Plectranthus barbatus: A Review of Phytochemistry, Ethnobotanical Uses and Pharmacology – Part 2

Authors
Rawiya H. Alasbahi 1, Matthias F. Melzig 2

Affiliations
1 Faculty of Pharmacy, Department of Pharmacognosy, University of Aden, Crater-Aden, Yemen
2 Institute of Pharmacy, Free University Berlin, Berlin, Germany

Abstract

Plectranthus barbatus Andr. is one of the most important species of the genus Plectranthus L’Herit. (Lamiaceae), with a wide variety of traditional medicinal uses in Hindu and Ayurvedic traditional medicine as well as in the folk medicine of Brazil, tropical Africa and China. The plant has therefore been an attractive target for intensive chemical and pharmacological studies up to now. This review presents data about the phytochemistry, ethnobotanical uses and pharmacology of Plectranthus barbatus as well as the pharmacology of its constituents. In addition to essential oil, abietane diterpenoids and 8,13-epoxy-labd-14-en-11-one diterpenoids are the main constituents found in Plectranthus barbatus. The major ethnobotanical uses are for intestinal disturbance and liver fatigue, respiratory disorders, heart diseases and certain nervous system disorders. Forskolin as one of the major constituents with its unique adenylyl cyclase activation that underlies the wide range of pharmacological properties could explain the different traditional uses of Plectranthus barbatus. Forskolin is involved in a number of patented pharmaceutical preparations used as over-the-counter drugs for the treatment of several ailments. However, the water-insoluble nature of forskolin limits its clinical usefulness. Forskolin thus served as a prototype for the development of 6-(3-dimethylaminopropionyl)forskolin hydrochloride (NKH477) as a potent water-soluble forskolin derivative that finds use in the therapy for a number of diseases especially of the cardiovascular system.

Pharmacology

Plectranthus barbatus

Studies on several extracts with various polarities obtained from different parts of P. barbatus revealed a number of pharmacological properties that may justify most of the traditional uses of P. barbatus, for example, organic extracts were reported to possess anti-inflammatory, antimicrobial [1,2], antioxidant [3], cytotoxic [4], hypotensive [5,6], spasmolytic [7], hepatoprotective [8] and antifeedant [9] activities as well as activity against Ehrlich’s ascites tumor in mice [10]. An alcoholic extract of the P. barbatus roots was shown to exhibit marked inhibitory action against Escherichia coli toxin-induced secretory response in rabbits and guinea pig ileal loops [11]. It has been shown that a hydroalcoholic extract of P. barbatus (880 mg/kg/day) exerted a variety of toxic effects on the different periods of pregnancy in rats; for example, in the period before embryo implantation, it caused a delay in fetal development and anti-implantation and, after embryo implantation, a delay in the development associated with maternal toxicity [12]. The water extract of P. barbatus leaves was found to exert hypoglycemic, hypotensive and antispasmodic activities [13]. It has been demonstrated that the water extract (WE) of the stems and leaves, at a dose of 1 g/kg p.o., shortened the sleeping time induced by pentobarbital by 37%, and at a dose of 2 g/kg p.o. enhanced the intestinal transit of charcoal by 30% in mice. The WE (2 g/kg intraduodenal) also reduced the gastric secretions (3.9 ± 1.0 to 0.5 ± 0.2 mL/4 h), and total acid secretion (34.4 ± 11.0 to 2.7 ± 0.5 mEq/L) and raised gastric pH (2.2 ± 0.3 to 6.5 ± 0.8) in rats. The treatment with WE (2 g/kg p.o.) was also found to protect against lesions induced by ethanol or cold-restraint stress, in pylorus-ligated rats [14]. Similar results were obtained by Schultz et al. [15] who reported that the WE of the leaves (0.5–0.1 g/kg) injected into the duodenal lumen decreased the volume (62 and 76%) and total acidity (23 and 50%) of gastric...
acid secretion in pylorus-ligated mice. The water extract of *P. barbatus* leaves administered by gavage to young rats with and without cholestasis was reported to reduce weight gain, feed ingestion, and energy utilization in both groups in the same proportion. However, the water extract was found to inhibit, partially, the increase in liver wet weight, liver fat content and the serum levels of cholesterol and triacylglycerides caused by cholestasis [16]. Furthermore, *P. barbatus* extract fed to ovariectomized rats was found to reduce body weight, food intake and fat accumulation [17]. The essential oil extracted from the leaves of *P. barbatus* and one of its major components, i.e., α-pinene, were reported to have a direct relaxant and spasmyloytic effect on the guinea pig ileum [13].

A variety of pharmacological activities of *P. barbatus* were the subjects of a number of patents, for example, anti-inflammatory effects on smooth muscle of the respiratory system, antiasthmatic, cough-relieving and phlegm-expelling [18–20], inhibition of the absorption of alveolar bones [21], reduction of the total body weight [22, 23], induction of lipolysis in rat adipose tissue [24] and inhibition of the α-glucosidase [25] as well as promotion of subcutaneous fat decomposition [26]. Other patents presented an antiallergic effect [27], hair-loss preventing effect, and activation of the process of melanogenesis [28], an antihypertensive effect [29] as well as antimicrobial activity of the essential oil, with a certain composition (at least 7.5% bornyl acetate, 3.5% 3-decanone, 3.75% of an azulene derivative, 1% α-pinene, and 0.75% β-pinene), extracted from *P. barbatus* root [30].

**Adverse effects of *Plectranthus barbatus***: *P. barbatus* was reported to cause perianal dermatitis [31].

**Forskolin**

Forskolin (26) (see Fig. 2 in Part 1 of our Review [DOI: 10.1055/s-0029-1240898]) is one of the most extensive studied constituents of *P. barbatus*. A great number of studies revealed the unique character of forskolin as a direct, rapid and reversible activator of adenylyl cyclase, which results in marked increases in the level of intracellular cyclic 3',5'-adenosine monophosphate (cAMP) in a variety of mammalian membranes, broken cell preparations and intact tissues [32–42]. Forskolin in the form of forskolin affinity columns has thus been used for the purification of the enzyme adenylyl cyclase [43, 44]. Adenylyl cyclase exists in at least nine different membrane-associated isoforms and each isoform shows distinct patterns of tissue distribution and biochemical/pharmacological properties. Forskolin is a general activator of all but one of the adenylyl cyclase isoforms, namely, adenylyl cyclase 9 [45, 46]. Forskolin, for example, was found to differ from isoprotorenol and prostaglandin E2 in the regulation of interleukin-10 (IL-10) and tumor necrosis factor alpha (TNF-α) in Kupffer cells, in which forskolin-insensitive adenylyl cyclase 9 mRNA is highly expressed and may be involved in the cAMP-mediated attenuation of TNF-α release. The strong CAMP activator forskolin was found to be no more potent than isoprotorenol in reducing TNF-α levels and significantly reduces IL-10 levels [47].

The discovery of forskolin as a direct, rapid and reversible activator of adenylyl cyclase and its ability to manipulate the intracellular levels of cAMP precisely and to elicit cAMP-dependent physiological responses and later on the disclosure of its ability to exert a number of cAMP-independent effects have made forskolin a target for intensive pharmacological research up to the present.

**Pharmacological effects of forskolin**

**cAMP-dependent effects**: A number of studies on the various pharmacological effects of forskolin have been conducted mainly on laboratory animals but a few on humans. The fact that forskolin directly activates adenylyl cyclase and thus increases cAMP levels is considered as the mechanism of action that underlies the various pharmacological effects of forskolin. The following is a summary of the main pharmacological effects of forskolin mediated by the increase of the CAMP.

