European Journal of Medicinal Plants
1(1): 1-9, 2011

SCIENCEDOMAIN *international*
www.sciencedomain.org

The Strategies for Production of Forskolin vis-a-vis Protection Against Soil Borne Diseases of the Potential Herb *Coleus forskohlii* Briq.

Selima Khatun[1], Narayan C. Chatterjee[1] and Ugur Cakilcioglu[2]*

[1]UGC Centre of Advanced Study, Department of Botany, University of Burdwan, Burdwan 713104, West Bengal, India
[2]Elazig Directorate of National Education, Dogukent IOO., Elazig 23100, Turkey

Received 12th December 2010
Accepted 19th December 2010
Available online 28th January 2011

Review Article

ABSTRACT

Coleus forskohlii is an important plant in Indian Ayurvedic medicine. It is the only source for forskolin among the plant kingdom. Forskolin has a unique property of activating almost all hormone sensitive adenylate cyclase enzymes in a biological system. This review article has highlighted on research developments of *C. forskohlii* for the production and to enhance the production of forskolin by employing various strategies, and also to protect the most potential herb against the soil borne wilt disease, causing a serious threat towards its propagation and cultivation by using effective integrated disease management technology.

Keywords: biosynthesis, Coleus forskohlii, forskolin, medicinal plant, tissue culture;

1. INTRODUCTION

Forskolin, a labdane diterpene is the active principle of the medicinal plant *Coleus forskohlii* (Willd.) Briq. [synonym *C. barbatus* (Andr.) Benth.] of family Lamiaceae. It is an ancient root drug of Indian origin (Shankaragowda, 2000) in Ayurvedic material medica (Shah, 1996). It is reported on morphology, phytochemistry and pharmacological aspects of *C. forskohlii* (Reddy et al., 2005; Kavitha et al., 2010). Forskolin has a unique property of activating almost all hormone sensitive adenylate cyclase enzymes in a biological system (De Souza and Shah, 1988). Forskolin is reported to be useful in the treatment of congestive heart failure, glaucoma, asthma and certain type of cancers (Bhat et al., 1993). It is an important plant used against various disorders in indigenous systems of medicine such as anti-aging, antioxidant, as a remedy for heart, abdominal and respiratory disorders. In addition, it has been shown to have anti-inflammatory property (Rupp et al., 1986). *C. forskohlii* is the only source for this compound. Apart from the anthropological stresses, the plants are facing continuously different types of pathogenic attack, among which wilt caused by *Fusarium* sp. is the most important one, occurring in severe form thereby posing a threat to its propagation and cultivation.

**Corresponding author: Tel.: +90 506 7936609; fax: +90 424 2332020; Email: ucakilcioglu@yahoo.com*

The pharmacological and biochemical investigations established that forskolin possesses multifaceted biological activities. The research & development of *C. forskohlii* by employing various strategies is necessary for the production and to enhance the production of forskolin. Also use of effective integrated disease management technology is required to protect the most potential herb against the soil borne wilt disease, which is causing a serious threat towards its propagation and cultivation.

2. FINDINGS AND DISCUSSIONS

2.1 ORIGIN AND GEOGRAPHICAL DISTRIBUTION

Indian sub-continent is considered as the place of origin of *C. forskohlii* (Valdes et al., 1987; Shankaragowda, 2000). 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 (Willemse, 1985) In India, it is grown in Gujarat, Bihar, Deccan Plateau, parts of Rajasthan, Maharashtra, Karnataka and Tamil Nadu (Somnath et al., 2005). 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 (Anon, 1950). Longitudinal and altitudinal range for the occurrence of the species is between 8^0 and 31^0 N and 600-800m, respectively.

2.2 PHYTOCHEMISTRY

The tuberous roots of the plant produce labdane diterpenoid forskolin (Bhat et al., 1977). 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). 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* (Gabetta et al., 1989). 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 (Hosono et al*.,* 1990). Newer compounds are being identified from the root extracts of *C*. *forskohlii*. Xu et al. (2005) obtained six compounds from the roots of *C*. *forskohlii* and identified structures as 14-deoxycoleon U, demethylcryptojaponol, alpha-amyrin, betulic acid, alpha-cedrol and beta sitosterol and the compounds *viz*., alpha-amyrin and betulic acid were isolated from *C*. *forskohlii* for the first time. Two new diterpenoids forskolin I (1 alpha, 6 beta diacetoxy-7 beta, 9 alpha-dihydroxy-8, 13-epoxylabd-14-en-11-one) and J, (1 alpha, 9 alpha-dihydroxy-6 beta,7 beta diacetoxy- 8,13-epoxylabd-14-en-11-one) were isolated from *C*. *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 *C*. *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.

