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Review Article

A REVIEW ON CHEMICAL CONSTITUENTS AND BIOLOGICAL ACTIVITIES OF THE GENUS *PICRORHIZA (SCROPHULARIACE)*

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ABSTRACT

Picrorhiza (family Scrophulariace), commonly known as 'kukti' is a small perennial herb found in the Himalayan regions of China, Pakistan, India, Bhutan and Nepal at an altitude of 3000-5200 m. Different plant parts and its extract have traditionally been used as a remedy of various ailments such as fever, asthma, jaundice, anemia, abdominal pain, dysentery, cold, stomach problems. Picrorihza has been investigated for its chemical composition and biological activities by various researchers. The major chemical constituents found in this plant were iridoid glycosides, cucurbitacins (triterpenoids) glycosides, phenylethanoid glycosides and phenolics. The Picrorihza has various pharmacological properties, including hepto-protective, antimicrobial, anti-mutagenic, cardio-protective, anti-malarial, anti-diabetic, anti-cancer, anti-inflammatory, anti-ulcer, and neuroprotective and antioxidant activities. A thorough bibliographic investigation was carried out by analyzing worldwide scientific databases including Pub Med, Science Direct, Google Scholar and Wiley online as well as offline sources. The Present review is aimed to provide an updated overview of traditional uses, chemical constituents and biological activities of Picrorihza to explore its therapeutic potentials and to provide bases for future research.

Keywords: Picrorihza, Traditional uses, Phytochemistry, Biological activity, Chemical constitutents

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INTRODUCTION

Natural products have been commonly used as an herbal drug for the treatment of various diseases and disorders from ancient times [1-3]. Natural products are substances or chemical compounds produced by living organisms, usually plants, that have many pharmacological activities [4-7]. Plants produce the vast and diverse array of structurally different organic compounds or secondary metabolites. Biosynthesis of the secondary metabolites is strongly affected by different abiotic and biotic factors. The stress conditions affects secondary metabolites or active ingredients that the plants produce, which are usually the basis for their medicinal activity [8-9]. Secondary metabolites have a wide spectrum of uses ranging from flavoring agents to medicinal values [10]. Thus, natural products (secondary metabolites) have been utilized in both traditional and modern medicine for treating various diseases [11-16]. The majority of rural population mainly depends upon the medicinal plants as a source of remedies [17-20].

The Genus Picrorhiza is well known for its medicinal values belonging to the family Scrophulariaceae having two important endangered medicinal plant species, *Picrorhiza kurrooa Royle ex Benth* and *Picrorhiza scrophulariiflora Pennel*, native of India, Nepal, China, Tibet and Pakistan. *P. kurroa* (Vernacular name-kutki) is predominant in the western Himalayas of Northern India, while *P. scrophulariiflora* is mainly occure in the Himalayan regions of Sikkim, Nepal and Tibet. In India genus Picrorhiza is distributed in alpine region of Kashmir to Sikkim Himalayas [21, 22].

In Ayurvedic medicine system, Picrorhiza is generally used for treatment of disorder of the liver, upper portion of the respiratory tract; to reduce fever, chronic diarrhea, dyspepsia, and scorpion sting [23]. There have been many reports to show a wide spectrum of biological activities having therapeutic importance of its extract and constitutents [24-27]. Different formulations of *Picrorrhiza Kurroa* extract and constituents are available viz-Kutku root powder, *Picrorrhiza kurroa* standardized extract containing 7-14% kutkin, Liver support and Arogya vardhani, etc. Picroliv, a standardized mixture of iridoid glycoside, prepared from alcoholic extract of Picrorhiza *Kurroa* root and rhizome has shown strong hepatoprotective activity against the liver damage caused by various hepato-toxins, it has also been investigated as anti-anaphylactic and anti-allergic [28, 29]. Picrorhiza *Kurroa* root and rhizome contain kutkin as active constitutent. Other identified active constituents are apocyanine, androcine and cucurbitacine glycoside [30, 31]. The constituents of Picrorhiza *kurroa* are reported to show a number of pharmacological activities such as hepatoprotective, anti-allergic, immunemodulatory properties, free radical scavenging, gastric ulcer, anti-allergic and many more [32-35]. P. scrophulariiflora is used for antioxidant and antiradical activities, antidiabetic, anti healing, antiasthmatic, cardioprotective, anticancer and antiulcer activity [36-40].

This study presents the current update on phytochemistry, medicinal uses, biological activities and toxicities of P. kurroa to reveal their pharmacological potentials and lacking that offer scope for future research.

About the genus picrorhiza

The *Picrorhiza* is small genera belonging to the family Scrophulariaceae, having two species namely *P. kurroa Royle ex Benth* and *P. Scorophulariiflora Pennell.* The name Picrorhiza is derived from the Greek word'picro'and 'rhiza', which means bitter root and it is used in native medicine. The specific name derived from Karu, the Punjabi name of the plant, which means bitter as well [41]. *P. kurroa* is a vulnerable, perennial medicinal herb prevalent in alpine region. The plant grows in Himalayan region in moist rock crevices as well as in organic soils. It grows typically on cliffy and sloppy mountains. It is chiefly abundant in Himalayan province i.e. from Garhwal to Bhutan, north Burma, west China and southeast Tibet. The species is found in large quantities in high altitudes ranged between 3000 to 5000 m [42]. The roots of *P. kurroa* are inflexible, almost 6-10 inches long, creeping and bitter in taste. The leaves are oval-shaped, 2-4 inches long, with a sharp apex or serrated. The flowers are pale purple or white in colour, occurring on a long spike. Furthermore, the fruit is about ½inch long and oval shaped. *P. Scorophulariiflora* is a species located in the moist eastern Himalayas having short stamens and a bilabiate corolla, upper lip of which is longer and the lower lip consists of three shorter lobes while *P. Kurroa* has long stamens with a short corolla and five sub-equal lobes [43].