**Cardiovascular effects**: Forskolin was found to exert positive inotropic actions on the isolated guinea pig heart, isolated rabbit heart and on the dog and cat heart in situ. In addition, forskolin augmented coronary blood flow in the isolated guinea pig heart. It was reported that forskolin increased the heart rate and lowered the blood pressure in dogs, cats, rats and rabbits and also in spontaneously hypertensive and renal hypertensive rats. The cardiovascular effects of forskolin such as the inotropic effect could be explained primarily by the increase of cAMP in heart muscle, which is known to increase its contractility via opening of the slow Ca2+-channels, thus leading to elevation of intracellular calcium, and the hypotensive effect by the increase of CAMP in the vascular smooth muscle, which causes a relaxation due to the lowering of the calcium sensitivity of the contractile system of smooth muscle cells [5, 48–50]. However, the inotropic and chronotropic effects of forskolin in conscious dogs were reported to be not only due to direct activation of adenylyl cyclase, but also mediated by neural mechanisms and potentiated by the prevailing level of sympathetic tone [51]. It has been demonstrated that forskolin exhibited concentration-dependent inhibitory effects on vascular contractility of rat aorta by decreasing the cytosolic Ca2+ level at a lower concentration (0.1 µM) and decreasing the sensitivity of contractile elements to Ca2+ at a higher concentration (1.0 µM) [52]. Repolarization and reduction in the intracellular Ca2+ sensitivity of force was found to be the primary mechanism of forskolin-induced relaxation of intact rat tail artery [53]. Forskolin as a vasodilator was reported to open the large-conductance calcium-activated potassium channels in coronary myocytes by cross-activation of protein kinase C. This signaling pathway represents a novel mechanism for regulation of potassium channel activity in various smooth muscle and other cells [54]. In addition, forskolin-induced relaxations of isolated rabbit aortic preaparations, accompanied by increased CAMP were found to interact with endothelium-derived relaxing factor-dependent relaxations [55].

It has been shown that forskolin is a potent, powerful activator of myocardial adenylyl cyclase in human cardiac tissue preparations. It produced maximal effects that were 26-fold greater than basal activity in normal functioning and failing left ventricles, and 4.82- (normally functioning left ventricle) and 6.13- (failing left ventricle) fold greater than those of isoprotorenol. Unlike isoprotorenol, forskolin did not appear to approach a true maximum at higher concentration ranges, and stimulated CAMP production in a linear-log dose manner between 10−7 and 10−4 M. The adenylyl cyclase stimulatory effect of forskolin was synergistic with isoprotorenol in preparations derived from a failing human heart. Forskolin was also found to produce a less potent positive inotropic effect (ED50 3.5 × 10−7 M) than isoprotorenol (ED50 2.4 × 10−8 M) in isolated human right ventricular trabeculae and papillary muscles derived from severely failing human hearts [56]. In a clinical study, forskolin has been reported to improve coronary blood flow and myocardial function without increasing the myocardial oxygen consumption in 6 patients undergoing diagnostic
Platelet aggregation inhibitory effect: Forskolin was reported to be a potent inhibitor of ADP-induced, arachidonate-induced and collagen-induced human, rat and rabbit platelet aggregation [5, 61]. Plasma adenosine was found to play an important role in the antplatelet activity of forskolin [61]. Platelet aggregation induced by collagen, ADP, arachidonic acid, or epinephrine is inhibited by elevations in cAMP. An increase in the cAMP levels has been found to correlate with the degree of inhibition of ADP-induced aggregation [5] as well as with the progressive inhibition of fibrinogen binding in thrombin-stimulated human platelets [62]. In addition to its direct effects, a low concentration of forskolin was found to markedly augment the efficacy and potency of prostaglandins [5, 63] and aspirin [64] in inhibiting platelet aggregation. The anti-aggregating activity of forskolin was thus attributed to both direct stimulation of adenyl cyclase and a marked enhancement of receptor-mediated stimulation of the enzyme [5]. Forskolin was found to exert an inhibitory effect in the excitatory signal transduction in the platelets at a site beyond phospholipase C at the level of the C kinase [65, 66]. Since C-kinase activation is one of the key events in excitatory signal transduction in the platelets, it was suggested that the inhibitory effect of forskolin on platelet secretion and aggregation might reside in its capacity to antagonize C-kinase activity [65]. Other targets for the mechanism of the anti-aggregating activity of forskolin were found to be the increase in the nitric oxide synthase activity of human platelets by cAMP/cAMP-activated protein kinase [67] and the inhibition of platelet-activating factor binding to platelet receptors independently of adenyl cyclase or G-protein involvement [68].

In a study using a subline of B16 murine melanoma, B16-F10 (highly metastatic to lungs), forskolin was reported to inhibit the melanoma cell-induced human platelet aggregation [69]. Moreover, the platelet anti-aggregating effect of forskolin was found to underlay the inhibitory effect of forskolin on hepatic metastasis from human colon cancer in nude mice during the metastatic tumor formation [70]. A 0.1% ethanolic solution of forskolin applied to the surface of polytetrafluoroethylene (PTFE) standard type grafts implanted into the superficial femoral arteries of ten healthy male Australian sheep was found to prevent platelet deaggregation (aggregation) on the surface of the PTFE grafts [71]. Moreover, addition of forskolin to platelet concentrates was found to inhibit the activation of platelets and therefore protect it from deleterious changes that may occur during storage [72].

Respiratory effects: It has been demonstrated that forskolin is able to relax airway smooth muscle in guinea pigs in vitro and in vivo [73–76] as well as in ovine isolated bronchioles [76]. In addition, forskolin was found to produce a partial reversal of tachyphylaxis to salbutamol- and isoproterenol-induced relaxation [76, 77]. Forskolin has been shown to inhibit the immunologically stimulated release of LTD4 and histamine from sensitized guinea pig lungs [74]. The antiarrhythmia effect of forskolin was identified by tests which measure the inhibition of anaphylactic bronchospasm in sensitized guinea pigs having antigen-induced bronchoconstriction. Forskolin was also found to inhibit allergen-induced histamine release from guinea pig and human sensitized tissue [78]. Inhalation of forskolin by asthmatics [79] as well as by healthy nonsmoker volunteers [80] was reported to improve respiration after provocation of bronchospasm with methacholine and acetylcholine, respectively. In a single-blinded clinical study in children and adult outpatients, forskolin capsules taken orally at 10 mg a day were found to be more effective than sodium cromoglycate (two inhalations every 8 h, three times a day) in preventing asthma attacks in patients with mild persistent or moderate persistent asthma [81]. Forskolin (as dry powder capsules) was found to produce bronchodilatation in 16 patients with asthma [82]. A number of studies, using animal models, demonstrated several mechanisms of forskolin to relax pulmonary smooth muscle such as the cAMP-dependent protein kinase (PKA) mediated inhibition of endothelin-1 stimulated generation of inositol phosphates and Ca2+ mobilization [83], the inhibition of the binding of inositol 1,4,5-trisphosphate (IP3) to its Ca2+-mobilizing intracellular receptor [84], the protein kinase C isoenzymes mediated activation of large-conductance, calcium- and voltage-activated potassium channels and the resulting pulmonary vasodilation [85], the decrease in the Ca2+ oscillation frequency of airway smooth muscle cells by reducing internal Ca2+ release through IP3 receptors [86], as well as the inhibition of myosin light chain (MLC) phosphorylation by reducing Ca2+ influx, Ca2+ release, by changing the MLC kinase/phosphatase balance and the inhibition of the MLC phosphorylation-independent regulatory mechanism [87]. It has also been reported that the relaxant effects of forskolin in cultured rat tracheal smooth muscle might be mediated, at least in part, by facilitating the sequestration of Ca2+ into intracellular stores by a mechanism involving guanosine 3',5'-cyclic monophosphate-dependent protein kinase [88]. Moreover, forskolin was shown to reverse airway hyperresponsiveness of bovine tracheal smooth muscle cells due to the inhibition of RhoA, a small G protein that plays an important role in the functional alterations of hyperresponsive tracheal smooth muscle cells [89].

