



Phytochemical and Pharmacological Properties of *Picrorhiza kurroa*

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Abstract

Picrorhiza kurroa of family Scrophulariaceae represents an endangered, small, hairy perennial medicinal herb indigenous to India, which grows in subalpine Himalayan province wild from Kashmir to Sikkim at an elevation of 3000–5000 m. It has got a wide range of medicinal properties which are attributed to presence bioactive phytoconstituents, like cucurbitacins, Picroside I and II, and phenolic components. As per various reports, the plant has been used traditionally and possesses significant antioxidant activity, and thus could be potentially

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helpful in the management of cancer, diabetes mellitus, and liver diseases. Besides, numerous studies have shown that *Picrorhiza* has got tremendous cardioprotective, anti-inflammatory, antimicrobial, immunomodulatory, and anti-malarial activity which are attributed due to the presence of kutkin, a principal active constituent of this plant. This chapter is an attempt to compile detailed literature available on scientific researches of phytochemical constituents, and pharmacological properties of the *P. kurroa*.

Keywords

Picrorhiza kurroa · Kutki · Phytoconstituents · Biological activities · Clinical trial

13.1 Introduction

Picrorhiza kurroa Royle ex. Benth (*P. kurroa*) also known as kutki, and Indian gentian, a member of Scrophulariaceae family, is an endangered, small, hairy, everlasting medicinal plant indigenous to India. It grows wild in Himalayan province ranging from Kashmir to Sikkim at an elevation of 3000–5000 m (Bhattacharjee et al. 2013; Soni and Grover 2019). It is chiefly found in Nepal's western region where it grows in the crevices of rock, facing slopes on the north, typically on cliffy and sloppy mountains cliffs and the turf of glacial flats. It is distributed from Kashmir to Kumaon in Himalayan region and Nepal to Garhwal north Burma, west China, and Southeast Tibet (Chhetri et al. 2005). Traditionally, it is known very well in Indian Ayurvedic system, in which mainly roots and rhizomes are used for the management of liver diseases, chronic fever, indigestion, cardiac ailments, and diarrhea (Bhandari et al. 2010; Dwivedi et al. 1992). International Union for Conservation of Nature and Natural Sources has declared *P. kurroa* as an endangered species because of its overutilization from natural habitat and has been included in Appendix II of the Convention on International Trade in Endangered Species (CITES) list (Bhat et al. 2012; Nayar and Sastri 1990). Its principal active constituent kutkin, constitutes Picroside I and II and the kutkoside (Bhandari et al. 2009; Sah and Varshney 2013). Small doses of *P. kurroa* mainly dried roots and rhizomes are used for stimulating appetite, stomachache, in small quantities as a laxative, and as purgative (Arya et al. 2013). In India, it is listed among top 15 species which are sold for its economic value (Ved and Goraya 2007). Approximately 500 tons of this plant are demanded globally per year and out of the total supply of 375 tons, only 75 tons/year is contributed alone by India (Thani 2018). Due to the presence of higher moisture content, materials collected in July and August is low rated, while materials collected in the month of September is high rated due to low moisture content. To fulfil the herbal drug industries demand, *Picrorhiza* is collected mostly from Sikkim, Uttarakhand, Kashmir, and Himachal Pradesh (Arya et al. 2013; Debnath et al. 2020; Uniyal et al. 2011).

Table 13.1 Taxonomical classification

Rank	Scientific name and common name
Kingdom	Plantae-plants
Phylum	Tracheophyta
Class	Dicotyledonae
Subclass	Asteridae
Order	Lamiales
Family	Scrophulariaceae-figwort
Genus	<i>Picrorhiza</i>
Species	<i>Picrorhiza kurroa</i> —Kutki, kadu, hellebore

13.1.1 Taxonomy

Binomial name: *Picrorhiza kurroa* Royle ex. Benth.

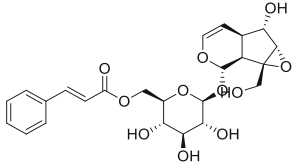
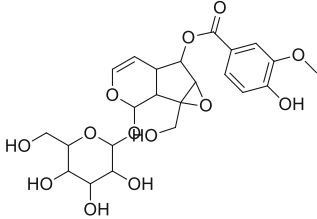
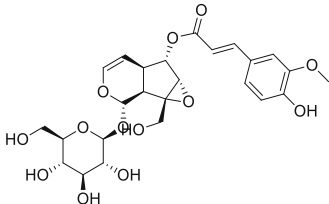
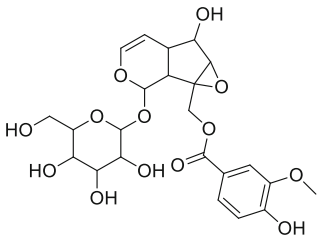
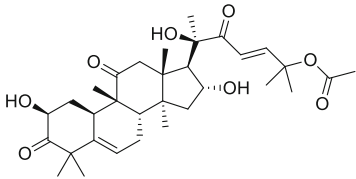
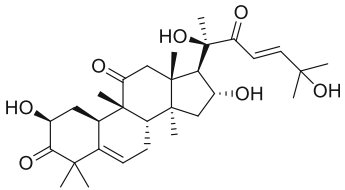
Synonym: *Picrorhiza lindleyana* (Wall.) Steud.

Around 200 genera and 3000 species of *Picrorhiza* (Table 13.1) are recognized in family Scrophulariaceae, which are mostly distributed in temperate regions of the world. *P. kurroa* is an everlasting plant with a slender, creeping rhizome along with basal and alternate leaves (5–10 cm in length) having a sharp apex. The flowers are present on a long spike which are either white or pale purple in color. The calyx splits up into five parts equally, and the corolla has got four to five lobes, 4–5 mm long with capitate stigma. Fruits are oval-shaped, tapered at the top, and 12 mm long with numerous ellipsoid seeds, along with transparent and thick seed coat. The rhizomes are thick, subcylindrical, or curved; grayish-brown in color externally; and presence of spherical scars of roots and furrows makes external surface coarse in texture. Root is elongated, tubular, straight, or curved marginally associated mostly with rhizomes. The flowering period of *Picrorhiza kurroa* (PK) is June to August.