Chemical constituents of picrorhiza

The main chemical constituents' isolated different parts of Picrorhiza species are listed and their bioactivities are described to demonstrate the development in the phytochemistry and therapeutic applications of Picrorhiza genus.

Iridoid glycosides

Medicinally important iridoid glycosides have been isolated and characterized from Picrorhiza: Picroside I, Picroside II, Picroside-III, Picroside-IV, Picroside-V, Veminoside, Catalpol, Veronicoside, Specioside, 6-feruloylcatalpol, Pikuroside, Aucubin etc [44, 45]. These iridoids belong to the family of terpenoids which has more than 30,000 members possessing important biological and physiological functions in plants. Kutkin and picroliv are the main herbal preparation of P. kurroa; Kutkin is a mixture of picroside I and kutkoside in a ratio of 1:2 and other minor glycosides whereas Picroliv is a similar but less purified fraction, containing about 60% of an equal mixture of Picrozide-I and kutkoside [46-48].

Cucurbitacins

These are triterpenoid compounds containing a cucurbitane skeleton characterized as 9β-methyl –19-nor lanosta-5-ene,. Cucurbitacins possess a wide range of biological activities and the present in the form of β-glycosides in plants. A large number of cucurbitacin glycosides have been isolated from Picrorhiza species, mainly from *P. kurroa* [49, 50].

Phenolics

They are precursors and degradation products of lignin, which provide sturdiness to the plant and a physical defense barrier against parasites. Various phenolics isolated from P. kurroa are vanillic acid, apocynin, androsin and picein [50, 51].

Phenylethanoid glycoside

P. scrophulariiflora contains cyclopentanoid monoterpenes, caffeoyl glycosides, phenylethanoid glycoside and plantamajoside [52, 53].

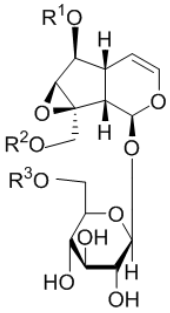
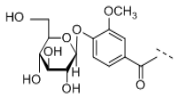
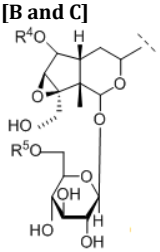
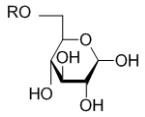
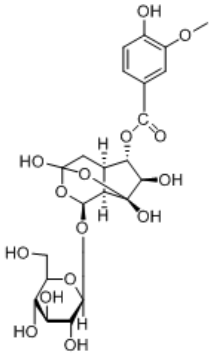
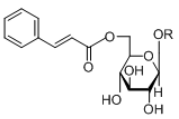
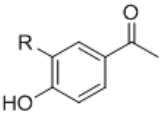
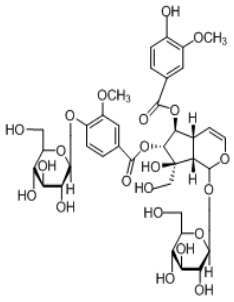
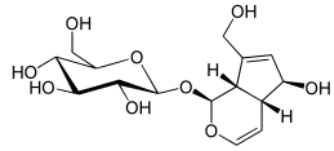
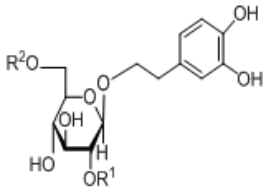
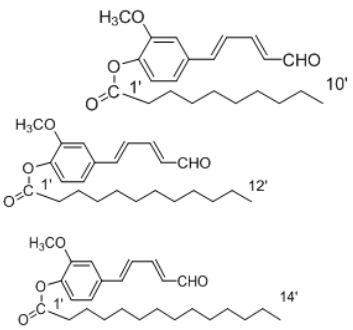
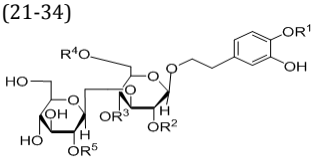
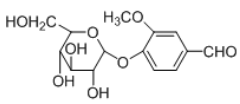
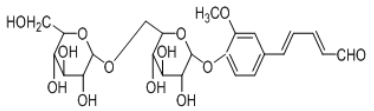
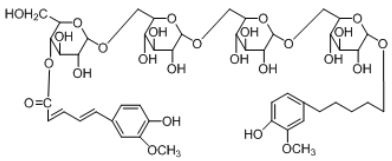
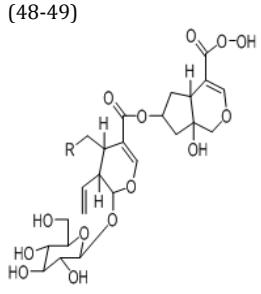
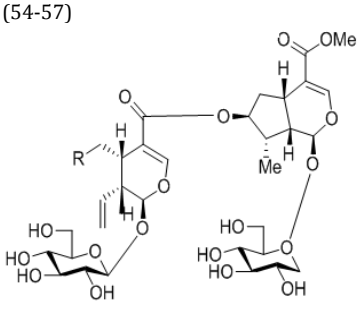
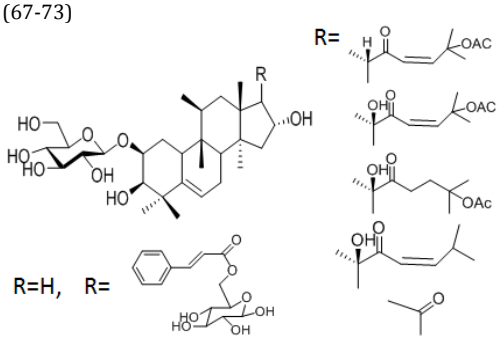
The major classes of chemical compounds isolated from Picrorhiza species-*P. kurroa (P. K)* and *P. Scorophulariiflora* (P. S*)* are listed in table 1.

