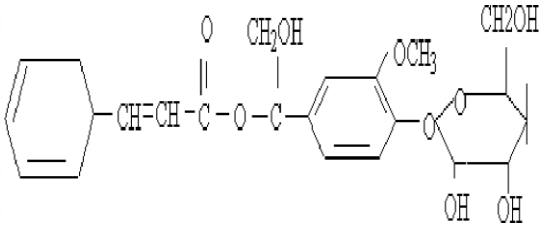
Picrorhiza has been extensively studied for its chemical properties, resulting in the extraction of numerous physiologically active compounds from its rhizomes, roots, seeds, stems, and leaves. This plant has produced over 65 secondary metabolites. The rhizomes and roots of *P. kurroa* yield a crystalline compound known as "Picroliv" or "Kutkin," which consists of two C9-IGs (C9-Iridoid Glycosides) referred to as kutkoside. Picroside-II and Picroside-I occur in a ratio of 2:1 [**19**]. Using HPLC (high-performance liquid chromatography) methods, the IGs (Iridoid Glycosides) Picrosides I, II, and III, cucurbitacins, and kutkoside were identified in *P. kurroa* rhizomes [**20**]. *P. kurroa* possesses a variety of bioactive compounds with pharmacological and therapeutic potential, including glycosides, iridoids, alkaloids, phenolics, terpenes, and cucurbitacins [**21-26**]. Apart from its purgative and emaciating qualities, picrorhiza also possesses cholagogue, digestive qualities, appetizing qualities, and actions that stimulate the liver and heart. Kutkin, the active ingredient in *P. kurroa*, is a combination of picroside and kutkoside. Pharmacologically, kutkin (picrosides and kutkosides) has demonstrated hepatoprotective qualities. Two additional bioactive compounds that were separated from this plant are drosin and apocyanin. One catechol that might inhibit neutrophils' oxidative response is apocynin [**27**]. *P. kurroa* contains cucurbitacins B, D, and R, which are well known for their cytotoxic and anti-tumorous qualities. Apocynin has anti-inflammatory and antioxidant qualities and is a strong inhibitor of NADPH (nicotinamide adenine dinucleotide phosphate) oxidase. There is an anti-asthmatic effect of androsin [**28**]. The 70 percent hydroalcoholic fraction has also been found to contain flavonoids like apocynin and vanillic acid, kutokoside, pikurosides, and picrosides I, II, III, and IV, according to LC ESI–MS/MS (liquid chromatography–electrospray ionization/multi-stage mass spectrometry) techniques [**29**]. Other significant substances found in *P. kurroa* include the carbohydrate D-mannitol and aromatic acids like ferulic acid, cinnamic acid, and vanillic acid [**30**,**31**]. A variety of *P. kurroa* secondary metabolites are displayed in Figure [**32**,**33**].



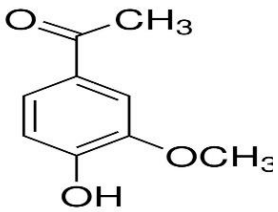
Picroside I ($C_{24}H_{28}O_{11}$) | Picroside II ($C_{23}H_{28}O_{13}$) | Picroside III ($C_{25}H_{30}O_{1}$)



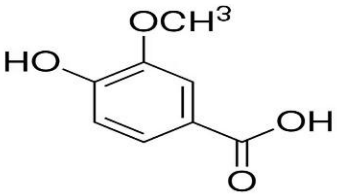
Picroside IV ($C_{24}H_{28}O_{12}$)



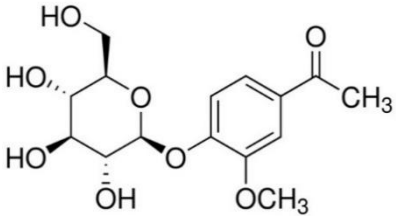
Kutkin ($C_{23}H_{28}O_{12}$)



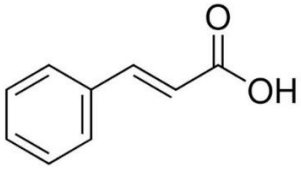
Apocynin ($C_9H_{10}O_3$)



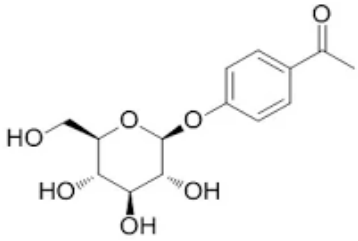
Vanillic acid ($C_8H_8O_4$)



