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A Review on Ethnobotany, Phytochemical and Pharmacological Dynamics of *Prangos pabularia* Lindl.

Nimisha Sharma[1]*, Praveen Kumar Ashok[1], Arvind Negi[1], Lakshmayya B[1]

Guru Ram Das (PG) Institute of Management & Technology, Dehradun, Uttarakhand, India

Abstract

Prangos pabularia Lindley is a hardy perennial herb widely distributed in the alpine and sub-alpine regions. The multidisciplinary pharmacological actions exhibited by the whole plant owe to the presence of diverse phytochemical constituents residing in the plant. The plant is used in traditional medicine systems as diuretic, antibacterial, anti-inflammatory and in the treatment of leukoplakia. The constituents liable to account for such dynamic behaviour comprise of osthol, isoimperatorin, coumarins and furanocoumarins viz. xanthotoxin etc. The reported biological activities and far reaching range of physiological effects present an exigency for the establishment of various pharmacopoeial standards and assay methods for this herb. This review is intended to put forward adequate background information on *P. pabularia* that will contribute in establishing the validity of this herb for its commercial exploitation.

Keywords: Allelopathic, Antibacterial, Diuretic, Furocoumarins, Leukoplakia, Osthol.

1. Introduction

The family 'Apiaceae' is well known for producing a large number of coumarins with isoprenoid units disposed in multifarious ways along with a relatively high concentration of secondary metabolites such as furocoumarins. *Prangos*, a genus of herbaceous, perennial distributed in the Mediterranean region and Western and Central Asia, belongs to this family. Among the 72 species of the genus *Prangos*, known till now, *P. pabularia* is indigenous to India.

Prangos pabularia Lindley is a widespread tall perennial herb and one of the most extensively studied species of the genus. It is commonly called as Djashire – Ulufei in Iran, Komal; Krungus in India, Silphium parsley, Hay plant [1–3]. The plant is valued for its medicinal uses and sometimes used as fodder. It is held in considerable repute in indigenous medicine for its roots and fruits. The roots and fruits have medicinal properties and are used in traditional medicine systems. The young leaves and flowers are used as insect repellent in paddy godowns. It is toxic to horses leading to temporary blindness [4]. This plant produces a large number of coumarins, and has been found to be relatively rich in secondary metabolic products.

2. Geographical Distribution

The plant is fairly well distributed from Afghanistan to India (Kashmir), Pakistan, Iran, Iraq, Russia, Turkey, Central Asia and Caucasian at an altitudinal range of 780–3300m. The plant is common around Dras in Ladakh, Banihal pass in Kashmir and Zanskar range (Western Himalaya). It can grow in semi-shade or no shade but requires moist soil and an average rainfall of 900–1300mm. This is a hardy perennial plant, mainly

*Corresponding author:
E-mail: nimihygiene@yahoo.co.in

suited for mountainous areas and limestone slopes. The plant grows in light (sandy) and medium (loamy), slightly acidic to neutral (pH – 6.3 to 7.3) well drained soil [5].

3. Collection

The plant flowers in the month of June. The fruits are collected in the months of August and September when they are just mature as they are liable to shedding if allowed to over-ripen on the plant. Umbels are cut by hand, dried, threshed and packed in cloth bags. The collection of roots is best carried out in the months of October and November when the aerial portions have dried up and the root lies in a dormant condition [5].

4. Botanical Features

P. pabularia L. is a bushy herb with stems reaching up to a height of 1m, branched and leafy. Leaves are long (30 –45cm), pinnate; many a time divided into linear filiform segments. Flowers are yellow in compound umbels (15–45cm) with linear bracts. Pedicels are 15–25 in number, 4–8mm, whereof 4–8 may produce fruits. Fruits are oblong or oval, upto 2cm x 1cm, with characteristic spongy undulate wings, commissure broad; carpels ½ - terete, dorsally compressed, inner face nearly plane but the epicarp thin, introflexed in a deep T-shaped groove; epicarp spongy; primary ridges large, subequal or the lateral larger; vittae small, numerous; carpophores 2–partite. The fruits have an aromatic odour and a sharp, sweet taste. When kept for long time the smell resembles that of cat's urine. Seeds are dorsally compressed (2–2.5mm), inner face slightly concave, with a deep narrow T – shaped groove. Roots strongly smell and have a bitter metallic taste [6–10].

