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Review Article

PHYTOPHARMACOLOGY OF *HOLMSKIOLDIA SANGUINEA* RETZ.: A REVIEW

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ABSTRACT

Holmskioldia sanguinea Retz. is a Sub-Himalayan plant that has been cultivated in the Americas, Europe, Indo-china, Asia-Pacific, and Southern Africa. It has been used traditionally to treat rheumatism and rheumatoid arthritis, dysentery, headaches, hypertension, boils, blain, ulcers, and gynaecological problems, as well as a blood purifying concoction. The botanical description of the plant, its phytochemical constituents, and its pharmacological activities are discussed, with an emphasis on antibacterial, antihepatotoxic, antifungal, anti-inflammatory, antioxidant, antimicrobial, analgesic, central nervous system depressant, diuretic, oestrogenic, anti-implantation, and anticancer properties. Most pharmacological effects are a result of plant constituents such as alkaloids, terpenoids, tannins, flavonoids, glycosides and phenols, to name a few. Conventional wisdom should be confirmed through in vitro and in vivo studies, as well as clinical trials. Herb's anti-tumor and anti-cancer properties have generated significant interest.

Keywords: *Holmskioldia sanguinea* Retz., Chinese hat plant, phytoconstituents, antioxidant, andrographolide, traditional, anti-microbial.

INTRODUCTION

Uttarakhand's Medicinal Plants

Human culture has been fascinated by medicinal plants since prehistoric times. India has a diverse range of medicinal plants at all three levels of biodiversity: species, genetic diversity, and habitat diversity[1]. The Himalayas are well-known for having some of the world's most diverse biodiversity hotspots[2]. The Himalayan region is rich in natural resources, particularly medicinal and aromatic plants. Asthma, diabetes, skin disorders, snake bites, fevers, and so on have all been treated with these plants by Indian traditional healers for centuries[3].

There are approximately 8644 plant species in the Indian Himalaya Region, divided into 1748 families. Uttarakhand, India's northernmost state, is a major contributor of medicinal and aromatic plant resources in the Indian Himalayan region, comprising 40.10 percent of all medicinal and aromatic plants discovered in the region[2,3].

Uttarakhand is in the Himalayan hotspot and is home to a vast array of wildlife. Hills cover 92.57% of the land and plains cover 7.43% of the total land area and covers 17.3 percent of India's total land area[4]. It is located between 77˚34′27″ to 81˚02′22″E longitude and 28˚53′24″ to 31˚27′50″N latitude. The Tons River divides it from Himachal Pradesh in the north-west, the Kali River divides it from Nepal in the east, and the greater Himalaya forms the state's northern boundary and international border with China[5]. The state is the habitat of major tribal communities such as Bhotias, Boaxas, Tharus, Jaunsaries, Shaukas, Kharvar, Mahigiri etc. which use medicinal plants for curing the diseases and ailments using natural medicines[6].

The state's climatic, topographic, and soil diversity has resulted in the discovery of several valuable and economically significant medicinal herbs with significant therapeutic potential. Uttarakhand is home to a varied array of medicinal plants that are heavily utilised by the pharmaceutical industry in the formulation of medications used in the Indian System of Medicine[7].

Residents in this region, particularly the elderly, tribal people, and women, heavily rely on these traditionally available medicinal plants for health care, believing that they are more accessible, less expensive, and have fewer side effects than modern drugs. Traditional knowledge is gradually eroding and disappearing from rural areas as a result of deforestation, the impact of tourism on the region's natural vegetation, population explosion and heavy construction in this region for development, and the changing climate in the Himalayan region, among other factors[8].

