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Review on Pharmacological effects of *Plectranthus forskohlii* (Willd) Briq.

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ABSTRACT

Plectranthus forskohlii (Willd). Briq. (Syn: *Coleus forskohlii*) is an important indigenous medicinal plant in India. It has been used in traditional Ayurveda medicine for curing various disorders and this is the only source of the diterpenoid forskolin. Forskolin is used for the treatment of eczema, asthma, psoriasis, cardiovascular disorders and hypertension, where decreased intracellular cAMP level is believed to be a major factor in the development of the disease process. A comprehensive account of the morphology, medicinal uses, phytochemistry, pharmacological activities, analytical methods and biotechnological approaches for forskolin production reported are included in view of the many recent findings of importance on this plant.

***Keywords*:** *Plectranthus forskohlii*; Phytochemistry; Pharmacology; Forskolin

1. INTRODUCTION

Plectranthus forskohlii (Willd) Briq. (Syn. *C. forskohlii*) that belongs to the family Lamiaceae, commonly known as *Coleus*, Pashanbedi (Sanskrit), Patharchur (Hindi), Manganiperu (Kannada), Marunthu koorkan (Tamil) which is grown throughout the country. Its tuberous roots are found to be a rich source of forskolin (Coleonol) used as a potential drug for hypertension, obesity, bronchitis, asthma, respiratory disorders, painful urination, insomnia and psoriasis.,(Ammon *et al*, 1982).

Clinical studies forskolin also indicate it may have therapeutic benefit in angina and prevention of cancer metastases (Ammon *et al*, 1985).

P. forskohlii is considered to be originated Himalaya of Kumaon in Nepal, Bihar and Deccan peninsular of south India as well as Srilanka, Apparently, it has been distributed to Egypt, Arabia, Ethiopia, Tropical East Africa and Brazil.

In India, the plant is found on dry, barren hills at an altitude of about 2400 m with moderate rainfall of 400-500 mm and a mean annual temperature of 18-27 °C. The crop is being commercially grown in large area in Madhya Pradesh, Maharashtra, Kerala, Karnataka and Tamil Nadu.

2. Taxonomic status

P. forskohlii is a member of mint family, Lamiaceae. It is indigenous to india and is recorded in Ayurvedic "Materia Medica" under the Sanskrit name "Makandi" and "Mayani" (Shah 1996). Taxonomic position of *P. forskohlii (C.forskohlii*) is as follows

Kingdom: Plantae
Class: Dicotyledones
Subclass: Gamopetalae
Series: Bicarpellatae
Order: Lamiales
Family: Lamiaceae
Genus: *Plectranthus*
Species: *forskohlii.* (Syn*: C.forskohlii*)

3. Botanical description

P. forskohlii is a perennial plant that grows to about 45-60 cm tall and aromatic in nature. It has four angled stems that are branched and nodes are often hairy. Leaves are 7.5 to 12.5 cm in length and 3 to 5cm in width, usually pubescent, narrowed into petioles. Inflorescence is raceme, 15-30 cm in length; flowers are stout, 2 to 2.5 cm in size, usually perfect and calyx hairy inside. Upper lip of calyx is broadly ovate. The blue or lilac corolla is bi labiate. Lower lobes are elongated and concave so that they enclose the essential organs. The ovary is four parted and stigma is two lobed and the flower is cross-pollinated by wind or insects (Bailey *et al,* 1942) The roots are tuberous, thick, fibrous, brown in colour, orange-red within and strongly aromatic. *P. forskohlii* is the only species of the genus to have fasciculated tuberous roots. The leaves and tubers have quite different odours. However, the growth habit of *P. forskohlii* is strikingly variable being erect, procumbent or decumbent; similarly, the root morphology in different populations is also fascinatingly diverse, being tuberous, semi tuberous or fibrous (Non tuberous).

