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PICRORHIZA KURROA ROYLE EX BENTH: UNLOCKING ITS HEPATOPROTECTIVE POTENTIAL THROUGH PHYTOCHEMICAL AND MOLECULAR INSIGHTS

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ABSTRACT

Picrorhiza kurroa Royle ex Benth. is an endangered medicinal herb of Himalayas used extensively in traditional medicine for the treatment of liver disorders. The review describes the botanical characters, ethnomedicinal uses, phytochemical constituents, pharmacological activities and hepatoprotective mechanisms. The plant is a good source of bioactive iridoid glycosides, especially picroside I, picroside II, kutkoside, apocynin and androsin, which show antioxidant, anti-inflammatory, antifibrotic, immunomodulatory and lipid regulating properties. These phytoconstituents offer hepatoprotective effects by decreasing oxidative stress, reducing inflammation, inhibiting apoptosis and regulating the lipid metabolism in the liver. Molecular docking studies also confirm the hepatoprotective potential of these compounds especially kutkoside by favorable binding to key liver related targets. Evidence-based therapeutic development of P. kurroa requires sustainable conservation, quality control standardization, and further pre-clinical and clinical studies.

KEYWORDS: *Picrorhiza Kurroa*, Hepatoprotective, molecular docking, Picroside I, Picroside II, Kutkoside.

INTRODUCTION

Picrorhiza kurroa Royle ex Benth. (Plantaginaceae family formerly Scrophulariaceae).[1,2] is a famous and highly valued medicinal herb found in the alpine regions of the Himalayas. The plant *Picrorhiza kurroa* is locally known as 'Kutki' or 'Katuka' in Ayurveda and has been traditionally used for the treatment of hepatic, gastrointestinal, inflammatory, respiratory and metabolic disorders.[3] The therapeutic fame of P. kurroa is based on its bitter-tasting rhizomes and roots with high concentration of bioactive iridoid glycosides called 'kutkin'.[4] The herb is described as a strong cholagogue, laxative, stomachic and antiperiodic agent in traditional systems of medicine, such as Ayurveda, Unani and Traditional Chinese Medicine (TCM).[5] Over the past few decades, numerous ethnobotanical claims have been increasingly validated by modern pharmacology, which has demonstrated the herb's robust hepatoprotective, immunomodulatory, anti-inflammatory, and antioxidant activities.[6] However, the increasing global demand for its bioactive secondary metabolites has resulted in indiscriminate harvesting and over-exploitation of natural populations, leading to a sharp decline of the species in its native Himalayan habitat.[15] P. kurroa occurs naturally in very specific and fragile alpine ecosystems, and ruthless uprooting has led to serious depletion of its native habitats, and it has been listed as an endangered species by the International Union for Conservation of Nature (IUCN).[7] The current review is focused on summarizing the available literature on the geographical distribution, botanical description, morphology, ethnobotanical uses, phytochemical profile, and pharmacological advances of P.kurroa to promote future conservation and clinical work.

Geographical Distribution

Picrorhiza kurroa is a native medicinal herb in the alpine and sub-alpine regions of the Hindu Kush–Himalayan mountain range with a natural distribution in northwestern India, Nepal, Bhutan, northern Pakistan, and southeastern Tibet (China).[8] Typically, the species is found between 3000 and 5000 m above mean sea level in moist alpine meadows, rocky slopes, glacial moraines and other high-altitude habitats above the tree line.[9,10] The natural populations in India are largely confined to the Himalayan states of Jammu and Kashmir, Himachal Pradesh and Kumaon and Garhwal regions of Uttarakhand including Chamoli, Tungnath and Ukhimath.[11,12] The plant is adapted to the cold alpine climatic conditions with low temperature and long-lasting snow cover affecting its growth, distribution and rhizome development. Such environmental conditions also contribute to the accumulation of bioactive metabolites in P. kurroa.[13]

