East and Central African Journal of Pharmaceutical Sciences
Vol. 13 (2010) 25- 32

Forskolin: A Successful Therapeutic Phytomolecule

M. B. PATEL

Atmiya Pharmacy College, Koyali-Sevasi road, Ankodia, District -Vadodara, Gujarat, India.

Forskolin, a labdane diterpene is the main active ingredient in the ayurvedic herb *Coleus forskohlii* (Labatiae) that has been used in India since ancient times. The root portion of the plant has been traditionally used for medicinal purposes and contains the active constituent, forskolin. Historically, it has been used to treat hypertension, congestive heart failure, eczema, colic, respiratory disorders, painful urination, insomnia, and convulsions. Clinical studies have justified these traditional uses and indicate its therapeutic potential in asthma, angina, psoriasis, and prevention of cancer metastases. The present review summarizes these reports along with the advancements in research on forskolin as a therapeutic molecule.

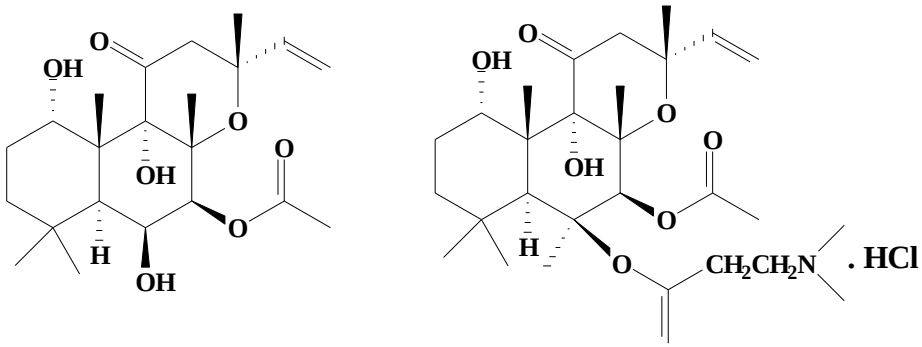
Key words: Forskolin, *Coleus forskohli,* labdane diterpene

INTRODUCTION

Coleus forskohlii is a perennial herb that grows in the subtropical temperate climates of India, Nepal, Sri Lanka, and Thailand. The common names for the plant in India are *makandi,mainmul* and *karpuravali*. The plant grows to 1-2 feet and its leaves are teardrop shaped, shimmering green framing a bright purple center. The leaf color varies depending on the amount of shade. A cluster of stalked pale purple or blue flowers branch off a single stem. It bears fasciculate tuberous roots. The root stock is typically golden brown, thick, fibrous and radially spreading. The roots are harvested in the fall, when the forskolin content is highest and the root color is brightest.

Coleus forskohlii and other related species were used in *Ayurvedic* medicine under the name *pashanabhedi* for heart and lung diseases, intestinal spasms, insomnia, and convulsions. It was studied for cardiovascular activity in 1974 by scientists from Hoechst India and the Central Drug Research Institute of India in screening programs that examined medicinal plants.

The diterpene forskolin (17-β-acetoxy-8, 13-epoxy-1α, 6-β, 9α-trihydroxylabd-14-en-11-one), derived from the root of the plant, is the primary constituent of clinical interest in *Coleus forskohlii* [1]. It was discovered by Finnish botanist, Forskal in 1974 and was initially referred to as coleonol. Since that time, as other coleonols and diterpenoids have been identified, the name was changed to forskolin [2]. Forskolin is responsible for virtually all pharmacological activities attributed to *Coleus forskohlii*. There is evidence, however, that other plant constituents, such as volatile oils and other diterpenoids and coleonols, may contribute to the pharmacological activity and absorption of forskolin [3]. Detailed analysis reveals approximately 20 constituents in various parts of the plant, but forskolin and other coleonols are present only in the root portion. The labdane diterpene glycosides, forskoditerpenoside C, D and E plus a novel labdane diterpene forskoditerpene A were isolated from the ethanol extract of the whole plant of *Coleus forskohlii* [4]. Presence of 14-deoxycoleon U, demethylcryptojaponol, α-amyrin, betulic acid, β-cedrol and β-sitosterol [5], 1-α, 6-β -diacetoxy-8, 13-epoxylabd-14-en-11-one, 1-α-hydroxy-6-β, 7-β-diacetoxy-8, 13-epoxylabd-14-en-11-one and



