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Review

The Therapeutic Potential of the Labdane Diterpenoid Forskolin

Bahare Salehi [1], Mariola Staniak [2], Katarzyna Czopek [2], Anna Stępień [2], Kamal Dua [3,4,5,*], Ridhima Wadhwa [6], Dinesh Kumar Chellappan [7], Oksana Sytar [8,9], Marian Brestic [9], Namrata Ganesh Bhat [10], Nanjangud Venkatesh Anil Kumar [10], María del Mar Contreras [11,*], Farukh Sharopov [12,*], William C. Cho [13,*] and Javad Sharifi-Rad [14,*]

1 Student Research Committee, School of Medicine, Bam University of Medical Sciences, Bam 44340847, Iran; bahar.salehi007@gmail.com
2 Institute of Soil Science and Plant Cultivation—State Research Institute, Czartoryskich Str. 8, 24-100 Puławy, Poland; staniakm@iung.pulawy.pl (M.S.); kczopek@iung.pulawy.pl (K.C.); astepien@iung.pulawy.pl (A.S.)
3 Discipline of Pharmacy, Graduate School of Health, University of Technology Sydney, Ultimo, NSW 2007, Australia
4 Centre for Inflammation, Centenary Institute, University of Newcastle, Callaghan, NSW 2308, Australia
5 Priority Research Centre for Healthy Lungs, Hunter Medical Research Institute (HMRI) & School of Biomedical Sciences and Pharmacy, University of Newcastle, Callaghan, NSW 2308, Australia
6 Faculty of Life Science and Biotechnology, South Asian University, Akbar Bhawan, Chanakyapuri, New Delhi 110021, India; rw4565@gmail.com
7 Department of Life Sciences, School of Pharmacy, International Medical University, Bukit Jalil, Kuala Lumpur 57000, Malaysia; Dinesh_Kumar@imu.edu.my
8 Department of Plant Biology Department, Taras Shevchenko National University of Kyiv, Institute of Biology, Volodymyrska str., 64, Kyiv 01033, Ukraine; oksana.sytar@gmail.com
9 Department of Plant Physiology, Slovak University of Agriculture, Nitra, A. Hlinku 2, 94976 Nitra, Slovak; marian.brestic@uniag.sk
10 Department of Chemistry, Manipal Institute of Technology, Manipal Academy of Higher Education, Manipal 576104, India; namrata.gb07@gmail.com (N.G.B.); nv.anil@manipal.edu (N.V.A.K.)
11 Department of Chemical, Environmental and Materials Engineering, University of Jaén, 23071 Jaén, Spain
12 Department of Pharmaceutical Technology, Avicenna Tajik State Medical University, Dushanbe 73400, Tajikistan
13 Department of Clinical Oncology, Queen Elizabeth Hospital, 30 Gascoigne Road, Hong Kong, China
14 Department of Pharmacology, Faculty of Medicine, Jiroft University of Medical Sciences, Jiroft 7861756447, Iran
* Correspondence: Kamal.Dua@uts.edu.au (K.D.); mmcontreras@ugr.es or mcgamez@ujaen.es (M.d.M.C.); shfarukh@mail.ru (F.S.); williamcscho@gmail.com (W.C.C.); javad.sharifirad@gmail.com (J.S.-R.)

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Abstract: Forskolin is mainly found in the root of a plant called *Coleus forskohlii* (Willd.) Briq., which has been used in the traditional medicine of Indian Ayurvedic and Southeast Asia since ancient times. Forskolin is responsible for the pharmacological activity of this species. Forskolin is a labdane diterpenoid with a wide biological effect. Several studies suggested a positive role of forskolin on heart complications, respiratory disorders, high blood pressure, obesity, and asthma. There are numerous clinical and pre-clinical studies representing the effect of forskolin on the above-mentioned disorders but more clinical studies need to be performed to support its efficacy.

Keywords: forskolin; plant secondary metabolites; *Coleus forskohlii*; cAMP pathway

1. Introduction

The fortitude of traditional medicine depends on the knowledge of plant medicinal characteristics. The major drivers of the pharmacological actions of medicinal plants are plant secondary metabolites [1,2]. Secondary metabolites are known as signal molecules for plant biosynthesis but also play defense role against herbivores, and other plants and microbes [3–5]. Terpenes are a diverse and big group of organic compounds, which are present in medicinal plants and may protect the plants that produce them by deterring herbivores and by attracting predators and parasites of herbivores [6]. The treatment of health disorders and infections with herbal medicines engages active natural products, mostly of low molecular weight, with great structural diversity such as terpenes and terpenoids [7,8].