2.3 BIOGENESIS

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. Engprasert et al. (2004) proposed

that forskolin was synthesised from Isopentenyl diphosphate (IPP), a common biosynthetic precursor via a non-mevalonate pathway. GGPP synthase is thought to be involved in the biosynthesis of forskolin, which is primarily synthesized in the leaves and subsequently accumulates in the stems and roots.

2.4 MEDICINAL USES

Forskolin showed positive effects against a wide range of conditions such as asthma (Lichey et al.,1984), glaucoma (Caprioli and Sears, 1983), hypertension (Dubey et al., 1981; De Souza et al., 2006), cancer (Agarwal and Parks, 1983; Li and Wang, 2006), heart diseases (Kramer et al., 1987), diabetes (Ammon et al.,1984; Gold et al., 1988) and obesity (Allen et al., 1986). It also showed inhibition of platelet activating factor (Nourshargh and Hoult, 1986; Dde-Chaffoy De et al., 1987), increase in the rate of sensory nerve regeneration in freeze-lesioned sciatic nerves (Kilmer and Carlsen, 1984), stimulation of water and cation permeability in aquaporin 1 water channels (Yool et al.,1996) and direct alteration of gating of a single class of voltage-dependent potassium channels from a clonal pheochromocytoma (PC12) cell line independent of adenylate cyclase activation (Hoshi et al., 1988). 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.

2.5 MECHANISM OF ACTION

Forskolin being the major chemical constituent of the tuber, herbal preparations of it act on various multiple pharmacologic mechanisms. The blood pressure lower-ing antispasmodic effects of extracts of *C. forskohlii* roots were reported by Dubey et al. (1974) based on the extensive screening of Indian plants for biological activity at the Central Drug Research Institute, Lucknow. De Souza (1977) found that the methanol extracted from the root tuber is helpful in lowering blood pressure and positive inotropic activities in animal models. Singh and Tandon (1982) compared physico-chemical properties of coleonol, forskolin and their derivatives and reported that the two compounds do not have the same structure and are stereoisomers that is, they differed only in the configuration of the acetate (-OAc) group at carbon 7; in forskolin it was β while in colenol it was α. The pharmacological studies of forskolin and coleonol indicated that they had identical properties (Seamon and Daly, 1981). The principle mechanism by which forskolin exerts its hypotensive activity is by stimulation of adenylate cyclase and thereby increasing cellular concentrations of the second messenger cyclic AMP (cAMP) (Seamon et al., 1981; Rupp et al., 1986). The mechanisms of interaction of forskolin were studied in detail (Zhang et al., 1997; Tesmer et al., 1997; Tang and Gilman, 1995). Forskolin directly activates almost all hormonesensitive adenylate cyclases in intact cells, tissues and even solubilised preparation of adenylate cyclase (Metzger and Lindner, 1981). The unique feature of this activation is that the site of action for forskolin is the catalytic subunit of the enzyme or a closely associated protein (Seamon and Daly, 1981). Of the 9 types of adenylate cyclase in humans, forskolin can activate all except type IX, which is found in spermatozoa (Iwatsubo et al., 2003). Stimulation of adenylate cyclase is thought to be the mechanism by which forskolin relaxes a variety of smooth muscles. This action of forskolin proved the potential use of the molecule, not only as an invaluable research tool for understanding cyclic AMP dependent physiological processes, but also as a potential therapeutic agent for diseases like cardiac insufficiency, hypertension, glaucoma, thrombosis, asthma and metastatic condition (Seamon, 1984). Forskolin, by increasing cAMP level in turn, inhibits basophil and mast cell degranulation and histamine release, (Marone et al., 1987) lowers blood pressure (Dubey et al., 1981) and intraocular pressure, (Caprioli et al., 1984) inhibits platelet aggregation, (Agarwal and Parks, 1983; Wong et al., 1993) promotes vasodilation, (Dubey et al., 1981; Wysham et al., 1986) bronchodilation, (Lichey et al., 1984) and thyroid hormone secretion and stimulates lipolysis in fat cells (Haye et al., 1985; Roger et al.,1987).