Forskolin Colforsin daropate hydrochloride

Figure 1: Chemical structures of forskolin and colforsin daropate hydrochloride

1-α ,9-α - dihydroxy-6-β,7-α -diacetoxy-8,13-epoxylabd-14-en-11-one has also been reported [6]. A diterpenoids, forskolins I (1-α, 6-β-diacetoxy-7-β, 9-α-dihydroxy-8, 13-epoxylabd-14-en-11-one) and forskolins J (1-α, 9-α-dihydroxy-6-β, 7-β-diacetoxy-8, 13-epoxylabd-14-en-11-one) were reported by Shem *et al* [7].

Forskolin ($C_{22}H_{34}O_7$, MW 410.5) is an off-white crystalline solid with a melting point of 228-230 ^{0}C and UV absorption maxima at 210 nm and 305 nm.

Medical research has shown that it can be used for treatment of allergies, respiratory problems, cardiovascular diseases, glaucoma, psoriasis, hypothyroidism and weight loss. Recently, it was reported as a natural remedy for urinary tract infections (UTI) by enhancing the ability of antibiotics to kill the bacteria that cause 90 % of infections in the bladder.

Isolation and Quality Control

As a result of screening programs, forskolin has been identified as the major active hypotensive principle of the roots of *Coleus forskohlii* [8]. The absolute stereochemistry of forskolin was determined by X-ray crystallography [9, 10]. The other most abundant diterpene in the plant, 1, 9-dideoxy-forskolin, had no hypotensive activity [11]. Subsequently several closely related diterpenes have been isolated from the roots and aerial portions of the plant including stigmasterol [11-14].Saleem *et al.* have described an isolation procedure that yields forskolin of 96.9% purity [15].

Because forskolin has been actively pursued as a drug development lead, there have been many analytical methods have been developed for analysis of the same. A gas-liquid chromatography (GLC) method was developed for quantitation of forskolin in plant tissues and in dosage forms [16]. Both thin layer and high performance liquid chromatographic (HPLC) methods have also been published [17]. The GLC method was more sensitive but the HPLC method was found to be more rapid [17]. The HPLC method has been used to monitor variation in forskolin content in different germplasms [18]. A monoclonal antibody specific for forskolin has been developed for affinity isolation of forskolin [19]. The same antibody also has been used for extremely sensitive quantitation of forskolin in plant tissues at different stages of development [20]

.Nuclear magnetic resonance (NMR) and gas chromatography-mass spectral methods have also been published for forskolin and its congeners [21, 22]. Tissue culture methods for forskolin production have been successfully explored because the low content of forskolin

in the plant has limited its development as a drug product [23, 24].

Recently HPLC-ELSD fingerprint of *Coleus forskohlii* was described by Wu *et al*. [25]. Forskolin being a biomarker is considered for quantification as a parameter for the quality control of products containing *Coleus forskohlii* root.

Mode of Action

Forskolin exerts most of its biological activity is by stimulation of adenylate cyclase, thereby increasing cellular concentrations of the second messenger cyclic AMP [26, 27]. Increased cellular cyclic AMP results in a broad range of physiological and biochemical effects, including inhibition of platelet activation, reduced release of histamine, increased force of contraction of the heart, relaxation of the arteries and other smooth muscles, increased thyroid function and increased lipolysis. Among the 9 types of adenylate cyclase in humans, forskolin activates all but type IX, which is found in spermatozoa [28]. Photoaffinity derivatives of forskolin have been shown to irreversibly react with type I adenylate cyclase [29] and the structure of forskolin bound to type II cyclase has been determined by X-ray crystallography [30]. Chemical modification of forskolin at the 6- and 7-positions has led to semisynthetic compounds with modest selectivity for particular adenylate cyclase isoforms, including the cardiac type V adenylate cyclase [28]. Stimulation of adenylate cyclase is thought to be the mechanism by which forskolin relaxes a variety of smooth muscles, inhibits basophil and mast cell degranulation and histamine release [31], lowers blood pressure [32] and intraocular pressure [28], inhibits platelet aggregation [33], promotes vasodilation [32], bronchodilation [34] and thyroid hormone secretion [35] and stimulates lipolysis in fat cells [36]. A number of diseases are characterized, in part, by decreased intracellular levels of cyclic AMP. These include asthma, eczema, psoriasis, angina, obesity and hypertension.