Description of genus

Bentham was the first to describe the genus *Picrorhiza Kurroa* Royle ex Benth. in Scrophularineae Indicae and classified it under the family Scrophulariaceae.[14] It is currently placed in the family Plantaginaceae, order Lamiales according to the APG IV classification and comprises two accepted species, P. kurroa Royle ex Benth. and P. scrophulariiflora Pennell.[15,16] *Picrorhiza kurroa* is a perennial, stoloniferous, rhizomatous alpine herb native to the north-western and central Himalayan ranges of India, Nepal, Bhutan, Pakistan and the Tibetan Plateau, at altitudes of approximately 3,000–5,000 m above sea level.[15] The plant has compact basal rosettes of simple, glabrous, serrate or crenate leaves on elongated creeping rhizomes. The flowering scape is erect, leafless and carries a dense terminal spike of many small, pale blue to purplish-blue, bisexual, zygomorphic flowers. The calyx is persistent and deeply five-lobed. The tubular bilabiate corolla contains four didynamous stamens and a bicarpellary superior ovary. The fruit is a small ovoid capsule with many minute seeds adapted for dispersal under alpine environmental conditions.[13,14,17] Anatomically, the rhizome is characterized by well developed vascular tissues, abundant parenchymatous storage cells and secretory structures that accumulate iridoid glycosides. These glycosides, especially picroside I, picroside II and kutkoside are responsible for the well known hepatoprotective and medicinal properties of the plant.[11,15]

Morphology of Picrorhiza Kurroa

Picrorhiza kurroa Royle ex Benth. is a small perennial herb with rhizomes, 10–20 cm in height, and is found in the alpine and subalpine regions of the Himalayas.[18] Rhizome elongated, creeping, sub-cylindrical, medicinally important, 2.5-12.0 cm long and 0.3-1.0 cm in diameter. It has fibrous roots and scale scars and the surface is greyish brown to dark brown and longitudinally wrinkled.[19] Leaves alternate, 5–10 cm, spathulate to oblanceolate, with short petiole, sharp apex and serrated edges. Fresh leaves are dark green but become blackish brown on drying.[2,19] The plant produces terminal spikes of small bisexual zygomorphic flowers, white, pale blue or purple. Flowers have four didynamous stamens which are exserted to help in pollination.[20] The fruit is a septicidally dehiscent ovate capsule with two valves 6–12 mm long containing a large number of small, ellipsoid, light-brown seeds with a thick reticulated seed coat.[21] Microscopical features of the rhizome include a multilayered cork of 20–25 rows of suberized cells, a parenchymatous cortex with an abundance of starch grains and a well-developed secondary xylem with lignified vessels and tracheids.[19]

Fig. 1. **Fig. 2.**

Fig. 1: The rhizome morphology of *Picrorhiza kurroa* & Fig.2: The whole morphology of *Picrorhiza kurroa.*

Ethanobotanical uses

Picrorhiza kurroa Royle ex Benth. Kutki is a very important medicinal herb used widely in the traditional health care systems of the Himalayan region especially in Ayurveda, Tibetan medicine and indigenous practices in India, Nepal and Bhutan.[22] In Ayurveda, rhizome of P. kurroa is described as Tikta Rasa (bitter) and Bhedana (purgative/cholagogue) and traditionally used in the management of Kamala (jaundice) and Yakrit Vikara (liver disorders).[22,23] It is also an ingredient in many classical Ayurvedic formulations for hepatobiliary disorders.[22] P. kurroa rhizome is traditionally used in powder or decoction form for the treatment of jaundice, digestive disorders and inflammatory conditions among Himalayan communities and is valued for its hepatoprotective properties.[24,25] P. kurroa has been used in Tibetan and other traditional medicine systems for the treatment of fever, gastrointestinal disorders, respiratory diseases and liver disorders.[1] Because of its high medicinal value, limited alpine distribution and increasing commercial demand, sustainable conservation and cultivation of P. kurroa is needed to prevent further depletion of its natural populations.[1,25]

Phytochemical Review

During the past few decades, a large number of phytochemical screening of *Picrorhiza kurroa* has resulted in the isolation and characterization of more than 130 different secondary metabolites from the rhizomes, roots, stems and leaves.[22,26] The main bioactive therapeutic matrix is represented by iridoid glycosides which are synthesized through the terpenoid metabolic pathway.[27] The main active ingredient, traditionally called 'kutkin', was found through modern chromatographic analyses to be a stable crystalline mixture of two main