5. Microscopical Characteristics

The pharmacognostic study of the roots of *P. pabularia* has been reported by Abrol and Kapur. The transverse section of fruit showed, the epicarp consisting of a single layer of thin walled rectangular and tangentially elongated cells with thick cuticle and absence of stomata. Five schizogenous secretory canals and five vascular bundles were embedded in the parenchymatous cells of mesocarp along with 20–26 vittae of various sizes. Endocarp consists of single layer of radially compressed and tangentially elongated cells. Endosperm consists of compact polygonal thick walled cells. Each cell is filled with granular material, oil globules, aleurone grains and prism shaped calcium oxalate crystals [11–12].

6. Phytochemistry

Phytochemical tests have shown that *P. pabularia* is a rich source of coumarin derivatives and terpenoids. Roots are good source of coumarins like prangenin. Fresh leaves contain 2% essential oil containing myrcene (48%), α-pinene (4%), borneol, dihydrocuminol and acetates (17.5%), resinous residue (28.8%) [13]. On dry weight basis the leaves are reported to contain protein – 10.4%; fat – 3.5%, crude fibre - 22.6% [9]. Dried fruit contains an essential oil, a trace of fixed oil, resins, traces of an alkaloid, quercitin in large amount and ethereal salt of valeric acid [2].

Prangosine is the only alkaloid so far obtained from the species [14]. A new furanocoumarin, pabularinone, has been isolated from roots [15]. Structures of pabularinone and pabulenol, two new minor furocoumarin constituents of *P. pabuaria* have been elucidated from spectral studies and chemical reactions and subsequently confirmed by their synthesis and correlation with compounds of known structure. Pabularinone, a linear furocoumarin, is an 8-phenoxyxanthotoxol derivative [16].

Osthol and its isomer are the two non-furanolactones isolated till date. Merancin, its hydrate, psoralen, 8-(3-chloro-2-hydroxy-3-methyl-butanoxy) psoralen, oxypeucedanin, oxypeucedanin hydrate, oxypeucedanin hydrate 3'-*O*-β-D-glucopyranoside, peucedanin, imperatorin, isoimperatorin, bergapten, heraclenin, heraclenol, heraclenol 3'-*O*- β-D-glucopyranoside, heraclenol 3'- Me ester, prangine, prangenine, prangenidine, suberosin, isopimpinellin, xanthotoxin have been isolated from roots, umbels and seeds. Heraclenin is the dextro form of imperatorin oxide [17–23].

Prangenidin was identified with alloimperatorin (prangenidin), by means of spectral data and chemical behaviour. Distillation of imperatorin in vacuo gave alloimperatorin [20]. Alloimperatorin was obtained from total alkaloids from the seeds of *P. pabulaira* [24]. Imperatorin oxide (prangenin) has been identified in