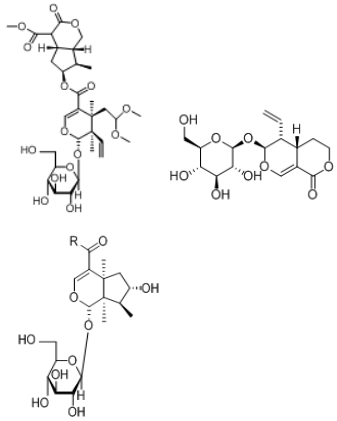
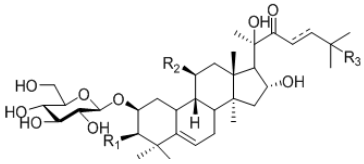
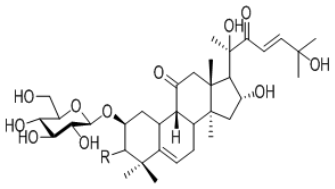
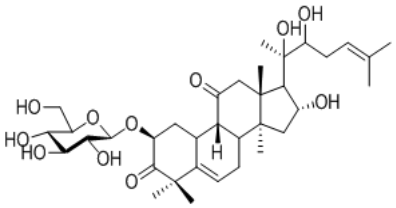
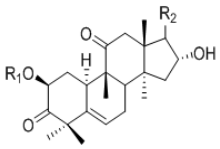
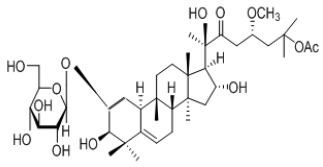
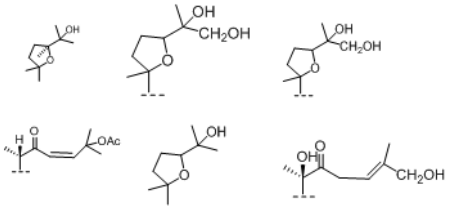
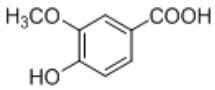
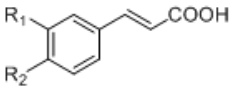
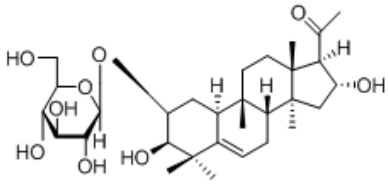
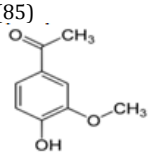
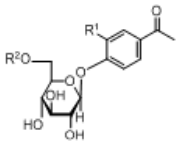
Table 1: Chemical constituents Isolated from picrorhiza species and bioacitives

Glycoside **Compound/ Name**	**Plant part/solvent of extraction**	**Bio-activities**	**Reference**
Iridoid Glycoside; Picroside-I: [(2R,3S,4S,5R,6S)-3,4,5-trihydroxy-6-[[(1S,2S,4S,5S,6R,10S)-5-hydroxy-2-(hydroxymethyl)-3,9-dioxatricyclo[4.4.0.02,4]dec-7-en-10-yl]oxy]oxan-2-yl]methyl (E)-3-phenylprop-2-enoate,(1)	Rhizomes of P. K/ Methanol, Methanol: water(1:1) P. S/Ethanol,	Hepto-Protective Activity, Collagenase Inhibitory Activities Anticancer Activity; Antiarthritis Activity; Antidiabetic Activity;	[44, 45, 54, 55, 56]
Iridoid Glycoside; Picroside-II: [(1*S*,2*S*,4*S*,5*S*,6*R*,10*S*)-2-(hydroxymethyl)-10-[(2*S*,3*R*,4*S*,5*S*,6*R*)-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]oxy-3,9-dioxatricyclo[4.4.0.0[2,4]]dec-7-en-5-yl] 4-hydroxy-3-methoxybenzoate, (2)	Rhizomes of P. K/ Methanol, Methanol: water (1:1) P. S/Ethanol	Collagenase Inhibitory Activities, Antiarthritis Activity, Antidiabetic Activity, Hepatoprotectiv Activity.	[57, 58]
Iridoid Glycoside; Picroside-III: [(1*S*,2*S*,4*S*,5*S*,6*R*,10*S*)-2-(hydroxymethyl)-10-[(2*S*,3*R*,4*S*,5*S*,6*R*)-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]oxy-3,9-dioxatricyclo[4.4.0.0[2,4]]dec-7-en-5-yl] (*E*)-3-(4-hydroxy-3-methoxyphenyl)prop-2-enoate (3)	Rhizomes of P. K/ Methanol; Ethanol P. S/Ethanol	Collagenase Inhibitory Activities Antimicrobial Activity; Anticancer Activity	[59]
Iridoid Glycoside; Picroside-IV: 2R,3S,4S,5R,6S)-3,4,5-trihydroxy-6-[[(1S,2S,4S,5S,6R,10S)-5-hydroxy-2-(hydroxymethyl)-3,9-dioxatricyclo[4.4.0.02,4]dec-7-en-10-yl]oxy]oxan-2-yl]methyl (E)-3-(4-hydroxyphenyl)prop-2-enoate,(4)	Rhizomes of P. S/ Butanol	Collagenase Inhibitory Activities antidiabetic Activity; Antimicrobial Activity	[63]
Iridoid Glycoside; Picroside-V: [6-M Methoxy benzoyl catalpol) (5)	Rhizomes of P. K/EtOAc	-----	[60]
Iridoid Glycoside; Catalpol: (1a*S*,1b*S*,2*S*,5a*R*,6*S*,6a*S*)-6-Hydroxy-1a-(hydroxymethyl)-1a,1b,2,5a,6,6a-hexahydrooxireno [2′,3′:4,5]cyclopenta[1,2-*c*]pyran-2-yl β-D-glucopyranoside, (6)	Rhizomes of P. S/ Butanol	------	[58, 88]
Iridoid Glycoside; 6-feruloyl catalpol: (2S,3R,4S,5S,6R)-2-[[(1S,2R,4S,5S,6R,10S)-5-[(E)-2-(4-hydroxy-3-methoxyphenyl) ethenoxy]-2-(hydroxymethyl)-3,9-dioxatricyclo[4.4.0.02,4]dec-7-en-10-yl]oxy]-6-(hydroxymethyl)oxane-3,4,5-triol, (7)	Rhizomes of P. K/ EtOAc	Collagenase Inhibitory Activities	[60, 61, 88]
Iridoid Glycoside; Minecoside: [(1*S*,2*S*,4*S*,5*S*,6*R*,10*S*)-2-(hydroxymethyl)-10-[(2*S*,3*R*,4*S*,5*S*,6*R*)-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]oxy-3,9-dioxatricyclo[4.4.0.0[2,4]]dec-7-en-5-yl] (*E*)-3-(3-hydroxy-4-methoxyphenyl)prop-2-enoate (8)	Rhizomes of P. K/ EtOAc	----	[61, 88]
Iridoid Glycoside; Kutkoside: [5-hydroxy-10-[3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]oxy-3,9-dioxatricyclo[4.4.0.0[2,4]]dec-7-en-2-yl]methyl 4-hydroxy-3-methoxybenzoate, (9)	Rhizomes of P. K/ Methanol	----	[62]
Iridoid Glycoside; Veronicoside: [(1*S*,2*S*,4*S*,5*S*,6*R*,10*S*)-2-(hydroxymethyl)-10-[(2*S*,3*R*,4*S*,5*S*,6*R*)-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]oxy-3,9-dioxatricyclo[4.4.0.0[2,4]]dec-7-en-5-yl] benzoate (10)	Rhizomes of P. S/ EtOAc	----	[62]
Iridoid Glycoside; Specioside: [(1*S*,2*S*,4*S*,5*S*,6*R*,10*S*)-2-(hydroxymethyl)-10-[(2*S*,3*R*,4*S*,5*S*,6*R*)-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]oxy-3,9-dioxatricyclo[4.4.0.0[2,4]]dec-7-en-5-yl] (*E*)-3-(4-hydroxyphenyl)prop-2-enoate, (11)	Rhizomes of P. S/Butanol	----	[63]