2.6 HISTOCHEMICAL LOCALIZATION OF FORSKOLIN AND OTHER TERPENOIDS

Histochemical analysis showed that forskolin is found in the cells of cork, cortex, medullary rays and xylem in roots and tuber of *C. forskohlii* (Narayanan et al., 2002; Khatun and Chatterjee, 2010a). Forskolin is reported to give violet coloration with vanillin in acetic acid and perchloric acid, which has been used as a spectrometric method for detection and quantification (Inamdar et al., 1984). TLC of

chloral hydrate washings showed presence of forskolin and other terpenoids in roots and tubers of *C. forskohlii.* Rf value of forskolin is 0.48 .This confirmed that the yellowish-red masses seen in the sections contain the terpenoids (Abraham et al., 1988).

2.7 EXTRACTION AND SEPARATION OF FORSKOLIN

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 (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 a gas chromatography-mass spectral method are also used for forskolin quantification (Demetzos et al., 2002). 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 (Schaneberg 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; Selima Khatun and Narayan Chandra Chatterjee, Department of Botany, Burdwan University, Burdwan, India, personal communication). Wu et al. (2007) reported that HPLC-ELSD fingerprint method can be used in quality control of *C*. *forskohlii.*

2.8 *IN VITRO* PROPAGATION

In vitro propagation is useful for mass multiplication and germplasm conservation of any plant species. *C. forskohlii* being succulent in nature responds well to *in vitro* propagation and various explants *viz*., nodal segments, shoot tip, leaf etc., are effectively used. Shoot tip explants from 30 days old aseptically germinated seedlings are also used for multiplication using 2 mg/l of 6-benzylaminopurine (Sen and Sharma, 1991). Reddy et al*.* (2001) developed a plant establishment protocol from leaf derived callus and found that the *in vitro* raised plants produce comparable quantity of forskolin with that of wild plants. Complete plantlets of *C. forskohlii* were developed within 35-40 days by culturing shoot tip explants in MS medium containing 0.57 µM IAA and 0.46 µM kinetin through direct multiplication at the rate of 12.5 shoots per explant (Rajasri and Sabita, 2001). The significance of the protocol is the formulation of growth regulators which affected very fast multiplication of the plant in less time that is, one-third time less of the hitherto known methods. Leaf explants of *C. forskohlii* induced callusing when cultured on MS media supplemented with 1 mg/L BAP with 2 mg/l NAA. Regeneration of shoot-lets is observed after 7 weeks of initial culture (Anbazhagan et al., 2005).

2.9 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 (Mukherjee et al., 2000). Forskolin was identified in shoot differentiating culture, micropropagated plants and root organ suspension by TLC and HPLC. Forskolin produced by shoot differentiating culture was similar as that of the micropropagated plants whereas root organ suspension showed only traces of forskolin (Sen et al., 1992). Krombholz et al. (1992) 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 were obtained following infection with *Agrobacterium*

tumefaciens (C58) were established in *C. forskohlii*. 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.

2.10 MASS PRODUCTION OF MYCORRHIZAL FUNGI INOCULUM AND YIELD OF FORSKOLIN

C. forskohlii have been used as host plants for their suitability to multiply VAM fungal inoculums in soil pot culture (Bagyaraj, 1992; Gracy and Bagyaraj, 2005). Influence of different AM-fungi on the growth, nutrition and forskolin content of *C. forskohlii* has been reported (Gracy and Bagyaraj, 2005). Seasonal variation of VAM colonization in roots and its associated rhizospheric soil of *C. forskohlii* have been reported (Khatun and Chatterjee, 2008). Application of Farm manure 0f 10 t ha^{-1} +40:60:50 NPK kg ha^{-1} or poultry manure of 3 t ha^{-1} resulted in significantly higher plant height, plant spread, laterals per plant, leaf area per plant, dry tuber yield (1.7 and 1.5 t ha^{-1}) and forskolin content (0.28-0.31%) is not affected by the sources of nitrogen (Vennila and Jayanthi, 2008). The forskolin yield at 60 cm × 30 cm of spacing was 154.59 mg/plant and harvested at 180 days after planting under irrigated condition is recorded to be significantly higher than other treatments (Mastiholi and Hiremath, 2009). However, if proper cultivation practices are applied, a yield of up to 2000 to 2200 kg ha^{-1} of dry tubers can be easily obtained (Rajamani and Vadivel, 2009). *C. forskohlii* is mainly cultivated under contract farming system in India. A study conducted by Agila et al. (2006) concluded that minimum risk in farming, assured price for the harvested produce, reduction in price risk, elimination of middle men, assured income and availability of financial support, technical guidance from the company, timely availability of inputs, awareness about appropriate technology are the major effective factors for better performance of the Coleus contract farming.

