POLICOSANOL

NATURALLY HEALTHFUL FROM THE INSIDE & OUT

presented by

SABINSA CORPORATION

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WHAT IS POLICOSANOL?

Policosanol is a natural mixture of higher aliphatic alcohols, found in plant waxes. Sugarcane wax is a common commercial source. The components of policosanol include 1-octacosanol, 1-dotriacontanol, 1-tetracosanol, 1-tetratria-contanol, 1-hexacosanol, 1-heptacosanol and 1-nonacosanol. This mixture of alcohols is clinically proven to be effective in maintaining normal cholesterol levels. Preclinical and clinical studies published in scientific literature reveal that Policosanol beneficially influences cholesterol metabolism (Gouni-Berthold, 2002; Menindez, 1994; Menindez, 1996).

The healthful role of policosanol in cosmetic and personal care formulations is described in a recent US Patent (Majeed, et al., 2007) that details a solvent free extraction process for policosanol from natural sources. This patent describes an innovative process for producing commercial quantities of policosanol containing 70 to 95 percent C_{28} fatty alcohol (Octacosanol) along with other lower chain length fatty alcohols, for use in cosmeceutical applications designed to control sebum, inhibit the growth of microbes and promote hydration and softening of the skin. Moreover, the process of extraction is solvent free so that it has low environmental impact.

CARDIOVASCULAR BENEFITS

Effects on cholesterol metabolism (Gouni-Berthold, et al.; 2002) and antioxidant benefits that prevent the oxidation of LDL-cholesterol, are reported to be responsible for the healthful effects of policosanol (Menindez, et al., 2000). In clinical studies, `Policosanol was shown to be effective in lowering both total cholesterol and low-density lipoprotein (LDL) cholesterol, the 'bad' cholesterol and to increase levels of the 'good' type of cholesterol, high-density lipoprotein (HDL) cholesterol (Gouni-Berthold, et al.; 2002). Other beneficial effects include inhibition of platelet aggregation, which in turn is helpful in maintaining cardiovascular health (Arruzazabala, 1995; Valdes, 1996).

BENEFITS IN HYPERCHOLESTEROLEMIA

A number of placebo controlled trials revealed that policosanol decreases total cholesterol, LDL, LDL/HDL, and TC/HDL along with raising HDL (Pons, 1992; Aneiros, 1993; Pons, 1994). Doses of policosanol at 40mg/day enabled lowering of triglyceride levels in hypercholesterolemic subjects (Castano, et al.; 2001).

The beneficial role of policosanol in hypercholesterolemic subjects with type II diabetes is also reported (Crespo, 1997; Torres, 1995; Crespo, 1999). It was also shown that policosanol outperformed lovastatin (20mg/day) with respect to raising HDL and lowering the LDL/HDL ratio (Crespo, 1999; Castano, 2003). Policosanol has also been shown to be effective in postmenopausal women with hyperlipidemia effecting decreased TC, LDL, LDL/HDL, and TC/HDL (Castano, 2000; Mirkin, 2001). Studies show that policosanol enables serum lipid profiles similar to simvastatin (Ortensi, 1997; Illnait, 1997), pravastatin (Castano, 1992; Benitez, 1997), lovastatin (Crespo, 1999; Mirkin, 2001; Cuebeddu, 2006), probucol (Pons, et al.; 1997), acipimox (Alcocer, et al.; 1999), and atorvastatin (Castano, et al.; 2003).

Interestingly, a meta-analysis of randomized controlled trials, revealed that policosanol outperforms the much publicized plant sterols and stanols in reducing LDL values and positively influencing lipid profiles in hypercholesterolemic individuals (Chen, JT et al.; 2005) approaching antilipemic drug efficacy. Response profiles of a total of 4596 patients from 52 eligible studies were reviewed.

INTERMITTENT CLAUDICATION AND ISCHEMIC HEART DISEASE

A comparative study with the commonly used statin drug Lovastatin on subjects suffering from intermittent claudication revealed significant benefits of policosanol in improving walking distance and pain symptoms. (Castano, 1999). A long term follow up study further established the beneficial role of policosanol in patients with intermittent claudication, with no untoward side effects. (Castano, 2001).

Ischemic heart disease refers to reduced blood supply to the heart, usually caused by atherosclerosis. One study found that subjects using policosanol and aspirin had significantly lower complications from ischemia along with greater exercise performance capabilities and improved left ventricular function (Batista, et al.; 1996). A small dose of policosanol (2 mg/day) was able to ameliorate anomalous ECG readings and reduce complications from angina (Batista, 1996). Policosanol is thus a potential natural intervention to support the management of ischemic heart disease, with an excellent safety profile.

