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Chemistry and Pharmacology of *Picrorhiza Kurroa* Royle ex Benth.

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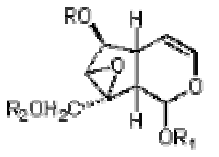
Abstract
Picrorhiza kurroa, commonly known as kutki, is having a remarkable reputation among the indigenous medical practitioners. It is well-known in the Ayurveda and has traditionally been used to treat disorders of the liver and upper respiratory tract. Recent studies proved the plant to be efficacious in various diseases and have good potential to reach clinic. These studies are focussed on the hepatoprotective, anti-cholestic, antioxidant and immunomodulatory activity. The present article comprises a review of the chemical constituents and pharmacological actions of the plant to emphasise its importance in medicine.

Key words: *Picrorhiza kurroa*, iridoid glycosides, picroliv, hepatoprotective, immunostimulant

Introduction
Picrorhiza kurroa Royle ex Benth. belongs to the family Scrophulariaceae. The dried roots and rhizome of the plant are used in traditional medicine by the name kutki, katurohini or titka. The plant is widely distributed in northwestern Himalayas at an altitude of 9000 - 15000 fts (1).

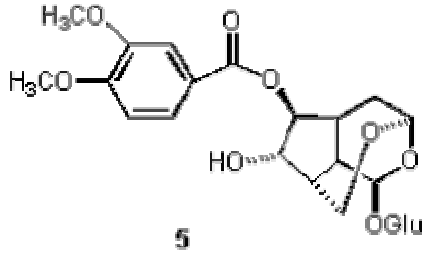
Traditional Uses
Traditionally, the roots and rhizome are used in Kapha. The root is reported to be bitter, cooling, cardiotonic, antipyretic, anthelmintic, laxative and appetiser. It is useful in biliousness, bilious fever, urinary discharges, asthma, hiccough, blood troubles, burning sensations, leucoderma and jaundice. In Ayurveda it is reported to purify the nurses milk. In China and Malaya, rhizome is widely used in bilious dyspepsia accompanied by fever (1). In Ayurveda, the practitioners often use it for the treatment of liver disorders and to treat the disorders of upper respiratory tract (2).

Chemical Constituents
First report on *Picrorhiza kurroa* is of isolation of bitter principle – glucoside kutkin along with a non-bitter principle kurrin and kutkiol (3). Kurrin was later identified as D-mannitol (4).
Structure of kutkin, which was proposed on hydrolysis and reaction studies, was 6-cinnamoyl-β-D-glucosidyl vanillate (5). Later on, the bitter principle- iridoid glycoside Picroside I (**1**) (6`-*o*-trans-cinnamoyl catalpol) was isolated as amorphous hygroscopic powder (6). Further studies reported that kutkin is a mixed crystal of Picroside I and Kutkoside (**2**), latter identified as 10-*o*-vanilloyl catalpol (7). Other iridoid glycosides Picroside II (**3**) (6-vanilloyl catalpol) and Picroside III (**4**) (6`-(4-hydroxy-3-methoxy cinnamoyl) catalpol) have also been isolated (8).



	R	R1	R2
1. Picroside I	H	6-cinnamoyl-β -D-glucopyranosyl	H
2. Kutkoside	H	β -D-glucopyranosyl	vanilloyl
3. Picroside II	vanilloyl	β -D-glucopyranosyl	H
4. Picroside III	H	6-feruloyl-β -D-glucopyranosyl	H

A new iridoid, pikuroside (**5**) has been isolated (9).



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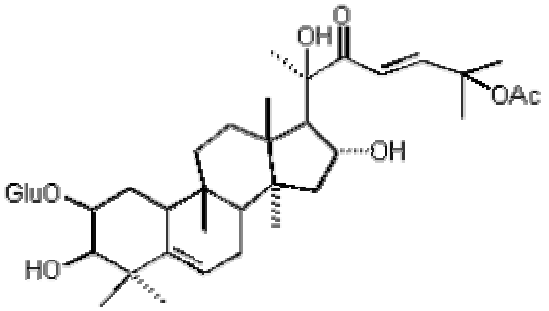
A cucurbitacin glycoside, 25-acetoxy-2-β-glucosyloxy-3,16,20-trihydroxy-9-methyl-19-norlanosta-5,23-dien-22-one (**6**), which is more bitter than Picroside I or Picroside II has been reported (10).



