

Effects of policosanol supplements on serum lipid concentrations: a systematic review

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SUMMARY

Motivation

The leading cause of death for several years has been diseases of the heart and blood vessels. At present, concerns regarding cardiovascular disease motivate several health practitioners to search for a product that has the ability to assist with improvement of lipid profiles with few or no adverse effects and is affordable and safe for use in all population groups. Over the past ten years nutritional supplements and nutraceuticals have become extremely popular amongst the general population. One such product that has been in the limelight is policosanol, a mixture of long-chain aliphatic primary alcohols.

Objectives

The objective of this study was to determine the efficacy of policosanol, a relatively new supplement primarily derived from sugar cane, in the reduction of total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) and increase in high-density lipoprotein cholesterol (HDL-C).

Methods

This study is presented in a systematic review format. Literature from January 1990 to May 2008 regarding the source, metabolism and mechanism of action of policosanol was reviewed and those randomised controlled trials focusing on the effect of policosanol on the lipid profile of humans were extracted onto predefined tables and the absolute data was then evaluated and results, recommendations and conclusions were provided.

Results

A total of 39 trials were identified. The majority of these indicated a beneficial link between the daily intake of policosanol and serum lipid level reduction. However, all of these studies were performed in Havana, Cuba prior to 2004. The initial studies (85%) indicated a mean percentage change of -17.57%, -29.5% and +19% in TC, LDL-C and HDL-C respectively within the experimental group. The dosage administered ranged from 1 mg/day to 80 mg/day, with the bulk between 5 and 20 mg/day, while the duration ranged from 30 days to 24 months. The more recent 15% of the trials were performed independently in various countries. These studies found no favourable effects with the use of policosanol. Reasons suggested to cause such diverse results include differences in composition of policosanol,

concentration of octacosanol, ethnic and environmental influences, however, these have been discarded as inconsistent factors.

Conclusion

Concern is raised regarding the results of the trials performed in Cuba, as these remarkable results have yet to be replicated in other areas of the world by independent research groups using the same or alternative extract of policosanol that was used in Cuba. Therefore, in order to ensure that the benefits of policosanol are in fact true, further studies using the original policosanol are required (although the results of some studies already indicated no difference between the composition and effect of original and alternative sources of policosanol). Future research should include long-term studies using controlled methods incorporating volunteers from countries around the world, focusing on the mechanism of action, rate and amount of absorption and different compositions of policosanol sources. Ideally, an interlaboratory study should be performed by experienced investigators in different international centres, coordinated from a central laboratory, using the original as well as an alternative policosanol in a double blind manner.

Key words

Policosanol; hypercholesterolaemia; octacosanol; cholesterol lowering; systematic review

OPSOMMING

Motivering

Die hooforsaak van dood is al verskeie jare siektes van die hart en bloedvate. Tans motiveer besorgdheid oor kardiovaskulêre siektes gesondheidspraktisyns in die soeke na 'n produk wat oor die vermoë beskik om lipiedprofile te verbeter met min of geen nadelige effekte, bekostigbaar en veilig vir gebruik in alle bevolkingsgroepe. Oor die afgelope tien jaar het voedingsaanplawwings en neutrasedutika uiters populêr geword onder die algemene bevolking. Een so 'n produk wat baie in die kollig is, is polikosanol, 'n mengsel van langketting primêre alifatiese alkohole.

Doelwitte

Die doel van hierdie studie was om die effektiwiteit van polikosanol, 'n relatief nuwe aanplawwing hoofsaaklik van suikerriet afkomstig, in die verlaging van totale cholesterol (TC) en lae-digtheid lipoproteïencholesterol (LDL-C) en verhoging in hoë-digtheid lipoproteïencholesterol (HDL-C) te bepaal.

Metodes

Die studie word in 'n sistematiese oorsigvorm aangebied. Literatuur vanaf Januarie 1990 tot Mei 2008 wat betrekking het op die bron, metabolisme en meganisme van werking van polikosanol is oorsigtelik bestudeer en die ewekansige gekontroleerde studies wat gefokus het op die effek van polikosanol op die lipiedprofiel van mense, is in vooraf gedefinieerde tabelle geëkstraheer, die absolute data is geëvalueer en resultate, aanbevelings en gevolgtrekkings is gemaak.

Resultate

'n Totaal van 39 studies is geïdentifiseer. Die meerderheid van hierdie studies het 'n voordelige verband tussen die daaglikse inname van polikosanol en serumlipiedverlaging getoon. Hierdie studies is egter almal in Havana, Kuba, voor 2004 uitgevoer. Die oorspronklike studies (85%) het 'n gemiddelde persentasie verandering van -17.57%, -29.5% en +19% in TC, LDL-C en HDL-C, respektiewelik in die eksperimentele groep aangedui. Die dosis toegedien het gewissel tussen 1 mg/dag en 80 mg/dag, met die meerderheid tussen 5 en 20 mg/dag terwyl die duur gewissel het van 30 dae tot 24 maande.

Die meer onlangse 15% van die studies is onafhanklik in verskeie lande uitgevoer. Hierdie studies het geen gunstige effek met die gebruik van polikosanol gevind nie. Redes aangevoer vir die oorsake van sulke diverse resultate sluit in verskille in samestelling van polikosanol, konsentrasie oktakosanol, etniese en omgewingsinvloede, maar hierdie is verwerp as inkonsekwente faktore.

Gevolgtrekking

Besorgdheid word uitgespreek oor die resultate van die ondersoeke in Kuba, omdat hierdie merkwaardige resultate tot dusver nie herhaal kon word in ander gebiede in die wêreld deur onafhanklike navorsingsgroepe met dieselfde of alternatiewe polikosanolekstrak as wat in Kuba gebruik is nie. Daarom, ten einde te verseker dat die voordele van polikosanol werklik waar is, is verdere studies met die oorspronklike polikosanol nodig (hoewel die resultate van sommige studies reeds geen verskil tussen die samestelling en effek van die oorspronklike en alternatiewe bronne van polikosanol aangedui het). Toekomstige navorsing behoort langtermyn studies met gekontroleerde metodes en vrywilligers van lande regoor die wêreld in te sluit, en te fokus op die meganisme van werking, snelheid en hoeveelheid geabsorbeer en verskillende samestellings van polikosanolbronne. Die ideaal is 'n interlaboratoriumstudie deur ervare ondersoekers uitgevoer in verskillende sentra, gekoördineer vanuit 'n sentrale laboratorium, met die gebruik van die oorspronklike sowel as 'n alternatiewe polikosanol op 'n dubbelblinde wyse.

Sleutelwoorde

Polikosanol; hipercholesterolemie; oktakosanol; cholesterolverlagend, sistematiese oorsig

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List of abbreviations

A: apo A-I

B: apo B-100

B-48: apo B-48

C: apo C_s

C: Carbon

CE: cholesterol ester

CETP: cholesterol ester transfer protein

CM: chylomicron

CMR: chylomicron remnant

CVA: Carotid vertebral atherosclerosis

CVD: Cardiovascular disease

CHD: Coronary heart disease

d: day

E: apo E

FFA: free fatty acid

GI: Gastro intestinal

GTPases: Guanosine triphosphatase.

H: Hydrogen

HC: Hypercholesterolaemic

HDL: High density lipoprotein

HDL-C: High density lipoprotein cholesterol

HDL:LDL: Ratio of high density lipoprotein to low density lipoprotein cholesterol

HL: hepatic lipase

HMG-CoA: 3-hydroxy-3-methylglutaryl-CoA

HPT: Hypertensive

IDL: Intermediate density lipoprotein

kg: kilogram

LDL: Low density lipoprotein

LDL-C: Low density lipoprotein cholesterol

LPL: lipoprotein lipase

mg: milligram

mg/day: milligram per day

MILD: Normal to mildly elevated cholesterol

NCEP: National Cholesterol Education Program

NIDDM: Non-insulin dependent diabetes mellitus

O: Oxygen

P: Placebo

PC: Policosanol

PMW: Post-menopausal women

TC: Total cholesterol

TG: Triglycerides

TxA₂: Thromboxane A₂

VLDL: Very-low density lipoproteins

α-HDL and preβ-HDL: HDL particles displaying α- and preβ-mobilities

CHAPTER 1
INTRODUCTION

1.1 Background and motivation

Two meta-analysis studies have been performed with a focus on policosanol and other alternative lipid lowering treatment and their effect on serum lipid profile. The first of these studies Chen *et al.* was published in 2005 and aimed at determining the effect of policosanol versus plant sterols and stanols. This study found that policosanol had a much more beneficial effect on LDL level reduction and thus promoted its use. The second study Nies *et al.*, which was performed in 2006 focused on a variety of alternative lipid lowering treatments including omega-3-fatty acids, plant sterols and stanols, flaxseed, red yeast rice, guggulipid, garlic, fiber, almonds and soy. This study concluded that further well-designed research is required with the use of policosanol. Since the completion of these two meta-analysis studies more recent, updated research has been performed and has found some controversy in the literature on the efficacy of policosanol, a mixture of long-chain aliphatic primary alcohols, as a cholesterol-lowering supplement therefore a revised systematic review is required to ensure recommendations are up-to-date. Some studies (Aneiros *et al.*, 1993; Canetti *et al.*, 1995; Castano *et al.*, 1995; Mas *et al.*, 1999; Menendez *et al.*, 2000) indicate a beneficial role in lipid-lowering while others (Lin *et al.*, 2004; Dulin *et al.*, 2006; Greyling *et al.*, 2006) were unable to obtain the same results. The evidence-based approach has recently been implemented as an objective framework in which to gather and review all available evidence in setting nutrition policy and practice, which will ensure that recommendations are based on evidence which has been assessed in an unbiased manner (Margetts *et al.*, 2002).

Egger and Smith (1997) regard a systematic review as "most appropriate for denoting any review of a body of data that uses clearly defined methods and criteria". Systematic reviewing is considered a field of research, although the data are derived from primary studies in the area of interest rather than from direct experimentation. A systematic review can be defined as a review of a clearly formulated question that attempts to minimise bias using systematic and explicit methods to identify, select, critically appraise and summarise relevant research (Needleman, 2002). The steps in conducting a systematic review include definition of a research question, development of study inclusion criteria, identification of studies with a search strategy, data collection and critical appraisal of information, pooling of information systematically in tables with columns constructed for each outcome, summarising of data, drawing conclusions and reporting new findings (Needleman, 2002).

According to Greenhalgh (1997), the advantages of systematic reviews are the following:

- Explicit methods limit bias in identifying and rejecting studies.
- Conclusions are more reliable and accurate because of methods used.

- Unmanageable quantities of research on a topic are found, summarised and appraised.
- Time between research discoveries and implementation of effective diagnostic and therapeutic strategies may be reduced.
- Results of different studies can be compared formally to establish generalisability of findings and consistency of results.
- Reasons for heterogeneity can be identified and new hypotheses generated about particular subgroups.
- Quantitative systematic reviews (meta-analyses) increase the precision of the overall result (Greenhalgh, 1997).

A meta-analysis and systematic review differ in the sense that a systematic review is an overview of primary studies that use explicit and reproducible methods while a meta-analysis is a mathematical synthesis of the results of two or more primary studies that address the same hypothesis in the same way (Greenhalgh, 1997). Studies should be combined in a meta-analysis only if they are sufficiently similar to produce a meaningful result (Feuer & Higgins, 1999).

Preparing a systematic review or meta-analysis is a complex process that comprises many judgements, as well as decisions about the process and the resources needed. As in any scientific endeavour, the methods should be established beforehand (Alderson *et al.*, 2004). Therefore, a well-planned and feasible protocol should be developed in order to assist the reviewer in conducting a review of good quality. As with any research, the first and most important decision in preparing a systematic review is to determine its focus by asking clearly framed questions. The key components of a research question should include the types of subjects/participants, comparisons/interventions, outcomes and study designs (Alderson *et al.*, 2004).

The next step in conducting a systematic review is to gather all the relevant literature using a structured search strategy. Predetermined standardised subject terms [a more complete description for key words, according to Alderson *et al.* (2004)] are useful because they provide a way of retrieving articles that may use different words to describe the same concept and they provide information beyond what is simply contained in the words and title of an article. Using the appropriate standardised subject terms, a simple search strategy can quickly identify articles pertinent to the topic of interest. However, a computer literature search alone will not guarantee an unbiased sample of studies because some smaller journals are not indexed on the major databases. To prevent publication bias and to obtain a suitable sample of studies, the reviewer should use a combination of search strategies (Alderson *et al.*, 2004).

Multiple search strategies may be necessary to locate relevant studies. An electronic database search on databases such as Medline, Web of Science, ScienceDirect, the Cochrane Central Register of Controlled Trials, SciSearch and PubMed is usually the first step. Handsearching involves a manual page-by-page examination of the entire contents of a journal issue to identify all eligible reports of trials, whether they appear in articles, abstracts, news columns, editorials, letters or other text (Durlak & Lipsey, 1991). Reviewers should check the reference lists of articles obtained (including those from previously published systematic reviews/meta-analyses) to identify relevant reports.

Quality assessment of the study is necessary before inclusion in order to reduce bias in the review. Scoring systems have been developed to appraise the quality of studies. Reasons for excluding articles may include inappropriate study designs or methodology (including methods of randomisation, concealment of allocation, blinded assessment to variables), types of subjects, exposures, outcomes, confounding factors or other variables in the particular study (Vorster *et al.*, 2003). Quality assessment might also help to gain insight into potential comparisons and to guide interpretation of findings (Alderson *et al.*, 2004).

For the data collection a well-designed data extraction form is essential. It forms a link between what the primary investigators report and what the reviewers ultimately report. Reviewers should consider which variables to collect before designing a data collection form. These forms should not be over detailed to prevent long and tedious forms to fill in. However, incomplete forms may lead to omission of key data and reviewers may have to re-abstract studies (Alderson *et al.*, 2004). It is not possible to specify all variables that should be coded. The ones usually coded for randomised controlled trials include: general information, participants (sampling random/convenience), exclusion criteria, total number and number in comparison groups, gender, age, weight, interventions (including placebos), dietary information, comparison interventions, wash out period, stabilisation period, assessment of compliance, withdrawals/losses to follow up (reasons/description for drop out), subgroups, statistical methods and key outcomes (effect sizes) (Adapted from Alderson *et al.*, 2003; Durlak & Lipsey, 1991; Vorster *et al.*, 2004).

Accurate coding is extremely important. To reduce errors, each study must be coded independently by at least two reviewers and controlled by a third reviewer if necessary. They need instructions and decision rules on the data collection form, which should have been pilot tested using a representative sample of the studies to be reviewed.

From this discussion it is clear that there is a place and need for well-constructed systematic reviews and meta-analyses in evidence-based nutrition. In recent years, these “tools” have rapidly gained an important place in aiding clinical decision-making in nutrition and an appropriate way in which the controversies regarding the usefulness of policosanols supplements for cholesterol lowering could be studied. This systematic review will uniquely contribute updated and recent scientific research that has not yet been included in a systematic review or meta-analysis focusing on policosanols.

1.2 Aim and objective

The aim of this study was to determine the efficacy of policosanols use in improving the serum lipid profile of diverse population groups. The objective was to establish the effects of policosanols on male and female subjects aged 20-75 years through the evaluation of randomised controlled trials reported in the literature up till May 2008 and thereby synthesising these papers in order to present the evidence and draw firm conclusions for the possible use of this supplement in future.

1.3 Structure of the mini-dissertation

This mini-dissertation is presented in article format of a systematic review. The first chapter is an introduction. The method of reference that was used is according to the requirements of the North-West University.

Chapter Two consists of a literature review that gives an overview of the published, available literature on the topic. The review covers in greater detail the possible mechanism of action of policosanols, composition and chemical characteristics. References are presented in fulfilment of the requirements of the North-West University.

Chapter Three is the systematic review article, focusing on the trials that have been published regarding the use of policosanols in the diet to assist in improving the lipid profile of those subjects who are healthy, hypercholesterolaemic, diabetic, postmenopausal and elderly. This review has been prepared for submission to the European journal of clinical nutrition. The references in this chapter were presented according to the European journal of clinical nutrition requirements.

In Chapter Four, a summary of the results of the study and general discussion are provided, with recommendations that will be beneficial for those subjects that wish to use policosanols in the future, or those in specialised fields e.g. dieticians and general practitioners that may

consider prescribing policosanol to their clients/patients. Recommendations for further research on the topic will also be made. The references in this chapter were also presented according to the North-West University requirements.

1.4 Contributions of authors

The systematic review that is reported in this dissertation was prepared and executed by three researchers and the contribution of each is listed below. A statement from the co-authors has also been included, confirming their responsibility in the study and providing their permission for the inclusion of this article in this mini-dissertation.

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B.Sc. Dietetics

Responsible for literature searches, article collection, data extraction table formation and text drafting.

Prof. C.S. Venter

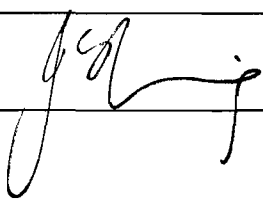
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CHAPTER 2

LITERATURE REVIEW

2.1 Introduction

It is well known and documented around the world that cardiovascular disease (CVD) is one of the leading causes of death and disability in many countries despite the remarkable gains in the treatment thereof (Mahan & Escott-Stump, 2004). Coronary heart disease (CHD) is the most familiar form of CVD and is usually associated with atherosclerosis and hypertension. The major risk factors that are associated with CHD include hypercholesterolaemia, hypertension, diabetes and insulin resistance, obesity, physical inactivity and smoking. The consequences as a result of CVD are usually heart disease (myocardial infarction and cardiac arrest) and stroke (Whitney & Rolfes, 2002). Most CVD deaths are linked to persons of 65 years and older, although at present a large number of deaths have been reported to occur prematurely (Mahan & Escott-Stump, 2004). Risk factor reduction has been shown to reduce CHD events (National Cholesterol Education Program, 2001; Kannel, 2002) and thus it is warranted for persons of all ages. According to statistics released by The Heart and Stroke Foundation SA (HSFSA) and Medical Research Council (MRC) between 1997 and 2004 in S.A. 195 people a day die due to some form of heart and blood vessel disease; about 33 people die per day due to heart attacks, 60 people due to strokes and 37 people per day due to heart failure. It is anticipated that in South Africa premature deaths due to heart and blood vessel diseases of people aged between 35 – 64 years are expected to increase by 41% between 2007 and 2030. The highest rates of cardiovascular disease in South Africa are found in the Indian community, followed by the coloured community. The white and black communities have the lowest and most similar rates, although the white population mainly have patterns of heart attacks, while the black group are more likely to suffer death due to stroke and high blood pressure (Donjeany, 2007).

One of the risk factors that is often influenced by dietary modification is hypercholesterolaemia (Mahan & Escott-Stump, 2004). Cholesterol is present in the daily diets of people around the world; it is commonly absorbed slowly from the gastrointestinal (GI) tract through to the intestinal lymph. It is highly fat-soluble and has very little water-soluble characteristics. The absorption that occurs via the GI tract is known as *exogenous cholesterol*, however, an even larger amount is formed by the cells of the body and is referred to as *endogenous cholesterol*. The majority of the *endogenous cholesterol* is formed in the liver. Other cells in the body have the ability to form at least some cholesterol, which thus explains the fact that many of the membranous structures of the cells are partially composed of this substance. As can be seen in **Figure 2.1** cholesterol is based on a sterol nucleus synthesised by multiple molecules of acetyl-CoA. This basis can be modified by various side chains thus forming cholesterol, cholic acid (the basis of bile acids formed in the liver) and valuable steroid hormones (Guyton & Hall, 2000).

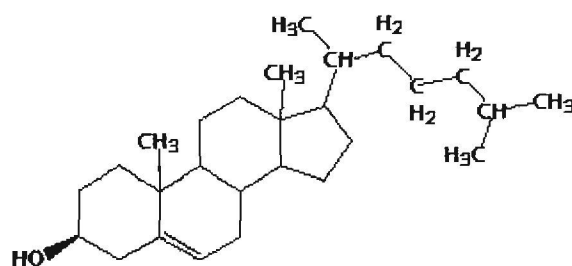


Figure 2.1 The chemical structure of cholesterol (Source: <http://www.cholesterol-and-health.com/Vitamin-D.html>)

The concentration of plasma cholesterol can be influenced by numerous factors, which include the amount of cholesterol ingested each day, a highly saturated fat diet and a lack of insulin or thyroid hormone (Guyton & Hall, 2000). The most imperative factor that is correlated in causing atherosclerosis is a high blood plasma concentration of cholesterol, mostly in the form of low-density lipoproteins (LDL) (Guyton & Hall, 2000). LDL is the principal cholesterol carrier in the blood and thus the correlation of LDL and total cholesterol (TC) level is very strong. After the LDL is formed as a result of the catabolism of very-low density lipoproteins (VLDL), around 60% is taken up by the LDL receptors, which are located on the liver, adrenals and other tissues. The remaining 40% is catabolised via nonreceptor pathways. The amount and activity of these receptors are a direct indication and determinant of the LDL cholesterol (LDL-C) level in the blood. Some LDL can be oxidised and taken up by the endothelial cells and macrophages in the arterial wall leading to the initial stages of atherosclerosis (Mahan & Escott-Stump, 2004) as seen in **Figure 2.2**.