13.2 Phytochemistry of *P. kurroa*

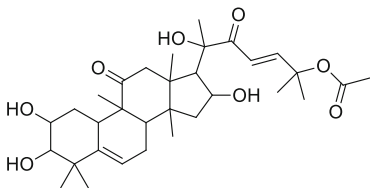
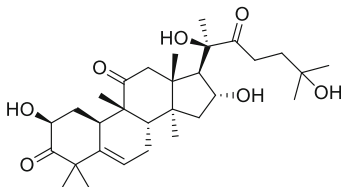
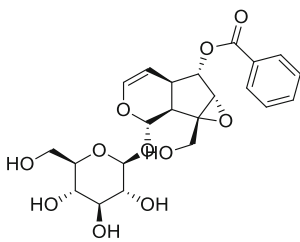
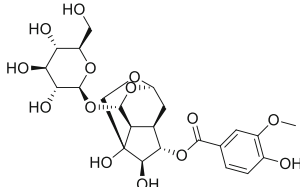
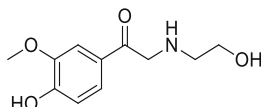
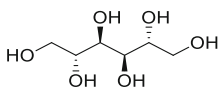
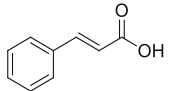
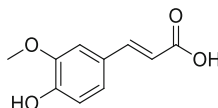
The phytochemical composition of PK has been widely researched and numerous studies have contributed to the discovery of 132 active ingredients from various parts of plant, including leaves, roots, branches, and seeds. An essential category of bioactive compounds of PK isolated (Table 13.2) from rhizomes are kutkoside, picroside I–III, and cucurbitacin, and elucidated by high-performance liquid chromatography (HPLC). Phytoconstituents like 4-hydroxy-3-methoxy acetophenone, pikuroside, veronicoside, and numerous phenolic compounds are also found in various extracts of PK (Sharma et al. 2012). Many other active compounds substances derived from PK include apocynin and drosine (Simons et al. 1989). *P. kurroa* consists of cucurbitacins that are known for having antitumor properties (Salma et al. 2017). Rhizomes of PK also contain kutkoside and glycosides. It also documented the occurrence of pikurosides, picrosides (I–IV), kutkosides, and flavonoids viz. vanillic acid and apocynin in the 70% hydroalcoholic fraction.

Table 13.2 Some essential bioactive compounds isolated from *Picrorhiza kurroa*

Phytoconstituent	Structure	References
Picoside I		Kitagawa et al. (1969), Weinges et al. (1972)
Picoside II		Singh and Rastogi (1972)
Picoside III		Weinges (1977)
Kutkoside		Singh and Rastogi (1972)
Cucurbitacin B		Laurie et al. (1985), Salma et al. (2017), Stuppner and Wagner (1989)
Cucurbitacin D		

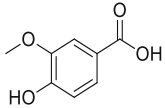
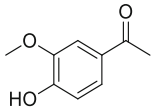
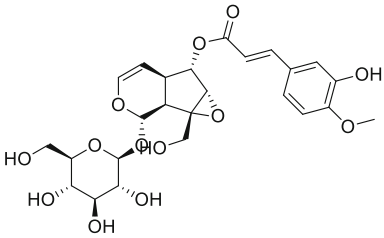
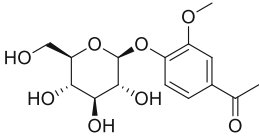
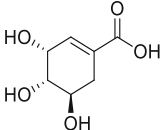
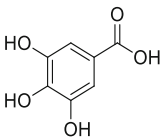
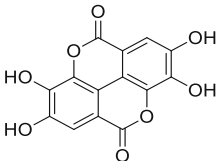
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Table 13.2 (continued)

Phytoconstituent	Structure	References
Cucurbitacin Q		
Cucurbitacin R		
Veronicoside		Stuppner and Wagner (1989)
Pikuroside		Jia et al. (1999)
4-Hydroxy-3-methoxyacetophenone		Sharma et al. (2012)
D-mannitol		Kumar et al. (2013)
Cinnamic acid		Kumar et al. (2013)
Ferulic acid		Kumar et al. (2013)

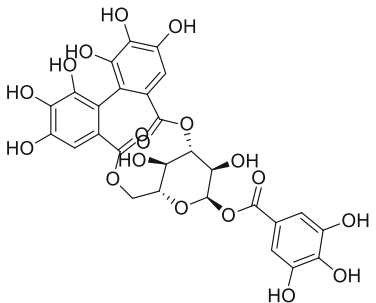
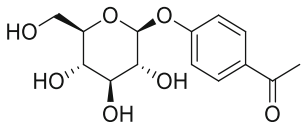
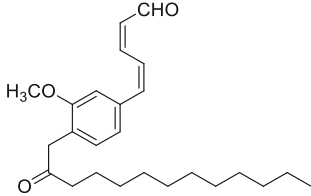
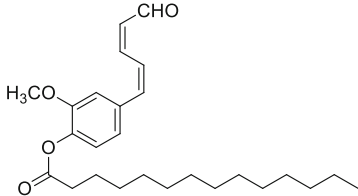
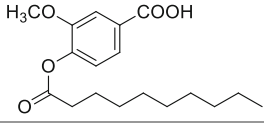
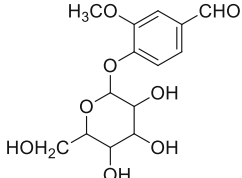
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Table 13.2 (continued)

Phytoconstituent	Structure	References
Vanillic acid		Rastogi et al. (1949)
Apocynin		Basu et al. (1971)
Minecoside		Stuppner and Wagner (1989)
Androsin		Stuppner and Wagner (1989)
Shikimic acid		Zhang et al. (2004)
Gallic acid		Zhang et al. (2004)
Ellagic acid		Zhang et al. (2004)