The role of traditional medicinal plants in promoting human health sustainability

The WHO categorises traditional medicines as including plants, animals, minerals, spiritual therapies, and various other health practises, approaches, knowledges, and beliefs that can be used singly or in combination to improve health and wellness, as well as to combat illness[9]. Medicinal plants form the foundation of traditional medicine, which means that over 3.3 billion people in less developed countries regularly use medicinal plants. These medicinal plants are regarded as a valuable source of ingredients for drug development and synthesis[10]. In China, India, Japan, Pakistan, Sri Lanka, and Thailand, traditional medicine is widely practised. Around 40% of total medicinal consumption in China is attributed to traditional tribal medicines alone[11]. Medicinal plants are widely used in India by all segments of the population, both as folk medicines in various indigenous systems of medicine such as Siddha, Ayurveda, and Unani, and as processed products

in the pharmaceutical companies. In India there are approximately 4.5 million plant species, but phytochemically for biological or pharmacological activity only 250 000 to 500 000 have been studied[12]. Because a growing number of people are looking for natural remedies with few or no side effects, many medicinal plants are seeing a rise in popularity in the marketplace[13]. Most traditional medicines were plant-based and widely available locally. While traditional medicines may have some benefits, they may also have some drawbacks. At the current state of our knowledge, it is impossible to tell whether most traditional medicines were helpful, harmful, or both[14]. Without a doubt, medicinal phytochemicals are critical natural resources for future drug discovery, but the phytochemical properties of only a small percentage of medicinal plants have been investigated[15]. The traditional applications of some therapeutic plants remain undocumented, causing declines in knowledge and trustworthiness. As a result, it has become necessary to document and share all knowledge in order to ensure their quality and preservation[16].

Plant chemical constituents are categorised according to their functions in essential metabolic processes: primary and secondary metabolites. Because primary plant metabolites are involved in fundamental life functions, they are found in all living cells. Secondary plant metabolites were instrumental in alleviating a variety of ailments in traditional medicine and folk medicine. They provided lead compounds for the manufacture of medications used to treat a variety of diseases ranging from migraine to cancer in modern medicine[17]. Indeed, secondary metabolites, whether used alone or in combination, can be effective and safe even when synthetic drugs fail. They may even enhance or synergize the effects of the medication's other active ingredients[18]. Alkaloids, glycosides, flavonoids, terpenoids, tannins, resins, lignin's, and saponins are just some of the metabolites[19]. These secondary metabolites are recognised as useful plant components for preventing and managing chronic diseases such as cancer, diabetes, and cardiovascular disease[20]. Lamiaceae, colloquially referred to as the mint family, is a diverse flowering plant family comprised of approximately 7136 species classified into 236 genera. Most species are herbaceous or shrubby, with few trees. Salvia is the most well-known genus (900 species), followed by *Scutellaria* (360 species), *Stachys* (300 species), *Plectranthus* (300 species), *Hyptis* (280 species), *Vitex* (250 species), *Teucrium* (250 species), *Thymus* (220 species), *Nepeta* (200 species), and *Clerodendrum* (150 species)[21].

Holmskioldia sanguinea Retz. Plant Description

Holmskioldia sanguinea Retz. is a large climbing shrub that grows to a height of 5000ft in the Himalayas. The plant is widely cultivated in India's gardens for its showy scarlet flowers. The plant requires little care and thrives in full sunlight. Layers, cuttings, and seeds are used to propagate it. Sheep and goats consume the plant. Due to the high yield of andrographolide, *Holmskioldia sanguinea* Retz. can be used as a cost-effective source for this important bioactive constituent. Andrographolide has been shown to be hepatoprotective[22].

Holmskioldia Sanguinea Retz. Plant Distribution

Holmskioldia sanguinea Retz. is a monotypic genus of the Lamiaceae family (formerly of Verbenaceae). It is a large scrambling shrub native to the subtropical and Himalayan regions from Kumaon to Bhutan, but it is also found widely in Pakistan, South Asia, Mauritius, Indonesia, and the West Indies. It has been widely distributed as an ornamental throughout the world, with cultivation records in the Americas, Europe, Indo-china, Asia-Pacific, and southern Africa[23,24,25].

Synonyms

Hastingia coccinea Sm.
Hastingia scandens Roxb.
Holmskioldia rubra Pers.
Holmskioldia sanguinea citrina Moldenke
Holmskioldia sanguinea f. *aurantiaca* Yin Yin Kyi & DeFilipps
Holmskioldia scandens Sweet, nom. nud.
Platunum rubrum A. Juss[26].

