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A Comprehensive Review : Coleus Forskohlii

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Abstract

Coleus forskohlii is an important indigenous medicinal plant in India. It has been used in traditional Ayurvedic medicine for curing various disorders and this is the only source of the diterpenoid forskolin. . Forskolin has a unique property of activating almost all hormone sensitive adenylate cyclase enzymes in a biological system & 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 disease process. This review article has through light on a comprehensive account of the morphology, distribution, medicinal uses, phytochemistry, pharmacological activities and biotechnological approaches for forskolin production.

Keywords: *Coleus forskohli*, medicinal uses, pharmacological activities.

Introduction

Plants are the first medicines for mankind and hundreds of plant species are harvested for their medicinal properties all over the world. In spite of modern development of sophisticated pharmaceutical chemicals to treat illnesse, medicinal plants remain an important tool for treating illness. The world market for plant derived chemicals viz., pharmaceuticals, fragrances, flavours and colour ingredients exceed several billion dollars per year. The demand for the products obtained from these plants such as phytochemical, steroidal, biologically active compounds, alkaloids, etc Classic examples of phytochemicals in biology and medicine include taxol,vincristine, vinblastine, colchicine as well as the Chinese antimalarial - artemisinin and the Indian ayurvedic drug -forskolin.

Forskolin obtained only from Indian species of Coleus forskholi. Forskolin has a unique property of activating almost all hormone sensitive adenylate cyclase enzymes in a biological system [1]. Forskolin is reported to be useful in the treatment of congestive heart failure, glaucoma, asthma and certain type of cancers [2]. In addition, it has been shown to have anti-inflammatory property [3].

C. forskohlii is the only source of forskolin & one of the most potential medicinal crops of the future, as its pharmacopieal properties have been discovered recently [4.] The pharmaceutical industries recognize it as most medicinally and economically important. It is said that the all plant parts of Indian herb *C. forskohlii* almost have traces of forskolin, the roots are the main source possessing 0.1 to 0.5 per cent and preferred for its extraction [5].The pharmaceutical industries are mainly dependent upon the wild population of the plant for the supply of tuberous roots for forskolin extraction. The large scale and indiscriminate collection of the wild material from the forests and inadequate attempts either to allow its replenishment or its cultivation has led to *C. forskohlii* being listed as endangered species [6]

Plant Profile

Coleus forskohlii Briq. [Synonym *C. barbatus* (Andr.) Benth.] Is a member of the mint, family Lamiaceae. It is indigenous to India and is recorded in Ayurvedic *Materia Medica* under the Sanskrit name 'Makandi' and 'Mayani", it is controversial drug mainly taken as Pashanabheda.

The taxonomic position
Kingdom - Plantae
Division - Magnolophyta
Class - Magnoliopsida
Order - Lamiales
Family - Lamiaceae
Genus - *Coleus*
Species – *forskohlii*

Vernacular names

Sanskrit- Pashanbhed

Hindi - Patharchur

Kannada - Makandiberu
English - Coleus
Gujarati - Garmalu
Marathi - Maimnul

Tamil - Koorkan kilangu[7]

VARIETIES

a) The genus *Coleus* consists of 150 species and the following species *viz., C. amboinicus, C. forskohlii, C. spicatus* and C. *malabaricus* occur naturally [13.]
b) Today there are more than 500 varieties of coleus in cultivation all over the world[9]
c) Mangani Peru- grown in Belgaum district in Karnataka [.8]
d) KARMAI- GROWN IN GUJRAT roots of medium size.[8]
e) "SELECTION-K"- A non-flowering type, has been found good under Karnataka & Tamilnadu conditions. All the growing areas are using this type only.[9]

Geographical Distribution

Indian sub-continent is considered as the place of origin of *C. forskohlii*. It is distributed over the subtropical warm temperate climatic zone on mountains of India, Nepal, Myanmar, Sri Lanka, Thailand and Africa. Apparently, it has been distributed to Egypt, Arabia, Ethiopia, tropical East Africa and Brazil in India, it is grown in Gujarat, Bihar, Deccan Plateau, parts of Rajasthan, Maharashtra, Karnataka and Tamil Nadu. In Tamil Nadu, it is approximately grown in Salem, Dharmapuri, Trichy, Erode, Coimbatore and Dindigul districts of 6000 acres. In India, plant is also found mostly on the dry and barren hills.Longitudinal and altitudinal range for the occurrence of the species is between 80 and 310 N and 600-800m, respectively.[7]