Forskolin has also been found to act through other mechanisms. Forskolin binds to the glucose transporter in adipocytes [37] to the P-glycoprotein drug efflux pump [38], alters potassium channel activity [39] and decreases GABA receptor chloride flux [40]. The compound is known to modulate the nicotinic acetylcholine receptor [41, 42]. The natural diterpene 1, 9-dideoxy-forskolin, which has no activity on the adenylate cyclase enzyme, shows activity through these other systems.

In addition to its cAMP-stimulating activity, forskolin inhibits the binding of platelet-activating factor (PAF), independently of cAMP formation. This may be a result of forskolin's direct effect on PAF or via interference with PAF binding to receptor sites. Forskolin acts on several membrane transport proteins and inhibits glucose transport in erythrocytes, adipocytes, platelets, and other cells [43].

PHARMACOLOGICAL ACTIONS

Cardiovascular Disease

The platelet aggregation and inhibiting effects of forskolin add to its value in cardiovascular disorders [54]. Forskolin significantly lowers blood pressure via relaxation of vascular smooth muscles [32, 44, 45]. It reduces diastolic blood pressure without increasing myocardial oxygen consumption [46]. Further it increases cerebral blood flow indicating it may be beneficial in cerebral vascular insufficiency and in enhancing post -stroke recovery [37]. Due to its vasodilating properties,forskolin has been proposed for intercarvenosal treatment of erectile dysfunction based on small scale clinical studies have been reported [67].

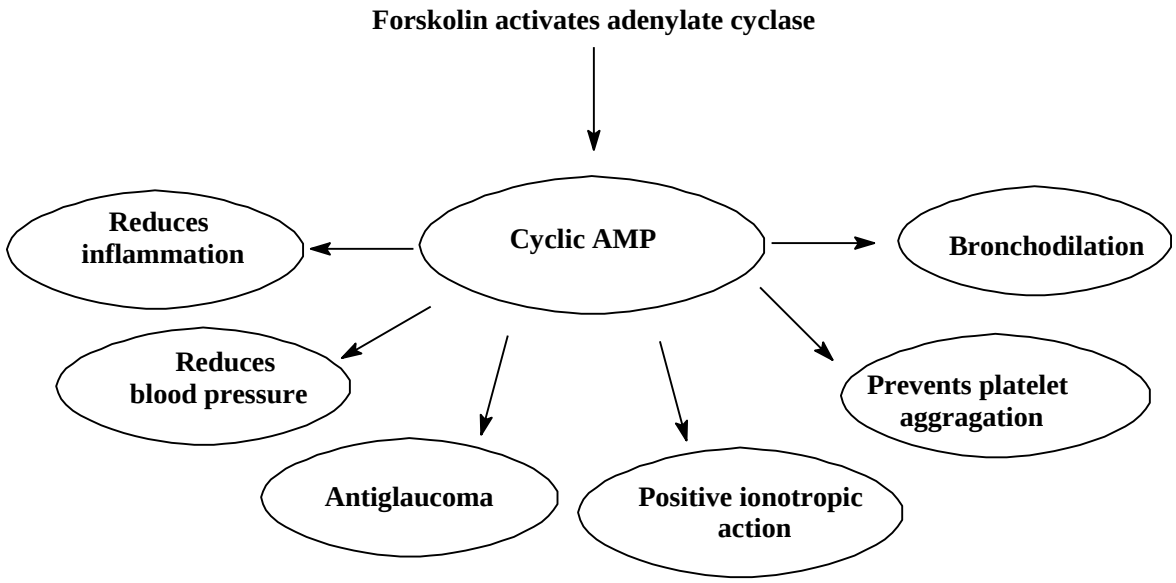


Figure 2: Effects of increased intracellular levels of cyclic AMP (cAMP) induced by forskolin