Androsin ($C_{15}H_{20}O_8$)



Cinnamic acid ($C_6H_5CH=CHCOOH$



Picein ($C_{14}H_{18}O_7$)

Figure: Various bioactive principles from P. kurroa

*P. kurroa has undergone a physicochemical analysis in certain investigations. The following were reported: moisture content (12.95% v/w), insoluble acid ash (2.14% w/w), water-soluble ash (3.35% w/w), total ash (5.92% w/w), and pH of 10% aqueous solution (12.95) [**34**–**36**]. P. kurroa roots were found to contain vanillic acid, the primary phenolic component, at a rate of 161.2 mg/100 g dry weight [**37**]. In a different study, the total phenolic content of aqueous and methanolic extracts at different concentrations (50, 100, P. kurroa has undergone a physicochemical analysis in certain investigations.*

*Total phenolics were more abundant in the methanolic extract (14.11–35.36 g GAE) than in the aqueous extract (10.79–24.87 g GAE) [**38**]. The total phenolic content of roots was found to be 3.14 mg/100 g of dry weight based on HPLC analysis [**39**]. In a related study, the total phenolics and flavonoids in a 70% ethanol extract of dry root were found to be 222 µg GAE/mg and 197 µg QE/mg. It was determined that the hydro methanolic extract of P. kurroa contained 400 mg RE of flavonoids and 544 mg GAE/g of total phenolics [**40**].*

7 Classical views of kutki (P. kurroa)

*Picrorhiza kurroa, commonly known as Kutki, has been recognized as a medicinal plant in the three major Ayurvedic treatises, namely Charaka Samhita, Sushruta Samhita, and Ashtanga Hridaya. [**41**-**44**]*

***Charaka Samhita**: Bhedaneeya, Lekhaneeya and Stanyashodhana Mahakashaya, Tikta Skandha.*

***Sushruta Samhita**: Patoladi, Pippalyadi, and Mustadi gana.*

***Ashtanga Hridaya**: Patoladi, Pippalyadi, and Mustadi gana.*

***Ashtanga Sangraha**: Stanyashuddhikaragana, Patoladi, Pippalyadi, and Mustadi gana.*

- *Furthermore, the continuous and extensive clinical use of Kutki (P. kurroa) is reflected in its inclusion in most of the medieval compendia, such as Nighantus:*
  - *Bhavaprakasha Nighantu (Hartikyadi varga) [17]*
  - *Madanapala Nighantu (Abhayadi varga) [45]*
  - *Raja Nighantu (Pippalyadi varga) [46]*

- *Dhanvantari Nighantu (Guduchyadi varga) [47]*
- *Kaiyadeva Nighantu (Aushadhi varga) [48]*
- *Ashtanga Nighantu (Mustadi gana) [49]*
- *Madanadi Nighantu (Panchadasha gana) [50]*
- *Sodhala Nighantu (Guduchyadi varga) [51]*
- *Paryayaratnamala [52]*

8 Properties and Properties [17]

Rasa: Tikta (Bitter)
Vipak : Katu (Pungent)
Guna: Ruksa, Laghu (Light to digest)
Veerya: Shita (Cold potency)
Karma: Hrudya, Deepaniya, Bhedini, Pittahara

In the Ayurvedic texts (Samhitas) and Nighantus, the properties and uses of *Kutki* are described as follows: (**Table no. 2)**