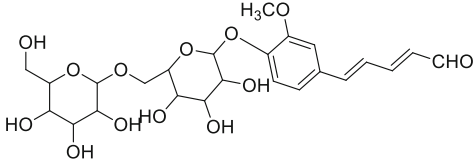
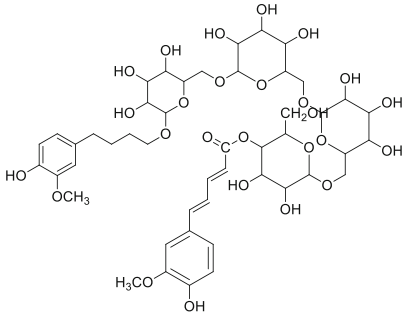
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Table 13.2 (continued)

Phytoconstituent	Structure	References
Isocorilagin		Zhang et al. (2004)
Picein		Stuppner and Wagner (1989)
Lauryl picraldehyde		Ali et al. (2017)
Myristyl picraldehyde		
Capryl vanillic acid		
Vanillin- α -D-glucoside		

(continued)

Table 13.2 (continued)

Phytoconstituent	Structure	References
Picaldehyde diglucoside		
Picrortetra-glucoside		

Other essential phytoconstituents derived from the PK are carbohydrates and aromatic acids (Kumar et al. 2013).

13.3 Pharmacological Activities of *P. kurroa* (PK)

Numerous pharmacological activities attributed to the presence of various phytoconstituents have been reported from the *P. kurroa* (Fig. 13.1).

13.3.1 Cardioprotective Effect of *P. kurroa*

Cardiovascular disease (CVD) is a blanket term for a group of pathological conditions involving cardiovascular system. It includes coronary heart disease, congenital heart disease, rheumatoid heart disease, peripheral arterial disease, cerebrovascular disease, etc. The various risk factors associated with the development of CVDs are obesity, dyslipidemia, diabetes, smoking, and hypertension (Stewart et al. 2017). CVD is a major concern in diabetic patients as it is a major cause of deaths among these people (Einarson et al. 2018).

Nandave et al. authenticated *P. kurroa* extract (PK) against cardiotoxicity induced by isoproterenol in male Wistar rats. Pretreatment with 200 mg/kg of an extract decreased the lipid peroxidation markedly. It preserved the cell membrane stability and integrity that consequently reduced the passage of enzymes in plasma, which are the hallmark of myocardial damage. The cardioprotective effect is due to the antioxidant effect of the extract (Nandave et al. 2013).

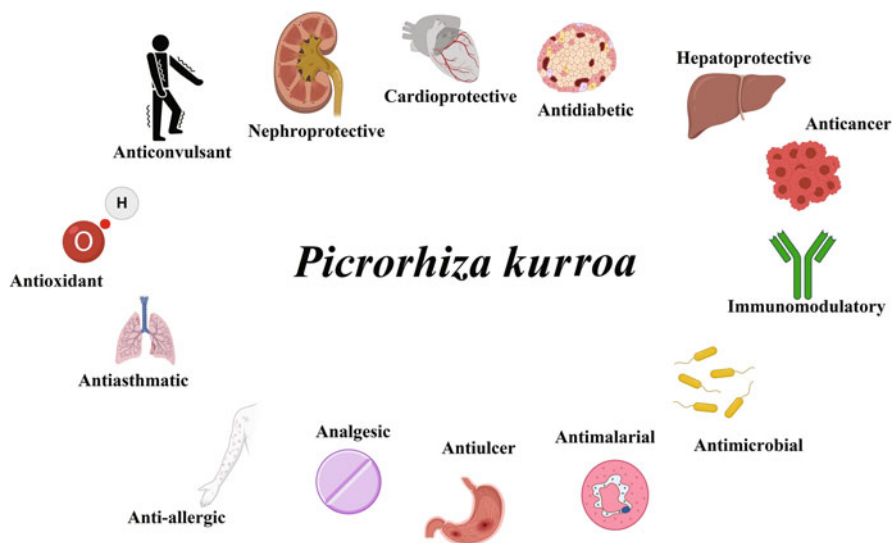


Fig. 13.1 Pharmacological activities reported from *P. kurroa*

Ethanollic extract of PK displayed reasonable protection against Adriamycin-challenged cardiomyopathy in male albino Wistar rat. The *Picrorhiza* (50 mg/kg) on oral administration daily for 15 days demonstrated the significant cardioprotective effect by decreasing lactate dehydrogenase (LDH), creatine phosphokinase (CPK), alanine aminotransferase (ALT), and aspartate aminotransferase (AST) levels in plasma and also prevents lipid peroxidation, which leads to the membrane instability and damage to heart tissue. Furthermore, the antioxidant enzyme profile was significantly increased as indicated by enhanced levels of superoxide dismutase, catalase, etc. Hence, the *Picrorhiza* efficiently alleviated all the harmful effects triggered by Adriamycin and preserved the myocardial membrane integrity and oxidative damage by strengthening the antioxidant mechanism in myocardial tissue (Rajaprabhu et al. 2007).

13.3.2 Antidiabetic Effect of *P. kurroa*

Diabetes mellitus (DM) happens to be one of the oldest, serious, and chronic disease governed by increased blood sugar levels resulting from either failure in production of insulin or increase in the insensitivity of the tissues toward insulin (Tan et al. 2019). The classic diabetic symptoms include polyuria (excessive urine passage), polyphagia (increased hunger), and polydipsia (intense thirst) (Ramachandran 2014). Diabetes is linked to multiple macrovascular and microvascular complications such as neuropathy, retinopathy, nephropathy, cardiovascular complications (like myocardial infarction), and cerebrovascular diseases (stroke) (Forbes and Cooper 2013).