Asthma and Allergies

Forskolin's activation of cAMP inhibits human basophil and mast cell degranulation [31], resulting in subsequent bronchodilation [34].Research has demonstrated aerosolized dry forskolin powder [49].

Psoriasis

Ammon *et al* [3] reported an improvement in symptoms of psoriasis in four patients treated with forskolin. The ability of forskolin to regulate cAMP levels in skin cells has been shown to have therapeutic benefit for sufferers of psoriasis.

Glaucoma and Increased Intraocular Pressure

There are clinical reports demonstrating the effect of forskolin on decrease of intraocular pressure both in animals and human patients [46, 54].Studies on human suggest forskolin may be of benefit in reducing intraocular pressure in glaucoma [50].

Depresion

Forskolin is thought to be acting as an antidepressant by increasing cAMP and inhibiting phosphodiesterase, although the results are limited to animal models [66].

Hypothyroidism

Forskolin has demonstrated the ability to increase thyroid hormone production and stimulate thyroid hormone release by increasing the quantity of stimulatory guanine nucleotide-binding proteins [52]. This mechanism of stimulating the thyroid to enhance metabolism may be one way in which forskolin promotes normal body weight. Forskolin's effects in normalizing thyroid function may also contribute to its antidepressant effects.

Cancer

Forskolin reduced tumor colonization (melanoma cell line – BF16F10) in the lungs by 70 % [55]. Applied with rolipram, forskolin provides a route to inhibition of colon cancer cell growth and survival [56].

Weight Loss

One clinical study reported forskolin's role in increasing lean mass, bone mass and testosterone in the subjects involved [57]. This research has led to companies marketing forskolin as a bodybuilding supplement. *In vitro* and animal studies demonstrate lipolysis in fat cells is stimulated by forskolin [36] via activation of adenylate cyclase and increased levels of cAMP. A patent claiming promotion of lean body mass and antidepressant activity of forskolin containing extract was granted to the supplement company Sabinsa in 1998 [65].

Other Clinical Indications

Forskolin has been shown to stimulate digestive secretions, including hydrochloric acid, pepsin, amylase, and pancreatic enzymes [3, 26, 62], suggesting clinical benefit in digestive disorders and malabsorption. An *in vitro* research has indicated forskolin has potent immuno-stimulation properties [60, 61]. Forskolin increases skin's natural resistance to UV light and stimulates a tanning response when applied topically.

Drug Interactions

Forskolin should be avoided in conjunction with anticoagulant medications [54] and with antihypertensive agents as it may have a potentiating effect on these drugs [32].

Contraindications

Caution should be used cautiously in patients suffering from ulcers [26], low blood pressure [32], bleeding disorders or those on blood-thinning medication [54] and in diabetics due to stimulation of lipid release and gluconeogenesis.

Forskolin derivatives

A water-soluble forskolin derivative, 6-(3-dimethylaminopropionyl) forskolin, colforsin daropate hydrochloride, has been shown to have relaxant effect on the acetylcholine-induced contraction of muscle strips of porcine coronary artery [68]. The same compound also possesses a potent anti-inflammatory activity [69]. Intraoperative administration of colforsin daropate hydrochloride had potent inotropic and vasodilatory activity and attenuated cytokine production and respiratory dysfunction after cardiopulmonary bypass [70]. The efficacy of this drug is approximately two times that of forskolin in membrane preparations of the guinea pig ventricle. A forskolin derivative, 6-[3-(dimethylamino)propionyl]-14,15-dihydro-forskolin (DMAPD) was studied for its adenylyl cyclase isoform selectivity using insect cell membranes overexpressing type II, III and V adenylyl cyclase isoforms. DMAPD stimulated type V more potently than types II and type III relative to forskolin [71].