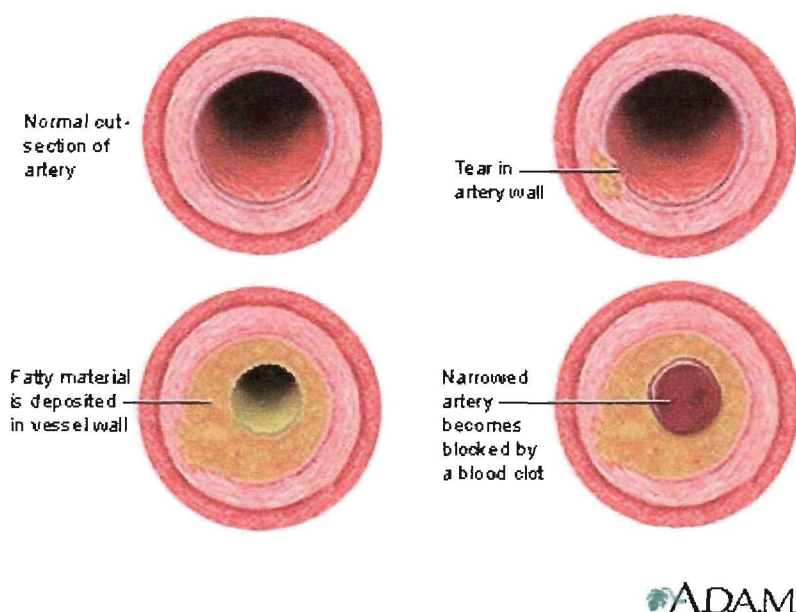


Figure 2.2 The developmental process of atherosclerosis (Source: www.nlm.nih.gov)

The benefits of decreasing the total serum cholesterol and LDL-C concentrations in the prevention of CVD both at the primary as well as the secondary stages has been proven indisputable (Scandinavian Simvastatin Survival Study Group, 1994; Shepherd *et al.*, 1995; Sacks *et al.*, 1996; The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group, 1998; Downs *et al.*, 1998; Heart Protection Study Collaborative Group, 2002; Shepherd *et al.*, 2002). In a recent meta-analysis it was shown that net absolute decreases in the TC and LDL-C of 1 mmol/L were associated with a 16% to 17% reduction in the relative risk of all-cause mortality, and reductions of 24% to 28% for the relative risk of CHD mortality (Gould *et al.*, 2007).

2.2 Existing lipid-lowering management

2.2.1 Therapeutic lifestyle changes

The first step that is taken in reducing the TC and LDL-C is the use of therapeutic lifestyle changes. These include the adherence to the guidelines set out by the National Cholesterol Education Program (NCEP), which was established in 1991. These recommendations were based on the Step 1 cholesterol-lowering diet and were created for children above two years of age as well as adolescents and adults. The recommendations that were agreed upon and voiced were to include a nutritionally adequate varied diet; adequate energy intake to ensure optimum growth and development, and maintenance of appropriate body weight; saturated fat intake of less than 10% of total kilojoules; total fat intake of an average of no more than 30% and dietary cholesterol of less than 300mg/day. Smoking cessation and increased physical activity are also encouraged (Mahan & Escott-Stump, 2004). The adherence to the adjustment of the therapeutic lifestyle allows many individuals, especially those with borderline or mildly elevated LDL-C (3.4 – 4.0 mmol/L) and TC (5.0 – 6.0 mmol/L) levels, to achieve desired ranges of these lipids (Shepherd *et al.*, 1995). However, in many individuals who suffer from mildly elevated TC and more than two of the nonlipid risk factors, or who are in the secondary prevention stage, therapeutic lifestyle changes may not be solely sufficient as more restricted goals are usually recommended for these patients (National Cholesterol Education Program Expert Panel 1988; Gotto *et al.*, 2000). Thus cholesterol-lowering drugs are encouraged in conjunction with the suggested therapeutic lifestyle changes in order to ensure that the recommended lipid levels are reached (Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults, 1993).

2.2.2 Pharmacological management

At present there are various effective and tolerable lipid-lowering treatments available. These include statins, fibrates, anionic exchange resins, niacin and probucol (Cubeddu *et al.*, 2006). Statins, also known as 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, work by inhibiting the synthesis of mevalonate, which is a rate-limiting step in the biosynthesis of cholesterol, thus leading to a reduction in the plasma LDL-C level (Shitara & Sugiyama, 2006) as shown in **Figure 2.3**.

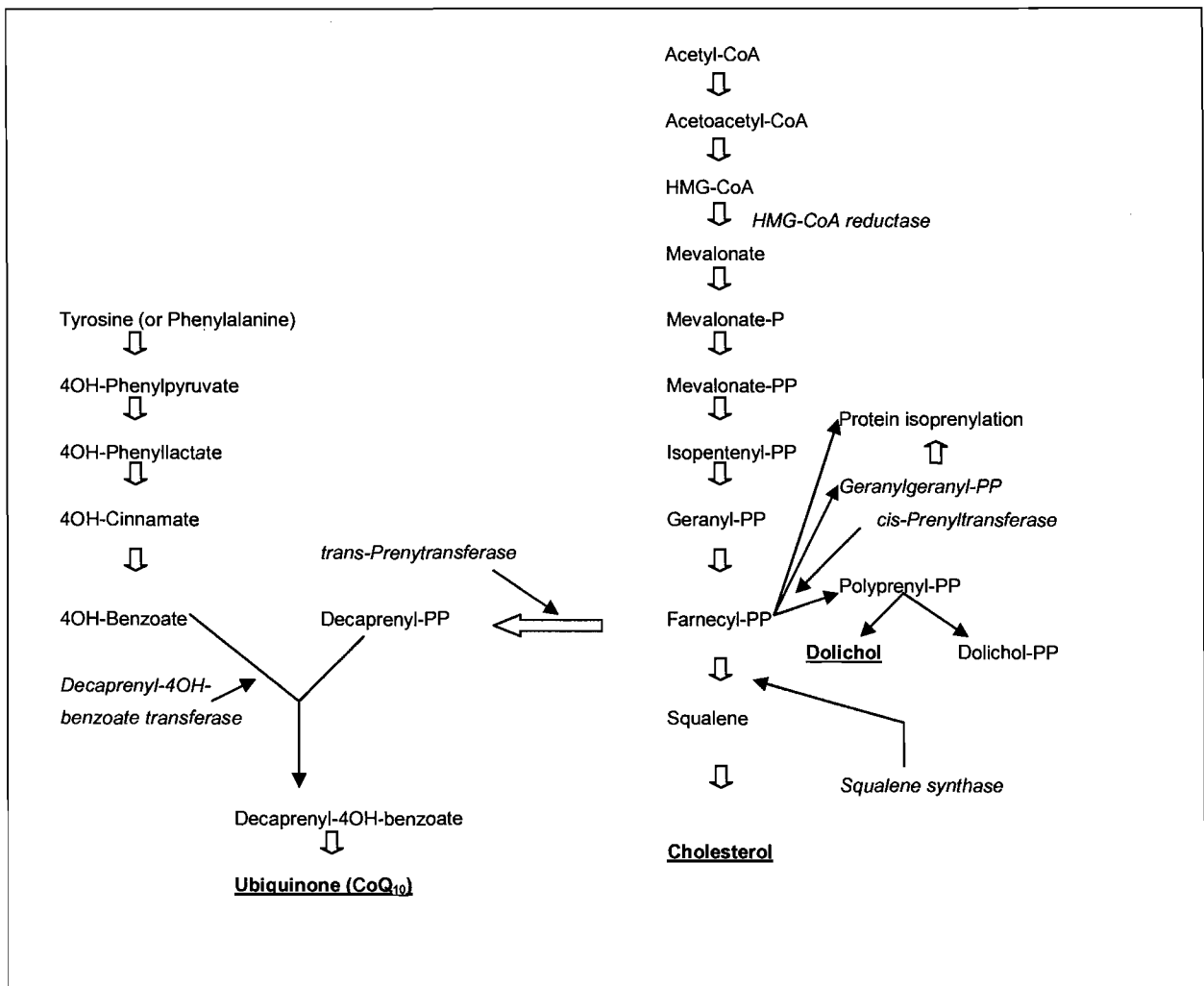


Figure 2.3 The biosynthesis of cholesterol (Brown & Goldstein, 1986)

The figure shows the pathway for the biosynthesis of cholesterol. HMG-CoA reductase-mediated production of mevalonate is a rate-determining step of cholesterol biosynthesis and thus the inhibition of this enzyme results in a decrease in the cholesterol level. A decline in the intracellular cholesterol level results in an upregulation of LDL-receptors by a transcriptional regulation to maintain the intracellular cholesterol by homeostasis (Brown & Goldstein, 1986;

Lennernas & Fager, 1997). However, the cytochrome P450 7A1 (CYP7A1, cholesterol 7 α -hydroxylase), which is specific to the liver, transforms the intracellular cholesterol to bile acids, thus leading to a reduction in the cholesterol in hepatocytes, although it is taken up via upregulated LDL-receptors. Biodegradation of cholesterol in the liver results in a reduction of total cholesterol in the body. In addition, the liver is known to have an important role in the biosynthesis of lipoprotein and catabolism of LDL (Brown & Goldstein, 1986).

There are randomised, controlled trials available that have shown that statins have the ability to lower cholesterol successfully (Scandinavian Simvastatin Survival Study Group, 1994; Shepherd *et al.*, 1995; Sacks *et al.*, 1996; The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group, 1998). However, there are numerous studies reporting a number of adverse effects including myopathy (inflammation or degeneration of the muscles that may cause pain or weakness) or rhabdomyolysis (serious and potentially fatal disease involving the destruction and degeneration of skeletal muscle, that can lead to kidney failure) (Staffa *et al.*, 2002; Thompson *et al.*, 2003).

As patients become wary of these drug treatments, their side effects, costs, as well as the patients' reluctance to be treated with chemically derived drugs, there is a clearer need for naturally derived, safe and as effective methods (Gouni-Berthold & Berthold, 2002). It was calculated in 2002 that a month of statin therapy in the United States would cost about a hundred dollars, excluding the charges for follow-up doctors appointments (McCarty, 2002). Therefore, is it important when considering a new lipid-lowering therapy cost and the balance of safety versus toxicity is essential (Shitara & Sugiyama, 2006).

2.3 Introduction of a potentially new lipid-lowering agent

Over the past ten years nutritional supplements and nutraceuticals (foods or dietary supplements that are believed to provide health benefits) have become extremely popular amongst the general population (Kato *et al.*, 1995; Saint John & McNaughton, 1986). One such product that has been in the limelight is policosanol. This supplement is a mixture of long-chain primary aliphatic alcohols, originally isolated by hydrolytic cleavage and purified from sugar cane wax (*Saccharum officinarum* L) (Janikula, 2002; Varady *et al.*, 2003) by Dalmer Laboratories in Havana, Cuba. It was approved for use as a cholesterol-lowering agent in Cuba in 1991. Presently there are over 40 countries worldwide that granted approval for use or are filing registration for utilisation (Francini-Pesenti *et al.*, 2007). Due to the highly beneficial effects found on the serum lipid levels by numerous well-designed clinical trials (Pons *et al.*, 1994; Anerios *et al.*, 1995; Canetti *et al.*, 1995a; Castano *et al.*, 1995a; Castano *et al.*, 2000), policosanol is being used in combination with dietary therapy to assist in the reduction of

elevated LDL-C as well as total serum cholesterol in patients suffering with type II hypercholesterolaemia (Canetti *et al.*, 1995b; Castano *et al.*, 1999b; Mas *et al.*, 1999; Castano *et al.*, 2000; Castano *et al.*, 2001c; Fernandez *et al.*, 2004) and dyslipidemia secondary to type 2 diabetes mellitus (Crespo *et al.*, 1997; Torres *et al.*, 1995). However, there are a few more recent studies that contradict this suggestion (Lin *et al.*, 2004; Berthold *et al.*, 2006; Dulin *et al.*, 2006; Greyling *et al.*, 2006; Kassis & Jones, 2006) and have found no significant advantage with the use of policosanol.

2.4 Chemical characteristics

Policosanol contains a mixture of eight primary aliphatic alcohols extracted from sugar cane (*Saccharum officinarum* L.). The extracted wax undergoes hydrolytic cleavage and subsequent purification. The resulting chemical formula is $\text{CH}_3 - (\text{CH}_2)_n - \text{CH}_2\text{OH}$ with varying lengths of each chain from between 24 – 34 carbon elements, as noted in **Figure 2.4**. Octacosanol is the predominant component, which is comprised of approximately 60 - 70% of the mixture. Triacontanol (10 - 15%) and hexacosanol (4.5 - 10%) are two of the other central components, while dotriacontanol (3 – 8%), heptacosanol (<5%), tetracosanol (<2%), nonacosanol (<2%) and tetratriacontanol (<2%) are the less major constituents (Laguna *et al.*, 1997; Mas, 2000; Gouni-Berthold & Berthold, 2002).

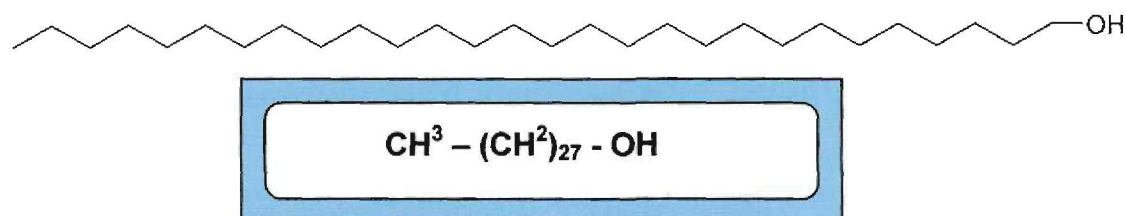


Figure 2.4 The chemical structure of octacosanol (Source Anon, 2004)

2.5 Sources of policosanol

At present, there are a number of dietary supplements available on the market containing policosanol. The bulk of these supplements available in the United States market are derived from beeswax or sugar cane extracts although wheat germ oil is also used as a source of policosanol (Irmak *et al.*, 2006).

2.5.1 Wheat

Policosanol is the section of the wax fraction that precipitates out from the crude oil during cold storage. Wheat straw has significantly higher total policosanol content than the other wheat-

milling fractions (wheat bran, germ, shorts and flour). It is understandable that this would be the case as policosanol is found in fruits, leaves and surfaces of plants and whole seeds (Tulloch & Hoffman, 1973). Policosanol is a component of the protective and waterproofing surface layer acting as the interface between plant tissue and the growth environment (Walton, 1990). Wheat flour is found to have a very low (<1 mg/kg) policosanol content, which can be explained by the association of policosanol with plant surface layers and other lipophilic plant components rather than the inner starchy endosperm. Wheat bran, on the other hand, has a much greater ($p < 0.05$) amount of policosanol than the germ. The possible explanation for this is higher oil content of wheat germ (about 11% w/w) than that of the bran (2-3% w/w). It has been suggested that the oil content may have diluted the policosanol in the germ extract. The highest policosanol composition in crude wheat germ oil solids is tetracosanol (C24) (34%, w/w, of the total policosanol), while the other two components found in large amounts include the hexa- and octacosanol (26% and 22% respectively). The main component of the wheat straw is octacosanol (C28) found in a total of 85% (Irmak *et al.*, 2006).

2.5.2 Sugar cane

Sugar cane is the most commonly used source of policosanol in commercial products. It was established that the sugar cane peel contained the highest amount of total policosanol (about 270 mg/kg), while the policosanol content that was found in sugar cane leaves (181 mg/kg) and wheat straw (164 mg/kg) were of very similar amounts. As with the wheat straw in wheat, the main component in the sugar cane plant was C28 even though the compositions varied considerable (Irmak *et al.*, 2006).

2.5.3 Beeswax

There are a few policosanol products available on the shelves derived from beeswax. The total content of policosanol in brown beeswax amounts to about 20 and 45 times higher than those of wheat germ oil and sugar cane, respectively (Irmak *et al.*, 2006). On the other hand, yellow beeswax contained a significantly ($p < 0.05$) lower policosanol content than the brown beeswax. The lower amount of policosanol in the yellow beeswax might have been due to several limitations involved in the complex formation of the hives and processing of the beeswax, including the lack of data available from the beeswax suppliers. The main component (>40 % of total policosanol) in both beeswax samples was found to be triacontanol (Irmak *et al.*, 2006). This was reiterated by the reports by Jimenez *et al.* (2003).

It is important to note that policosanol extracted from rice bran wax is also a potential candidate for use in foods, medicine and cosmetics (Chen *et al.*, 2007). Rice bran wax is a component in

rice bran oil extracts. Its composition is that of 46 up to 60 carbon atoms (C) forming esters (Tulloch, 1976). It has been reported to be one of the best sources containing octacosanol and has been suggested to play a role in health, such as blood lipid or cholesterol lowering and improving athletic performance without adverse side effects (Shimura *et al.*, 1987; Kato *et al.*, 1995; Rapport, 2000).

It seems as if beeswax has the highest concentration of policosanol. Wheat straw contains more policosanol than the wheat milling fraction and the total amount of policosanol in sugar cane peel is equal to that in the wheat straw (Irmak *et al.*, 2006).

2.6 Metabolism and mechanism of action

2.6.1 Metabolism of policosanol

There have been numerous reports of the potential benefits of octacosanol on the cardiovascular system (Varady *et al.*, 2003; Kabir & Kimura, 1993). However, there has been very little data published on the exact mechanism of their actions (Xu *et al.*, 2007). However, Kabir and Kimura (1993, 1994, and 1995) have investigated systemic distribution and metabolism of radiolabeled octacosanol in rats after oral dosing. They found that *in vivo* there is a conversion of octacosanol to its corresponding acid. They also suggested that once octacosanol is in the liver it is degraded to fatty acids (FA) and then integrated into triglycerides, sterols and phospholipids. A considerable level of radioactivity found in the muscle suggested that the octacosanol or a metabolic product (possibly FA) were eventually transported out of the liver to be utilised for energy via β -oxidation. A study by Menendez and co-workers in 2005 focused on the *in vitro* and *in vivo* metabolism of octacosanol. They demonstrated that octacosanoic acid is formed after the incubation of fibroblasts with ^3H -octacosanol. This was performed to determine if such acid was actually a metabolite formed from octacosanol *in vitro*. They found that the ^3H -octacosanol was consumed, used and transformed into metabolites. The results *in vivo* showed that after oral doses with policosanol to rats, octacosanoic acid was present in both the liver and plasma, but to a higher degree in the liver. This group used GC-MS to determine the plasma levels of octacosanol from an oral dose of 10mg/kg policosanol in monkeys. Results indicated plasma levels of over 400 ng/ml at 1 hour after ingestion. They also tested the plasma levels of rats that were administered 60mg/kg of policosanol and found maximum concentrations of 30.4 ng/ml in the plasma and 68.4 ng/ml in the tissues. When comparing the dosage of policosanol given, the amount absorbed is diminutive. It was thus suggested by this group that octacosanoic acid is formed within 15 min of administration of octacosanol, indicating a quick uptake and transformation in the rat liver while ^3H -octacosanoic acid is generated in cultured cells less than 30 minutes after the addition of labeled octacosanol

(Menendez *et al.*, 2005). Octacosanol has been suggested to have the ability to reduce lipid levels, inhibit platelet aggregation, prevent endothelial damage and reduce the development of foam cells (Varady *et al.*, 2003). It has also been proposed that methods by which octacosanol may have an effect includes the down-regulation of the cellular expression of HMG-CoA reductase activity (much the same as statins) (McCarthy, 2002) or an increase in lipid catabolism and, therefore, a reduction in plasma TC levels (Shimura *et al.*, 1987). Increasing the breakdown of LDL has also been put forward (Varady *et al.*, 2003).

2.6.2 Down-regulation of HMG-CoA reductase cellular expression and increased lipid catabolism and breakdown of LDL cholesterol

The link between LDL-C reduction and the prevention of coronary disease is well recognized (Scandinavian Simvastatin Survival Study Group, 1994; Shepherd *et al.*, 1995; Sacks *et al.*, 1996). Agents that have the ability to reduce this marker by inhibiting HMG-CoA reductase are associated with numerous vascular protective effects independent of cholesterol modulation (Gaw, 1996; Vaughan *et al.*, 1996; Bellosta *et al.*, 1998; Endres & Laufs, 1998; Jarvisalo, 1999; Sotiriou & Cheng, 2000; Laufs & Liao, 2000a). These effects are partly the result of a down-regulation of isoprenylation reactions, which allow a reduction in the membrane association and, therefore, suppress the activation of GTPases of the Rho family (Van Aelst & D'Souza-Schorey, 1997) that influences the expression of proteins that are of functional importance in the vascular wall and platelets (Laufs & Liao, 2000a; Laufs & Liao, 2000b). It has been proposed that policosanols does not directly inhibit HMG-CoA reductase but rather decreases the expression in fibroblasts in a dose-dependent manner. *In vivo* studies in rats and rabbits have suggested that policosanols decreases hepatic cholesterol synthesis and thus increases hepatic expression of LDL receptors (Menendez *et al.*, 1996; Menendez *et al.*, 1997). The obstruction that occurs is at a point proximal to mevalonic acid (the product of HMG-CoA reductase) and, therefore, does not inhibit the liver's ability to convert exogenous mevalonic acid to cholesterol (Menendez *et al.*, 2001). Policosanols was also found not to decrease HMG-CoA expression by more than 50% thus indicating safety in animal toxicity (Parker *et al.*, 1993; Elson *et al.*, 1999). In a study by Menendez *et al.* (2001) on the policosanols modulatory effect of HMG-CoA reductase activity in cultured fibroblasts, it was proposed that the inhibitory effect of policosanols on cholesterol biosynthesis, especially when cultured fibroblasts were exposed to a lipid-free medium, could be explained by a depression of *de novo* synthesis of HMG-CoA reductase and/or by stimulation of its degradation. Therefore, this reiterates the hypothesis that policosanols may inhibit cholesterol biosynthesis by down-regulating the cellular expression of HMG-CoA reductase (Varady *et al.*, 2003). However, it has been important to consider the fact that the absorption of policosanols in the small intestine is low (Hargrove *et al.*, 2004), thus breaching a gap for doubt on this proposed mechanism. A recent study by Wang *et al.* (2003) on hamsters

also casts doubt on this proposed mechanism, as they did not support the initial animal trials indicating the possibility of these mechanism.

