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48 *Coleus forskohlii* Extract in the Management of Obesity

Muhammed Majeed, PhD

CONTENTS

Introduction.....	703
<i>Coleus forskohlii</i> : Origin and Botanical Aspects	704
Taxonomic Position.....	704
Traditional and Ethnomedicinal Uses	705
Cultivation of <i>Coleus forskohlii</i> for Forskolin Extraction	706
Chemistry of <i>Coleus forskohlii</i> Root Extract and Its Bioactive Constituent, Forskolin	707
Stereochemistry.....	708
Analytical Methods	708
Spectroscopic Details.....	709
Biological Effects of Forskolin.....	712
Cardiovascular Effects	713
Anti-Platelet Aggregation Activity	714
Effects on the Airways/Bronchodilation	714
Anti-Inflammatory Effects	714
Ocular Effects.....	714
Acute Eye Irritation Study	715
Antiglaucoma/Intraocular Pressure-Lowering Effect.....	715
Forskolin in Promoting Lean Body Mass: Mode of Action and Supporting Research.....	715
Safety of ForsLean as a Dietary Ingredient	716
Clinical Studies with ForsLean in Promoting Lean Body Mass.....	719
Concluding Remarks: Forskolin in Weight Management.....	724
References.....	726

INTRODUCTION

Coleus forskohlii Briq. is an aromatic herb from the family of mints and lavenders, which is indigenous to India. The herb has received a lot of attention over the past 40 years, from medical researchers, as the only significant plant source of forskolin, a bioactive compound with diverse pharmacological benefits. These research efforts helped to scientifically validate the versatile health benefits of this herb that have long been known in folk medicine. Interestingly, the roots of the plant have a long history of food use in India, in the form of a pickle or condiment.

The Sami/Sabinsa group pioneered the natural extracts of *Coleus forskohlii* (CF), for use in nutritional and cosmetic applications, in the early 1990s. These include forskolin-enriched extracts from the roots (trademarked ForsLean[®], an award-winning ingredient) as well as extracts featuring

an aromatic essential oil composition from the roots. Both types of extracts have clinically validated health benefits and are currently used in a wide range of dietary supplements and cosmetics. In another facet of research on forskolin, the group developed novel delivery systems for forskolin, paving the way for the use of the molecule as a natural drug, for example, in the management of glaucoma (Ocufors®). Earlier efforts by pharmaceutical companies were unsuccessful in this regard, because forskolin is insoluble in water.

To ensure a steady and reliable supply of CF roots, the Sami/Sabinsa group also pioneered cultivation efforts for the plant, based on varieties and techniques, developed through focused research, targeting the promotion of “green” practices and sustainability.

A major breakthrough in research on forskolin was the discovery that ForsLean (CF root extract) is a clinically effective natural ingredient in weight management.

A majority of ingredients available for weight management support are designed to decrease body weight or fat with little regard for, and often at the expense of, lean body mass. It is comprehensible that an increase in muscle mass upregulates the body’s metabolism, as muscle requires energy to sustain its mass and in turn helps burn additional body fat throughout the day. This plays a major role in not only optimizing body composition more favorably but helps maintain body fat reduction. Based on preclinical studies, it was hypothesized that forskolin could possibly enhance anabolic (lean body mass–building) functions in the body to increase muscle mass. Subsequent clinical studies supported the positive effects of branded ForsLean in enhancing lean body mass, promoting fat loss, and improving the overall body composition.

COLEUS FORSKOHLII: ORIGIN AND BOTANICAL ASPECTS



CF is available for centuries as a medicinal herb in India, which is also considered to be the place of origin. It grows in the wild in warm subtropical temperate regions of India, Nepal, Burma, Sri Lanka, and Thailand. Apparently, it has been distributed to Egypt, Arabia, Ethiopia, tropical East Africa, and Brazil as well. In India, wild CF is found mostly on the dry and barren hills. Latitudinal and altitudinal range for the occurrence of the species is between 8°–31°N and 600–800 m, respectively.¹

TAXONOMIC POSITION

Coleus (genus) was first described by Loureiro in 1790, and the generic name was derived from the Greek word “coleos” meaning sheath.¹ The genus *Coleus* comprises of nearly 200 species distributed in the tropical and subtropical regions. About eight species of *Coleus* are recorded in India. It is classified along with 13 other genera under the subfamily Ocimoideae.^{2,3} Of the 13 genera, *Plectranthus* is taxonomically closest to *Coleus*. Among the 200 species of

Coleus, only CF contains the most significant compound forskolin, and, therefore, this herb occupies a unique position in the chemical taxonomy of the family Labiatae (Lamiaceae).²

Coleus forskohlii Briq. (synonyms, *C. barbatus* Benth., *Plectranthus forskohlii* Willd., *P. barbatus* Andr.) belongs to the Lamiaceae family, popularly known as the mint or “Tulasi” family. CF is recorded in Ayurvedic *Materia Medica* under the Sanskrit name “Makandi” and “Mayani.”¹ The taxonomical classification of *Coleus forskohlii* Briq. syn. *C. barbatus* Benth.³ is as follows:

Kingdom	Plantae
Division	Magnoliophyta
Class	Magnoliopsida
Order	Lamiales
Family	Lamiaceae
Genus	<i>Coleus</i>
Species	<i>forskohlii</i>

Description^{1,3}

CF is a perennial, branched, aromatic herb and grows to about 45–60 cm (1–2 ft high) tall, with a thick root stalk. It has four angled stems that are branched and nodes are often hairy.



Leaves are 7.5–12.5 cm in length and 3–5 cm in width, usually pubescent, narrowed into petioles. Inflorescence is raceme, 15–30 cm in length; flowers are stout, 2–2.5 cm in size, usually perfect; calyx is hairy inside.

The root is typically golden brown, thick, fibrous, and radially spreading. Roots are tuberous, fasciculate, 20 cm long and 0.5–2.5 cm in diameter, conical fusiform, straight, orangish within.

CF has been used since ancient times in traditional medicine. The root portion of the plant has been used for medicinal purposes and contains the active constituent forskolin. Forskolin, a diterpenoid, was named after the Finnish botanist Forskel.¹

TRADITIONAL AND ETHNOMEDICINAL USES

Traditional knowledge about medicinal plants remains a very important tool for treating illnesses. According to the World Health Organization (WHO, 2003), it has been estimated that approximately 80% of the world’s population is dependent on traditional medicines for their health needs.¹

Coleus forskohlii Briq. (family Lamiaceae) has several ethnomedicinal uses,² which have been transmitted by word of mouth from generation to generation. Historically, it has been used to treat

heart diseases, respiratory disorders, insomnia, asthma, bronchitis, intestinal disorders, burning sensation, constipation, and skin diseases.¹

In the northern parts of India, the paste of fresh roots of the plant is used by local people as topical application on tumors and boils. Ground fresh roots are mixed with mustard oil and are applied on eczema and skin infections.

In south India, the decoction of roots is used as a tonic by the tribals of Trichigadi (Kotas).

The plant is known to pacify vitiated pitta with benefits in supporting the management of fever, burning sensation, inflammation, muscular spasm, hypertension, diabetes, cardiac debility, allergy, anaphylaxis, high cholesterol, and bronchial asthma.¹

The active phytochemical forskolin in CF was discovered in 1974 and has been the subject of many laboratory studies ever since. The compound has a vast array of effects on the body, working primarily on an enzymatic level, raising the level of cAMP (cyclic adenosine 3'5'monophosphate), a substance that activates a gamut of other cellular enzymes.²

CULTIVATION OF *COLEUS FORSKOHLII* FOR FORSKOLIN EXTRACTION

Medicinal plants form the major resource base of our indigenous health-care traditions. They have the additional advantages of simplicity, effectiveness, a broad spectrum of activity, and emphasis on preventive rather than curative drug action. Herbal remedies are fast becoming mainstream consumer products manufactured by multinational corporations among others and sold in supermarket chains and a variety of outlets worldwide. Another parallel development is the incorporation of herbs into an increasing number of health foods and dietary products. Studies have shown that medicinal plants have contributed considerably to economic welfare of people by providing and generating reasonable income.

Moreover, export of value added items requires product development, setting up of processing facilities, and quality assurance. Increasing concerns of unsustainable collection from the wild, disappearance of certain species on one hand, and concerns of quality and standardization on the other make it imperative to promote cultivation of species critical to herbal industry.

Plant tissue culture, touted as the most dynamic discipline of biotechnology, is a versatile cloning technique that offers the benefits of scale, scope, and uniformity. In plant tissue culture, the harvesting of living cells from any plant part (*explants*) facilitates growth of new plants in the sterile laboratory environment under aseptic conditions. It allows exact replication in many locations on a large scale, that is, it can create multiple clones from a single explant. With the objective of becoming a technology-driven, environmentally responsible manufacturer of herbal ingredients and to maintain a sustainable source of herbal raw materials, Sami Labs has adopted tissue culture as an enabling technology for its key raw materials. The adoption of plant tissue culture technology has ensured pathogen-free, disease-resistance, and high-yielding planting material in case of CF, which has helped to increase the yield, productivity, uniformity of produce, and reduced harvesting time and wastage.

Sami Labs has developed premium-quality planting material and established protocols for the micropropagation of *Coleus* by use of tissue culture technology. The "rooted cuttings" of *Coleus* developed through tissue culture technology have been transferred to the farmers and are reaping encouraging results.