Joy and Kuttan researched antidiabetic activity of hydroalcoholic extract of *P. kurroa* using Wistar albino strain of rats. The extract has been shown to diminish the level of glucose. *Picrorhiza* extract (75 and 150 mg/kg) administered orally considerably reduced the blood glucose level over 10 days in alloxan-induced diabetes in rats. A 75 mg/kg dose reduced the blood sugar by 43%, while 60% reduction was observed with 150 mg/kg. The levels of urea in blood and lipid peroxides as an indicator of kidney and liver injury respectively was assessed, and a significant decrease was observed with *Picrorhiza* extract-treated animals in comparison to diabetic control groups (Joy and Kuttan 1999).

In a study done by Husain et al., where they administered aqueous extract of PK, in streptozotocin–nicotinamide-induced diabetic rats administered orally at doses of 100 and 200 mg/kg for 14 days elevates insulin levels in plasma. Histopathological examination revealed the more population of β pancreatic cell in *Picrorhiza*-treated group as compared to the diabetic control group (Husain et al. 2014).

Administration of aqueous extract of PK via oral route in streptozotocin–nicotinamide-induced rats at of 100 or 200 mg/kg dose for 2 weeks markedly reduced the fasting glucose levels and hence enhanced the glucose tolerance. The glycogen level in all the groups was compared, and *Picrorhiza* was found to restore the reduced levels of glycogen in liver, which is an indication of enhancement in the liver glycogenesis. The *Picrorhiza* extract also reversed the weight loss observed in diabetic rats (Husain and Singh 2009).

Chauhan et al. examined the antidiabetic activity of alcoholic and aqueous extract of PK rhizome at a concentration of 250, 500 mg/kg for 15 days in alloxan-induced diabetes in Wistar albino rats. The *Picrorhiza* extract-treated group showed decreased levels of glycosylated hemoglobin (HbA_{1C}) and blood sugar. Furthermore, increase in the levels of insulin in plasma and hemoglobin content was noticed in extract-treated group. Also, reduction in oxidative stress markers, such as malondialdehyde (MDA), peroxide, superoxide and nitric oxide radicals, and increase in antioxidant profile, that is, catalase (CAT), superoxide dismutase (SOD), glutathione oxidase, and glutathione-S-transferase, was associated with *Picrorhiza* extract treatment group. Moreover, the decrease in the weight of animals in diabetes animals was brought to normal by *Picrorhiza* (Chauhan et al. 2008).

Immune-mediated destruction of pancreatic beta cells decreases the efficiency of these cells and hence resulted in diabetes mellitus. Therefore, regeneration of the beta cell is one of the promising approaches to tackle the disease. Kumar et al. showed the antidiabetic effect of hydroalcoholic extract of PK on autoimmune diabetes mellitus elicited by streptozotocin in male Wistar rats. The hydroalcoholic extract decreased the blood glucose level and demonstrated significant ability to regenerate the pancreatic β cells and has the potential to cause insulin release. Alterations in ST, ALP, SOD, ALT, and catalase levels were normalized. The extract showed efficacy toward streptozotocin-mediated β -cell destruction and also showed an inhibitory effect on glucagon signaling through suppressing the expression of glucagon receptor in liver and kidney tissues and results in hypoglycemia. The hypoglycemic effect is due prevention of glucagon binding to these receptors, which is responsible for gluconeogenesis and glycogenolysis. The extract also

enhances the proliferation of Rin5f cells (insulin-producing cells) and increases the cellular uptake of glucose (Kumar et al. 2017).

13.3.3 Hepatoprotective Effect of *P. kurroa*

Various essential physiological functions of metabolism, storage, and secretion are mainly operated through liver. Hepatic disorders are highly prevalent disease and death, causing disorder in the world (Khan et al. 2019). Hepatotoxicity is caused by various agents such as viruses, parasites, environmental pollutants, alcohol abuse, and chronic administration of drug that leads to the development of various hepatic disorders including cirrhosis, alcohol liver disease (ALD), hepatitis B & C (HCC) (Khan et al. 2019; Saha et al. 2019; Shakya 2020). The various pathways involved in pathogenesis of hepatotoxicity are cell membrane destruction, modulation of various cellular pathways involved in metabolism of drugs, activation of immune system response, free-radical accumulation, inflammation, lipid peroxidation, and subsequently cell death (Cichoż-Lach and Michalak 2014; Del Campo et al. 2018; Khan et al. 2019; Mohi-Ud-Din et al. 2019).

Sinha et al. examined the hepatoprotective effect of aqueous extract of *P. kurroa* in vitro, utilizing mouse liver slice culture harvested from the liver of mice. The hepatotoxicity was induced using alcohol. The extract decreases the lipid peroxidation as indicated by decrease in the MDA products. The elevated lactate dehydrogenase (LDH), serum glutamic pyruvic transaminase (SGPT), and serum glutamic oxaloacetic transaminase (SGOT) levels of liver damage markers were inhibited. Furthermore, antioxidant enzyme activities was found to be increased (Sinha et al. 2011).

The rhizome extract of PK in combination with honey demonstrated fruitful results against acetaminophen-induced liver toxicity by altering the activity of hepatic enzymes and synergistically function in boosting the hepatoprotection and hepato-regeneration ability in liver toxicity. Histopathological study revealed that either *Picrorhiza* or honey alone or as combinational approach exhibit reduction in the deleterious effect of acetaminophen. Furthermore, the elevated levels of SGOT and SGPT in the injured liver were also normalized (Gupta et al. 2016).

Dwivedi et al. performed an experiment to evaluate the protective effect *Picrorhiza* extract (12.5 and 25 mg/kg) in thioacetamide-induced hepatic injury and concluded that the extract was equally effective in reducing the enhanced levels of serum SGOT and SGPT as that of silymarin. Moreover, the level of alkaline phosphatases was also reduced but no effect was observed on the bilirubin. Increase in the levels of δ -glutamyl transpeptidase and decrease in succinate dehydrogenase and glucose 6-phosphatase were observed (Dwivedi et al. 1991).

Picrorhiza extract has also been reported as an anti-hepatotoxic agent against carbon tetra chloride (CCl₄)-induced injury in mice. The results from the experiment revealed that the less alterations in the levels of alanine aminotransferases (ALT), alkaline phosphatase (ALP), reduced glutathione (GSH), catalase (CAT), and Na⁺/K

+ ATPase after *Picrorhiza* administration. The histological studies showed decrease in liver lesions in extract-treated group (Santra et al. 1998).