4. Uses in folklore medicine

In India, the major medicinal species of *Plectranthus* is the tuberous *P. forskohlii*. *P. amboinicus, P. blumei, P. malabaricus* and *P. scutellaroides* are other species and are mainly used to treat dysentery and digestive disorders (De Souza *et al*., 1983). *P. forskohlii* is widely used in different countries for various ailments. In Egypt and Africa, the leaf is used as an expectorant, emmenagogue and diuretic. In Brazil, it is used as a stomach aid and in treating intestinal disorders (Valdes *et al.,* 1987). It is used as a condiment in India and the tubers are prepared as pickle and eaten. In traditional Ayurvedic systems of medicine, *P. forskohlii* has been used for treating heart diseases, abdominal colic, respiratory disorder, insomnia, convulsions, asthma, bronchitis, intestinal disorders, burning sensation, constipation, epilepsy and angina (Ammon and Muller, 1985). The roots are also used in treatment of worms and to alleviate burning in festering boils. When mixed with mustard oil, the root extract is applied to treat eczema and skin infections. The plant is also used for veterinary purposes (De Souza and Shah, 1988). Forskolin is also used in the preparation of medicines preventing hair greying and restoring grey hair to its normal color. Though grouped as a medicinal plant, it also contains essential oil in tubers, which has very attractive and delicate odour with spicy note (Misra *et al*., 1994). Essential oil has potential uses in food flavoring industry and can be used as an antimicrobial agent (Chowdhary and Sharma, 1998).

5. Phytochemical properties of *P. forskohlii*

The tuberous root extracts of *P. forskohlii* contain minor diterpenoids *viz.*, deactylforskolin, 9-deoxyforskolin, 1,9-deoxyforskolin, 1,9-dideoxy-7-deacetylforskolin in addition to forskolin (7-acetoxy-8,13-epoxy-1,6,9-trihydroxylabd-14-en-11-one) (Ammon and Kemper, 1982; De Souza and Shah, 1988).

Forskolin was discovered in the year 1974 and was initially referred to as Coleonol. After the identification of other coleonols and diterpenoids the name was later changed to forskolin (Saksena *et al.*, 1985). Shah *et al.* (1980) reported that forskolin occurred exclusively in *P. forskohlii* and could not be detected in other *Plectranthus* species viz., *P. amboinicus*, *P. blumei*, *P. canisus*, *P. malabaricus*, *P. parviflorus* and *P. spicatus*, *P.coesta*, *P. incanus*, *P. melissoides*, *P. mollis*, *P. rugosus* and *P. stocksii*. Studies carried out using one hundred samples belonging to species of *Plectranthus* and *Orthosiphon* of the sub family Ocimoideae at Japan also revealed the absence of forskolin in all the samples. Second generation forskolin derivatives *viz.*, 5-6-deoxy-7-deacetyl-7-methyl amino carbon forskolin (HIL568), a potential anti glaucoma agent and 6- (3-dimethylamino propionyl) forskolin hydrochloride (NKH477), a potential cardio tonic agent were developed (Hosono *et al.*,1990). Newer compounds are being identified from the root extracts of *P. forskohlii*. Xu *et al.* (2005) obtained six compounds from the roots of *P. forskohlii* and identified structuresas14-deoxycoleon U, demethyl crypto japonol, alpha-amyrin, betulic acid, alpha-cedrol and beta-sitosterol and the compounds *viz*., alpha-amyrin and betulic acid were isolated from *P. forskohlii* for the first time. Two new diterpenoids forskolin I (1alpha, 6-beta-diacetoxy-7-beta, 9-alpha-dihydroxy-8,13-epoxylabd-14-en-11-one) and J, (1alpha, 9-alpha-dihydroxy-6-beta, 7-beta-diacetoxy-8,13-epoxylabd-14-en-11-one) were isolated from *P. forskohlii* plants collected in Yunnan Province (Shen and Xu, 2005).

Recently, two more new labdane diterpene glycosides, forskoditerpenoside A, B were also isolated from the ethanol extract of the whole plant (Shan *et al.*, 2007). This was the first report about the occurrence of glycosides derived from labdane diterpene in the nature and these compounds showed relaxative effects on isolated guinea pig tracheal spirals *in vitro*. Later, three new minor labdane diterpene glycosides, forskoditerpenoside C, D and E and a novel labdane diterpene forskoditerpene A from the ethanol extract of the whole plant of *P. forskohlii* were isolated (Shan et al.,2008). Forskoditerpenoside C, D and E showed relaxative effects on isolated guinea pig tracheal spirals *in vitro* and an unusual 8,13-epoxy-labd-14-en-11-one glycoside pattern. Forskoditerpene A is the first known labdane derivative with a spiro element. Forskolin is in great demand in Japan and European countries for its medicinal use and related research purposes.