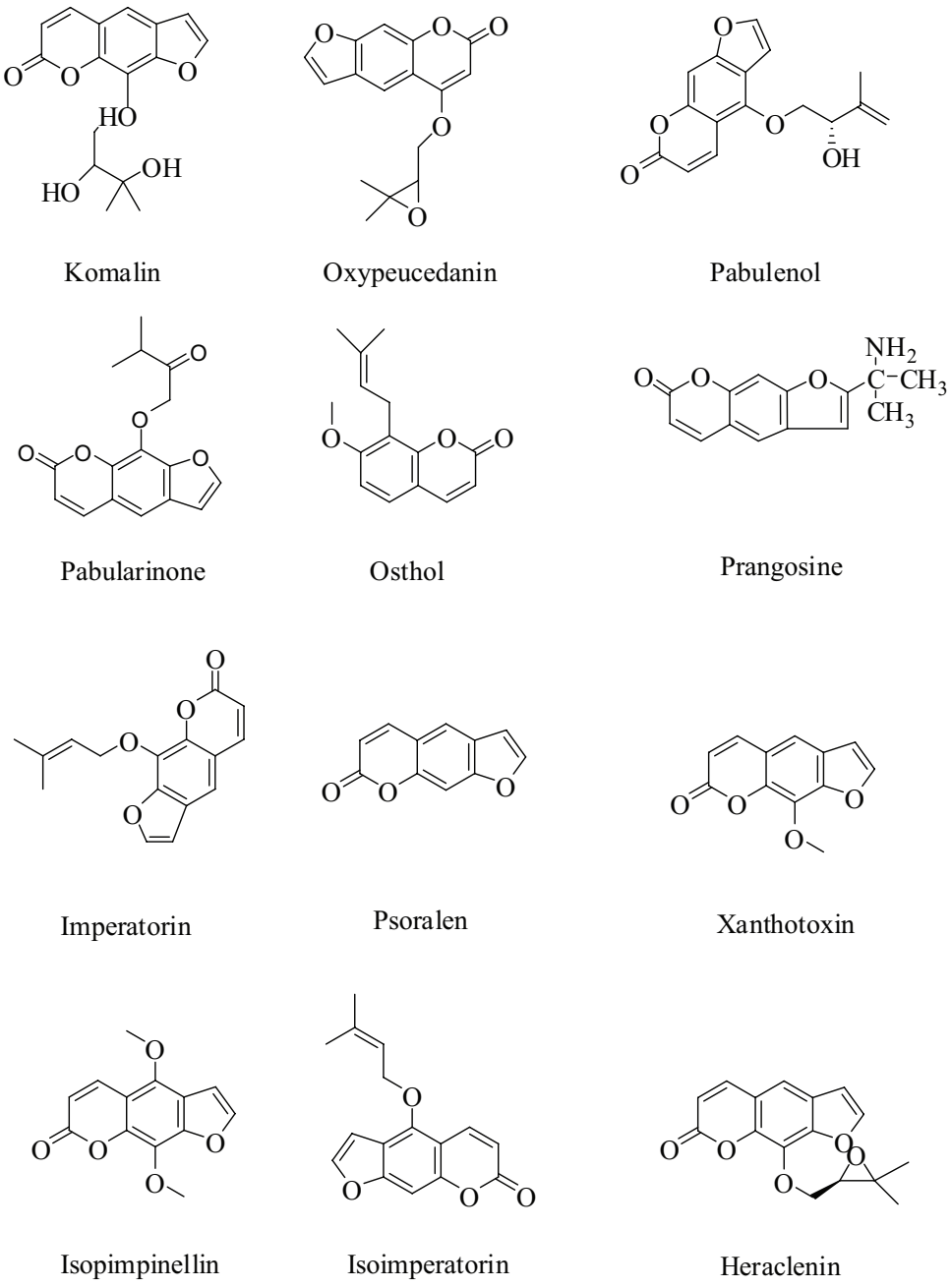

Fig. 1 Structures of some of the chemical constituents of *Prangos pabularia*

P. pabularia roots [25]. Prangenin is neither the normal nor the sec-butyl ether of xanthotoxol. It may be the t-butyl ether; however, the butyl ethers of phenols are very rare in nature [26].

Prangolarin, an optical isomer of oxypeucedanin, has been isolated from the roots [27]. It is dextrorotatory. The UV and IR spectral results suggest it to be a furo-coumarin. Two furanocoumarins – aviprin & komalin have also been isolated from the roots. The structure of aviprin has been elucidated as a linear furanocou-marin substituted at C8 with an oxygenated prenyl re-sidue or oxypeucedanin hydrate and that of komalin as δ-lactone of 7-(2,3-dihydroxy-3-methylbutoxy)-6-hyd-roxy-5-benzofuran acrylic acid or heraclenin glycol [28].

The repeated column chromatography of the methanol extract gave a mixture of two inseparable compounds

which on acetylation and subsequent fractionation were isolated and on deacetylation gave coumarin glucosideviz. 4-[3-(β-D-glucopyranosyloxy)-2-hydroxy-3-methyl butoxy]-7H Furo [3, 2-g] [1] benzopyran-7-one, 9-[3-(β-D-glucopyranosyloxy)-2-hydroxy-3-methyl butoxy]-7H Furo [3, 2-g] [1] benzopyran-7-one along with methyl ether of alloimperatorin [29].