Forskolin was found to reduce the expression of inflammatory mediators such as the surface adhesion molecules including ICAM-1 and the release of granulocyte-macrophage colony-stimulating factor (GM-CSF) and interleukin-8 (IL-8) secreted by airway smooth muscle cells in diseases such as asthma [90]. It has been demonstrated that forskolin reduced airway smooth muscle cell mitogenesis and attenuated smooth muscle growth (that play a potential role in the generation of airway smooth muscle hyperplasia) by suppressing cyclin D1 expression [91] and through an EPAC (exchange protein directly activated by cAMP) or an EPAC-like cAMP-dependent mechanism [92]. Moreover, for-
skolin was reported to increase the isometric contraction of the isolated hemidiaphragm in the presence of calcium [93].

**Gastrointestinal tract:** A number of studies reported that forskolin stimulated acid formation in rabbit and rat parietal cell preparations [94,95], in intact amphibian gastric mucosa [96], and both acid formation and pepsinogen secretion in isolated rabbit gastric glands [96,97], and, in vivo, rat gastric acid secretion [95]. Treatment of rabbit gastric glands and gland homogenates as well as dispersed rabbit parietal cells with forskolin resulted in an increase in cAMP levels [94–97], indicating the major role of cAMP in gastric secretion. As reported by Modlin et al. [98], the enhancement of phosphorylated bands around 92 kilodaltons by forskolin in isolated gastric glands illustrated the intracellular regulatory mechanisms of gastric secretion. Moreover, forskolin, at 1 mg/loop, was found to be able to exhibit almost similar anti-secretory (antidiarrheal) activity as loperamide (anti-secretory opiate agonist) 1 mg/loop, against Escherichia coli enterotoxins-induced secretory response in animal ileal loop models [11].

**Gastrointestinal tract:** Intra-arterial injection of forskolin (3–100 µg) in blood-perfused dog pancreas was reported to cause a dose-dependent increase in the secretion of pancreatic juice mediated through an increase of intracellular cAMP concentration [99]. Forskolin was shown to relax smooth muscles of cat intestine, rat intestine and uterus as well as rabbit duodenum and guinea pig ileum [5,100]. A combination of forskolin and saponin was reported to improve bowel movement without side effects such as abdominal pain and habit formation [101].

**Genitourinary tract system:** It has been demonstrated that forskolin caused a concentration-dependent relaxation of rabbit and porcine detrusor muscle [102,103], as well as a stimulation of rennin release from isolated perfused rat kidney [104]. As reported by Bishop and coauthors [105], forskolin, injected directly into the bladder or administered intravenously to type 1 fimbriated uropathogenic Escherichia coli infected mice, induced exocytosis of bladder epithelial cells fusiform vesicles in which E. coli is incorporated and thus reduced the number of intracellular E. coli and exposed the bacteria to the antibiotics. The inhibitory effect of forskolin on the contractions of the uterine rings from rats at 16 days of gestation was found to involve the activation of adenylyl cyclase, the adenosine triphosphate-dependent potassium channels and, to a greater extent, calcium-dependent potassium channels [106]. Moreover, intrarenal infusion of forskolin in anesthetized dogs was reported to cause natriuresis with an increase in intracellular cAMP levels [94–97], indicating the major role of cAMP in the regulation of gastric secretion. Moreover, forskolin, injected directly into the bladder or administered intravenously to type 1 fimbriated uropathogenic Escherichia coli infected mice, caused exocytosis of bladder epithelial cells fusiform vesicles in which E. coli is incorporated and thus reduced the number of intracellular E. coli and exposed the bacteria to the antibiotics. The inhibitory effect of forskolin on the contractions of the uterine rings from rats at 16 days of gestation was found to involve the activation of adenylyl cyclase, the adenosine triphosphate-dependent potassium channels and, to a greater extent, calcium-dependent potassium channels [106]. Moreover, intrarenal infusion of forskolin in anesthetized dogs was reported to cause natriuresis with an increase in intracellular cAMP levels [94–97], indicating the major role of cAMP in the regulation of gastric secretion. Moreover, forskolin, injected directly into the bladder or administered intravenously to type 1 fimbriated uropathogenic Escherichia coli infected mice, caused exocytosis of bladder epithelial cells fusiform vesicles in which E. coli is incorporated and thus reduced the number of intracellular E. coli and exposed the bacteria to the antibiotics. The inhibitory effect of forskolin on the contractions of the uterine rings from rats at 16 days of gestation was found to involve the activation of adenylyl cyclase, the adenosine triphosphate-dependent potassium channels and, to a greater extent, calcium-dependent potassium channels [106]. Moreover, intrarenal infusion of forskolin in anesthetized dogs was reported to cause natriuresis with an increase in intracellular cAMP levels [94–97], indicating the major role of cAMP in the regulation of gastric secretion. Moreover, forskolin, injected directly into the bladder or administered intravenously to type 1 fimbriated uropathogenic Escherichia coli infected mice, caused exocytosis of bladder epithelial cells fusiform vesicles in which E. coli is incorporated and thus reduced the number of intracellular E. coli and exposed the bacteria to the antibiotics.

**Eye:** Topical ocular administration of 1% forskolin suspension in rabbits, monkeys and human volunteers, who were free from eye disease, was reported to lower the intraocular pressure as a result of a reduction of the net aqueous flow without significant change in outflow facility [108–112]. Nevertheless, lowering the intraocular pressure in rabbits by forskolin was also ascribed to increasing renal blood flow and glomerular filtration rate, which is due to the ability of forskolin to preferentially dilate the afferent arterioles [107].

**Eye:** Topical ocular administration of 1% forskolin suspension in rabbits, monkeys and human volunteers, who were free from eye disease, was reported to lower the intraocular pressure as a result of a reduction of the net aqueous flow without significant change in outflow facility [108–112]. Nevertheless, lowering the intraocular pressure in rabbits by forskolin was also ascribed to increasing renal blood flow and glomerular filtration rate, which is due to the ability of forskolin to preferentially dilate the afferent arterioles [107].

**Eye:** Topical ocular administration of 1% forskolin suspension in rabbits, monkeys and human volunteers, who were free from eye disease, was reported to lower the intraocular pressure as a result of a reduction of the net aqueous flow without significant change in outflow facility [108–112]. Nevertheless, lowering the intraocular pressure in rabbits by forskolin was also ascribed to increasing renal blood flow and glomerular filtration rate, which is due to the ability of forskolin to preferentially dilate the afferent arterioles [107].

**Skin:** It has been reported that forskolin after a relatively long lag period, induced the production of melatonin in cultured Syrian hamster pineal glands [118]. Forskolin was found to cause a significant increase in human hair follicle melanogenic activity and consequently a significant increase in pigmented hair follicles [119], and to stimulate the growth of hair follicular keratinocytes and melanogenesis in vitro [120,121]. In addition, it has been demonstrated that compositions containing solubilized 2% w/w of forskolin and 5% freeze-dried liquid endosperm of Cocos nucifera or 1% forskolin and 1% 9,10-dimethoxy-2-mesitylimino-3-methyl-2,3,6,7-tetrahydro-4H-pyrimido[6,1-a]isoquinolin-4-one hydrochloride were able to promote hair growth in animal models [122,123]. Moreover, forskolin was found to protect keratinocytes from UVB-induced apoptosis and increase DNA repair independent of its effects on melanogenesis. Although the induction of new pigment synthesis requires several days, the action of forskolin on DNA repair appears to be efficient when applied only a few minutes before UVB exposure [124,125]. A composition based on labdane diterpenoids including forskolin was found to provide better photoprotection against both UV A and UV B radiation in the HaCaT human keratinocyte cell lines and to enhance melanogenesis in B16F1 mouse melanoma cells and to act as a tanning inducer/accelerator both in the presence or absence of sunlight [126]. It has been demonstrated that topical application of a cream containing forskolin to the skin of patients with hyperplastic disease for 5 days caused healing to slight erythema or full recession [127]. Moreover, forskolin was reported to improve symptoms in 4 patients with psoriasis [48].