The *P. kurroa* hydroalcoholic extract exhibited considerable hepatoprotective effect in against high fat diet (HFD)-induced nonalcoholic fatty liver disease (NAFLD) at a dose of 200 and 400 mg/kg for a duration of 4 weeks. The extract reduced the ALT and ALP levels and also decreased the lipid content of liver in the treatment group. Histopathological examination revealed that treatment with PK extract showed minimal damage to liver and maintains the structure and morphology of the liver (Shetty et al. 2010).

The other studies that established the hepatoprotective activity of PK against various adversities like exposure to aflatoxin B1 (Dwivedi et al. 1993), cadmium (Yadav and Khandelwal 2006), galactosamine (Dwivedi et al. 1992), alcohol (Rastogi et al. 1996), oxytetracycline (Saraswat et al. 1997), and monocrotaline (Dwivedi et al. 1991) have been reported.

13.3.4 Anticancer Effect of *P. kurroa*

Cancer is a global concern, responsible for eight million deaths annually, and is predominantly prevailing in developing nations as about 63% deaths are outlined due to cancer from these countries (Abbas and Rehman 2018; Wani et al. 2021). Cancer development is a multistep process which involves three phases: initiation, promotion, and progression (Chakravarthi et al. 2016), resulting from modifications at genetic and epigenetic level by altering various signaling pathways (Li et al. 2020; Trosko 2005).

A research was conducted to investigate the anticancer property of extract of rhizome of PK (both alcoholic and aqueous) on multiple cell lines namely (MDA-MB-435S), (Hep3B), and (PC-3). The study concluded the potential cytotoxicity of the extract in all the cell lines through induction of apoptosis. Ferric ion-reducing antioxidant power (FRAP) and thiobarbituric acid (TBA) assays revealed the radical scavenging property of both alcoholic and aqueous extract with maximum effect exhibited by aqueous extract of *P. kurroa* (Rajkumar et al. 2011b).

Anticancer activity of Picroliv, an important constituent obtained from root extract of PK, was explored in Sprague Dawley rat subjected to 1,2-dimethylhydrazine hydrochloride (DMH). The oral administration of different doses (40 and 200 mg/kg) of Picroliv showed promising result in liver carcinogenesis and liver necrosis. The elevated level of liver γ -glutamyl transpeptidase (Y-GT), a marker of neoplastic events induced by DMH gets reduced in Picroliv treatment group. Normalization of the levels of catalase and superoxide dismutase and reduction in lipid peroxidation was found with Picroliv administration (Rajeshkumar and Kuttan 2003).

Rajeshkumar and Kuttan (2000) identified the antitumor potential of Picroliv against N-nitrosodiethylamine (NDEA) prompted liver cancer in mice model. Orally given Picroliv (200 mg/kg) reduced the raised gamma-glutamyl transpeptidase

(gamma-GT) levels in liver and plasma at a comparable level as that of normal group. Also, the substantial reductions in increased levels of ALP, serum peroxidases, and bilirubin was observed in Picroliv treatment group (Rajeshkumar and Kuttan 2000).

Methanolic extract (75%) of PK (150 and 750 mg/kg orally) in Swiss albino mice resulted in inhibition of sarcoma induced by administration of 20-methylcholanthrene. Dose-dependent reduction in volume of implanted solid tumor was observed and increase in survival ascites tumor-bearing mice. *Picrorhiza* extract also demonstrated inhibitory effect on topoisomerase I and II in *S. cerevisiae* mutant strain cell culture; however, no effect was observed with cdc2 kinase, which is an enzyme that regulates cell cycle (Joy et al. 2000).

Rathee et al. conducted a study on (MCF-7) to explore the anticancer property of *Picrorhiza* extract and Kutkin, Picroside I, and Kutkoside. Treatment with this extract showed potential cytotoxicity in a dose-dependent pattern. The extract and isolated glycosides possessed anti-invasive and anti-migratory effect through suppression of metalloproteases, matrix metalloproteinase 2 (MMP-2), 9 (gelatinases) and MMP-1, 13 (collagenases) that are involved in the process (Rathee et al. 2013).

Evaluation of picroside II, an iridoid glycoside obtained from PK, revealed its antimetastatic, and antiangiogenic properties. The matrix metalloproteinase 9 (MMP-9) is an important player responsible for cancer metastasis through degradation of extracellular matrix was reduced. Also, the angiogenic marker, cluster of differentiation (CD31) was also suppressed (Lou et al. 2019).

13.3.5 Immunomodulatory Effect of *P. kurroa*

For protection from various infections and pathogens in humans, immune system plays an important role. Innate and adaptive systems are the two branches of immune system, among which the innate immune functions with distinct mechanism for protection against pathogen, while the nonadaptive trigger the stimulation of antimicrobial defense mechanism by sensing pathogen through well-recognized receptors. However, the relation between various immune components is not fully understood (Turvey and Broide 2010).

Amit et al. evaluated biopolymeric fraction RLJ-NE-205 isolated from *P. kurroa* rhizomes for immunomodulatory effect and studied parameters like phagocytic index, HA titre, DTH reaction, PFC assay, proliferation of lymphocytes, and analysis of cytokines in serum. Pretreatment with 50 mg/kg fraction RLJ-NE-205 significantly increases lymphocytes and cytokine levels in serum and significantly strengthens the immune system (Gupta et al. 2006).

Arshad et al. examined the immunomodulatory response of ethanolic and aqueous extract of PK against cyclophosphamide-induced immunosuppression in rats. The immunomodulatory effect was authenticated by studying humoral antibody response to sheep red blood cells (SRBC) and was concluded that both the ethanolic and aqueous extract of PK showed significant increase in delayed type hypersensitivity response among which ethanolic extract was more potent (Hussain et al. 2013).