Terpenes and terpenoids are the main components of the essential oils of many types of plants and flowers. Their biosynthesis occurs within specific tissues or at specific stages of development in plants [9]. Many terpenoids also possess pharmaceutical properties and are currently being used in clinical practices. Nowadays, terpenoids intensively applied in traditional drugs are taxol (diterpene) from *Taxus baccata* L. and artemisinin (sesquiterpene lactone) from *Artemisia annua* L. as malaria and cancer medicines, respectively, and forskolin (Figure 1a) from *Coleus forskohlii* (Willd.) Briq. (also known as *Plectranthus forskohlii* Willd.) (Lamiaceae) [10–13]. Forskolin is known to treat conditions such as heart complications, respiratory disorders, and asthma [14,15].

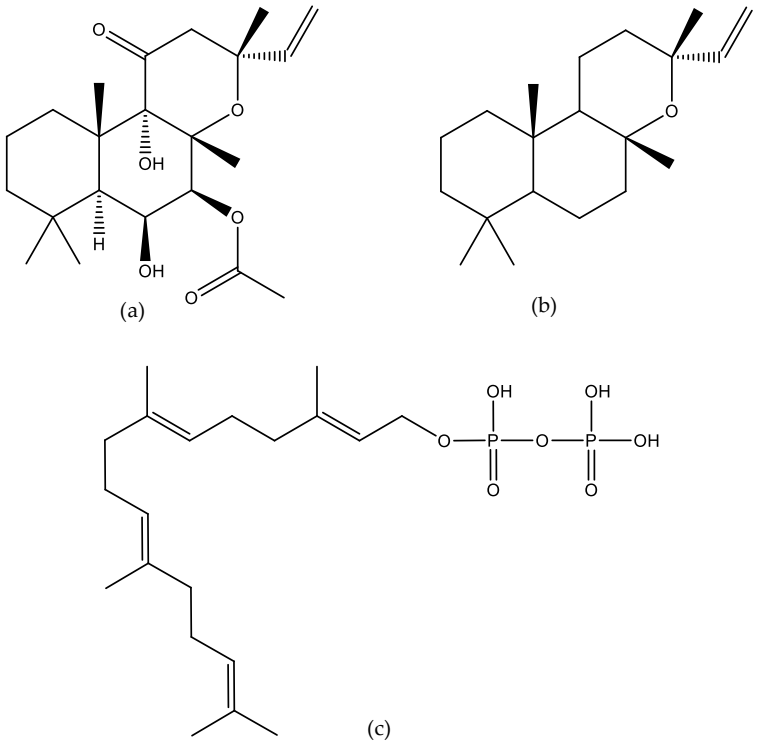

Figure 1. The chemical structure of: (**a**) forskolin; (**b**) geranyl geranyl diphosphate; and (**c**) 13R-manoyl oxide.

In particular, forskolin, which is exclusively found in the root of *C. forskohlii*, has been used in traditional Indian Ayurvedic, under the name "Makandi" or "Mayani", and Southeast Asian medicine since ancient times [15]. In African countries, it is commonly known as a drug in diseases of the digestive, urinary and respiratory tracts [16]. *C. forskohlii* is commonly found in Nepal, Burma, Thailand, and India. It is also grown in many East African countries [16–18]. India is a leading exporter of *C. forskohlii* extracts and its products to various countries, mainly USA, Poland, South Korea, Australia, Japan, Italy, Spain, South Africa, and Canada [19]. Chemically, the whole plant is rich in alkaloids, but the most desirable part of the plant is the roots, because they contain the highest concentrations

of forskolin. In the extracts obtained from the *C. forskohlii*, the presence of α-amyrin, β-sitosterol, betulinic acid, α-cedrol, citronellal and α-cedren was also identified. Other diterpenoids such as forskoditerpenoside A and B were also detected in the ethanolic extract from *C. forskohlii*, while in the essential oil obtained from the roots of the plant were identified, among others: borneol, α-humulene, 1-octadecanol, 1-decanol, decanoic acid, 4-terpineol, 1,8-cineol, α- and β-pinene, camphene, α-cedrol, α-ylangene, and γ-terpinene [15,16,18]. However, the latter compounds have a weaker therapeutic effect compared to forskolin. Hence, the research results show that forskolin is mainly responsible for the pharmacological activity of herbal materials obtained from this species [20].