SUGGESTED DOSE LEVELS AND POSTULATED MECHANISMS OF ACTION

The recommended starting dose is 5 mg once a day with the evening meal, since cholesterol biosynthesis is increased at night. Daily doses used in clinical studies range from 10 mg to 24 mg. Policosanol from sugarcane is absorbed with peak absorption at 30-120 minutes and stored in the liver and excreted through the bile.

Literature reports suggest that policosanol inhibits cholesterol synthesis at a point between the formation of acetate and mevalonate. Unlike statins, policosanol exerts no direct inhibitory effects on HMG-CoA reductase. Policosanol may facilitate increased incorporation of LDL into hepatocytes and the resultant stimulation of its catabolism. Policosanol is also an effective antioxidant in preventing LDL oxidation.

FACTORS INFLUENCING CLINICAL EFFICACY

In a randomized, double blind study published in the International Journal of Clinical & Pharmacological Research, physicians investigated the efficacy and tolerability of policosanol at doses of 20 mg a day compared with 40 mg a day (Castano, et al.; 2001). Patients with high cholesterol had been on a cholesterol-lowering diet, but failed to achieve desired results. The patients were instructed to continue the cholesterol-lowering diet and were allocated to receive either placebo, policosanol 20 mg/day, or 40 mg/day. After 28 weeks, policosanol at 20 and 40 mg/day lowered LDL cholesterol by 27.4% and 28.1%, while total cholesterol was reduced by 15.6% and 17.3% respectively. Most impressive was the finding that beneficial HDL cholesterol was increased by 17.6% in the 20 mg/day and 17% in the 40 mg/day policosanol groups. There were no significant changes in the placebo group. The conclusion of this study was that 20 mg a day of policosanol provides about the same cholesterol lowering efficacy as 40 mg a day. Consistent with previous studies, no adverse effects were observed.

In another recent study, the effects of policosanol were measured on menopausal women in a randomized, double blind, multi-center placebo-controlled trial (Mirkin, et al.; 2001). These women showed elevated total and LDL cholesterol despite a six-week standard lipid-lowering diet. Eligible patients were randomized to receive placebo or policosanol 5 mg/day for eight weeks and the dose was doubled to 10 mg/day during the next eight weeks. Results determined that policosanol at doses of 5 and 10 mg/day significantly decreased LDL-cholesterol (12.9%, 26.7%), total cholesterol (12.9%, 19.5%), LDL-cholesterol:HDL-cholesterol (17.2%, 26.5%) and total cholesterol:HDL-cholesterol (16.3%, 21.0%) when compared with baseline and placebo. The study concluded that policosanol was effective in hypercholesterolemic postmenopausal women.

Some studies reveal that race related genetics may play a role in the efficacy of policosanol in cholesterol lowering. While some studies unequivocally demonstrated the benefits of policosanol, others have been inconclusive. One such study done outside Cuba used authentic Cuban sugarcane policosanols in healthy hypercholesterolemic volunteers for a period of 28 days. The results of the study showed no affect on plasma lipid values, no difference between treatment and control groups in plasma lipid values, no difference between treatment and control groups in plasma total, LDL-, HDL-cholesterol, and triacylglycerol concentrations (Kassis, et al.; 2006).

Another study found that Policosanol (20 mg/d for 12 weeks) did not significantly alter plasma total cholesterol, LDL-C, high-density lipoprotein cholesterol, or triglyceride levels when judged against baseline values or with values of the placebo group. Atorvastatin given 10 mg/d for 12 weeks decreased total cholesterol by 27% and LDL-C by 35%. Policosanol combined with atorvastatin failed to result in any further reduction in lipid levels compared to atorvastatin alone.

A recent study conducted in India (Sami Labs Ltd, 2006) with subjects of South Asian origin revealed beneficial effects of policosanol in lipid levels and inflammatory markers. Policosanol (15 mg/day) was compared to Atorvastatin (10 mg/day) in a randomized, double-blind study on 40 patients with hypercholesterolaemia (type IIa) mixed dyslipidemia (type IIb) and/or primary hypertriglyceridemia for 24 weeks. Policosanol compared favorably with Atorvastatin in improving the serum lipid profile. All the 40 subjects completed the study implying that both the groups benefited positively. Policosanol was well tolerated and no drug-related adverse drug reactions were observed. It is concluded that Policosanol is a safe and effective supplement for lowering of LDL, triglycerides and VLDL levels with high degree of safety and can be used to lower several cardiovascular disease risk factors.

STUDY SUMMARY: POLICOSANOL VS. ATORVASTATIN

40 subjects, men and women, aged 18-65 years, with hypercholesterolemia (type IIa) mixed dyslipidemia (type IIb) and/or primary hypertriglyceridemia were identified were selected. Patients under treatment with cholesterol reducing agents were given a 1-week wash out period before being included in the study.

The patients received oral medication of 15 mg of Policosanol or Atorvastatin (10mg) capsule daily before bed time for 24 weeks. Hepatic synthesis of cholesterol is thought to occur primarily at night, thus once daily doses of Policosanol were given in the evening.

