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**FORSKOLIN: ITS THERAPEUTIC APPLICATIONS****KAUSHIK PURANAM AND SUREKHA RANI.H****Department of Genetics, Osmania University, Hyderabad, Telangana state, India***ABSTRACT**

Medicinal herbs are moving from fringe to mainstream use with a greater number of people seeking remedies. Forskolin, is a diterpene, the main active ingredient in the ayurvedic herb *Coleus forskohlii* has been used in India since prehistoric times in ayurvedic traditional medicine. *Coleus forskohlii* is a perennial aromatic herb found in subtropical regions of India, Nepal and Srilanka. Forskolin activates the enzyme adenylate cyclase, results in increased cAMP in cells. Cyclic AMP is involved in several biological processes, including inhibition of platelet activation, reduced release of histamine, increased force of contraction of the heart, relaxation of the arteries and other smooth muscles, and increased lipolysis and also cures various diseases like asthma, eczema, psoriasis, angina, obesity, hypertension, glaucoma, acts as anti-metastatic and protect cells from UV induced damage, ageing of skin. Studies are warranted to understand the effect of forskolin on various diseases for its utility in therapeutics.

KEYWORDS: Forskolin, *Coleus forskohlii*, Adenylate cyclase, cAMP activator, Medicinal importance, Therapeutic applications.

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INTRODUCTION

Plants are the first medical solution for mankind and thousands of plant species are selected for their medicinal properties all over the world. World Health Organization (2003) estimates that 80% of the world's population wants to tend towards traditional phyto medicine. In modern development of erudite pharmaceutical chemicals to cure various diseases, it is possible that medicinal plants from ayurveda play a distinct role in treating illness. In many developed countries, traditional herbal remedies are making retaliation as alternatives to modern medicine. India has a very long, safe and continuous usage of many herbal drugs in the officially documented alternative systems of health. Such a classic example of potent phytochemical in the medicine is the Indian ayurvedic drug – forskolin¹. Forskolin, is a diterpene, the main active ingredient in the ayurvedic herb *Coleus forskohlii* from family Labatae that has been used in India since prehistoric times in ayurvedic traditional medicine. It's commonly known as Coleus and sanskrit name is Pashanbedi, Makandi, Karpuravali and Sughandabalu. And the parts clinical interest is roots only. Forskolin is extracted from the root proportion of the plant which has been traditionally used for medicinal purposes and is the prime component of clinical interest in *Coleus forskohlii*. It was discovered by Finnish botanist Forskal in 1774. Forskolin (C₂₂H₃₄O₇) is an off-white crystalline solid with a molecular weight of 410.5 and melting point of 228- 230 °C and UV absorption maxima at 210 nm and 305 nm².

ORIGIN AND GEOGRAPHICAL DISTRIBUTION

Coleus forskohlii is a perennial branched aromatic herb; found in subtropical western Himalayas, Nilgiri hills, Gujarat and Bihar, and grows wild in sun-exposed arid and semi-arid hill slopes of the Himalayas in Uttar Pradesh, from Shimla eastward to Sikkim and Bhutan, the Deccan Plateau, Eastern Ghats, Eastern Plateau and rain shadow regions of the Western Ghats in India^{1,3}.

REGULATION OF MAMMALIAN ADENYLYL CYCLASE BY FORSKOLIN

Forskolin has served as a very important tool in molecular pharmacology and endocrinology, which is mediated by activation of adenylyl cyclase and increased concentration of cyclic adenosine monophosphate (cAMP)⁴. Cyclic AMP is one of the most important "second messengers" and cell-regulating compounds. Amid its many roles, cAMP activates various other enzymes involved in assorted cellular functions. Cyclic AMP is a master regulator of innate immune cell function. It arbitrates several biological processes like memory, metabolism, gene regulation, and immune function. Increased cellular cyclic AMP results in a broad range of physiological and biochemical effects, including inhibition of platelet activation resulting in decreased possibility of blood clots, reduced release of histamine (resulting in decreased allergy symptoms), increased force of contraction of the heart, relaxation of the arteries and other smooth muscles, increased thyroid function, and increased lipolysis.⁵ Hormones and neurotransmitters also activate adenylyl cyclase, but Forskolin appears to be able to activate adenylyl cyclase by itself, without the assistance of hormones or neurotransmitters. The ability of forskolin to stimulate adenylyl cyclase in intact cells in the absence of hormonal agonists has been exploited by many laboratories for investigation of the role of cyclic AMP in various physiological functions. Nine isoforms of adenylyl cyclase have been identified. With the exception of one, all of them are stimulated by forskolin^{6, 7}. Forskolin is a hydrophobic activator of all the mammalian adenylyl cyclases but type IX⁷. Type IX Adenylyl cyclase is non-responsive to forskolin because of amino acid changes in its binding pocket (Ser to Ala and a Leu to Tyr). When these changes are reversed by site-directed mutagenesis, the resulting type IX mutant can be activated by forskolin as well as other adenylyl cyclases. Forskolin activates Adenylyl cyclase in all tissues as up till now tested¹⁰. Forskolin also interacts with certain proteins, including glucose transporters and

ion channels, in addition to activation of adenylatecyclase.