S. No.	***Roghaghnata* (Indication)**	**C.S. [42]**	**S.S. [43]**	**A.H. [44]**	**A.S. [45]**	**B.N. [18]**	**M.N. [46]**	**R.N. [47]**	**D.N. [48]**	**K.N. [49]**	**M.N [51]**
1	*Asrajit* (useful in bleeding disorders)					+		+	+		
2	*Dahajit* (relieves burning sensation)					+	+	+	+	+	+
3	Aruchinashak (Anti-anorexic/Appetizer)		+	+	+			+	+		
4	Vishamajvara (useful in chronic recurrent fever)								+		+
5	*Bhedani*, (piercing, causes purgation)					+				+	
6	*Rechani* (Purgative)							+			+
7	*Deepani* (Appetizer)		+			+				+	
8	*Hrudya/Hrudyaroga* (good for heart and useful in heart diseases)					+		+			+
9	*Jwraghna/Kapha* Pitta *Jwarapaha* (Antipyretic/ useful in fever of *Kapha* and *Pitta* origin)			+	+	+	+	+		+	+
10	*Pramehahara* (useful in urinary tract disorders, diabetes)					+				+	
11	*Shvasahara* (useful in asthma, dyspnoea)					+	+	+		+	
12	*Kasa* (useful in cough, cold)					+				+	
13	*Kushtahara* (useful in skin disorders)			+	+					+	
14	*Chardinashana* (Anti-emetic)		+	+	+						
15	*Hikkanashana* (Useful in Hiccups)		+								
16	*Kamalanashak* (Alleviating jaundice)			+	+						+
17	*Vishaghna* (Detoxicant)		+	+							+
18	*Krumighna* (Antimicrobial)					+	+			+	
19	*Sheetapittaghna* (Anti-urticarial)							+			
20	*Stnyashodhana/Stnyadoshahara* (Improving the quality of breast milk)	+	+	+	+						
21	*Yonidoshahara* (Vaginal disorders)		+	+	+						
22	*Pratishyaya roga* (Nasal disorders)		+	+	+						
23	*Arsha roga* (Hemorrhoids)									+	

9 Formulations of *Picrorhiza kurroa*

Arogya vardhini, Tiktaka Ghruta, Mahatiktaka Ghruta, Sarivadyasava, Mahayograj Guggulu, Sudarshan choorna, Katukadyavaleha, Tiktadi kwath, Sarvajvarahara Lauha are some of the multi-ingredient formulations mentioned in the samhitas, containig Kutki (P. Kurroa) as one of the components, which could be present in a significant or minor amount.

10 Pharmacological Activities of *P. kurroa*

Pharmacological Characteristics of *P. kurroa* Rhizomes

Pharmacological Activity	Action	Concentration	Study Model	Reference
Hepatoprotective	Prevents biochemical alterations in the liver and serum of galactosamine-intoxicated animals	12 mg/kg/day for 7 days	Rats	[111]
Anti-diabetic	Reduces blood glucose levels under normal and high glucose conditions	75 mg/kg extract of body weight	Rats	[14]
Anti-diabetic	Assesses glucose tolerance in normal, non-diabetic rats	100 mg/kg – 200 mg/kg, p.o.	Rats	[72]
Anti-diabetic	Increases GLUT-4 levels in the soleus muscle membrane fractions	100 mg/kg/day – 200 mg/kg/day	Rats	[73]
Anticancer	Provides protection against hypoxic damage	-	Hep3B and glioma cells	[90]
Anticancer	Suppresses FMuLv-induced erythroleukemia	-	BALB/c mice	[86]
Anticancer	Counteracts DMH-induced liver carcinogenesis	40 mg/kg and 200 mg/kg	Rats	[87]
Anticancer	Prevents Hepatocarcinogenesis caused by N-Nitrosodiethylamine	200 mg/kg body weight	Rats	[88]
Anticancer	Inhibits sarcoma and papilloma formation induced by specific carcinogens	100 mg/kg – 200 mg/kg, p.o.	BALB/c mice	[89]
Anticancer	Induces cell toxicity and reduces levels of MMP-1, MMP-13, MMP-2, and MMP-9	50 µg/mL and 100 µg/mL	MCF-7 cell lines (Human breast cancer)	[85]
Anticancer	Demonstrates maximum cytotoxic effects	50 mg/kg for 10 days	Ehrlich ascites carcinoma tumor-bearing mice	[84]
Antitumor & Anti-carcinogenic	Inhibits yeast topoisomerase I and II enzymes	250 µg/mL	Tumor-bearing mice	[7]
Anticarcinogenic	Affects serum and tissues of tumor-bearing animals	150 mg/kg – 750 mg/kg body weight	Rats	[78]
Cytoprotection	Reduces adriamycin-induced cardiomyopathy	50 mg/kg body weight	Rats	[53]
Anti-HBsAg Activity	Exhibits hepatoprotective properties	-	Serum	[91]
Anti-anaphylaxis	Suppresses passive cutaneous anaphylaxis	25 mg/kg p.o.	Mice/Rats/Guinea Pig	[106]