**Tumor:** Forskolin was found able to inhibit pulmonary tumor colonization and metastasis in mice. A single dose of forskolin (82 µg/mouse) administered intraperitoneally 30 or 60 minutes prior to tail vein injection of cultured B16-F10 cells (2 or 3 × 10⁵ cells/mouse) reduced tumor colonization in the lungs by more than 70% [69]. Forskolin also inhibited the growth of the human gastric adenocarcinoma cell line AGS with a half-maximal inhibition achieved at 20 µM [128]; also it prevented the growth and induced apoptosis of myeloid and lymphoid cells [129]. In studies using human gastric cancer cell lines BGC-823 and SCC-7901, forskolin was reported to inhibit cell growth by decreasing the activity of protein kinase C (PKC) and inhibiting the gene expression of PKC subunits (PKC β and γ) and of some oncogene proteins such as Ha-ras and c-jun [130,131] and by down-expression of the rasp21 protein and p53 protein [132], respectively. In addition, forskolin has been demonstrated to partially inhibit cytokine-driven colony formation and proliferation of CD34⁺ bone marrow
cells (NBM\textsuperscript{CD44\textsuperscript{+}}) without inducing either apoptosis or protein phosphatase 2A (PP2A) activity. Thus, the effects of forskolin on NBM cells most likely depend on its ability to activate adenyl cyclase and induce cAMP, which inhibits cytokine-dependent proliferation of normal myloid progenitors [133]. Addition of rolipram (10 µmol/L), known to maximally inhibit cyclic nucleotide phosphodiesterase type 4, to a low dose of forskolin (1 µmol/L) enhanced the growth suppression induced by forskolin and caused complete growth cessation of chemoresistant KM12C colon cancer cells, despite rolipram having no effect on its own [134]. A composition containing adenyl cyclase activators such as forskolin, theophylline, and isobutylmethylxanthine with carboxamidotriazole was found to display synergistic antitumor effects and to inhibit the proliferation of tumor cells [135]. Contradictory to the above studies, a combination of forskolin and theophyllin (as cAMP increasing agents) was reported to attenuate the execution of the apoptotic process generated by etoposide, camptothecin, heat shock, cadmium chloride and X radiation in promonocytic leukemia cells. This anti-apoptotic action is explained by the ability of the forskolin/theophylline combination to inhibit retinoblastoma (type 1) phosphatase and ICE/CED-3-like protease activities, and the abrogation of c-myc expression in myeloid cells [136]. Moreover, other studies indicated that forskolin prevented the generation of apoptosis in human leukemia U937 cells [137] and stimulated cell growth, increased cAMP in the cells and enhanced the metastasis-related phenotypes including adhesion to laminin (Ln) and human umbilical vein epithelial cells (HUVEC), chemotactic migration and invasion in the H7721 human hepatocarcinoma cell line [138].

**Weight management:** The lipolytic activity of forskolin was reported to be mediated by the cAMP activity [40, 139]. However, it has been demonstrated that forskolin-induced lipolysis in intact rat fat cells and the cell-free system consisting of intact lipid droplets and the lipase was not correlated with cyclic AMP content [140]. Some other studies also indicated the inconsistencies observed when the intracellular cAMP levels are correlated with lipolysis. They demonstrated that the cAMP concentration required to reach maximum lipolysis was higher for forskolin than for isoproterenol in digitonin-permeabilized adipocytes [141] and in intact adipocytes [142], as well as in isolated rat fat cells [143, 144]. A similar observation was made by Schimmel [145] in hamster white adipocytes, who also reported that isoproterenol potentiation of forskolin’s lipolytic action was not accompanied by increasing the cAMP content and persisted in the absence of extracellular K\textsuperscript{+}, even though the lipolytic response to isoproterenol alone was absent in K\textsuperscript{+}-free media. It has been shown that forskolin induced lipolysis in rat fat cells by stimulating the translocation of hormone-sensitive lipase from the cytosol to its substrate on the surface of the lipid droplets in fat cells [146]. It is postulated that the lipolytic responses of adipose tissue are more complex and other cyclic AMP-independent lipolytic mechanisms may be involved in the regulation of lipolysis in adipocytes [140, 144, 145].

In an animal model of obesity, forskolin – given by means of gastric intubation at 2 mg/mice/day in a divided dose – was found to reduce the body weight and fat significantly [147]. Some studies [148, 149] reported that topical application of forskolin cream reduced the local fat from the thigh of obese women without diet or exercise.

Miscellaneous pharmacological activities

Forskolin was found to be able to inhibit interleukin-2 (IL-2)-secreting T helper 1 lymphocytes in vitro and decrease IL-2 production and IL-2Rα (IL-2 receptor α-chain) expression and thus be able to suppress immunological responses to allografts and prevent acute allograft rejection. The increase in cAMP induced by forskolin is also considered to have an inhibitory effect on the generation of cytotoxic T lymphocytes, which are considered to play a role in the course of acute allograft rejection [150]. However, in various in vitro and in vivo test methods, forskolin was found to be able to increase the immunological activity of the recipient (mice) by stimulating the antibody response, increasing the cellular immune response (DTH response), and the macrophage activity [151]. Forskolin has been shown to protect the mouse neuronal cell line, Neuro 2A, against dispropyl fluorophosphate, a surrogate of the organophosphate chemical warfare agents soman and sarin induced toxicity. This protective effect was found to be due to the ability of forskolin to activate the acetylcholinesterase promoter and upregulate its expression [152].

In an animal model using rats, repeated oral administration of forskolin (50 mg/kg) was reported to reduce the alcohol consumption significantly [153]. Moreover, forskolin was found to protect cultured cerebellar granule neurons (from wild-type mice) against alcohol-induced cell death by promoting the expression of neuronal nitric oxide synthase and increasing its activity [154]. It has also been demonstrated that forskolin showed anti-passive cutaneous anaphylaxis and mast cell stabilizing activity [155] and caused an inhibition of IgE-mediated release of histamine and peptide leukotrienes C4 from human basophils and lung mast cells [156]. Testing forskolin for anti-inflammatory activity using procedures such as the acute carrageenin-induced rat paw edema test, croton oil-induced rat ear inflammation test, and adjuvant-induced arthritis test in rats revealed that forskolin displayed an anti-inflammatory effect with ED\textsubscript{50}: 4.80 mg/kg/ i.p., ED\textsubscript{50}: 1.15 mg/ear and ED\textsubscript{50}: 2.5–2.4 mg/kg/ i.p. (ca. 23–27% inhibition of developing and established arthritis) respectively, [157, 158].