2.7 Effects of policosanol on cholesterol and lipoprotein metabolism

2.7.1 Introduction

Cholesterol is an important constituent in the cell membranes and the body but high levels lead to hypercholesterolaemia resulting in arteriosclerosis and coronary heart disease (Mahan & Escott-Stump, 2004). Cholesterol is transported throughout the body and removed from the bloodstream by five main lipoprotein transporters, namely, high-density lipoprotein (HDL), low-density lipoproteins (LDL), intermediate-density lipoproteins (IDL), very-low density lipoproteins (VLDL) and chylomicrons. HDL is the component that transports cholesterol from the peripheral tissues to the liver and plays an essential role in the maintenance of cholesterol homeostasis in the body (Mahan & Escott-Stump, 2004), thus these levels are encouraged to be high. LDL is the main lipoprotein that is responsible for the transportation of the cholesterol and assists in the incorporation of cholesterol into the cell membranes. The pathway of metabolism of LDL-C is eluded in **Figure 2.5**.

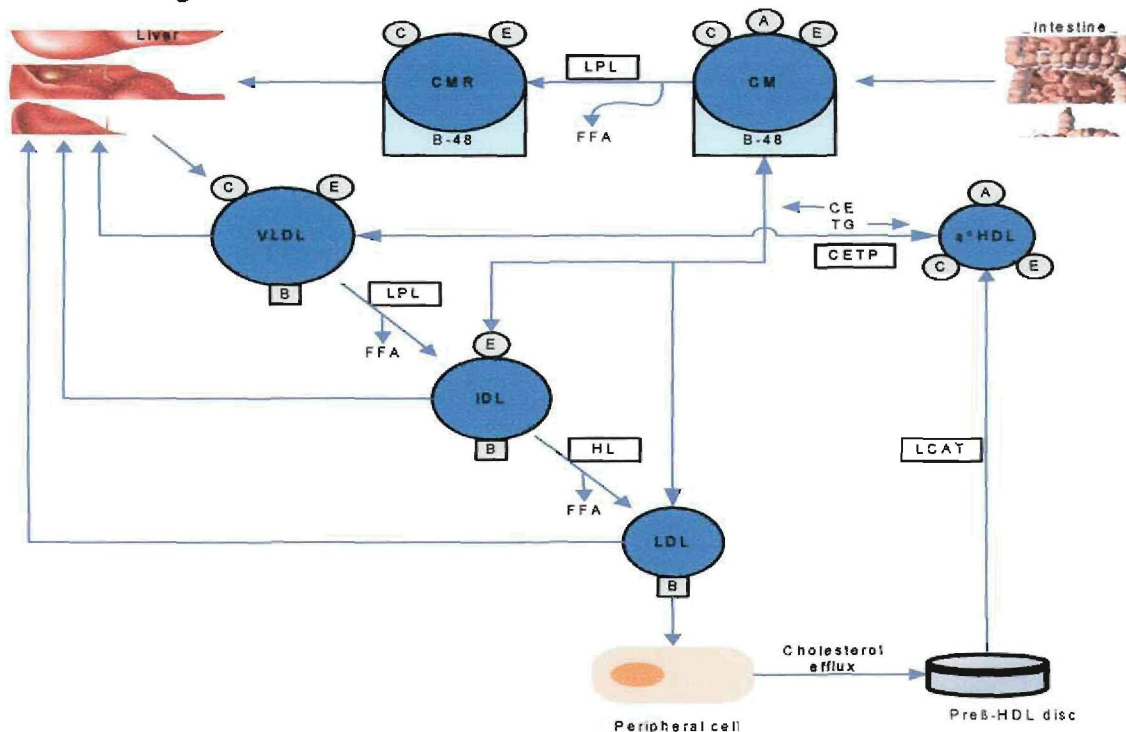


Figure 2.5 The metabolism of lipoprotein in the human body (Source: ethesis.helsinki.fi/julkaisut/l/lindbohm/review.html)

(A, apo A-I; B, apo B-100; B-48, apo B-48; C, apo C-3; CE, cholesterol ester; CETP, cholesterol ester transfer protein; CM, chylomicron; CMR, chylomicron remnant; E, apo E; HL, hepatic lipase; LPL, lipoprotein lipase; TG, triglycerides; α-HDL and preβ-HDL, HDL particles displaying α- and preβ-mobilities; VLDL, very-low density lipoprotein; HDL, high density lipoprotein; FFA, free fatty acids; IDL, intermediate density lipoprotein; LCAT, lecithin:cholesterol acyltransferase)

LDL receptors on cells take up the LDL via a mechanism known as endocytosis in order to perform a process known as steroid biosynthesis. There are, however, receptors that bind to the LDL and remove it from the blood. The more of these receptors available results in lower cholesterol. Increased LDL can result in a deficiency in the binding mechanisms; this is known as type II hypercholesterolemia. This hypercholesterolaemia can be genetic or may be the result of a combination of genetics, diet and lifestyle. Most treatment that is available for hypercholesterolaemia is aimed at increasing the HDL available and decreasing the total and LDL cholesterol present (Castano *et al.*, 2000; Craig & Sitzel, 1994).

The possible ability that policosanols may have on lowering of lipids has been recorded in several clinical trials in animal and human models in different population groups (Pons *et al.*, 1992; Torres *et al.*, 1995; Castano *et al.*, 1999b; Mas *et al.*, 1999; Castano *et al.*, 2000; Mirkin *et al.*, 2001; Castano *et al.*, 2002b) including healthy volunteers, postmenopausal women, patients diagnosed with mild hyperlipidaemia and those with type II hypercholesterolaemia with or without diabetes mellitus (Mesa *et al.*, 1994; Castano *et al.*, 1995b; Torres *et al.*, 1995; Crespo *et al.*, 1997; Menendez *et al.*, 1997; Mirkin *et al.*, 2001; Arruzazabala *et al.*, 2002). Of these studies the largest effect is found on LDL-C, with the LDL end points resulting in a decrease of 19 to 31% (Gouni-Berthold & Berthold, 2002; Janikula, 2002). However, there are more recent studies that have found no benefit with the use of policosanols (Lin *et al.*, 2004; Berthold *et al.*, 2006; Cubeddo *et al.*, 2006; Greyling *et al.*, 2006; Dulin *et al.*, 2006; Kassis & Jones, 2006; Francini-Pesenti *et al.*, 2007).

2.7.2 Animal trials examining the efficacy of policosanols as lipid-lowering agents

Policosanols has previously been shown to assist in lipid lowering, reduction of lipofundin-induced atherosclerotic lesions (Noa *et al.*, 1995), foam cell formation (Noa *et al.*, 1995) and smooth muscle cell proliferation (Rodriguez-Echenique *et al.*, 1994; Noa *et al.*, 1996) and to be non-toxic in a number of animals including rabbits and other rodents (Aleman, 1994; Rodriguez *et al.*, 1994), beagle dogs (Mesa *et al.*, 1994) and monkeys (Rodriguez-Echenique *et al.*, 1994). In rats and rabbits it decreased the development of atherosclerotic lesions, including foam cell formation (Noa *et al.*, 1995; Noa *et al.*, 1996) and neointimal formation (smooth muscle cell proliferation) (Noa *et al.*, 1998).

However, it is essential to note that recent animal studies did not confirm the cholesterol-lowering properties reported in original trials. Kassis *et al.* (2007) compared the cholesterol-lowering effect of the Cuban (Dalmar) sugar cane policosanols with an alternative mixture of similar policosanols composition in hamsters and reported that neither of the two policosanols treatments had any significant effect on plasma lipids. Another recent study performed by

Dullen and co-workers (2008) on heterozygous LDL receptor deficient mice found that individual policosanols as well as the natural policosanols mixture showed no signs of any potential for reducing coronary heart disease as a result of the effects on serum LDL concentrations (Dullens *et al.*, 2008). Furthermore, Marinangeli *et al.* (2007) also found that neither the original (Cuban) policosanols nor the alternative sources of policosanols were detectable in the small intestine, liver, adipose tissue or plasma in hamsters fed these supplements and no changes in serum lipid levels were noted. It is of interest that the absorption of nutrients with long-chain carbon backbones like that of fatty acids and a high degree of saturation is normally low (Jones *et al.*, 1985; Sallee & Dietschy, 1973; Bernard & Carlier, 1991). In the study by Menendez *et al.* (2005) they found the free octacosanol and octacosanoic acid levels in the liver after a single dose of octacosanol (60 mg/kg) to rats. The peak octacosanoic acid occurred at 30 minutes with a concentration of 300 ng/g tissue. It then dropped to 125 ng/g at 60 minutes and slightly above 100 ng/g at 90 minutes. The octacosanol hovered between the 25 and 50 ng/g tissue marker. In comparison the plasma concentrations of octacosanol peaked at 20 minutes at a value of 30 ng/ml and slowly lowered to 20 ng/ml and 15 ng/ml at 60 and 90 minutes respectively. Octacosanoic acid only peaked after 90 minutes reaching just below 20 ng/ml. The authors speculated that these findings indicated that octacosanol peaks quicker in the plasma while octacosanoic acid has a higher and quicker pinnacle in the liver.

In order for further validation regarding the effects of policosanols, human trials are, however, also necessary.

2.7.3 Human clinical trials examining lipid-lowering potential of policosanols

In the literature survey a total of 39 studies were identified, mostly composed of randomised, controlled, blinded trials, 33 of which have shown that there is a possibility that policosanols may play a beneficial and substantial role in the lowering of serum lipid values and improving the HDL-C value in the treatment of hypercholesterolaemia, two of which were open-labelled, uncontrolled trials. The vast majority of these impressive results were performed in Cuba, conducted by the same research group. Six of the studies aimed at determining the possible benefits of policosanols did not find affirmative results. The first of these was performed in Germany on 143 hypercholesterolaemic subjects using Cuban sugar cane policosanols (Berthold *et al.*, 2006). The second was a study performed in South Africa on 19 patients with hypercholesterolaemia and 16 with heterozygous familial hypercholesterolaemia using sugar cane policosanols Lesstanol Octa-60 provided by Garuda International Inc, Lemon Cove, California, USA (Greyling *et al.*, 2006). A study performed in the Netherlands on 58 subjects with normal to mild hypercholesterolaemia using sugar cane policosanols also found no significant change in lipid levels (Lin *et al.*, 2004). A further two studies were performed in

Charlotte, NC (Dulin *et al.*, 2006) and Canada (Kassis & Jones, 2007), both of which used sugar cane policosanol. The Kassis and Jones (2007) group used policosanol in the form of margarine instead of tablet form. All these indicated a lack of significant effect. The last study was performed in Italy by Francini-Pesenti *et al.* (2007), who administered Cuban sugar cane policosanol (Dalmar Laboratories, Havana, Cuba) at a dose of 20 mg/day for 8 weeks. They also reported a lack of improvement in the lipid levels of the subjects with hypercholesterolaemia. The results of these trials performed are shown in **Tables 2.1, 2.2 and 2.3** respectively.

The trials included studies performed on hypercholesterolaemic patients (**Table 2.1**), volunteers with normal to mild cholesterol levels (**Table 2.2**) and patients with diabetes mellitus (**Table 2.3**). The dosage of policosanol that has been administered amongst human studies ranged between 1 and 40 mg/day, predominantly 5 to 10 mg/day, over a period ranging from 28 days through to 24 months. The same research group performed the initial studies all performed prior to 2004 in Havana, Cuba. These early trials all indicated a very beneficial role in the use of policosanol in the daily intake of patients diagnosed with hypercholesterolaemia. The percentage change ranges of the TC, LDL-C, HDL-C, TG and the ratio of HDL: LDL in these studies were -30% to +10.5%; -44.8% to 3.01%; -5.93% to +68.5%; -36.5% to +17.5% and -62.7% to +17% respectively.

Figure 2.6 schematically presents the percentage change in LDL-C and HDL-C that was reported between the experimental and control groups in the trials performed on hypercholesterolaemic, mild to normocholesterolaemic, post-menopausal and diabetic subjects. Four trials were, however, excluded from the data integrated in the figure due to numerous reasons. Pons *et al.* (1993) was excluded, as this trial studied the effects that policosanol had on TC and no other lipid markers, Reiner *et al.* (2005) employed a cross-over study design, the results of which only indicated the experimental group. Castano *et al.* (1998) and Castano *et al.* (1999) both used an open-labeled study design and did not have control groups, only experimental groups to be studied. The study performed by Batista and co-workers in 1996b reported the effects found on the LDL-C but not that of the HDL-C.

It was noted throughout the review that the studies conducted have all been considerably varied. The mean reduction of LDL-C amongst the Cuban studies was 22.5%, while the mean increase in HDL-C was 14.27%. The mean dose that was issued to the subjects to be taken daily was 12 mg/day, with a range of between 1 to 80 mg/day.

Table 2.1 The effects of policosanol on hypercholesterolaemic patients

Reference	Study population	Study design	Policosanol duration	Dosage	Physiological effects	p-value**
Pons <i>et al.</i> , 1992	29 placebo, 27 policosanol primary type II hypercholesterolaemic volunteers	Parallel, randomised, double-blind, placebo-controlled	6 weeks dietary stabilisation. Studied for 8 weeks	5mg/d	TC - 13.1% LDL-C - 17.7% HDL-C - 3.3%	p< 0.0001 p< 0.0001 NS
Aneiros <i>et al.</i> , 1993	17 placebo, 16 policosanol primary hypercholesterolaemic volunteers	Parallel, randomised, double-blind, placebo-controlled	4 weeks dietary stabilisation. Studied for 12 weeks	2 * 5 mg	TC - 16.6% LDL-C - 21.2% HDL-C + 2.9%	p< 0.0001 p< 0.001 NS
				20 mg/d	TC - 20.9% LDL-C - 30% HDL-C + 7.7%	NS p< 0.001 NS
				1mg/d	TC - 16.8%	p< 0.05
Pons <i>et al.</i> , 1993	8 placebo, 12 policosanol (1 mg/d), 6 policosanol (10 mg/d) primary hypercholesterolaemic volunteers	Parallel, randomised, single-blind, placebo-controlled	4 weeks dietary stabilisation. Studied for 24 weeks	10 mg/d	TC - 21.8%	p< 0.01
Pons <i>et al.</i> , 1994a	31 placebo, 28 policosanol type II hypercholesterolaemic volunteers	Parallel, randomised, double-blind, placebo-controlled	12 weeks dietary stabilisation. Studied for 12 months	5 mg/d	TC - 16.4% LDL-C - 24.6% HDL-C + 2.2%	p< 0.0001 p< 0.0001 NS
Pons <i>et al.</i> , 1994b	10 placebo, 12 policosanol hypercholesterolaemic volunteers with high risk cardiovascular disease	Parallel, randomised, double-blind, placebo-controlled	12 weeks dietary stabilisation. Studied for 24 weeks	5mg/d initially, increased to 10mg/d, then 20 mg/d	TC - 23.5% LDL-C - 32.4% HDL-C + 5.9%	p< 0.01 p< 0.01 NS
Aneiros <i>et al.</i> , 1995	23 placebo, 22 policosanol type II hypercholesterolaemic volunteers	Parallel, randomised, double-blind, placebo-controlled	5 weeks dietary stabilisation. Studied for 6 weeks	2 * 5 mg	TC - 16.2% LDL-C - 21.5% HDL-C + 14%	p< 0.0001 p< 0.0001 NS
Batista <i>et al.</i> , 1995	11 placebo, 11 policosanol type II hypercholesterolaemic volunteers with mild carotid-vertebral atherosclerosis	Pilot study, parallel, randomised, double-blind, placebo-controlled	Studied for 12 months	2 * 5mg	TC - 15.8% LDL-C - 17.3% HDL-C + 6.2%	NS NS NS
Canetti <i>et al.</i> , 1995a	50 placebo, 47 policosanol type II hypercholesterolaemic volunteers	Parallel, randomised, double-blind, placebo-controlled	12 weeks dietary stabilisation. Studied for 12 months	2 * 5 mg	TC - 15.9 LDL-C - 26.8% HDL-C + 16%	p< 0.0001 p< 0.0001 p < 0.001
Canetti <i>et al.</i> , 1995b	37 placebo, 32 policosanol type II hypercholesterolaemic volunteers	Parallel, randomised, double-blind, placebo-controlled	12 weeks dietary stabilisation. Studied for 24 months	2 * 5 mg	TC - 18.3% LDL-C - 24.2% HDL-C + 5.4%	p< 0.0001 NS NS
Castano <i>et al.</i> , 1995b	38 placebo, 36 policosanol type II hypercholesterolaemic volunteers	Parallel, randomised, double-blind, placebo-controlled	12 weeks dietary stabilisation. Studied for 12 months	2 * 5 mg	TC - 17.2% LDL-C - 26.4% HDL-C + 13.6%	p< 0.00001 p< 0.00001 p< 0.01
Castano <i>et al.</i> , 1995a	34 placebo, 28 policosanol elderly type II hypercholesterolaemic volunteers	Parallel, randomised, double-blind, placebo-controlled	12 weeks dietary stabilisation. Studied for 12 months	10mg/d	TC - 16.3% LDL-C - 24% HDL-C + 6.3%	p< 0.00001 p< 0.00001 NS

Reference	Study population	Study design	Policosanol duration	Dosage	Physiological effects	p-value**
Batista <i>et al.</i> , 1996a	14 placebo, 12 policosanol, 15 policosanol and aspirin ischaemic volunteers	Parallel, randomised, double-blind, placebo-controlled	4 weeks dietary stabilisation. Studied for 20 months	2 * 5 mg	TC - 10.5% LDL-C - 10.9% HDL-C + 2.8%	p< 0.01 NS NS
				2 * 5 mg plus 125mg aspirin	TC - 8.8% LDL-C - 12.6% HDL-C + 2.9%	NS p< 0.05 NS
Batista <i>et al.</i> , 1996b	11 placebo, 12 policosanol type II hyperlipidaemic and borderline hypercholesterolaemic volunteers	Parallel, randomised, single-blind, placebo-controlled	Studied for 14 months.	2 * 1mg/d	TC - 14.9% LDL-C - 15.7%	p< 0.001 p< 0.05
Castano <i>et al.</i> , 1996	28 placebo, 30 policosanol type II hypercholesterolaemic volunteers	Parallel, randomised, double-blind, placebo-controlled	12 weeks dietary stabilisation. Studied for 12 months	10mg/day	TC - 13% LDL-C - 19.1% HDL-C + 17.1%	p< 0.00001 p< 0.00001 p< 0.01
Castano <i>et al.</i> , 1997	20 placebo, 20 policosanol (2*5 mg), 20 policosanol (1*10 mg) type II hypercholesterolaemic volunteers	Parallel, randomised, double-blind, placebo-controlled	4 weeks dietary stabilisation. Studied for 10 weeks	2 * 5 mg	TC - 14.1% LDL-C - 21.1% HDL-C + 17.9%	p< 0.0001 p< 0.0001 p< 0.01
				1 * 10 mg	TC - 14.6% LDL-C - 23.2% HDL-C + 28.9 %	p< 0.0001 p< 0.00001 p< 0.01
Castano <i>et al.</i> , 1998	54 policosanol type II hypercholesterolaemic volunteers	Open-labelled, uncontrolled	5 weeks dietary stabilisation. Studied for 8 weeks	20mg/d	TC - 16.9% LDL-C - 22.6% HDL-C + 20 %	p< 0.00001 p< 0.00001 p< 0.01
Castano <i>et al.</i> , 1999c	68 policosanol type II hypercholesterolaemic volunteers	Open-labelled, uncontrolled	5 weeks dietary stabilisation. Studied for 12 months	20 mg/d	TC - 30 % LDL-C - 44.8% HDL-C + 68.5%	p< 0.00001 p< 0.00001 p< 0.00001
Mas <i>et al.</i> , 1999	218 placebo, 219 policosanol type II hypercholesterolaemic volunteers with additional coronary risk factors	Parallel, randomised, double-blind, placebo-controlled	5 weeks dietary stabilisation. Studied for 24 weeks	5mg/day initially	TC - 13% LDL-C - 18.3 HDL-C + 15.5%	p< 0.001 p< 0.001 p< 0.001
				10mg/day after 12 wks	TC - 17.4% LDL-C - 25.6% HDL-C + 28.4%	p< 0.001 p< 0.001 p< 0.001
Castano <i>et al.</i> , 2000	122 placebo, 122 policosanol postmenopausal type II hypercholesterolaemic volunteers	Parallel, randomised, double-blind, placebo-controlled	6 weeks dietary stabilisation. Studied for 24 weeks	5mg/day initially	TC - 12.6% LDL-C - 17.7% HDL-C + 16.5%	p< 0.0001 p< 0.0001 p< 0.05
				10mg/day after 12 wks	TC - 16.8% LDL-C - 25.4% HDL-C + 29.3%	p< 0.0001 p< 0.0001 p< 0.0001