BOTANICAL DESCRIPTION

C. forskohlii is a perennial plant However, the growth habit of *C*oleus is strikingly variable being erect, procumbent decumbent. Similarly, the root morphology in different populations is also fascinatingly diverse, being tuberous, semi tuberous or fibrous [11]

Height	45-60 cm tall.
Stem	It has four angled stems that are branched & nodes are often hairy.
Leaves	Leaves are 7.5 to 12.5 cm in length &3-5 cm in width, usually pubescent, narrowed into petioles.
Inflorescence	Raceme, 15 to 30 cm in length.
Flowers	Are stout,2-2.5 cm in size, usually perfect &calyx hairy inside
Calyx	The upper lip of calyx is broadly ovate.
Corolla	The blue or lilac corolla is bilabiate. Lower lobes are elongated and concave so that they enclose the essential organs.
Ovary	It is four parted & stigma is two lobed & flowers are cross pollinated by insects or wind.
Root	The root is typically golden brown, thick, fibrous &radially spreading. Roots are tuberous, fasciculate, 20 cm long &0.5 to2.5 cm in diameter, conical fusiform, straight, organish within an strongly aromatic. C.forskohlii is the only species of genus to have fasciculate tuberous roots.
Odour	The leaves and tubers have quite different odours, the latter being reminiscent of but quite different from Ginger.

Active Constituents

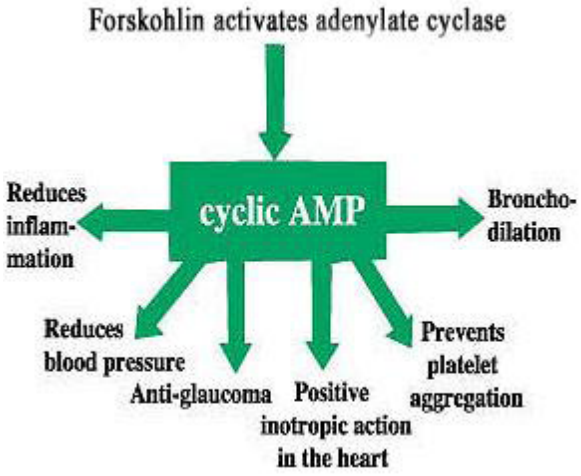
The diterpene forskolin, derived from the root of the plant, is the primary constituent of clinical interest in *Coleus forskohlii*.[12] It was discovered by Western scientists in 1974 and was initially referred to as coleonol. Since that time, as other coleonols and diterpenoids have been identified, the name was changed to forskolin.[13] There is evidence, however, that other plant constituents, such as volatile oils and other diterpenoids and coleonols, may contribute to the pharmacological activity and absorption of forskolin.[14] Detailed analysis reveals approximately 20 constituents in various parts of the plant, but forskolin and other coleonols are present only in the root portion.[15]

MEDICINAL USES

Forskolin showed positive effects against a wide range of conditions such as asthma [16],glaucoma [17], hypertension [18].cancer[19], heart diseases[20] diabetes [21] and obesity [22]. It also showed inhibition of platelet activating factor [23] increase in the rate of sensory nerve regeneration in freeze-lesioned sciatic nerves [24],. Its foliage is also employed in treating intestinal disorders and used as a condiment since long. Flavonoids are present in both the roots and tubers of *C. forskohlii* as flavonoids are known to act as antioxidant.[25]

