RESEÑA

Cuban sugar cane wax policosanol: Is it an aid in metabolic syndrome treatment?

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Recibido: 22 de marzo de 2017 Aceptado: 26 de octubre de 2017

Key words: metabolic syndrome, policosanol, adenosine monophosphate protein kinase, VLDL
Palabras clave**:** síndrome metabólico, policosanol, proteína kinasa de monofosfato de adenosina, LMBD

ABSTRACT. The objective of the present review is to present evidences supporting the proposal of the potential benefits of cuban sugar cane wax Policosanol for concomitant use in metabolic syndrome treatment. Cuban Policosanol is a mixture of very long chain saturated fatty alcohols; that decreases serum total cholesterol, low density lipoprotein cholesterol and, also diminishes triglycerides serum concentrations in different preclinical and clinical assays while, significantly increases high density lipoprotein cholesterol. Early investigations demonstrated that Cuban Policosanol modulate cholesterol synthesis by inhibiting mevalonic acid formation. Later on, it was confirmed that cuban Policosanol activates Adenosine Monophosphate Protein Kinase, which once activated, inhibits Hydroxyl Methyl Glutaryl Coenzyme A Reductase, and Acetyl CoA Carboxylase. Changes in life style, including healthy dietary regimens and increased physical activity are the first line measures for prevention and therapy of metabolic syndrome. Additionally, a number of therapeutic agents had been proposed to treat metabolic syndrome. However, some of those therapies present low efficacy, low influence durability and, side effects. Beside changes in serum lipid profile, activated Adenosine Monophosphate Protein Kinase, ameliorates high blood pressure, decrease body weight, while prevents pro-thrombotic state, oxidative stress, insulin resistance, inflammatory processes and, improves physical fitness. Thus, Adenosine Monophosphate Protein Kinase, is considered as a therapeutic target for new agents with potential use in the metabolic syndrome treatment. This paper evaluates some findings about the effect of Policosanol in pre-clinical research and clinical assays, demonstrating positive effects on several symptoms presents in metabolic syndrome. In conclusion, the use of cuban Policosanol may be beneficial as a concomitant treatment of the metabolic syndrome treatment.

RESUMEN. El objetivo de la presente revisión es presentar evidencias que sustentan la hipótesis del beneficio potencial del Policosanol cubano de cera de caña de azúcar para su uso concomitante en el tratamiento del síndrome metabólico. El Policosanol cubano es una mezcla de alcoholes grasos de cadena muy larga; que disminuye la concentración de colesterol total, colesterol unido a lipoproteína de baja densidad, y también disminuye la concentración de los triglicéridos del suero en diferentes en distintos ensayos preclínicos y clínicos mientras que, por otro lado, incrementa significativamente el colesterol unido a las lipoproteínas de alta densidad. Tempranamente se demostró que el Policosanol cubano modula la síntesis del colesterol mediante la inhibición de la síntesis de mevalonato. Más tarde se confirmó que el Policosanol cubano activa la Proteína Kinasa de Monofosfato de Adenosina, la cual, una vez activada, inhibe las enzimas Hidroximetil Glutaril Coenzima A Reductasa y Metil Glutaril Coenzima A Carboxilasa las cuales regulan, respectivamente, la síntesis de colesterol y ácidos grasos. Los cambios en el estilo de vida, incluyendo los regímenes dietéticos saludables y el incremento de la actividad física, son las medidas de primera línea para la prevención y terapéutica del síndrome metabólico. Adicionalmente, se han propuesto un número de agentes terapéuticos para el tratamiento del síndrome metabólico. Sin embargo, estos agentes presentan baja eficiencia y durabilidad además de efectos colaterales. Además de los cambios que promueve la Proteína Kinasa de Monofosfato de Adenosina activada sobre el perfil de los lípidos del suero, también mejora la hipertensión arterial, disminuye el peso corporal, previene el estado pro-trombótico, el estrés oxidativo, la resistencia a la insulina, los procesos inflamatorios y mejora la capacidad física. Así, la Proteína Kinasa de Monofosfato de Adenosina es considerada como diana terapéutica de nuevos agentes farmacológicos con uso potencial en el tratamiento del síndrome metabólico. Este artículo evalúa algunos hallazgos sobre el efecto del Policosanol en

investigaciones preclínicas y ensayos clínicos, demostrando efectos positivos sobre varios síntomas presentes en el síndrome metabólico. En conclusión, el uso del Policosanol cubano pudiera ser beneficioso como tratamiento concomitante en el síndrome metabólico, para lo cual se necesita investigar su seguridad y eficacia en estos pacientes.