Forskolin, or coleonol, is a labdane diterpene synthesized in the plastid of plant cells. In the higher plant, the non-mevalonic acid pathway takes place in plastids and synthesizes hemi-, mono-, sesqui-, and diterpenes along with carotenoids and phytol tail of chlorophyll [21]. Forskolin is synthesized by diterpene synthases via the substrate protonation at the 14,15-double bond of the initial precursor geranyl geranyl diphosphate (Figure 1b) [22]. Forskolin contains some unique functional elements, notably the tetrahydropyran-derived heterocyclic ring [23].

Forskolin is stored inside cells within the bark of the root in structures called oil bodies, which are similar to oil drops. A technique called RNA sequencing was used to identify several genes that are highly active in oil body's cells and encoded five cytochrome P450s and two acetyltransferases involved in a cascade of chemical reactions that convert a molecule called 13R-manoyl oxide (Figure 1c) into forskolin [24].

The *C. forskohlii* plant, due to forskolin presence, is used for prevention of cancer metastases, where the decreased level of activated cyclic adenosine monophosphate (cAMP) may play a main role in the disease development [25]. This ability to directly activate the adenylate cyclase enzyme resulting in elevated levels of the cAMP from adenosine-5′-triphosphate (ATP) is also related to other pharmaceutical characteristics of forskolin [26]. In this context, the present review is focused on the health-promoting effects of forskolin elucidated through modern research.

2. Pharmacological Activities of Forskolin

Forskolin is a naturally derived diterpenoid that can interact with the cAMP pathway. This interaction endows forskolin with significant therapeutic benefits against several metabolic diseases, cancers and others. According to a number of clinical studies reported on clinicaltrials.gov, the effects of forskolin have been studied in conditions such as asthma, cystic fibrosis, homozygous F508DEL mutation, chronic obstructive pulmonary disease (COPD), metabolic syndrome, obesity and glaucoma [27–34]. Notable clinical and preclinical studies, along with their pharmacological actions, are discussed below. Moreover, a summary of the effects of forskolin is shown in Figure 2.

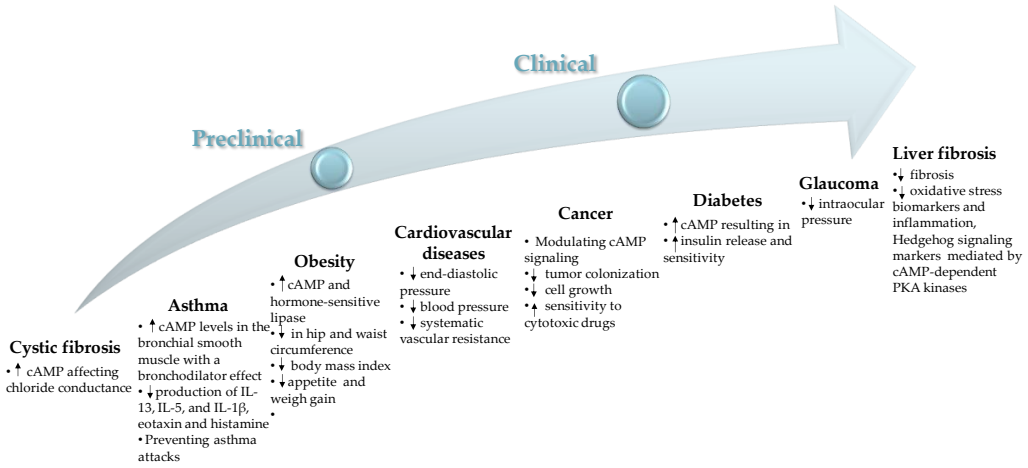

Figure 2. Effects of forskolin in human health.