Glycoside Compound/ Name	**Plant part/solvent of extraction**	**Bio-activities**	**Reference**
Iridoid Glycoside; Pikuroside: [(1*R*,4*S*,5*R*,6*S*,7*R*,8*S*,9*S*)-4,5-dihydroxy-9-[(2*S*,3*R*,4*S*,5*S*,6*R*)-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]oxy-2,10-dioxatricyclo[5.3.1.0[4,8]]undecan-6-yl] 4-hydroxy-3-methoxybenzoate, (12)	Rhizomes of P. K/ EtOAc	----	[64]
Iridoid Glycoside; Aucubin: [(2*S*,3*R*,4*S*,5*S*,6*R*)-2-[[(1*S*,4*aR*,5*S*,7*aS*)-5-hydroxy-7-(hydroxymethyl)-1,4*a*,5,7*a*-tetrahydrocyclopenta[c]pyran-1-yl]oxy]-6-(hydroxymethyl)oxane-3,4,5-triol, (13)	Rhizomes of P. S/ Methanol	----	[58]
Iridoid Glycoside; Picrorhizaoside-A, (14) Iridoid Glycoside; Picrorhizaoside-B, (15) Iridoid Glycoside; Picrorhizaoside-C, (16) Iridoid Glycoside; Picrorhizaoside-D, (17) Iridoid Glycoside; Picrorhizaoside-E,(18) Iridoid Glycoside; Picrorhizaoside-F, (19) Iridoid Glycoside; Picrorhizaoside-G, (20)	Rhizomes of P. K/methanol	Hyaluronidase inhibitory activity	[66]
Phenylethanoid Glycosides; Kurroaoside-A,(21) Phenylethanoid Glycosides; Kurroaoside-B, (22) Phenylethanoid Glycosides; Kurroaoside-C,(23)	Rhizomes of P. K/methanol	Collagen synthesis-promoting and collagenase inhibitory activities	[67, 101,
Phenylethanoid Glycosides: Calceolarioside-A, (24) Phenylethanoid Glycosides: Calceolarioside-B, (25)	Rhizomes of P. K/methanol	Antibacterial scavengers of reactive oxygen species	102]
Phenylethanoid Glycosides: Plantamajoside (26)	Roots of P. S/Butanol	----	[63]
Phenylethanoid Glycosides: Isoplantamajoside, (27)	Roots of P. S./Butanol	----	
Phenylethanoid Glycosides: Scroside D (2-(3-Hydroxy-4-methoxyphenyl)ethyl 3-O-β-B-glucopyranosyl-β-D-glucopyranoside 4-[(2E)-3-(4-Hydroxy-3-methoxyphenyl)prop-2-enoate] (28)	Stems of P. S/EtOAc	Immunomodulatory activity	67
Phenylethanoid Glycosides: Scroside E (2-(3-Hydroxy-4-methoxy phenyl)ethyl-3-O-β-D-Glucopyranosyl-β-D-glucopyranoside 6-[(2E)-3-(4-Hydroxy-3-methoxyphenyl)prop-2-enoate] (29)			
Phenylethanoid Glycosides: Scroside A, 6-[(2E)-3-(3-hydroxy-4-methoxyphenyl)-2-propenoate]2-(3-hydroxy-4-methoxyphenyl)ethyl O-β-D-glucopyranosyl-(1→2)-O-β-D-glucpyranosyl-(1→3)-β-D-glucopyranoside (30)	Root s of P. S/Butanol	---	[88]
Phenylethanoid Glycosides: Scroside B, 6-[(2E)-3-(3-hydroxy-4-methoxyphenyl)-2-propenoate] 2-(3-hydroxy-4-methoxy phenyl)ethyl 3-O-β-D-glucopyranosyl-β-D-glucopyranoside (31)			
Phenylethanoid Glycosides: Scroside C, 4-[(2E)-3-(3-hydroxy-4-metho xyphenyl)-2-propenoate]2-(3-hydroxy-4-methoxyphenyl)ethyl O-β-D-glucopy ranosyl-(1→2)-O-β-D-glucopyranosyl-(1→3)-β-D-glucopyranoside (32)			
Phenylethanoid Glycosides: Hemiphroside-A, 2-(3-Hydroxy-4-methoxyphenyl) ethyl 3-O-β-D-Glucopyranosyl-β-D-glucopyranoside 4-[(2E)-3-(4-Hydroxy-3-methoxyphenyl)β-prop-2-enoate (33)	Stems of P. S/Methanol	---	[67]
Phenylethanoid Glycosides: ChionosideJ, (34)		----	
Glycopyranoside: 6-O(E) Cinnamoyl β-D glycopyranoside, (35)	Roots of P. S/Methanol	----	
Glycopyranoside: Methyl 6-O(E) feruloylyl β-D glycopyranoside, (36)		---	
Glycopyranoside: 6-O(E) Cinnamoyl β-D glycopyranoside, (37)		---	
Quninol Glycoside: Herbitol III. (38) Quninol Glycoside: Scrophuloside (39)	Roots of P. S/Methanol	---- ----	
4 hydroxy acetophenone (40)	Roots of P. S/Methanol	----	
4-hydroxy, 3 methoxy acetophenone (41)	Roots of P. S/Methanol/Ethanol	Antidiabetic	
Capryl vanillic acid); 3-methoxy-4-decanoxy benzoic acid (42)	Rhizomes of P. K/methanol	----	[68]
Lauryl picraldehyde; 3-methoxy-4-dodecanoxyphenyl-n-pent7, 9-dien-11-al (43)		----	
Myristyl picraldehyde); 3-methoxy-4-tetradecanoxy-phenyl n-pent-7, 9–diene-11-al (44)		----	
α-glucovanillin; vanillin-α-D-glucopyranoside (45)		----	
Picraldehyde α-D-diglucoside; picraldehyde 4-O-α-Dglucopyranosyl-(6′→1′′)-O-α-D-glucopyranoside (46)		----	
Picrortetra-glucoside; (47)		----	
3-methoxy-4-hydroxyphenyl-nbutanyl-α-O-D-glucopyranosyl-(6a→1b)-α-O-Dglucopyranosyl-(6b→1c)-α-O-D-glucopyranosyl-(6c→1d)-αO-D-glucopyranosyl-4d-3′-methoxy-4′-hydroxyphenyl n-pent7′,9′-dien-11′-oate			