iridoid glycosides: Picroside-I (6-O-trans-cinnamoyl-catalpol) and Picroside-II (6-O-vanilloyl-catapol).[4,28] Other minor iridoids isolated from rhizome matrix are Picroside-III, Picroside-IV, kutkoside, minecoside and specioside.[29] In addition to iridoid glycosides, P. kurroa contains a high amount of highly functionalized acetophenones, mainly apocynin (4-hydroxy-3-methoxyacetophenone) and androsin.[30] This herb has a major effect on anti-inflammatory and cellular antioxidant effects, and apocynin is a well-studied catechol derivative and known as a very selective NADPH oxidase inhibitor.[31] The plant also produces a series of highly oxygenated tetracyclic triterpenoids called cucurbitacins (i.e., cucurbitacin B, I, D, and E) which can be responsible for their strong cytotoxic properties.[32] The phenolic acids (vanillic acid, cinnamic acid, ferulic acid, and caffeic acid) and a range of phytosterols (beta-sitosterol and daucosterol) as well as lipophilic terpenes make up a complex chemical architecture that defines the multi-target pharmacological synergy of Kutki.[1,33]

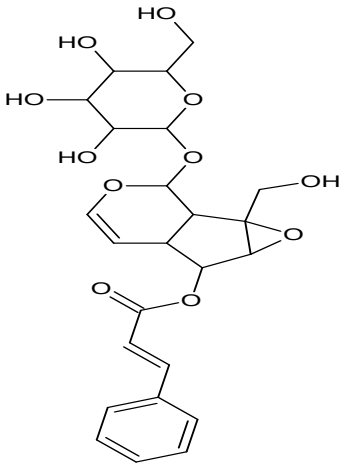

Fig. 3: Picroside I.

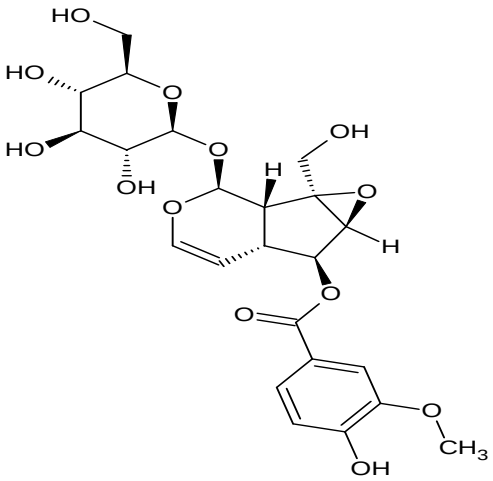

Fig.4: Picroside II

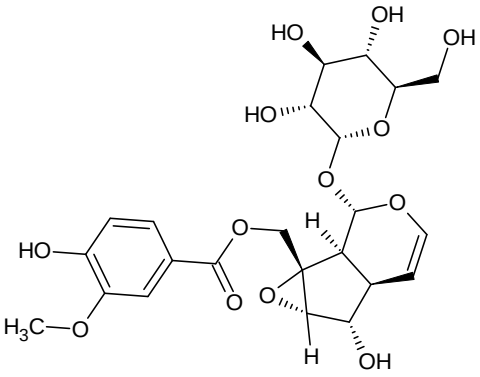

Fig. 5: Kutkoside.

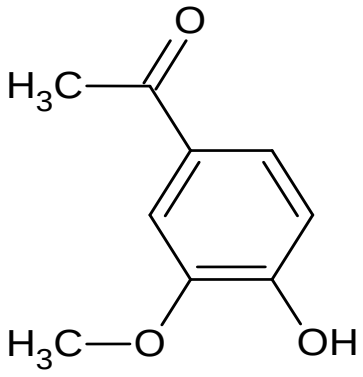

Fig.6: Apocynin

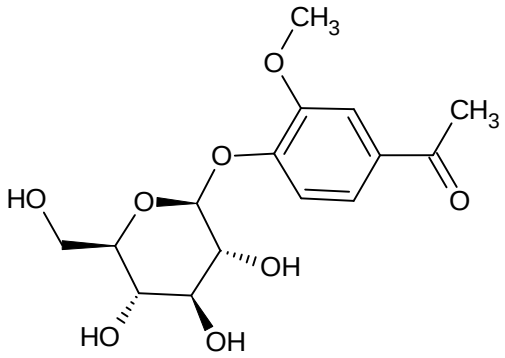

Fig. 7: Androsin.