As reported by Maeda et al. [159], forskolin (0.01 mg/kg) displayed a potential antidepressant effect, stronger (150 times) than that produced by amitriptyline (15 mg/kg) in the forced swimming test. At a high dose (1.0 mg/kg) of forskolin, the duration of immobility was returned to control level. Subcutaneous injection (1 mg/kg) and intracerebroventricular administration (10 and 100 µg) of forskolin into mice was found to prevent seizures induced by pentylentetrazole [160] and depress spontaneous locomotor activity [161], respectively. A preliminary study demonstrated that intravenous infusion of forskolin (75 minutes) to four depressed and five schizophrenic patients caused a transient mood elevation in all four depressed patients and in two of the five schizophrenic patients [162]. It has been reported that forskolin reversed the inhibitory effect of amyloid beta-peptide on the protein kinase A/activated cAMP response element binding protein (PKA/CREB) pathway in cultured hippocampal neurons and consequently promoted the recovery of long-term potentiation formation. Forskolin therefore has been found able to reverse some of the risks related to higher amyloid beta levels that play a crucial role in Alzheimer’s disease [163]. It was found that forskolin enhanced the function of fibroblast growth factor 8 on dopaminergic differentiation from human fetal mesencephalic neural progenitor cells and thus increased the production of dopaminergic neurons, which can be used in the therapy for neurodegenerative diseases [164].
Forskolin was reported to stimulate the release of insulin and glucagon from the pancreatic islets both in vitro and in vivo. Stimulating the release of insulin by forskolin required the presence of a stimulatory glucose concentration of about 5.6 mM [165, 166]. Furthermore, it has been demonstrated that feeding forskolin to normal rats caused an increase in blood glucose, serum insulin, glucagon and free fatty acid levels with a corresponding increase in glucose-6-phosphatase activity and depletion of liver glycogen. This effect is due to the predominant stimulation of pancreatic α-cells and the cAMP formation. The increase in blood glucose level and glucagon amount in forskolin-fed alloxan diabetic rats compared to untreated alloxan diabetic controls was explained by the stimulatory effect of forskolin on glucagon and the release and/or increase formation of cAMP [165]. In addition, forskolin was found to augment the insulinotropic action of glibizide (a hypoglycemic sulfonylurea) in the perfused pancreas of normal and Goto-Kakizaki rats at a low concentration of glucose (2.8 mM) as well as to disclose the glucagonotropic potential of glibizide that was otherwise not detected in diabetic animals [167].

In a clinical investigation in 31 patients with vasculogenic impotence resistant to standard 3-agent pharmacotherapy, an overall 61% improvement in rigidity and/or erection duration without adverse events, was reported by using intracavernosal forskolin (98 µg/mL) in combination with papaverine (29 mg/mL), phenolamine (0.98 mg/mL) and prostaglandin E1 (9.8 µg/mL) [168]. Forskolin was also reported to increase the progressive motility and the percentage of motile cells of human sperm in vitro in a dose-dependent manner [169, 170]. It has been shown that forskolin, using dog thyroid slices, potentiated as well as mimicked the effect of thyrotropin-releasing hormone (THS) on iodide organification and secretion [171].

cAMP-independent effects of forskolin

In addition to cAMP-dependent effects, forskolin exerts a number of cAMP-independent effects through a mechanism that does not involve the production of cAMP [172] such as the inhibition of a number of membrane transport proteins, for example, the inhibition of glucose transporter in rat and human adipocytes [173, 174], human erythrocytes [175], human platelets [176], and bacterial galactose- H+ transport protein GalP [177] as well as the modulation of ion channels such as voltage-dependent K+ [178, 179], Na+ [180] and Ca2+ channels [181, 182], and inhibition of nicotinic acetylcholine receptor currents [183, 184] and the 5-hydroxytryptamine receptor mediated current [185, 186]. Further examples of cAMP-independent effects of forskolin are the partial reversal of doxorubicin resistance in multidrug resistance (MDR) lines in a dose-dependent fashion by enhancing the accumulation of doxorubicin in resistant cells [187], the increase of the adriamycin cytotoxicity in human ovarian carcinoma cells by inhibiting the P-glycoprotein multidrug transporter [188], the partial protection of LS29 cells against tumor necrosis factor-alpha mediated cytotoxicity (intraneosomal DNA fragmentation) [189], and the activation of cytchrome P450 3A1 and 3A4 (CYP3A1 and CYP3A4) gene expression [190, 191].

Forskolin was found to accelerate the desensitization of GABA_A and glycine receptors by a cAMP independent mechanism presumably by acting directly on extracellular sites of the receptors [192]. It has been demonstrated that forskolin modulated the desensitization of the nicotinic acetylcholine receptor by both cAMP-dependent [193, 194] and cAMP-independent mechanisms when used at concentrations above 20 µM [195, 196].

Studies of the bone anti-resorptive property of forskolin on rat osteoclasts showed that forskolin exerted a bimodal cAMP-independent effect on superoxide anion (O2−) generation by bone-resorbing rat osteoclasts, being stimulatory at a low dose (1 µM) and having an inhibitory effect at a higher dose (10 µM) [197] although the dual effect of forskolin in earlier studies was believed to be due to the elevation of cAMP [198]. The inhibition of platelet-activating factor binding to platelet receptors by forskolin was found to be independent of adenyl cyclase or G-protein involvement [68].

Recently, it has been found that forskolin is a potent protein phosphatase 2A (PP2A) activator, it induced marked apoptosis, reduced proliferation, impaired colony formation, inhibited tumorigenesis and restored differentiation of BCR/ABL-transformed cells regardless of their degree of sensitivity to imatinib. The antileukemic effects of forskolin appear to depend on the induction of PP2A activity rather than an increased intracellular cAMP and/or PKA activation, as exposure of BCR/ABL-transformed cells to the AMP inducer theophylline or to a PKA inhibitor did not alter BCR/ABL expression/activity [133].

Adverse effects of forskolin

Large doses of forskolin were found to cause a depressant action on the central nervous system in mice [100]. Due to the ability of forskolin to induce CYP3A gene expression in primary hepatocytes by functioning as pregnane X receptor ligands and thus be more likely to interfere with the metabolism of other drugs, Ding and Staudinger [199] suggested that herbal therapy with P. barbatus extract should be approached cautiously in patients on combination therapy. Moreover, Putnam et al. [200] recommended that patients with autosomal dominant or recessive polycystic kidney disease (PKD) should avoid using forskolin in any form because a forskolin-like substance has been identified within the cyst fluid of 15 patients out of 18 patients with PKD.

Pharmacological effects of forskolin analogues and other natural occurring constituents of Plectranthus barbatus

Isoforskolin [35] (see Fig. 2 in part 1) was reported to stimulate cAMP mildly [49, 201] and thus decrease blood pressure and produce an inotropic effect less than that of forskolin [49, 202, 203]. Isoforskolin was found to be able to relax guinea pig tracheal spirals [204], and at 1 mg/loop to exhibit a comparable antisecretory (antidiarrheal) activity as loperamide (1 mg/loop) against E. coli toxin-induced secretory response in animal ileal loop models [11]. A composition based on labdane diterpenoids including iso-forskolin was reported to protect HaCaT human keratinocyte cells lines against both UV A and UV B radiation, enhance melanogenesis in B16F1 mouse melanoma cells and act as a tanning inducer/accelerator both in the presence or absence of sunlight [126]. Isoforskolin – given by means of gastric intubation at 2 mg/mice/day in a divided dose – was found to reduce the body weight and fat significantly [147].

1-Acetylforskolin [34] (see Fig. 2 in part 1) was found to stimulate the adenylyl cyclase slightly and to suppress rabbit ocular hypertension [201].

7-Deacetylforskolin [37] (see Fig. 2 in part 1) was shown to display a blood pressure lowering effect less potent than that of forskolin in anesthetized cats [5, 49, 202], but equipotent with forskolin in spontaneously hypertensive rats [5]. 7-Deacetylforskolin (1%) was found to suppress rabbit ocular hypertension [201]. It has been reported that 7-deacetylforskolin was able to activate...
adenyl cyclase mildly [49, 201, 205], and to exert a cAMP-independent inhibition of glucose transport and cytochalasin B binding in rat adipocyte plasma membranes [205]. In an animal model, 7-deacetylforskolin was found to reduce the body weight and fat significantly [147].

**9-Deoxoforskolin (27)** (see Fig. 2 in part 1) was found to retain some activity on cyclic AMP generating systems but was inactive in lowering blood pressure even at a high dose (1 mg/kg) in anesthetized cats [49].