6. Extraction and separation of Forskolin

Forskolin is extracted from the root tuber of *P. forskohlii*. The tubers are harvested at 75 to 85% moisture level on wet basis and stored at less than 12% moisture after drying. Sun drying required longer period than mechanical drying and recorded the lowest recovery of forskolin. Tubers mechanically dried at 40°C with tuber slice thickness of 0.5 cm and packed in poly ethylene lined gunny bag retained the highest amount of forskolin (Rajangam,2005). Different chromatographic methods are employed for quantification of forskolin and gas-liquid chromatography (GLC) method is the first developed method (Inamdar *et al.*,1980). Later, thin layer and high performance liquid chromatographic (HPLC) methods are employed. HPLC method is found to be more rapid and less sensitive than GLC and used to monitor variation in forskolin Content in different germplasm (Inamdar *et al.*,1984). A

monoclonal antibody specific for forskolin has been developed for affinity isolation of forskolin and it has been used for extremely sensitive quantification of forskolin in plant tissues at different stages of development (Yanagihara *et al*.,1996). Nuclear magnetic resonance data and gas chromatography-mass spectral method are also used for forskolin quantification (Demetzos *et al*., 2002). Reversed-phase liquid chromatography with a photo diode array detector at 210 nm is successful in the qualitative and quantitative evaluation of forskolin in plant material and in market products claiming to contain forskolin (Schanebera and Khan, 2003). A simple, safe, rapid and economical reverse phase high performance liquid chromatography (RP-HPLC) method using activated charcoal as an adsorbent in column is developed for the isolation of high-purity forskolin (Saleem *et al*.,2006). Wu *et al.* (2007) reported that HPLC-ELSD finger print method can be used in quality control of *C. forskohlii.*

7. Anti-Obesity

Henderson *et al.* (2005) suggested that *C. forskohlii* does not appear to promote weight loss but may help mitigate weight gain in over weight females with apparently no clinically significant side effects. The anti-obesity effects of *C. forskohlii were* investigated in ovariectomized rats (Han *et al*., 2005) and the administration of *C. forskohlii* extracts reduced body weight, food intake and fat accumulation in those rats suggesting that *C. forskohlii* may be useful in the treatment of obesity.

8. Heart disorder and Hypertension

In, Modern medicine, through pharmacological studies it was established that Forskolin has a positive inotropic action on cardiac tissue via increased cAMP levels. Which lowered normal or elevated blood pressure in different animal species through a vasodilatory effect (De Souza *et al*.1983; Dubey *et al* 1981).

C. forskohlii has traditionally been used to treat hypertension, congestive heart failure, and angina. Coleus's basic cardiovascular action is to lower blood pressure, while simultaneously increasing the contractility of the heart. This is believed to be due to forskolin's Cyclic AMP-elevating ability, which results is relaxation of the arteries, and increased force of contraction of the heart muscle. A preliminary trial found that *Coleus* reduced blood pressure and improved heart function in people with cardiomyopathy. Coleus also increases cerebral blood flow, indicating that it may be beneficial in cerebral vascular insufficiency, and in enhancing post-stroke recovery. The platelet aggregation-inhibiting effects of coleus also add to its value in cardiovascular disorders.

9. Glaucoma

Glaucoma is characterized by elevated intraocular pressure (IOP). Glaucoma is a condition in which the pressure in the eye is too high, due to an imbalance between the formation of aqueous humour in the eye and its absorption in or drainage out of the eye. Eventually, as the pressure builds up, the blood vessels nourishing the optic nerve are constricted, resulting in irreversible damage to the nerve and impaired vision culminating in blindness, if left untreated. Several animal and human studies have demonstrated the ability of forskolin to lower IOP, possibly via cAMP activation and a reduction in aqueous flow.

The effect of forskolin on aqueous humour dynamics and intraocular pressure was first described by Capriole and Sears. The topical application of forskolin lowered the intraocular pressure in rabbits, monkeys and healthy human volunteers and it was associated with a reduction in aqueous inflow and no change in outflow facility indicating the potential of

forskolin as a therapeutic agent in the treatment of glaucoma. However, Lee *et al*, reported that forskolin had no lasting effect on intraocular pressure in monkeys with glaucoma. It also showed no effect on humans in reducing aqueous flow when apply topically to the eye (Brubaker *et al*, 1987).

10. Asthma

Asthma and other allergic conditions are characterized by decreased cAMP level in bronchial smooth muscle, as well as high levels of PAE. In response to allergenic stimuli, mast cells degranulate, histamine is released and bronchial smooth muscle contracts. Forskolin's activation of cAMP inhibits human basophil and mast cell degranulation, resulting in subsequent bronchodilation.

Forskolin was studied as bronchodilator for its potential use in the treatment of asthma (Bruka *et al*, 1986). The blocked bronchospasm, the chief characteristic of asthma and bronchitis in guinea pigs caused by histamine and leukotriene C-4 (Marone *et al*, 1987). A study involving human revealed that inhaled forskolin powder formulations were capable of causing brochodilation in asthma patients (Bauer *et al*, 1993). Forskolin seems to be a promising drug if used in an appropriate dosage for treatment of patients with congestive heart failure, glaucoma and asthma (Rupp *et al*, 1986).