Reference	Study population	Study design	Policosanol duration	Dosage	Physiological effects	p-value**
Menendez <i>et al.</i> , 2000a	10 placebo, 10 policosanol type II hypercholesterolaemic volunteers with high coronary risk	Parallel, randomised, double-blind, placebo-controlled	6 weeks dietary stabilisation. Studied for 12 weeks	5mg/ day	TC - 15.7% LDL-C - 19.6% HDL-C + 5.4%	p< 0.05 p< 0.05 p< 0.05
Castano <i>et al.</i> , 2001a	30 placebo, 29 policosanol (20 mg), 30 policosanol (40 mg) primary type II hypercholesterolaemia	Parallel, randomised, double-blind, placebo-controlled	6 weeks dietary stabilisation. Studied for 24 weeks	20 mg/d	TC - 15.6% LDL-C - 27.4% HDL-C + 17.6%	p< 0.00001 p< 0.05 p< 0.001
				40 mg/d	TC - 17.3% LDL-C - 28.15% HDL-C + 17%	p< 0.00001 p< 0.00001 p< 0.001
Castano <i>et al.</i> , 2001b	21 placebo, 20 policosanol (10 mg), 21 policosanol (20 mg) type II hypercholesterolaemic volunteers	Parallel, randomised, double-blind, placebo-controlled	4 weeks dietary stabilisation. Studied for 8 weeks	2 * 10 mg	TC - 16% LDL-C - 35.9% HDL-C + 38%	p< 0.001 p< 0.001 p< 0.001
				1 * 20 mg	TC - 20% LDL-C - 37.8% HDL-C + 39.4%	p< 0.001 p< 0.001 p< 0.001
Castano <i>et al.</i> , 2001c	89 placebo, 90 policosanol elderly, type II hypercholesterolaemic volunteers	Parallel, randomised, double-blind, placebo-controlled	6 weeks dietary stabilisation. Studied for 24 weeks	5mg/d	TC - 12.8 % LDL-C - 16.9% HDL-C + 14.6%	p< 0.001 p< 0.001 p< 0.01
				10mg/d	TC - 16.2% LDL-C - 24.4% HDL-C + 29.1%	p< 0.001 p< 0.001 p< 0.001
Mas <i>et al.</i> , 2001	140 placebo, 140 policosanol elderly hypercholesterolaemics with CHD	Parallel, randomised, double-blind, placebo-controlled	6 weeks dietary stabilisation. Studied for 12 months	5 mg/d	TC - 15.9% LDL-C - 21.3% HDL-C + 18.2%	p< 0.00001 p< 0.00001 p< 0.001
Mirkin <i>et al.</i> , 2001	28 placebo, 28 policosanol postmenopausal hypercholesterolaemic volunteers	Parallel, randomised, double-blind, placebo-controlled	6 weeks dietary stabilisation. Studied for 16 weeks	5mg/day initially	TC - 12.9% LDL-C - 17.3% HDL-C + 3.6%	p< 0.0001 p< 0.0001 NS
				10mg/day after 12 wks	TC - 19.5% LDL-C - 26.7% HDL-C + 7.4%	p< 0.001 p< 0.0001 NS
Castano <i>et al.</i> , 2002b	293 placebo and 296 policosanol type II hypercholesterolaemic and hypertensive volunteers	Parallel, randomised, double-blind, placebo-controlled	6 weeks dietary stabilisation. Studied for 12 months	5 - 10 mg/d	TC - 15.4% LDL-C - 20.5% HDL-C + 12.7%	p< 0.00001 p< 0.00001 p< 0.00001
Reiner <i>et al.</i> , 2005	70 type II hypercholesterolaemic volunteers	Cross-over, randomised, double-blind, placebo-controlled	8 weeks dietary stabilisation. Studied for 16 weeks	10 mg/d	TC - 5.2% LDL-C - 2.5% HDL-C - 1.5%	p< 0.07 NS NS

Reference	Study population	Study design	Policosanol duration	Dosage	Physiological effects	p-value**
Berthold <i>et al.</i> , 2006	29 placebo, 114 policosanol hypercholesterolaemic and hyperlipidaemic volunteers	Parallel, randomised, double-blind, placebo-controlled	6 weeks dietary stabilisation. Studied for 12 weeks	10 mg/d	TC - 5.7% LDL-C - 8% HDL-C + 2.3%	NS NS NS
				20 mg/d	TC - 3.5% LDL-C - 4.3% HDL-C - 0.7%	NS NS NS
				40 mg/d	TC - 2.5% LDL-C - 2.8% HDL-C + 3.9%	NS NS NS
				80 mg/d	TC - 3.4% LDL-C - 8.3% HDL-C + 7.8%	NS NS NS
Greyling <i>et al.</i> , 2006	19 hypercholesterolaemic and 16 familial hypercholesterolaemic volunteers	Cross-over, randomised, double-blind, placebo-controlled	4 weeks washout. Studied for 12 weeks	20 mg/d - Familial hypercholesterolaemic	TC + 0.98% LDL-C + 3.0% HDL-C + 2.50%	NS NS NS
				20 mg/d - Hypercholesterolaemic	TC - 6.1% LDL-C - 8.6% HDL-C - 5.5%	p< 0.03 p<0.009 NS
Francini-Pesenti <i>et al.</i> , 2007	32 placebo, 31 policosanol hypercholesterolaemic volunteers	Parallel, double-blind randomised, placebo-controlled	Studied for 8 weeks	2*10 mg	TC - 1% LDL-C - 0.4% HDL-C + 2.6%	NS NS NS

Physiological change: the difference in percentage change between experimental groups

-: net effect was a decrease

CHD: Coronary heart disease

TC: Total cholesterol

HDL-C: High density lipoprotein cholesterol

NS: Non-significant

+: net effect was an increase

LDL-C: Low density lipoprotein cholesterol

TG: Triglycerides

**percentage difference from baseline to end value

Table 2.2 Studies performed on volunteers with normal to mild hypercholesterolaemia

Reference	Study population	Study design	Policosanol duration	Dosage	Physiological effects	p-value**
Hernandez <i>et al.</i> , 1992	13 placebo, 15 policosanol (10 mg), 10 policosanol (20 mg) healthy volunteers	Parallel, randomised, double-blind, placebo-controlled	Studied for 4 weeks	10 mg/d	TC - 10.7% LDL-C - 10.1% HDL-C + 2.6%	p< 0.05 NS NS
				20 mg/d	TC - 11.3% LDL-C - 23% HDL-C + 23.9%	p< 0.05 p< 0.01 p< 0.05
Menendez <i>et al.</i> , 2000b	23 placebo, 46 policosanol normocholesterolaemic volunteers	Parallel, randomised, double-blind, placebo-controlled	Studied for 8 weeks	5 mg/d	TC - 10.5% LDL-C - 16.7% HDL-C + 9%	p< 0.0001 p< 0.0001 p< 0.05
				10 mg/d	TC - 12.4% LDL-C - 20.2% HDL-C + 15.2%	p< 0.0001 p< 0.0001 p< 0.001
Arruzazabala <i>et al.</i> , 2002	15 placebo, 15 policosanol (20 mg/d), 15 policosanol (40mg/d) healthy and hypercholesterolaemic volunteers	Parallel, randomised, double-blind, placebo-controlled	4 weeks dietary stabilisation. Studied for 30 days	20mg/d	TC - 12.4% LDL-C - 15.9% HDL-C + 5.4%	p< 0.01 p< 0.001 p< 0.05
				40mg/d	TC - 12.3% LDL-C - 17% HDL-C + 5.1%	p< 0.001 p< 0.01 p< 0.05
Castano <i>et al.</i> , 2003	50 policosanol, 50 placebo borderline to mildly elevated cholesterolaemic volunteers	Parallel, randomised, double-blind, placebo-controlled	6 weeks dietary stabilisation. Studied for 8 weeks	5mg/ day	TC - 12.3% LDL-C - 19.9% HDL-C + 10.5%	p< 0.001 p< 0.001 p< 0.001
Lin <i>et al.</i> , 2004	29 placebo, 29 policosanol normal to mildly elevated cholesterolaemia	Parallel, randomised, double-blind, placebo-controlled	Studied for 4 weeks	20mg/d	TC - 2.2% LDL-C - 2.5% HDL-C - 1.6%	NS NS NS
Dulin <i>et al.</i> , 2006	20 placebo, 19 policosanol mild hypercholesterolaemic volunteers	Parallel, randomised, double-blind, placebo-controlled	Studied for 8 weeks	20 mg/d	TC - 2.5% LDL-C - 7.7% HDL-C - 3.3%	NS NS NS
Kassis & Jones, 2006	21 mild hypercholesterolaemic volunteers	Cross-over, randomised, double-blind, placebo-controlled	28 days washout phase, 28 days each treatment	10mg/d	TC + 1.8% LDL-C + 4.5% HDL-C - 2.7%	NS NS NS

Physiological change: the difference in percentage change within the experimental group from baseline to end value

-: net effect was a decrease

CHD: Coronary heart disease

TC: Total cholesterol

HDL-C: High density lipoprotein cholesterol

NS: Non-significant

+: net effect was an increase

LDL-C: Low density lipoprotein cholesterol

TG: Triglycerides

**percentage difference from baseline to end value

Table 2.3 Studies performed on hypercholesterolaemic patients with diabetes mellitus

Reference	Study population	Study design	Policosanol duration	Dosage	Physiological effects	p-value**
Torres <i>et al.</i> , 1995	15 placebo, 14 NIDDM, hypercholesterolaemic volunteers	Parallel, randomised, double-blind, placebo-controlled	6 weeks dietary stabilisation. Studied for 12 weeks	2 * 5 mg	TC - 16.9% LDL-C - 21.7% HDL-C + 6.5%	p< 0.01 p< 0.01 NS
Crespo <i>et al.</i> , 1997	9 placebo, 10 NIDDM, hypercholesterolaemic volunteers	Parallel, randomised, double-blind, placebo-controlled	6 weeks dietary stabilisation. Studied for 12 weeks	2 * 5 mg	TC - 28.9% LDL-C - 44.4% HDL-C + 23.5%	p< 0.01 p< 0.05 p< 0.05

Physiological change: the difference in percentage change between experimental groups

-: net effect was a decrease

CHD: Coronary heart disease

TC: Total cholesterol

HDL-C: High density lipoprotein cholesterol

NS: Non-significant

+: net effect was an increase

LDL-C: Low density lipoprotein cholesterol

TG: Triglycerides

NIDDM: Non-insulin dependent diabetes mellitus

**percentage difference from baseline to end value

Figure 2.6 and Table 2.4 Percentage change in LDL-C and HDL-C between the experimental and control groups (page 29)

Footnotes:

HC: Hypercholesterolemia

MILD: Normal to mildly elevated cholesterol

DM: Diabetes Mellitus

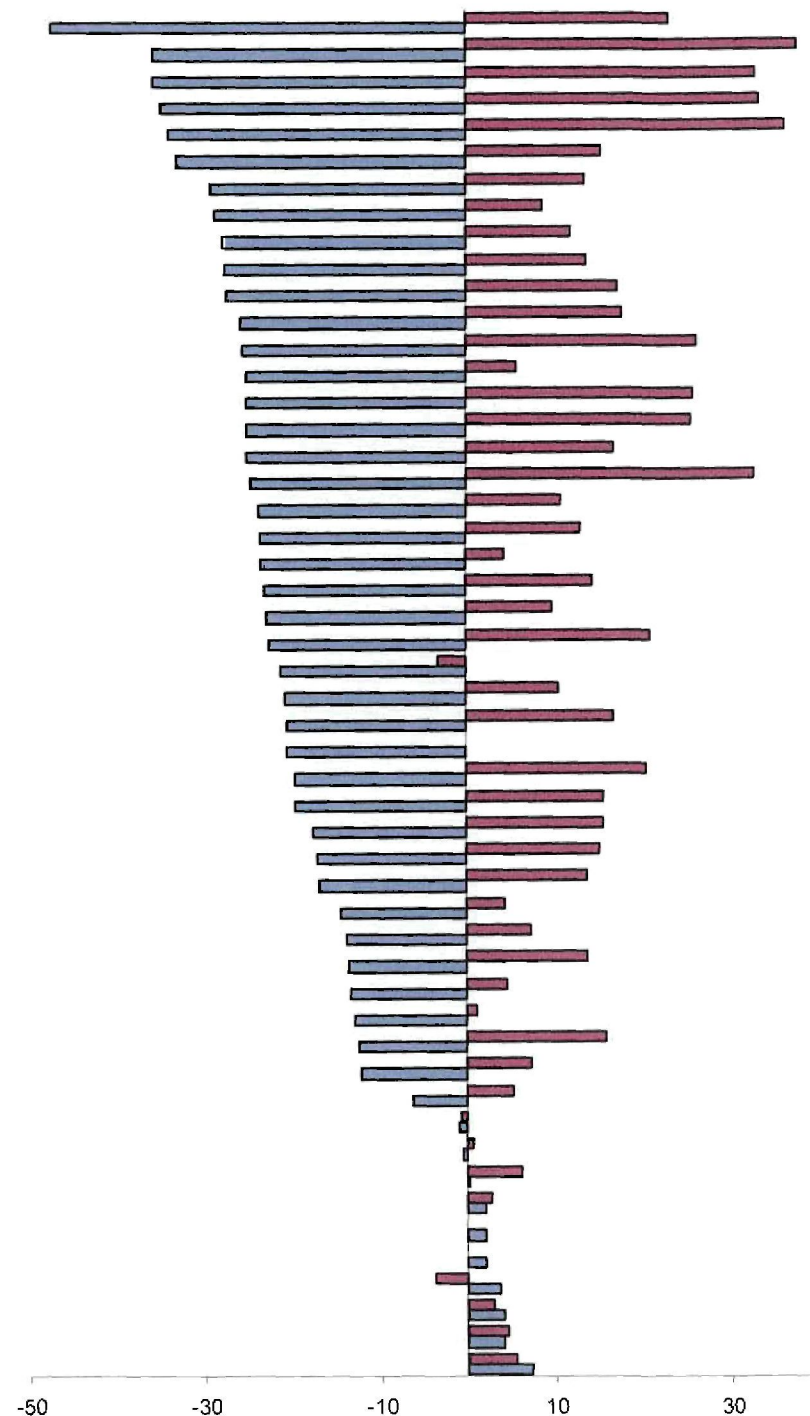
HPT: Hypertensive

PMW: Post-menopausal women

P: Placebo

PC: Policosanol

Author	Group	No of patients	Dosage (mg/day)	Duration (weeks)	% change LDL-C	% change HDL-C
Crespo <i>et al.</i> , 1997	HC, DM	19 (9 P, 10 PC)	10	12	-47.8	22.8
Castano <i>et al.</i> , 2001b	HC	82 (21 P, 21 PC) 1*20mg	20	8	-36.1	37.8
Castano <i>et al.</i> , 2001a	HC	89 (30 P, 30 PC)	40	24	-36	32.8
Castano <i>et al.</i> , 2001a	HC	89 (30 P, 29 PC)	20	24	-35.2	33.4
Castano <i>et al.</i> , 2001b	HC	82 (21 P, 20 PC) 2*10mg	20	8	-34.2	35.4
Torres <i>et al.</i> , 1995	HC, DM	29 (15 P, 14 PC)	10	12	-33.2	15.3
Pons <i>et al.</i> , 1994b	HC	22 (10 P, 12 PC)	10	24	-29.5	13.5
Castano <i>et al.</i> , 1995a	HC, elderly	82 (34 P, 28 PC)	10	52	-29	8.6
Castano <i>et al.</i> , 1995b	HC	74 (35 P, 36 PC)	10	52	-28	11.9
Mirkin <i>et al.</i> , 2001	HC	56 (28 P, 28 PC)	10	16	-27.7	13.6
Menendez <i>et al.</i> , 2000b	MILD	59 (23 P, 46 PC)	10	8	-27.5	17
Canetti <i>et al.</i> , 1995a	HC	97 (50 P, 47 PC)	10	52	-26	17.5
Castano <i>et al.</i> , 2000	HC, PMW	244 (122 P, 122 PC)	10	24	-25.8	26
Castano <i>et al.</i> , 1996	HC, HPT	58 (28 P, 30 PC)	10	52	-25.2	16.6
Castano <i>et al.</i> , 1997	HC	60 (20 P, 20 PC) 1*10mg	10	10	-25.2	25.3
Mas <i>et al.</i> , 1999	HC	437 (218 P, 219 PC)	10	24	-25.2	25.5
Castano <i>et al.</i> , 2001c	HC, elderly	179 (89 P, 90 PC)	10	24	-24.8	32.7
Aneiros <i>et al.</i> , 1993	HC	33 (17 P, 16 PC)	20	12	-24.6	12.8
Menendez <i>et al.</i> , 2000b	MILD	59 (23 P, 46 PC)	5	8	-24	10.8
Pons <i>et al.</i> , 1994a	HC	59 (31 P, 28 PC)	5	52	-23.6	4.3
Castano <i>et al.</i> , 1997	HC	60 (20 P, 20 PC) 2*5mg	10	10	-23.1	14.3
Canetti <i>et al.</i> , 1995b	HC	59 (37 P, 32 PC)	10	104	-23	12.9
Menendez <i>et al.</i> , 2000a	HC	20 (10 P, 10 PC)	5	12	-22.9	9.7
Mas <i>et al.</i> , 2001	HC, elderly	280 (140 P, 140 PC)	5	52	-22.8	20.8
Pons <i>et al.</i> , 1992	HC	58 (29 P, 27 PC)	5	8	-21.4	-3.3
Castano <i>et al.</i> , 2003	MILD	100 (50 P, 50 PC)	5	8	-21	10.5
Hernandez <i>et al.</i> , 1992	Healthy	38 (13 P, 10 PC)	20	4	-20.6	5.9
Aneiros <i>et al.</i> , 1993	HC	33 (17 P, 16 PC)	10	12	-20.6	16.6
Bastista <i>et al.</i> , 1996b	HC	23 (11 P, 12 PC)	2	56	-20.6	***
Aneiros <i>et al.</i> , 1995	HC	45 (23 P, 22 PC)	10	6	-19.8	20.3
Castano <i>et al.</i> , 2002	HC, HPT	589 (293 P, 296 PC)	5	52	-19.7	15.4
Castano <i>et al.</i> , 2000	HC	244 (122 P, 122 PC)	5	24	-18.2	15
Mas <i>et al.</i> , 1999	HC	437 (218 P, 219 PC)	5	24	-17.4	15.5
Castano <i>et al.</i> , 2001c	HC, elderly	179 (89 P, 90 PC)	5	24	-17	13.6
Arruzazabala, 2002	Healthy	45 (15 P, 15 PC)	40	4	-14.5	4.3
Bastista <i>et al.</i> , 1996a	HC	41 (14 P, 15 PC)	10	80	-13.9	7.2
Bastista <i>et al.</i> , 1995	HC	22 (11 P, 11 PC)	10	52	-13.6	13.6
Arruzazabala, 2002	Healthy	45 (15 P, 15 PC)	20	4	-13.4	4.6
Mirkin <i>et al.</i> , 2001	HC	56 (28 P, 28 PC)	5	16	-12.8	1.1
Bastista <i>et al.</i> , 1996a	HC	41 (14 P, 15 PC)	10	80	-12.2	7.2
Hernandez <i>et al.</i> , 1992	Healthy	38 (13 P, 15 PC)	10	4	-7.7	-15.4
Lin <i>et al.</i> , 2004	MILD	58 (29 P, 29 PC)	20	4	-0.9	-4
Berthold <i>et al.</i> , 2006	HC	143 (29 P, 32 PC)	80	12	-0.7	9.4
Dulin <i>et al.</i> , 2006	MILD	39 (20 P, 19 PC)	20	8	-0.5	0.6
Berthold <i>et al.</i> , 2006	HC	143 (29 P, 28 PC)	10	12	-0.4	3.8
Francini-Pesenti, 2007	HC	68 (34 P, 34 PC)	20	8	1.9	2.8
Greyling <i>et al.</i> , 2006	FH	16 (16 P, 16 PC)	20	24	2.04	-0.13
Kassis <i>et al.</i> , 2006	Healthy	21 (21 P, 21 PC)	10	4	2.9	4.7
Berthold <i>et al.</i> , 2006	HC	143 (29 P, 27 PC)	20	12	3.3	0.86
Berthold <i>et al.</i> , 2006	HC	143 (29 P, 27 PC)	40	12	4.8	5.5
Greyling <i>et al.</i> , 2006	HC	19 (19 P, 19 PC)	20	24	6.1	6.4



2.8 Comparison with other lipid lowering therapies

The first step in the treatment of high cholesterol should be a change in therapeutic lifestyle, which includes moderate exercise, a balance, low fat diet and cessation of smoking. If there is little improvement then there are various effective drugs available and marketed for the management of hyperlipidaemia, including statins, nicotinic acid, ionic exchange resins, fibrates and probucol (NCEP expert panel, 1988). There are many statins available on the market, such as atorvastatin, fluvastatin, pravastatin and simvastatin (Taylor *et al.*, 2003). They have very different pharmacokinetic profiles, which are associated with their physicochemical properties (Shitara & Sugiyama, 2006). These all work in more or less the same way by competitively inhibiting 3-hydroxy-3-methylglutaryl coenzyme A reductase in the process of cholesterol synthesis (BMA/RPSGB, 2001). There have been numerous randomised clinical trials that have been performed indicating the effective cholesterol-lowering ability of statins to assist in the reduction of cardiovascular diseases (Scandinavian Simvastatin Survival Study Group, 1994; Shepherd *et al.*, 1995; Sacks *et al.*, 1996; Bertolini *et al.*, 1997; The Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID) Study Group, 1998). The tolerabilities of these substances are, however, questionable. Several articles are available that indicate that these products are associated with several long-term side effects including hepatotoxicity and myopathy (Yale, 1992; Bhatnagar, 1998; Bolego *et al.*, 2002). These supplements are, therefore, contraindicated for patients suffering from renal failure or those who consume high quantities of alcohol whose liver function may be compromised (Taylor *et al.*, 2003).

Table 2.5 highlights a few studies that compare policosanols to drug therapy in hypercholesterolaemic patients. In the earlier studies policosanols were shown to have greater beneficial effects on lipid profile than statins. Drug therapy was also associated with numerous side effects which include skin rash, gastric pain, blurred vision as well as an increase in levels of serum transaminase, possibly indicating an association with muscle deterioration and a risk of hepatotoxicity (Fernandez *et al.*, 2001; Alcocer *et al.*, 1999). These initial studies found that administration of 10 mg/day showed modest advantages (Benitez *et al.*, 1997). One of the studies found no significant effect on HDL-C with the use of policosanols or simvastatin, but a marked improvement in TC and LDL-C values (Ortensi *et al.*, 1997). The study by Castano *et al.* (2000) found similar effectiveness with both policosanols and lovastatin treatment.