The field performances of rooted cuttings and seedlings have been studied extensively. It has been found that vegetatively propagated planting stock had higher field growth performance than seedlings.^{4,5} Rooted cuttings had good survival and grew well in the field.⁶

According to Kavitha et al. [1], CF is propagated by seeds as well as vegetatively by terminal stem cuttings.¹ Because seed propagation is difficult and slow, propagation by terminal stem cutting is easy and economical. Terminal cuttings of 10–12 cm length with three to four pairs of leaves are planted in nursery beds to induce rooting. When the 1 month old cuttings have produced sufficient roots, they are transplanted to the main field. The best period of planting in South India is during the

month of June and July and during September to October. Rooted cuttings are planted at an interval of 60 cm. Proper irrigation methods, weeding, and plant protection should be adopted.⁷

The forskolin content of the roots obtained from natural habitats ranges from 0.04% to 0.60% of dry cell weight, 0.5% being most common.⁸

CHEMISTRY OF COLEUS FORSKOHLII ROOT EXTRACT AND ITS BIOACTIVE CONSTITUENT, FORSKOLIN

Forskolin: identity and nomenclature:

Chemical Abstract Number (CAS No): 66575-29-9.

Synonyms: Colforsin.

Chemical name: (3R, 4aR, 5S, 6S, 6aS, 10S, 10aR, 10bS)-5-(acetyloxy)-3-ethenyldodecahydro-6, 10, 10b-trihydroxy-3, 4a, 7, 7, 10a, pentamethyl-1H-naphtho[2,1-b]pyran-1-one. It is also referred by the chemical name 7-β-acetoxy-8, 13-epoxy-1α, 6β, 9γ, trihydroxylabd-14-en-11-one.⁹

Chemical family: Forskolin belongs to the class of labdane diterpenoids. It contains three six-membered rings (one of them being a pyran ring) condensed in the form of a naphthopyran system. It has two secondary hydroxyl groups, one tertiary hydroxyl group, a keto group, and an O-acetyl group. It also has an exocyclic double bond (see Figure 48.1).

Diterpenoids that occur in plants contain 20 carbons from the assembly of four isoprene units (C₂₀ unit). The four isoprene units assemble to form geranylgeranyl pyrophosphate in the plant, which is acted upon by several enzymatic pathways to lead to a variety of diterpenoids. Depending on the biosynthetic pathway, a wide diversity of linear as well as cyclized diterpenoids result in the plant kingdom. This rich structural variety is in turn manifested by a broad spectrum of biological and pharmacological actions of these diterpenoids.

Each structural variety of diterpenoids has yielded some familiar compounds in use today. An example of an acyclic diterpene is phytol, a simple reductive product from geranylgeraniol. The phytol structural component occurs in chlorophyll and vitamin K and E structures. One of the famous cyclic diterpenoids is paclitaxel, a well-known anticancer agent, with a taxane skeleton. Another well-known diterpene is salvinorin A, active component of traditional medicine of Mexican Indians. Abietic acid is another example of a different diterpenoid skeleton. Forskolin belongs to the class of labdane diterpenoids, presumably arising from the quenching of labdanyl cation with water and further cyclization.

While two rings of forskolin are carbocyclic, the third ring is heterocyclic. Hence, it is usually associated with labdane bicyclic system. Forskolin skeleton is uniquely oxygenated, with each face of the molecule containing two hydroxyl groups, one of them being acetylated.

Unlike triterpenoids (C₃₀ unit), the diterpenoids generally do not occur as glycosides. Thus, their functional groups such as hydroxylic groups especially are not glycosylated. Their occurrence without ligation with carbohydrates makes them generally highly water insoluble in their native form.

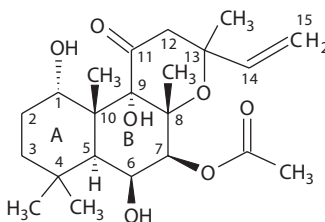
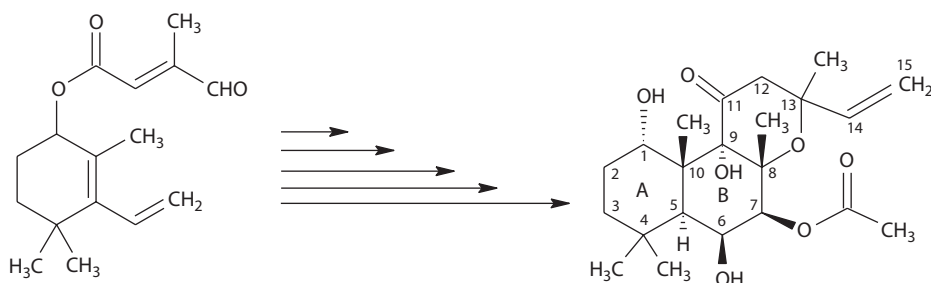


FIGURE 48.1 Chemical structure of forskolin.

Synthetic methods



The total synthesis of forskolin was achieved by starting from an ester aldehyde. Then the development of new carbon–carbon and carbon–oxygen bonds with enduring stereochemistry resulted from several key steps: a stereospecific intramolecular Diels–Alder reaction, a facially selective osmylation, a base-catalyzed intramolecular conjugate addition, a Lewis acid–mediated cuprate addition to a β -substituted dihydropyran-4-one, and a stereo- and regioselective allene photoaddition.¹⁰

Ester aldehyde Forskolin

Partial synthesis¹¹ (from 9-deoxyforskolin) and total synthesis¹² of (\pm) forskolin have been reported.

STEREOCHEMISTRY

The absolute stereochemistry of forskolin was determined by x-ray crystallography.¹³ The trans stereochemistry of the A/B ring junction and of the β -configuration at C-10 was obtained from circular dichroism data on 14,15-dihydroforskolin and 1-oxo-analog. The change in cotton effect ($\Delta \Sigma$) values from -0.71 , for the former, to -0.76 , for the latter, was conclusive. The *cis* orientation of the C-1 and C-9 hydroxy groups was further confirmed by facile formation of the sulfite ester on treatment of forskolin with $\text{SOCl}_2/\text{pyridine}$.

Formation of the hemiacetal acetate via ozonolysis of 1,6-diacetyl-forskolin, followed by acetylation, provided additional data in support of the 13α -configuration of the vinyl group. Application of Mill's rule to the Δ^5 -compound shown, $(M)_D + 347.17^\circ$, derived by thionyl chloride/pyridine treatment of 1-methyl-forskolin, and to the corresponding deacetyl compound, $(M)_D - 32.03^\circ$, established the β -configuration of the 7-acetoxy substituent.

Nuclear Overhauser effect difference spectroscopy (NOEDS) confirms the α -orientation of the 7-proton following irradiation at the $8\beta\text{-CH}_3$ and the β -orientation of the 1-proton following irradiation at $10\beta\text{-CH}_3$. A two-dimensional correlated spectroscopy spectrum of forskolin has vividly reconfirmed the connectivities of the coupled protons. The absolute configuration of forskolin was finally confirmed by x-ray analysis of forskolin and of its 1-benzyloxy-7-deacetyl-7-bormoisobutyryl derivative.^{14–16}

The other most abundantly present diterpene in the plant is 1,9-dideoxy-forskolin.¹⁷ Subsequently, several closely related diterpenes have been isolated from the roots and aerial parts of the plant including stigmaterol.^{18,19} Saleem et al. described an isolation procedure that yields 96.9% pure forskolin.²⁰

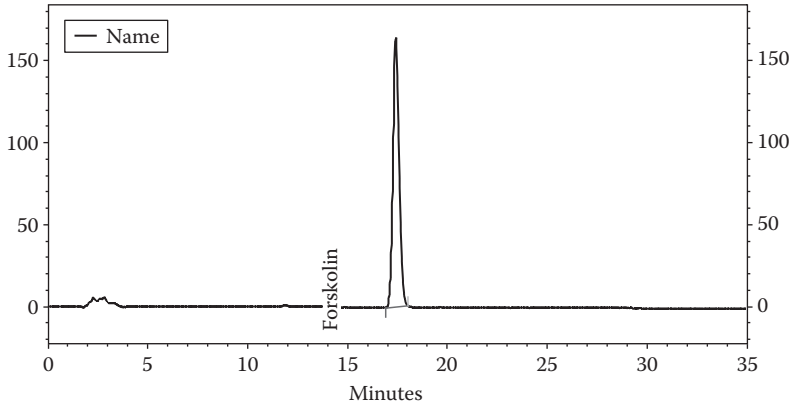
ANALYTICAL METHODS

Many analytical methods have been developed to elucidate the characteristics and attributes of forskolin primarily because of its pharmacological value. A gas–liquid chromatography (GLC) method was developed for quantifying forskolin in plant tissues and in dosage forms.²¹ Inamdar et al. [22] have reported the thin layer and high-performance liquid chromatographic (HPLC) methods. The GLC method had better sensitivity, but the HPLC method was found to be more rapid.²²

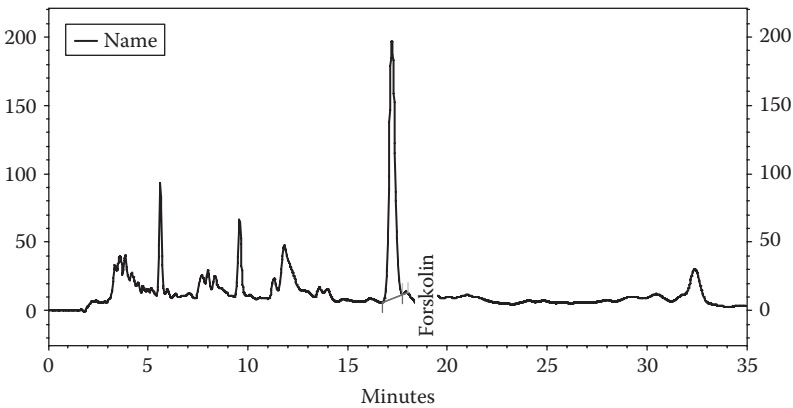
SPECTROSCOPIC DETAILS

HPLC data of ForsLean (forskolin 10%) and HPLC, FTIR, mass, and NMR spectroscopic data of pure forskolin are being illustrated in the following section.