Pharmacological activity

In vitro and in vivo studies have confirmed the diverse spectrum of pharmacological activities of *Picrorhiza kurroa*. It reveals a strong hepatoprotective effect through reduction of hepatocellular injury, oxidative stress and lipid peroxidation and improvement of endogenous antioxidant defense. The plant also possesses significant anti-inflammatory activity by inhibition of pro-inflammatory cytokines and modulation of COX-2, NF-κB and MAPK signaling pathways. Moreover, P. kurroa demonstrates antioxidant, immunomodulatory, anti-diabetic, antimicrobial, anti-asthmatic, anti-ulcer, nephroprotective and anticancer activities, which is mainly due to its major bioactive constituents like picroside I, picroside II, kutkoside and apocynin. These pharmacological effects justify the traditional medicinal use and therapeutic potential of the plant in the management of liver diseases, metabolic disorders, inflammatory conditions and oxidative stress related).[1,34,35]

Indepth Review of *Picrorhiza Kurroa*

The most investigated pharmacological property of *Picrorhiza kurroa* is its hepatoprotective activity. P. kurroa and its major bioactive constituents picroside I, picroside II, kutkoside and androsin have exhibited protective effects against various experimental models of CCl_4, D-galactosamine, paracetamol, alcohol, thioacetamide, LPS and high-fat diet induced NAFLD. Standardized extracts like Picroliv (picroside I + kutkoside) maintain hepatic architecture, lower serum levels of ALT, AST, ALP, GGT, LDH and bilirubin and improve liver histology. These effects are mainly attributed to the antioxidant, anti-inflammatory, anti-apoptotic, mitochondrial protective, lipid-regulating and anti-fibrotic mechanisms.[36-42]

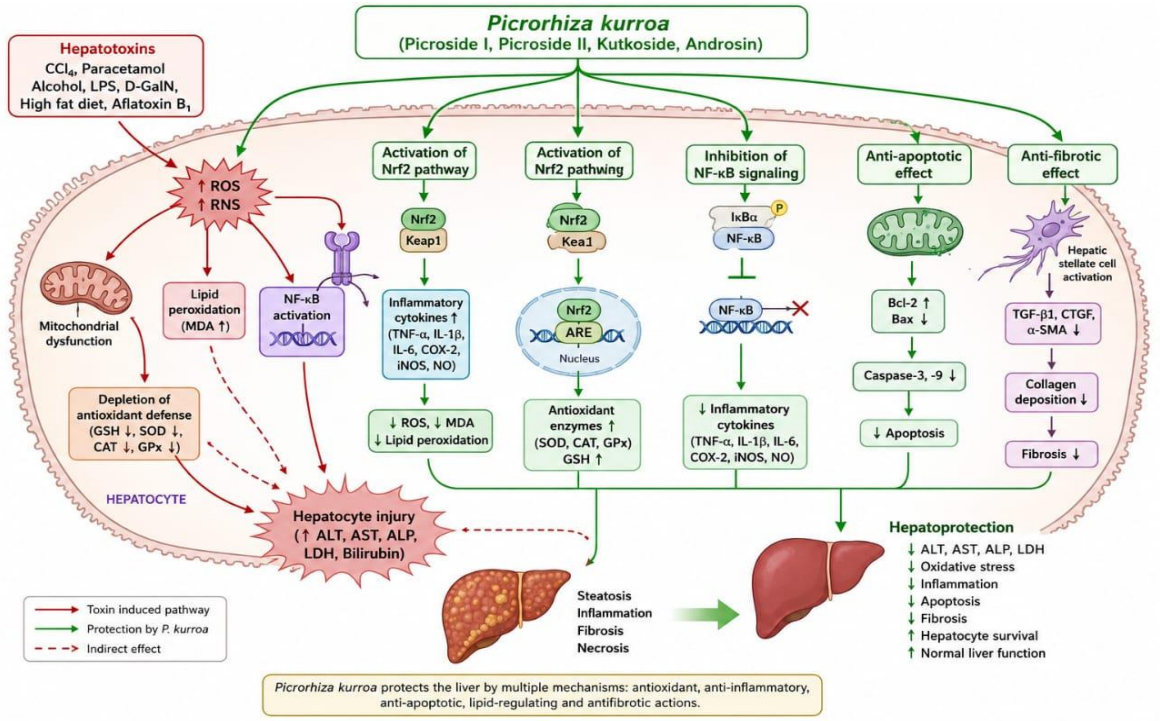

Fig. 8: A Schematic diagram represents mechanism of hepatoprotective action for *Picrorhiza Kurroa.*