Results of the study show that the policosanol group showed significant decreases in total cholesterol, triglyceride levels, LDL levels, and VLDL levels, as did the atorvastatin group. Both groups had increases in HDL. ESR (erythrocyte sedimentation rate) an early indicator of inflammation, decreased significantly in the policosanol group. hs-CRP (high sensitivity C-reactive protein) is a useful indicator of major tissue damage and coronary heart disease, and the reduction of this marker in the policosanol group was significantly greater than that in the atorvastatin group.

An improvement in the liver function test, represented by a decrease in the SGOT (serum glutamic oxaloacetic transaminase) levels in the Policosanol treated group (18.38%, $p < 0.023$)) in comparison with the Atorvastatin treated group (14.07%) was observed.

Significant reduction in Uric acid levels was also observed in Policosanol and Atorvastatin treatment groups (14.09 and 20.10%, significant at $p < 0.01$ and 0.005). No treatment related toxicity symptoms were observed in the Policosanol group during the duration of the study.

COSMECEUTICAL APPLICATIONS

Research efforts by Sabinsa Corporation revealed novel applications of policosanol in supporting healthy keratinous tissues. Policosanol was found to have antimicrobial and sebum control effects that are potentially useful in managing inflammatory skin conditions, particularly acne.

Acne is a follicular disorder of the skin occurring predominantly in specialized pilosebaceous units on the face and neck. There is excessive secretion of sebum by the sebaceous glands and alterations in the sebaceous ducts, leading to their blockage. Localized sebum accumulation encourages proliferation and colonization by microbes, particularly the anaerobic follicular bacterium *Propionibacterium acnes*, which under normal circumstances, is part of the normal cutaneous microflora. Further action by microbial agents such as Staphylococci results in serious infection, inflammation and lesion formation.

Recent research data demonstrate that the skin is in fact a steroidogenic tissue. The human sebaceous gland can synthesize cholesterol from acetate and can further metabolize steroids such as dehydroepiandrosterone into potent androgens (Thiboutot, et al.; 2003). Acne is known to be an androgenic skin disorder. It therefore follows that agents that beneficially affect cholesterol metabolism may have a potential role in the management of acne. Policosanol was found to inhibit cholesterol biosynthesis and enhance LDL processing in cultured human fibroblasts (Menindez, et al.; 1994). Policosanol was found to favorably influence sebum levels in the skin and efficiently inhibit the growth of *Propionibacterium acnes* (Majeed, et al. , 2007).

POLICOSANOL FAVORABLY INFLUENCES SEBUM LEVELS

Sixteen healthy subjects of between 18 and 25 years of age were included in the study after they had signed the informed consent form. The main inclusion criterion was those with oily skin (scores >4 on a 0-5 scale). All the subjects were required to abstain from taking drugs, applying cosmetic products to their skin and exposing themselves to sunlight or any other source of ultraviolet radiation throughout the duration of the study.

Policosanol, 2% or 5% colloidal solution in 1,2-hexanediol was applied (0.2 ml) for seven days, twice daily, on the forehead. One side of forehead being treatment and the other side being the control (1,2-hexanediol treatment).

The efficacy was evaluated based on self-assessment and on the assessment of a panel of five independent cosmetologists, visually, using Sebutape (CuDerm Corp., Dallas, Texas). The sebutape is made of microporous, hydrophobic polymeric film composed of many tiny air cavities. The surface of the film is coated with a lipid porous adhesive layer that enables the tape to adhere to the skin surface. The tape is applied to the skin test site for optimal period of one hour. Sebum is absorbed into the tape, displacing the air in the microcavities. As this occurs, the lipid-filled cavities become transparent to light. Through this process, the sebum output from each follicle forms a sharply defined clear spot, its size roughly corresponding to the sebum volume. When the sebutape is placed on the black background of the score card, the sebum on the tape becomes clearly visible as black spots. These spots are scored by a panel of cosmetologists on a scale of 0-5. These are pooled and from the mean of the scores, the percentage change is calculated from the control treatment site.

(i) 2% and 5% Policosanol colloidal solution was found to be safe for local application. No untoward side effects were observed.

(ii) Topical application of the Policosanol colloidal solution was found to decrease the sebum secretion in a concentration dependent manner. 2% Policosanol solution reduced the sebum levels by about 11%, while 5% solution reduced sebum secretion by 27%.

(iii) Both self-assessment and assessment by the panel of cosmetologists revealed that 100% of the subjects showed marked decrease in sebum release. (Table 1)

(iv) The colloidal solution was found to be effective in people with moderately high oily skin (scores >3.5).

(v) Additionally, one surprising observation was that Policosanol treatment protected the 1,2-Hexanediol induced dryness of skin and made the skin smooth and soft.