2.1. Cystic Fibrosis

Cystic fibrosis is caused due to a mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene [35]. Two potential drug targets can be used to treat cystic fibrosis; namely, potentiator VX-770 and corrector VX-809 linked to CFTR gene [36]. CRE sequence (TGACaTCA) present in the promoter CFTR gene has thrown more light on the processes from cAMP regulation to gene expression [37]. Around 45–50% of cystic fibrosis patients suffer from a homozygous mutation named, F508DEL [36]. In 1991, Drumm et al. reported that the association between CFTR and chloride conductance is sensitive to forskolin (Figure 3), where the order of sensitivity occurs at a similar level as the disease severity [38]. Several clinical studies are reported for cystic fibrosis, such as NCT03652090, NCT03390985, NCT03894657 and NCT02807415, where forskolin is used to analyze drug sensitivity and classification of cystic fibrosis [27,28,32,34].

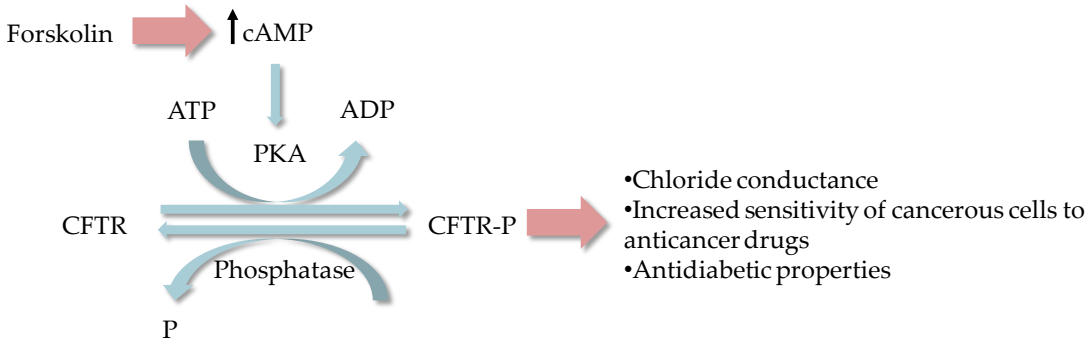

Figure 3. Potential modulation effect of forskolin based on [36]. ADP, adenosine diphosphate; ATP, adenosine triphosphate; cAMP, cyclic adenosine monophosphate; PKA, cAMP-dependent protein kinase; CFTR, cystic fibrosis transmembrane conductance regulator; CFTR-P, phosphorylated CFTR.

2.2. Cardiovascular Diseases

Forskolin has a particularly beneficial effect on the cardiovascular system. It works via vasorelaxation, causing relaxation of smooth muscles in the walls of blood vessels, which results in increasing the overall volume of the circulatory system while maintaining the volume of blood. Thanks to this, it improves the blood circulation process, the blood supply to internal organs and increases the efficiency of the myocardium. In 1983, Bristow et al. reported the pharmacological effects of forskolin in cardiovascular diseases. They reported positive inotropic effects of forskolin in membrane preparations derived from failing and normal functioning human left ventricles [39]. Several clinical and preclinical studies have been carried out, which provide sufficient evidence for the involvement of forskolin in cardiovascular diseases. In isolates of guinea pig hearts, an increase in the forskolin dose resulted in amplified contractions. However, changes in the heart rate were low. The simultaneous increase in the coronary flow and oxygen consumption represents additional vasodilator effects of this drug on the coronary circulation [40]. A clinical study conducted by Kramer et al., in 1987, reported that 15 patients with dilated cardiomyopathy were administered with forskolin (10 µg/kg) for a duration of 10 min in the first course of administration. The data were then compared with those data with dobutamine administration [41]. In the second course, 3 µg/kg/min forskolin was administered for 10 min before and at the end of each infusion period where the heart rate was maintained constant by atrial pacing [41]. The study concluded that forskolin can inhibit the decrease of end-diastolic pressure in the left ventricle. Schlepper et al. suggested, in their study, that the effect of forskolin lies in its ability to cause vasodilation. They further elaborated that the dose of forskolin needs to be high to produce positive effects in cardiovascular diseases, in addition to the decrease in the blood pressure and systematic vascular resistance observed [42].