INTRODUCTION

The Metabolic Syndrome (MS) is a major increasing public-health and, clinical challenge worldwide, related with unhealthful life style and a group of metabolic disturbances. MS confers a five fold increase in the risk of type II diabetes mellitus and two fold the risk of developing cardiovascular disease (CVD) in the following 5 to 10 years after MS diagnosis. Patients with the MS are at 2 to 4 fold increased risk of stroke, a 3 to 4 fold increased risk of myocardial infarction (MI), and two fold the risk of dying from such events compared with those without the MS, regardless a previous history of cardiovascular events. Safe and sufficiently effective drugs for treating metabolic syndrome are needed.[1]

Beyond a lipid profile controlling agent, there are enough experimental and clinical research evidences supporting the proposition of cuban Policosanol (CPco) as aid in MS treatment

Policosanol: Definition, Composition and, Biological Importance.

Policosanol is a term employed originally in Cuba to name a particular sugar cane wax extract, containing eight Very Long Chain Fatty Alcohols (VLCSFAls) (1-tetracosanol, 1-hexacosanol, 1-heptacosanol, 1-octacosanol, 1-nonacosanol, 1-triacontanol, 1-dotriacontanol, 1-tetratriacontanol). The term is also used, by extension, to name any mixture of VLCSFAls regardless of their composition and concentration of fatty alcohols or sources.

Although Octacosanol is the mayor component of CPco, exhibiting some of the mains pharmacological effects, the activity of the mixture seems to be superior in some experimental models.[2]

Recent results indicate that minor VLCSFAls component of CPco, converted into VLCFAs in endoplasmic reticulum (ER), are also very important for health.[3-5] Conversely, patients suffering peroxisomes diseases, which cannot metabolize VLCSFAs, undergo severe metabolic disturbances, mental retardation, and others symptoms, deeply affecting their lives, [6-7] indicating the biological importance of VLCSFAl as well as VLCSFA.

Biochemistry

After intestinal absorption, VLCSFAls are up taken by the liver; converted into carboxylic acids;[8] released into plasma as triglycerides as component of lipoproteins and, distributed in different organs; mainly in muscle, adipose tissue, brain and, heart.[9]

VLCSFAls are reversibly converted into VLCSFAs in ER through a fatty alcohol cycle described by Rizzo W.B.[10,11] VLCSFAs initiates ω oxidation in ER and continue β oxidation in peroxisome to an appropriate chain length, or used for synthesis. Eventually, they are completely β oxidized in mitochondria.[12]

VLCSFAs are considered as natural and potent PPARα agonists.[13,14] Fibrates which are, well known ligands for PPARα, stimulate the production of apolipoprotein (Apo) A-I.[15] Consequently, it seems possible that VLCFAs may also induce the synthesis of Apo A1.

It was demonstrated that CPco inhibits cholesterol synthesis in the firth step of its metabolic pathway through activation of AMPK, which in turn inhibit HMGCoA-R.[16-20]

Activated AMPK also inhibit Acetyl CoA Carboxylase (ACC). The inhibition of ACC increases fatty acid oxidation and reduces lipid synthesis, protecting in this way, muscle, heart, and others tissues from lipotoxicity.[21, 22]

In addition, AMPK activation is associated with a wide array of beneficial effects on metabolic syndrome related diseases. Its potential benefits include pancreatic β cells, hepatocytes, striated muscle cells, adipocytes and other two special cell types: endothelial cells, and leukocytes.[23] The β oxidation in peroxisomes is not only a catabolic but also a synthetic path way. The intermediates products of β oxidation participates in the synthesis of bile acids and plasmalogens (Pls).

Increased VLCFAs peroxisome β oxidation, contributes to eliminate cholesterol by increasing bile excretion [24] as well as controlling intestinal bile reabsorption.[25] Moreover, bile has a hormone like behaviour, limiting the cholesterol synthesis transcription enzyme.[26] The only way to eliminate cholesterol is its excretion through the bile, as free cholesterol or as bile salts following conversion in bile acids in the liver.