Antileishmanial	Boosts lymphocyte proliferation and enhances antileishmanial activity	20–5 mg/kg dose for 12 days and 10 mg/kg for further experiments	Leishmania donovani/Hamster	[106]
Antifungal Activity	Inhibits the growth of dermatophytic fungi	5% and 10% alcoholic solvent extracts of root and rhizome	Solidified agar plates	[15]
Immunomodulatory	Increases cytokine levels (IFN-γ, IL-4) and promotes lymphocyte proliferation	12.5 mg/kg, 25 mg/kg, and 50 mg/kg body weight for 14 days	Balb/c mice	[5]
Immunomodulatory	Enhances both cell-mediated and humoral immune responses	-	Mice and rats	[97]
Immunomodulatory	Modulates hypersensitivity reactions	100 mg/kg body weight	Albino mice	[96]
Antioxidant & Anti-neoplastic	Exhibits antioxidant effects by scavenging free radicals and inhibiting lipid peroxidation	-	Hep3B, PC-3, MDA-MB-435S	[62]
Anticonvulsant	Reduces seizure intensity and mortality in various chemically and electrically induced convulsions	100 mg/kg	Mice	[108]
Anti-arthritic	Decreases joint inflammation and downregulates inflammatory cytokines (IL-1β, IL-6, TNF-R1, VEGF) in arthritis models	*Picrorhiza kurroa* rhizome extract (PKRE)	Rats	[11]

10.1 Hepatoprotective

In comparison to hepatoprotective substances like catapol, silymarin, and rographolide, picroliv, which was derived from *P. kurroa*, has been evaluated for its effects against ethanol-induced toxicity in rats. The findings indicated a minimal hepatoprotective effect, as evidenced by the reduced levels of marker enzymes such as alkaline phosphatase, glutamic-oxaloacetic transaminase, glutamic pyruvic transaminase, and aldehyde dehydrogenase [**3**].

A methanol extract derived from the rhizomes of *Picrorhiza kurroa Royle ex Benth*. (Plantaginaceae) showed hepatoprotective properties against liver damage in mice induced by D-galactosamine (D-GalN)/lipopolysaccharide (LPS) [**55**].

The active component of the plant *Picrorhiza kurroa*, known as picroliv, was evaluated for its protective effects on the liver in rats suffering from ethanol-induced liver damage. Administration of alcohol (3.75 g/kg for 45 days) altered liver markers (lipid, glycogen, and protein) and certain serum markers (AST, ALT, and ALP) by 20–114%. Furthermore, the treatment reduced the viability of ex vivo isolated hepatocytes (by 44–48%) as measured by oxygen uptake rate and Trypan blue exclusion [**56**].

In the liver and kidneys of the test rats, Picroliv exhibited hepatoprotective effects against AFB1 toxicity, comparable to that of standard silymarin [**57**].

The liver-protecting properties of Enliv, an herbal formulation that includes *P. kurroa*, were enhanced by counteracting the decline in glutathione levels induced by paracetamol and elevating lipid peroxidation levels in liver tissue [**58**].

10.2 Antioxidant

Kant et al. (2013) investigated the antioxidant potential of *P. kurroa* leaves, aiming to discover a new natural source of antioxidants. Various solvent extracts, including ethanol, butanol, and ethyl acetate, along with an isolated compound, luteolin-5-O-glucopyranoside, were evaluated for their

antioxidant activities using DPPH and ABTS assays. The results showed that luteolin-5-O-glucopyranoside exhibited an IC50 value comparable to that of standard ascorbic acid, indicating that P. kurroa leaves may serve as a natural source of antioxidants [**9**].

The antioxidant activities of two Picrorhiza species, *P. kurroa* and *P. scrophulariiflora*, were compared at a concentration of 0.1 mg/ml, and the results showed that *P. scrophulariiflora* had higher radical scavenging activity (34.30%) than *P. kurroa* (37.70%) [**59**].

The 70% hydroalcoholic extract of *P. kurroa* was found to exhibit antioxidant activity by inhibiting DNA damage and lipid peroxidation induced by hydrogen peroxide, with IC50 values of 75.16 and 55.50 µg/ml in DPPH and metal chelating antioxidant assays [**60**].

Rajaprabhu et al. (2007) found that *P. kurroa* extract exhibited significant antioxidant and protective effects when administered orally to rats (50 mg/kg body weight/day for 15 days), countering the detrimental effects of adriamycin [**61**].

Extracts of *P. kurroa* exhibited exceptional antioxidant potential in scavenging radicals and inhibiting lipid peroxidation, as evidenced by assays such as DPPH, FRAP, and TBA [**62**]

Choi et al. (2008) conducted a study to evaluate the antioxidant activity of enzymatic extracts of *P. kurroa* against hydroxyl radical-induced DNA damage using ESR spectroscopy, and their findings suggest that *P. kurroa* may emerge as a valuable natural source of antioxidants [**63**].