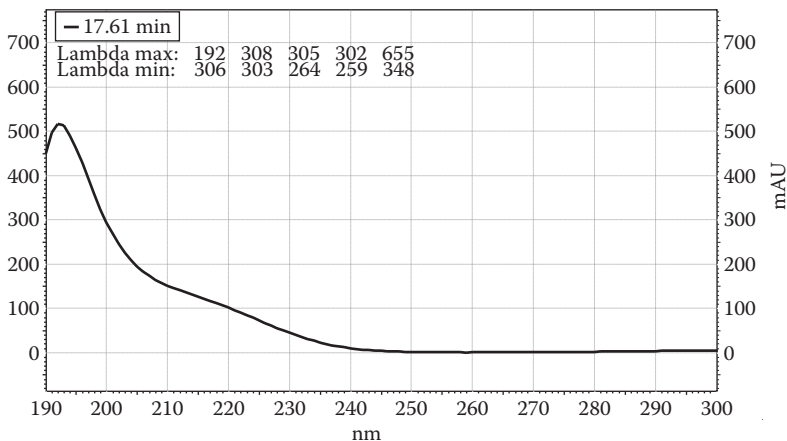
HPLC chromatogram of forskolin (pure)



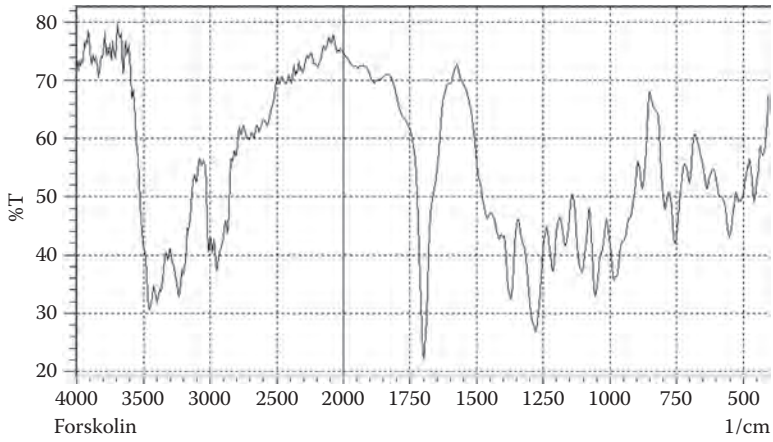
HPLC chromatogram of ForsLean (forskolin 10% extract)



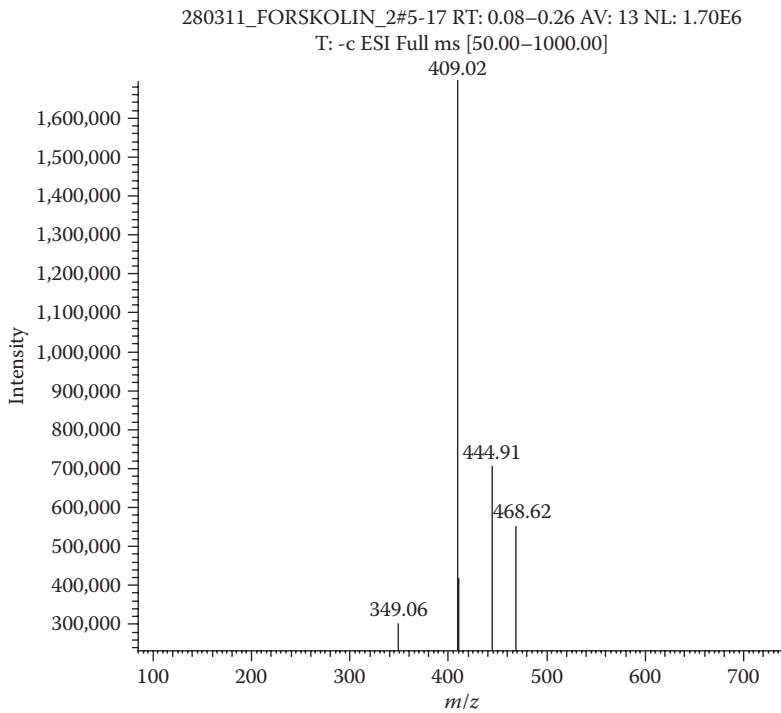
UV spectrum of forskolin (pure)



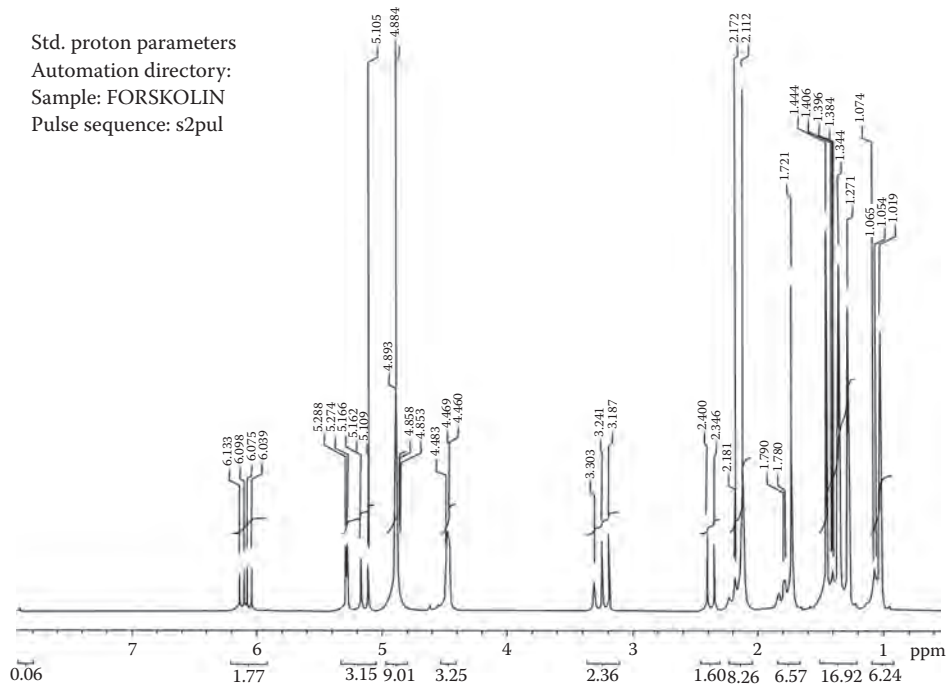
FTIR spectrum of forskolin (pure) in KBr



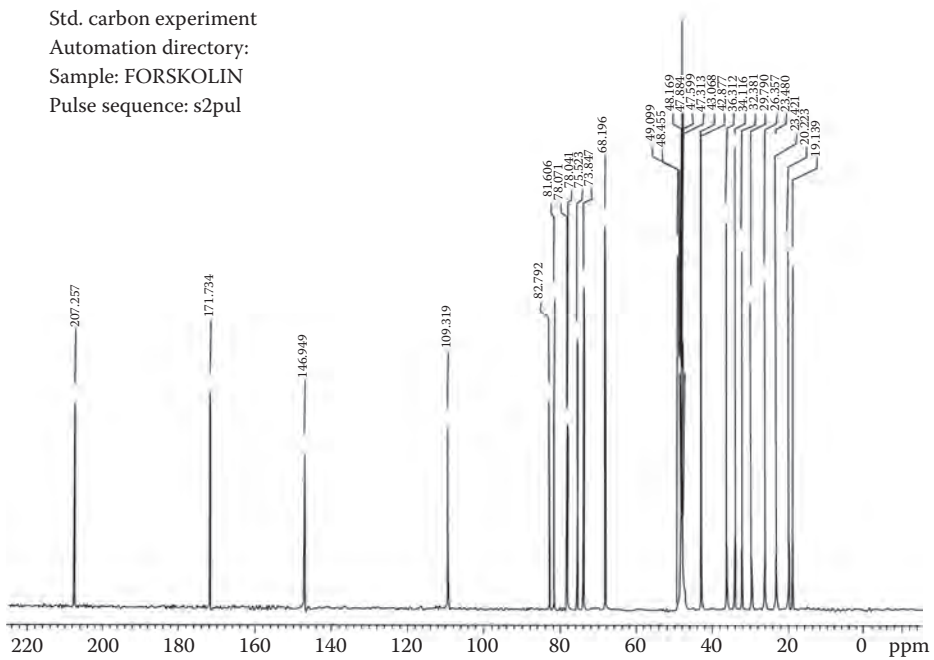
Mass spectrum of forskolin (pure)



¹H NMR spectrum of forskolin (pure) in CDCl₃



¹³C NMR spectrum of forskolin (pure) in CDCl₃



Forskolin, a diterpenoid compound (having a labdane chemical structure), is present in CF roots as the major component, along with isoforskolin, deacetylforskolin, 9-deoxyforskolin, 1,9-dideoxyforskolin, and 1-deoxy deacetyl forskolin.

Conventionally, forskolin is isolated from the roots of CF by hot extraction with solvents like ethyl alcohol, toluene, and similar organic solvents. The pasty oleoresin thus obtained (containing 7%–11% forskolin) is further purified by treatment with mixture of solvents to a brown powder containing 28%–32% forskolin. This powder is then crystallized using organic solvents to upgrade to 95% forskolin and then to an API grade of >98%.

Forskolin can be extracted using the following three processes, all of which have been used by Sami Labs in commercial processes. The current extraction is using continuous extraction technique.

1. Batch-wise solvent extraction
2. Continuous solvent extraction technique
3. Supercritical carbon dioxide extraction

Among these three processes, the continuous extraction process has several advantages over the other two processes, such as the following: (a) large tonnage of roots can be processed in a day, (b) solvent loss is much less, and (c) reduced batch cycle time.

BIOLOGICAL EFFECTS OF FORSKOLIN

Researchers in the early 1970s isolated forskolin from the roots of CF. The unique activity of forskolin as a nonadrenergic stimulator of adenylate cyclase attracted attention of medical researchers to start their work using forskolin in their research. Some of the pharmacological effects of forskolin that have been validated in preclinical and clinical studies are summarized in Figure 48.2.