**1,9-Dideoxyforskolin (28)** (see Fig. 2 in part 1) was reported to lack an adenyl cyclase activating function and therefore does not exhibit any of effects mediated by cAMP [37, 49]. On the other hand, the inhibition of contractions of uterine rings from rats at 16 days of gestation by 1,9-dideoxyforskolin was attributed to an activation of adenyl cyclase and calcium-dependent potassium channels [106]. Testing the anti-inflammatory effect of 1,9-dideoxyforskolin – using procedures such as carrageenin-induced rat paw edema test, croton oil-induced rat ear inflammation test and adjuvant-induced arthritis test in rats – indicated that 1,9-dideoxyforskolin displayed an anti-inflammatory effect with ED₅₀ values of 2.2 mg/kg/i.p., 1.6 mg/ear, and 3.0 mg/kg/i.p., respectively. 1,9-Dideoxyforskolin was also found to exert an analgesic effect with an ED₅₀ of 9.0 mg/kg/s.c. by using the acetic acid induced writhing test in mice [157, 158].

It has been demonstrated that 1,9-dideoxyforskolin is able to produce many cAMP-independent effects such as inhibition of glucose transport and cytochalasin B binding in rat adipocyte plasma membranes [205], augmentation of late voltage-dependent Na⁺ channel activity in cardiac ventricular myocytes [180], inhibition of the basal cardiac L-type Ca²⁺ current [181] as well as inhibition of Ca²⁺ influx induced by K⁺ in the rat pheochromocytoma cell line (PC12) [182], and in rat cerebellar granule cells [206] and by K⁺ or nicotine in chromaffin cells [183]. 1,9-Dideoxyforskolin was found to inhibit the nicotinic acetylcholine receptor in chromaffin cells [183] and in rat pheochromocytoma cells [184], and to accelerate the desensitization at GABAₐ and glycine receptors in amacrine-like cells of carp (Carassius auratus) retina [192]. Moreover, 1,9-dideoxyforskolin (10 µM) was reported to partially reverse the resistance to doxorubicin in multidrug resistance lines in a dose-dependent manner by enhancing drug resistance lines in a dose-dependent manner by enhancing the uptake of doxorubicin in resistant cells [187], to partially inhibit the in vitro proliferation of human airway smooth muscle cells [92], and to reduce the binding of platelet-activating factor to platelet receptors in isolated rabbit platelets [68]. In addition, 1,9-dideoxyforskolin was shown to enhance the activity of protein phosphatase 2A (PP2A) and therefore restore its activity in the BCR/ABL⁺ cell line, which consequently leads to the impairment of the BCR/ABL leukemogenic potential in imatinib-sensitive and resistant cell lines. Similarly, the clonogenic potential of myeloid CML-Bcr/abl-D34⁺ cells was also dramatically reduced by 1,9-dideoxyforskolin treatment (80–95% inhibition). Importantly, in vivo administration of the PP2A activator 1,9-dideoxyforskolin severely impacted and efficiently modulated the development of the wild-type and T315I BCR/ABL-induced acute leukemia-like disease process [133].

**FSK88**, a forskolin derivative, extracted and purified from cultured roots, was reported to induce apoptotic death of human gastric cancer BGC 823 cells through multiple cellular and molecular pathways such as the upregulation of pro-apoptotic Bax and Bad gene expression and downregulation of anti-apoptotic Bcl-2 gene expression, dissipation of mitochondrial potential ΔΨₘ, mitochondrial release of cytochrome c, caspase-3 and caspase-9 activation [207].

**13-Epi-9-deoxyforskolin (55)** (see Fig. 3 in part 1) was reported to produce a blood pressure-lowering activity on anesthetized cats [208].

**13-Epi-sclareol (59)** (see Fig. 4 in part 1) was found to produce antiproliferative activity in breast and uterine cancers in vitro. The antiproliferative activity of 13-epi-sclareol (IC₅₀: 11.056 µM) in the breast cancer cell line MCF-7 was found to be comparable to that of tamoxifen (IC₅₀: 14.34 µM) and devoid of cytotoxicity in normal cells, namely the Vero cell line and primary osteoblast cells. The compound also inhibited the growth of endometrial adenocarcinoma ( Ishikawa) cells where tamoxifen failed to show any such effect. Moreover, 13-epi-sclareol (10 µM and 20 µM) showed concentration-dependent increased apoptotic changes in the breast cancer cell line MCF-7 [209].

**Forskoditerpenosides** A (64), B (65), C (66), D (67), E (68) (see Fig. 5 in part 1) were found to relax guinea pig tracheal spirals [204, 210].

**Barbatin** (6) (see Fig. 1 in part 1) was found to demonstrate an inhibitory effect against Lewis lung carcinoma and lymphotoxic leukemia P 388 in mice [10].

**Barbatosul (25)** (see Fig. 1 in part 1), at a dose of 3 mg/kg (i.v. in rats), was found to induce a potent lowering of blood pressure associated with discrete bradycardy [6].

**Coleon C (15)** (see Fig. 1 in part 1) was reported to inhibit tumor growth and proliferation with a low toxicity to normal cells [211].

**Plectrin (5)** (see Fig. 1 in part 1) was reported to display anti-feedant activity against the green bug *Schizaphis graminum* and the pink bollworm *Pectinophora gossypiella* [9].

**Plectrinon A (12)** (see Fig. 1 in part 1) was found to inhibit the gastric H⁺K⁺-ATPase with an IC₅₀ value about 10-fold greater than that of the classic proton pump inhibitor omeprazole. This result may account for the antisecretory acid effect and reputed antiviral activity of *P. barbatus* [15].

**Second generation forskolin derivatives**

Although the biological profile of forskolin is characterized by various pharmacological properties such as the positive inotropic, hypotensive, bronchospasmyotic and antiglaucoma activities that have been proved in vitro and in vivo using mainly laboratory animals and few humans, forskolin has not been available as an approved drug due to its low water solubility (ca. 0.001%) [212] and low oral activity that limit its clinical usage as an intravenous formulation and an oral one, respectively [213], as well as the concern that forskolin as a nonspecific adenylyl cyclase activator may be too toxic for clinical use. Forskolin has, therefore, been considered as a useful prototype for the development of similar agents with better water solubility and more selective effects on adenylyl cyclase types. Several attempts were tried to increase the aqueous solubility of unmodified forskolin by dissolving it in solutions of solubilizing agents such as α-, β- and γ-cyclodextrins and their derivatized products such as hydroxypropyl-gamma-cyclodextrin [212, 214], and a block copolymer Pluronic F-127 [215]. The solubility of such forskolin solutions was increased to some extent and was found to be especially useful for topical application to treat intraocular pressure. Further synthetic and structure–activity studies, such as the introduction of water-soluble substituents onto forskolin, were carried out, and of the active analogues produced, the 6-(3-dimethylaminopropionyl) forskolin hydrochloride (NKH477) (79) (see Fig. 7 in part
the scope of this review. In a number of wide-ranging pharmacological activities of NKH477 is beyond the treatment of cardiovascular diseases and on some examples of its clinical applications for NKH477 in the cardiovascular system.

In this review, we focus briefly on the cardiovascular effects of NKH477 and on some examples of its clinical applications for the treatment of cardiovascular diseases – as evaluating the wide-ranging pharmacological activities of NKH477 is beyond the scope of this review. In a number of in vivo and in vitro animal model studies, NKH477 was found to produce a similar cardiovascular profile (positive inotropic, positive chronotropic, and coronary vasodilatory effects) [219,226,227] to that of forskolin, except for the duration of actions; in which, NKH477 was longer-acting than forskolin [228]. In anesthetized dogs, NKH477 administered intravenously produced dose-related increases in left ventricular dp/dtmax, cardiac output, coronary and femoral blood flow, heart rate and myocardial oxygen consumption, and dose-related decreases in blood pressure, pulmonary arterial diastolic pressure and total peripheral resistance [213,229]. In addition, in some animal heart failure models, NKH477 was reported to improve cardiac function [230,231]. Moreover, NKH477 was found to be effective on the β-receptor desensitized heart model in which the effects of β-adrenoceptor agonists and phosphodiesterase inhibitors were attenuated [219,227,232]. In clinical studies [227,233], an NKH477 infusion (0.4 to 0.8 µg/kg/min) was found to improve the hemodynamics as well as subjective and objective symptoms in patients with heart failure and was also effective in catecholamine-resistant heart failure patients. A number of clinical applications of NKH477 [Colforsin daropate HCl; (Adehl®Inj., Nihon Kayaku, Ltd., Tokyo, Japan)] – a recently available forskolin derivative in Japan [234,235] – has demonstrated the usefulness of NKH477 as the first clinically available adenylyl cyclase activator for preoperative management [234,236,237] of patients undergoing cardiac surgery. Iranami et al. [235] reported a case in which the continuous infusion of NKH477 (0.25 µg ·kg−1 ·min−1) successfully permitted the weaning of a neonate from cardiopulmonary bypass after correction of a complex congenital cardiac defect, under conditions in which better known inotropic agents [e.g., milrinone (phosphodiesterase inhibitor) in combination with epinephrine and isoproterenol] had failed. NKH477 administration to 9 patients after open heart surgery was found to improve the hemodynamics through positive inotropic and vasodilator effects without hypotension. However, side effects such as tachycardia and arrhythmia have been observed [238].