10.3 Anti-inflammatory

Rohit Kumar et al. (2016) found that PKRE, a hydroalcoholic extract of *P. kurroa* rhizome, exhibited anti-inflammatory effects by attenuating paw oedema, granuloma formation, and proinflammatory mediator production in macrophages, achieved by inhibiting the iNOS and NF-κB signalling pathway [**64**].

The anti-inflammatory effect of *Picrorhiza Kurroa* extract (PK) was confirmed to be mediated by β-adrenergic blockade, suggesting that PK treatment alters cell-surface biology. Furthermore, the blockade of protein synthesis by cycloheximide pretreatment reduced the effect of PK, indicating that protein mediation plays a role. Additionally, the metabolic inhibitor dinitrophenol equally inhibited inflammatory edema in both control and PK-treated animals, leading to the conclusion that PK's effect is masked [**65**].

B.L. Pandey et al. investigated anti-inflammatory action of *P. kurroa* extract (PK) in albino rats. Research showed that the anti-inflammatory effect of PK treatment was reversed at specific time intervals (1 hour, 3 hours, and 5 hours) following the depletion of mast cells, neutrophils, and macrophages, respectively [**66**].

Apocynin, a key constituent of *P. kurroa* roots, has been found to exhibit anti-inflammatory properties by inhibiting thromboxane A2 formation, stimulating prostaglandin release, and ultimately preventing bovine platelet aggregation in arachidonic acid-induced inflammation [**67**].

Kutkin, a bioactive compound present in the alcoholic root extract of *P. kurroa*, has been identified as the primary contributor to its anti-inflammatory effects in animal models [**68**].

10.4 Anti-asthmatic

Studies have shown that androsin, a constituent of *P. kurroa*, significantly reduced allergen-induced bronchial obstruction in guinea pigs. The plant extract also inhibited histamine release in vitro [**70**]. Additionally, an iridoid glycoside fraction isolated from *P. kurroa* roots and rhizomes demonstrated anti-allergic properties by inhibiting passive cutaneous anaphylaxis and preventing mast cell degranulation in rats and mice [**70**,**71**].

10.5 Anti-diabetic

Research has found that *P. kurroa* extract reduces serum lipid peroxide levels and blood urea nitrogen in diabetic rats induced by alloxan, while also inhibiting weight loss and leukopenia. This suggests that *P. kurroa* extracts may mitigate metabolic damage caused by alloxan [**14**].

Moreover, studies have provided in vivo evidence that standardized extracts of *P. kurroa* exhibit considerable antidiabetic activity in rats with type-2 diabetes [**72**].

Another study has elucidated the mechanism of antidiabetic activity of *P. kurroa* extract, revealing its ability to enhance insulin-mediated glucose uptake in skeletal muscle [**73**].

Nirja et al. investigated the antidiabetic properties of *P. kurroa* extract in a male Wistar rat model. The results of the study demonstrated a significant reduction in blood glucose levels, as well as improvements in lipid profile levels. These findings suggest that *P. kurroa* extract may have a beneficial effect on glucose metabolism and lipid profiles. Furthermore, the extract showed promising results in both in-vitro and in-vivo studies, indicating its potential as a natural remedy for the treatment and management of diabetes [**74**].

The methanolic extract of *Picrorhiza kurroa* has been found to possess high total phenolic content (TPC) and total flavonoid content (TFC), as well as exceptional antioxidant potential. This is attributed

to its high scavenging capacity, as demonstrated by its performance in DPPH, ABTS, and FRAP assays. Furthermore, the extract's significant α-amylase and α-glucosidase inhibitory activities suggest its potential as a natural therapeutic agent for the treatment and management of diabetes [**75**].

A study found that administering an herbal formulation containing *P. kurroa* to streptozotocin-induced diabetic rats resulted in decreased levels of malondialdehyde and NADPH-oxidase dependent superoxide formation in the diabetic kidney. This indicates that *P. kurroa* may play a protective role in diabetic nephropathy by mitigating oxidative stress and inflammation [**76**].

A study found that KT fraction of PKE enhanced adipogenesis, improved lipid metabolism, and increased insulin sensitivity in adipocytes. KT activated PPARγ, PI3K/Akt signalling, and upregulated adiponectin, while reducing TNFα expression. Additionally, KT promoted insulin-mediated glucose uptake and activated PI3K/Akt axis even in the presence of a PI3K inhibitor [**104**].