Research on the *in vivo* effects of forskolin revealed a number of significant biological effects in animal models. Such effects were dose dependent and varied with the route of administration. Some of these researches are summarized here for general information purposes.

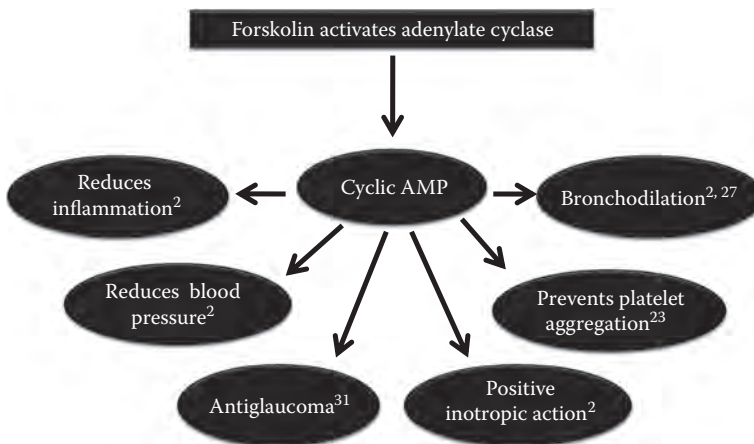


FIGURE 48.2 Spectrum of potential therapeutic activities of forskolin.

CARDIOVASCULAR EFFECTS

Forskolin has significant effect on the cardiovascular system. Dohadwalla [2] reported the following:²

1. In the preliminary set of acute experiments using anesthetized cats, hypotensive effect was observed on intravenous (i.v.) administration of forskolin. The duration of action was 16 min when the i.v. dose was 50 µg/kg (Table 48.1).
 The cardiovascular responses to bilateral carotid occlusion and vagal and preganglionic sympathetic nerve stimulation to challenges with acetylcholine, epinephrine, norepinephrine, and isoprenaline were not affected by 2 mg/kg of forskolin given i.v. to anesthetized cats. These evidences suggest that the hypotensive action of forskolin may not be due to inhibition of central vasomotor tone or alpha or beta adrenoceptor inhibition.
2. The hypotensive effect of forskolin was studied in detail using normotensive anesthetized dogs.² Within 1–5 min of i.v. administration of 0.1 mg/kg of forskolin, a sharp fall in systolic and diastolic blood pressure of about 70 mmHg was recorded. Simultaneously, the left ventricular pressure (dp/dt) was increased from 3100 to 4100 mmHg/s. This steep rise in left ventricular pressure demonstrates its positive inotropic property. There was only marginal increase in heart rate. The duration of action lasted for about 30 min.
3. The hypotensive effect of forskolin was further investigated in conscious spontaneously hypertensive (SH) rats.² Forskolin, in doses ranging from 2.5 to 10 mg/kg given intraperitoneally (i.p.) daily for 5 days, showed dose-dependent fall in systolic blood pressure. At a dose of 10 mg/kg, the maximum fall of 48 mmHg in systolic blood pressure was observed on the third day of experiment.

The results obtained from these studies show that forskolin is a potent hypotensive agent in anesthetized cats, dogs, and conscious SH rats. The results also suggest the possibility that the hypotensive property of forskolin is due to its vasodilatory activity on peripheral resistance.

Dohadwalla [2] carried out perfusion studies to find out the underlying mechanism of the hypotensive action of forskolin. Experimental results suggest that the hypotensive action of forskolin may be due to its direct smooth muscle relaxation property. Forskolin stimulates adenylate cyclase, resulting in increase of cAMP levels in smooth muscles of peripheral vessels. This in turn mediates vasodilation and the ensuing hypotension.

Forskolin was also demonstrated to possess strong positive inotropic activity in isolated guinea pig heart (Langendorff) preparation.² The compound at a dose of 0.25 µg exhibits positive inotropic activity with marginal increase in the rate of contraction. The rate of coronary blood flow in the guinea pig heart was also increased at a dose of 2 µg of forskolin.

TABLE 48.1
Hypotensive Action of Forskolin
in Anesthetized Cats

Dose (µg/kg)	Fall in Mean BP (mm Hg)	Duration (min)
50	49.7 ± 3.2	16.7 ± 2.1
100	63.7 ± 5.5	55.0 ± 3.9
250	72.2 ± 6.2	97.5 ± 5.6

In experiments using isolated guinea pig atrium and electrically driven left atrium and the papillary muscle of cat heart, forskolin produced dose-dependent positive inotropic effect. Results showed that this positive inotropic action is independent of its hypotensive action and is related to its adenylate cyclase stimulation property.

ANTI-PLATELET AGGREGATION ACTIVITY

From the experiments performed in male SH rats, it is evident that forskolin at doses ranging from 2.5 to 10 mg/kg given i.p. caused dose-dependent inhibition of ADP-induced platelet aggregation. A dose-dependent fall in systolic pressure was also observed. Thus, it is apparent that the percentage inhibition of ADP-induced platelet aggregation by forskolin is correlated with the magnitude of fall in systolic blood pressure.²

Siegl et al. [23] reported that inhibition of platelet aggregation is due to the elevation of intracellular cAMP.²³ Therefore, it can be reasonably assumed that the hypotensive and anti-platelet aggregation properties of forskolin are due to its ability to stimulate adenylate cyclase.

Forskolin inhibits the binding of platelet-activating factor (PAF) by directly binding to PAF receptor sites. Platelet-activating factor is a key factor in allergic and inflammatory pathways. It also acts on several membrane transport proteins and inhibits glucose transport in erythrocytes, adipocytes, platelets, and other cells.^{1,24}

EFFECTS ON THE AIRWAYS/BRONCHODILATION

Forskolin relaxes guinea pig airways, both *in vitro* and *in vivo*.² Kreutner et al. [25] reported that forskolin blocked bronchospasms, the chief characteristic of asthma and bronchitis in guinea pigs caused by histamine and leukotriene C4.²⁵

Forskolin, when administered i.v. in anesthetized guinea pigs, produced dose-dependent abolition of bronchospasms induced by histamine, acetylcholine, and serotonin. It is suggested that the bronchospasmolytic effect may also be brought about through stimulation of adenylate cyclase.²

Marone et al. [26] reported that forskolin blocked the release of histamine and leukotriene C4 in human basophils and mast cells,²⁶ resulting in subsequent bronchodilation.²⁷

Studies in dogs suggest that active ion transport across the airways epithelium toward the lumen can be enhanced by β -adrenergic agonists. In amphibian skin and rat colon, forskolin stimulated unidirectional transepithelial transport of sodium and chloride. Therefore, forskolin is likely to have similar effects in the airways. Higher water content of mucus secretion in lumen alters the viscoelastic properties of the mucus and thus facilitates mucociliary clearance.

Bauer et al. [23] reported that in a randomized double-blind placebo-controlled trial, patients with a single inhaled aerosolized dry forskolin powder (10 mg) showed a significant relaxation of bronchial muscles and relief of asthma symptoms compared to the placebo or fenoterol (0.4 mg).²⁸

ANTI-INFLAMMATORY EFFECTS

Forskolin exhibits potent anti-inflammatory effect in various animal models. When administered i.p., forskolin significantly inhibited carrageenan-induced paw edema in a dose-dependent manner. Similar effects were also observed in croton oil-induced local inflammation and adjuvant-induced polyarthritis in rats. All these studies are reported in rats. However, the exact mechanism underlying these effects remains unclear.²

OCULAR EFFECTS

Neufeld and Sears reported that cAMP plays a pivotal role in mediating the action of catecholamines on aqueous humor dynamics and on the lowering of intraocular pressure (IOP).²⁹ Since forskolin has a distinctive ability to stimulate adenylate cyclase, the ocular effects of this molecule have attracted the attention of investigators.

ACUTE EYE IRRITATION STUDY

Forskolin ophthalmic solution (Ocufors), containing 1.05% forskolin and manufactured by Sami Labs Limited, was tested for its eye irritation potential in New Zealand white rabbits. A volume of 0.1 mL of the undiluted test item was instilled into the conjunctival sac of the left eye. Similarly, the placebo (blank) preparation was instilled into the conjunctival sac of the right eye. The effects on the conjunctiva, cornea, and iris were scored by Draize's evaluation method at 1, 24, 48, and 72 h postinstillation. Results indicated that Ocufors did not cause any irritation in the eye of the test animals.³⁰

ANTIGLAUCOMA/INTRAOCULAR PRESSURE-LOWERING EFFECT

Several studies have demonstrated the effect of forskolin to lower IOP both in animals and humans. Caprioli and Sears [31] reported that forskolin suspension (1% forskolin) lowers the IOP in rabbits, monkeys, and humans by reducing the net aqueous inflow.³¹

The Sami Labs/Sabinsa research groups developed a stable aqueous formulation of forskolin (with patents granted in the United States and several other countries, pending approval in others) for use in the management of ocular hypertension and glaucoma. An Investigational New Drug Application for this product was successfully approved, with the product gone through clinical trials yielding positive results in relation to Timolol, the comparative standard drug. The product has since been approved for marketing in India by Drug Controller General of India (DCGI).

