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Policosanol and Human Health

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Abstract

Policosanol (PC) is a mixture of very long chain aliphatic alcohols derived from the wax constituent of plants. Sugar Cane Policosanol (SCP) was used in Cuba as dietary supplement since the early 1990s. Today, Cuban SCP and PC isolated from other sources are widely used in supplements for hypercholesterolemia. The oral absorption and bioavailability of PC are limited and their exact lipid-lowering mechanisms have not been adequately elucidated. Cuban authors showed that SCP inhibits hepatic cholesterol synthesis prior to the formation of mevalonate, reducing synthesis and increasing degradation of 3-Hydroxy-3-Methylglutaryl-Coenzyme A (HMGCoA). Other studies demonstrated that SCP reduces HMGCoA activity via AMP-kinase phosphorilation.

Cuban trials reported that 5 to 20 mg/day of the SCP significantly reduce Total Cholesterol (TC), Low Density Lipoprotein Cholesterol (LDL-C) and LDL peroxidation and are effective in improving endothelial cell dysfunction, platelet aggregation and intermittent claudication and pre-hypertension. Research groups outside of Cuba have failed to validate the cholesterol-lowering and antioxidant efficacy of PC. The lack of independent studies confirming the therapeutic benefits of PC in cardiovascular disease prevention and treatment raises questions regarding their true efficacy.

Keywords: Policosanol; Long-chain aliphatic alcohols; Octocosanol; Cholesterol

Abbreviations

HMG-CoA: Hydroxy-3-Methylglutaryl-Coenzyme A; HDL-C: High-Density lipoprotein Cholesterol; LDL: Low Density Lipoproteins; LDL-C: Low-Density Lipoprotein Cholesterol; PC: Policosanol; SCP: Sugar Cane Policosanol; TC: Total Cholesterol.

Introduction

Policosanol (PC) is the generic term used for a mixture of long-chain aliphatic primary alcohols (C_{24}-C_{34}, Figure 1), originally isolated from sugar cane (*Saccharum officinarum L.*) wax [1,2]. The major components of the mixture are octacosanol (60-70%, w/w), triacontanol (10-20%, w/w) and hexacosanol (4-10%, w/w). The mixture can also be extracted from a variety of other natural sources such as bee wax, rice bran and wheat germ [3,4], but the commercial availably supplements contain primarily Sugar Cane Policosanol (SCP). SCP has been used in Cuba in several human populations for its cholesterol-lowering properties and actually, PC supplements have been approved as a cholesterol-lowering supplement in many countries [5].

Dietary supplements containing PC extracted by sources other than sugar cane have been marketed in recent years. Their composition in long-chain aliphatic primary alcohols differs little among the different sources and octacosanol is the main aliphatic primary alcohol in all policosanol mixtures and it is thought to be the most active component.

In addition to improving serum lipids, some studies evaluated policosanol in reduction of low-Density Lipoproteins (LDL) oxidation, platelet aggregation, smooth muscle proliferation and blood pressure.

Metabolism and Mechanism of Action

Cuban SCP consist mainly of 66% octacosanol (CH_3-CH_2 (26)-CH_2-OH), 12% triacontanol, and 7% hexacosanol. Other alcohols, namely tetracosanol, heptacosanol, nonacosanol, dotriacontanol, and tetratriacontanol, are minor components [1]. Pharmakinetic data in humans are unpublished except for one study that used tritiated octacosanol where only total radioactivity was measured [6].

Thus there is no certainty that significant amounts of the intact aliphatic alcohols are absorbed from the intestinal tract and are available for human tissues. Absorption in rodents after oral administration is assumed to range between 10% and 35% and bioavailability between 5% and 12%. Studies after oral administration of 14C-labeled octacosanol in rats show that the absorbed fraction is distributed between several tissues [7].