In another study, an experiment was carried out to evaluate the immunomodulatory activity of *P. kurroa*, *Asparagus racemosus*, and *Withania somnifera*, against cyclophosphamide immunosuppressive agent in male Swiss albino mice. The finding of this experiment uncovered that all these herbs demonstrated footpad thickness in Delayed Type Hypersensitivity (DTH). The results further revealed that among all the three herbs, *W. somnifera* enhances humoral antibody response (Siddiqui et al. 2012).

Sharma et al. evaluated the immune-stimulatory activity of *P. kurroa* leaf extract against sheep RBC (SRBC)–induced hypersensitivity reaction in mice serum. Pretreatment with 50% ethanolic extract of PK significantly elevates humoral and cell-mediated components of the immune system in mice and rats and also stimulate the phagocytosis in reticuloendothelial cells of mice (Sharma et al. 1994).

The root and rhizome extract of PK (Picroliv) in combination with paromomycin and miltefosine revealed fruitful results used against *Leishmania donovani*/hamster model. The results of this study revealed that the antileishmanial efficacy and lymphocyte proliferation was significantly enhanced by Picroliv on combination with paromomycin and miltefosine and thus was concluded that Picroliv can be used as adjunct to anti-leishmanial chemotherapy (Sane et al. 2011).

13.3.6 Antimicrobial Effect of *P. kurroa*

Antimicrobial means potency of drugs or chemical by virtue of which they can kill or inhibit the growth of disease causing microbes and may be classified as antibiotics, antifungal, or antiviral based on the microorganism primarily they act against (Salma et al. 2017).

Vinoth et al. authenticated the antimicrobial activity of acetone, ethanol, methanol, aqueous, and hexane extract of *P. kurroa* against selected gram-negative and gram-positive bacterial strain. The result of the study demonstrated that ethanolic extract of PK rhizome possesses significant antimicrobial activity against *K. pneumoniae*, *S. typhi*, and *S. pyogenes*, followed by methanolic extract showing potent activity against *P. aeruginosa*. This study also suggested that acetone and aqueous of *P. kurroa* possess moderate antibacterial active against *S. aureus*, *K. pneumoniae*, *B. cereus*, and *S. pyogenes*, and therefore concluded that ethanolic and methanolic extracts of *P. kurroa* rhizomes comprise of compounds that can be used for development of novel broad spectrum antibacterial formulation (Kumar et al. 2010).

Surendra and Naresh studied the antimicrobial activity of chloroform, methanol, and aqueous extract of PK rhizome against bacterial and fungal strain using cup–plate method and ciprofloxacin and Fluconazole were used as standards. The results demonstrated that the methanolic extract showed significant antibacterial activity comparable to ciprofloxacin and aqueous extract showed potent antifungal activity as comparable to fluconazole hence concluded that *P. kurroa* rhizome extract possess significant antimicrobial activity (Sharma and Kumar 2012).

P. kurroa ethanolic extract was authenticated for its antimicrobial activity via agar well diffusion model. PK was found active against *B subtilis* and *P. aeruginosa* with minimum inhibitory concentration (MIC) values ranging from 65 to 260 mg / mL (Usman et al. 2012).

Diksha et al. evaluated antimicrobial activity of endophytes isolated from PK against human pathogens *S. typhimurium* (MTCC98), *S. aureus* (MTCC 96), *E. coli* (MTCC 1697), and *P. aeruginosa* (MTCC741). The results of the study concluded that MB-05 and MB-03 possess potent activity against *P. aeruginosa* whereas MB-09 and MB-15 showed potent activity against *S. typhimurium* and *S. aureus*. On the basis of antimicrobial potential, methanolic and chloroform extract of MB-05 were subject to HPLC analysis for the active metabolite identification (Raina et al. 2018).

A study was carried out to study antimicrobial activity of *P. kurroa* Benth rhizomes. Antimicrobial effect of the methanolic and aqueous extract was authenticated against *Micrococcus luteus*, *P. aeruginosa*, *B. subtilis*, *E. coli*, and *Staphylococcus aureus* bacterial strains. From the study, it was concluded that the extracts possess the significant antimicrobial activity but methanolic extract was found more potent against *S. aureus* and *P. aeruginosa*, which proved its traditional use in skin treatment, GIT infection, diarrhea, and urinary tract infection (UTI). Further, the iridoids, picroside I, and kutkoside were estimated using HPLC which was found to be 3.66 ± 0.11 and 4.44 ± 0.02 respectively (Rathee et al. 2016).

13.3.7 Antimalarial Effect of *P. kurroa*

Malaria, caused by *Plasmodium* parasites, a single-celled microorganism, which is transmitted from person to person through infected female *Anopheles* mosquitoes called “malarial vectors.” Symptoms usually develop after 10–15 days after mosquito bite (World Health Organization 2016).

An in vivo study was carried out by Banyal et al. to evaluate the antimalarial effect of ethanolic extract of *P. kurroa* roots and leaves against *Plasmodium berghei* for 4 days. From the study it was found that after day 4, the ethanolic extract of PK significantly inhibited the malarial parasite and parasitemia. Root extract of PK showed potent activity as compared to leaves (Banyal et al. 2014).

Saba Irshad et al. evaluated the in vitro antimalarial activity of *Artemisia absinthium*, *P. kurroa*, and *Caesalpinia bonducella* at a dose of 2 mg/mL against *Plasmodium falciparum*. Maceration and percolation extraction procedures were used for the preparation of different extracts from different parts of these plants. Cold alcoholic, hot alcoholic, and aqueous extracts of PK at a dose of 2 mg/mL significantly inhibit the growth of *P. falciparum* viz. 100%, 90%, and 34%, respectively. Cold alcoholic, hot alcoholic, and aqueous extract of *Caesalpinia bonducella* at the same dose showed 56%, 70%, and 65% growth inhibition *P. falciparum*, respectively. Similarly, Cold alcoholic, hot alcoholic, and aqueous extract of *Artemisia absinthium* showed 55%, 21%, and 35% inhibition, respectively, at the same concentration. The study was concluded that among these plants PK possess good

antimalarial activity and also proved its traditional uses as antimalarial drug (Irshad et al. 2011).