FORSKOLIN IN PROMOTING LEAN BODY MASS: MODE OF ACTION AND SUPPORTING RESEARCH

The primary mode of action of forskolin is by increasing the cellular concentrations of cAMP and cAMP-mediated functions via the activation of the enzyme adenylate cyclase.²

Adenylate cyclase is the enzyme involved in the production of cAMP, a very important molecule, known as "second messenger," referring to its broad range of activities in the body's life sustaining reactions. Normally, cAMP is formed when a stimulatory hormone (e.g., epinephrine) binds to a receptor site on the cell membrane and stimulates the activation of adenylate cyclase. The receptors on each cell are specific to the activating hormone. The unique feature of this activation is that the site of action of forskolin is the catalytic subunit of the enzyme or a closely associated protein and not the receptors. Of the nine types of adenylate cyclase in humans, forskolin can activate all except type 9, which is found in spermatozoa. Stimulation of adenylate cyclase is thought to be the mechanism by which forskolin relaxes a variety of smooth muscles.¹

Forskolin appears to *bypass* the hormone-receptor interactions and activates adenylate cyclase. Adenylate cyclase activation induces a rise in intracellular cAMP levels.²

In many hormone-sensitive systems, the hormone itself does not enter the target cell but binds to a receptor and indirectly affects the production of another molecule within the cell, which then diffuses intracellularly to the target enzymes or a receptor inside the cell to produce the response. This intracellular mediator is called the second messenger. cAMP is a "second messenger" hormone signaling system. Therefore, cAMP and forskolin have marked physiological effects through such "second messenger" actions on various biochemical processes in the body.

The biochemical mechanism of maintaining or increasing lean body mass is related to the availability of cAMP. By facilitating hormonal action, cAMP may regulate the body's thermogenic response to food, increase the body's basic metabolic rate, and increase utilization of body fat (since thermogenesis is preferentially fueled by fatty acids derived from body fat and/or food).

Typically, an increase in cAMP levels leads to subsequent activation of protein kinase. Protein kinase has been shown to activate the hormone-sensitive lipase that is involved in the breakdown of triglycerides, known as building blocks of fatty tissue.³²

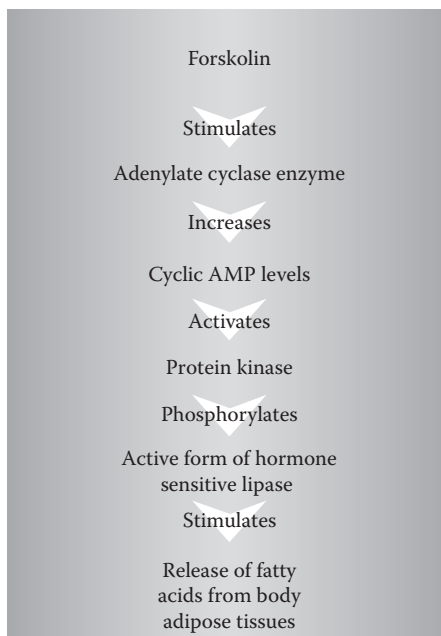


FIGURE 48.3 Mechanism of action of forskolin in promoting a healthy body composition.

The other factor relevant to the weight loss mechanism of forskolin involves its thyroid stimulating action, comparable in strength to thyrotropin or TSH.³³ The thyroid stimulating action of forskolin may also contribute to the increase in the metabolic rate and thermogenesis.

Forskolin may also be involved in regulating insulin secretion.³⁴ Insulin, although well recognized for its metabolism of carbohydrates, is also involved in the metabolism of fats and proteins that are major contributors to body composition (Figure 48.3).

In summary, forskolin increases cAMP levels, inhibits mast cell degranulation and histamine release, increases force of contraction of heart muscle, relaxes the arteries and other smooth muscles, increases insulin secretion, increases thyroid function, and increases lipolysis (breakdown of fat). The therapeutic implications of CF extract based on the pharmacological effects of forskolin are therefore immense.

SAFETY OF FORSLEAN AS A DIETARY INGREDIENT

Botanicals or phytomedicines have always been a major component of the traditional system of healing in developing countries and have been an integral part of their history and culture. But even though plants have a long history of use in Ayurveda and other traditional medicine, natural products or plant extracts are not altogether exempted from the quintessential safety evaluation. Ideally, rodents in adequate number of cohorts are employed for conducting suitable acute, subacute, and chronic toxicity studies from which toxicological information and data are collated that approve the test sample to be escalated for potential human use.

CF extracts and forskolin have an excellent safety profile and are generally considered safe, nontoxic, and without any side effects at the recommended dosage. Animal studies with forskolin indicate an extremely low order of toxicity for forskolin. Prolonged topical application of forskolin is well tolerated and is not associated with overt toxicity, as judged directly by behavioral observation or by growth and development, and was apparently found to be of no untoward clinical significance.

The safety of ForsLean for use as a dietary supplement was established by means of detailed toxicological evaluation of the product. Tests performed include the following:

- *Acute oral toxicity (LD₅₀):*³⁵ Acute oral toxicity of CF extract 10% (ForsLean) was done in Sprague Dawley rats. The test substance suspended in 0.1% aqueous carboxymethyl cellulose was administered by oral route, and the experimental animals were observed for 14 days for product-related symptoms. The test substance did not produce any signs of toxicity after the dosing, and all animals survived the study period of 14 days. The LD₅₀ value of the test substance in rats by oral route was found to be greater than 2000 mg/kg body weight.
- *Subacute oral toxicity (28 Days):*³⁶ Subacute oral toxicity was designed and conducted to determine the toxicity profile of CF extract 10% (ForsLean) when administered daily for 28 days in Sprague Dawley rats. The test substance suspended in 0.1% aqueous carboxymethyl cellulose was administered once daily to animals at various dose levels. Hematological and biochemical analysis were carried out at the end of the experiment. The test substance did not cause any signs of intoxication. Based on these findings, the no observed effect level (NOEL) of this product administered to rats over a period of 28 days was found to be 1000 mg/kg body weight for male and female animals.
- *Chronic oral toxicity (180 days):*³⁷ Chronic oral toxicity study with CF extract 10% (ForsLean) was conducted in Wistar rats to examine toxicity and mortality profiles. Groups of 20 male and 20 female rats were subjected to daily administration of 10% forskolin by oral gavage for 180 days at the dose levels of 500 and 1000 mg/kg body weight. Clinical examinations were done daily. The clinical signs that were observed are abdominal breathing, wet perineum, diarrhea, and circling disorder. Results showed that there was no treatment-related mortality in rats treated with the substance at 500 mg/kg and at 1000 mg/kg body weight, and clinical results showed that there were no significant changes in the rats. Ophthalmoscopic and neurological examinations conducted did not show any remarkable changes or neurotoxic effects of the substance. Body weights of the treated rats did not change significantly and had the same level of food intake as the control group of animals.

At the end of 3 months when the hematological tests were performed, rats treated with ForsLean at doses up to 1000 mg/kg were comparable to normal rats in all parameters. Hematological parameters measured were hemoglobin, packed cell volume, total and differential WBC counts, total RBC count, platelet count, and clotting time. The test substance also did not induce changes in plasma levels of total protein, albumin, alanine aminotransferase, aspartate aminotransferase, cholesterol, alanine phosphatase, glucose, creatinine, urea, urea nitrogen, total bilirubin, calcium, phosphorus, sodium, and potassium. Urine samples examined at the end of the study revealed that there were no significant differences between the treated and nontreated groups. Organ weights were also comparable to control, and the treatment did not induce any gross alterations in the tissues. Based on the findings of this study, it was concluded that the NOEL of ForsLean in Wistar rats, following administration for 180 days, was found to be greater than 1000 mg/kg body weight.

- *Single-dose oral toxicity in rats/LD₅₀ in rats:*³⁸ Single-dose oral toxicity study with CF extract 10% (ForsLean) was conducted in Wistar rats. Groups of five healthy male and five healthy female rats were dosed orally with CF extract at 2000 mg/kg body weight. The rats were observed 1, 2, and 4 h postdose and once daily for 14 days for toxicity, general behavior, and pharmacological effects. The animals were observed for mortality. Body weights were recorded immediately—pretest, weekly, at death, and at termination of the survivors. All animals were examined for gross pathology.

Results:

1. All animals survived the 2000 mg/kg oral dose.
2. Body weight changes were normal in seven tenths of animals. Three females lost weight during the second week of the study.
3. Necropsy results were normal in all animals.

Conclusion: The oral LD₅₀ of CF extract 10% was found to be greater than 2000 mg/kg.

- *Coleus forskohlii* bacterial reverse mutation assay of extract 10% with an independent repeat assay:³⁹ Bacterial reverse mutation assay with CF 10% extract (ForsLean) was conducted using *Salmonella typhimurium* tester strains TA98, TA100, TA1535, and TA1537 and *Escherichia coli* tester strain WP2 *uvr* A in the presence and absence of Aroclor-induced rat liver S9.

The assay was performed in two phases using the plate incorporation method:

1. First phase, the preliminary toxicity assay, was used to establish the dose range for the mutagenicity assay.
2. Second phase, the mutagenicity assay (initial and independent repeat assays), was used to determine the mutagenic potential of the test article.

Dimethyl sulfoxide (DMSO) was selected as the solvent of choice based on compatibility with the target cells and solubility of the test article. Concentrations of 50–75 mg/mL were considered as workable suspensions.

In the preliminary toxicity assay, the maximum dose tested was 5000 µg/plate; this dose was achieved using a concentration of 100 mg/mL and 50 µL plating aliquot. Concentrations from 6.7 to 100 mg/mL were workable suspensions, concentrations from 0.67 to 2.0 mg/mL were soluble but cloudy solutions, and concentrations from 0.13 to 0.20 mg/mL were soluble and clear solutions. Neither precipitation nor appreciable toxicity was observed. Based on the findings of the toxicity assay, the maximum dose plated in the mutagenicity assay was 5000 µg/plate.

In the mutagenicity assay, no positive response was observed. Precipitation was observed beginning at 1800 or 3333 µg/plate in the presence and absence of rat S9 activation. Toxicity was observed in the initial mutagenicity assay at 5000 µg/plate with tester strain TA98 in the absence of S9 activation and beginning at 3333 µg/plate with tester strains TA100 and TA1535 in the absence of S9 activation.