2.11 ENDANGERED WITH DISEASES - A MAJOR PROBLEM

Indiscriminate collection of *C. forskohlii* has led to rapid depletion of wild populations resulting in its listing as a plant vulnerable to extinction in India (Gupta, 1988). The plant is highly susceptible to root rot and wilt caused by *Fusarium chlamydosporum,* causing serious losses but inoculation with *Trichoderma viride* and *Glomus mosseae* will give the best result in controlling the disease (Boby and Bagyaraj, 2003). The root rot caused by *Macrophomina phaseolina* affects the tuber yield up to 100% and application of bioformulation viz., *Trichoderma harzianum* and zinc sulphate exerted maximum reduction in root rot incidence (Kamalakannan et al., 2006). *Glomus fasciculatum* and *Pseudomonas fluorescens* are most effective treatments that reduced 56-65% and 61-66%, under lower and higher levels of pathogen *F. chlamydosporum* (Singh et al., 2009). The plant also suffers tremendously from a wilt pathogen, *Fusarium oxysporum* (ITCC No.6933.08) which results in great economic loss to our country like India during its cultivation. But successful use of root infection with an AM fungus, *G. fasciculatum,* is found to be a potentially effective protection against *F. oxysporum* (Khatun and Chatterjee, 2010b). The leaf eating caterpillars, mealy bugs and root knot nematodes are the important pests that attack this crop.

3. CONCLUSION

In the present review, an attempt has been made to know the distribution, medicinal uses, phytochemistry, analytical methods and various aspects of *C. forskohlii*. The present study also indicates that it 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 very badly modern integrated disease management technology for their survival against diseases 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.

ACKNOWLEDGEMENT

First author Selima Khatun acknowledges the UGC, Government of India, New Delhi for granting Meritorious Fellowship as financial assistance.

REFERENCES

Abraham, Z., Srivastava, A.K., Bagchi, G.D. (1988). Cytoplasmic vesicles containing secondary metabolites in the root of *Coleus forskohlii.* Current Sci., 57, 1337–1339.

Agarwal, K.C., Parks J.R.E. (1983). Forskolin: a potential antimetastatic agent. Int. J. Cancer, 32, 801-804.

Agila, R., Manoharan, M., Ravi, K.C. (2006). Performance of Coleus under contract farming. In: Proc.: Int. Conf. on Globalization of Traditional, Complementary and Alternative Systems of Medicine held at Tamil Nadu Agric. Univ., Coimbatore, India, pp. 24.

Allen, D.O., Ahmed, B., Naseer, K. (1986). Relationships between cyclic AMP levels and lipolysis in fat cells after isoproterenol and forskolin stimulation. J. Pharmacol. Exp. Therapeut., 238, 659-664.

Ammon, H.P., Müller, A.B., Schmiedebergs, N. (1984). Effect of forskolin on islet cyclic AMP, insulin secretion, blood glucose and intravenous glucose tolerance in rats. Naunyn-Schmiedeberg's Arch. Pharmacol., 364-367.

Anbazhagan, K., Sathish, K. N., Hemavathi, V., Sathyanarayana, B.N. (2005). *In vitro* morphogenesis in *Coleus forskohlii.* J. Medicinal Aromatic Plant Sci., 27, 253-256.

Anonymous, (1950). *Coleus forskohlii*. In: Wealth of India – Raw materials, Vol. II. Council of Scientific and Industrial Research, New Delhi, India, p. 308.

Bagyaraj, D.J. (1992). Vesicular-arbuscular mycorrhiza: Application in agriculture, in: Norris, J.R., Read, D.J., Varma, A.K. (Eds.), Methods in Microbiology. Academic Press, London, pp. 359-373.