2.3. Obesity

Obesity is a multifactorial condition, generally related to unhealthy lifestyle and metabolic diseases such as diabetes, cardiac diseases, etc. Hormone-sensitive lipase (HSL) is known to be involved in moving stored triglycerides and releasing fatty acids for metabolic consumption [43]. HSL is activated by cAMP, which helps forskolin to increase the production of HSL. There are numerous clinical and pre-clinical studies representing the effect of forskolin in promoting lean body mass and decreasing body fat. Shivaprasad et al. showed that *C. forskohlii* extract halted increase in food intake and weight gain on cafeteria diet-induced obesity in rats as well as inhibited the development of dyslipidemia [44]. Moreover, one of the significant studies was done by Loftus et al., where a group of 41 obese patients were administered forskolin along with 250 mg of *C. forskohlii* extract for 12 weeks with assessments in the 4th, 8th, and the 12th weeks [45]. No significant changes in the weight were observed in comparison with the control group, but changes in hip and waist circumference were significant, suggesting a decrease in fat mass and an increase in bone mass [45]. Godard et al., in 2005, reported a similar result in a study conducted on 12 men, who were administered with the same dose of *C. forskohlii.* They observed decreases in body fat percentage and fat mass, and increases lean body mass and serum free testosterone in overweight and obese men [43]. Several other early studies suggested a positive role of forskolin in body composition [46–52]. Henderson et al. (2005) demonstrated its effectiveness in weight reduction in women [51]. The interest in the appetite suppressant properties of *C. forskohlii* extract was also revealed in the clinical trial NCT02143349 [30].

2.4. Asthma, COPD, and Other Allergies

During asthmatic conditions, forskolin acts by increasing the cAMP levels in the bronchial smooth muscle, which reduces bronchial reactivity and subsequent bronchodilator effect [53]. Notably, cAMP is also known to be involved in Na^+/K^+ regulation. In 1984, Hiramitsu et al. explained the role of forskolin in tracheal muscles [54]. Forskolin also possesses an activity that inhibits the production of interleukins (IL-13, IL-5, and IL-1β), eotaxin and histamine. It also acts as an anti-oxidant [55–69]. González-Sánchez et al. reported the findings obtained for forskolin in 20 patients administered with the 10 mg oral forskolin (capsules) daily (for six months) resulting in positive control of asthma attacks. Moreover, the values of forced expiratory volume in 1 s and forced expiratory flow were similar to those using inhalations of the drug sodium cromoglycate [70]. In 2010, Hureta et al. reported about a clinical study conducted on 30 patients with mild or moderately persistent adult asthma, where forskolin was administered orally (10 mg) once a day on an empty stomach. The report suggests that there was no significant difference between the treatment with this compound and the drug beclomethasone for any studied lung function parameter. The authors indicated that more studies are necessary in this regard [71]. Furthermore, Bauer et al. [72] and Kaik et al. [73] reported that the forskolin capsules (10.0 mg) facilitate bronchodilatation in asthma patients.

2.5. Cancer

Generally, cAMP signaling, through protein kinase A (PKA)-dependent and/or independent pathway is crucial for cancer and it could provide an anti-tumor drug target [74]. Thus, forskolin has raised interest. In 1983, Agarwal et al. reported a reduction of tumor colonization in the lungs by 70% in a mouse model after a dose of 82 µg/mouse [75]. Forskolin also provides a potential pathway to inhibit colon cancer cell growth and survival [76]. Perrotti and Neviani reviewed that forskolin activates protein phosphatase-2A (PP2A) and antagonize leukemogenesis in multiple solid tumors (both in vitro and in vivo) [77]. Recent studies suggest that forskolin can increase the antitumoral effects of some anticancer drugs [74,78,79]. In this regard, the treatment with forskolin increased the sensitivity of Aromatase inhibitor-breast cancer cells to everolimus [78] and human triple negative breast cancer cells to doxorubicine [79] through activating PP2A and a mechanism dependent on the cAMP/PKA mediated extracellular-signal-regulated kinase (ERK) inhibition, respectively (Figure 3).

Moreover, reports from several other animal studies are available online [74]. However, clinical studies need to be performed to support its efficacy as an anti-cancer drug, as well as its therapeutic potential to increase the sensitivity to cytotoxic drugs.