The overall evaluation and dose ranges tested are as follows:

	Overall Evaluation and Dose Range Tested (µg/Plate)										
	TA98		TA100		TA1535		TA1537		WP2 <i>uvr</i> A		
	Low	High	Low	High	Low	High	Low	High	Low	High	
<i>S9</i> Activation											
<i>None</i>	Negative		Negative		Negative		Negative		Negative		
	25	5000	25	5000	25	5000	25	5000	25	5000	
<i>Rat</i>	Negative		Negative		Negative		Negative		Negative		
	25	5000	25	5000	25	5000	25	5000	25	5000	

Conclusion: CF extract (ForsLean) was concluded to be negative in the bacterial reverse mutation assay with an independent repeat assay (AMES test).

- *Repeated insult patch test*:⁴⁰ Repeated insult patch test was done using forskolin 2% w/w solution in wickenol. The study was performed with adherence to ICH Guideline E6 for Good Clinical Practice and requirements provided for in 21 code of federal regulations (CFR) parts 50 and 56 and in accordance to standard operating procedures and applicable protocols.

Fifty-six qualified subjects, male and female ranging in the age from 17 to 75 years, were selected. Forty-five subjects completed the study, and the observations remained within the normal limits throughout the test interval. Hence, forskolin 2% w/w solution in wickenol did not show dermal irritation or allergic contact sensitization.

In this context, topical forskolin has been used with success in the treatment of cellulite. Topical fat reduction in specific areas of the body is a common concern for women.⁴¹ Ronsard popularized the term “cellulite” to describe the dimpling and “orange peel” external appearance of the thighs, the cause of which was attributed to the aging process by later researchers.⁴² It has been postulated that the structure of subcutaneous adipose tissue accounts for the development of the “orange peel” appearance. Groups of fat cells are attached to the ventral side of the dermis by fibrous connective tissue. As fat cells enlarge, the fibers are stretched and pull down on the underlying skin. This causes the indentation or dimpling of the skin called cellulite. It has been demonstrated that adipose tissue metabolism varies from one region of the body to another; for example, in severely obese women losing weight after the jejunoileostomy, fat was seen to be absorbed or reduced more slowly in the thigh region than the abdominal region.⁴³ These differences lead to the hypothesis that localized application of forskolin triggers lipolysis or fat reduction.

Forskolin has been reported to potentiate topical fat reduction in combination with yohimbine and aminophylline.⁴⁴ This study proved that topical fat loss for women’s thighs can be achieved without diet or exercise.

CLINICAL STUDIES WITH FORSLEAN IN PROMOTING LEAN BODY MASS

Abstracts of several studies are being presented in the following section, encompassing the lean body mass–promoting, antiobesity effects of ForsLean. Readers are reminded that the beneficial effects of forskolin are best obtained when the supplement is used in concurrence with a sensible diet and healthy lifestyle measures.

Study 1: Majeed et al. [45]

Diterpene forskolin (Coleus forskohlii, Benth.): A possible new compound for reduction of body weight by increasing lean body mass

An extract of *Coleus forskohlii*, Benth. root standardized for diterpene forskolin (ForsLean) was tested in an open-field study for weight loss and lean body mass increase. The study’s hypothesis was based on the recognized role of diterpene forskolin as a plant-derived compound, which stimulates the enzyme adenylate cyclase and subsequently cAMP (3′5′adenosine monophosphate). cAMP may release fatty acids from the adipose tissue depots, which may result in enhanced thermogenesis, loss of body fat, and theoretically increased lean body mass.

Six overweight, but otherwise healthy, women were selected for the trial. Each participant was informed about the purpose of the study and was asked to sign an informed consent before entering the study. Each participant was examined by a physician at the inception and after 4 and 8 weeks of the study. Their body composition was determined by bioelectrical impedance analysis. ForsLean was prepared in the form of two-piece hard-shell capsules. Each capsule contained 250 mg of the extract standardized for 10% forskolin. The participants were instructed to take one capsule in the morning and one in the evening, half an hour before a meal. They were asked to maintain their previous daily physical exercise and eating habits. In addition, physical activity was monitored based on a questionnaire before and during the trial. The study was performed in an outpatient bariatric clinic at Hilton Head, S.C., and supervised by a physician specializing in bariatric medicine for over 30 years.

During the 8 week trial, the mean values for body weight and fat content were significantly decreased, whereas lean body mass was significantly increased as compared to the baseline (Wilcoxon matched pairs test). Weight loss was statistically significant ($p < 0.05$) after 4 and 8 weeks, and the mean amounted to 4.3 and 9.17 lb, respectively. The body fat values expressed as % body fat were as

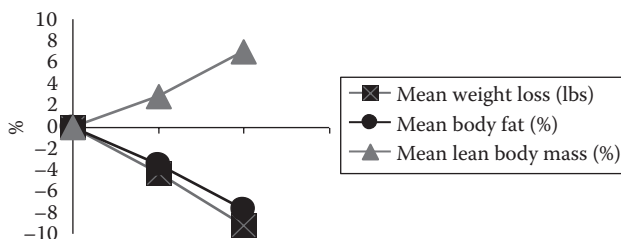


FIGURE 48.4 Open-field study, six overweight women subjects, 500 mg ForsLean corresponding to 50 mg forskolin/day for 8 weeks.

follows: 0 weeks, 33.63 ± 3.02 ; 4 weeks, 30.10 ± 4.34 (statistically not significant or n.s.); and 8 weeks, 25.88 ± 4.77 ($p < 0.05$). The lean body mass values expressed as % lean body mass were as follows: 0 weeks, 67.07 ± 3.02 ; 4 weeks, 69.90 ± 4.34 (n.s.); and 8 weeks, 74.13 ± 4.77 ($p < 0.05$) (Figure 48.4).

The 8 week therapy with 50 mg of forskolin per day did not adversely affect the systolic/diastolic blood pressure or the pulse rate. Systolic pressure (mm Hg) values were as follows: 0 weeks, 113.67 ± 14.50 ; 4 weeks, 110.00 ± 18.93 (n.s.); and 8 weeks, 104.50 ± 17.54 (n.s.). Diastolic pressure (mmHg) values were as follows: 0 weeks, 71.00 ± 12.76 ; 4 weeks, 69.33 ± 9.93 (n.s.); and 8 weeks, 66.00 ± 8.49 (n.s.). Pulse rates (beats/min) were as follows: 0 weeks, 66.33 ± 8.02 ; 4 weeks, 69.00 ± 7.97 (n.s.); and 8 weeks, 74.67 ± 11.55 (n.s.). These preliminary data obtained with 250 mg b.i.d. of ForsLean 10% extract indicate that this composition bears promise as a safe and effective weight loss regimen. The effect of ForsLean is particularly valid in the absence of change in frequency and intensity of physical exercise and without diet restrictions during the course of the trial. This study warrants a double-blind clinical trial evaluating the effects of forskolin on body composition and its possible thermogenic mechanism.

Study 2: Tsuguyoshi [46]

Clinical report on root extract of Perilla Plant (Coleus forskohlii) ForsLean® in reducing body fat: Asano Institute, Tokyo, Japan

A standardized extract of CF roots known as ForsLean (10% diterpene forskolin) was evaluated in a 12 week open-field study in overweight volunteers, 1 male and 13 females; average weight, 74.7 ± 11.98 kg; average BMI (body mass index), 29.9 ± 4.31 ; and average body fat, $38.2\% \pm 4.87\%$. ForsLean was administered in a dose of 125 mg twice a day. Total daily intake of ForsLean was calculated as 25 mg of diterpene forskolin. Each patient was examined in the physician's office, and body composition measurements were taken with an infrared analyzer Futorex 6200 on day 0, 1st, 2nd, and 3rd month. Total body weight showed tendency to decrease from an average 74.7 kg at the onset of the study to 73.5 kg on the 3rd month ($p < 0.05$). BMI improved from an initial average value of 29.9–29.4 ($p < 0.05$) at conclusion of the study. The body fat was decreased from an initial average value of 38.2%–37.1% ($p < 0.01$) at conclusion of the study. Lean body mass was preserved in the course of 12 week ForsLean administration (average 45.8 kg vs. 45.9 kg). The 12 week regimen with 25 mg of forskolin per day did not significantly change blood pressure parameters, that is, average systolic blood pressure, 135.7 mmHg versus 128 mmHg; average diastolic blood pressure, 85.3 mmHg versus 83.6 mmHg. This 12 week open-field study of ForsLean on 14 overweight Japanese subjects indicates its usefulness in weight loss management with no apparent subjective and objective side effects of the regimen.

Study 3: Krieder et al. [47]

Effects of Coleus forskohlii extract supplementation on body composition and markers of health in sedentary overweight female

In a double-blind and randomized manner, 23 females were made to supplement their diet with ForsLean 250 mg of 10% CF extract or a placebo group two times per day for 12 weeks. Body

composition (dual energy x-ray absorptiometry—DEXA), body weight, and psychometric instruments were obtained at 0, 4, 8, and 12 weeks of supplementation. Fasting blood samples and dietary records (4 days) were obtained at 0 and 12 weeks. Side effects were recorded on a weekly basis. Data were analyzed by repeated measures ANOVA and are presented as mean changes from baseline for the CF and placebo groups, respectively. No significant differences were observed in caloric or macronutrient intake. CF tended to mitigate gains in body mass (-0.7 ± 1.8 , 1.0 ± 2.5 kg, $p = 0.10$) and scanned mass (-0.2 ± 1.3 , 1.7 ± 2.9 kg, $p = 0.08$) with no significant differences in fat mass (-0.2 ± 0.7 , 1.1 ± 2.3 kg, $p = 0.16$), fat-free mass (-0.1 ± 1.3 , 0.6 ± 1.2 kg, $p = 0.21$), or body fat ($-0.2\% \pm 1.0\%$, $0.4\% \pm 1.4\%$, $p = 0.40$). Subjects in the CF group tended to report less fatigue ($p = 0.07$), hunger ($p = 0.02$), and fullness ($p = 0.04$). No clinically significant interactions were seen in metabolic markers, blood lipids, muscle and liver enzymes, electrolytes, red cells, white cells, hormones (insulin, TSH, T_3 , and T_4), heart rate, blood pressure, or weekly reports of side effects. Results suggest that CF may help mitigate weight gain in overweight females with apparently no clinically significant side effects.