Water-soluble forskolin and 7-deacetylforskolin derivatives with an aminoacetyl, a 3-aminopropionyl or a 4-aminobutyryl group at the 6- or 7-positions showed positive inotropic as well as vasodilative activities when evaluated in anesthetized dogs. Among the 6-aminoacylforskolins, 6-(3-dimethylaminopropionyl) forskolin and 6-(4-dimethylaminobutyryl) forskolin exhibited potent positive inotropic and vasodilative activities comparable to those of forskolin. The effects of the soluble forskolins on adenylate cyclase activity were also examined *in vitro* whereby 6-aminoacylforskolins exhibited potent adenylate cyclase-stimulating activity, comparable to that of forskolin [72].

CONCLUSION

Forskolin, being a molecule that elevates cAMP in turn is responsible for most of the pharmacological actions of *Coleus forskohlii* root. This herb is used in various traditional medicine and thousands of products are available in market. Products are standardized on account of their forskolin content. Many of its derivatives have been synthesized in an effort to improve efficacy and safety. Molecules having effect on cardiovascular system, bronchodilatory effect, prevention of platelet aggregation, anti inflammatory effect have enjoyed market success in the past.

Forskolin possesses all these properties and due to its versatility may be made into many formulations. This molecule can be taken as lead compound and could be further improved via quantitative structure activity relationship studies. It provides a vast scope of research in a variety of therapeutic areas.

REFERENCES

[1] N.J. De Souza, A.N. Dohadwalla, J. Reden, Med. Res. Rev. 3 (1983) 201-219.

[2] A.K. Saksena, M.J.Green, H.J.Shue et al, Tetrahedron Lett. 26 (1985) 551-554.

[3] H.P. Ammon and A.B. Muller, Planta Med. 6 (1985) 473-477.

[4] Y. Shan, L. Xu, Y. Lu, X. Wang, Q. Zheng Q, L. Kong, M. Niwa,Chem. Pharm. Bull. (Tokyo) 56 (2008) 52-6. [84] S Namkoong, C.K. Kim, Y. L. Cho, J.H. Kim, H. Lee, K.S. Ha, J. Choe, P.H. Kim, M.H. Won, Y.G. Kwon, E.B. Shim, Y.M. Kim, Cellular signalling (Cell Signal) 21 (2009) 906-915.

[5] L.L Xu , J. Lu, W.J. Li, L.Y. Kong, Zhongguo Zhong Yao Za Zhi. 30 (2005) 1753-5.

[6] Q.R. Yang, H.Z. Wu , X.M. Wang, G.A. Zou, Y.W. Liu, J. Asian Nat. Prod. Res. 8 (2006) 355-360.

[7] Y.H. Shen, Y.L. Xu, J. Asian Nat. Prod. Res. 7 (2005) 811-815.

[8] S.V. Bhat, B.S. Bajwa, H. Dornauer, N.J. De Souza, Tetrahedron Lett. 1977 (1977) 1669-1672.

[9] E.F. Paulus, Z. Kristallogr . 152 (1980) 239-245.

[10] E.F. Paulus, Z Kristallogr. 53 (1980) 43.

[11] R. Roy, A. Mishra, N. Varma, J.S. Tandon, M. Saux, A. Carpy, Phytochemistry 34 (1993) 1577-1580.

[12] Y. Khandelwal, B.R. Jotwani, P.K. Inamdar, N.J. De Souza, R.H. Rupp, Tetrahedron 45 (1989) 763-766.

[13] J.S. Tandon et al, Bioorg. Med. Chem. Lett. 2 (1992) p249.

[14] V.C. Shah, A.S. D'Sa AS, N.J. De Souza, Steroids 53 (1989) 559-565.

[15] A.M. Saleem, P.B. Dhasan, M.R. Rafiullah, J. Chromatogr A. 1101 (2006) 313-314.