Earlier reports described the presence of some coumarins and terpenoids in this plant. The n-hexane and ethyl acetate extracts of the stems and the ethyl acetate extracts of roots from *P. pabularia* afforded an γ-pyrone derivative; maltol-(6-*O*-acetyl)-β-D-glucopyranoside, and furanocoumarin derivatives with three glucose and γ-pyrone (pabularin A, B and C), along with 26 previously known compounds (18 coumarins, six terpenoids and two glycosides). Their structures were established on the basis of spectroscopic studies. Known compounds - Oxypeucedanin methanolate, oxypeucedanin hydrate-2'-*O*-monoacetate, tamarin, auraptenol, osthol, paniculal, majurin, rivurobirin E, loliolide, 2,3,4-trimethylbenzylalcohol-*O*-β-D-glucopyrano-side, 1,1,5-trimethyl-2-hydroxymethyl-(2,5)-cyclohexadien-(4)-one-*O*-β-D-glucopyranoside, 1,1,5-trimethyl-2-hydroxymethyl-(5)-cyclohexene-(4)-one-*O*-β-D-glucopyranoside, spathulenol, kauranol, β-sitosterol- β-D-glucopyranoside and 1-*O*-isopropyl-β-D-glucopyranoside have for the first time been isolated from *P. pabularia* [30].

The presence of behenic, arachidic, stearic, palmitic, oleic and petroselenic acids in saponifiable and β-carotene, a coumarin derivative and some pigments in non-saponifiable part of seed oil have been reported [31].

The rhizomes of *P. pabularia* on hydrodistillation yielded 1.2% of a brown coloured oil. The TLC and GLC analysis of the essential oil has led to the identification of camphene, limonene, Δ - carene, phellandrene, terpinolene, camphor, carvone, β and γ – elemene, β – caryophyllene, β – selinene, citronellyl, geranyl acetate, eudesmol, elemole, β – caryophyllene oxide, myrcene, α – pinene, p – cymene, borneol, cinnamaldehyde, osthol and imperatorin [32et–33].

The composition of the essential oils isolated from leaves, fruits and umbels of this plant was analyzed using GC-MS. The results showed that the leaves' oil was dominated by sesquiterpene derivatives with spathulenol, α-bisabolol, and (Z)-4-methoxycinnamaldehyde as major constituents. The fruits and umbels oil were characterized by monoterpenes comprising of α-pinene and santalene and p-methoxyacetophenone as the main compounds. The essential oils of the fruits and leaves of the plant were also dominated by α-humulene and camphene respectively. Essential oil of the plant leaves was dominated by the oxygenated sesquiterpenes and sesquiterpene hydrocarbons while the oils of fruits and umbels of the plant were characterized by monoterpene hydrocarbons. The composition of the chemical constituents varies among plants due to different chemotypes, environmental and genetic factors, and the nutritional status of the plants or any other factors that can influence the oil composition [34].

The resin obtained by the alcoholic extraction of roots and leaves+stalks of *P. pabularia* yielded oxypeucedanin hydrate and osthol, pabulin respectively. Pabulin is a furocoumarin derivative and could be an isomer of prangenin [35].

7. Therapeutic Potential

The fruit is used as carminative, laxative, stomachic, stimulant, emmenagogue, alexiteric, tonic to the liver; lessens inflammation and griping pain; used in lumbago and in the treatment of leukoplakia, in Indian system of medicine. It is said to promote expulsion of the foetus [6-9]. It also possesses diuretic properties. The seed is used as an aphrodisiac. The roots are a valuable remedy in the cure of itch; they are used as diuretic and emmenagouge. Infusion of roots is given for indigestion and irregularity in menses. Root infusion is given twice a day in small doses up to one week or more to cure indigestion [36]. Extracts of the genus *Prangos* were reported to stop bleeding and heal scars when applied externally [37].

The roots, in combination with *Terminalia chebula*, *Emblica officinalis* and other plants are used orally in the form of tablets; 3 tablets thrice daily for 8 to 10 days or till recovery, against all kinds of kidney and urinary disorders, soothing and controls urine discharge, inflammation and bleeding in the kidney [38].

