

Isoforskolin from Native Plant *Coleus forskohlii* of Yunnan, China Plays Multiple Biological Roles

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Abstract

Isoforskolin (ISOF) was isolated from *Coleus forskohlii* native to Yunnan in China. It is identified as one analog of diterpene forskolin (FSK) which comes from the Indian plant *Coleus forskohlii*. Researches found that the Yunnan native plant *Coleus forskohlii* contained rich ISOF but not FSK. ISOF was reported to activate adenylyl cyclase (AC) isoforms. The ophthalmologic and cardiovascular effects of ISOF were firstly reported in the 1990s. The researchers in Kunming, China, found ISOF could lower blood pressure and intraocular pressure. Recent researches found the respiratory tract effects of ISOF, and showed that ISOF significantly elevated cyclic adenosine monophosphate (cAMP) levels in rat lung homogenate, and relaxed the histamine-induced contraction of isolated guinea pig trachea and lung smooth muscle, isoforskolin pretreatment attenuates acute lung injury induced by lipopolysaccharide (LPS) in several models, lowered LPS-induced secretion of the inflammatory cytokine in human monocytes.

Keywords

Coleus forskohlii, Natural Compound, Isoforskolin, Bioactivity

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1. Introduction

Chinese materia medica is popular nationally, as well as being used worldwide. According to recent data from the World Health Organization, the market of Chinese materia medica is substantial. The output of Chinese materia medica was estimated to a more than 20% increase from the past [1]. However, it is still possible that wild plants in China may contain unknown active principles which may be useful drugs and tools for natural sciences and medicine.

A classic example of phytochemicals used extensively in biology and medicine is isoforskolin (ISOF), which is also known as Coleonol B, 6-acetyl-7-deacetyl forskolin, and is isolated from *Coleus forskohlii* native to Yunnan in China. There are few Chinese medicine's records of *Coleus forskohlii* in books of previous dynasties. It was found in the northeast area of Yunnan Province in China in 1989 [2]. ISOF is identified as one analog of diterpene forskolin (FSK) which comes from the Indian plant *Coleus forskohlii*. Phytochemists found that the Yunnan native plant *Coleus forskohlii* contained rich ISOF but not FSK [3]. Forskolin (also called coleonol) is labdane diterpene that is produced by the plant Indian Coleus (*Coleus forskohlii*) from Ayurveda. Forskolin has been commonly used to activate adenylyl cyclase, which provides investigators with a means for researches of the role of cyclic AMP (cAMP) in cell physiology and pathogenesis of several diseases. Recent researches show that ISOF plays multiple biological roles [4]. In this review, we briefly summarize the varied pharmacological effects of ISOF.

2. Pharmacological Actions (Table 1)

2.1. Ophthalmologic Effects

The Ophthalmologic effects of ISOF were firstly reported in the 1990s [5], a study of 40 big-eared Japanese rabbits with ISOF administered, indicated that both normal IOP (intraocular pressure) and water-induced OHT (ocular hypertension) were decreased by the ocular hypotensive effect of ISOF when compared with control. Additionally, ISOF suspension at 0.25% exerted little topical irritating actions, which showed the security and reliability of the ocular hypotensive effect of ISOF. With further research on the screened OHT rabbits and water-induced OHT rabbits with ISOF and FSK suspensions respectively at 0.25%, the ocular hypotensive effect of ISOF was more significant than FSK [6]. To study the mechanisms of the ocular hypotensive effect of ISOF, levels of cAMP reflecting AC activity were assayed by protein-binding method of radioimmunoassay in isolated SD rat livers added into the mixture containing isoforskolin and forskolin, respectively. The results demonstrated that isoforskolin and forskolin stimulated adenylate cyclase in vitro with almost equal activity [7].

On the basis of the above-mentioned animal experiments, a study conducted in 20 healthy Chinese population aged among 23 - 50 years old without eye diseases, investigated the effects of ISOF on the acute increase of intra ocular pressure (IOP) induced by water-drinking (14 ml/kg), showed that ISOF (0.5%) as suspension eye drops also played the ocular hypotensive role [8].