Conclusion

The potential role of Plectranthus barbatus in traditional medicine – for the treatment of several diseases – and the disclosure of some of its pharmacological activities, has provoked the selection of this plant for strategically planned research programs starting in India and then in East Africa, Brazil and China over the past decades that have continued up to now, and led to the isolation of a number of new compounds including those with unusual structural and pharmacological profiles. Besides essential oils, 25 abietane diterpenoids and 43 labdane diterpenoids were the main constituents isolated from different parts of P. barbatus. The pharmacological profile of the constituents is wide ranging, and could justify the ethnobotanical uses of P. barbatus. The essential oils were found to have antimicrobial and spasmodic activities, some of the abietane diterpenoids such as barbatonis, coleon C were characterized by antitumor activity, barbutinol by a hypotensive effect, plecetroxin A by a gastric proton pump inhibitory effect and plectrin by an antifeedant activity. Of the 43 labdane diterpenoids, 27 were distinguished by the typical 8,13-epoxy-labd-14-en-11-one skeleton, among them forskolin was found to possess the optimal structural requirements for a direct, high activation of adenylyl cyclase. Forskolin was therefore the most important and extensively studied compound. The unique character of forskolin, as a direct activator of adenylyl cyclase, was considered to account for the broad in vivo and vitro, proven pharmacological activities of the compound. However, the low aqueous solubility and low oral bioavailability and the nonspecific activation of adenylyl cyclase prevent forskolin from being clinically used. Nevertheless, forskolin remains, so far, a valuable tool to study the role of cAMP in cellular processes. Compared to forskolin, NKH477 [6-(3-dimethylaminopropionyl) forskolin hydrochloride], a synthetic water-soluble forskolin derivative, has better characteristics as it is orally and intravenously active and possesses high affinity for adenylyl cyclase, especially type V in the myocardium. Many in vivo, in vitro, animal models and clinical studies have provided experimental evidence indicating that NKH477 is effective as a cardiotonic and vasodilator. NKH477 [Colforsin daropate HCl; (Adehl®Inj.)] is available as an approved drug in Japan and is used for the treatment of heart failure. This review illustrates an example of how the selection of a proper plant for a planned mission-oriented research can lead to the development of a potential drug.

References


Alasbahi RH, Melzig MF. Plectranthus barbatus: A Review... Planta Med 2010; 76: 753–765


Daly JW. Forskolin, adenylate cyclase, and cell physiology: an overview. Adv Cyclic Nucleotide Protein Phosphorylation Res 1984; 17: 81–89


Pfeuffer E, Mollner S, Pfeuffer T. Adenylate cyclase from bovine brain cortex: purification and characterization of the catalytic unit. EMBO J 1985; 4: 3675–3679


Lindner E, Metzger H. The action of forskolin on muscle cells is modified by hormones, calcium ions and calcium antagonists. Arzneimittelforschung 1983; 33: 1436–1441


Melzig MF. Plectranthus barbatus: A Review... Planta Med 2010; 76: 753–765
Alasbahi RH, Melzig MF. *Planteans barbatus*: A Review... *Planta Med* 2010; 76: 753–765


73 Pavia DS, Caprioli J, Sears M. Protective effect of forskolin in acetylcholine provoked responses in the dog pancreas. *Arch Intern Pharmacodyn Ther* 1987; 286: 320–328


78 Bai Y, Sanders MJ. Airway smooth muscle relaxation results from a reduction in the frequency of Ca2+ oscillations induced by a CAMP-mediated inhibition of the IP3 receptor. *Respir Res* 2006; 7: 34


82 Prostran M, Varagaj VM. The effect of forskolin on the isometric contraction of the isolated hamster mesentery. *Respir Res* 2006; 7: 34


84 Collinson PW, Caprioli J, Sears M. Protective effect of forskolin in acetylcholine provoked responses in the dog pancreas. *Arch Intern Pharmacodyn Ther* 1987; 286: 320–328


120 Burstne NL, Sears ML, Mead A. Aqueous flow in human eyes is reduced by forskolin, a potent adenylyl cyclase activator. Exp Eye Res 1984; 39: 745–749

121 Caprioli J, Sears M. The adenylyl cyclase receptor complex and aqueous humor formation. Yale J Biol Med 1984; 57: 283–300

122 Sears ML. Regulation of aqueous flow by the adenylyl cyclase receptor complex in the ciliary epithelium. Am J Ophthalmol 1985; 100: 194–198


131 Hayashi T. Application of a new botanical ingredient ‘Coleus extract’ to hair growth products. Fragra J 2000; 28: 45–49


141 Mooney RA, Swicegood CL, Marx RB. Coupling of adenyl cyclase to lipolysis in peroxisomized adipocytes: direct evidence that an anti-polycyclic effect of insulin is independent of adenyl cyclase. Endocrinology 1986; 119: 2240–2248


144 Allen DG, Queesney JT. Quantitative differences in the cyclic AMP-lipolysis relationships for isoprotenerol and forskolin. J Pharmacol Exp Ther 1988; 244: 852–858

145 Schimmel RJ. Stimulation of cAMP accumulation and lipolysis in hamster adipocytes with forskolin. Ann J Physiol 1984; 246: C63–C68


151 Schorlemmer HU, Dickneite G, Sedlacek HH, de Souza NJ, Dohadwalla AN. Use of the diterpene derivative forskolin for immunomodulation. US Patent 4578399; 1986

152 Curtin BF, Pal N, Gordon RK, Nambiar MP. Forskolin, an inducer of cAMP, upregulates acyclcylcinesterase expression and protects against organophosphate exposure in neuro 2A cells. Mol Cell Biochem 2006; 290: 23–32

153 Morazzoni P, Bombardelli E. Use of forskolin or extracts containing it in the manufacture of a medicament for the treatment of alcohol addiction. PCT Int Appl WO 9636332 A1; 1996

154 Karagay B, Li C, Pantuzis NJ, Bonbiss OJ. Stimulation of the cAMP pathway protects cultured cerebellar granule neurons against alcohol-induced cell death by activating the neuronal nitric oxide synthase (nNOS) gene. Brain Res 2007; 1143: 34–45
155 Gupta PP, Srimal RC, Verma N, Tandon JS. Passive cutaneous anaphylactic
inhibitory and mast cell stabilizing activity of coleonol and its de-
rivatives. Indian J Pharmacol 1994; 26: 150–152

156 Marone G, Columbo M, Triggiani M, Cirillo R, Genovese A, Formisano S.
Inhibition of IgE-mediated release of histamine and peptide leuko-

157 Dohadwala AN, Mandrekar SS, Dedkar NK, Khandelwal Y, Rupp RH, de Souza NJ. Labdan derivatives and their use as drugs. Patent DE
3502686A1; 1986

158 Dohadwala AN, Mandrekar SS, Dedkar NK, Khandelwal Y, Rupp RH, de Souza NJ. Method of treating inflammatory diseases with labdan deri-
atives. US Patent 4724238; 1988