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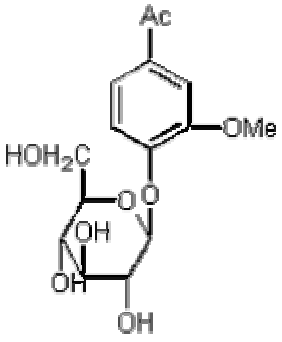
Minor iridoids (veronicoside and minecoside), phenolics (picein and androsin (**7**)) and several cucurbitacin glycosides have also been isolated. The cucurbitacin glycosides isolated are 2-β-glucosyloxy-3,16,20,25-tetrahydroxy-9-methyl-19-norlanosta-5,23-dien-11,22-dione (**8**); 2-β-glucosyloxy-16,20,22-trihydroxy-9-methyl-19-norlanosta-5,24-dien-3,11-dione (**9**); Arvenin III (**10**); 25-acetyloxy-2-β-D-glucopyranosyloxy-3,16-dihydroxy-9-methyl-19-norlanosta-5,23-dione (**11**); 25-acetyloxy-2-β-D-gluco pyranosyloxy-3,16,20-trihydroxy-9-methyl-19-norlanosta-5,23-dione; 25-acetyloxy-2-β-D-glucopyranosyloxy-3,16-dihydroxy-9-methyl-19-norlanosta-5-en-22-one; 2-β-D-glucopyranosyloxy-3,16,20-trihydroxy-9-methyl-19-norlanosta-5,24-dien-22-one; 2-β-D-glucopyranosyloxy-3,16-dihydroxy-4,4,9,14-tetramethyl-19-norpregn-5-en-20-one; 2,3,16,20,25-pentahydroxy-9-methyl-19-norlanosta-5-en-22-one; 2-(6-o-cinnamoyl-β-D-glucopyranosyloxy)-3,16,20,25-tetrahydroxy-9-methyl-19-norlanosta-5-en-22-one (8,11,12).



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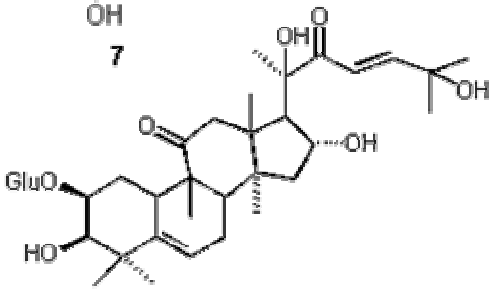

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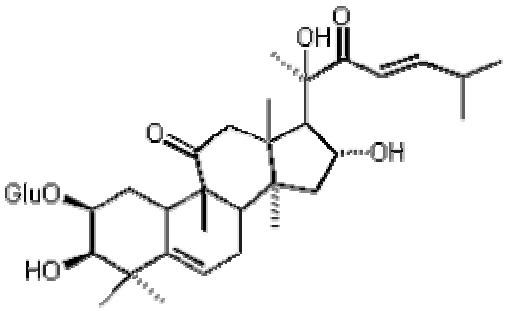

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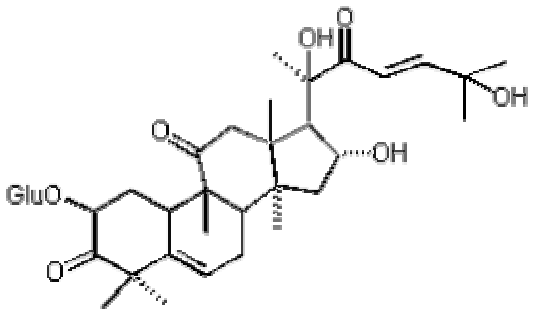
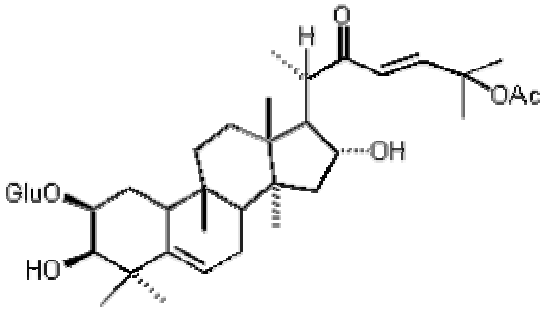