[16] P.K. Inamdar, H. Dornauer, N.J. De Souza, J. Pharm. Sci. 69 (1980)1449-1451.

[17] P.K. Inamdar, P.V. Kanitkar, J. Reden, N.J. De Souza, Planta Med. 50 (1984): 30-34.

[18] R.A Vishwakarma, B.R. Tyagi, B. Ahmed, A. Hussain, Planta Med. 54 (1988) 471.

[19] H Yanagihara et al, Anal. Chim. Acta. 335 (1996) 63.

[20] H. Yanagihara, R. Sakata, Y. Shoyama, H. Murakami, Planta Med. 62 (1996) 169-172.

[21] O. Prakash O et al, Magn. Reson. Chem. 26 (1988) 117.

[22] C. Demetzos, A. Kolocouris, T. Anastasaki, Bioorg. Med. Chem. Lett. 12 (2002) 3605-3609.

[23] R. Mersinger, H. Dornauer, E. Reinhard, Planta Med . 54 (1988) 200-204.

[24] Mukherjee S, Ghosh B, Jha S. Establishment of forskolin yielding transformed

[25] H.Z. Wu, Q.R. Yang, Y.F. Yang, Y.W. Liu, Zhong. Yao. Cai. 30 (2007) 1370-1374.

[26] K.B. Seamon, W. Padgett, J.W. Daly, Proc. Natl. Acad. Sci. U S A. 78 (1981) 3363-3367.

[27] H. Metzger, E. Lindner, Arzneimittel forschung 31 (1981) 1248-1250.

[28] K. Iwatsubo, T. Tsunematsu, Y. Ishikawa, Expert Opin. Ther. Targets 7 (2003) 441-451.

[29] E.M. Sutkowski, J.D. Robbin, W.J. Tang, K.B. Seamon, Mol. Pharmacol. 50 (1996) 299-305.

[30] G. Zhang, Y. Liu, A.E. Ruoho, J.H. Hurley, Nature. 386 (1997) 247-253.

[31 G. Marone, M. Columbo, M. Triggiani et al, Agents Actions 18 (1986) 96-99.

[32] M.P. Dubey, R.C. Srimal, S. Nityanand, B.N. Dhawan, J. Ethnopharmacol. 3 (1981) 1-13.

[33] K.C. Agarwal, R.E. Parks Jr, Biochem. Pharmacol. 31 (1982) 3713-3716.

[34] I. Lichey, T. Friedrich, M. Priesnitz, Biamino G, Usinger P, Huckauf H Lancet 2 (1984) 167.

[35] B. Haye, J.L. Aublin., S. Champion, B. Lambert, C. Jacquemin, Mol. Cell Endocrinol. 43 (1985) 41-50.

[36] H. Okuda, C. Morimoto, T. Tsujita, J. Lipid Res. 33 (1992) 225 - 231.

[37] A. Kashiwagi, T.P. Hueckstead , J.E. Foley, J. Biol. Chem. 258 (1983) 13685-13692.

[38] D.I. Morris, L.A. Speicher, A.E. Ruoho, K.D. Tew, K.B. Seamon, Biochemistry 30 (1991) 8371-8379.

[39] T. Hoshi, S.S. Garber, R.W. Aldrich, Science 240 (1988) 1652-1655.

[40] G. Heuschneider, R.D. Schwartz, Proc. Natl. Acad. Sci. U S A. 86 (1989) 2938-2942.

[41] E.X. Albuquerque, S.S Deshpande, Y. Aracava, M. Alkondon, J.W. Daly, FEBS Lett. 199 (1986) 113-120.

[42] P.K. Wagoner, B.S. Pallotta, Science 240 (1988) 1655-1657.

[43]I. Mills, F. J. Moreno, J.N. Fain, Endocrinology 115 (1984) 1066-1069.

[44] W. Kramer, J. Thormann, M. Kindler, M. Schlepper, Arzneimittelforschung 37 (1987) 364-367.

[45] Schlepper M, Thormann J, Mitrovic V, Basic Res Cardiol 84 (1989), S197-S212.