Hepatoprotective effects are mediated through the following mechanisms:

Antioxidant activity and restoration of endogenous antioxidant defense: *Picrorhiza kurroa* mainly acts as a hepatoprotective agent by decreasing the oxidative stress. Therefore, its scavenged bioactive constituents of reactive oxygen species (ROS) and reactive nitrogen species (RNS) reduced lipid peroxidation and malondialdehyde (MDA) levels. The extract restored intracellular glutathione (GSH) and increased the endogenous antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx). P. kurroa also activates the Nrf2/ARE signaling pathway, which upregulates the expression of antioxidant genes and protects hepatocytes against oxidative damage.[43,44]

Inhibition of inflammatory signaling: Liver injury activates Kupffer cells, which release inflammatory mediators. *Picrorhiza kurroa* suppressed tumor necrosis factor-alpha (TNF-alpha), interleukin-1 beta (IL-1 beta), interleukin-6 (IL-6), nitric oxide (NO), cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS). It also inhibits NF-κB activation, thus reducing hepatic inflammation and preventing the transition of acute liver injury into chronic liver damage.[1,43]

Hepatocyte apoptosis inhibition: Oxidative stress activates the mitochondrial pathway of apoptosis. Picroside II inhibits apoptosis of hepatocytes by up-regulating the expression of anti-apoptotic protein Bcl-2, down-regulating the expression of pro-apoptotic protein Bax, inhibiting the activation of caspase-3 and caspase-9, stabilizing the mitochondrial membrane potential, and reducing TNF-α-mediated hepatocyte death. These actions maintain viable liver cells during toxic injury.[38,43]

Stabilization of liver cell membrane: Free radicals damage the hepatocyte membranes and this causes leakage of liver enzymes. *Picrorhiza kurroa* protects the integrity of plasma and mitochondrial membranes and prevents leakage of ALT, AST, ALP and LDH, thus maintaining the integrity of the cell and liver functions in the presence of toxin exposure.[1,36]

Regulation of lipid metabolism in NAFLD: *Picrorhiza kurroa* decreases hepatic triglyceride accumulation, de novo lipogenesis, hepatic steatosis and lipid deposition, increases fatty acid β-oxidation, and improves insulin sensitivity in non-alcoholic fatty liver disease (NAFLD). These effects preclude the progression of fatty liver to steatohepatitis.[1,44]

Antifibrotic effect: Continuous liver injury leads to the activation of hepatic stellate cells and fibrosis. *Picrorhiza kurroa* inhibits the activation of hepatic stellate cells, reduces collagen deposition, inhibits profibrotic mediators such as the transforming growth factor-β1 (TGF-β1) and limits extracellular matrix accumulation, thus retarding development towards cirrhosis.[1,44]

Protection against various hepatotoxins: *Picrorhiza kurroa* has been shown to protect against liver damage induced by carbon tetrachloride (CCl4), D-galactosamine, lipopolysaccharide (LPS), paracetamol (acetaminophen), alcohol, high fat diet, isoniazid and rifampicin, and aflatoxin B1 in experimental studies. Combined antioxidant, anti-inflammatory and anti-apoptotic mechanisms are responsible for protection.[1,36,44]

Insilico Molecular Docking Studies

The *in-silico* molecular docking study was conducted using CB-Dock2 to evaluate the hepatoprotective potential of the major phytoconstituents of *Picrorhiza kurroa* (picroside I, picroside II, kutkoside, and apocynin) against seven liver-associated therapeutic protein targets (PDB IDs: 8BHE, 5LDO, 2R3X, 3NXU, 4IQK, 2C6U, and 2HI4). The binding affinities, binding poses and protein-ligand interactions were discussed and compared with

the standard hepatoprotective drugs (ursodeoxycholic acid, N-acetylcysteine, metadoxine and bifendate) to elucidate their molecular interactions and to evaluate their hepatoprotective potential.