11. Cancer metastases

Research has shown *Coleus* to be a potent inhibitor of tumor colonization in mice. It is theoretically possible that coleus could be used in human to prevent or inhibit tumor metastases. Many metastasizing tumour cell lines induce platelet aggregation both *in vitro* and *in vivo*. Upon the aggregation, platelets release substances that promote tumour growth. Researchers have demonstrated forskolin's ability to block platelet aggregation via its stimulation of platelet adenylate cyclase and increase of intracellular cAME. 82ulg of forskolin to mice 30-60 minutes prior to injection with a highly metastastic melanoma cell line (B16 F10) reduced tumour colonization in the lungs by 70 percent (Agarwal *et al*, 1983).

12. Antithrombotic effect

Forskolin inhibits platelet aggregation through adenylatecyclase stimulation, augmenting the effects of prostaglandins (Adnot *et al*, 1982 and Siegl *et al*, 1982). Its antithrombotic properties may be enhanced by cerebral vasodilation and it was observed in rabbits. This vasodilation was not potentiated by adenosine (Wysham *et al*, 1986). The use of crude *C. forskohlii* extract as a rational phyto-therapeutic antithrombotic has been proposed (De Souza *et al*, 1988).

13. Psoriasis

In Psoriasis, cell divide about 1,000 times faster than normal. Coleus helps to alleviate psoriasis by normalizing the cAMP/cGMP ratio. Like asthma, psoriasis is characterized by decreased levels of cAMP in the skin in relation to another regulating substance, cyclic guanosine monophosphate (cGMP)., Ammon *et al* reported an improvement in symptoms of psoriasis patients supplemented with forskolin. The ability of forskolin to regulate cAMP levels in skin cells has been shown to have therapeutic benefit for the sufferers of psoriasis (Ammon and Muller, 1985).

14. Depression

Depression is believed to be associated with an imbalance of neurotransmitters in the brain, serotonin and dopamine primarily. Where there is a shortage of serotonin, the supplements 5-HTP or tryptophan or the SSRI drugs like Prozac or Zoloft may be beneficial. If the catecholamine neurotransmitters (epinephrine, norephinephrine) are deficient the amino acids L-Phenylalanine or L-Tyrosine, or monoamine oxidase inhibitors like Gerovital (GH3) or Deprenyl may be helpful. Recent research has also been evaluating drugs that increase cAMP as a means of elevating the catecholamines. Since forskolin elevates cAMP, it may improve neurotransmitter function and thereby relieve depression. Clinical trials using coleus to treat depression have not been done.

15. Increasing Lean Body Mass

The health promoting value of increasing lean body mass can be directly appreciated due to the known benefits derived from the use of forskolin drugs as a supplementary building lean body mass and stamina. The abdominal fatty tissue is a significant risk factor for cardiovascular disease, and it has been demonstrated that by stimulating cyclic AMP by forskolin may increase the circulation of anabolic hormones and enhance their utilization which would theoretically lead to increased lean body mass.

Studies have shown that selective inhibitors of phosphodiesterase (PD) enzymes (group of enzymes inactivating cyclic AMP) and forskolin are the potent activator of the hypothalamo-pituitary-adrenal (HPA) axis when given orally or intra peritoneally to rodents. The content of cyclic AMP in hypothalamic tissue increased in response to forskolin. At the same time CRH (corticotropin or ACTH releasing hormone) was released and steroid hormones were synthesized. The selective inhibitors of PD enzymes worked synergistically with forskolin increasing steroidogenesis.

16. CONCLUSION

The present review has been done to disseminate knowledge of *Plectranthus forskohlii* the distribution, medicinal uses, phytochemistry, analytical methods and various aspects of forskolin. The pharmacological and biochemical studies reviewed in this paper through widely exposed that forskolin possesses multifaceted biological activities of forskolin. This Indian drug plant needs very badly modern integrated disease management technology and improved agriculture practices to increase the area of cultivation of this medicinal plant to satisfy the growing demand in pharmaceutical industry on one side, and at the same time the wild plants may be saved from indiscriminate exploitation. The selection of suitable molecular tools may also help to increase the produce of *P. forskohlii* in future. To argument the knowledge about *P. forskohlii* for future research this review paper information provides a complete knowledge and information about *P. forskohlii*.

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