Infusion of the fruit (1 in 20); decoction of the root (1 in 20) are used in doses of 1 to 2 fluid ounces; given in urinary diseases, gravel, strangury and dyspepsia; also in dropsy and gonorrhoea [39]. Fresh leaves are crushed

into a thick paste and this paste is applied on scorpion bites with ghee to relieve pain [40].

The essential oil of *Prangos pabularia* is possibly of therapeutic importance [41]. B-caryophyllene possesses cytotoxic effects with IC_{50} values comparable to the commercial drug vinblastine. However, different constituents of the oil though present in small amount, could synergistically contribute towards the inhibition of the cell population growth [42]. The oil imparts antimicrobial activity too [43].

Coumarins are considered phytoalexins since they are produced by the plant as a defence mechanism against attack by other organisms [44–45]. They have a variety of bioactivities including anticoagulant, estrogenic, dermal photosensitising, antimicrobial, vasodilator, molluscacidal, antithelmintic, sedative and hypnotic, analgesic and hypothermic activity. Coumarin-containing plants are valuable as dietary supplements on the basis of their mild antimicrobial and anti-inflammatory effects.

Furanocoumarins have a high spectrum of cytotoxic, phytotoxic, photosensitizing, insecticidal, antibacterial, antifungal, antiproliferative, antioxidant, anticonvulsant and anticoagulant activities. They are inhibitors of different enzymes and block the synthesis of some metabolites [46–47].

The coumarins that have been isolated have moderate antibiotic activity. An interesting compound, Osthol, has been isolated from *P. pabularia*. This coumarin is able to inhibit P-388 D1 cells *in vivo* and to induce apoptosis in HeLa and HL-60 cells *in vitro*, demonstrating it to be a good lead compound for developing antitumour drugs [48]. It has also been found to possess antioxidant properties [49]. Osthol raised blood pressure and stimulated respiration. It caused stimulation of cardiac muscles and constriction of peripheral blood vessels. It antagonized to some extent action of respiratory depressants such as phenobarbital, pentobarbital and morphine. It inhibited activity of smooth muscles of intestine and uterus and showed antagonism to acetylcholine and histamine. Osthol showed analeptic action on respiration and heart, stimulated brain functions and had antiacetylcholine and antihistaminic actions. In dogs and rabbits, toxic doses caused convulsions, vomiting and stimulation of respiration [50–51]. It is also used as an antidote in the poisoning due to hypnotics and anti-inflammatory agent [52–53].

Osthol has a high therapeutic window and is free from any chronic toxicity [54]. In an attempt to overcome the insolubility, absorption, syringeability problems it faces, a micellar solubilization of osthol in dimethylacetamide-water mixture (50% v/v) with the help of Brij 35 (10% w/v) has been worked out. The mixture remained clear and possessed good flow properties and could thus be injected easily. The formulation tested on rabbits showed that the drug was well absorbed from the vehicle. The solubilised form could effectively reverse the depression of respiration caused. Comparison of bioavailability of osthol from solubilised formulation and from a solution in propylene glycol: water mixture showed that, osthol is about 50% more effective in the solubilised formulation [55].

Free 6-OH in the coumarin nucleus has been found to be important for antifungal activity, while the free hydroxyl group at position 7 is important for antibacterial activity [56]. Psoralen exhibited inhibitory effect on *Staphylococcus aureus* by disc-diffusion [57]. Four (oxypeucedanin methanolate, oxypeucedanin, imperatorin & osthol) of the sixteen coumarin derivatives isolated from the stems and roots of *P. pabularia*, screened for antibacterial activity by the disc-diffusion test for methicillin-sensitive *S. aureus* (MSSA), methicillin-resistant *S. aureus* (MRSA), *E. coli* and *Pseudomonas aeruginosa* showed weak activity, but were inactive against the gram negative organism *Escherichia coli*. However, osthol showed significant activity against *S. aureus* and *P. aeruginosa*. The isolated compounds were also tested for inhibition of cytokine (IL-1, IL-4, IL-1β and TNF-α) release. Twelve compounds i.e. oxypeucedanin hydrate, oxypeucedanin, heraclenol, heraclenol-3'-Me ester, imperatorin, isogospherol, ulopterol, tamarin, osthol, majurin, 1,1,5-trimethyl-2-hydroxymethyl-(5)-cyclohexene-(4)-one-*O*-β-D-glucopyranoside and 1-*O*-isopropyl- β-D-glucopyranoside, inhibited produ-ction of IL-1, IL-4, IL-1β and TNF-α. Ten of these significantly affected the production of TNF-α thus proving them effective immunosuppressive agents [30, 58].