10.6 Anti-arthritic

R. Kumar et al. evaluated the anti-arthritic activity of *Picrorhiza kurroa* (PK) in rat models of formaldehyde and adjuvant-induced arthritis (AIA). The study found that administration of *Picrorhiza kurroa* rhizome extract (PKRE) resulted in significant reductions in joint inflammation and inflammatory cytokine expression, including IL-1β, IL-6, TNF-R1, and vascular endothelial growth factor, in AIA-induced arthritic rats. These results suggest that PKRE may exert its anti-arthritic effects by suppressing the expression of inflammatory cytokines and modulating the inflammatory response in arthritic joints [**11**].

10.7 Anti-cancer

A study investigated the antineoplastic and antioxidant properties of methanolic extracts and aqueous extracts of *P. kurroa* rhizomes. The extracts were tested for their cytotoxic effects on human breast carcinoma, human hepatocellular carcinoma, and human prostate cancer cell lines using the XTT assay. The results demonstrated that both extracts exhibited significant antineoplastic activity by inducing apoptosis in all three cancer cell lines, suggesting their potential as natural anticancer agents [**77**].

Rathee et al. (2013) found that iridoid glycosides, including picroside-I, kuthkoside, and kutkin, isolated from *P. kurroa*, exhibited anti-invasive and anti-migratory effects on MCF-7 breast cancer cells by reducing the activity of matrix metalloproteinases (MMP-2, 9, and MMP-1,13). These compounds also suppressed the expression of MMPs at both protein and mRNA levels, leading to the inhibition of inflammatory mediators and the suppression of cancer cell invasion and migration [**85**].

Additionally, Mallick et al. (2015) found that the dichloromethane fractions of *P. kurroa* rhizome exhibited significant anticancer effects, including a reduction in tumor cell count and restoration of haematological parameters, which were attributed to the presence of cucurbitacin B, cucurbitacin E, picroside-I, picroside-II, betulinic acid, and apocynin [**84**].

The extract of *P. kurroa* was found to significantly inhibit hepatocarcinogenesis induced by N-nitrosodiethylamine, suggesting its potential as a chemopreventive agent against liver cancer [**78**].

Kong et al. demonstrated that Cucurbitacin E (CuE) inhibits the growth of human breast cancer cells in vitro by inducing apoptosis and cell cycle arrest. The study suggested that CuE's anti-cancer effects are mediated through the inhibition of STAT3 function. Additionally, the results showed that low-dose CuE enhances the efficacy of cisplatin in inhibiting breast cancer cell growth, highlighting its potential as an adjunctive therapy for breast cancer [**79**].

Another study revealed that combining cucurbitacin B (CuB) at a relatively low concentration with either Docetaxel (DOC) or Gemcitabine (GEM) exhibits significant antiproliferative activity against breast cancer cells, without increasing toxicity [**80**].

Another study's findings strongly suggest that picroliv is a beneficial agent for reducing damage caused by chemotherapy and radiation [**81**].

Jun-shan zhu et al. discovered that CuB exhibits antitumor activity in Jurkat cells, inhibiting their growth in a dose-dependent manner. Treatment with CuB arrested cell cycle progression at the G2/M phase, inducing both apoptotic cell death and autophagy [**82**].

Duangmano et al. demonstrated that cucurbitacin B possesses strong antiproliferative properties against breast cancer cells, inhibiting their growth in a dose-dependent manner. The mechanism of action involves disruption of microtubule polymerization and nucleophosmin/B23 translocation, resulting in cell cycle arrest at the G2/M phase and apoptosis. These results indicate that cucurbitacin B may be a promising agent for breast cancer therapy [**83**].

10.8 Anti-microbial

Methanol extract of *P. kurroa* rhizomes exhibited significant antimicrobial activity, comparable to the standard antibiotic Ciprofloxacin, as determined by the cup plate method. Additionally, the aqueous extract demonstrated antifungal activity against fungal strains, similar to the standard antifungal agent Fluconazole [**92**].

A study has demonstrated that acetone and methanol extracts of dried stolons of *P. kurroa* exhibit potent antimicrobial activity against a broad range of microorganisms, including bacteria and fungi. The extracts showed dose-dependent inhibitory effects against Bacillus subtilis, Erwinia chrysanthemi, Escherichia coli, Gloeocercospora sorghi, Fusarium oxysporum, Rhizoctonia solani, and Sporisorium scitamineum. Significantly, the extracts demonstrated greater antibacterial activity against B. subtilis than the standard antibacterial agent used in the study, highlighting their potential as natural antimicrobial agents [**93**].