Taxonomical classification

Domain: Eukaryota
Kingdom: Plantae
Phylum: Spermatophyta
Subphylum: Angiospermae
Class: Dicotyledonae
Order: Lamiales
Family: Lamiaceae
Genus: *Holmskioldia*
Species: *Holmskioldia sanguinea* Retz.

Common Names

International (English): Chinese hat plant, Cup-and-Saucer-plant, Mandarin hat, Parasol Flower.
India: Hindi: Kapni
Assamese: Hurmuli, Chatra-puspa, Manu-kata-phul
Manipuri: Kharamleithong
Garo: Misi-nasil
Kach: Khemjuta-phang
Khasi: Dieng-skor-khnai, Jermei-snam-khmut, Mei-da-kyna
Others: Arnamamir, Long-i-arong, Wo-so
Nepal: Jhule phool, Aputo
Puerto Rico: Platillo
Cuba: Farolito Japones, Paraguita chino
Haiti: Bonnet chinois, Chapeau chinois [25,26].

Holmskioldia sanguinea Retz. Morphological characters

Holmskioldia sanguinea Retz. is a straggling evergreen shrub that grows slowly but steadily to a height of 3-9m **Fig.1**. Its leaves are simple and opposite or subopposite, ovate, acuminate, serrated, or entire, and reach a length of approximately 10 cm [27]. Stem obtusely quadrangular or cylindrical, puberulent, greyish; stipules absent[25]. Inflorescence **Fig.2** with foliaceous bracts, axillary or terminal, a dense thyrse composed of 2-6 opposite cymes; cymes three-flowered or reduced to a single long-pedicellate central flower and two sterile lateral bracteoles; pedicels extremely short and s Calyx is shallowly cone-shaped, orange or red, with five lobed lobes. Tubular corolla, brick red, scarlet to orange or red-brown, 1.5-2.5 cm long, five-lobed; four anterior lobes, one enlarged posterior lobe. Four didynamous stamens attached to or slightly below the corolla throat, briefly exserted **Fig.3**. Anthers are dorsifixed and longitudinally dehiscing. Fruit with an incomplete division into four nutlets and a brown, frequently verrucose, surface[28].

Figure 1: *Holmskioldia sanguinea* Retz. Plant

Figure 2: *Holmskioldia sanguinea* Retz. Inflorescence

Figure 3: *Holmskioldia sanguinea* Retz. Flower

Ethnopharmacological uses

There are reports to indicate that it is in use in traditional medicine. Its freshly crushed leaves and shoots are used to treat rheumatism and rheumatoid arthritis, as well as boils, blain, ulcer, and gynaecological problems[29,30]. The stem and stembark extracts are used to treat dysentery, headaches, and hypertension, while the leaves are boiled as part of a blood purifying concoction. Additionally, leaves and flowers are believed to have magical and ritual significance, particularly in the treatment of children's diseases[25].

PHYTOCHEMICAL CONSTITUENTS

Pal *et al.* reported presence of alkaloids, carbohydrate, tannins, terpenoids, flavonoids, phenols and glycosides in alcoholic extracts of *Holmskioldia sanguinea* Retz. leaves[31].

Bhardwaj *et al*. isolated a pigment from *Holmskioldia sanguinea* Retz. and proposed its structure as 3,6-dimethoxy-5,7,3',4'-tetrahydroxyflavone. The pigment was identified as flavone: axillarin[32]. **Fig.4**

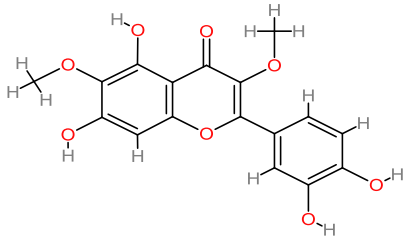


Figure 4: Axillarin[33]

Following a chemical screening of *Holmskioldia sanguinea* Retz., Chaudhuri *et al.* isolated two known active diterpenoids: andrographolide and neoandrographolide **(Fig.5-6)** as well as wogonin, oroxindin, friedelin, friedelinol, β-sitosterol glucoside, β-amyrin, **(Fig.7-12)** and a new lipid 27-methylnonaeicosanol along with twelve know lipids reported first time: Propionic (0.3%), malonic (0.3%), succinic (0.3%), myristic (1%), azelaic (1%), tricosanoic (1.3%), arachic (2.8%), heneicosanoie (1%), behenic (2.5%), lignoceric (10.8%), pentacosanoic (6%), and hexacosanoic (70%) acids were identified by GC±MS. Several previously isolated diterpenoids and triterpenoids were also isolated in the laboratory[34].