MEDICINAL IMPORTANCE

Forskolin serves as a very important tool in molecular pharmacology and endocrinology. Diterpenoid forskolin form a large class of secondary metabolite isolated from plants that possess a wide spectrum of important biological activities to cure a number of diseases characterized, in part, by decreased intracellular levels of cyclic AMP. These include asthma, eczema, psoriasis, angina, obesity and hypertension. Hence increase in cAMP levels by activation of Adenylyl cyclase enzyme by forskolin cures various diseases. In addition to its adenylyl cyclase stimulating actions, forskolin also appears to have actions that are not due to this mechanism, but are due to its ability to alter a number of membrane transport proteins.^{11& 12}

CARDIOVASCULAR EFFECTS OF FORSKOLIN

Many reports have extensively shown that several classes of diterpenoids exert significant cardiovascular effects. The platelet aggregation and inhibiting effects of forskolin add to its value in treatment of cardiovascular disorders. Forskolin significantly lowers blood pressure via relaxation of vascular smooth muscles. It reduces diastolic blood pressure without increasing myocardial oxygen consumption. Further it increases cerebral blood flow indicating it may be beneficial in cerebral vascular insufficiency and in enhancing post stroke recovery. In a study it has been shown that forskolin administration dramatically improved left ventricular function and overall cardiovascular performance. These findings show the diterpenoids as a promising source of new way for the discovery and advancement of novel cardiovascular therapeutic systems¹¹.

FORSKOLIN ANTI-GLAUCOMA MOLECULE

Glaucoma is characterized by increased intraocular pressure (IOP) but in some patients with glaucoma have normal IOP but poor circulation, resulting in damaging of optic nerve¹³. Forskolin stimulates adenylatecyclase which stimulates the ciliary epithelium to produce cyclic adenosine

monophosphate (cAMP) that results in decreased aqueous humor inflow there by decrease in IOP¹⁴. In a study conducted by Josephetal1984, intravitreal doses and topical application of forskolin resulted in a significant decrease in IOP compared with baseline in rabbits¹⁵.

FORSKOLIN AS ANTI-METASTATIC COMPOUND

Forskolin has been examined for its effects on tumor induced human platelet aggregation and pulmonary tumor colonization in mice employing a subline of 816 murine melanoma and B16-F10 cells (highly meta- static to lungs). Results have shown that forskolin strongly constrains the melanoma cell-induced human platelet aggregation and a single dose of forskolin (82 µg/mouse) administered peritoneally 30 or 60 min prior to tail vein injection of cultured B16-F10 cells reduced tumor colonization in the lungs by more than 70 % . These findings promote the possibilities that forskolin could prove of value in for the deterrence of cancer metastasis¹⁶.

PSORIASIS

Patients with psoriasis have decreased cAMP and increased GMP in affected areas. Increased cGMP levels are associated with cell proliferation. This imbalance results in a much higher rate of cell division which is 1,000 times greater than normal, resulting in psoriatic outbreaks. Ammon et al reported an improvement in symptoms of psoriasis in patients supplemented with forskolin. The ability of forskolin to regulate cAMP levels in dermatocytes has been shown to have therapeutic benefit in alleviation of psoriasis^{17&18}.

ULTRAVIOLET RADIATION, AGING AND SKIN

As forskolin, is a skin-permeable compound, it directly activates adenylatecyclase to induce production of cAMP, D'Orazioetal(2006) showed that topical application of forskolin promotes UV-independent production of eumelanin in an MC1R-defective fair-skinned animal model¹⁸. Pullar, C.E etal(2005) showed that

pharmacologic incitement of cAMP using forskolin protects the skin in ways other than through melanin induction, i.e., through enhancement of keratinocyte migration to promote wound healing and to decrease blister formation^{20& 21}. cAMP-promoting agents like forskolin also protect the skin against UVB-induced apoptosis and by promoting epidermal thickening also aids in resisting UV damage^{22&23}. It has also been reported that forskolin protected against the generation of oxidative stress by decreasing levels of nitric oxide and enhancing the stimulation of the cytoplasmic antioxidant enzyme copper/zinc superoxide dismutase^{24&25}.

ASTHMA AND ALLERGIES

Allergic processes, such as asthma and eczema, are characterized by a relative reduction in the cAMP levels in cells in the intestine and bronchial muscles. Forskolin mediated increase of cAMP levels and cAMP dependent phosphorylation could lessen the asthma attacks through bronchial muscle relaxation via activation of membrane maxi-K channels. Forskolin has anti-inflammatory and antioxidant activity, which has been useful in the treatment of the tachyphylaxis. Forskolin has been shown to have inhibitory effects on the production of interleukins (IL-13, IL-5 and IL-1b), eotaxin and histamine. Forskolin exerts an inhibitory action on macrophages with subsequent decrease in thromboxane-2 and superoxide levels describing its antioxidant and bronchial anti-inflammatory actions. On this basis, forskolin might be useful as an anti-spasmodic drug at the level of the intestine or bronchi and subsequently for long-term use in the treatment of asthma²⁶.

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OBESITY AND LIPOLYSIS

Obesity results from consuming more energy than is used or from placing the body in a positive energy balance²⁶. As a cyclic adenosine monophosphate (cAMP) stimulator, forskolin induces the production of the active form of hormone-sensitive lipase (HSL). HSL is directly involved in the deployment of triglyceride stores that release free fatty acids to be used for fuel within the body.²⁸

ANTI-DEPRESSIVE ACTIVITY

The mechanisms of the antidepressant activity of forskolin were studied by *Maeda et al*, (1997) using the forced swimming method in rats. Forskolin, when administered dose-dependent decrease of immobility ratings was observed, which are similar to the effects of amitriptyline treatment. The maximum effects of forskolin were observed at very low dose which is 150 times more potent than the higher dose of amitriptyline. Data from this study indicates that forskolin has strong anti-depressive strength, reliable with the hypothesis that elevation of the cAMP cascade system may have an important role in anti-depressive effects²⁹.

CONCLUSION

Herbal drugs are an excellent alternative to pharmaceutical chemicals of modern medicine in curing various diseases. Studies are warranted to understand the effect of forskolin on the molecular mechanisms of pathology of various diseases for its utility in the therapeutics.

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