Table 2.5 Trials comparing policosanols to other lipid-lowering therapies

Reference	Aim	Study design; n	Duration and dosage	Lipid profile	Treatment	Baseline value	End value	Delta (Percentage change)	p-value
Benitez <i>et al.</i> , 1997	Compare the short term efficacy and tolerability of policosanol and pravastatin in type II hypercholesterolaemic patients	Randomised, double-blind; n= 24	6wks-dietary stabilisation; 6wk-5mg policosanol or 10mg pravastatin twice daily with evening meal and breakfast	TC	Policosanol	7.19	6.02	-1.17 (-15.7%)	p<0.01
					Pravastatin	7.19	6.08	-1.11 (-15.3%)	p<0.01
				LDL-C	Policosanol	4.96	3.75	-1.21 (-24.2)	p<0.01
					Pravastatin	4.99	4.01	-0.98 (-19.6)	p<0.01
				HDL	Policosanol	0.94	1.06	+0.12 (+13.6%)	p<0.01
					Pravastatin	0.97	1.01	+0.04 (+4.7%)	p=0.05
Ortensi <i>et al.</i> , 1997	Compare the tolerability and efficacy of policosanol and simvastatin in elderly patients with primary hypercholesterolaemia	Randomised, double-blind; n= 53	6wks-dietary stabilisation; 8wk-10mg policosanol or 10mg simvastatin twice a day with meals	TC	Policosanol	7.5	6.43	-1.07 (-14.7%)	p<0.0001
					Simvastatin	7.39	6.29	-1.1 (-15.2%)	p<0.0001
				LDL-C	Policosanol	4.97	4.07	-0.9 (-17.9%)	p<0.0001
					Simvastatin	5.03	4.05	-0.98 (-19.8%)	p<0.0001
				HDL	Policosanol	1.45	1.42	-0.03 (-1.7%)	NS
					Simvastatin	1.46	1.39	-0.07 (-2.9%)	NS

Reference	Aim	Study design; n	Duration and dosage	Lipid profile	Treatment	Baseline value	End value	Delta (Percentage change)	p-value
Castano <i>et al.</i> , 2000	Compare the efficacy and tolerability of policosanol and lovastatin in type II hypercholesterolaemic patients at high risk for coronary events	Randomised, double-blind; n= 59	4wks-dietary stabilisation; 12wk-10mg policosanol or 20mg lovastatin once daily with evening meal	TC	Policosanol	6.92	5.37	-1.55 (-22.4%)	p<0.0001
					Lovastatin	6.73	5.40	-1.33 (-19.8%)	p<0.0001
				LDL-C	Policosanol	4.69	3.17	-1.52 (-32.4%)	p<0.0001
					Lovastatin	4.56	3.30	-1.26 (-27.6%)	p<0.0001
				HDL	Policosanol	1.33	1.52	+0.19 (+14.3%)	p<0.05
					Lovastatin	1.36	1.41	+0.05 (+3.7%)	NS
Fernandez <i>et al.</i> , 2001	To compare the efficacy and tolerability of policosanol and fluvastatin in elderly hypercholesterolaemic women	Randomised, single-blind; n= 70	4wks-dietary stabilisation; 8wk-10mg policosanol or 20mg fluvastatin once daily	TC	Policosanol	6.52	5.24	-1.28 (-19.3%)	p<0.01
					Fluvastatin	6.67	5.57	-1.1 (-16.7%)	p<0.001
				LDL-C	Policosanol	4.80	3.37	-1.43 (-29.26%)	p<0.001
					Fluvastatin	4.93	3.79	-1.14 (-22.9%)	p<0.001
				HDL	Policosanol	1.04	1.24	+0.2 (+19.8%)	p<0.001
					Fluvastatin	1.05	1.15	+0.1 (+9.2%)	p<0.001

Reference	Aim	Study design; n	Duration and dosage	Lipid profile	Treatment	Baseline value	End value	Delta (Percentage change)	p-value
Cubeddu <i>et al.</i> , 2006	To evaluate the efficacy of policosanol, given alone and in combination with atorvastatin, in patients with dyslipidemia	Randomised, double-blind; placebo-controlled; n= 99	8wks-no statin therapy; 12wks-pts assigned to 1 of 4 groups receiving policosanol 20mg, atorvastatin 10mg, combination therapy (policosanol 20mg plus atorvastatin 10mg) or placebo	TC	Policosanol	4.08	4.05	-0.03 (-0.74%)	p<0.01
					Atorvastatin	4.3	2.64	-1.66 (-38.6%)	p<0.01
					Policosanol+ Atorvastatin	3.89	2.56	-1.3 (-33.4%)	p<0.01
					Placebo	4.05	3.77	-0.28 (-6.9%)	p<0.01
				LDL-C	Policosanol	6	6.2	+0.2 (+3.33%)	p<0.01
					Atorvastatin	6.49	4.74	-1.75 (-26.96%)	p<0.01
					Policosanol+ Atorvastatin	6.1	4.59	-1.51 (-24.75%)	p<0.01
					Placebo	6.18	5.92	-0.26 (-4.2%)	p<0.01
				HDL-C	Policosanol	1.35	1.34	-0.01 (-0.7%)	NS
					Atorvastatin	1.36	1.38	+0.02 (+1.47%)	NS
					Policosanol+ Atorvastatin	1.35	1.34	-0.01 (-0.74%)	NS
					Placebo	1.30	1.33	0.03 (2.3%)	NS

n- number of subjects, NS- non significant, pt patient, wk-weeks, mg-milligrams

The more recent trial by (Cubeddu *et al.*, 2006) found that there were no advantageous effects displayed by policosanol, while 10 mg/day of atorvastatin resulted in significant reductions in TC and LDL-C from baseline to 12 weeks. The reduction of TC that was reported by this group was 27% and a 35% reduction in LDL-C. It was also found that neither of the treatments had any effect on HDL-C serum lipid levels. This group proposed that policosanol should be added to the list of nutritional supplements that lack appropriate scientific validity to support their use.

2.9 Safety and adverse effects

Several preclinical (Mesa *et al.*, 1994; Rodriguez-Echenique *et al.*, 1994) as well as clinical (Pons *et al.*, 1992; Pons *et al.*, 1994b; Canetti *et al.*, 1995a; Canetti *et al.*, 1995b; Castano *et al.*, 1995b; Torres *et al.*, 1995; Castano *et al.*, 1996; Canetti *et al.*, 1997; Crespo *et al.*, 1997; Ortensi *et al.*, 1997) trials have indicated that policosanol is safe and well tolerated amongst the population. Policosanol has not been linked to any adverse effects of clinical, haematologic or blood biochemical nature. One study focused on the nature and incidence of adverse effects in over 20 000 policosanol treated individuals (Fernandez *et al.*, 1998). Patients were included in the study based on the indications of the supplement use and not on sex, age or associated pathology. The recommended duration of treatment was required to be no less than two consecutive months. An adverse effect was described as any undesirable occurrence, whether it was to be related to the policosanol or not. The adverse effects were further divided into mild, moderate or severe. The effects were considered mild if withdrawal of policosanol therapy was required, moderate when transient or definitive withdrawal of treatment was necessary and severe or fatal when fatal, life threatening or disabling, or when hospitalisation or prolongation of any hospitalisation stay was required. The results of this study are shown in **Table 2.6**.

Table 2.6 Overall reported incidence of adverse events in policosanol treated patients (N = 27 879) (Fernandez *et al.*, 1998).

Body system	Incidence	
	n	%
Nervous system		
Headache	8	0.03
Insomnia	15	0.05
Somnolence	1	<0.004
Excitability	1	<0.004
Dizziness	6	<0.02
Cardiovascular system		
Hypertension with concomitant epistaxis	1	<0.004
Skin		
Rash	1	<0.004

Body as a whole		
Polyphagia	13	0.05
Polyuria	19	0.07
Weight loss	21	0.08
Total	86	0.31

The overall incidence of adverse effects was 0.31%, all of which were considered to be drug associated. The total number of subjects that discontinued the treatment amounted to only 31 (0.1%), of these only 7 (0.03%) due to experiencing adverse effects. The adverse effect that was most commonly reported was weight loss (represented 24.4% of the adverse effects), reported by 0.08% of the population group. The decrease in weight is not an expected adverse effect for cholesterol-lowering drugs and is not illustrated in the general safety profile of these drugs. In most other therapies, simvastatin for example, weight gain has been reported (Ortensi *et al.*, 1997). Polyuria (0.07%), insomnia (0.05%) and polyphagia (0.05%) were other reported adverse events.

Another study (Mas *et al.*, 1999) that was performed on 6611 patients to determine the nature and incidence of adverse events found that 163 patients in the policosanol group and 177 patients in the control group reported > 1 adverse event, the most frequent of which were weight loss (1.75%), polyuria (0.68%), headache (0.61%), dizziness (0.44%) and polyphagia (0.36%). Between the groups there were no significant differences recorded. Twenty-six of the patients (0.72%) discontinued the therapy due to adverse events, which included weight loss (0.42%), asthenia (0.08%) and somnolence (0.06%). This study concluded that policosanol was extremely well tolerated in terms of type and nature of adverse events. When taking policosanol into consideration it is of interest to note that once treatment has ceased there are no noted rebound effects (Canetti *et al.*, 1995a; Canetti *et al.*, 1995b; Canetti *et al.*, 1997).

The relative composition of the original (Cuban) policosanol supplement has been stated to have a purity of greater than 90%, with octacosanol (60 – 70%) as the most abundant trailed by triacontanol (10 – 15%), hexacosanol (4.5 – 10%), dotriacontanol (3 – 8%), heptacosanol (<5%), tetracosanol (<2%), nonacosanol (<2%) and tetratriacontanol (Mas, 2000a). It is assumed that due to the fact that octacosanol is the highest available component, it must be the responsible factor for lowering cholesterol levels (Mas, 2000a). It has been pointed out by the original researchers that their results are so striking due to the exclusive purity and relative composition of the Cuban supplement (Castano *et al.*, 2002a). However, Marinangeli *et al.* (2007) compared the

purity and relative composition of the Cuban and alternative sources of sugar cane policosanol and reported similar results. The similar composition between brands is indicative of consistent manufacturing practices, no matter where the product is sold. Thus the other policosanol sources should possess the same cholesterol-lowering properties as that of the original policosanol (Marinangeli *et al.*, 2007). The metabolism of policosanol has also come under the spotlight as a subject of controversy, as its hydrophobicity would appear to result in poor absorption (Hargrove *et al.*, 2004; Dullens *et al.*, 2008), which has been confirmed in studies performed on both rats (Kabir & Kimura, 1995; Menendez *et al.*, 2005) and monkeys (Menendez *et al.*, 2005) using radiolabelled [8-¹⁴C] octacosanol (Kabir & Kimura 1995) and policosanol supplements (Menendez *et al.*, 2005). It has been suggested that as a result of the low absorption rate there may be a lipid-lowering effect at the level of the intestine (Gouni-Berthold & Berthold, 2002).

2.10 Recommended dosage

Policosanol in dosages from 5 mg to 20 mg daily has been suggested to be effective in lowering levels of TC and LDL-C and increasing HDL-C levels (Gouni-Berthold & Berthold, 2002; Chen *et al.*, 2005), thus indicating dose dependency with a maximal response after 6 – 8 weeks (Aneiros *et al.*, 1993; Pons *et al.*, 1994a; Pons *et al.*, 1994b; Canetti *et al.*, 1995a; Canetti *et al.*, 1995b). **Figure 2.7** and **Figure 2.8** indicate the dose dependency of the trials that found a positive correlation with policosanol supplementation in relation to the effect on LDL and HDL cholesterol respectively of all of the trials compiled.

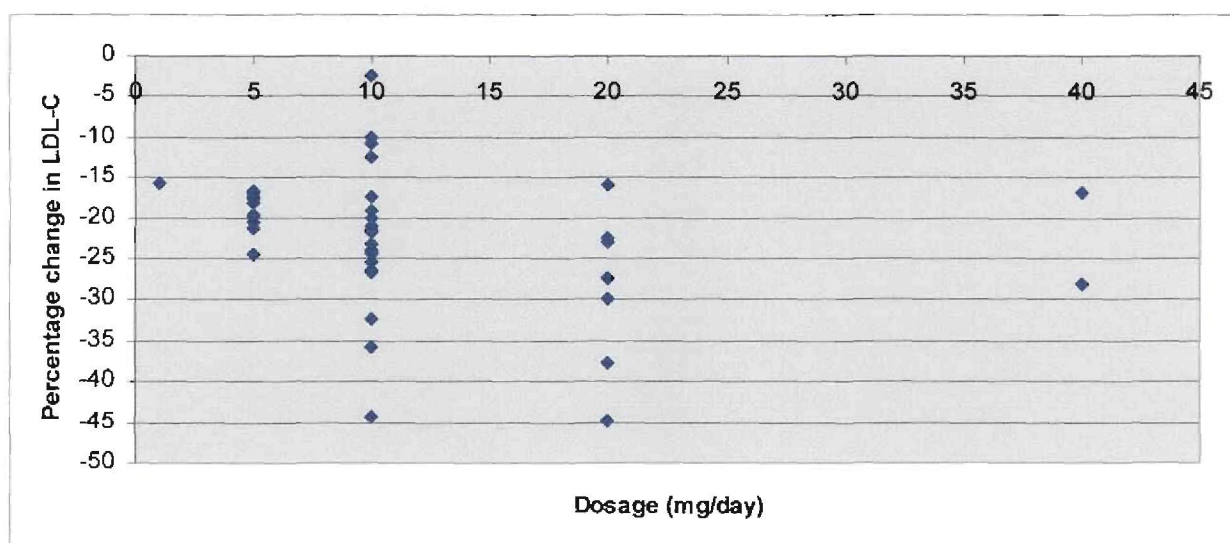


Figure 2.7 Dose dependency of LDL cholesterol

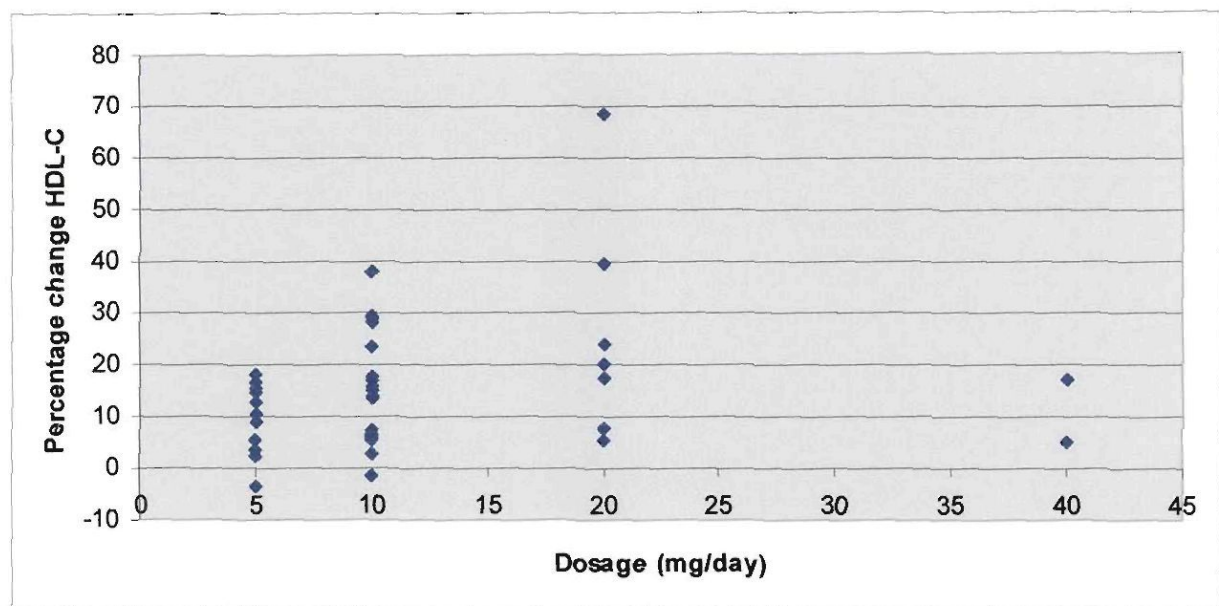


Figure 2.8 Dose dependency of HDL cholesterol

It has been suggested to start with a 5 mg once a day dose to be taken with an evening meal, which is gradually increased. Doses higher than 20 mg per day up to 80 mg per day are currently being studied. Policosanol is contraindicated during pregnancy. However, there have been no teratogenic effects found in performed animal studies (Rodriguez- Echenique *et al.*, 1994; Rodriguez *et al.*, 1997; Rodriguez *et al.*, 1998).

Policosanol is also not recommended during lactation as no studies have been performed to determine whether the drug or its metabolites pass into human milk. The use in children is also not encouraged due to the lack of studies available in this population group. While there has been no dose reduction suggested for patients with liver dysfunction, no studies have yet been performed on patients suffering from impaired kidney function (Gouni-Berthold & Berthold, 2002) and thus recommendations for the use of policosanol in these patients are unavailable.

2.11 Other possible benefits of policosanol

2.11.1 Antiplatelet and antithrombotic effect

In conjunction with the lipid-lowering functions of policosanol, a number of trials have focused on the potential antiplatelet effect that policosanol may have in both human trials and animal studies (Arruzazabala *et al.*, 1996; Valdes *et al.*, 1996; Arruzazabala *et al.*, 1997; Carbajal *et al.*, 1998; Arruzazabala *et al.*, 1998; Castano *et al.*, 1999b).

The mechanism of action differs from that of aspirin and does not significantly affect coagulation time (Arruzazabala *et al.*, 1997). Policosanol has shown evidence of an effect on platelet activation, endothelium turnover as well as foam cell formation (Varady *et al.*, 2003). The activation of platelets is one of the primary steps that are involved in the occurrence of ischaemic insult (Shah *et al.*, 1985).

The consistency of blood should enable a smooth, non-obstructive flow through the body, avoiding any possible damage to the blood vessels or clots. It is when blood platelets aggregate that the blood becomes a thicker form or even possibly a clot (causing deep-vein thrombosis or cerebral ischaemia), thus resulting in a life-threatening event. The aggregation that occurs in the blood may be due to exogenous agents such as arachidonic acid, collagen and adenosine diphosphate. These aggregated platelets then release thromboxane A₂ (TxA₂, a potent platelet aggregatory agent in both human and nonhuman species), which encourages further platelet aggregation (Arruzazabala *et al.*, 1993). Inhibition of platelet aggregation is thought to reduce the formation of thrombus and, therefore, prevent the development of atherosclerosis (Arruzazabala *et al.*, 1998; Castano *et al.*, 1999a).

A study that was performed randomly and in double blind conditions on healthy volunteers investigated the effects that policosanol and aspirin had on platelet aggregation (Arruzazabala *et al.*, 1997). Policosanol was given daily at 20 mg and indicated a significant decrease in platelet aggregation induced by adenosine diphosphate, epinephrine and collagen. The aspirin at 100 mg per day demonstrated significant decreases in collagen and epinephrine induced platelet aggregation. Aspirin is widely used for the prevention of thrombosis and cerebral ischaemia, but there are numerous side effects noted, including headache, epigastralgia, nose and gum bleeding (Arruzazabala *et al.*, 1997). The mechanism by which policosanol affects platelet aggregation is by directly inhibiting the TxA₂ synthesis. Prostaglandin synthesis is, therefore, unaffected and thus there are fewer side effects recorded, leading to an advantage above that of aspirin. The results of this study indicated that 20 mg/d of policosanol is as effective as 100 mg/d of aspirin, with no side effects.

Policosanol has also been associated with antiplatelet effects in animal models, while there is evidence that a decrease in thromboxane B₂ and an increase in prostacyclin levels are involved (Arruzazabala *et al.*, 1992; Arruzazabala *et al.*, 1993; Carbajal *et al.*, 1994). These effects have been also been linked to the anti-ischaemic action of policosanol in cerebral ischaemic animal models (Molina *et al.*, 1999).

It is important to consider policosanol as a possible effective treatment in the inhibition of platelet aggregation, but overdose could be associated with problems such as haemorrhage. Policosanol in excess is thought to have the possible ability to increase blood coagulation time and, in patients that are unaware of injury, it could lead to gastric ulcers or bleeding in the brain. It is, therefore, important to refrain from using policosanol with anti-coagulation treatment such as warfarin (Taylor *et al.*, 2003).

2.11.2 Cytoprotective effect

Due to the common occurring gastric side effects (gastric irritation or ulcers) that are associated with continuous use of aspirin, which causes the blocking of the protective effects of prostaglandins acting in the stomach as protection for the gastric mucosa, it is suggested that policosanol may be a favourable alternative as the mechanism of action does not interfere with prostaglandin production of this kind (Taylor *et al.*, 2003). A study by Carbajal *et al.* in 1995 aiming at determining whether octacosanol may have anti-ulcer activity used a mixture of higher primary alcohols of wax called D-002, which contains triacontanol, octacosanol (concentration of which 17.49%), dotriacontanol, hexacosanol and tetracosanol as major components. Administered orally to rats it was found to induce a mild anti-inflammatory effect. The effect of D-002 was monitored on indomethacin-induced and ethanol-induced gastric ulcers. Those induced by indomethacin were significantly inhibited with D-002 administration in doses of 25 and 50 mg/kg. In the case of ethanol-induced ulcer, maximum inhibition was recorded at 66.9% with a dose of 50 mg/kg (Carbajal *et al.*, 1995).

Another study was based on the fact that ulceration is caused as a result of gastric acid (Carbajal *et al.*, 1996). It was found in this study that D-002 was independent of gastric acid and thus the mode of action differs from cimetidine, which is an H₂ antagonist and acts by blocking H₂ receptors that produce acid in the stomach. It was proposed that the cytoprotective role of D-002 was related to its prostaglandin effect rather than that of inhibition of the gastric acid.

It was, therefore, found that due to the gastric irritation that is caused with the use of aspirin, policosanol might be the favourable option because of the cytoprotective effect, especially in patients where aspirin is contraindicated (Taylor *et al.*, 2003).

2.12 Summary and conclusion

As CVD has been recognised as one of the leading causes of death and a major health issue around the world (Mahan & Escott-Stump, 2004), there is a genuine need to explore treatments of diverse sources and fields of wellbeing. Amongst most population groups it is accepted that diet is the first line of action and is usually tried before drug therapy against hypercholesterolaemia. Changes in therapeutic dietary intake and lifestyle of the patient, which include physical activity, a low saturated fat and cholesterol diet and striving for adequate weight reduction are necessary (NCEP, 2001).