2.6. Diabetes

Diabetes is a metabolic syndrome that is dependent on insulin level and insulin sensitivity. The levels of cAMP are elevated due to the administration of forskolin. This elevated cAMP levels further activate two signaling pathways: PKA and guanine exchange by cAMP (Figure 3) [80]. This results in a glucose-mediated response to pancreatic beta cells and insulin release [81]. An in vivo study on rats also supported the evidence for forskolin, causing a decrease in serum glucose levels, which decreased the severity of fasting hyperglycemia [82]. A clinical study on forskolin administration (250 mg of standardized *C. forskohlii* extract to 10% forskolin for 12 weeks) in conjunction with a hypocaloric diet in 41 patients revealed glucose-dependent insulin release (Figure 4) and insulin sensitivity. This was related to a decreased abdominal fat mass as indicated by a reduction of waist circumference [45]. Moreover, forskolin (50 mg/kg per week for 12 consecutive weeks) has also shown an attenuation of retinal inflammation in diabetic mice by means of limiting glucose transport into the retina. It downregulated glucose transporter 1 expression and decreased inflammatory factor expression levels [83].

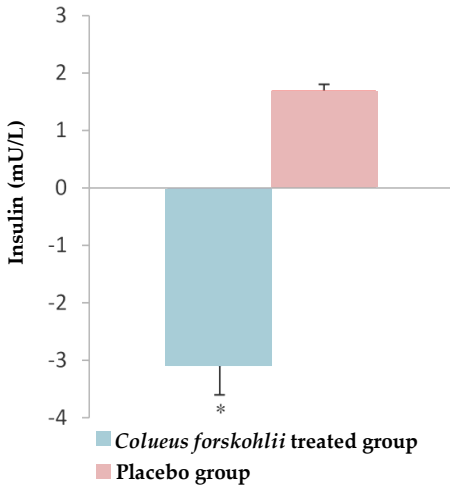

Figure 4. Reduction of fasting plasma insulin concentration by *Coleus forskohlii* extract. * Significant at $p < 0.05$ (adapted from [45]).

2.7. Intraocular Pressure in Glaucoma

Intraocular pressure (IOP) plays a critical role in regulating the changes in aqueous humor volume [84]. The rate of production and drainage of aqueous humor by ciliary epithelium must be balanced, as a small change in the aqueous humor can influence intraocular pressure. Forskolin has been studied for IOP in glaucoma due to aqueous flow regulation by adenylate cyclase receptor complex in the epithelium. The potential to modify retinal nerve fibers layers have also been studied in the clinical trial NCT01254006 [33]. Witte et al. reported a double blind intra-individual study of forskolin eye drops (0.3%, 0.6%, and 1.0% suspension) in 18 healthy males (in groups of six). It was observed that forskolin reduced IOP by 23–28% and the concentration influenced the duration by 3–5 h [85]. Another double-blind, control, randomized, comparative and non-crossover study was conducted with 90 trial subjects. Forty-five individuals were given 1% (*w*/*v*) forskolin, which was efficient in reducing IOP in mild open-angle glaucoma [86]. Badian et al. reported that the forskolin-eyedrops decreased IOP in healthy male subjects. Sensations in less degree were observed in subjects for a brief period [87]. Majeed et al. recruited 90 adult male/female patients suffering from open-angle glaucoma

with IOP of more than 24 mm Hg. They observed that 1% forskolin eye drops reduced IOP to less than 5.4 mm Hg [88].

2.8. Liver Fibrosis

Liver fibrosis has been associated with high rates of morbidity and mortality worldwide due to limited therapeutics. New therapies have been under development to arrest or reverse fibrosis. Studies focusing the anti-fibrotic effect of Hedgehog (Hh) pathway and forskolin were elucidated [89,90]. Calcium tetrachloride was used to induce hepatic fibrosis in male Sprague-Dawley rats until six weeks. Induction of fibrosis was confirmed by a reduction in ALT, AST, TC and TG levels. Treatment with forskolin improved all changes in the hepatocytes [91]. The role of forskolin was observed by oxidative stress markers (GSH, GPx, and lipid peroxides), inflammatory markers (NF-κB, TNF-α, COX-2, IL-1β, and TGF-β1) and Hh signaling markers (Ptch-1, Smo, and Gli-2). This was confirmed by α-SMA expression, which indicates that forskolin reduces hepatic stellate cells (HSCs) expression and further fibrogenesis. Co-treatment with forskolin significantly reduced oxidative stress biomarkers and inflammation, which has been studied by mRNA expression of Hh signaling markers and cAMP-dependent PKA kinases. Thus, this study proves that forskolin has an antifibrotic effect.