Pls are a variety of ether phospholipid characterized by the presence of a vinyl ether linkage at the sn-1 position and an ester linkage at the sn-2 position. In mammals, the sn-1 position is typically occupied by fatty alcohols (C16:0, C18:0, or C18:1), while the sn-2 position is most commonly occupied by polyunsaturated fatty acids.[27] VLCFALs are transformed in Pls through a metabolic path way initiated in peroxisome and completed in ER. They are found in numerous human tissues, with particular enrichment in the nervous, immune, and cardiovascular systems. Pls are 30 - 40 % of the choline glycerophospholipids in human heart tissue; almost 30 % of the glycerophospholipids in the adult human brain, and up to 70 % of the myelin sheath ethanolamine.[28]

It has been demonstrated that Pls can protect mammalian cells against the damaging effects of reactive oxygen species. In addition; they had been implicated as signaling molecules and modulators of membrane dynamics and are involved in several cellular functions, for instance: vesicles formation, membranes fusion, ions transport, and generation of secondary signals mediators such as platelet activation factor.[29]

Pls deficit in brain tissue are involucrate in Alzheimer disease and other nervous system derangements; in addition, low serum concentration of Pls is associated with CVD.[30]

Pls are delivered from the liver into circulation as a component of lipoproteins.[31] Low Density Lipoprotein Cholesterol (LDL-C) of animals treated with CPco exhibits higher resistance to oxidation.[32,33] They also improve High Density Lipoprotein Cholesterol (HDL-C) functionality; making more efficient the reverse cholesterol transport[34] and in many other aspects associated with HDL function,for instance:

-Vascular dilatation by stimulation of nitric oxide synthesis;
-Protection of endothelial cell, and macrophages;
-Promotion of anti-trombogenic effect;
-Improve its anti-inflammatory action;
-Upgrades protection from infections;
-Enhances the modulation of glucose metabolism;[35]
-Cholesterol handling in the brain[36] and,
-AMPK activation.[37]

The Pls concentration in HDL, are inversely associated with coronary artery disease and anti-apoptotic activity.[38,39]

Toxicology

The toxicological evaluation of CPco included acute systemic toxicity testing, repeated-doses and sub-chronic and chronic studies, genes toxicity, reproductive toxicity and carcinogenicity in different rodents and non-rodent species, demonstrating no toxic effect in any of the performed tests. Data from short and long term clinical studies indicate that CPco is safety and very well tolerated by most patients, including elders[1] and children.[40]

A post marketing surveillance study, participating 27 897 subjects, treated with CPco, during four years, showed a slight but significant weight loss as one of the most frequent report.[41]

Weight loss was also the most a frequent report in other controlled surveillance study. It was considered a drug related effect, even though no statistical significance difference with control group was found.[42]

METABOLIC SYNDROME

Concept

From the late 1980s, Reavens described a cluster of abnormalities, whose combined risk of developing diabetes and cardiovascular risk is greater than that of its individual components.[43]

This cluster was termed "Syndrome X" by Reaven. Later, the cluster came to be known by others names such as Metabolic Syndrome (MS) or Insulin Resistance Syndrome.The original concept of MS included hyperinsulinemia, impaired glucose tolerance, hypertriglyceridemia, low HDL cholesterol, and hypertension. New concepts of MS also include central obesity, microalbuminuria, endothelial dysfunction, inflammation, and pro-thrombotic state. It is on debate whether the presence of non-alcoholic fatty liver disease (NAFLD) should be included.[44-46]

The international associations attending MS problem are: The International Diabetes Federation (IDF); American Diabetes Association (ADA); World Health Organization (WHO); European Group for Insulin Resistance (EGIR); The NCEP ATP III; and AACE: The American association of clinical Endocrinologist (AACE).

Those associations define MS according different criteria, including or not, symptoms suggested to be MS connected. IDF propose the most inclusive criteria, considering that MS is characterized by symptoms and physical or biochemical findings coexisting more often than could be explained by chance alone. On the other hand, The AACD focuses its definition only on the presence of insulin resistance (not diabetes). According the WHO criteria MS is defined by the presence of: insulin resistance, impaired glucose tolerance or diabetes mellitus type II, as well as two of the following conditions: 1st: Reduced high density lipoprotein (HDL) plus increased triglycerides, 2nd: Hypertension and, 3rd: Micro-albuminuria.[47]

Prevention and Therapy

Changes in lifestyle including healthy dietary regimens and increased physical activity should be the first lines measures for prevention and also MS management.