Mechanism of action

1) Forskolin is a diterpene that acts directly on adenylate cyclase [(26).] Adenylate Cyclase is an enzyme that activates Cyclic Adenosine Monophosphate, or Cyclic AMP (cAMP) in the cell. An intracellular second messenger responsible for inducing the cellular response to hormonal activation. Because forskolin effectively activates cAMP, it has been used in numerous research studies to explore the mechanisms and effects of cAMP. Within the body, hormones bind to extracellular membrane receptors on their target cells. Following hormone-receptor binding, adenylate cyclase is activated from the inner cellular membrane. Adenylate cyclase catalyzes the conversion of adenosine triphosphate (ATP) to cAMP. This conversion fosters the activation of cAMP-dependent enzymes. The cAMP-dependent enzymes in turn activate or inhibit the specific enzymes within the cell, thereby eliciting the response associated with the binding hormone. Catecholamine's, adrenocorticotropic hormone, and vasopressin are among the many hormones that elicit action via the cAMP second messenger system.[27]



EXTRACTION AND SEPARATION OF FORSKOLIN

1) Forskolin is extracted from tuber. 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 polyethylene lined gunny bag retained the highest amount of forskolin [28].
2) Different chromatographic methods are employed for quantification of forskolin and gas-liquid chromatography (GLC) method is the first developed method 65. 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[29.]
3) 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[30].
4) Nuclear magnetic resonance data and a gas chromatography-mass spectral method are also used for forskolin quantification[31]. Reversed-phase liquid chromatography with a photodiode 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 [32].
5)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 [33].

BIOGENESIS

1) The forskolin is biosynthesized from acetate-mevalonate pathway. In the postulated biosynthetic pathway 8,13- epoxy-labd-14-en-11-one is the first mono oxygenated labdane type diterpene to be formed on biosynthetic pathway leading from the labdane diterpene skeleton, subsequent addition of oxygen gives 1,9-dideoxy forskolin, 9-deoxyforskolin and forskolin with other terpenes. Forskolin is the last compound to be formed in the biogenetic sequence. Molecular cloning and functional expression of geranylgeranyl pyrophosphate synthase from *C. forskohlii* have been demonstrated.[9]

PHYTOCHEMISTRY

1) The tuberous roots of the plant produce labdane diterpenoid forskolin [34]. Forskolin (7β-Acetoxy-8, 13-epoxy-1α, 6 β, 9 α-trihydroxy-labd-14-ene-11-one) a labdane diterpene compound is the active principle (Shah et al., 1980)36. Minor diterpenoids, deacetylforskolin, 9-deoxyforskolin, 1, 9- deoxyforskolin, 1, 9-dideoxy-7-deacetylforskolin, and four other diterpenoids, have been reported to be present in the roots of *C. forskohlii* [35]
2) Second generation forskolin derivatives *viz*., 5-6-deoxy-7-deacetyl-7-methyl amino carbon forskolin (HIL 568), a potential antiglaucoma agent and 6-(3-dimethylamino propionyl) forskolin hydrochloride (NKH 477), a potential cardiotonic agent were developed [37].

IN VITRO FORSKOLIN PRODUCTION

Study on tissue culture methods for forskolin production was carried out because of the relatively modest
Content of forskolin in the plant has limited its development as a drug[38]. Forskolin was identified in shoot differentiating culture, micro propagated plants and root organ suspension by TLC and HPLC. Forskolin were obtained following infection with *Agrobacterium tumefaciens* (C58) were established in produced by shoot differentiating culture was similar as that of the micro propagated plants whereas root organ suspension showed only traces of forskolin [39]. reported that root cultures of *C. forskohlii* initiated from primary callus or IBA-treated suspension cultures and maintained on Gamborg's B5 medium containing 1 mg l-1 IBA produced forskolin and its derivatives in amounts ranging from 500 to 1300 mg kg-1 dry weight, corresponding to about 4

to 5 mg l-1.Suspension cultures derived from gall calli which *C. forskohlii*.40 Studies on cell line selection following single cell cloning or cell aggregate cloning were carried out to select cell lines capable of fast growth and for producing high level of forskolin. A fast growing cell line (GSO-5/7) was found to accumulate 0.021% forskolin in 42 days. The effect of cultural conditions on cell growth was studied to identify factors influencing biomass yield. Cell growth in suspension was found to be influenced significantly by carbon source, initial cell density and light or dark condition. Optimal cell growth (20 fold increase in biomass in a 42 day period) was obtained when the cells were grown in dark condition in B5O media containing 3% sucrose as sole carbon source with an initial cell density of 1.5 x 10(5) cells per ml. Forskolin accumulation was maximum (0.021%) in the stationary phase of cell growth.[8]

Pharmacological activities

Coleus forskohlii has been used to treat hypertension, congestive heart failure, eczema, colic, respiratory disorders, painful urination, insomnia, and convulsions. Clinical studies of the plant and the forskolin constituent support these traditional uses, but also indicate that it may have therapeutic benefit in asthma, angina, psoriasis, and prevention of cancer metastases[40].