A regimen that combines both diet and drug use is said to achieve more improved blood lipid goals than diet alone (Cobb *et al.*, 1991). At present there are numerous pharmacological treatments available, dependent on the risk category and the attainment of the TC and LDL-C goal. These drugs have been found to lower serum lipid levels significantly, however, they are also expensive and have been associated with several side effects. In the modern age there is also a movement towards naturally derived products instead of chemically developed, as each individual becomes more aware and knowledgeable about good health and natural merchandise it is essential that health care providers remain up-to-date and open-minded to the possibilities of benefits of these products (Nies *et al.*, 2006).

Therefore, the naturally derived policosanol has come to light. Various medical researchers have studied this extract of sugar cane, beeswax or wheat germ. Studies have been performed on different population groups including normal to mildly elevated cholesterolaemic, hypercholesterolaemic, elderly, postmenopausal and diabetic volunteers. There have been numerous studies performed in Havana, Cuba; these were performed in this area on the surrounding population using the same extract of policosanol. This group of researchers have reported many studies showing positive effects of policosanol on the lipid profile. It is, however, important to be aware that a number of more recent studies performed elsewhere in the world, including South Africa, Germany, the United States of America, Canada, the Netherlands and Italy, have not been able to replicate the serum lipid-lowering effects of policosanol.

Of utmost importance to consider is the fact that studies that were performed in areas other than Cuba have not had the same correlation with beneficial results and thus numerous questions are raised and high alert is raised. One therefore questions the

methods and motivation behind the Cuban studies. Firstly, Cuba is a leading country in the production of sugar cane. The Cuban economy is based on one crop of cane sugar and hence it is sensitive to the international fluctuation in prices. The remarkable development of sugar cane cultivation in Cuba is reasoned by a number of factors. Sufficient rainfall of 100 cm to 175 cm, high temperature of 21°C to 27°C and calcareous soil make 4 to 8 harvests from a single planting possible. Thus sugar cane is an essential source of revenue for the country and benefits other than initially anticipated would be advantageous. Secondly, the results of the Cuban studies, including the percentage changes soars far above the placebo, thus indicating policosanol as a miracle lipid-lowering agent, with no liberty for question about the product. Results with such large differences are rare to come by. Challenging this is the fact that researchers in other countries, including South Africa and Italy, did not find any correlation between serum lipid reduction and the use of policosanol. If this supplement did have such outstanding qualities one would at least expect a correlation, even if it were a diminutive one.

When results of other countries did not find the same favourable outcome the Cuban researchers reported that the composition of the specific original policosanol was the cause of dispute, however, this argument was challenged by Marinangeli and co-workers in 2007 when they compared the different compositions and absorption of various sugar cane derived policosanols and found that the original Cuban policosanol supplement has a purity and relative percentage of policosanol composition that is consistent with other sources of the same supplement used in other trials. Thus it was suggested by this group that the cholesterol-lowering properties should be the same. The metabolism of the different sources compared to the original Cuban policosanol was, however, suggested by this group to be studied further before firm conclusions could be made (Marinangeli *et al.*, 2007).

Another possible reason for the differences in the results of the diverse groups was the fact that the population of volunteers used in the Cuban studies were from the surrounding area and, therefore, it was suggested that ethnic and environmental factors could play a role. This theory was once again confronted by an Italian research group (Francini-Pesenti *et al.*, 2007) who reasoned that ethnic differences could not explain differences in the Cuban and other studies as diet and lipid-lowering agents, such as statins, have been shown to have similar effects in different populations. In a recent study by Dullens *et al.* (2007) it was found that neither the individual policosanol components nor the natural policosanol mixture lowered serum cholesterol

concentrations in LDL receptor knock-out mice. They also found that there was no significant effect on gene expression profiles of LDLr, ABCA1, HMG-CoA synthase 1 and apolipoprotein A-I (apo A-I) in hepatic and small intestinal tissue of female mice after a 7-week intervention phase. It was concluded by this group that policosanol had no potential for reducing LDL concentrations and increasing HDL-C concentrations (Dullens *et al.*, 2008). Therefore, answers to the questions regarding the possible lipid lowering of policosanol are still unclear.

Regarding the safety of policosanol numerous reports have found that the adverse effects are lacking or mild. The most commonly reported was a loss of weight although headaches were also mentioned. These effects are minimal when compared to the side effects that have been associated with the daily use of statins, which include myopathy, rhabdomyolysis and occasionally death. In order to have the possible benefits of policosanol, a dosage of between 5 – 10 mg/day has been suggested by the trials that have been performed, once or twice daily, preferably in the evening.

From the studies performed on policosanol it seems reasonable to encourage the use of policosanol as an alternative therapy or in conjunction with the currently available statins in patients with hypercholesterolaemia. It is, however, important to recognise the possible downfalls in the current available data. Therefore, it is concluded that further studies are recommended in order to clarify the numerous potential advantages and metabolism of various sources of policosanol (Marinangeli *et al.*, 2007). These studies should be controlled with large population groups over a long period of time. The objectives should include the efficacy, mechanism of action, absorption rate and amount as well as the recommended dosage for effect. It is suggested that an interlaboratory study by experienced investigators in different international centres, coordinated from a central laboratory, and using the original as well as an alternative policosanol in a double blind manner, should be performed.

In order to summarise the results of all the studies that have been done so far in different parts of the world systematically, a systematic review was compiled and will be presented in an article format in the next chapter.

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CHAPTER 3
ARTICLE

Systematic review:
Effects of policosanol supplements on serum lipid
concentrations

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Abstract

Policosanol, a mixture of long-chain primary aliphatic alcohols isolated and purified from the wax constituent of plants, has been reported to play a favourable role in the treatment of hypercholesterolaemic patients by numerous Cuban trials. More recent studies have, however, contradicted these original proposals. The objective of this study was to review systematically all the available peer-reviewed data investigating the effects of policosanol on total serum cholesterol (TC), low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C). Peer-reviewed literature from January 1992 to May 2008 was re-evaluated and assessed. Trials were required to reach pre-compiled inclusion, exclusion and quality criteria in order to be considered. Thirty-nine good quality trials of over 3400 volunteers were included in the review of which 85% (n=33) encouraged the use of policosanol in improving lipid profile, while the remaining 15% (n=6) found no advantageous correlation. Dosage varied from 1 mg/day to 80 mg/day, where 5 to 20 mg/day yielded the most benefits. Percentage change ranges for TC, LDL-C and HDL-C from baseline to end value were between +1.29 and -29.3%; +0.2 and -45.7% and -3.3 and +37.8% respectively. Policosanol was well tolerated with few or no adverse effects. This review established that although initial results encouraged the use of policosanol for reduction of TC and LDL-C, independent trials performed subsequent to 2004 found a lack of any effect on serum lipid levels. Reasons suggested to cause such diverse results include differences in composition of policosanol, concentration of octacosanol, ethnic and environmental influences. However, these have been discarded as inconsistent factors. Therefore, this review supports independent studies showing no cholesterol-lowering effects. Further controlled, long-term research with globally accepted methods is required in varying population groups across the world focusing on efficacy, amount and rate of absorption and dosage in order to conclude the true benefits of policosanol and the possibility of inclusion in the daily intake amongst hypercholesterolaemic subjects. An international, interlaboratory study, coordinated from a central laboratory, may provide the answer.

KEY WORDS: policosanol octacosanol hypercholesterolaemia clinical trials
cardiovascular disease

Introduction

Cardiovascular disease (CVD) is still one of the leading causes of death and hindering in many countries around the world despite the extraordinary gains in the treatment thereof (Falk *et al.*, 1995; Singh & Mehta, 2002). Dyslipidaemias with high plasma level of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C) and triglycerides (TG) as well as low levels of high-density lipoprotein cholesterol (HDL-C) play an etiological role in CHD (Singh & Mehta, 2002). The benefits of decreasing the TC and LDL-C in the prevention of CVD both at the primary as well as the secondary stages have been proven indisputable (Gould *et al.*, 2007).

The first step in TC and LDL-C reduction is therapeutic lifestyle changes. These include the adherence to the National Cholesterol Education Program (NCEP), which encourages the step 1 cholesterol-lowering diet, smoking cessation as well as regular systematic physical exercise (Expert Panel of Detection, Evaluation and Treatment of High Blood Cholesterol in Adults, 2001). In many individuals who suffer from elevated TC and more than two of the nonlipid risk factors, or those who are in the secondary prevention stage, may find therapeutic lifestyle changes not solely sufficient, as more restricted goals are usually recommended (National Cholesterol Education Program Expert Panel 1988; Gotto *et al.*, 2000). Therefore, cholesterol-lowering drugs are usually prescribed in conjunction with the therapeutic lifestyle changes in order to ensure that the recommended lipid levels are reached (Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults, 1993).

Available lipid-lowering treatments include statins, fibrates, anionic exchange resins, niacin and probucol. Statins are reported to be the favoured and most successful method of LDL-C reduction. The addition of second or third agents is often required (Conti, 2002; Scandinavian Simvastatin Survival Group, 1994) as these combination treatments utilise complimentary mechanisms of action ensuring adequate effects on serum lipid levels in combination with minimal adverse events are met (Downs *et al.*, 1998; The LIPID study group, 1998). Due to the ever increasing reluctance of patients to comply with chemically derived drug therapies, the use of alternative natural therapies have become more popular over the past few years (Eisenberg *et al.*, 1998; MacLennan *et al.*, 2002).

Policosanols are a mixture of long-chain primary aliphatic alcohols originally isolated and purified from sugar cane wax (*Saccharum officinarum* L) (Janikula, 2002; Varady *et al.*, 2003). Octacosanol is the largest component, which comprises approximately 60 – 70% of the mixture. Triacosanol (10 - 15%) and hexacosanol (4.5 - 10%) are the other two significant components (Laguna *et al.*, 1997; Mas, 2000; Gouni-Berthold & Berthold, 2002), while tetracosanol, heptacosanol, nonacosanol, dotriacontanol and tetratriacontanol are the less major constituents (Pepping, 2003). Different sources of policosanol contain varying amounts of the extract, beeswax being the richest source, followed by wheat straw, sugar cane peel and wheat milling fractions (Irmak *et al.*, 2006).

It has been suggested that the cholesterol-lowering effect is mainly mediated by a decrease in serum LDL-C levels, due to inhibition of hepatic cholesterol synthesis and stimulation of receptor-mediated LDL uptake by the liver (Menendez *et al.*, 1994; Menendez *et al.*, 1996; Menendez *et al.*, 1997; Fernandez *et al.*, 2001). Cholesterol synthesis was studied *in vitro* by measuring the enrichment of tritiated water into human fibroblasts (Fernandez *et al.*, 2001) and animals *in vivo* (Menendez *et al.*, 1997). Synthesis was reduced as a result of supplementation with policosanol. In human cultured fibroblasts policosanol interfered with the cholesterol biosynthesis pathway at a step between acetate and mevalonate production (Menendez *et al.*, 1994; Fernandez *et al.*, 2001). Decreased cholesterol biosynthesis is related to an increase in LDL-receptor expression in hepatocytes (Basu *et al.*, 1976; Junker & Davis, 1989). According to Menendez *et al.* (1994), the effects on serum LDL-C are a result of LDL binding uptake or degradation. However, in a recent study by Kassis and Jones (2008), who examined the effect of sugar cane policosanol *in vivo* using deuterium incorporation into red blood cell cholesterol, cholesterol synthesis was not inhibited by policosanol.

The aim of this systematic review was to analyse all the peer-reviewed literature investigating the efficacy of policosanol supplements in improving the serum lipid profile (reduction of TC and LDL-C as well as an increase in the HDL-C) of male and female volunteers aged 20 – 75 years.

Methods

Search strategy

A systematic review of the published literature from January 1990 to May 2008 was performed using the *Cochrane Library* and the search engines MEDLINE, *Web of Science* and *Science Direct* as well as hand searching for key articles using referenced lists. Key words or search terms that were used included 'policosanol', 'octacosanol', 'hypercholesterolemia', 'hypercholesterolaemia', 'cholesterol', 'randomized', 'randomised' and 'placebo-controlled'. The starting year of 1990 was used to ensure the literature was up-to-date and relevant. The first study found within this range was from the year 1992.

Study selection and data extraction

Exclusively randomised, blind or double blind, peer reviewed trials were located and required to meet various inclusion, exclusion and quality criteria. Two open-labelled studies were included that did not reach this criteria, namely Castano et al., 1998 and Castano et al., 1999, this is due to the contribution that they made in the overall results. Each article was rated according to a criteria checklist adapted from the Delphi list (Verhagen *et al.*, 1998). Population criteria included volunteers diagnosed with hypercholesterolaemia and/or diabetes, healthy individuals with mild to borderline cholesterol as well as hypercholesterolaemic post-menopausal women. Subjects were required to be within the age ranging from 20 to 75 years. Exclusion criteria included trials performed on patients with hepatic or renal dysfunction and acute myocardial infarction or stroke. These were excluded as most of the trials considered the safety of the volunteers and thus these criteria were abided by. Those studies comparing policosanol intake to other lipid-lowering therapies were also excluded in order to establish a clearer outcome of the effect of policosanol as a lipid lowering therapy. It is understood that the effects that lipid lowering drug therapy, especially statins, have is already accepted as beneficial and potent (Scandinavian Simvastatin Survival Study Group, 1994; Shepherd *et al.*, 1995; Sacks *et al.*, 1996, Bertolini *et al.*, 1997, The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study group, 1998) Studies reported in languages other than English were also excluded. Similar baseline characteristics and suitable and justifiable sample size was fundamental, with only a few confounding factors or methods utilised to ensure confounders were controlled for. Compliance was also required to be of high quality with few dropouts.

Two assessors screened the studies identified to determine eligibility for inclusion into the review. Using a standardised form, data was extracted to determine the quality of

all the identified intervention studies. Once all of the articles were composed, reviewed and extracted onto data forms they were interpreted and a systematic report was formulated.

Results

Thirty-nine trials qualified and met eligible criteria, of these 34 were parallel in design (Pons *et al.*, 1992; Hernandez *et al.*, 1992; Aneiros *et al.*, 1993; Pons *et al.*, 1993; Pons *et al.*, 1994a; Pons *et al.*, 1994b; Torres *et al.*, 1995; Aneiros *et al.*, 1995; Batista *et al.*, 1995; Canetti *et al.*, 1995a; Canetti *et al.*, 1995b; Castano *et al.*, 1995a; Castano *et al.*, 1995b; Batista *et al.*, 1996a; Batista *et al.*, 1996b; Castano *et al.*, 1996; Crespo *et al.*, 1997; Castano *et al.*, 1997; Mas *et al.*, 1999; Menendez *et al.*, 2000a; Menendez *et al.*, 2000b; Castano *et al.*, 2000; Castano *et al.*, 2001a; Castano *et al.*, 2001b; Castano *et al.*, 2001c; Mas *et al.*, 2001; Mirkin *et al.*, 2001; Castano *et al.*, 2002b; Arruzazabala *et al.*, 2002; Castano *et al.*, 2003a; Lin *et al.*, 2004; Berthold *et al.*, 2006; Dulin *et al.*, 2006; Francini-Pesenti *et al.*, 2007;), while the remaining five were cross-over (Reiner *et al.*, 2005; Greyling *et al.*, 2006; Kassis & Jones, 2006;) and open labelled (Castano *et al.*, 1998; Castano *et al.*, 1999a) studies.

The most common source of policosanols used was extracted from sugar cane. Exceptions included Reiner and colleagues (2005) who used rice policosanols and Lin *et al.* (2004) who used wheat germ policosanols. The duration of the studies varied from 4 weeks to 14 months (mostly 4 to 12 weeks) with a dietary stabilisation period of four to 12 weeks. The number of patients in each study were between 19 to 589 with four relatively large studies namely 244 (Castano *et al.*, 2000), 280 (Mas *et al.*, 2001), 437 (Mas *et al.*, 1999) and 589 (Castano *et al.*, 2002b). The dosage administered ranged from 1 mg/day to 80 mg/day, mostly 10 or 20 mg/day. The effect that the policosanols had on the total cholesterol, LDL-cholesterol and HDL-cholesterol values is summarised in **Table 1**, **Table 2** and **Table 3** respectively. It can also be seen from the tables where the majority of the studies have been performed.

Figure 1 schematically presents the percentage change in LDL-C and HDL-C that was reported between the experimental and control groups in the trials performed on hypercholesterolaemic, mild to normocholesterolaemic, post-menopausal and diabetic subjects. Four trials were, however, excluded from the data integrated in the figure due to numerous reasons. Pons *et al.* (1993) was excluded, as this trial studied the effects

that policosanol had on TC and no other lipid markers, Reiner *et al.* (2005) employed a cross-over study design, the results of which only indicated the experimental group. Castano *et al.* (1998) and Castano *et al.* (1999) both used an open-labeled study design and did not have control groups, only experimental groups to be studied. The study performed by Batista and co-workers in 1996b reported the effects found on the LDL-C but not that of the HDL-C.

It was noted throughout the review that the studies conducted have all been considerably varied. The mean reduction of LDL-C amongst the Cuban studies was 22.5%, while the mean increase in HDL-C was 14.27%. The mean dose that was issued to the subjects to be taken daily was 12 mg/day, with a range of between 1 to 80 mg/day.

Table 1 Studies determining the effect of policosanol on total, LDL and HDL cholesterol in hypercholesterolaemic patients

Reference [Quality score]** Location of study	Duration; n; daily dosage	TC		LDL		HDL	
		Difference between change in experimental and change in control group (mmol/L) [percentage difference]	p-value	Difference between change in experimental and change in control group (mmol/L) [percentage difference]	p-value	Difference between change in experimental and change in control group (mmol/L) [percentage difference]	p-value
Pons <i>et al.</i> , 1992 [13] Havanna, Cuba	8wk; n=56; 5mg/d	1.02 (14%)	NS	1.08 (21.4%)	NS	-0.05 (3.3%)	NS
Aneiros <i>et al.</i> , 1993a [13] Havanna, Cuba	12wk; n=33; 2 * 5mg	0.92 (13.2%)	NS	1.04 (20.6%)	NS	-0.19 (16.6%)	NS
	20 mg/d	1.19 (17.2%)	NS	1.24 (24.6%)	NS	-0.14 (-12.8%)	NS
Pons <i>et al.</i> , 1993 [11] Havanna, Cuba	24wk; n=26; 1mg/d	1.53 (23.3%)	NS	Not determined			
	10mg/d	1.81 (28.3%)	NS	Not determined			
Pons <i>et al.</i> , 1994a [13] Havanna, Cuba	12mo; n=59; 5mg/d	1.04 (14.5%)	NS	1.15 (23.6%)	NS	-0.06 (4.3%)	NS
Pons <i>et al.</i> , 1994b [11] Havanna, Cuba	24wk; n=22; 5,10, 20mg***	1.78 (22.6%)	0.01	1.69 (29.5%)	0.01	-0.18 (13.5%)	NS
Aneiros <i>et al.</i> , 1995 [13] Havanna, Cuba	6wk; n=45; 2 * 5mg	0.95 (12.1%)	0.001	1.09 (19.8%)	0.00001	-0.18 (-20.3%)	0.05

Reference [Quality score]** Location of study	Duration; n; daily dosage	TC		LDL		HDL	
		Difference between change in experimental and change in control group (mmol/L) [percentage difference]	p-value	Difference between change in experimental and change in control group (mmol/L) [percentage difference]	p-value	Difference between change in experimental and change in control group (mmol/L) [percentage difference]	p-value
Batista <i>et al.</i> , 1995 [11] Havanna, Cuba	12mo; n=22; 2 * 5mg	-0.98 (15.3%)	NS	-0.61 (13.6%)	NS	0.2 (-13.6%)	NS
Canetti <i>et al.</i> , 1995a [13] Havanna, Cuba	12mo; n=97; 2 * 5 mg	1.32 (17.3%)	0.001	1.42 (26%)	NS	-0.22 (17.5%)	NS
Canetti <i>et al.</i> , 1995b [13] Havanna, Cuba	24mo; n=69; 2 * 5 mg	1.2 (15.9%)	0.01	1.27 (23%)	NS	-0.17 (12.9%)	NS
Castano <i>et al.</i> , 1995a [13] Havanna, Cuba	12mo; n=62; 10mg/d	1.49 (20%)	0.0001	1.55 (29%)	NS	-0.11 (-8.6%)	NS
Castano <i>et al.</i> , 1995b [13] Havanna, Cuba	12mo; n=74; 2 * 5 mg	1.2 (18%)	0.0001	1.37 (28%)	0.0001	-0.14 (-11.9%)	0.01

Reference [Quality score]** Location of study	Duration; n; daily dosage	TC		LDL		HDL	
		Difference between change in experimental and change in control group (mmol/L) [percentage difference]	p-value	Difference between change in experimental and change in control group (mmol/L) [percentage difference]	p-value	Difference between change in experimental and change in control group (mmol/L) [percentage difference]	p-value
Batista <i>et al.</i> , 1996a [13] Havanna, Cuba	20mo; n=41; 2 * 5 mg	0.5 (8.3%)	NS	0.45 (12.2%)	NS	-0.08 (-7.2%)	NS
	2 * 5 mg plus 125mg aspirin	0.41 (6.6%)	NS	0.5 (13.9%)	NS	-0.08 (7.3%)	NS
Batista <i>et al.</i> , 1996b [11] Havanna, Cuba	14mo; n=23; 2 * 1mg/d	1.27 (18.1%)	NS	0.96 (20.6%)	NS	Not determined	
Castano <i>et al.</i> , 1996 [13] Havanna, Cuba	12mo; n=58; 10mg/day	1.18 (16.5%)	0.01	1.22 (25.2%)	0.001	-0.15 (-16.6%)	NS
Castano <i>et al.</i> , 1997 [13] Havanna, Cuba	10wk; n=60 2 * 5 mg	1.17 (16.6%)	0.00001	1.24 (23.1%)	0.00001	-0.12 (-14.3%)	0.01
	1 * 10 mg	1.25 (17.1%)	0.00001	1.41 (25.2%)	0.00001	-0.21 (25.3%)	0.01