3. Other Effects

Forskolin has been reported to be a potent activator of adenylate cyclase in the thyroid gland and as well, stimulating thyroid secretion [92,93]. Laurberg et al. compared the effects of 10^{-5} M forskolin and 100 μunits/mL thyroid stimulating hormone (TSH) over T_3 and T_4 secretion of perfused dog thyroid lobes. An ethanol concentration of 0.2% was used in forskolin containing medium [92]. Forskolin elevated the cAMP levels within 5 min post forskolin infusion. A lag phase resulted from the increase in cAMP levels. Thus, it activated cAMP generation to interact with the catalytic subunit of adenylate cyclase [94]. Bersudsky et al. reported that forskolin helps in transient mood elevation or stimulation in schizophrenic patients with negative symptoms [95]. Moreover, Doorn et al. reported forskolin induces alkaline phosphatase and insulin-like growth factor-1, thereby increasing bone formation by human mesenchymal stromal cells [96].

4. Bioavailability of Forskolin

The administration form of forskolin depends on the tissue target, but it is a poorly water-soluble compound, which limits both its topical and its oral bioavailability. Despite this low bioavailability, forskolin has shown to be more potent than natural and synthetic analogs [97].

Some studies have evaluated different forms of administration than suspension to improve ocular bioavailability when administered to eyes. In this respect, Saettone et al. (2009) tested several solubilization eye-compatible polymeric agents. Polyoxyethylene-polyoxypropylene block copolymer (Pluronic^R F-127) increased 40 times the drug solubility in water (up to 120 mg/100 mL). It also prolonged the duration of the hypotensive effects of forskolin with respect to a 1.0% traditional suspension of this compound in rabbits presenting increased IOP [98]. More recently, a formulation based on forskolin nanocrystals stabilized by poloxamer 407 and Noveon AA-1 polycarbophil/poloxamer 407 gel was able to reduce IOP in rabbits around 31% and lasted for 12 h, better than the effect produced by traditional suspension (18%, up to 6 h) [99]. Proper vehicles, such as in situ gel forming systems, may also increase the contact time of this compound on the cornea [100], while nanoencapsulation within polymeric system provided sustained drug release and enhanced permeation profile with maximum depth penetration [101]. Other potential vehicles are through the formation of forskolin nanoemulsions [102] and cocrystals able to enhance the water solubility properties of forskolin [103].

Concerning oral bioavailability, recent studies suggest that forskolin could be absorbed in all segments of the intestine with an effective permeability in the range of drugs with high intestinal permeability, but it was a saturable transport process mediated by P-glycoprotein. The authors estimated that, after oral administration in humans, the absorbed fraction of dissolved forskolin could

be close to 100% [104]. Moreover, forskolin can bind to human serum albumin, which could play a role in the pharmacokinetics of this compound [105] and it could be the basis of nanoparticles [106].

5. Conclusions

Forskolin is a natural diterpenoid with a wide biological effect. The mechanism of action of forskolin is based on the activation of the adenylyl cyclase enzyme, which results in the synthesis of cAMP. Forskolin increases the level of intracellular cAMP, which is a transmitter of intracellular signals that regulates and affects the activity of many enzymes in the cell [83,84]. This is particularly important in disease entities with reduced levels of this transmitter, such as asthma, cardiovascular disorders and obesity, among others. The Indian nettle *C. forskohlii* is the natural source of forskolin. Beneficial effects of forskolin have been reported in preclinical and clinical studies on the treatment cystic fibrosis, cardiovascular disease, obesity, allergies, asthma, COPD, diabetes, cancer, thyroid disorders, IOP in glaucoma, and liver fibrosis. Forskolin can interact with the cAMP pathway. More clinical and pre-clinical studies need to be performed to support forskolin efficacy since both the plant extract and forskolin exhibit low toxicity [75,107].

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