Clinical conditions

Antithrombotic effect

Forskolin inhibits platelet aggregation through adenylate cyclase stimulation, augmenting the effects of prostaglandins [42]. Its antithrombotic properties may be enhanced by cerebral vasodilation and it was observed in rabbits. This vasodilation was not potentiated by adenosine [43].

Asthma and Allergies

Asthma and other allergic conditions are characterized by decreased cAMP levels in bronchial smooth muscle, as well as high levels of PAF. In response to allergenic stimuli, mast cells degranulation, histamine is released and bronchial smooth muscle contracts. Forskolin's activation of cAMP inhibits human basophil and mast cell degranulation, resulting in subsequent bronchodilation.14 Research has demonstrated aerosolized dry forskolin powder results in significant relaxation of bronchial muscles and relief of asthma symptoms.[42]
1) Alcohol extracts of fourteen plants traditionally used in India for antiallergic disorders were evaluated for their antiallergic activity. *Coleus forskohlii, Nyctanthes arbortristis, Pterocarpus santalinus, Rubia cordifolia* and *Momordica dioica* were found to inhibit passive cutaneous anaphylaxis (PCA) in the mouse and rat[44].

Antiobesity activity

Oral ingestion of forskolin (250 mg of 10% forskolin extract twice a day) for a 12-week period was shown to favourably alter body composition while concurrently increasing bone mass and serum free testosterone levels in overweight and obese men. The results indicate that forskolin is a possible therapeutic agent for the management and treatment of obesity[45].

Anti-inflammatory

The extracts of Coleus forskohlii prepared by using hexane, chloroform, methanol, 80% methanol and water as solvents were screened for secondary metabolites and for its in vitro anti-inflammatory activity. Of all the extracts methanolic and aqueous extracts showed maximum activity[46]

Obesity and Weight Loss

A number of recent studies have shown that the active ingredient in *coleus forskohlii* can help patient's burn excess body fat more efficiently. The herb's active ingredient stimulates signalling agents within adipose tissue, leading to the breakdown of triglycerides and the subsequent release of fatty acids and glycerol into the bloodstream.[47]

Drug/Botanical Interactions

1) Because forskolin has an inhibitory effect on platelet aggregation, it should be avoided or used With caution in conjunction with anticoagulant medications.[43]

2) Caution should be used when giving forskolin with antihypertensive agents as it may have a potentiating effect on this drugs.[18]

Side Effects and Toxicity

Coleus forskohlii and forskolin extracts have an excellent safety profile and are generally without toxicity or side effects at the recommended dosage.[42]

Conclusion

In the present review, an attempt has been made to congregate the morphology, distribution, medicinal uses, phytochemistry, and various aspects of *C. forskohlii*. The available evidence indicates that *C. forskohlii* is the only known natural source of the diterpenoid forskolin. The pharmacological and biochemical investigations established that forskolin possesses multifaceted biological activities. This Indian drug plant needs attention for their degradation of germplasm by pharmaceutical industries and other stresses. However, the screening of the herb is needed to identify, isolate, design, develop, modify or to prepare new pharmacologically active compounds other than forskolin. The mechanisms of action of various secondary metabolites isolated from this potential medicinal herb are yet to be elucidated. But most of the studies used concentrated extract of forskolin in a non-oral delivery form for treating various disorders in animal models only and the effect of oral forskolin in humans has not been well established. Moreover still, there is paucity for the mechanism of other bioactive principles present in the herb except forskolin. Further researches in view of applicability of forskolin for treating human ailments without side effects and activity of other bioactive principles other than forskolin are needed.

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