13.3.8 Antiulcer Effect of *P. kurroa*

An ulcer is an eruption on stomach or small intestine lining caused by sloughing out of inflamed necrotic tissues. The causes for ulcers in stomach include *Helicobacter pylori* (*H. pylori*) infection and prolong use of nonsteroidal anti-inflammatory drugs (NSAIDs) like aspirin, ibuprofen, or naproxen. Sometimes a body increases its acid production due to unknown leads to stomach and intestinal ulcers which is commonly known as Zollinger–Ellison syndrome. Burning sensations or pain between chest and belly button are some common symptoms of this disease (Shiotani and Graham 2002). Debashish et al. investigated the antiulcer activity of PK20 mg/kg against acute stomach ulceration induced by indomethacin male Swiss albino mice and evaluated its potential to balance oxidative stress, prostaglandin (PGE₂) levels and EGF during the study. The methanolic extract of PK resulted in reduction of ulcer indices by 45.1% as compared by the standard drug Omeprazole (76.3%). Furthermore, extract reduces protein carbonyl (37.7%) and thiobarbituric acid reactive substances (TBARS) (32.7%), levels, and elevated mucosal PGE₂ (21.4%), mucin (42.2%), cyclooxygenase-1 and 2 (COX-1 and -2) expressions (26.9 and 18.5%), epidermal growth factor (EGF) (149.0%), and vascular endothelial growth factor (VEGF) (56.9%) levels in the body. Hence, concluded that PK can be used an effective antiulcer agent, which can act by decreasing ROS-mediated stress and stimulate prostaglandin synthesis, mucin secretion promoting, and increasing cyclooxygenase enzymes and growth factors expression (Banerjee et al. 2008).

Arun et al. evaluated the antioxidant potential of PK at the concentration of 20 mg/kg for 10 days against indomethacin-induced acute gastric ulcers in rats. In gastric tissue, lipid peroxidized level in terms of TBARS and antioxidant enzymes, viz. SOD, catalase, and total tissue sulfhydryl group were studied during the investigation. The study concluded that the ethanolic extract of PK significantly enhanced the healing process in indomethacin-induced gastric ulcers. Furthermore, the extract also significantly increased the antioxidant enzymes. Therefore, ethanolic extract of PK rhizomes accelerate stomach wall healing in indomethacin-induced gastric ulceration probably by free radical scavenging action (Ray et al. 2002).

13.3.9 Analgesic Activity of *P. kurroa*

Analgesia, which results due to disruption in nervous system pathway, and the drugs which are used to get relief from pain are known as analgesic drugs or painkillers (Cregg et al. 2013). Neha et al. evaluated the analgesic and antipyretic activity of methanolic and hydroalcoholic extracts of *P. kurroa* rhizomes at a dose of 260 and 520 mg/kg using hot plate and yeast-induced pyrexia models. It was concluded from the results that the methanolic extract of *P. kurroa* at the dose of 260 and 520 mg/kg

possesses potent analgesic and antipyretic active as compared to hydroalcoholic extract which showed activity only on 520 mg/kg (Kaila and Dhir 2019).

Shid Rupali et al. evaluated the analgesic potential of PK roots at the concentration of 250 and 500 mg/kg for 7 days. The study was conducted using acetic acid-induced writhing and hot plate methods in albino mice. The results revealed that PK at 500 mg/kg showed similar analgesic effect as shown by standard drug pentazocine at ½ h. Furthermore, extract at 500 mg/kg significantly decreases the number of writhing that were induced by acetic acid, and concluded that *P. kurroa* possesses significant analgesic activity at the dose of 500 mg/kg (Shid Rupali et al. 2013).

13.3.10 Antiallergic Effect of *P. kurroa*

Allergies or allergic diseases are a group of conditions triggered by hypersensitivity of the immune system or allergen-induced unfavorable immune response typically to harmless substances from the environment, which typically could not be controlled completely by modern medicine (Kubo et al. 2017).

Baruah et al. investigate anti-anaphylactic and antiallergic activity of Picroliv (25 mg/kg). The results of the study showed that Picroliv significantly inhibits passive cutaneous anaphylaxis (82%) in mice and (50–85%) in rats. Further, it also protects mast cells from degranulation (60–80%) (Baruah et al. 1998).

13.3.11 Antiasthmatic Effect of *P. kurroa*

Asthma is a condition wherein the airway of the human respiratory system is constricted and narrowed. It occurs usually in reaction to a cause like cold, dust, allergen, exercise, or emotional stress affecting about 7% of total population, which approximately accounts for 300 million people worldwide. Asthma is associated with difficulty in breathing because of the inflammation of airways which occurs due to constriction of smooth muscle cells in bronchi (Ranjeeta et al. 2009).

Antiasthmatic activity of *P. kurroa* root ethanolic extract has been studied by in vitro and in vivo experimental model in guinea pigs by inducing histamine stimulated bronchoconstriction. A significant protection was observed with the extract (52.16%) which was comparable to that of salbutamol (65.83%). The molecular mechanism behind the muscle relaxant activity of the extract was also analyzed. The extract was found to be effective at a dose of 100 mg/mL against acetylcholine- and histamine-induced contraction. The result further revealed that antiasthmatic activity of the extract was due to presence of flavonoids and saponins (Sehgal et al. 2013).

13.3.12 Anti-Inflammatory Effect of *P. kurroa*

Inflammation is a defense mechanism wherein the human body responds to harmful stimuli like tissue injury or exposure to various allergy-causing substances (allergens). On the contrary, an uncontrolled response to inflammation is the reason for the vast number of diseases including allergies CVD dysfunctions, cancer, autoimmune disorders, etc. (Bagad et al. 2013; Mir et al. 2019, 2020).

It was reported that *P. kurroa* is an active anti-inflammatory drug due to the inhibition of edema at the rate of 29.8% (Kantibiswas et al. 1996). Similarly, application of *P. kurroa* rhizome extract was shown to considerably inhibit inflammation of joints against chemically induced inflammation. Owing to its anti-inflammatory activity it may be regard as a high-quality naturally occurring analgesic.