Glycoside **Compound/ Name**	**Plant part/solvent of extraction**	**Bio-activities**	**Reference**
Iridoid Glycoside; Abeloside A (48) Iridoid Glycoside; Abeloside B, (49) Iridoid Glycoside; Sylvestroside IV dimethyl acetal, (50) Iridoid Glycoside; Sweroside, (51) Iridoid Glycoside; 8-Epi-Loganin, (52) Iridoid Glycoside; 8-Epi-Loganic acid, (53) Bis-Iridoid Glycoside; Saungmaygaoside A, (54) Bis-Iridoid Glycoside; Saungmaygaoside B, (55) Bis-Iridoid Glycoside; Saungmaygaoside C, (56) Bis-Iridoid Glycoside; Saungmaygaoside D, (57)	Stems of P. K/n-butanol	Anti-Vpr activity	[69, 104]
Cucurbitacins glycosides			
2-O-glycoside of cucurbitacin B: (25-acetoxy-2-beta-glucosyloxy-16,20-dihydroxy-9-methyl-19-norl anosta-5, 23-diene-3,11,22-trione) (58)	Roots of P. K/EtOAc	-----	[65]
2-O-glucoside of 23,24 didydrocucurbitacin B: (25-acetoxy-2-beta-glucosyloxy-16,20-dihydroxy-9-methyl-19-norl anost-5-ene-3, 11-22-trione) (59)		-----	
2-beta-glucosyloxy-3,16,20,25-tetrahydroxy-9-methyl-19-norlanos ta-5, 23-diene-22-one, (60)		-----	
2-beta-glucosyloxy-3,16,20,25-tetrahydroxy-9-methyl-19-norlanos t-5-ene-22-one, (61)		-----	
the 2-O-glucoside of cucurbitacin Q (25-acetoxy-2-beta-glucosyloxy-3,16,20-trihydroxy-9-methyl-19-norlanosta-5, 23-diene-11,22-dione), (62)		-----	
2-O-glucoside of deacetoxycucurbitacin B (2-beta-glucosyloxy-16,20-dihydroxy-9-methyl-19-norlanosta-5, 24-diene-3,11,22-trione) (63)		-----	
Arvenin III: 2β-glucosyloxy-3,16,20,25-tetrahydroxy-9-methyl-19-norlanosta-5,23-diene-11,22-dione and 2β-glucosyloxy-16,20, 22-trihydroxy-9-methyl-19-norlanosta-5,24-diene-3,11-dione, are new and one, (64)	Roots of P. K/Butanol	-----	[70]
2 β-glucosyloxy-3,16,20,25-tetrahydroxy-9-methyl-19-norlanosta-5,23-diene-11,22-dione (65)		-----	
2-β-glucosyloxy-16,20,22-trihydroxy-9-methyl-19-norlanosta-5,24-diene-3,11-dione (66)		-----	
25-(acetyloxy)-2-(β-D-glucopyranosloxy)-3,16,-dihydr oxy-9-methyl-19-norlanosta-5,23-dien-22-one (67)	Roots of P. K/EtOAc	-----	[63]
25-(acetyloxy)-2-(β-D-glucopyranosyloxy)-3,16,20-trihydr oxy-9-methyl-19-nor lanosta-5, 23(Z)-dien-22-one (68)		-----	
25-(acetyloxy)-2-(β-D-glucopyranosyloxy)-3,16,20-trihy droxy-9-methyl-19-norlanost-5-en-22-one (69)		-----	
2-(β-D-glucopyranosyloxy)-3,16,20 trihydroxy-9-methyl-19-norlanosta-5, 24-dien-22-one (70)		-----	
2-(β-D-glucopyranosyloxy)-3,16-dihydroxy-4,4,9,14-tetra methyl-19-norpregn-5-en-20-one (71)		-----	
2,3,16,20,25-pentahydroxy-9-methyl-19-norlanost-5-en-22-one (72)		-----	
2-(6-O-cinnamoyl-β-D-glucopyranosyloxy)-3,16,20, 25-tetrahydroxy-9-methyl-19-norlanost-5-en-22-on (73)		-----	
(2β,9β,10α,16 α,20ϵ,24 ϵ)-20, 24-epoxy-2-(β-D-glucopyranosyloxy)-16,25-dihydroxy-9-methyl-19-norl anost-5-ene-3,11-dione (74)	Roots of P. K/methanol	-----	[64]
2 β,3β,9β,10α,16α,20ϵ, 24ϵ)-20,24 epoxy-2-(β-D-glucopyranosyloxy)3,16,25-trihydroxy-9-methyl-19-norla nosta-5-ene-11-one (75)		-----	
(2β,9 β,10α,16α,20ϵ,24ϵ)-20,24-epoxy-2-(β-D-glucopyrano-syloxy)-16,25,26-trihydroxy-9-methyl-19-norlanost-5-en-3,11-dione (76)		-----	
(2β,3β,9β,10α,16α, 20ϵ,24ϵ)-20,24-epoxy-2-(β-D-glucopyranosyloxy)-3,16, 25, 26-tetrahydroxy-9-methyl-19-norlanost-5-en-11-one (77)		-----	
(2β,9β,10α,16α,20β,24Z)-2-(β-D-glucopyranosyloxy)-16,20,26-trihydroxy-9-methyl-19-norlanost-5,24-diene-3,11-dione (78)		-----	
(2 β,9β,10α,16α,20β,24Z)-2-(β-D-glucopyranosyloxy)-3,16,20, 26-tetrahydroxy-9-methyl-19-norlnost-5,24-diene-11-one (79)		-----	
Cucurbitane-type triterpene glycoside; Kurroaoside D, (80)	Roots of P. K/methanol	Collagenase inhibitory activities	[67]
Nortriterpene glycoside; 25-acetoxy-2-β-D-glucopyranosyloxy-3,16,20-trihydroxy-9-methyl-19-norlanosta-5-en-22-one, (81)	Roots P. K/methanol	Anti-tumorous activities and collagenase inhibitory activities	[67]
Phenolics			
Vanillic acid: 4-hydroxy-3-methoxybenzoic acid (82)	Rhizomes of P. K/methanol, P. S with ethanol	----	[49]
Ferullic acid: (E)-3-(4-hydroxy-3-methoxyphenyl) prop-2-enoic acid (83)	Rhizomes of P. K/95% ethanol	----	[72, 73]
Isoferullic acid: (E)-3-(3-hydroxy-4-methoxyphenyl) prop-2-enoic acid (84)	Rhizomes of P. K/95% ethanol	----	[72, 73]
Apocynin: 1-(4-Hydroxy-3-methoxyphenyl)ethan-1-one	Rhizomes of P.		[74]