A study on the leaf extracts of *Picrorhiza kurroa* revealed significant antibacterial and antioxidant activity. The acetone extract demonstrated notable antibacterial potency against S. aureus, S. mutans, E. coli, K. pneumoniae, and P. aeruginosa. Although the antioxidant activity of the extracts was moderate compared to ascorbic acid, the findings suggest that *Picrorhiza kurroa* leaf extracts may be a valuable source of natural antimicrobial and antioxidant agents [**94**].

Rathee et al. conducted a study to evaluate the antimicrobial activity of methanolic and aqueous extracts of *P. kurroa* against various fungi and bacteria. The study involved in vitro testing against two fungal strains (Aspergillus niger and Candida albicans) and five bacterial strains (Escherichia coli, Pseudomonas aeruginosa, Staphylococcus aureus, Micrococcus luteus, and Bacillus subtilis). The results showed that the methanolic extract exhibited significant activity against P. aeruginosa and S. aureus, and moderate activity against E. coli, B. subtilis, and M. luteus. In contrast, the aqueous extract had no activity against any of the tested fungi [**6**].

10.9 Immunomodulatory

A study conducted by Hussain et al. demonstrated the immunomodulatory properties of *Picrorhiza kurroa* in an in vivo model of immunosuppressed mice. Cyclophosphamide was employed to induce immunosuppression, and the results showed that the alcoholic extract of the plant significantly augmented immunostimulant activities [**95**].

A study evaluated the immunomodulatory properties of RLJ-NE-205, a biopolymeric fraction isolated from *P. kurroa*, in a murine model. The results demonstrated a statistically significant increase in cytokine levels (IFN-γ and IL-4) and lymphocyte proliferation at a dose of 50 mg/kg, suggesting that RLJ-NE-205 may function as a biological response modulator, influencing the immune response in a dose-dependent manner [**5**].

Research has shown that a 50% ethanolic extract of *P. kurroa* leaves possesses immunomodulatory effects, enhancing both cellular and humoral immune components, as well as phagocytic activity, in animal models. Specifically, the extract was found to augment humoral immune responses in rats and mice, and increase phagocytic activity in the reticuloendothelial system of mice, indicating its potential as an immunoenhancing agent [**97**].

This study demonstrated the efficacy of AEV01 in treating COVID-19 patients. The results showed significant improvements in oxygen saturation and cough relief, with a reduced recovery time of 4.5 days compared to 9.1 days in the placebo group. Additionally, AEV01 treatment led to improvements in key biomarkers, including ESR, LDH, serum ferritin, and inflammatory cytokines. Overall, the study suggests that AEV01 is a promising treatment for COVID-19, offering rapid and sustained improvements in clinical outcomes [**98].**

10.10 Cardioprotective

A study examined the cardioprotective effects of *P. kurroa* in rats with adriamycin-induced cardiomyopathy. Adriamycin treatment resulted in elevated plasma marker enzymes, lipid peroxidation, and decreased glutathione levels and anti-peroxidative enzymes in cardiac tissue. Conversely, oral administration of *P. kurroa* effectively counteracted these changes, returning the rats to a normal state [**53**]

Research has shown that an ethanolic extract of P. kurroa's rhizome and roots effectively reversed myocardial stress induced by isoproterenol in mice, highlighting its potential as a cardioprotective agent. [**54**]

10.11 Anti-ulcer

A study assessed the gastroprotective effects of an ethanol extract of *P. kurroa* roots and rhizomes against ethanol/HCl-induced gastric ulceration in rats. The extract's effects on gastric mucosal pepsin, antioxidant status, glycoproteins, and proteins were evaluated. The results showed that oral treatment with the extract for 10 days resulted in a significant reduction in ulceration, suggesting its potential as a gastroprotective agent [**99**].

A study investigated the gastroprotective effects of the methanol extract of *P. kurroa* rhizomes on indomethacin-induced gastric ulcers in mice. The

results showed that the extract accelerated ulcer healing by modulating key physiological processes, including mucin secretion, oxidative stress reduction, prostaglandin production enhancement, and cyclooxygenase enzyme expression upregulation, thereby demonstrating its potential as a therapeutic agent for gastric ulcer treatment [**100**].