Oxypeucedanin methanolate, xanthotoxin and bergapten have growth inhibitory capacity for a number of malignant cell lines *in vitro*; against human gastric adenocarcinoma MK-1 cell growth [59].

Interestingly, coumarins have also inhibitory effect on DNA gyrase which may be linked to the anti-HIV (human immunodeficiency virus) activity [60], xanthotoxin was first introduced in the treatment of vitiligo over 50 years ago [61].

The phototoxicity of linear furanocoumarins (also referred to as psoralens) has been turned into a useful property when combined with controlled UVA irradiation, this PUVA treatment has been widely used for psoriasis. Administration of oral or topical psoralens (such as xanthotoxin) followed by irradiation with long wave ultraviolet radiation in the 320–400 nm range (UVA) is now a widely used, frequently convenient and effective systemic treatment of psoriasis with well-characterised and controllable side effects [62–63]. PUVA suppresses the accelerated proliferation of the keratinocytes, another mechanism of action in psoriasis is suggested to be a result of its direct lymphotoxic effects. In case of major acute adverse reactions associated with PUVA and xanthotoxin (nausea, vomiting, pruritus and erythema), xanthotoxin can be replaced with bergapten. Besides psoriasis, skin diseases like cutaneous T-cell lymphoma, atopic dermatitis, alopecia areata, urticaria pigmentosa and lichen planus [64–65] are treated with the photochemotherapy with linear furanocoumarins and UVA.

The results of phytotoxic assay showed that the oil of *P. pabularia* could play an allelopathic role for the plant. Allelopathic potential of the *P. pabularia* oil is dependent to the presence of spathulenol and bisabolol that compose the main fractions of the oil. Accordingly, the oil can be used for the control of weeds as a bioherbicide [34].

Aviprin is a bioactive compound that exhibits profound antibacterial, antifungal and phytotoxic activities. Phytotoxic assays showed that aviprin significantly reduced seed germination of lettuce in a dose dependent manner. The germination was completely stunted at an IC_{50} value of 0.270 mg/ml. This implies that it can be utilised for the purpose of managing weeds, pathogens, and to combat pathogenic bacteria, fungi and herbivorous insects. It displayed potent antifungal effects against *Sclerotinia sclerotiorum* and antibacterial activity on both bacilli and cocci gram positive bacteria. It is more bioactive than aviprin glucoside (aviprin-3"-*O*-glucoside) that might be attributed to the presence of sugar moiety [66].

Bergapten and umbelliferone demonstrated both anti-inflammatory and analgesic activities in mice [67]. Osthol and xanthotoxin revealed only anti-inflammatory activity, and isoimperatorin only analgesic effect. Interestingly, coumarins can also possess pro-inflammatory effects: lower doses of psoralen and imperatorin have shown an anti-inflammatory effect but at higher doses they have a pro-inflammatory effect.

Woo and co-workers (1983) investigated the effects of coumarins on the drug-metabolising enzymes and found imperatorin, isoimperatorin, oxypeucedanin, isooxypeucedanin, and oxypeucedanin methanolate (in decreasing order) to retard the drug metabolism both *in vitro* and *in vivo*. Xanthotoxin, psoralen and bergapten inhibited monoamine oxidase (mouse brain) [68].

Apart from the above mentioned effects coumarins display a wide variety of industrial uses, primarily due to strong fragrant odour [69]. 6-methylcoumarin is mainly used as a flavour enhancer, and 7-hydroxycoumarin in sunscreens.

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