Glycoside Compound/ Name	Plant part/solvent of extraction	Bio-activities	Reference
(85) Picein 1-[4-[(2*S*,3*R*,4*S*,5*S*,6*R*)-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]oxyphenyl]ethanone (86) Androsin 1-[3-methoxy-4-[(2*S*,3*R*,4*S*,5*S*,6*R*)-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]oxyphenyl]ethanone (87)	K/methanol, Rhizomes of P. K/methanol, Rhizomes of P. K/methanol,	Anti-inflammatory ---- anti-asthmatic properties	[61] [61, 58]
(1-20)  **[A]**  **[B and C]**  B: R_4=H, R_5=Cin C: R_4= Fer R_5=H  35: R= Cin, 36: R= Fer	**(1):** R^1= H, R^2=H,R^3=Cin, **(2)** R^1= Van, R^2=H,R^3=H, **(3):** R^1= H, R^2=H,R^3=Fer, **(4):** R^1= H, R^2=H,R^3=Cin **(5):** R^1= m-MeO-benzoyl, R^2=H,R^3=H, **(6):** R^1= H, R^2=H,R^3=H, **(7):** R^1=Fer, R^2=H,R^3=H, **(8):** R^1= IFer, R^2=H,R^3=H, **(9):** R^1= H, R^2=Van,R^3=H **10):** R^1=benzoyl, R^2=H,R^3=H, **(11):** R^1=p-hydroxy Cin, R^2=Van,R^3=H, **(14):** R^1= Van, R^2=H,R^3= α-Glc, **(15):** R^1= α-Gal, R^2=H,R^3=Cin, **(16):** R^1= H, R^2=H,R^3=A, **(18):** R^1= Van, R^2=B,R^3=H, **(19):** R^1= Van, R^2=H,R^3=B, **(20):** R^i=Van, R^2=H,R^3=C, (12)   37: R= CH_3 38: R=1-O mannityl  40: R= H, 41: R= OCH_3	(17)  **24: R^1= H, R^2=Caf** **25: R^1= Caf, R^2=H**   (42-44) 	(21-34)  (21)-R^1= H, R^2=H, R^3=Fer, R^4=H, R^5=β-Glc (22)-R^1= H, R^2=H, R^3= H, R^4= Fer, R^5=β-Glc, (23)-R^1=C H_3, R^2= β-Gal, R^3=Fer,R^4=H, R^5= H, (26)-R^1= H, R^2=H, R^3=Caf,R^4=H, R^5=H, (27)-R^1= H, R^2=H, R^3=H,R^4=Caf, R^5=H, (28)-R^1= H, R^2=H, R^3=Fer,R^4=H, R^5=H,, (29)-R^1= H, R^2=H, R^3=H,R^4=Fer,R^5=H, (30)-R^1= CH_3, R^2=H, R^3=H,R^4=Fer, R^5=β-Glc, (32)-R^1= CH_3, R^2=H, R^3=H,R^4=Fer, R^5=β-Glc, (33)-R^1= CH_3, R^2=H, R^3=Fer,R^4=H, R^5=H (34)-R^1= H, R^2=H, R^3=Caf, R^4=H, R^5=β-Glc. [Cin; Cinnamoyl; Van: Vanillyl, Fer: Feruloyl; Cou: p-coumaroyl, IFer: Isoferuloyl; Caf: caffeoyl] α-Glc: α-D-glucopyranosyl, β-Glc: β-D-glucopyranosyl, α-Gal: α-D-galactopyranosyl, β-Gal: β-D-galactopyranosyl, (45-47)   
(48-49)  R= CHO, R=CH(OMe)$_2$	(54-57)  R=COOH, R= CHO, R=CH_2OH R=CH(OMe)$_2$	(67-73)  64:R=O, 65: R=OH
(50-53)	(58-63)	