Bhat, S.V., Minale, L., Ricco, R., Zollo, F. (1993). Forskolin and congeners. In: Progress in the chemistry of organic natural products (Herz, W., Kirby, G.W., Moore, R.E., Steglich, W., Tamm, C.H., eds.) Springer-Verlag, New York, pp. 1-60.

Bhat, S.V., Bajwa, B.S., Dornauer, H., De Souza, N.J., Fehlababer, H.W. (1977). Structures and stereochemistry of new labdane diterpinoids from *Coleus forskohlii* Briq. Tetrahedron Lett., 18, 1669-1672.

Bhattacharya, R., Bhattacharya, S. (2001). *In vitro* multiplication of *Coleus forskohlii* Briq.: An approach towards shortening the protocol. In Vitro Cellular and Developmental Biology – Plant, 37, 572-575.

Boby, V.U., Bagyaraj, D.J. (2003). Biological control of root-rot of *Coleus forskohlii* Briq. using microbial inoculants. World J. Microbiol. Biotechnol., 19, 175-180.

Caprioli, J., Sears, M. (1983). Forskolin lowers intraocular pressure in rabbits, monkeys and man. Lancet, 1, 958–960.

Caprioli, J., Sears, M., Bausher, L., Gregory, D., Mead, A. (1984). Forskolin lowers intraocular pressure by reducing aqueous inflow. Investigative Ophthalmology and Visual Sci., 25, 268-277.

Dde-Chaffoy, De C., Roevens, P., Belle, H.V. (1987). Prostaglandin E1 and forskolin antagonize C-kinase activation in the human platelet. Biochemical J., 244, 93-99.

De Souza, N.J. (1977). In: Proceedings of the Third Asian symposium on medicinal plants and species. Colombo, Sri Lanka, UNESCO, pp. 83-92.

De Souza, N.J., Dohadwalla, A.N., Reden, U. (2006). Forskolin: A labdane diterpenoid with antihypertensive, positive inotropic, platelet aggregation inhibitory, and adenylate cyclase activating properties. Medicinal Res. Rev., 3, 201-219.

De Souza, N.J., Shah, V. (1988). Forskolin – an adenylate cyclase activating drug from an Indian herb. Economic and Medicinal Plant Res., 2, 1-16.

Demetzos, C., Kolocouris, A., Anastasaki, T. (2002). A simple and rapid method for the differentiation of C-13 manoyl oxide epimers in biologically important samples using GC-MS analysis supported with