Reference [Quality score]** Location of study	Duration; n; daily dosage	TC		LDL		HDL	
		Difference between change in experimental and change in control group (mmol/L) [percentage difference]	p-value	Difference between change in experimental and change in control group (mmol/L) [percentage difference]	p-value	Difference between change in experimental and change in control group (mmol/L) [percentage difference]	p-value
Castano <i>et al.</i> , 1998 [8] Havanna, Cuba	8wk; n=54; 20mg/d	Open labelled, uncontrolled					
Castano <i>et al.</i> , 1999a [8] Havanna, Cuba	12mo; n=68; 20mg/d	Open labelled, uncontrolled					
Mas <i>et al.</i> , 1999 [13] Havanna, Cuba	24wk; n=437; 5mg/day initially	0.78 (12.1%)	0.001	0.91 (17.4%)	0.001	-0.16 (-15.5%)	NS
	10mg/day after 12 wks	1.11 (17.2%)	0.001	1.28 (25.2%)	0.001	-0.26 (-25.5%)	NS
Castano <i>et al.</i> , 2000 [13] Havanna, Cuba	24wk; n=244; 5mg/day initially	0.85 (12.9%)	0.0001	0.97 (18.2%)	0.0001	-0.16 (-15%)	0.01
	10mg/day after 12 wks	1.16 (17.3%)	0.0001	1.35 (25.8%)	0.0001	-0.26 (-26%)	0.0001
Menendez <i>et al.</i> , 2000a [13] Havanna, Cuba	12wk; n=20; 5mg/ day	1.22 (19.4%)	0.001	1.24 (22.9%)	0.01	-0.06 (-9.7%)	0.05

Reference [Quality score]** Location of study	Duration; n; daily dosage	TC		LDL		HDL	
		Difference between change in experimental and change in control group (mmol/L) [percentage difference]	p-value	Difference between change in experimental and change in control group (mmol/L) [percentage difference]	p-value	Difference between change in experimental and change in control group (mmol/L) [percentage difference]	p-value
Castano <i>et al.</i> , 2001a [13] Havanna, Cuba	24wk; n=89; 20 mg/d	1.01 (14.9%)	0.001	1.49 (35.2%)	0.00001	-0.47 (-33.4%)	0.0001
	40 mg/d	1.16 (16.6%)	0.00001	1.54 (36%)	0.00001	-0.45 (-32.8%)	0.0001
Castano <i>et al.</i> , 2001b [13] Havanna, Cuba	8wk; n=62; 2 * 10 mg	0.98 (13.8%)	0.001	1.37 (34.2%)	0.001	-0.49 (-36.4%)	0.001
	1 * 20 mg	1.29 (17.8%)	0.001	1.59 (36.1%)	0.001	-0.45 (-37.8%)	0.001
Castano <i>et al.</i> , 2001c [13] Havanna, Cuba	24wk; n=179; 5mg/d	0.81 (12.4%)	0.001	0.91 (17%)	0.001	-0.14 (-13.6%)	NS
	10mg/d	1 (15%)	0.001	1.25 (24.8%)	0.001	-0.33 (-32.7%)	NS

Reference [Quality score]** Location of study	Duration; n; daily dosage	TC		LDL		HDL	
		Difference between change in experimental and change in control group (mmol/L) [percentage difference]	p-value	Difference between change in experimental and change in control group (mmol/L) [percentage difference]	p-value	Difference between change in experimental and change in control group (mmol/L) [percentage difference]	p-value
Mas <i>et al.</i> , 2001 [13] Havanna, Cuba	1yr; n=280; 5 mg/d	1.01 (13.1%)	0.00001	1.05 (22.8%)	0.00001	-0.23 (-20.8%)	0.001
Mirkin <i>et al.</i> , 2001 [13] Havanna, Cuba	16wk; n=56; 5mg/day initially	0.62 (10.6%)	0.001	0.56 (12.8%)	0.05	-0.02 (-1.1%)	NS
	10mg/day after 12 wks	0.95 (18.5%)	0.0001	1.07 (27.7%)	0.0001	-0.11 (-13.6%)	0.01
Castano <i>et al.</i> , 2002b [13] Havanna, Cuba	12mo; n=589; 5 - 10 mg/d****	1 (14.4%)	0.001	0.95 (19.7%)	0.001	-0.11 (-15.4%)	0.01
Reiner <i>et al.</i> , 2005 [13] Zagreb, Croatia	8wk/tm; n=70; 10 mg/d	0.38 (5.2%)	0.007	0.12 (2.5%)	NS	0.02 (1.47%)	NS

Reference [Quality score]** Location of study	Duration; n; daily dosage	TC	LDL	HDL			
		Difference between change in experimental and change in control group (mmol/L) [percentage difference]	p-value	Difference between change in experimental and change in control group (mmol/L) [percentage difference]	p-value	Difference between change in experimental and change in control group (mmol/L) [percentage difference]	p-value
Berthold <i>et al.</i> , 2006 [13] Cologne, Germany	12wk; n=143; 10mg/d	-0.05 (-1.1%)	NS	0.06 (0.4%)	NS	-0.05 (-3.8%)	NS
	20 mg/d	-0.23 (3.3%)	NS	-0.15 (-3.3%)	NS	-0.01 (-0.86%)	NS
	40 mg/d	-0.66 (-4.3%)	NS	-0.22 (-4.8%)	NS	-0.07 (-5.46%)	NS
	80 mg/d	-0.23 (-3.4%)	NS	0.05 (0.7%)	NS	-0.03 (-9.36%)	NS
Greyling <i>et al.</i> , 2006 [13] Potchefstroom, South Africa	12wk/tm; n=35; 20 mg/d - Familial hyperchol	0.16 (2.3%)	NS	-0.11 (-2.04%)	NS	0 (0.13%)	NS
	Hyperchol	0.35 (5.32%)	NS	0.29 (6.1%)	NS	0.07 (6.4%)	NS
Francini- Pensenti <i>et al.</i> , 2007 [13] Padua, Italy	8wk; n=63; 2* 10 mg/d	0.03 (0.4%)	NS	0.09 (1.9%)	NS	0.04 (2.8%)	NS

TC: total cholesterol wk: weeks NS: Non-significant d: number of days HDL: high density lipoprotein cholesterol mo: months n= number of volunteers per trial tm: per treatment

LDL: low density lipoprotein cholesterol yr: years mg: milligram -: net effect was an increase +: net effect was a decrease hyperchol: hypercholesterolaemia

**Quality score-criteria includes: blind/double blind conditions (controlled); compliance (drop-outs); similar baseline characteristics; randomization; suitable sample size,

volunteers received either 5, 10 or 20mg policosanol per day *volunteers received either 5 or 10 mg policosanol per day

Table 2 Studies determining the effect of policosanol on total, LDL and HDL cholesterol in normocholesterolaemic or mild hypercholesterolaemia volunteers

Reference [Quality score]**	Duration; n; daily dosage	TC		LDL		HDL	
		Difference between change in experimental and change in control group (mmol/L) [percentage difference]	p-value	Difference between change in experimental and change in control group (mmol/L) [percentage difference]	p-value	Difference between change in experimental and change in control group (mmol/L) [percentage difference]	p-value
Hernandez <i>et al.</i> , 1992 [13] Havanna, Cuba	4wk; n=38; 10 mg/d	0.78 (16.6%)	NS	0.23 (7.7)	NS	0.2 (15.4%)	NS
	20 mg/d	0.79 (17.2%)	NS	0.61 (20.6%)	NS	-0.04 (-5.9%)	NS
Menendez <i>et al.</i> , 2000b [13] Havanna, Cuba	8wk; n=69; 5 mg/d	0.67 (14.9%)	0.0001	0.67 (24%)	0.0001	-0.11 (-10.8%)	0.05
	10mg/d	0.75 (16.8%)	0.0001	0.77 (27.5%)	0.0001	-0.14 (-17%)	0.01
Arruzazabala <i>et al.</i> , 2002 [13] Havanna, Cuba	30d; n=45; 20mg/d	0.63 (16.2%)	0.05	0.6 (13.4%)	0.05	-0.04 (-4.6%)	0.05
	40mg/d	0.65 (16.1%)	0.001	0.66 (14.5%)	0.05	-0.04 (-4.3%)	0.01
Castano <i>et al.</i> , 2003a [13] Havanna, Cuba	8wk; n=100; 5mg/ day	0.7 (13.4%)	0.001	0.75 (21%)	0.001	0 (-10.5)	0.05
Lin <i>et al.</i> , 2004 [13] Vlaardingen, Netherlands	4wk; n=58; 20mg/d	0.13 (2.4%)	NS	0.03 (0.9%)	NS	0.05 (4%)	NS

Reference [Quality score]**	Duration; n; daily dosage	TC		LDL		HDL	
		Difference between change in experimental and change in control group (mmol/L) [percentage difference]	p-value	Difference between change in experimental and change in control group (mmol/L) [percentage difference]	p-value	Difference between change in experimental and change in control group (mmol/L) [percentage difference]	p-value
Dulin <i>et al.</i> , 2006 [13] Charlotte, NC, USA	8wk; n=39; 20mg/d	-0.11 (-1.6%)	NS	0.01 (0.5%)	NS	0 (-0.6%)	NS
Kassis & Jones, 2006 [11] Quebec, Canada	28d/tm; n=21; 10 mg/d	-0.17 (-5.8%)	NS	-0.08 (-2.9%)	NS	-0.04 (-4.7%)	NS

TC: total cholesterol

wk: weeks

NS: Non-significant

d: number of days

HDL: high density lipoprotein cholesterol

mo: months

n= number of volunteers per trial

tm: per treatment

LDL: low density lipoprotein cholesterol

yr: years

mg: milligram

-: net effect was an increase

+: net effect was a decrease

**Quality score-criteria includes: blind/double blind conditions (controlled); compliance (drop-outs); similar baseline characteristics; randomization; suitable sample size,

***volunteers received either 5, 10 or 20mg policosanol per day

****volunteers received either 5 or 10 mg policosanol per day

Table 3 Studies determining the effect of policosanol on total, LDL and HDL cholesterol in Type II diabetic and hypercholesterolaemic patients

Reference [Quality score]**	Duration; n; daily dosage	TC		LDL		HDL	
		Difference between change in experimental and change in control group (mmol/L) [percentage difference]	p-value	Difference between change in experimental and change in control group (mmol/L) [percentage difference]	p-value	Difference between change in experimental and change in control group (mmol/L) [percentage difference]	p-value
Torres <i>et al.</i> , 1995 [13] Havanna, Cuba	12wk; n=29; 2 * 5 mg	1.67 (23%)	0.01	1.76 (33.2%)	0.01	-0.17 (-15.3%)	NS
Crespo <i>et al.</i> , 1997 [11] Havanna, Cuba	12wk; n=19; 2 * 5 mg	2.23 (29.3%)	0.01	2.46 (47.8%)	0.05	-0.1 (-22.8%)	0.05

TC: total cholesterol

wk: weeks

NS: Non-significant

d: number of days

HDL: high density lipoprotein cholesterol

mo: months

n= number of volunteers per trial

tm: per treatment

LDL: low density lipoprotein cholesterol

yr: years

mg: milligram

-: net effect was an increase

+: net effect was a decrease

**Quality score-criteria includes: blind/double blind conditions (controlled); compliance (drop-outs); similar baseline characteristics; randomization; suitable sample size,

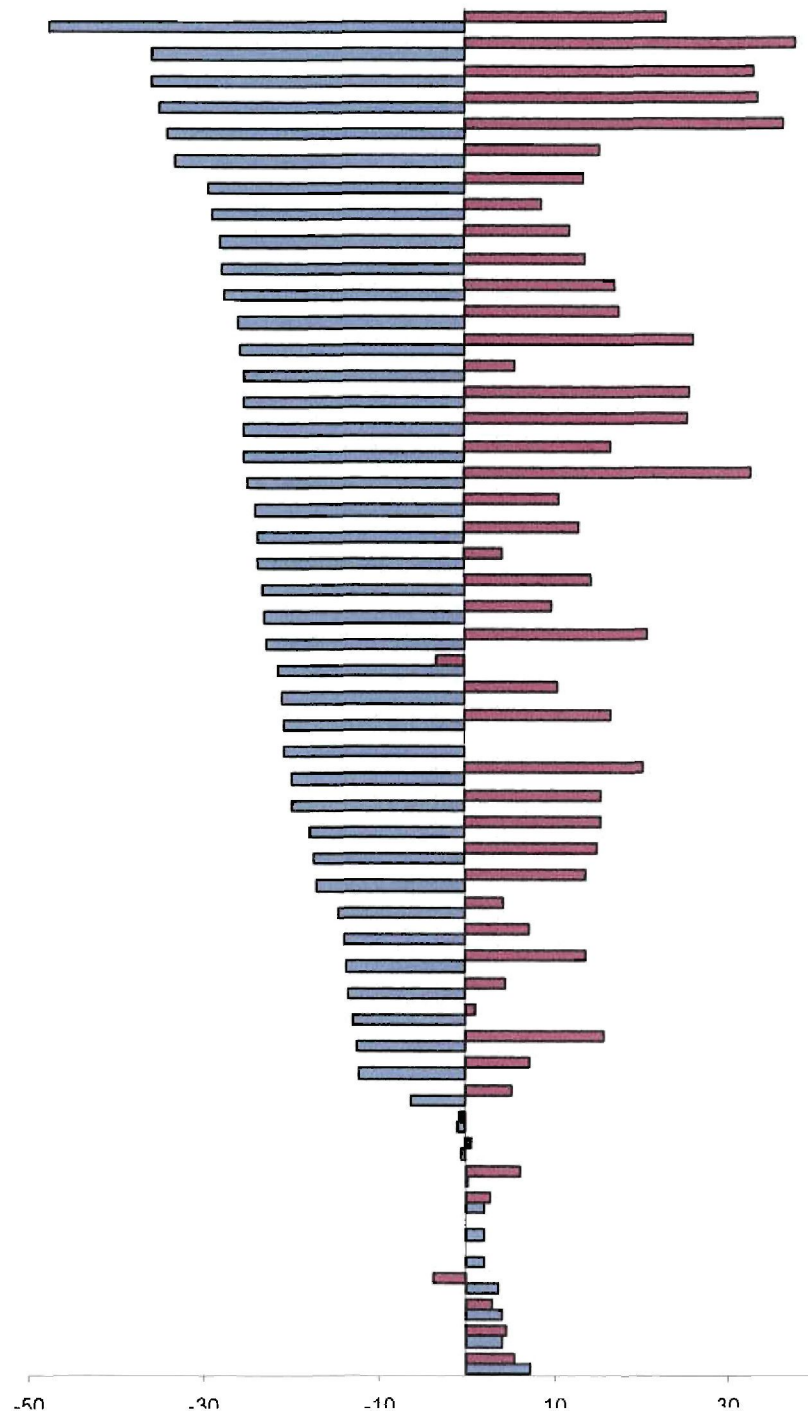
***volunteers received either 5, 10 or 20mg policosanol per day

****volunteers received either 5 or 10 mg policosanol per day

Note: Differences between changes extracted from data.

Figure 1 The percentage change in LDL-C and HDL-C between the experimental and control groups (Page 78)

Author	Group	No. of patients	Dosage (mg/day)	Duration (weeks)	% change LDL-C	% change HDL-C
Crespo <i>et al.</i> , 1997	HC, DM	19 (9 P, 10 PC)	10	12	-47.8	22.8
Castano <i>et al.</i> , 2001b	HC	62 (21 P, 21 PC) 1*20mg	20	8	-36.1	37.8
Castano <i>et al.</i> , 2001a	HC	89 (30 P, 30 PC)	40	24	-36	32.8
Castano <i>et al.</i> , 2001a	HC	89 (30 P, 29 PC)	20	24	-35.2	33.4
Castano <i>et al.</i> , 2001b	HC	62 (21 P, 20 PC) 2*10mg	20	8	-34.2	36.4
Torres <i>et al.</i> , 1995	HC, DM	29 (15 P, 14 PC)	10	12	-33.2	15.3
Pons <i>et al.</i> , 1994b	HC	22 (10 P, 12 PC)	10	24	-29.5	13.5
Castano <i>et al.</i> , 1995a	HC, elderly	62 (34 P, 28 PC)	10	52	-29	8.6
Castano <i>et al.</i> , 1995b	HC	74 (38 P, 36 PC)	10	52	-28	11.9
Mirkin <i>et al.</i> , 2001	HC	56 (28 P, 28 PC)	10	16	-27.7	13.6
Menendez <i>et al.</i> , 2000b	MILD	69 (23 P, 46 PC)	10	8	-27.5	17
Canetti <i>et al.</i> , 1995a	HC	97 (50 P, 47 PC)	10	52	-26	17.5
Castano <i>et al.</i> , 2000	HC, PMW	244 (122 P, 122 PC)	10	24	-25.8	26
Castano <i>et al.</i> , 1996	HC, HPT	58 (28 P, 30 PC)	10	52	-25.2	16.6
Castano <i>et al.</i> , 1997	HC	60 (20 P, 20 PC) 1*10mg	10	10	-25.2	25.3
Mas <i>et al.</i> , 1999	HC	437 (218 P, 219 PC)	10	24	-25.2	25.5
Castano <i>et al.</i> , 2001c	HC, elderly	179 (89 P, 90 PC)	10	24	-24.8	32.7
Aneiros <i>et al.</i> , 1993	HC	33 (17 P, 16 PC)	20	12	-24.6	12.8
Menendez <i>et al.</i> , 2000b	MILD	69 (23 P, 46 PC)	5	8	-24	10.8
Pons <i>et al.</i> , 1994a	HC	59 (31 P, 28 PC)	5	52	-23.6	4.3
Castano <i>et al.</i> , 1997	HC	60 (20 P, 20 PC) 2*5mg	10	10	-23.1	14.3
Canetti <i>et al.</i> , 1995b	HC	69 (37 P, 32 PC)	10	104	-23	12.9
Menendez <i>et al.</i> , 2000a	HC	20 (10 P, 10 PC)	5	12	-22.9	9.7
Mas <i>et al.</i> , 2001	HC, elderly	280 (140 P, 140 PC)	5	52	-22.8	20.8
Pons <i>et al.</i> , 1992	HC	56 (29 P, 27 PC)	5	8	-21.4	-3.3
Castano <i>et al.</i> , 2003	MILD	100 (50 P, 50 polic)	5	8	-21	10.5
Hernandez <i>et al.</i> , 1992	Healthy	38 (13 P, 10 PC)	20	4	-20.6	5.9
Aneiros <i>et al.</i> , 1993	HC	33 (17 P, 16 PC)	10	12	-20.6	16.6
Bastista <i>et al.</i> , 1996b	HC	23 (11 P, 12 PC)	2	56	-20.6	***
Aneiros <i>et al.</i> , 1995	HC	45 (23 P, 22 PC)	10	6	-19.8	20.3
Castano <i>et al.</i> , 2002	HC, HPT	589 (293 P, 296 PC)	5	52	-19.7	15.4
Castano <i>et al.</i> , 2000	HC	244 (122 P, 122 PC)	5	24	-18.2	16
Mas <i>et al.</i> , 1999	HC	437 (218 P, 219 PC)	5	24	-17.4	15.5
Castano <i>et al.</i> , 2001c	HC, elderly	179 (89 P, 90 PC)	5	24	-17	13.6
Arruzazabala, 2002	Healthy	45 (15 P, 15 PC)	40	4	-14.5	4.3
Bastista <i>et al.</i> , 1996a	HC	41 (14 P (aspirin), 15 PC)	10	80	-13.9	7.2
Bastista <i>et al.</i> , 1995	HC	22 (11 P, 11 PC)	10	52	-13.6	13.6
Arruzazabala, 2002	Healthy	45 (15 P, 15 PC)	20	4	-13.4	4.6
Mirkin <i>et al.</i> , 2001	HC	56 (28 P, 28 PC)	5	16	-12.8	1.1
Bastista <i>et al.</i> , 1996a	HC	41 (14 P (aspirin), 12 PC)	10	80	-12.2	7.2
Hernandez <i>et al.</i> , 1992	Healthy	38 (13 P, 15 PC)	10	4	-7.7	-15.4
Lin <i>et al.</i> , 2004	MILD	58 (29 P, 29 PC)	20	4	-0.9	-4
Berthold <i>et al.</i> , 2006	HC	143 (29 P, 32 PC)	80	12	-0.7	9.4
Dulin <i>et al.</i> , 2006	MILD	39 (20 P, 19 PC)	20	8	-0.5	0.6
Berthold <i>et al.</i> , 2006	HC	143 (29 P, 28 PC)	10	12	-0.4	3.8
Francini-Pesenti, 2007	HC	58 (34 P, 34 PC)	20	8	1.9	2.8
Greyling <i>et al.</i> , 2006	FH	16 (16 P, 16 PC)	20	24	2.04	-0.13
Kassis <i>et al.</i> , 2006	Healthy	21 (21 P, 21 PC)	10	4	2.9	4.7
Berthold <i>et al.</i> , 2006	HC	143 (29 P, 27 PC)	20	12	3.3	0.86
Berthold <i>et al.</i> , 2006	HC	143 (29 P, 27 PC)	40	12	4.8	5.5
Greyling <i>et al.</i> , 2006	HC	19 (19 P, 19 PC)	20	24	6.1	6.4



From the 39 studies that were included in this review, 85% of them found that policosanol had a beneficial effect on the lipid profile, while 15% of the studies did not confirm benefits. The latter incorporated the more recent (independent) studies performed after 2004. The same research group in Cuba performed those studies reporting positive beneficial association with policosanol intake. Of these initial studies the largest percentage decrease of total cholesterol, at 29.3% was reported in the study by Crespo *et al.* (1997) who gave each of the test subjects in the policosanol group 10 mg of policosanol twice daily and monitored them for 12 weeks. This study also reported the largest decrease in the LDL-C level by 47.8%. The effect that policosanol had on the total cholesterol of both normocholesterolaemic volunteers as well as those with hypercholesterolaemia indicated that the effect was of a larger degree on those volunteers with hypercholesterolaemia, thereby indicating that policosanol may not have prophylactic qualities. The study performed by Castano *et al.* in 2001 resulted in the most significant increase of HDL-C, where a percentage change of 37.8% was reported.