2.2. Heart-Vascular Effects

The Cardiovascular effects of ISOF were also firstly reported in the 1990s [9], researchers in Kunming, Yunnan Province of China, found that isoforskolin could reduce blood pressure and benefit heart. Whole platelet aggregation in vitro of 20 Wistar rats induced by adenosine diphosphate (ADP)/arachidonic acid (AA) and 10 guinea pigs induced by platelet activating factor (PAF) was suppressed by ISOF (5, 10 mg/kg). The maximal inhibitory effects appeared at 10 minutes after drug administration, and the inhibitory effects lasted for 2 hours. In view of the inhibition of platelet aggregation and hypotensive effect, ISOF could be used for prevention and treatment of hypertension with platelet aggregation. Furthermore, ISOF could also effectively decrease the blood pressure in anaesthetized rats without influencing the heart rate (HR), electrocardiograph (ECG), left ventricular pressure (LVP), rate of change of left ventricular pressure (LVdp/dt) and left ventricular end diastolic pressure (LVEDP) [10]. Recent study on general pharmacology of ISOF in animal models indicated that ISOF has no significant influence on heart rate, breathing, systolic blood pressure, mean arterial pressure, diastolic blood pressure of SD rats [11]. Thus, the safety of ISOF has been proved through the animal models.

2.3. Respiratory Tract Effects

As ISOF, as an effective AC activator, induces increasing intracellular cAMP, researcher also found that ISOF

Table 1. The biological effects of ISOF.

bioactivities	descriptions
ophthalmologic effects	ISOF decreasing ocular pressure effect by stimulating adenylate cyclase
heart-vascular effects	ISOF show the potentiality for prevention and treatment of hypertension with platelet aggregation
respiratory tract effects	ISOF, as an effective AC activator, induces increasing intracellular cAMP, may plays a significant role in immune modulation of inflammatory reaction; ISOF significantly inhibit the contraction of isolated guinea pig trachea induced by histamine diphosphate and acetylcholinium chloride; ISOF pretreatment attenuates acute lung injury induced by lipopolysaccharide (LPS)

plays a significant role in immune modulation of inflammatory reaction, such as mitigating acute lung injury (ALI). ISOF (25, 50, 100 $\mu\text{mol/L}$) inhibited human polymorphonuclear cell (PMNC) recruitment, expression of PMN adhesion molecules, and TNF- α released from PMNC. The effects that ISOF increased the intracellular cAMP might be associated with the mechanism of its mitigating ALI [12]. ISOF was reported to activate adenylyl cyclase (AC) isoforms 1, 2 and 5. The study by Yang *et al.* demonstrated that ISOF increased cyclic adenosine monophosphate (cAMP) level in rat lung homogenate, and relaxed the histamine-induced contraction of isolated guinea pig trachea and lung smooth muscle. ISOF pretreatment attenuates acute lung injury induced by lipopolysaccharide (LPS). ISOF (50, 100, and 200 μM) and dexamethasone (10 μM) pre-incubation lowered LPS (2 $\mu\text{g/mL}$)-induced secretion of the cytokine TNF- α , and interleukins IL-1 beta, IL-6, and IL-8 In human mononuclear leukocyte. The pretreatment with ISOF attenuates LPS-induced acute lung injury in several models, which is involved in down-regulation of inflammatory responses and proinflammatory cytokines TNF- α , IL-1 beta, IL-6, and IL-8 [13].

Recent research showed that ISOF played the relaxation effects on isolated bronchioles in guinea pig, and significantly inhibited the contraction of isolated guinea pig trachea induced by histamine diphosphate and acetylcholinium chloride [14].

3. Conclusion

ISOF from plant *Coleus forskohlii* native to Yunnan Province, which is the main diterpene from the native plant, plays multiple biological roles. The increasing number of new diterpenes isolated from *Coleus forskohlii* has been reported, and they are definitely worth exploring for further study [15]. The antioxidant activity in tubers of *Coleus forskohlii* was reported recently, which might protect against oxidant and free radical injures [16]. *Coleus forskohlii*, which contains multiple bioactive compounds, is a medicinal plant with significant value [17].

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