Glycoside Compound/ Name	Plant part/solvent of extraction	Bio-activities	Reference
 R=-O-, R= OH (74-79)	 (58)R_1=O,R_2=O,R_3=OAc (59)R_1=O,R_2=O,R_3=OAc (60)R_1=OH,R_2=OH,R_3=OAc (61)R_1=OH,R_2=OH,R_3=OAc (62) R_1=OH,R_2=H,R_3=OH (63) R_1=OH,R_2=O,R_3=OAc	 (66)  (81)	
 R_1= β-D-Glc R_2= (80) 	 (82)  (83): R^1= OCH3, R^2=OH 84: R^1= OH, R^2=OCH3, 	 (85)  **86:** R^1= H, R^2=H,  87: R^1= OCH_3, R^2=H, 39: R^1= OCH_3, R^2=Cou,	

Biological activates

The wide range of biological activities of extracts and isolated chemical constitutents of P. kurroa include anti microbial [75], hepato protective [76], antioxidant activity [77], anticancer [78], anti arthritic [80], anti diabetic [87], anti-mutagenic, cardio-protective, anti-malarial, anti-inflammatory, anti-ulcer, anti-asthmatic activity [79], immunomodulatory activity, hypo lipemic activity and nephro-protective activity.

Antimicrobial activity

An antimicrobial activity was observed in the ethanol and methanol extracts of Picrorhiza kurroa rhizome against selected bacterial strains. Ethanol extract of Picrorhiza kurroa rhizome showed high antibacterial activity against E. coli, B. cereus, S. aureus, K. pneumoniae, S. Typhi and, S. pyogens. The methanol rhizome extracts showed high antibacterial activity against S. aureus and P. aeruginosa, whereas acetone and hexane extract showed intermediate activity against E. coli, S. aureus, B. cereus, K. pneumoniae, S. typhi, P. aeruginosa and S. pyogens by P. Vinoth Kumar *et al.* [81] Usman *et al.*, evaluated the antimicrobial potential of Picrorhiza. They conducted an *in vitro* study on different bacterial starins such as gram-positive bacteria-Staphylococcus aureus and Bacillus subtilis and gram-negative bacteria-Escherichia coli and Pseudomonas aeruginosa and Aspergillus niger, Malasseiza furfur and Candida albicans fungal strains. It was observed that ethanolic extract of this plant showed efficient action against all the used strains of microbes, which suggests its use an anti-microbial [82]. Antimicrobial activity of methanol extract of Picrorhiza kurroa was also investigated by Sharma *et al.*, [83] observed that it was more potent actions against bacterial strain (E. coli, B. subtilis, S. aureus) than antibacterial drug ciprofloxacin and aqueous extract was found to be more effective against fungal strain (A. niger, C. albicans) than Fluoconazole which is a standard antifungal drug.

Hepatoprotective activity

Picroliv, possess hepatoprotective activity. Alcohol-fed rats reduced the viability of isolated hepatocytes, reduced the levels of alcohol-metabolizing enzymes (acetaldehyde dehydrogenase, aldehyde dehydrogenase) in rat hypatocytes and also produced cholestasis, as indicated by the reduction in bile volume, bile salts and bile acids. After treatment with Picroliv all these altered parameter were restored. A hydroalcholic extract of P. kurroa has been shown to be effective against

non-alcoholic fatty liver disease by reversal of the fatty infiltration of the liver and a lowering of the quantity of hepatic lipids [84].

P. Kurroa alcoholic extract have also show hepatoprotective activity. Plant is a potent immune stimulant of both hormonal immunity and cell-mediated and shows choleretic activity in dogs. Picrorhiza kurroa is also beneficial in the management of bronchial asthma. The crude extract, and the isolated bioactive of the roots have shown to protect the liver from various types of drug-induced injury [85]. Hepatoprotective activity of Picrorhiza kurroa was investigated by Shetty *et al.*, on male Wistar rat models. The administration of hydroalcoholic extract for 4 w at the dosage of 200 mg/kg and 400 mg/kg showed potent hepatoprotective actions by restoring all the changes in the liver induced in the liver [86].