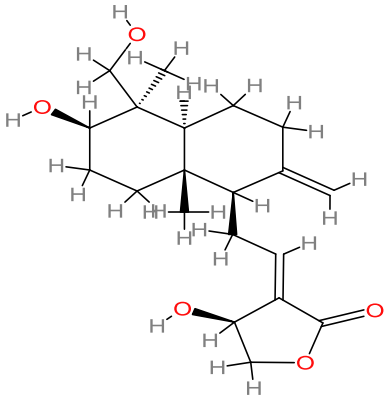


Figure 5: Andrographolide[35]

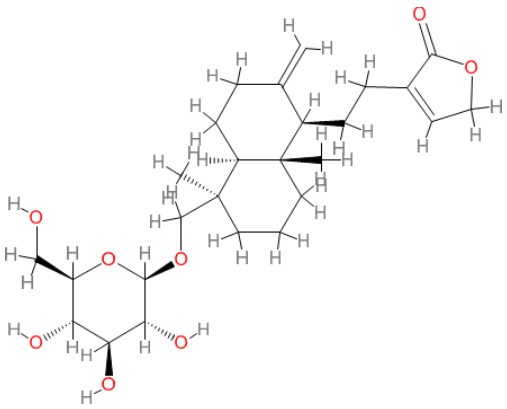


Figure 6: Neoandrographolide[36]

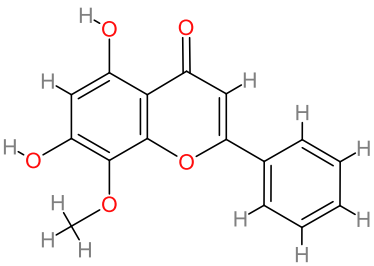


Figure 7: Wogonin[37]

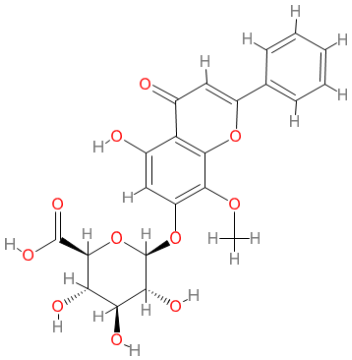


Figure 8: Oroxindin[38]

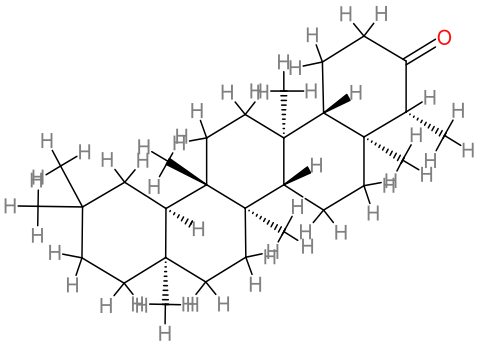


Figure 9: Friedelin[39]

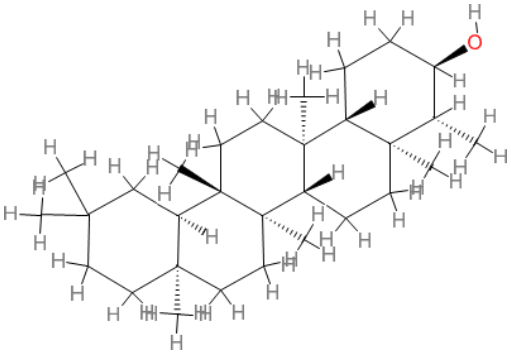


Figure 10: Friedelinol[40]