Table No. 1: Binding affinity for phytochemicals with target enzymes.

Target Enzymes	Picroside-I	Picroside II	Kutkoside	Ursodeoxycholic Acid	N-Acetylcysteine	Metadoxine	Bifendate	Silymarin
2HI4	-10.2	-9.8	-10.6	-7.1	-4.9	-6.6	-7.6	-9.0
8BHE	-10.5	-9.1	-8.1	-9.5	-5.0	-5.5	-7.6	-8.6
5LD0	-7.5	-7.8	-8.0	-7.1	-4.8	-5.7	-7.0	-7.9
2R3X	-9.7	-9.7	-9.7	-9.7	-4.9	-5.8	-7.3	-10.0
3NXU	-9.6	-8.7	-8.3	-9.2	-4.8	-5.5	-6.7	-8.9
4IQK	-10.5	-10.5	-11.8	-9.7	-4.8	-6.4	-7.6	-10.4
2C6U	-8.0	-8.0	-7.7	-7.9	-4.3	-5.4	-5.8	-8.1

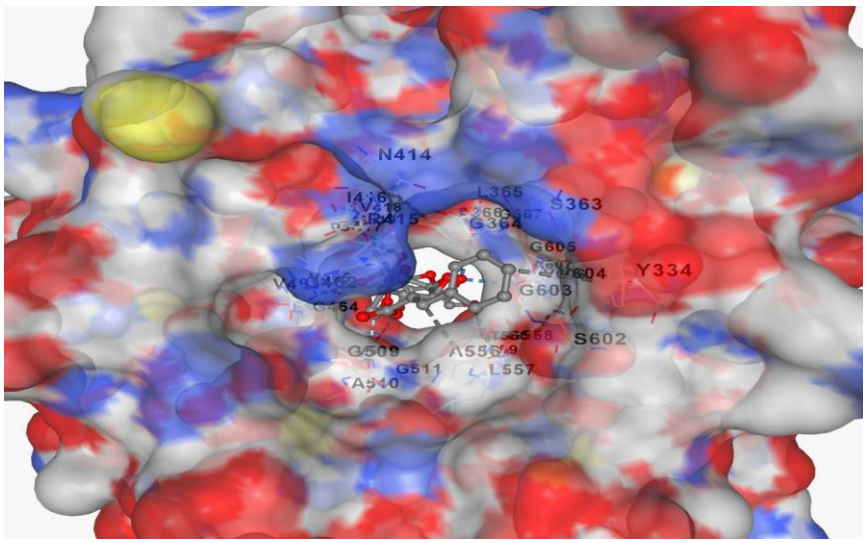

Fig. 9: The Binding Affinity of Picroside1 in 4IQK Target Enzyme.

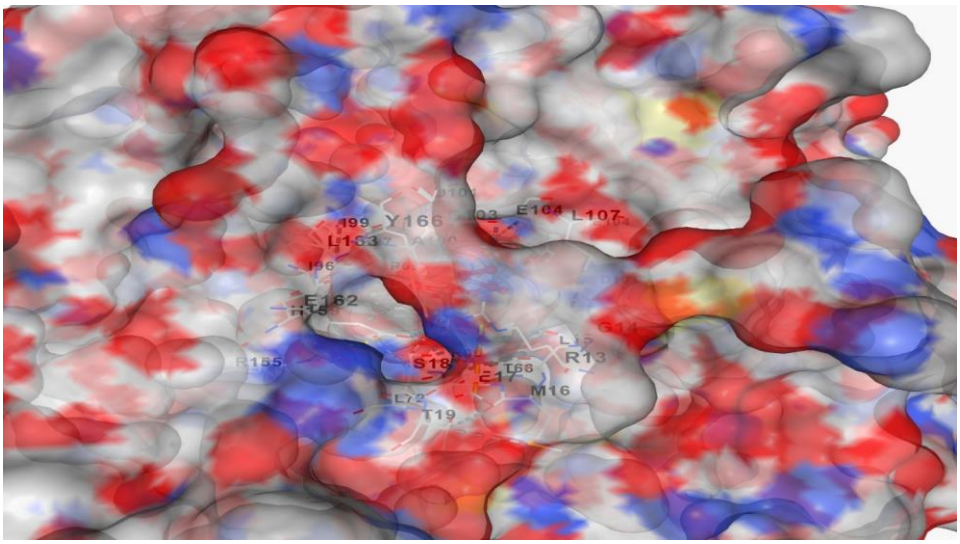

Fig: 10: The Binding Affinity of Kutkoside in 2R3X Target enzyme.