Diet:

Successful dietary strategies include energy restriction and weight loss such as changing proportions of dietary macronutrients, either through restriction of carbohydrates and fat, or by means of enrichment in beneficial fatty acids, functional foods, and bioactive nutrients.[48-50]

A large prospective study provides evidence that a better adherence to traditional Mediterranean diet may help in reducing MS incidence, mediated by its beneficial association with several MS components (waist circumference, hypertension, high concentration of blood serum triglycerides, low serum HDL-cholesterol concentration and, type II diabetes.[51]

A diet containing low refined carbohydrates, red wine and fish are known characteristics of Mediterranean diet. Addition of red wine polyphenols to obese rat receiving high fat diet diminished oxidative stress in different tissues,

showing an antioxidant effect and a better control of metabolic syndrome. These findings support the use of antioxidants as adjunctive nutritional aid for MS treatment.[52]

To evaluate the association between dietary polyphenol intake and prevalence of MS, a cross-sectional population-based survey including 8 821 adults (51.4 % female) was conducted in Krakow, Poland. Dietary polyphenols were inversely associated with MS and some of its component,[53] showing the importance of antioxidant in the diet of MS patients.

Antioxidants are bioactive nutrients often not sufficiently consumed. A study demonstrated that women with MS presenting low intake of antioxidants vitamins (A, C and D) could be beneficiated with prescriptions of that vitamins.[54]

Long chain polyunsaturated fatty acid, present in sea fish, may also improve some symptoms associated to metabolic syndrome features such as obesity, insulin resistance, hypertension and dyslipidemia (hypertriglyceridemia). Moreover, the blood pressure-lowering, the anti-inflammatory properties and, their benefits in vascular function of these fatty acids might confer cardio-protection.[55]

Physical activity

Together with good nutritional habits, exercise is other important component of a healthy life style. Increasing intensity and volume of physical activity and decreasing time spent at sedentary level of physical activity, reduces the probability of developing the MS. Intensive and supervised exercise interventions objectively measured, are recommended to obtain better results instead of self-report.[56-59]

The molecular bases of beneficial effect of physical activity rest on AMPK activation. AMPK is activated by muscle contractions in an intensity dependent manner. The activation of AMPK during exercise occurs in response to increased binding of Adenosine monophosphate (AMP) and decreased binding of Adenosine triphosphate (ATP) to γ subunit of the enzyme. The cellular increase of AMP over ATP concentration in the ratio AMP: ATP activates AMPK. Activated AMPK increases the energy production processes, while decreases energy consuming processes.

It is known the effect of exercise in prevention and treatment of several common diseases, the increase insulin sensitivity, and reduction of overall mortality. In contrast, inactivity is a powerful risk factor for many diseases.[60]

CPco: CANDIDATE FOR MS TREATMENT

MS is a complex metabolic derangement, associated with inappropriate life styles, and genetic conditions that are responsible for biochemical, physiological, organic, and differences of symptoms components between patients. MS is also defined as a constellation of an interconnected physiological, biochemical, clinical and, metabolic factors that directly increases the risk of atherosclerotic CVD, type II diabetes mellitus, and all-cause mortality.

Different therapeutic measures have been proposed to treat each of the symptoms components of MS:

-To avoid hyperglycemia, it has been proposed to reduce excessive hepatic glucose production, by enhancing glucose-stimulate insulin secretion; or activating insulin signaling pathway.

-To control obesity, it is suggested to act on lipid metabolism and lipotoxicity

-To enhance tissue sensitivity by insulin it is recommended PPARS ligands[61]

However, beside low efficacy and effect durability; some of the proposed symptomatic agents present side effects.[62]

EFFECTS OF POLICOSANOL ON SYMPTOMS COMPONENTS OF MS

Two population studies support the possible use of VLCSFAs in MS and, CVD risk patients:

A population study held in S. Korea in 2013 demonstrated the association of each and sum of VLCFA intake with the improvement of MS. The results indicated that higher intake of VLCFA is significantly associated with favorable metabolic status including lower levels of circulating TG and negatively associated with MS risk as compared to subject with lower intake of VLCFA.[3]