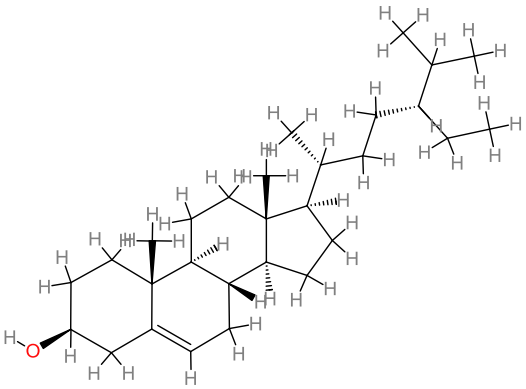


Figure 11: β-sitosterol[41]

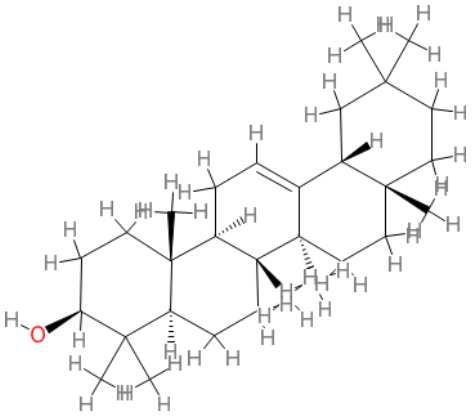
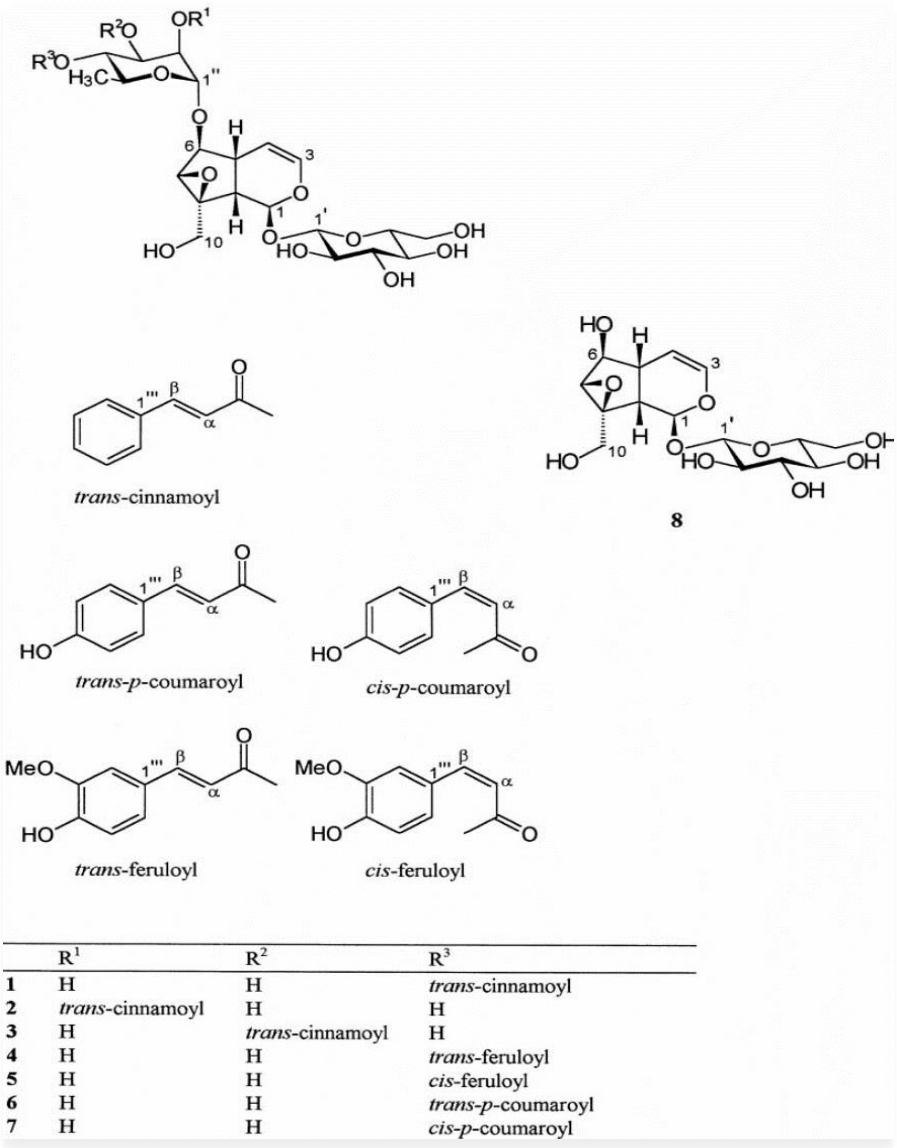