Study 4: Bhagwat et al. [48]

A randomized double-blind clinical trial to investigate the efficacy and safety of ForsLean® in increasing lean body mass

Shri C. B. Patel Research Center for Chemistry and Biological Sciences, Mumbai, India

In a 12 week double-blind and randomized study, 60 overweight male and female volunteers, 25–45 years old with a BMI between 28 and 40 and/or body fat concentration above 30% in males and 40% in females, received 25 mg of diterpene forskolin b.i.d in the form of ForsLean (250 mg of 10% CF root extract) or a matching placebo. The volunteers receiving the ForsLean on average shed 1.73 kg or 4.02% of their total body weight, while the placebo group gained an average of 250 g (0.29%) of the total body weight. The volunteers treated with the placebo gained 0.32% of body fat, while the ForsLean group lost 0.87% of body fat. The difference in the weight and fat reduction was statistically significant between the active and placebo groups. The tests for thyroid function were performed, assessing levels of hormones T_3 , T_4 , and TSH before and after the completion of the study. It was observed that the levels of all three hormones remained within normal range in both active and placebo-treated groups after 12 weeks of the regimen. The blood lipid profile, performed at the onset and at the conclusion of the study, included triglycerides, total cholesterol, HDL, LDL, and VLDL. Ratio of total cholesterol to HDL was also calculated. At the end of 12 weeks, the placebo-treated volunteers did not show any significant change in any of the lipid parameters recorded. However, those volunteers on the active compound ForsLean showed a significant rise in the concentrations of HDL at the end of the study, while triglycerides, total cholesterol, LDL, and VLDL levels remained unchanged in this group as compared to baseline and placebo group levels (Figure 48.5).

In conclusion, based on this 12 week clinical study, ForsLean may be said to have a weight and fat reduction property. In addition, as compared with the placebo-receiving group, ForsLean may help preserve lean body mass. The 12 week treatment did not produce any subjective or objective side effects in the active compound. The laboratory data indicated that ForsLean regimen did not alter the thyroid hormones and blood lipid profile, with exception of increase in the HDL serum levels and significant decrease of total cholesterol/HDL ratio as compared to the control group.

Study 5: Godard et al. [49]

Body composition and hormonal adaptations associated with forskolin consumption in overweight and obese males

Department of Health Sports and Exercise Sciences, Applied Physiology Laboratory, University of Kansas, Specialized University Center, United States

A study published in the peer-reviewed medical journal, Obesity Research, reports that a dose of 250 mg of ForsLean twice daily significantly increased lean body mass and decreased body fat in obese male subjects (Figure 48.6).

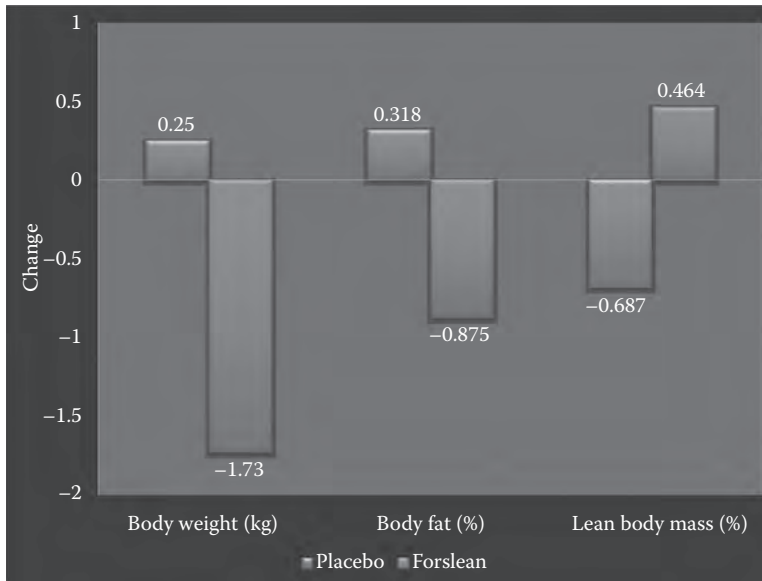


FIGURE 48.5 Change in body weight, body fat, and lean body mass of volunteers treated with ForsLean® and placebo. Change is statistically significant.

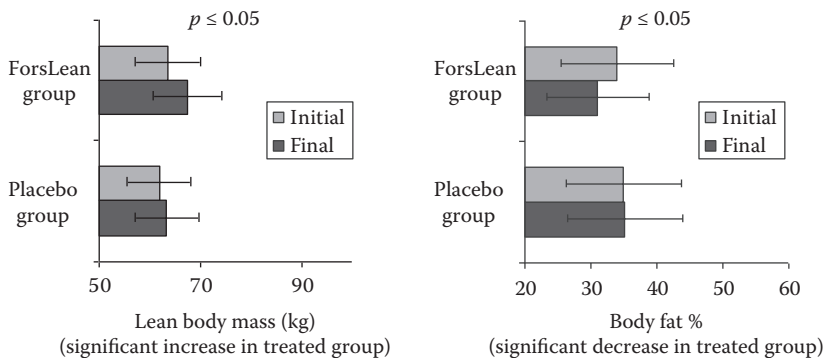


FIGURE 48.6 Changes in lean body mass and body fat ($n = 30$).

This randomized, double-blind, placebo-controlled 12 week study examined the effect of forskolin on body composition, testosterone, metabolic rate, and blood pressure in 30 overweight and obese ($\text{BMI} \geq 26 \text{ kg/m}^2$) men. Fifteen subjects received ForsLean (250mg twice daily) and 15 subjects received a matching placebo.

ForsLean administration elicited favorable changes in body composition by significantly decreasing body fat percentage and fat mass as determined by DEXA, compared with the placebo group ($p \leq 0.05$). Additionally, forskolin administration resulted in an increase in bone mass compared with the placebo group ($p \leq 0.05$). There was a trend toward a significant increase for lean body mass in the forskolin group compared with the placebo group ($p \leq 0.097$).

Serum free testosterone and total testosterone levels were significantly increased in the forskolin group compared to the placebo group ($p \leq 0.05$). The total testosterone increased $16.77\% \pm 33.77\%$ in the forskolin group compared with a decrease of $1.08\% \pm 18.35\%$ in the placebo group (Figure 48.7).

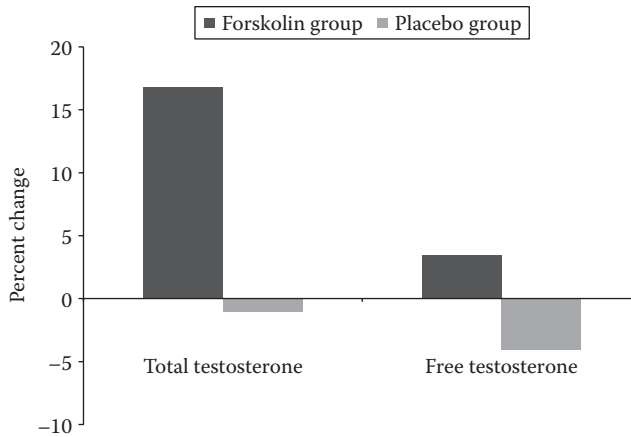


FIGURE 48.7 Percent changes in total testosterone and free testosterone levels.

Study 6: Kamath [50]

Efficacy and Safety of ForsLean® in Increasing Lean Body Mass

Department of Ayurvedic Medicine, Kasturba Medical College, Manipal, India

Fifty subjects, male and female, were randomized to receive 250mg of ForsLean or placebo capsules twice a day (morning and evening) half an hour before meals for 12 weeks. A significant decrease in body weight and fat content and a significant increase in lean body mass were observed (Figure 48.8).

The mean percentage lean body mass increased by 1.78% in the ForsLean group, while the placebo group showed a mean decrease of 0.2% of LBM from baseline values. No significant changes in blood biochemistry profiles were observed in either ForsLean or placebo-receiving groups.

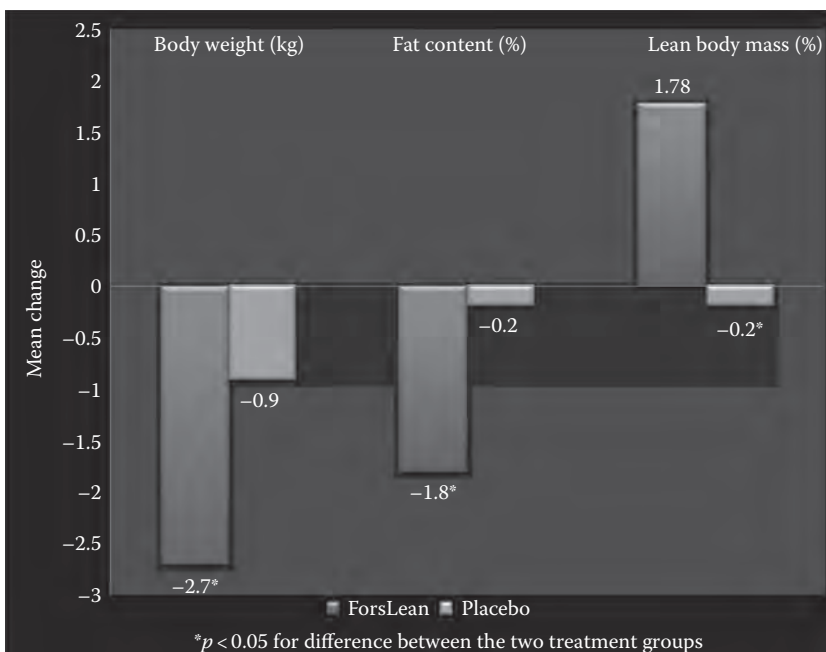


FIGURE 48.8 Mean change in lean body mass, fat content, and body weight (n = 50).