Other study held in U.S. confirmed that circulating serum VLCSFAs were independently associated with favorable profiles of blood lipids (lower TG and increased HDL); others CVD risk markers and, a lower CVD risk by 52 %, erythrocyte not showing VLCSFAs significant trends of lower CVD risk.[4]

The results of experimental and clinical research suggest the possibility that CPco is able to improve, at least most of the symptoms constellation present in MS

Dislipoproteinemia

Many experiments *in vitro*, in animal models and, clinical trials demonstrated beneficial effects of CPco on serum lipids profile in different animal species, normal humans with different ages as well as with different physiological and pathological conditions.[1] A number of clinical assays shows that CPco (10 - 20 mg.) significantly reduces TC (18 - 22.9 %), LDL-C (26.1 - 31.2 %), and increased HDL-C (7.2 - 10.4 %) serum concentration.[1] CPco also modestly, but systematically, decreases TG serum concentration in clinical assays.[63-73]

A double-blind placebo-controlled trial was conducted in 29 non-insulin dependent diabetes mellitus patients with hypercholesterolemia. After stable glycemic control, achieved by diet and/or oral glucose lowering drugs, patients were instructed to follow a cholesterol-lowering diet for six-week previous treatment. Patients who met entry criteria received, under double-blind conditions, CPco (10 mg/d) or placebo tablets, twice a day for 12 weeks. CPco

significantly reduced total cholesterol by 17.5 % and LDL-C by 21.8 % compared with baseline and placebo. Furthermore, HDL-C was raised by 11.3 %, and triglycerides showed a statistically non-significant decrease of 6.6 %. These changes in lipid profile were similar to those induced by policosanol in nondiabetic patients with type II hyperlipoproteinemia.[74]

Hyperglycemia: It was suggested the possibility that CPco could have a metformine like effect on glycemic control.[18]

A report provides new evidence that tetracosanol, a minor component of CPco, induces insulin receptor kinase activity and improvement of glucose uptake.[5] Long-term supplementation of policosanol in a rat model, results insignificant decrease concentration of blood cholesterol, glucose and triglycerides.[70] Hypoglycemic effect was also reported in other clinical trial,[73] and a slight, non-significant, reduction in blood glycosylated hemoglobin, was observed in a clinical trial in diabetic patients even under glycemic control measures.[75]

In a clinical assay, conducted with fatty liver disease patients, treated with Policosanol, revealed a significant reduction in total cholesterol, LDL-C and HOMA (Homeostatic Model Assessment) index ($p < 0.002$), indicating effect on insulin resistance and glucose metabolism. It was also found a not statistically significant trend for a marked reduction in serum transaminases, triglycerides, and BMI.[76]

Pro-thrombotic State

CPco decrease thromboxane A_2 and increase prostaglandin I_2.[77,78] Moreover, *ex vivo* and *in vivo* experiments in rats have demonstrate that CPco significantly inhibited ADP and collagen induced platelet aggregation, platelet count and, malondialdehide concentration.[79,80] The antiplatelet effect of CPco was also demonstrated in normal people,[81,82] as well as in hypercholesterolemic patients.[83]

The activation of AMPK or PPARγ by rosiglitazone and pioglitazone inhibit platelet aggregation responsive to aggregation stimuli such as collagen, ADP, and thrombin.[84] Probably, the activation of AMPK by CPco could also contribute to its anti-aggregator effect.

Inflammation:

A chronic low-grade inflammation and activation of the immune system observed in abdominal obesity may have a role in the pathogenesis of obesity-related metabolic disorders.[85]

Consuming Mediterranean diet, even in the absence of weight loss, but with waist circumference reduction significantly reduces inflammation.[86]

Beside a healthy diet and weight loss there are necessary aerobic exercises to improve reduction of serum inflammatory markers.[87]

CPco prevents the development of foam cells in carrageenan-induced granulomas (extravascular medium) in rats, evidencing its anti-inflammatory effect.[88]

Policosanol induced a remarkable reduction in the density and number of foam cells and improved the intimal lesions of the aorta in animal models and, exerted hypoglycemic effect along with an inhibition of inflammation, oxidative stress and, calcium deposition.[89]

The combination of Policosanol with exercise significantly improves serum inflammatory markers and leptin in obese women.[90] In addition, policosanol exhibit an anti-inflammatory effect in hyperlipidemic subjects, resulting in a significant decrease of hemoxigenase and C reactive protein in serum.[91]

Physical Fitness

Physical inactivity has a major health impact all over the world. Elimination of physical inactivity would remove from 6 % to 10 % of the major non communicable diseases such as CVD, type 2 diabetes; breast and colon cancers and, increase life expectancy.[92]

Higher total mean volume or intensity of activity measured as metabolic equivalents were negatively associated with the risk of MS and separate components of MS, while the time spent at sedentary level of physical activity (PA) was positively associated with MS.[55]

It is very well known that the practice of PA is able to activate AMPK, but the effect of activated AMPK on PA is less reported in scientific literature.