Figure 12: β -amyrin[42]

Rimpler *et al.* isolated Four new iridoids **Fig.13**:
6-O-a-L-(20-O-trans-cinnamoyl)rhamnopyranosylcatalpol**(1)**
6-O-a-L-(30-O-trans-cinnamoyl)rhamnopyranosylcatalpol**(2)**
6-O-a-L-(40-O-trans-cinnamoyl)rhamnopyranosylcatalpol**(3)**
and
6-O-a-L-(40-O-cis-feruloyl)rhamnopyranosylcatalpol**(5)**, along with three known monoacyl rhamnopyranosylcatalpol derivatives:
6-O-a-L-(40-O-trans-feruloyl)rhamnopyranosylcatalpol**(4)**
6-O-a-L-(40-O-trans-p-coumaroyl)rhamnopyranosylcatalpol**(6)**
and
6-O-a-L-(40-O-cis-p-coumaroyl)rhamnopyranosylcatalpol**(7)**
was isolated from *Holmskioldia sanguinea* Retz. aerial parts. Catalpol**(8)** was identified by GC and GC±MS analysis. Three well characterized phenolic glycosides **Fig.14** were isolated in trace amounts, were identified as methyl salicylate glucoside**(9)**, osmanthuside H**(10)**, and icariside F2**(11)**and concluded that rhamnopyranosylcatalpol esters are the main iridoid constituents present in this species[43].



	R^1	R^2	R^3
1	H	H	*trans*-cinnamoyl
2	*trans*-cinnamoyl	H	H
3	H	*trans*-cinnamoyl	H
4	H	H	*trans*-feruloyl
5	H	H	*cis*-feruloyl
6	H	H	*trans-p*-coumaroyl
7	H	H	*cis-p*-coumaroyl

Figure 13: Structure of isolated four new iridoids (1-4) along with three known monoacyl rhamnopyranosylcatalpol derivatives (5-7) and catalpol(8)[43]

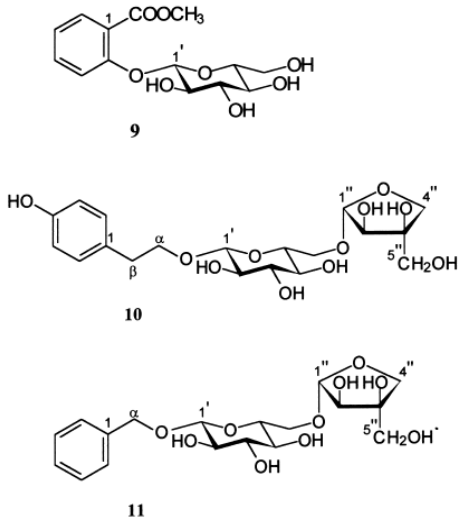


Figure 14: Structure of isolated three known phenolic glycoside: Methyl salicylate Glucoside (9), Osmanthuside H (10), and Icariside F2 (11)[43].