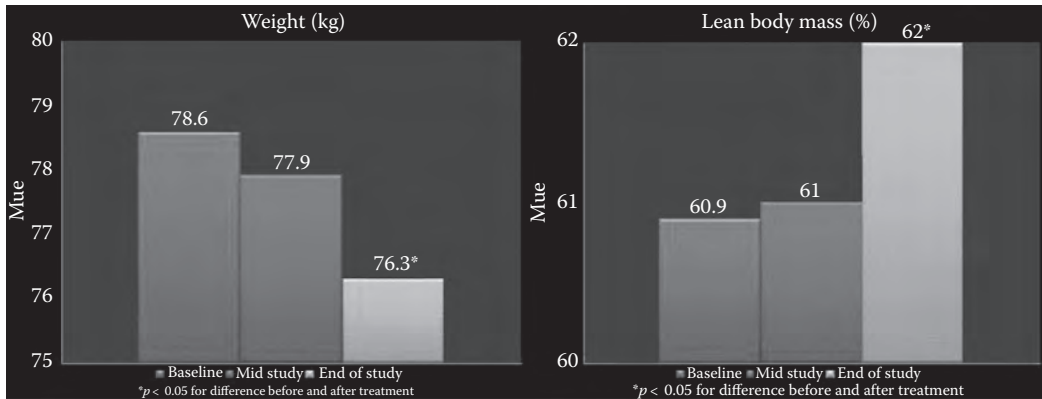


FIGURE 48.9 Effect of forskolin treatment on weight (kg) and lean body mass (%) ($n = 24$).

Study 7: Dr. Pankaj Gandhi and Dr. Parekh [51]

Body composition and hormonal adaptations associated with forskolin consumption in overweight and obese women

This clinical trial evaluated the effect of forskolin on the hormonal levels, particularly testosterone, and the BMD (bone mineral density), along with its effect on lean body mass and weight loss. The study was conducted with compliance to Good Clinical Practice guidelines (Figure 48.9).

Twenty-four obese female subjects, aged 25–35 years, and with BMI ranging from 28 to 45 (I degree to III degree obesity) were enrolled in the study. Subjects were assessed at baseline for demographic and baseline characteristics. Physical examination including blood pressure, weight, BMI, and % body fat measurement (using bioelectrical impedance monitor) were done. Laboratory tests like estrogen, progesterone, testosterone, luteinizing hormone (LH), and BMD were also recorded before the subjects received the study drug. Subjects were given 250 mg of ForsLean capsules twice daily half an hour before breakfast and dinner for 3 months.

The follow-up schedules were fixed at visit 1 (23rd day), visit 2 (46th day), visit 3 (69th day), and visit 4 (92nd day), that is, the final visit. Forskolin demonstrated a significant increase in lean body mass with a corresponding reduction in body weight, BMI, and fat content. There was no effect on hormonal levels or BMD. There were no significant differences across time for daily caloric intake as obtained with the dietary recall. There was no effect on blood pressure or heart rate with forskolin treatment. Neither the systolic nor the diastolic blood pressure showed any significant difference at baseline or during any of the follow-up visits. The good tolerability of ForsLean along with its weight loss efficacy makes it an attractive option in the treatment of obesity.

CONCLUDING REMARKS: FORSKOLIN IN WEIGHT MANAGEMENT

The active ingredient in ForsLean, forskolin, facilitates a cascade of biochemical events in the body that allows fat cells to be used as energy and helps utilize readily available hormones to maintain and/or increase lean body mass.

Specifically, forskolin activates adenylate cyclase, the main enzyme involved in the production of cAMP. cAMP is directly responsible for triggering essential lean body mass–building hormones at the expense of nonessential body fat.

Lean body mass is composed of muscle, vital organs, bone and bone marrow, connective tissue, and body water. The percentage of lean body mass to fat not only determines the body's aesthetic appearance but it is also an index of physical fitness, health status, susceptibility to disease, and

premature mortality. Because the body’s metabolic rate is directly proportional to the amount of lean body mass, there is substantial interest in products that safely increase lean body mass because they are most likely to work.

Forskolin effectively increases lean body mass and supports fat loss without manifesting the adverse side effects associated with ephedrine and synephrine, which have been used as weight loss agents. Ephedrine and synephrine (bitter orange extract) are sympathomimetics. They stimulate adrenergic receptors, which can increase blood pressure and pulse rate and lead to high blood pressure and anxiety. Ephedrine stimulates adrenergic receptors (which is the primary mechanism for ephedrine, even though this process is not totally accountable for its fat-burning effects) before it reaches cAMP. Unfortunately, many negative side effects can be experienced when some of these adrenergic receptors are stimulated, such as increased blood pressure, anxiety, and cardiovascular distress. Fortunately, forskolin is not a sympathomimetic agent; it bypasses the adrenergic receptors and stimulates the release of fatty acids by increasing cAMP levels directly. As evident from Figure 48.10, both ephedrine and forskolin can reduce adipose tissue. However, in essence, while their final results are similar, the mechanism of action for each differs significantly.

The safety and efficacy of ForsLean are evident from the results in more than seven clinical trials, which showed an overall trend to increase lean body mass and decrease body fat content, weight, and BMI (mean BMI).

ForsLean shifts the proportion between lean body mass and adipose, or fatty, tissue in favor of lean body mass, which improves overall health. The effect can be measured by decreases in the waist–hip ratio and the BMI.

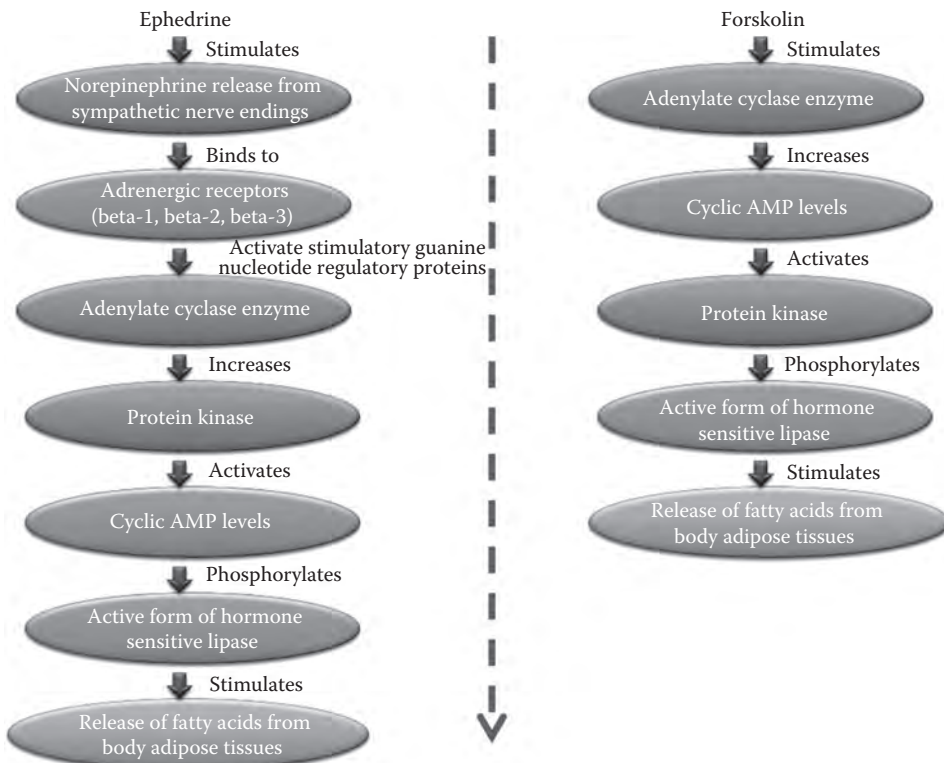


FIGURE 48.10 Mechanism of thermogenic action and its significant differences. Same end result, different pathways. (Adapted from an update on the world’s most underestimated supplement for attacking body fat and increasing muscle mass...what is it, is it safe, and should you be taking it?, *Real Solutions Magazine*, Supplement Breakthrough. 2002.)

Although results vary from individual to individual and from study to study, ForsLean helps maintain healthy body weight. Participants in clinical trials shed between 2 and 9 lb over an 8–12 week period or did not gain body weight; more importantly, the participants preserved or increased their lean body mass as compared to the placebo-receiving group.

Based on the results in these studies, it is recommended that individuals desiring maximum benefits take products that contain 250 mg of ForsLean (standardized to 10% forskolin) approximately 30 min before meals twice daily. For best results, Sabinsa recommends integrating ForsLean with a sensible diet along with an exercise regimen lasting 30–45 min, at least 3–5 days a week. Based on effects in clinical studies, perceptible benefits are observed in 3–4 weeks on supplemental ForsLean.

ForsLean can also be used in conjunction with hydroxycitric acid (available in branded GarCitrin), L-carnitine, white kidney bean extract (Fabenol), and BioPerine® (a bioavailability enhancer) in multi-ingredient compositions for weight management support.

The safety of CF has been proved clinically, and so far, it has not been observed to cause any adverse reactions in humans. However, it is not recommended during pregnancy or for nursing/lactating mothers. Those with severe liver or kidney disease should probably avoid it until more research has demonstrated its safety during such conditions. It is contraindicated for ulcers. Those taking blood pressure medications, such as beta-blockers, clonidine, or hydralazine, or blood-thinning drugs, such as coumadin (warfarin), heparin, or Trental (pentoxifylline), should seek medical guidance before starting a forskolin regimen.

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