10.12 Hypolipidemic Effect

Lee et al. assessed the hepatoprotective and hypolipidemic potential of *P. kurroa* root extract (PKRE) in a murine model of high-fat diet-induced hyperlipidaemia. The results demonstrated that PKRE supplementation significantly reduced serum levels of total cholesterol, LDL cholesterol, triglycerides, and liver enzymes (ALT and AST), while also decreasing liver weight. Conversely, PKRE did not exert any significant effects on serum HDL cholesterol levels, suggesting a neutral impact on HDL metabolism [**101**].

A study investigated the hepatoprotective and hypolipidemic effects of the water extract of *P. kurroa* (PR) in mice with hyperlipemia induced by poloxamer (PX)-407. The efficacy of PR was compared to that of simvastatin, a standard lipid-lowering agent. The results demonstrated that PR extract and simvastatin treatment resulted in dose-dependent reductions in serum triglycerides, LDL cholesterol, and total cholesterol levels [**102**].

A study on *Picrorhiza kurroa* plant extract showed it significantly reduced cholesterol and triglyceride levels in hyperlipidaemic rats, with high-dose (200mg/kg) extract being most effective, comparable to standard drug Atorlip-20 [**103**]

10.13 Antileishmanial activity

The synergistic potential of Picroliv in enhancing the antileishmanial efficacy of conventional drugs has been elucidated in various studies. Specifically, the combination of Picroliv with ketoconazole and miltefosine resulted in a significant augmentation of antileishmanial activity, with efficacy increasing from 72% to 82% against visceral leishmaniasis [**12**].

Picroliv also showed significant enhancement of anti-leishmanial effects when combined with paromomycin and miltefosine [**105-106**].

10.14 Antimalarial activity

An in vivo study evaluated the antimalarial efficacy of the ethanolic extract of *Picrorhiza kurroa* roots and leaves against Plasmodium berghei in a murine model. The results demonstrated that the root extract possessed significant antimalarial activity, with a more pronounced inhibitory effect on malaria parasites compared to the leaf extract [**107**].

10.15 Anticonvulsant effect

An in vivo study evaluated the anticonvulsant activity of the ethanolic root extract of *Picrorhiza kurroa* in a mouse model of maximal electroshock-induced seizures and pentylenetetrazole, picrotoxin-induced seizures. The findings revealed that administration of the extract at a dose of 100 mg/kg significantly attenuated convulsive seizures and mortality, thereby confirming its anticonvulsant properties [**108**]

11 TOXICITY STUDY

A study was conducted to evaluate the oral toxicity of *Picrorhiza kurroa* root extract (PKRE) in Wistar rats. A single high dose of 2000 mg/kg was administered, and the rats were observed for 14 days. The results showed no signs of toxicity, and the rats exhibited weight gain, indicating a high LD50 value [**109**].

The results of the acute oral toxicity study indicated that the maximum non-lethal dose of *Picrorhiza kurroa* (*P. kurroa*) in rats is less than 2000 mg/kg of body weight per day, administered in two fractional doses. Moreover, the study showed that *P. kurroa* exhibits thermal stability, retaining its properties when stored at temperatures up to 50°C for a duration of three months [**110**].

Despite its diverse applications, *Picrorhiza kurroa* has been subjected to limited toxicity studies. Consequently, further toxicological investigations are warranted to elucidate the potential adverse effects associated with its use. These studies are essential for ensuring the safe handling, production, and utilization of its bioactive extracts and secondary metabolites.

12 CONCLUSION & FUTURE PERSPECTIVES

This comprehensive review aims to provide an updated overview of the versatile applications of *Picrorhiza kurroa*, an herb characterized by its diverse pharmacological properties and widespread inclusion in herbal preparations. As a cornerstone of traditional Indian medicine, *Picrorhiza kurroa* presents a promising alternative to conventional therapeutic modalities. Its profound ethnomedical significance underscores the need for further research to delineate the bioactive compounds and molecular mechanisms of action responsible for its therapeutic efficacy. A substantial body of evidence from in vitro and in vivo studies has substantiated the pharmacological relevance of the bioactive secondary metabolites present in *Picrorhiza kurroa*. However, a critical knowledge gap persists due to the scarcity of human clinical trials to validate these preclinical findings. Thus, there is an urgent need for well-designed human clinical trials to confirm the efficacy and safety of *P. kurroa*, which will ultimately

inform the development of novel therapeutic applications.

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