Yadava *et al.* isolated new compound from ethanolic extract of stems parts of this plant which is reported as 3,4′-dihydroxy-5,7-dimethoxyflavone-3-O-β-D-galactopyranosyl(1→4)-O-β-Darabinopyranosyl-4′-O-α-L-rhamnopyranoside **Fig:15**.[44]

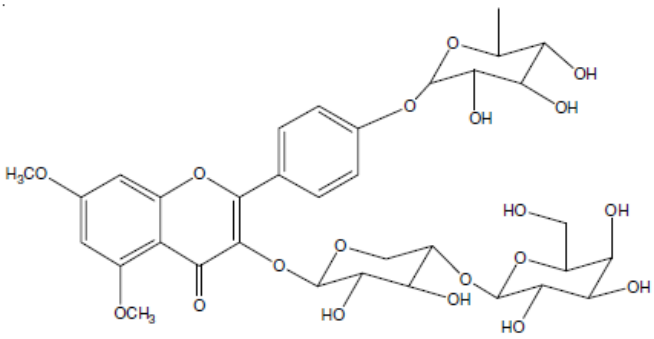


Figure 15: Chemical Structure of 3,4′-dihydroxy-5,7-dimethoxyflavone-3-O-β-D- galactopyranosyl(1→4)- O-β-Darabinopyranosyl-4′-O-α-L-rhamnopyranoside [44].

PHARMACOLOGICAL ACTIVITES

Antihepatotoxic Activity

Pal *et al.* investigated the anti-hepatotoxic effect of an alcoholic extract *of Holmskioldia sanguinea* Retz. aerial part on rats with hepatic damage caused by carbon tetrachloride (CCl4). Serum glutamate pyruvate transaminase (SGPT), alkaline phosphates (ALP), serum glutamate oxaloacetate transaminase (SGOT), total bilirubin, and gamma glutamate transpeptidase (GGTP) activity were determined. A liver sample was compared to a control liver sample for histopathological changes. The alcoholic extract exhibited significant hepatoprotective activity, implying that the hepatoprotective effect of *Holmskioldia sanguinea* Retz. may be a result of the flavonoids and terpenoids found in the plant[31].

Antibacterial Activity

Yadava RN and Raguvansi J. isolated 3,4′-dihydroxy-5,7-dimethoxyflavone-3-O-β-D-galactopyranosyl(1→4)-O-β-D-arabinopyranosyl-4′-O-α-L-rhamnopyranoside and reported that the compound exhibited significant antibacterial activity, indicating that it could be used as a potent antibacterial agent against a variety of Gram positive and Gram negative bacteria-related diseases[44].

Phytotoxic and Antifungal Activity

Pal *et al.* reported that they determined the antifungal activity of wogonin isolated from *Holmskioldia sanguinea* Retz. against four different fungal organisms (*Aspergillus niger*, *Penicillium notatum*, *Penicillium frequentans* and *Botrytis cinerea*). The compound's effects were compared to those of the standard antifungal agent griseofulvin. The pure compound wogonin showed inhibitorius reactions to all organisms tested in order *A. niger* > *P. frequentans* > *B. cinerea* > *P. notatum* when it was tested by the use of turbidity or spore-germination techniques and concluded that the compound wogonin isolated from *Holmskioldia sanguinea* Retz. leaves are an effective antifungal agent[45]. Chaudhuri *et al.* reported that the flavonoid wogonin possesses phytotoxic and antifungal properties, while oroxindin significantly reduced the inhibitory potency against *A. alternata* and *F. fusiformis* seed growth, germination, and fungal growth[24].

Antioxidant and Antimicrobial Activity

Ajaib *et al.* reported methanol and chloroform extracts of *Holmskioldia sanguinea* Retz. exhibited significant antioxidant activity. Their IC_{50} values were determined to be 18.12±1.32 and 32.52±0.12µg/ml, respectively, in comparison to BHT, a reference standard, which has an IC_{50} value of 12.52 ± 0.89. Methanol extract exhibited the highest total antioxidant activity, measuring 1.142±0.08 units. Additionally, it demonstrated a high FRAP value (92.15±1.06 TE µM/mL), the highest total phenolic content (74.83±1.14 GAE mg/g), and the highest percent inhibition of lipid peroxidation (49.13±0.37 vs. standard BHT, 62.93 ± 0.78). Methanol extract formed the largest zone of inhibition, measuring 47±1.72mm against E. coli. The MIC results indicated that the methanolic extract is more resistant to *E. coli*, at 0.010 µg/ml, and concluded that methanol and chloroform extracts of this plant can be used to develop antioxidant and antimicrobial agents[46].