NMR spectroscopy and computational chemistry results. Bioorg. Medicinal Chem. Lett., 12, 3605-3609.
Dubey, M.P., Srimal, R.C., Nityanand, S., Dhawan, B.N. (1981). Pharmacological studies on coleonol, a hypotensive diterpene from *Coleus forskohlii*. J. Ethnopharmacol., 3, 1-13.
Dubey, M.P., Srimal, R.C., Patnaik, G.K., Dhawan, B.N. (1974). Blood pressure lowering and antispasmodic effects of *C. forskohlii* Briq. Indian J. Pharmaceut. Sci., 6, 15.
Engprasert, S., Taura, F., Kawamukai, M., Shoyama, Y. (2004). Molecular cloning and functional expression of geranylgeranyl pyrophosphate synthase from *Coleus forskohlii* Briq. BMC Plant Biol. 4, 18.
Gabetta, B., Zini, G., Daniele, B. (1989). Minor diterpenoids of *Coleus forskohlii*. Phytochem., 28, 859–862.
Gold, G., Qian, R.L., Grodsky, G.M. (1988). Insulin biosynthesis in HIT cells. Effects of glucose,forskolin, IBMX and dexamethasone. Diabetes, 37, 160-165.
Gracy, L.S., Bagyaraj, D.J. (2005). Influence of different AM fungi on growth, nutrition and forskolin content of *Coleus forskohlii*. Mycological Res., 109, 795-798.
Gupta, R. (1988). Genetic resources of medicinal plants. Indian J. Plant Genetic Resour., 1, 98-102.
Haye, B., Aublin, J.L., Champion, S. (1985). Chronic and acute effects of forskolin on isolated thyroid cell metabolism. Molecular and Cellular Endocrinol., 43, 41-50.
Hoshi, T., Garber, S.S., Aldrich, R.W. (1988). Effect of forskolin on voltage-gated K+ channels is independent of adenylate cyclase activation. Sci., 240, 1652-1655.
Hosono, M., Takahira, T., Fujita, A., Fujihara, R., Ishizuka, O., Ohio, I., Tatee, T., Nakamura, K. (1990). Cardiovascular effects of NICH 477, a novel potent water soluble forskolin derivative. European J. Pharmacol., 183, 2110.
Inamdar, P.K., Dornauer, H., De Souza, N.J. (1980). GLC method for assay of forskolin, a novel positive inotropic and blood pressure-lowering agent. Journal of Pharmaceutical Sci., 69, 1449-1451.
Inamdar, P.K., Kanitkar, P.V., Reden, J., De Souza, N.J. (1984). Quantitative determination of forskolin by TLC and HPLC. Planta Med., 50, 30-34.
Iwatsubo, K., Tsunematsu, T., Ishikawa, Y. (2003). Isoform-specific regulation of adenylyl cyclase: A potential target in future pharmacotherapy. Experts Opinion Therapeutics Targets, 7, 441-451.
Kamalakannan, K., Mohan, L., Samiyappan, R., Chandrasekaran, A., Valluvaparidasan, V. (2006). Development of inoculum dependent management strategies for the control of Coleus (*Coleus forskohlii*) root rot caused by *Macrophomina phaseolina.* In: Proceedings of International conference on Globalization of Traditional, Complementary and Alternative Systems of Medicine held at Tamil Nadu Agricultural University, Coimbatore, p. 45.
Kavitha, C., Rajamani, K., Vadivel, E. (2010). *Coleus forskohlii*: A comprehensive review on morphology, phytochemistry and pharmacological aspects. Journal of Medicinal Plants Res., 4(4), 278-285.
Khatun, S., Chatterjee, N.C. (2008). Seasonal variation of VAM colonization in roots of a medicinal plant *Coleus forskohlii*. Plant Arch., 8(2), 919-922.
Khatun, S., Chatterjee, N.C. (2010a). Phytochemical constituents vis-a-vis histochemical localization of forskolin in a medicinal plant *Coleus forskohlii*. J. Medicinal Plants Res., 4(24) in press.
Khatun, S., Chatterjee, N.C. (2010b). *Glomus fasciculatum* in defense responses to fusarial wilt of *Coleus forskohlii*. Acta Agriculturae Scandinavica Section B- Soil Plant Sci., In press.
Kilmer, S.L., Carlsen, R.C. (1984). Forskolin activation of adenylate cyclase *in vivo* stimulates nerve regeneration. Nature, 307, 455-457.
Kramer, W., Thormann, J., Kindler, M., Schlepper, M. (1987). Effects of forskolin on left ventricular function in dilated cardiomyopathy. Arzneimittel Forsch., 37, 364-367.
Krombholz, R., Mersinger, R., Kreis, W., Reinhard, E. (1992). Production of forskolin by axenic *Coleus forskohlii* roots cultivated in shake flasks and 20-l glass jar bioreactors. Planta Med., 58, 328-333.
Li, Z., Wang, J. (2006). A forskolin derivative, FSK 88, induces apoptosis in human gastric cancer BGC 823 cells through caspase activation involving regulation of Bcl-2 family gene expression, dissipation of mitochondrial membrane potential and cytochrome c release. Cell Biol. Int., 30 (11), 940-946.
Lichey, I., Friedrich, T., Priesnitz, M., Biamino, G., Usinger, P., Huckauf, H. (1984). Effect of forskolin on methacholine-induced bronchoconstriction in extrinsic asthmatics. Lancet, 2, 167.

Marone, G., Columbo, M., Triggiani, M., Cirillo R., Genovese, A., Formisano, S. (1987). Inhibition of IgE-mediated release of histamine and peptide leukotriene from human basophils and mast cells by forskolin. Biochemical Pharmacol., 36, 13-20.

Mastiholi, A.B., Hiremath, S.M. (2009). Influence of spacing and time of harvest on forskolin content and yield in *Coleus forskohlii*. J. Medicinal and Aromatic Plant Sci., 31, 101-104.