Table 1: Effect of Policosanol on the sebum secretion in human volunteers

Groups	Sebum secretion (Mean scores of sebutape by a 5 member panel	% reduction of sebum release
Control	4.2+0.49	---
2% Policosanol (n=8)	3.71+0.41	11.6%
5% Policosanol (n=8)	3.29+0.33	27.66%

Policosanol colloidal solution was found to be effective in people with moderately high oily skin. Additionally, the treatment was found to offer protection against 1,2-Hexanediol induced dryness of skin, and made the skin smooth and soft.

ANTIMICROBIAL EFFECT OF POLICOSANOL

Reinforced clostridial agar medium was prepared, sterilized and poured into plates. Propionibacterium acnes culture was inoculated [0.3 ml / plate] and dispersed on the plate. After 30 minutes, antibacterial sterile discs [6 mm] were dispensed (2/plate). 2.5, 5.0, 7.5 and 10 µl of the prepared samples and controls were dispensed onto the discs. The plates were incubated inside the anaerobic chamber at 37°C for 48 hours. Policosanol in different concentrations (0.1-2%) prepared in 1,2-Hexanediol was used as vehicle for the study with 1,2-Hexanediol as control. Clindac A (Clindamycin Phosphate Gel 1% w/w) was used as positive control. The clearance zones formed around the discs were measured and expressed in mm. (Table 2)

Table 2: Efficacy of Policosanol in inhibiting the growth of *Propionibacterium acnes*

Sl. No.	Conc. Of the sample (%)	Zone inhibition (mm) Policosanol	Zone inhibition (mm) Clindamycin
1	2.0	12.0	11.0
2	1.5	9.0	9.0
3	1.0	8.0	8.0
4	0.5	0.0	0.0
5	0.01	0.0	0.0

As seen in Table 2, Policosanol effectively inhibits Propionibacterium acnes in concentrations above 1% and the activity is comparable with that of Clindamycin gel.

Inhibition of anaerobic organisms complemented by decrease in sebum secretion and skin moisturizing effects suggests the potential utility of policosanol in cosmetic formulations to support the management of acne, as anti-seborrhic agent, as antimicrobial agent, and as a moisturizer.

SAFETY OF POLICOSANOL

In published literature, at oral dosages of up to 20 mg per day, policosanol is reported to be safe and well tolerated, even in long-term studies (> three years) (Gouni-Berthold, et al.; 2002). The topical studies outlined above showed that policosanol does not induce erythema, edema or sensitization in human volunteers. It is therefore safe for topical use at the suggested levels.

SAMPLE COSMETIC FORMULATION CONTAINING POLICOSANOL

Policosanol could be used alone or in combination with other actives such as antibacterials, blemish erasers, sunscreens, and sunscreen boosters in skin care formulations that are beneficial in the management of acne. Suggested levels of use are 1% to 5% by weight in cosmetic creams, lotions, gels; hair care, lip care and nail care products. Additionally, the moisturizing and skin smoothing benefits of policosanol suggest its potential use as a substitute for lanolin and other animal fats in cosmetic formulations.

Sebum Modulating Anti-acne Cream:

	Ingredient	**% by weight**
A.	Cetyl alcohol	10.0%
	Cetostearyl alcohol	3.0
	Glyceryl monostearate SE	4.0
	Isopropyl myristate	3.0
	caprylic/capric triglycerides	2.0
	Cetyl esters	3.0
	Stearyl stearate	0.5
	Cetyl palmitate	0.5
	Myristyl myristate	0.5
Paraffinum liquidum		2.0
B.	Carbomer (Carbopol 940, BFGoodich)	0.1
	Dimethiconol	1.5
	Sodium methylparaben	0.25
	Sodium propylparaben	0.1
	Imidazolidinyl urea	0.15
	Sodium benzoate	0.1
	Tetrasodium EDTA	0.02
	Glycerin	2.5
	Water (aqua)	qs 100.0
C.	Policosanol	1.0
	Coleus forskohlii oil (Sabinsa Corp.)	1.0
	Tetrahydrocurcuminoids (Sabinsa Corp.)	0.5
	Tetrahydropiperine (Cosmoperine®, Sabinsa Corp.)	0.01 – 0.1

Procedure: In separate containers, heat A and B to 65-75°C. At this temperature, add C to A, mix thoroughly, and combine with B under homogenization. Cool to fill temperature.

CONCLUSIONS

Thus as a nutritional intervention to support cardiovascular health and wellness, Policosanol appears to work well in populations such as Latinos and South Asians who are in the higher risk group for cardiovascular disease development. As a cosmeceutical, Policosanol is an effective natural approach in modulating sebum levels in the skin and scalp, a natural antimicrobial adjunct in anti-acne formulations, and a non-animal derived emollient - a potential substitute for wool-derived lanolin in cosmetic formulations.

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