159 Mueda H, Ozawa H, Saijo T, Irie T, Takahata N. Potential antidepressant
properties of forskolin and a novel water-soluble forskolin (NRK477) in the forced swimming test. Life Sci 1997; 61: 2435–2442

160 Sano M, Seto-Ohshima A, Mizutani A. Forskolin supresses seizures in-
duced by pentylenetetrazole in mice. EXPERIENIA 1984; 40: 1270–1271

521–524

162 Berzdorff Y, Kotler M, Shiffin M, Belmaker RH. A preliminary study of possible psychoactive effects of intravenous forskolin in depressed and
schizophrenic patients. Short communication. J Neural Transm 1996; 103: 1463–1467

163 Vitolo OV, Sant’Angelo A, Costanzo V, Battaglia F, Arancio O, Shenks M.
Amyloid beta-peptide inhibition of the PKA/CREB pathway and long-term potentiation: reversibility by drugs that enhance cAMP sig-

362: 117–121

165 Ahmad F, Khan MM, Rastogi AK, Kidwai JR. Insulin and glucagon release
controlling activity of coleonol (forskolin) and its effect on blood glucose level in normal and alloxan diabetic rats. Acta Diabetol Lat 1991;
28: 71–77

166 Yamamoto S, Nakadate T, Uzumaki H, Kato R. Lipoxgenase inhibitors and
cyclic AMP- mediated insulin secretion caused by forskolin, theo-
ophylline and dibutyryl cyclic AMP. J Pharmacol Exp Ther 1985; 253:
176–180

273: E52–E58

168 Mulhall JF, Dallier M, Trish MA, Gupta S, Park K, Salimpoor P, Payton TR,
Krate RJ, Goldstein I. Intracavernosal forskolin: role in management of
impotence resistant to standard 3-agent pharmacotherapy. Urology 1998;
51: 861–865

169 Li JH, Li Y, Cao ZG, Ye ZQ. Effect on superoxide anion generation in isolated osteoclasts. Exp Physiol 2002; 404: 293–301

170 Sander RA, Kreek MJ, McMillan RE, Belliveau SJ, Huganir RL. Regulation of
intracellular cAMP. J Neurosci 1988; 8: 3405–3413

171 Putnam WC, Swenson SM, Reif GA, Wallace DP, Helmkamp Jr GM, Gran-
tham JJ. Method of treating inflammatory diseases with labdan deriva-
tives. US Patent 4724238; 1988

172 Sano M, Seto-Ohshima A, Mizutani A. Forskolin supresses seizures in-
duced by pentylenetetrazole in mice. EXPERIENIA 1984; 40: 1270–1271

173 Hashi T, Garber SS, Aldrich RW. Effect of forskolin on voltage-gated K+
channels is independent of adenylate cyclase activation. Science 1988;
240: 1652–1655

174 Matthias K, Seifert G, Reinhardt S, Steinhäuser C. Modulation of volt-
age-gated K(+)-channels Kv11 and Kv14 by forskolin. Neuropharma-
cology 2002; 43: 444–449

175 Oto K, Fozard JA, Hankck DA. A direct effect of forskolin on sodium channel bursting. Pfugers Arch 1995; 429: 561–569

176 Mukherjee T, Pelzer S, McDonald TF. Cyclic AMP-independent inhibition of cardiac calcium current by forskolin. Mol Pharmacol 1996;
50: 1262–1272

177 Park TJ, Kim KT. Cyclic AMP-independent inhibition of voltage-sensi-
tive calcium channels by forskolin in PC12 cells. J Neurochem 1996;
66: 83–88

178 Gandía I, Vitale ML, Villarroya M, Ramírez-Lavergne C, García AG, Tri-
faró JM. Differential effects of forskolin and 1,9-dideoxyforskolin on nicotinic receptor- and K+- induced responses in chromaffin cells. Eur J
Pharmacol 1997; 329: 189–199

179 Shii LJ, Liu LA, Wang CA. Effect of forskolin on acetylcholine-induced
21: 281–285

180 Fan P. Antagonism by forskolin of the 5-HT3 receptor-mediated cur-
nent in rodose ganglion neurons is independent of cyclic AMP. Brain Res 1994; 650: 16–19

181 Oz M, Zhang L, Spivak CE. Direct noncompetitive inhibition of 5-HT3 recep-
tor-mediated responses by forskolin and steroids. Arch Biochem Biophys 2002; 404: 293–301

182 Waerter W, Ostermann MH, Pfeiffer A. Partial reversal of doxorubicin resistance by forsko-

183 Morris DL, Speicher LA, Rizzo JR, Seaman KB. Interaction of forskolin with the P-glycoprotein multidrug transporter. Biochemis-
try 1991; 30: 8371–8379

184 Zubillaga DA, Savage N. The adenylyl cyclase activator forskolin partially
protects L929 cells against tumour necrosis factor-alpha-mediated cytotoxicity via a cAMP-dependent mechanism. Cytokine 2002; 19:
250–258

185 Sidhu JS, Omiecinski CJ. Forskolin-mediated induction of CYP3A1 mRN
expression in primary rat hepatocytes is independent of elevated intracellular cyclic AMP. J Pharmacol Exp Ther 1996; 270: 238–245

186 Dowless MS, Barbee JL, Borchert KM, Bocchino WP, Houch KA. Cyclic

187 Li Ping, Yang XL. Forskolin modulation of desensitization at GABAA and
glycine receptors is not mediated by cAMP-dependent protein ki-
nase in isolated carp amacrine-like cells. Pfugers Arch 2001; 441:
73–78

188 Middleton P, Jaramillo F, Schwartz SM. Forskolin increases the rate of
cytochrome P450 inhibition that occurs in rat soleus endplates. Proc Natl Acad Sci USA 1986; 83: 4967–4971

189 Miles K, Anthony DT, Rubin LL, Greenberg P, Huganir RL. Regulation of
nicotinic acetylcholine receptor phosphorylation in rat myotubes by forskolin and cAMP. Proc Natl Acad Sci USA 1987; 84: 6591–6595

190 Wagoner PK, Pullotla BS. Modulation of acetylcholine receptor desen-
sitization by forskolin is independent of cAMP. Science 1988; 240:
1655–1657

191 Middleton P, Rubin LL, Schwartz SM. Desensitization of acetylcholine recep-
tors in rat myotubes is enhanced by agents that elevate intracel-
lular cAMP. J Neurosci 1988; 8: 3405–3412

192 Berger CE, Datta HK. Forskolin has a bidomal cAMP-independent ef-
flect on superoxide anion generation in isolated osteoclasts. Exp Phys-
iol 2000; 85: 57–60

193 Kreiger NS, Stern PH. Effect of forskolin on bone in organ culture. Am J
Physiol 1987; 252: E44–E48

194 Ding X, Staudinger JL. Induction of drug metabolism by forskolin: the role of the pregnane X receptor and the protein kinase A signal trans-
duction pathway. J Pharmacol Exp Ther 2005; 312: 849–856

195 Putnam WC, Swenson SM, Reif GA, Wallace DP, Helmkanp Jr CM, Gran-
tham JJ. Identification of a forskolin-like molecule in human renal cy-

196 Yang W, Li X, Chen Z, Nie L, Wang B, Shen Z. Adenylate cyclase stimula-
tion and ocular hypertension inhibition by forskolin analogs. Yanke
Yanjiu 2001; 20: 1–4
hydrochloride, inhibits the decrease in cortical renal blood flow induced by noradrenaline or angiotensin II in anesthetized rats. Nephrol Physiol 2004; 96: 59–64


231 Sambe A, Takeo S. Effects of NKH477, a water-soluble forskolin derivative, on cardiac function in rats with chronic heart failure after myocardial infarction. J Pharmacol Exp Ther 1995; 274: 120–126