Metzger, H., Lindner, E. (1981). The positive inotropic-acting forskolin, a potent adenylate cyclase activator. Arzneimittel Forsch., 31, 1248-1250.

Mukherjee, S., Ghosh, B., Jha, S. (2000). Establishment of forskolin yielding transformed cell suspension cultures of *Coleus forskohlii* as controlled by different factors. J. Biotechnol., 76, 73-81.

Narayanan, P., Laddha, K.S., Akamanchi, K.G. (2002). Histochemical localization of forskolin and other terpenoids in *Coleus forskolii.* Current Sci., 83, 945-946.

Nourshargh, S., Hoult, J.R.S. (1986). Inhibition of human neurophil degranulation by forskolin in the presence of phosphodiesterase inhibitors. Eur. J. Pharmacol., 122, 205-212.

Rajagam, J. (2005). Studies on the effect of planting methods and growth regulators on growth, tuber development, yield and quality, and standardization of postharvest technology of Coleus (*Coleus forskohlii* Briq.). Ph.D. Thesis, Tamil Nadu Agricultural University, Coimbatore, India.

Rajamani, K., Vadivel, E. (2009). Marunthu Kurkan – Medicinal *Coleus*. In: Naveena Mulikai Sagupaddi Thozhil Nuttpangal, Tamil Nadu Agricultural University, Coimbatore, India, 17-22.

Reddy, C.S., Desireddy, R.B., Ciddi, V. (2005). A review on forskolin: a cyclic AMP modulator from tissue cultures of *Coleus forskohlii.* Pharmacognosy Mag., 1 (3), 85-88.

Reddy, P.S., Rodrigues, R., Rajasekharan, R. (2001). Shoot organogenesis and mass propagation of *Coleus forskohlii* from leaf derived callus. Plant Cell Tissue Organ Cult., 66, 183-188.

Roger, P.P., Servais, P., Dumont, J.E. (1987). Regulation of dog thyroid epithelial cell cycle by forskolin and adenylate cyclase activator. Experimental Cell Res., 172, 282-292.

Rupp, R.H., De Souza, N.J., Dohadwalla, A.N. (1986). Proceedings of the International Symposium on Forskolin: Its chemical, biological and medical potential. Hoechst India Ltd., Bombay, 19-30.

Saleem, A.M., Dhasan, P.B., Rafiullah, M.R. (2006). Simple and rapid method for the isolation of forskolin from *Coleus forskohlii* by charcoal column chromatography. J. Chromatogr. - A, 1101, 313-314.

Schaneberg, B.T., Khan, I.A. (2003). Quantitative analysis of forskolin in *Coleus forskohlii* (Lamiaceae) by reversed-phase liquid chromatography. J. AOAC Int., 86, 467-470.

Seamon, K.B. (1984). Forskolin and adenylate cyclase: New opportunities in drug design. In: Annual Report on Medical Chemistry. (D.M., Bailey eds.). Academic Press, New York, 19, 293-302.

Seamon, K.B., Daly, J.W. (1981). Forskolin: a unique diterpene activator of cyclic AMP-generating systems. Journal of Cyclic Nucleotide Res., 7, 204-224.

Seamon, K.B., Padgett, W., Daly, J.W. (1981). Forskolin: unique diterpene activator of adenylate cyclase in membranes and in intact cells. Proceedings of the National Academy of Sci., USA, 78, 3363-3367.

Sen, J., Sharma, A.K. (1991). *In vitro* propagation of *Coleus forskohlii* Briq. for forskolin synthesis. Plant Cell Rep., 9 (12), 696-698.

Sen, J., Sharma, A.K., Sahu, N.P., Mahato, S.B. (1992). Production of forskohlin in *in vitro* cultures of *Coleus forskohlii*. Planta Med., 58, 324-327

Shah, V. (1996). Cultivation and utilization of medicinal plants (supplement), RRL and CSIR, Jammu – Tawai, 385-411.

Shah, V., Bhat, S.V., Bajwa, B.S., Dornaeur, H., De Souza, N.J. (1980). The occurrence of forskolin in Labiatae. Planta Med., 39, 183-185.