Pandey et al. also observed the anti-inflammatory activity of *P. kurroa* and confirmed that this activity was due to β -adrenergic blockade, suggesting that the plant extract was responsible for changes in biology of cell and it was also concluded that *P. kurroa* extract selectively have role in activation methods related to the membrane in inflammatory effect or cells which could be the cause of anti-inflammatory activity (Kumar et al. 2016).

13.3.13 Antioxidant Activity of *P. kurroa*

Antioxidants are the compounds that prevent or inhibit the oxidation and generally extend the life of the oxidizable matter (Kokate et al. 2003). Free radicals are produced in many biochemical processes and several diseases are allied to oxidative stress owing to free radical generation (Velavan et al. 2007). Antioxidant agents are radical scavengers that prevent the human body from various disorders (Kalaivani and Mathew 2010).

Antioxidant property of *P. kurroa* extract suggest its active role toward different oxidative stress-related diseases. Deshpande et al. reported that following the treatment with the extract of *P. kurroa*, the liver enzyme activities are reduced among the patients suffering from liver cirrhosis (Deshpande et al. 2015).

Rajkumar et al. reported the antioxidant effectiveness of extracts of *P. kurroa* by employing various methods, viz. ferric-reducing antioxidant activity, radical scavenging assays, and thiobarbituric acid assay for evaluating lipid peroxidation inhibition (Rajkumar et al. 2011a). Ray et al. established that the administration of PK rhizome ethanolic extract (20 mg/kg) promptly cured abdominal wall of gastric ulcerated rats (induced by indomethacin) (Ray et al. 2002). Krupashree et al. used diverse antioxidant testing methods to determine the antioxidant efficacy of the leaf fractions of PK. They found that the extract of *P. kurroa* demonstrated radical scavenging property and metal chelating activities (Krupashree et al. 2014). Sinha et al. evaluated the antioxidant properties of PK using in vitro methods and authenticated that *P. kurroa* aqueous extract has potent antioxidant activity. Furthermore, the addition of aqueous extract *P. kurroa* along with ethanol helped in the

re-establishment of antioxidant enzyme activity and suppression of lipid peroxidation (Sinha et al. 2011).

13.3.14 Anticonvulsant Activity of *P. kurroa*

Convulsion or epilepsy is the most common and foremost neurological disorder and around 5% of total population of the world acquires convulsion in their lifetime. Convulsions/epilepsy often causes transitory damage of perception, thereby leaving a person at the risk of physical harm (Kee et al. 2012).

Dilnawaz et al. studied the anticonvulsant activity of *P. kurroa* and ethanolic extract of its roots in mice using various inducing agents, viz. picrotoxin, pentylenetetrazole-induced seizures and electroshock-induced seizure. The convulsion latency and the number of animals protected from convulsions were noted and it was observed that the plant at a dose of 100 mg/kg exhibited substantial rise in clonic convulsion latency and also reduced the mortality (Pathan and Ambavade 2014).

13.3.15 Nephroprotective Effect of *P. kurroa*

The main functions of the kidneys include urine formation, water and electrolyte balance maintenance, as well as hormones and enzyme production. Kidneys also play an important role in the maintenance of endocrine, acid–base balance, and blood pressure. Nephrotoxicity is a renal dysfunction that develops in response toward exposure to external agents such as drugs and chemicals present in the environment (Priyadarasini et al. 2012; Sundararajan et al. 2014). An enormous number of chemicals that are commonly used nowadays are harmful to our kidneys (renal toxins). Administration of such chemicals/renal toxins into the body might trigger mechanical trauma to the kidneys and selectively interfere with some functions of the renal tubules.

Siddiqi et al. studied the effectiveness of *P. kurroa* against the toxicity induced by nimesulide. The in vitro study was performed on mice which were divided into four groups at National Institute of Health. One group was given only the plant extract while the other three groups were given a potential nephrotoxic drug, nimesulide, to induce nephrotoxicity for 3 days at a dose of 750 mg/kg. The serum urea and creatinine levels were measured by performing biochemical analysis of kidney. The results showed that out of total 20 mice, only 1 mouse could not survive while 19 mice of nimesulide group survived. The nimesulide group exhibited mean serum urea of 60 mg/dl, which reduced to 23 and 25 mg/dL with two doses of the plant extract. In the other group, mean creatinine level observed was 0.55 mg/dL, which was reduced to 0.21 and 0.19 mg/dL with two doses of the plant extract (Siddiqi et al. 2015).

Yamgar et al. studied nephrocurative and nephroprotective activity of the extract of *P. kurroa* rhizome (ethanolic extract) in mice against toxicity induced by cisplatin, through the evaluation of the levels of urea in blood and creatinine levels in serum.

On treatment with the ethanolic extract of the PK rhizome, the high levels of urea in blood and creatinine levels in serum were significantly reduced at a dose of 600 mg/kg. An Ayurvedic preparation, Arogyawardhini, containing PK as a basic constituent was also reviewed for the nephroprotective and nephrocurative actions against nephrotoxicity induced by cisplatin. This preparation was established to have better results in comparison to the rhizomic extract (Surekha et al. 2010).

13.4 Conclusion

From the above discussion it can be concluded that *P. kurroa* is valuable plant with range of ethnomedicinal and pharmacological significance. Due to the overexploitation of this plant it has been placed in list of endangered species by International Union for Conservation of Nature (IUCN). Therefore, the plant has a desperate need to be conserved. Varied pharmacological activities and presence of many bioactive compounds have been confirmed by studies, though many of them are yet to be quantified. The phytoconstituents and its biological activities reviewed in this study can help researchers to investigate this plant to further extent. Its utilization in different other diseases as well as its toxicity can be tested. Results have been based mostly on in vitro bioassay, but in vivo study employing humans is also required. Consequently, clinical trials should form a standard for safe therapeutic applications of this species.

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