The mechanism behind PC-induced cholesterol lowering has not yet been fully elucidated. Some authors reported that PC seems to cause decreased synthesis and increased degradation of 3-Hydroxy-3-Methylglutaryl-Coenzyme A (HMG-CoA), the rate-limiting step in cholesterol synthesis [8,9]. Further studies have demonstrated that PC could lower blood cholesterol via the promotion of AMP-kinase phosphorylation in the liver of mice and hepatoma cells [10,11]. AMP-kinase, a HMGCoA inhibitor, is activated by triacontanol, aliphatic alcohol contained in PC mixtures between 10 and 20% [10]. It should be noted that the doses of PC used in mice ranging from

$$CH_3 - (CH_2)_n - CH_2 - OH$$

Figure 1: Policosanol structural formula.

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10 to 100 mg/kg by body weight and were about one-hundred-fold higher than those used in clinical studies. PC has also demonstrated improvement in LDL metabolism by increasing LDL binding, uptake, and degradation in human fibroblasts [12].

Studies on humans and rats show that PC decreases *in vitro* LDL oxidation using multiple oxidation models [13]. Independent research outside of Cuba examining the antioxidant activity of SCP failed to support previous positive findings, reporting no significant change of oxidation state in LDL from humans treated with a SCP supplements [14,15].

Finally, some Cuban studies reported that SCP decreased neointimal formation, indicating decreased smooth muscle cell proliferation [16,17] and platelet aggregation, by decreasing the synthesis of platelet-aggregating thromboxane B2, with no effect on prostacyclin [18].

Clinical Studies and Safety

Despite low bioavailability, many studies originating in Cuba have shown the efficacy of SCP supplements in the treatment of cardio-vascular related conditions, including hypercholesterolemia, arterial function, LDL oxidation, and intermittent claudication. SCP has been used as lipid-lowering agent in Cuba since 1991. Early clinical studies have shown that oral administration of sugar cane policosanol within a range 5-20 mg/d reduces plasma Total Cholesterol (TC), low-density lipoprotein cholesterol (LDL-C) levels and increases High-Density Lipoprotein Cholesterol (HDL-C) in healthy, hypercholesterolaemic and diabetic patients [19-22].

Reports comparing SCP with statins showed the same efficacy in LDL-C lowering, whereas SCPs have a greater efficacy than statins in increasing HDL-C [23-26]. SCP-induced cholesterol lowering seems to be dose dependent in a dose range of 5-20 mg/day.

Independent authors outside of Cuba have not been able to reproduce the same evidences regarding PC supplementation. Indeed, the effects of PC on plasma cholesterol levels have been questioned by the results of several randomized controlled trials performed in Europe and the US that failed to find any significant effect of PC on plasma cholesterol levels in different clinical settings [27-30].

The lack of cholesterol-lowering efficacy has been confirmed for both Cuban SCP and for PC extracted from other sources [31,32]. In 2011, EFSA rejected a claim on the beneficial effects of SCP for the lack of evidence of a cause–effect relationship between SCP supplementation and cholesterol-lowering [33].

Given the protective effects of showed on vascular function and on platelet aggregation, SCP supplementation was tested in patients diagnosed with intermittent claudication. Some Cuban trials evidenced that SCP supplementation was able to improve walking distances, while in the placebo group remained unchanged [34,35].

In a more recent study, Reiner et al. failed to find any effect on blood coagulation after 8 weeks of treatment with 10 mg/d of rice PC in hypercholesterolaemic patients [36].

Recently, a Korean study reported that long-term PC supplementation in patients with pre-hypertension reduced in a dose-dependent manner blood pressure, blood renin, LDL-C, plasma glucose, increasing HDL-C at doses of 10 and 20 mg/d [37].

Clinical trials as well as toxicological studies in animal models have not demonstrated any serious adverse effects or biochemical changes indicative of cell damage during PC supplementation [36-40].

Conclusion

Studies conducted mainly by Cuban researchers in the local population report that SCP supplementation is effective in improving hypercholesterolemia, LDL-C peroxidation, arterial endothelial cell dysfunction, platelet aggregation, intermittent claudication and pre-hypertension. In most cases, external research groups have been unable to reproduce the same results in different populations.

Some aspects of PC such as absorption, pharmacokinetics, and mechanism of action remain to be clarified. This uncertainty on their metabolism and the disparity in results between research groups raise doubts about the use of PC as cardio-protective nutraceutical.

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