The amount of voluntary exercise was significantly higher in octacosanol fed animals than in controls[93] and, a supplementation with omega 3 fatty acids plus Policosanol to eighteen karateka showed a reduced reaction time and increased vigor sensation with a reduction of latency of the movement-related brain macropotencials.[94]

A CPco containing nutritional complement (Vasoactol), used in Cuba for aged people and persons with special physiological conditions, significantly increases VO_2 max (maximum oxygen consumption), mean power, and total exercise time, being the final values significantly higher than placebo group.[95] Also, a mixture of VLCFA extracted from Cuban sugar cane wax VLCFA (D-003), in a randomized, double blinded, placebo controlled clinical assay, conducted in middle aged and older subject, improved $VO_{2max,}$ pain/discomfort, health perception (Euro-Qol score) and, cardiovascular capacity (Specific Activity Scale).[96]

Obesity

Adipose tissues in markedly obese insulin resistant individuals, uniformly show decreased AMPK activity and increased oxidative stress compared with insulin sensitive patients.[97]

Phosphorylated AMPK inactivates ACC and lowers the intracellular malonyl-CoA level, which is the substrate for fatty acid synthesis and at the same time, the inhibitor of carnitine palmitoyl transferase, the rate-limiting enzyme of mitochondrial fatty acid oxidation.[98]

Significant reduction of perirenal adipose tissue weight, without decrease in cell number was observed in octacosanol treated rats, fed with high fat diet.[99]

In a number of assays, a significant body weigh decrease was not always present in subject treated with CPco. However, a slight, non-significant reduction of body weight was observed in hypercholesterolemic obese patients, treated with policosanol during one year[100] and, in two pharmacologic surveillance studies.[41,42]

Endothelial Dysfunction

Endothelial dysfunction is defined as an alteration of vascular relaxation induced by reduction of endothelium derived relaxing factors, mainly nitric oxide (NO). These abnormal vasomotor responses occur in the presence of various risk factors for atherosclerosis. The metabolic syndrome is considered a state of chronic inflammation accompanied by endothelial dysfunction.[101]

NO, synthesized by endothelial Nitric Oxide Synthase (eNOS) is an important regulator of cardiovascular homeostasis. Endothelium derived NO promotes vasodilatation and inhibit platelet aggregation, leucocyte adherence and, vascular smooth muscle proliferation. Experimentally, CPco is able to inhibit smooth muscle proliferation.[102]

Endothelial AMPK may play important physiological functions, such as modulation of endothelial cell energy supply, protection from apoptosis and, mediation of endothelial NOS activation in response to shear stress and regulation of inflammation, angiogenesis and maintenance of perfusion.[103]

The association of AMPK with NOS demonstrated in different studies indicates that AMPK is capable to directly phosphorylate eNOS.[104]

Some experimental models and clinical assays suggest the beneficial effect of VLCFAl and VLCFA in endothelium function: Sodium citrate injection significantly ($p < 0, 05$) increased the circulating endothelial cells count compared with the control. However, treatment with D-003 (5, 25, 100 and 200 mg/kg) decreased significantly ($p < 0.05$) and dose-dependently circulating endothelial cells by 23.6, 35.4, 53.3 and 57.1 %, respectively in animals treated with sodium citrate. These results provide evidences about the VLCFA protective effects on vascular endothelium.[105]

CPco also prevents endothelium injury and significantly reduces intimal thickness of rabbit arteries damaged with forceps.[106]

A clinical assay conducted in older patients with hypercholesterolemia type II demonstrated the CPco (10 mg/d) diminishing effect on blood circulating endothelial cells beside improvement of lipid profile.[107] It was also demonstrated in clinical assays the beneficial effect of CPco on endothelial protection in patients with cardio-vascular disease.[108-110]