10. Arvenin III



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Several cucurbitacins with unusual side chains have been reported by Stuppner and Muller. These are (2β, 3β, 9β, 10α, 16α, 20ε, 24ε)-20,24-epoxy-2-(β-D-glucopyranosyloxy)-3,16,25-trihydroxy-9-methyl-19-norlanosta-5-en-11-one; (2β, 9β, 10α, 16α, 20ε, 24ε)-20,24-epoxy-2-(β-D-glucopyranosyloxy)-16,25-dihydroxy-9-methyl-19-norlanosta-5-en-3,11-dione; (2β, 9β, 10α, 16α, 20ε, 24ε)-20,24-epoxy-2-(β-D-gluco pyranosyloxy)-16, 25, 26-trihydroxy-9-methyl-19-norlanosta-5-en-3, 11 dione; (2β, 3β, 9β, 10α, 16α, 20ε, 24ε)-20,24-epoxy-2-(β-D-glucopyranosyloxy)-3,16,25,26-trihydroxy-9-methyl-19-norlanosta-5-en-11-one; (2β, 9β, 10α, 16α, 20ε, 24ε)-20,24-epoxy-2-(β-D-glucopyranosyloxy)-16,20,25-trihydroxy-9-methyl-19-nor lanosta-5,24-dien-3,11-dione and (2β, 9β, 10α, 16α, 20ε, 24ε)-20,24-epoxy-2-(β-D-glucopyranosyloxy)-3,16,20,26-tetrahydroxy-9-methyl-19-norlanosta-5,24-dien-11-one (13). The iridoid glycoside fraction, named as 'Picroliv' has also been isolated and been tested for various biological activities (14).

Pharmacological Activities

Hepatoprotective activity

P. kurroa and Picrolive are investigated in great deal for the hepatoprotective activity. Picroside II and related glycosides have been shown to protect liver against intoxication by carbon tetrachloride in mice (15). Kutkin also possesses the hepatoprotective activity against liver damage induced by galactosamine in rats and against the damage induced by *Plasmodium berghei* in mastomys (16).

Hepatoprotective activity of Picroliv has been studied against various hepatotoxic agents like paracetamol,

alcohol-carbon tetrachloride, thioacetamide, galactosamine, ethanol, aflatoxin B_1 and rifampicin (17, 18, 19, 20, 21, 22, 23, 24, 25). Picroliv when given orally to rats 6 - 12 mg/kg for 7 days caused significant reversal of the paracetamol induced biochemical changes which include changes in activities of γ-glutamyl transpeptidases, 5`-nucleotidase, succinate dehydrogenase, glucose-6-phosphatase, cytochrome P_{450} and contents of glycogen and cholesterol in liver. Picroliv was also found to reverse the biochemical changes induced by thioacetamide, galactosamine, aflatoxin B_1, oxytetracycline, alcohol-carbon tetrachloride, rifampicin and ethanol (14, 17, 22, 26). One report suggested that the hepatoprotective activity is due to kutkin and kutkin free fractions are devoid of any activity (16).

Recent reports show that picroliv also prevents the renal ischemia-reperfusion-injury in rats and picroliv preconditioning protects the rat liver against ischemia-reperfusion injury (27, 28).

In clinical studies on patients of infective hepatitis with jaundice, *P. kurroa* led to a rapid fall in serum bilirubin levels towards normal range and quicker clinical recovery with no untoward effect (29).

Anti-inflammatory activity

Kutkin, Picroside I and Kutkoside possess dose dependant anti-inflammatory activity in several acute and chronic test models (30). In adjuvant induced and formaldehyde arthritis in rats and mice, kutkin, Picroside I and Kutkoside were shown to possess significant activity. In carrageenan induced oedema, inhibitory activity was remarkably enhanced upon intra peritoneal treatment in rats. It also inhibited the acetic acid induced vascular permeability in mice and leukocyte migration in rats. Kutkin lacked analgesic, antipyretic or ulcerogenic effect (30). The anti-inflammatory activity is reported to be mediated by a non-neural augmentation of β-adrenoceptor function or consequent cellular events (31, 32, 33). However, recent report shows that the extracts of *P. kurroa* have cyclooxygenase-2 (COX-2) inhibitory activity (34).

Hypolipidaemic activity

Picroliv in albino rats has shown hypolipidaemic activity in normal as well as in triton- and cholesterol-fed rats. Serum lipids were lowered by picroliv (25 mg/kg body weight) in triton WR-1339 induced hyperlipemia. Chronic feeding (6 mg/kg) in normal rats and in animals simultaneously treated with cholesterol (25 mg/kg) for 30 days caused lowering in the lipid and protein levels constituting β-lipoproteins followed by an increase in high density lipoprotein cholesterol in experimental animals. Picroliv altered the lipolytic activities in plasma, liver, heart and adipose tissues and stimulated receptor mediated catabolism of low density lipoproteins. The lipid lowering action is mediated through inhibition of cholesterol biosynthesis in liver, increased faecal bile acid excretion and enhanced plasma lecithin:cholesterol acyl transferase activity (35). In another study, the extracts produced marked reduction in serum cholesterol and coagulation time (36).