[46] C. Seto, S. Eguchi, M. Araie, S. Matsumoto, M. Takase, Jpn. J. Ophthalmol. 30 (1986) 238-244.

[47] B.H. Meyer, A.A. Stulting, F.O. Muller FO, M. BAdian, S. Afr. Med. J. 71 (1987) 570-571.

[48] H.K. Kim, K.S. Song, J.H. Chung, K.R. Lee, S.N. Lee, Br. J. Haematol. 124 (2004) 376-384.

[49] K. Bauer, F. Dietersdorfer, K. Sertl, G. Kaik, Clin. Pharmacol. Ther. 53 (1993) 76-83.

[50] J. Caprioli, M. Sears, L. Bausher, D. Gregory, A. Mead, Invest. Opthalmol. Vis. Sci. 25 (1984) 268-277.

[51] J. Caprioli, M. Sears M, Lancet 1 (1983) 958-960.

[52]B. Saunier, J. Biol. Chem. 265 (1990) 265: 1994 2-6.

[53] V. Badmaev, M. Majeed, A. Conte, J.E. Parker, Townsend Lett. (2001) June: 115.

[54] A.M. Siegl, J.W. Daly, J.B. Smith, Mol. Pharmacol. 21 (1982) 680-687.

[55] K. C. Agarwal, R.E. Parks Jr., Int. J. Cancer. 32 (1983) 801-804.

[56] D.G. McEwan, V.G. Brunton, G.S.Baillie GS, Leslie NR, Houslay MD, Frame MC. Cancer Research 67 (2007) 5248-5257.

[57] P.G. Michael, A.J. Brad, R.R. Scott, Obesity Research 13 (2005) p8.

[58] L.F. Martin C.M. Klim, S.J. Vannucci et al, Surgery 108 (1990) 228-234.

[59] S. Adnot, M. Desmier, N. Ferry, J. Hanoune, T. Sevenet, Biochem. Pharmacol. 31 (1982) 4071-4074.

[60] H.U. Schorlemmer, Chem. Abstr. 102 (1985) ,p1009.

[61] J.F. Krall, E.I. Fernandez, M. Connelly-Fittingoff, Proc. Soc. Exp. Biol. Med. 184 (1987) 396-402.

[62] S.J. Hersey, A. Owirodu, M. Miller, Biochim. Biophys. Acta. 755 (1983) 2963-299.

[63] P.Y. Lee, S.M. Podos, J.B. Serle, C.B. Camras, C.H. Severin, Arch. Ophthalmol. 105 (1987) 249-252.

[64] R.F. Brubaker, K.H. Carlson, L.J. Kullerstrand, J.W. McLaren, Arch. Ophthalmol. 105 (1987) 637-641.

[65] M. Majeed et al., US patent 5804596 (1997).

[66] H. Maeda, H. Ozawa, T. Saito, T. Irie, N. Takahata, Life Sci. 61 (1997) 2435-2442.

[67] S.E. Drewes, J. George, F. Khan, Phytochemistry 62 (2003) 1019-1025.

[68] J. Shafiq, S. Suzuki, T. Itoh, H. Kuriyama, Circ. Res. 71 (1992) 70-81.

69] N. Hayashida, S. Chihara, E. Tayama, T. Takaseya, N. Enomoto, T. Kawara, S. Aoyagi, Ann. Thorac. Surg. 71 (2001) 1931-1938.

[70] M. Hosono, T. Takahira, A. Fujita, R. Fujihara, O. Ishizuka, T. Tatee, K Nakamura, J. Cardiovasc. Pharmacol. 19 (1992) 625–634.

[71] Toya Y, Schwencke C, Ishikawa Y, Journal of Molecular and Cellular Cardiology 30 (1998) 97-108.

[72] T. Tatee T, A. Narita., K. Narita, G. Izumi, T. Takahira, M. Sakurai, A. Fujita, M. Hosono, K. Yamashita, K. Enomoto, A. Shiozawa, Chem. Pharm. Bull. 44 (1996)2274-2279.[