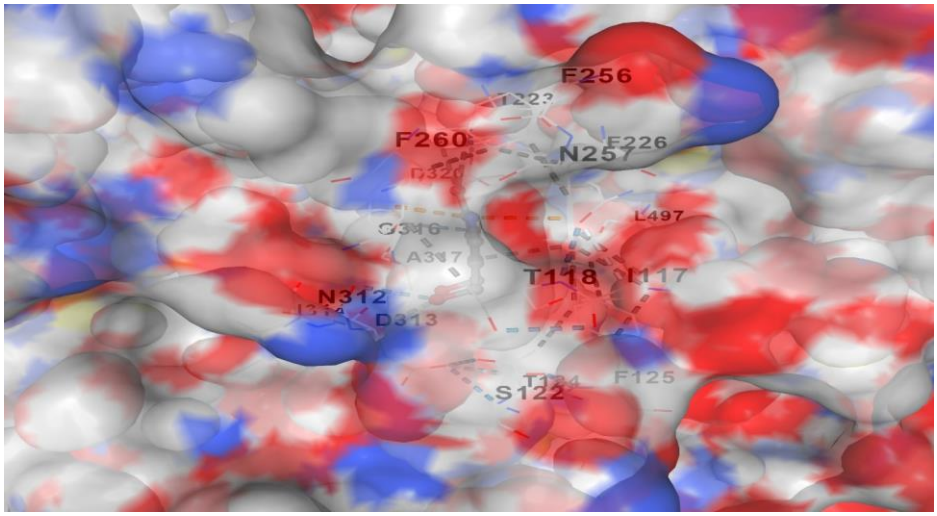

Fig. 11: The Binding Affinity of metadoxine in 2HI4 Target enzyme.

Molecular docking studies showed that the natural iridoid glycosides Picroside I, Picroside II and Kutkoside exhibited better binding affinities (more negative docking scores) than the standard hepatoprotective drugs N-Acetylcysteine, Metadoxine and Bifendate against most of the seven selected liver associated target enzymes. In addition, the three phytoconstituents showed similar or better binding affinities compared to Ursodeoxycholic Acid and Silymarin against various protein targets. Among the tested compounds, Kutkoside had the highest overall binding potential, giving the best docking score of −11.8 kcal/mol against the 4IQK target and also showing better affinity towards 2HI4 (−10.6 kcal/mol). Picroside I consistently showed excellent binding with most targets, with docking scores ranging from -7.5 to -10.5 kcal/mol. Picroside II also showed strong and stable interactions, with docking scores ranging from -7.8 to -10.5 kcal/mol. All three phytoconstituents showed binding affinities equal to or better than several standard drugs against major targets such as 2HI4, 8BHE, 3NXU and 4IQK and comparable with best performing standards against 2R3X. In general, the order of binding strength was Kutkoside > Picroside I > Picroside II but all the three natural compounds showed excellent molecular interactions with the selected hepatoprotective targets. This study strongly supports the potential hepatoprotective efficacy of phytoconstituents of *Picrorhiza kurroa* and provides an insight that the phytoconstituents of *Picrorhiza kurroa* may be a promising lead molecule for novel liver protective therapeutics.

CONCLUSION

Picrorhiza kurroa Royle ex Benth. is an important medicinal herb of Himalayas having high hepato-protective potential. Its major bioactive compounds such as picroside I, picroside II,

kutkoside, apocynin and androsin protect the liver via antioxidant, anti-inflammatory, anti-apoptotic and lipid-regulating mechanisms while inducing hepatocellular regeneration. Molecular docking also supported the therapeutic potential of these phytoconstituents especially kutkoside, by revealing strong interactions with liver associated targets. The promising pharmacological profile of P. kurroa, coupled with its threatened status, warrants sustainable cultivation, conservation and standardized quality control. Additional pharmacokinetic, toxicological and clinical studies are needed to determine its efficacy and to guide its development into evidence-based hepatoprotective therapies.

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