Immunostimulant activity

The ethanolic extract showed potent immunostimulatory activity, stimulating both cell-mediated and humoral immunity (37). It also stimulated phagocytosis in experimental animals without producing mitogenic activity (38). The alcoholic extract was shown to inhibit the mast cell anaphylaxis. Mast cell-IgE binding, assessed from induction of passive sensitisation was not affected. Calcium independent early activation events in mast cell anaphylaxis indicated the inhibitory influence of Picrorhiza kurrooa treatment. It also inhibits the membrane protease release. Thus, it was suggested that Picrorhiza kurrooa act as immunostimulant through the alteration of membrane structure function (33).

Oral administration of Picroliv (10 mg/kg for 7 days) in mice prior to immunisation with sheep red blood cells (SRBC) was found to significantly increase hemagglutinating antibody (HA) titre, plaque forming cells (PFC) and delayed hypersensitivity response to SRBC. Picroliv also enhances the non-specific immune response characterised by an increase in macrophage migration index (MMI), (^{14}C) glucosamine uptake, phagocytosis of (^{14}C) leucine labelled E. coli, chemiluminescense of peritoneal macrophages and higher uptake of [^3H] thymidine in the lymphocytes of treated mice (39). Picroliv also selectively augmented human T cell response to mycobacterial protein antigens suggesting it can be used as adjunct to chemotherapy (40).

Antioxidant activity

Picroliv, Picroside I and Kutkoside were studied for their antioxidant activity. These inhibited the non-enzymatic generation of superoxide anion as studied in Phenazine/NADH system. Similarly, it also inhibits the superoxide anion generation in xanthin - xanthine oxidase system and the MDA generation in rat liver microsomes stimulated with ascorbate-ferric system. Thus the activity of these glycosides is like that of superoxide dismutase, metal ion chelators and xanthine oxidase inhibitors (41). The extract of *P. kurroa* has also been reported to have free radical scavenging activity, reducing the hydrogen peroxide-induced cytotoxicity and DNA damage in human non-immortalized fibroblasts. The extracts show a dose-dependent free radical scavenging capacity and a protective effect on DNA cleavage (42).

Antiasthmatic activity

Picrorhiza extracts have beneficial results in management of bronchial asthama (43). Through different chemical and pharmacological methods, phenol glycoside - androsin - was shown to be the active compound preventing allergen and platelet-activating factor induced bronchial obstruction *in vivo* (10 mg/kg,

per oral, 1 hr prior to inhalation challenge) (12). Study of molecular mechanisms suggest that picroliv may act as a protective agent against hypoxia/reoxygenation induced injuries and the mechanism underlying such protection involves a novel signal transduction pathway evidenced by reduction in Protein Kinase C (PKC) and inhibition of protein tyrosine kinase (44).

Anti-allergic effect

Picroliv has anti-allergic and anti-anaphylactic activity. It inhibited passive cutaneous anaphylaxis in mice and rats and protected mast cells from degranulation in a concentration dependant manner independent of histamine receptor blocking activity (45).

Antileishmanial activity

Picroliv was studied for protective effect against *Leishmania donovani* infections in *Mesocricetus auratus* and showed significant antileishmanial activity (39, 46).

Anticancer activity

Cancer chemoprevention of chemically induced tumours by Picroliv, has been studied on 20-methylcholanthrene (20-MC)-induced sarcoma model and 7,12-dimethylbenz-[α]-anthracene (DMBA)-initiated papilloma formation in BALB/c mice. Picroliv at the dose of 100 and 200 mg/kg, p.o inhibited the sarcoma development and exhibited anti-tumour-promoting activity on a two-stage carcinogenesis test on mouse skin using DMBA as an initiator and croton oil as a promoter (47).

Summary

Picrorhiza kurroa is a widely used medicinal plant in traditional and folklore medicine. The main chemical constituents that have been studied in great detail and found to possess the various pharmacological activities are the glycosides, mainly the iridoid glycosides. Picroliv, the standardised glycoside fraction shows most of the activities entitled for the drug. The plant has hepatoprotective, anti-inflammatory, antilipidaemic, immunostimulant, antiallergic and antiasthamatic activity. The plant has the potency and may thus be explored further to the clinic level.

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