Shan, Y., Wang, X., Zhou, X., Kong, L., Niwa, M. (2007). Two minor diterpene glycosides and an eudesman sesquiterpene from *Coleus forskohlii*. Chemical and Pharmaceutical Bull., 55, 376-81

Shan, Y., Xu, L., Lu, Y., Wang, X., Zheng, Q., Kong, L., Niwa, M. (2008). Diterpenes from *Coleus forskohlii*. Chemical and Pharmaceutical Bull., 56, 52-56.

Shankaragowda, P. (2000). Evaluation of genotypes and standardization of production technology of *Coleus forskohlii* Briq. Ph.D. Thesis, University of Agricultural Sci., Bangalore.

Shen, Y.H., Xu, Y.L. (2005). Two new diterpenoids from *Coleus forskohlii*. J. Asian Natural Products Res., 7, 811-815.

Singh, R., Parameswaran, T.N., Prakasa Rao, E.V.S., Puttanna, K., Kalra A., Srinivas, K.V.N.S., Bagyaraj, D.J., Divya, S. (2009). Effect of arbuscular mycorrhizal fungi and *Pseudomonas*

fluorescens on root-rot and wilt, growth and yield of *Coleus forskohlii*. Biocontrol Sci. Technol., 19(8), 835-841.

Singh, S., Tandon, J.S. (1982). Coleonal and forskolin from *Coleus forskohlii*. Planta Med., 45, 62-63.

Somnath, S., Bhaskar, S., Sreenivasamurthy, C.A. (2005). Influence of Farmyard manure, inorganic fertilizers (NPK) and sources of potassium on the yield of *Coleus forskohlii.* J. Medicinal Arom. Plant Sci., 27, 16-19.

Tandon, J.S., Katti, S.B., Ruedi, P., Eugster, C.H. (1979). Crocetin-dialdehyde from *Coleus forskohlii* Briq. Labiatae. Analytica Chimica Acta, 62, 2706-2707.

Tang, W.J., Gilman, A.G. (1995). Construction of a soluble adenylyl cyclase activated by Gs alpha and forskolin. Sci., 268, 1769-1772.

Tesmer, J.J., Sunahara, R.K., Gilman, A.G., Sprang, S.R. (1997). Crystal structure of the catalytic domains of adenylyl cyclase in a complex with Gsalpha-GTPgamaS. Sci., 278, 1907-1916.

Valdes, L.J., Mislankar, S.G., Paul, A.G. (1987). *Coleus barbatus* (*C. forskohlii*) (Lamiaceae) and the potential new drug forskolin (Coleonol). Economic Bot., 44, 474-483.

Vennila, C., Jayanthi, C. (2008). Growth and yield of *Coleus forskohlii* as influenced by sources of nitrogen. Journal of Medicinal and Aromatic Plant Sci., 30:347-349.

Willemse, R.H. (1985). Notes on East African *Plectranthus* species (Labiatae). Kew Bul., 40, 93-96.

Wong, S., Mok, W., Phaneuf, S., Katz, S., Salari, H. (1993). Forskolin inhibits platelet-activating factor binding to platelet receptors independently of adenylyl cyclase activation. European J. Pharmacol., 245, 55-61.

Wu, H.Z., Yang, Q.R., Yang, Y.F., Liu, Y.W. (2007). Studies on HPLC-ELSD fingerprint of the *Coleus forskohlii* introduced in Tongcheng. Zhong Yao Cai, 30, 1370-1374.

Wysham, D.G., Brotherton, A.F., Heistad, D.D. (1986). Effects of forskolin on cerebral blood flow: implications for a role of adenylate cyclase. Stroke, 17, 1299-1303.

Xu, L.L., Lu, J., Li, W.J., Kong, L.Y. (2005). Studies on the chemical constituents in root of *Coleus forskohlii*. Zhongguo Zhong Yao Za Zhi, 30, 1753-1755.

Yanagihara, H., Sakata, R., Shoyama, Y., Murakami, H. (1996). Rapid analysis of small samples containing forskolin using monoclonal antibodies. Planta Med., 62, 169-172.

Yool, A.J., Stamer, W.D., Regan, J.W. (1996). Forskolin stimulation of water and cation permeability in aquaporin 1 water channels. Sci., 273, 1216-1218.

Zhang, G., Liu, Y., Ruoho, A.E., Hurley, J.H. (1997). Structure of the adenylyl cyclase catalytic core. Nature, 386, 247-253.