Hypertension

AMPK-mediated vascular relaxation is present and enhanced in arteries of spontaneously hypertensive rats, suggesting that activation of AMPK may be a potential strategy to prevent vasomotor dysfunction by suppressing enhanced endoperoxide mediated contraction and increasing NO-mediated relaxation and/or enhanced COX-mediated contraction.[111]

It is hypothesizing that AMPK is a dual sensor for energy and redox status within a cell and, may be a therapeutic target for protecting vascular endothelial function. In this way, a safe compound that directly and effectively activates AMPK in endothelial cells, yielding the same beneficial therapeutic effects of existing drugs while avoiding unwanted side-effects, may prove to have substantial practical value for promoting vascular health.[112]

Blood pressure lowering effect of CPco was observed in different clinical assays. [3,113-117]

Oxidative stress

In addition to its lipid profile improvement effect, Policosanol is able to reduce the potential of lipoprotein to undergo lipid peroxidation.[118]

When policosanol was administered orally (100 and 250 mg/kg) for up to four weeks, a partial prevention of rat *in vitro* microsomal lipid peroxidation was noted. The formation of TBARS in microsomes isolated from treated rats was significantly decreased by about 50 %. [119] Moreover, Policosanol, significantly rise the lag time (20.9 %) of Cu+2-induced LDL peroxidation and total plasma antioxidant activity (24.2 %) ($p< 0.05$) in a double blinded study and, dietary octacosanol ameliorates hyperlipemia and diabetes with oxidative stress in KKAy mice with type 2 diabetes.[120]

Albuminuria

It is suggested that AMPK activation could serve as a potential therapeutic strategy to prevent and/or treat the development of chronic kidney disease in patients with established proteinuria.[121]

The reduction of albuminuria during treatment with CPco in nephrotic syndrome was reported in a single clinical assay, [122] indicating the need of more research on the effect of CPco in this aspect.

Fatty Liver Disease

An early clinical assay was conducted in patients with hypercholesterolemia, exhibiting increased serum levels of alanine amino transferase, gamma-glutamil-transpeptidase or alkaline phosphatase. The treatment with CPco, besides acting on serum lipid profile, was capable to significantly decreases the concentration of those serum indicators of hepatic function, suggesting a liver protective capacity.[123]

CPco, prevent the damage induced by carbon tetrachloride in the Sprague-Dawley rat liver. This result was attributed to an attenuation of hepatic reactive oxygen species metabolism by octacosanol, the mayor component of CPco.[124]

A clinical trial demonstrated the reduction of liver echogenicity in non-alcoholic fatty liver disease patients treated with Policosanol.[76]

CONCLUDING REMARKS

The inhibition of TC synthesis by CPco increases LDL receptor activity in the liver and, consequently, the LDL-C up take from the blood. This effect is accompanying by an HDL-C reinforced reverse cholesterol transport. Moreover, Policosanol attenuated the degradation of LDL-C receptor promoted by subtilisin/kexin type 9 levels, increased during statin treatment receptor.[125]

Doses of CPco below 5 mg are not able to inhibit the synthesis of cholesterol. On the other hand, at largest doses of policosanol between 40 - 50 %, do not decrease more than 50 % HMG-Co.A-R expression, but this inhibition level is considered sufficient to obtain protective health benefits, avoiding possible side effect.[126] The effect of CPco on cholesterol synthesis is described by Menéndez as a modulatory effect.[127]

A dose effect (non-published study), shows that dose 5 mg/d (or below) of CPco do not significantly decrease TC serum concentration. Progressive dose increase of CPco over 5 mg shows a dose dependent decreasing curve of TC, LDL-C, and TG, reaching the highest effects at doses between 40 to 50 mg whereas shows an increasing curve in the concentrations of HDL-C in blood serum. Others clinical trials confirm those relations at effective recommended dose (5-20 mg/d.)[73,128,129]

CPco also decrease TC, LDL-C and TG in a time dependent manner, along one-year, and even more, whereas HDL-C concentration increases with time of treatment.[130,131]

AMPK activation by CPco provides a wide range of health benefits beyond lipid controlling effect. Nevertheless, it is not enough, a healthy life style is crucial to obtain more rapid and better results in any MS treatment and CPco treatment is not an exception. CPco could be a whole, efficient, safety and tolerable aid for MS patient's treatment, but accurate researches on the effect of CPco are needed to confirm its security and efficacy in MS patients

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