Anti-inflammatory Activity

Chaudhuri *et al*. compared and elucidated the anti-inflammatory effects of three fractions (CHCl3, n-BuOH, and H2O) extracted from *Holmskioldia sunguinea* Retz. aerial parts using a carrageenin-induced oedema model. The H2O (20 and 40 mg) and n-BuOH (200 mg) fractions were found to be effective in comparison to standard hydrocortisone. The effective and lethal dose (LD_{50} > 1 g/kg) values indicated that the extract was non-toxic, implying that the plant possesses significant anti-inflammatory activity[47].

Anticancer Activity

Pal *et al.* studied the protective effects of *Holmskioldia sanguinea* Retz. extract on Ehrlich ascites carcinoma (EAC) and Dalton's ascites lymphoma (DAL) in Swiss albino mice, as well as the potential mechanisms of action. The antioxidant status of the compound was investigated in tumor-bearing mice, which demonstrated the compound's potential for significant free radical scavenging activity, as well as significant tumour regression and prolonged survival time. When the isolated bioactive molecule andrographolide from *Holmskioldia sanguinea* Retz. is subjected to HPTLC/HPLC analysis, it yields (2.5 percent). The cellular defence system, which is catalysed by superoxide dismutase, was enhanced, resulting in a greater restriction of lipid peroxidation. *Holmskioldia sanguinea* Retz. has shown its effectiveness in the therapy of cancer as a new source of andrographolide[48].

Analgesic activity

Asolkar *et al.* investigated the analgesic properties of various parts of *Holmskioldia sanguinea* Retz.

Diuretic and CNS depressant Activity

Asolkar *et al.* discovered that the aerial parts of *Holmskioldia sanguinea* Retz. possessed diuretic and central nervous system depressant properties[49].

Oestrogenic and Anti-implantational Activity

Singh *et al*. isolated Wogonin, a 5,7-dihydroxy-8-methoxyflavone from *Holmskioldia sanguinea* Retz., and tested it in rats for oestrogenic and anti-implantational activity. Wogonin had a mild oestrogenic effect but was effective against implantation. The wet uterine and vaginal weights increased significantly after three days of uterotrophic bioassay at a dose level of 10mg/kg body weight per day, intramuscularly. Wogonin at same dose level was effective in inhibiting implantation when given intramuscularly on days 1-3, 4-6, and 1-7 post coitum and orally on days 1-7 post coitum. However, when the drug was administered between days 7-9 post coitum, it had no effect on implantation, but interfered with embryonic development, resulting in foetus resorption, and stated Wogonin, a mild oestrogenic compound, was found to be an interceptor at all stages of pregnancy[50].

CONCLUSION

Holmskioldia sanguinea Retz. extract has phytotoxic and antifungal activities. Its bioactive component can be isolated and substituted for synthetic fungicides. Due to *Holmskioldia sanguinea* Retz. anti-inflammatory properties, the extract may be used in place of synthetic anti-inflammatory drugs. A number of previous studies have concluded that various extracts of *Holmskioldia sanguinea* Retz. have a pharmacological effect, including antihepatotoxic, antibacterial, phytotoxic and antifungal activity, anticancer activity, analgesic, diuretic, and central nervous system depressant activity, as well as oestrogenic and anti-implantational activity. *Holmskioldia sanguinea* Retz. phenolic content may be beneficial in the treatment of stress, depression and free radical balance due to its antioxidant and anti-inflammatory properties. *Holmskioldia sanguinea* Retz. extract contained chemical bioactive molecules such as carbohydrates, alkaloids, terpenoids, tannins, flavonoids, glycosides, and phenols among others, that have been shown to be useful in the treatment of diseases such as diabetes, Alzheimer's disease, Parkinson effect and more. It possesses antifungal, antimicrobial, anti-inflammatory, anti-cancer, and antioxidant properties, which may be related to the presence of a bioactive constituent.

Additional research on *Holmskioldia sanguinea* Retz. is required to confirm its medicinal properties and to develop formulations containing this plant for practical clinical applications benefiting mankind.

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