Anti-inflammatory activity

Anti-inflammatory activity of extract of Picrorhiza kurroa was evaluated by Kumar *et al.*, on rat models, suggested that this plant is a potent source of anti-inflammatory drug [87]. Apocynin possess anti-inflammatory properties. The rhizome of Picrorhiza scrophulariiflora is used to treat inflammatory diseases as a traditional medication and its ethanol extract improves accelerated atherosclerosis through inhibition of redox-sensitive inflammation in rabbits [89].

Immunomodulatory activity

The effect of an ethanolic extract of the drug was studied on delayed type hypersensitivity, skin allograft rejection, humoral responses to sheep RBC and phagocytic activity of the reticuloendothelial system in mice. Picrorhiza kurroa was found to be a potent immune stimulant of both cell-mediated and humoral activity [103]. As per the Hussain *et al.*, *in vivo* study report Picrorhiza kurroa is associated with immunomodulatory activities. The study was carried out on immunosuppressed mice models. Cyclophasphamide was induced in the models for immunosuppression. The study concluded that the alcoholic plant extract is significantly works on the enhancement on immunostimulant activities [90].

Antioxidant activity

Kalaivani *et al.*, conducted an *in vitro* study to evaluate the antioxidant and free radical scavenging potential of Picrorhiza kurroa. It was observed that ethanolic extract of this plant showed significant anti-oxidant properties due to the presence of flavonoid and phenolic compounds [91]. The butanol extract of P. kurroa leaves were evaluated for antioxidant activity against two assays, 2,2-diphenyl-1-picrylhydrazyl radical and 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulphonic acid) assay. Compounds, luteolin-5-O-glucopyranoside and picein were also shown the antioxidant activity by kant *et al.* [92]

Anti-diabetic activity

Anti-diabetic activity of Picrorhiza extract was found to lower blood glucose in laboratory animals. Chronic administration of the extract significantly reduced blood sugar in alloxan-induced diabetic rats for 10 d. The extract was also to find to reduce the increased blood urea nitrogen and serum lipid peroxides in alloxan-induced diabetic animals and to inhibit the bodyweight reduction and leukopenia induced by alloxan administration [93]. Kumar *et al.*, evaluated the antihyperglycemic effects and improved renal and hepatic functions in the hydroalcoholic extract of *P. kurroa* rhizome. It is observed that extract possesses increased insulin-stimulated glucose uptake potential [94]. Husain *et al.*, conducted an *in vivo* study on rat models to investigate the antidiabetic potential of Picrorhiza kurroa. The models were administered with streptozotocin nicotinamide to induce diabetes mellitus. The oral administration of standardized aqueous extract effectively helped in restoring all the changes induced by streptozotocin nicotinamide which suggests Picrorhiza kurroa use as an antidiabetic agent [95, 96].

Anticancer

Rajeshkumar *et al.*, conducted an *in vivo* study on BALB/c mice models for the evaluation of the anti-cancer activity of Picrorhiza kurroa. Sarcoma was induced by 20- methylcholanthrene (20- MC) in models and papilloma formation was initiated by 7,12 dimethylbenz[a]anthracene (DMBA) in the models. The oral administration of picroliv (100 and 200 mg/kg, p. o) showed inhibitory actions against 20 - MC and DMBA by decreasing sarcoma and papilloma. This study suggested that picroliv is a potent anti-cancer agent [97].

Anti-mutagenic

As per the reported study conducted by Zaberi *et al.*, hydroalcoholic extract of Picrorhiza kurroa is associated with antimutagenic actions. It was found that hydroalcoholic extract exhibited inhibitory actions against Salmonella typhimurium MTCC 1251 and MTCC 1252 strains by direct-acting mutagen of sodium azide [98].

Antiviral activity

The n-butanol extract of Picrorhiza kurroa stems was assayed for anti-Vpr activity using TREx-HeLa-Vpr cells. Among the isolates, sylvestroside IV dimethyl acetal, saungmaygaoside D and sweroside were the most potent inhibitors with effective doses of 5 and 10 μM, respectively, without showing any notable cytotoxicities [99].

Anti-collagenase activity

A methanol extract of Picrorhiza kurroa rhizomes along with picrosides I II, III, and IV and 6-feruloylcatalpol, phenylethanoid glycosides, triterpene glycosides, cucurbitacin B 2-O-β-D-glucopyranoside and 25-acetoxy-2-β-D-glucopyranosyloxy-3,16,20-trihydroxy-9-methyl-19-norlanosta-5-en-22-one, and an acetophenone glycoside, picein, exhibited collagenase inhibitory activity at 10–30 μM, with no cytotoxicity being observed at the effective concentrations [67].

RESULTS AND DISCUSSION

Genus Picrorhiza (family Scrophulariaceae) has great importance in Ayurvedic system of medicines. Picrorhiza species accumulate cucurbitacin glucosides, iridoid glucosides, phenylethanoid glucosides, and phenolics. Its two species P. kurroa and P. scrophulariiflora have so much similarity due to the presence of similar active constituents like picroside-I, picroside-II, kutkoside while P. scrophulariiflora contains some additional phenylethanoid glycoside and plantamajoside, which are absent in the species P. kurroa. So, the P. scrophulariiflora is closely related to P. kurroa and used as a substitute or adulterants. Thus, reviewing the genus Picrorhiza it is clear that the lot of work has been done on species P. kurroa in comparison to other species P. scrophulariiflora. However, more research is needed to know about the chemical constituents of P. scrophulariiflora and its biological activities.

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Nil

AUTHOR CONTRIBUTION

All the work has been carried out by me.

CONFLICTS OF INTERESTS

Declared none

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