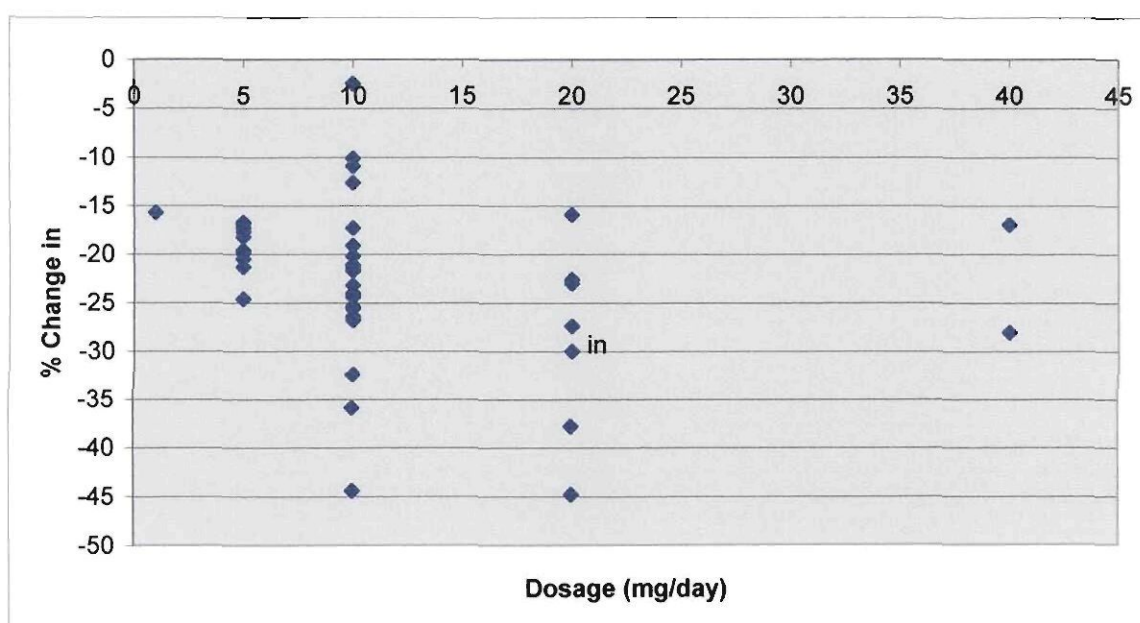


Figure 2 The response of dosage on percentage change of LDL-C on initial Cuban studies

The cholesterol-lowering effect of policosanol is mainly noted when there is a decrease in LDL-C (Menendez *et al.*, 1996). A dosage of 2 mg/day was found to reduce the TC and LDL-C by 14.8% and 15.6% respectively (Bastita *et al.*, 1996b). Castano *et al.* (2000) found that 5 mg/day resulted in a 1.29 percentage decrease in LDL-C while 10 mg/day decreased LDL-C by 17.3%. The most significant changes in percentage in TC

between the policosanol and placebo groups occurred at a dosage of between 5 – 10 mg per day. The study performed by Castano *et al.* (2002) found the LDL-C mean percent reduction from baseline were 27.4% and 28.1% for the 20 and 40 mg/day groups, respectively and almost identical in changing the lipid profile in all the other parameters. Therefore according to this study dosage above 20 mg/day may have beneficial effects but need to be studied further. **Figure 2** clearly indicates that the most significant effect found on the LDL levels is at dosages of between 10 to 20 mg/day. Dosage administered at quantities of greater than that are less effective. Therefore, a sensible recommendation would be to start with 5 mg daily and increase gradually to 10 mg twice daily or more as necessary (Anon, 2004). Policosanol was found to be as effective in once-off regimes as twice daily after 4 weeks of use (Castano *et al.*, 2001b). The once-off dosage was administered in the evening based on the proposal that policosanol decreases the cholesterol by inhibiting biosynthesis of cholesterol and increasing the receptor dependent LDL catabolism and due to the increased rate of cholesterol biosynthesis at night (Parker *et al.*, 1982).

Most of the trials focused on female subjects (73.4%) while the remaining 26.6% were male volunteers. This may be due to the reflecting patterns of behaviour in the population group as in Cuba, middle-aged and older women tend to adhere more to long-term treatment than men. This factor was noted to be unlikely to limit conclusions due to the lack of significant differences between groups in sex composition (Castano *et al.*, 2001b).

Diet

The majority of the selected studies encouraged a diet stabilisation period prior to the beginning of the trial where volunteers were encouraged to follow a step 1 cholesterol-lowering diet throughout the trial, but with no control or monitoring of the diet. Only five studies encouraged habitual or normal eating patterns (Hernandez *et al.*, 1992; Menendez *et al.*, 2000; Dulin *et al.*, 2006; Kassis & Jones, 2006; Lin *et al.*, 2006). The step 1 cholesterol-lowering diet includes a varied, balanced and nutritious consumption of the food groups, daily intake of < 300 mg/day cholesterol, total fat intake of less than 30%, saturated fats <10% of total energy and the ratio of polyunsaturated: saturated fatty acids between 0.75 to 1 (NCEP, 2001; Torres *et al.*, 1995). Some of the studies encouraged a habitual diet with no changes in dietary intake or frequency (Hernandez *et al.*, 1992; Menendez *et al.*, 2000b; Lin *et al.*, 2004; Kassis & Jones, 2006; Dulin *et al.*, 2006). Very long chain fatty alcohols are also widely available in plants and oils that

constitute a large part of the human diet (Hargrove *et al.*, 2004) as it is found in products commonly consumed such as rice, wheat, apple, apples, plums, spinach and a large variety of nuts and seeds (Hargrove *et al.*, 2004). Therefore, a habitual diet that already provides a high concentration of octacosanol may have the potential ability to mask the effect of the supplementation (Kassis & Jones, 2006). Therefore, the possibility of a confounding effect of food cannot be ruled out.

Compliance, tolerability and safety

Policosanol was mostly issued in capsule or tablet form, varying in strengths. Kassis and Jones (2006) used the original policosanol from Havana, Cuba, crushed it and incorporated it into margarine served on a slice of bread to evaluate policosanol's integration with food. The fatty matrices were also presumed to assist with mixing and distribution of policosanol due to the insolubility of policosanol in water. Lin *et al.* (2004) issued chocolate pellets containing wheat germ policosanol and found compliance in both experimental and placebo groups to be excellent.

Most of the trials measured compliance using tablet or pill count while some used tablet count in addition to an interview or even solely an interview. The policosanol was well tolerated in all the population groups, including the elderly, postmenopausal and diabetic patients. Good compliance was recorded with few dropouts. Dropouts were mainly due to personal reasons, change of address, refusal or unwillingness to continue treatment, travel abroad and lack of compliance. More than 60% of the dropouts were from the placebo group while the remaining 40% fell into the experimental groups. Throughout the studies the adverse effects/ events were reported and monitored in both the placebo and policosanol groups. Of the total number of volunteers studied in the policosanol groups the most common adverse effects reported were gastrointestinal disturbances (gastritis, flatulence, nausea and increase bowel movement) (1%) headache (1%), cardiovascular complications (uncontrolled hypertension) (1%) and nervousness (1%). Other adverse effects noted included dizziness (0.72%), insomnia (0.72%), somnolence (0.52%), dry skin or rash (0.39%), muscle cramps (0.4%), asthenia (0.32%), abdominal pain (0.19%) and fatigue (0.13%).

Discussion

This systematic review found that although there are numerous peer-reviewed, controlled trials available from Cuba indicating beneficial uses for policosanol in the treatment of hypercholesterolaemia, more recent external clinical trials (Lin *et al.*, 2004; Berthold *et al.*, 2006; Dulin *et al.*, 2006; Greyling *et al.*, 2006; Kassis & Jones., 2006; Francini-Pesenti *et al.*, 2007) have found only contradicting results even when the original sugar cane derived supplement was used (Berthold *et al.*, 2006; Kassis & Jones, 2006; Francini-Pesenti *et al.*, 2007).

The duration of the clinical trials varied from 4 weeks to 24 months with effects noted already by the fourth week (Hernandez *et al.*, 1992). The external studies performed varied from four to 24 weeks but still no significant effects were noted with dosages similar to the Cuban studies. From **Figure 3** it is possible to see the effects on total cholesterol were noted over the duration of from 6 weeks through to 21 months. Even at the longer duration there was an effect found with the use of policosanol supplementation.

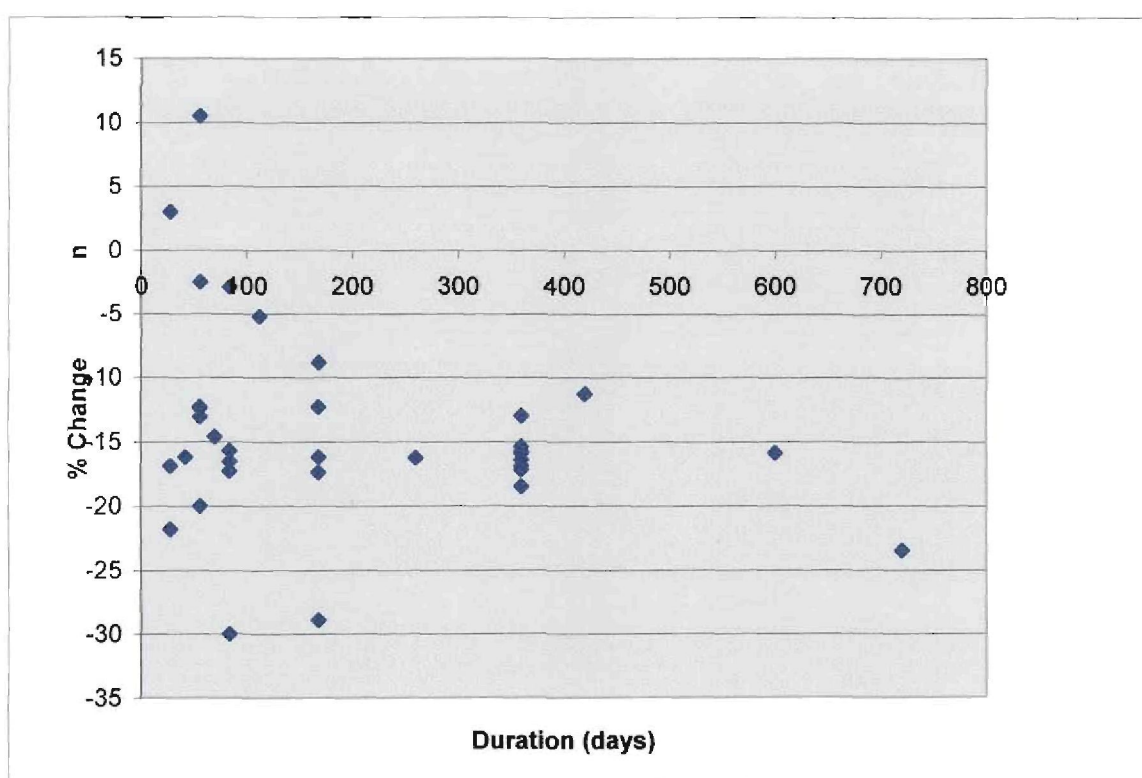


Figure 3 Duration (days) and the response to total cholesterol

Current available lipid-lowering therapies e.g. statins, nicotinic acid, ionic exchange resins, fibrates and probucol have been associated with a number of long term side effects, namely hepatotoxicity and myopathy as indicated in available data (Yale, 1992; Bhatnagar, 1998; Bolego *et al.*, 2002). It was found that at 10 mg/day policosanol had a much more advantageous effect in HDL-C and was better tolerated than lovastatin at 20 mg/day (Crespo *et al.*, 1999). Policosanol also exhibited a more beneficial effect in comparison to pravastatin at 10 mg/day, notably increasing the HDL-C (Castano *et al.*, 1999b). When acipimox, 750 mg/day was compared to policosanol it resulted in a decrease in both TC and LDL-C in both groups after an 8 week treatment duration, but the policosanol group was found to have a larger decrease in the LDL: HDL ratio and the TC: HDL ratio (Alcocer *et al.*, 1999). However, the results of a recent study by Cubeddu *et al.* (2006) contradict these findings. They reported a 27% reduction of TC and 35% reduction of LDL-C in hypercholesterolaemic patients when atorvastatin was administered whilst addition of policosanol to atorvastatin failed to produce any further reduction in lipid levels. Policosanol alone (or in combination with atorvastatin) did not reduce LDL-C or TC levels. The authors proposed, "policosanol should be added to the list of nutritional supplements lacking scientific validity to support their use" (Cubeddu *et al.*, 2006).

With a 10 % reduction of the level of total serum cholesterol there may be a reduction in the 5-year risk of ischaemic heart disease by around 25% (Law *et al.*, 1994). A meta-analysis by Gould and colleagues (Gould *et al.*, 1998; Gould *et al.*, 2007), which included eight clinical trials of lipid-lowering therapy, found that every 10% reduction in serum TC level significantly decreased the risk of CHD mortality by 15% and total mortality by 11%. In the policosanol studies they found twenty-eight had at least a 10% reduction in serum TC (Pons *et al.*, 1992; Hernandez *et al.*, 1992; Aneiros *et al.*, 1993a; Pons *et al.*, 1994a; Pons *et al.*, 1994b; Aneiros *et al.*, 1995; Batista *et al.*, 1995; Canetti *et al.*, 1995a; Canetti *et al.*, 1995b; Castano *et al.*, 1995a; Castano *et al.*, 1995b; Torres *et al.*, 1995; Castano *et al.*, 1996; Zardoya *et al.*, 1996; Crespo *et al.*, 1997; Castano *et al.*, 1997; Mas *et al.*, 1999; Menendez *et al.*, 2000a; Menendez *et al.*, 2000b; Castano *et al.*, 2000; Castano *et al.*, 2001a; Castano *et al.*, 2001b; Castano *et al.*, 2001c; Mas *et al.*, 2001; Mirkin *et al.*, 2001; Arruzazabala *et al.*, 2002; Castano *et al.*, 2002b; Castano *et al.*, 2003). In addition to the reduction in TC and LDL-C levels there was a mean increase of 12.7% in the HDL found and a reduction in the LDL: HDL ratio (-33.8%) and triglycerides (-5.7%). All of these blood lipid levels resulted in a clear reduction in the risk for cardiovascular disease.

Reasoning for the exceptionally impressive initial results of the majority of the studies by research groups in Cuba while researchers elsewhere in the world have been unable to reproduce the initial reports (Lin *et al.*, 2004; Reiner *et al.*, 2005; Berthold *et al.*, 2006; Dulin *et al.*, 2006; Greyling *et al.*, 2006; Kassis & Jones, 2006) raises alertness. The Cuban researchers suggested that it is the exclusive purity and relative composition of their policosanols supplement that is responsible for its ability to improve the serum lipid profile (Castano *et al.*, 2002a). However, Marinangeli *et al.* (2007) compared the relative percentage purity and policosanol composition of both the original Cuban and alternative sources of policosanol. Their results indicated that the alternative policosanol formulations have a composition that is highly consistent with the original supplement and they concluded that if the cholesterol-lowering efficacy of policosanol is dependent on its purity and composition, then sugar cane derived alternative sources should possess similar therapeutic properties as the original supplement. It was also found in the study by Kassis and Jones (2006) who used the authentic Cuban sugar cane policosanol that there were no significant effects on serum lipids. The original supplement was also used in a recent study by Berthold *et al.* (2006), administered at 10, 20, 40 and 80 mg/d to four different treatment groups over a 12-week period. They could not demonstrate a reduction in lipid levels beyond the placebo. Nonetheless, the original policosanol in the Berthold *et al.* (2006) study was purchased as a raw material, and then subsequently manufactured into tablets.

It was thought that due to the high content of the main alcohol octacosanol in the primary policosanol source, it may be the primary factor that is responsible for the assistance in the reduction of lipid levels (Mas, 2000). However, the octacosanol concentration of wheat germ, rice and Lesstanol Octa-60 policosanol is similar to the original supplement (Lin *et al.*, 2004; Reiner *et al.*, 2005; Greyling *et al.*, 2006). In a study by Dullens *et al.* (2008) it was found that neither the individual policosanol components nor the natural policosanol mixture lowered serum cholesterol concentrations in LDL receptor knockout mice. They also found that there was no significant effect on gene expression profiles of LDLr, ABCA1, HMG-CoA synthase 1 and apolipoprotein A-I (apo A-I) in hepatic and small intestinal tissue of female mice after a 7-week intervention phase. It was concluded by this group that policosanol had no potential for reducing LDL concentrations and increasing HDL-C concentrations (Dullens *et al.*, 2007).

As policosanols are oxidised after ingestion to fatty acids through β -oxidation (Singh & Poulos, 1986; Singh *et al.*, 1987; Wanders *et al.*, 1987; Kabir & Kimura, 1993; Kabir &

Kimura, 1995) very long chain fatty acids (VLCFA) are implicated as the active form of policosanols influencing cholesterol metabolism. Long-chain aliphatic alcohols are not well absorbed in the intestine (Bernard & Carlier, 1991). Marinangeli *et al.* (2007) recently fed Syrian hamsters a diet containing 0.275 mg/g policosanols of either the original Cuban source or an alternative sugar cane product to study the intestinal absorption. Policosanols were undetectable in the small intestine, liver, adipose tissue or plasma in animals fed either source. Hamsters fed the original policosanols excreted octacosanol (C28) more rapidly than hamsters receiving the alternative source. Furthermore, no changes in serum lipids were noted (Marinangeli *et al.*, 2007). The hypothesis regarding the mechanism for lowering HMG-CoA reductase activity in the liver would require that adequate amounts of the supplement are absorbed and, therefore, be detected in both the plasma and hepatocytes (Marinangeli *et al.*, 2007). Prior to this Wang *et al.* (2005) performed a study on 75 male Golden Syrian hamsters. They also found that the VLCFA had no significant lipid-lowering effects in hamsters and thus found policosanols ineffective.

Most of the Cuban studies were performed on the surrounding population. It was, therefore, suggested that ethnic and environmental factors could be responsible for the remarkable results found by this group. Francini-Pesenti and co-workers (2007) discussed the possibility of this and reasoned that ethnic differences could not explain differences in the Cuban and other studies as diet and lipid lowering agents, such as statins, have been shown to have similar effects in different populations (Howard *et al.*, 1995; Tan *et al.*, 2003). With more recent data being published questions are raised regarding the methods used and the motivation driving the reasons for this phenomenon.

The strengths of the studies included in this review embraces the sufficient number of test subjects that are randomised into groups, the varying dosages and durations that subjects are observed for and the control that is ensured throughout the period of the study. However, it is of importance to recognise that a major potential weakness to consider is the fact that most of the studies reporting positive, beneficial results were performed amongst the same study population and by the same authors located in Cuba before 2004. Studies performed elsewhere did not confirm these results.

Conclusion

It was revealed by this systematic review of the available data that the earlier studies performed on policosanol found a significant decrease in the LDL-C. Some of these also found a decrease in TC and an increase in HDL-C indicating a large benefit in the use of policosanol in hypercholesterolaemic individuals. However, more recent independent studies have not been able to replicate these beneficial results and have found that the daily consumption of policosanol plays no role in the reduction of serum lipid levels. Reasons for these contradicting results included the differences in the type and concentration of policosanol used and the ethnic and cultural groups studied. These justifications were, however, invalidated as the concentration of octacosanol was found to be similar in all policosanol products and other drug therapy results in lipid reduction in all population groups. Therefore, in order to guarantee that there are benefits in using policosanol to assist in serum lipid reduction further research on the efficacy and advantages is required. Future research should include long-term, double blind, placebo-controlled studies, with large population groups from various areas of the world. Methods to be used should be discussed amongst researchers to ensure a standard of quality. Studies should be done using both the original as well as other sources of policosanol. The focus of this research should include efficacy of policosanol, dosage required to ensure adequate results, the influence of therapeutic diet and lifestyle and the rate and amount of absorption of policosanol in the body.

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CHAPTER 4
SUMMARY, CONCLUSIONS AND RECOMMENDATIONS

4.1 Introduction

This chapter serves as a summary of the results that were found in the preceding chapters. The details, therefore, are only broad discussions and conclusions, as the more comprehensive results are found in these prior chapters.

The main findings will be presented for easy conclusions to be made for all those patients and specialised health professionals that are involved with serum lipid-lowering techniques and possible supplementation and for researchers for further studies on the topic.

4.2 Summary of main findings

Due to the high prevalence of CVD worldwide it is continuously essential that new, potential lipid-lowering products be researched for efficacy and tolerability. Policosanol is one such product that has caused a stir amongst researchers in the cardiovascular field.

4.2.1 Effects on serum lipid levels

According to the initial studies conducted and included in the systematic review, there is evidence that the daily inclusion of policosanol into the diet may assist in the reduction of total cholesterol, LDL-C and the increase of HDL-C. However, the more recent, independent studies have contradicted this proposal. It is thus imperative to be aware that the same research group in Havana, Cuba performed the initial studies. It was suggested by Castano *et al.* (2002) that the differences in results were due to different sources of policosanol and thus different compositions and, therefore, mechanism of action. However, Marinangeli *et al.* (2007) recently found that the original policosanol supplement and the alternative sources had consistent purity and percentage composition thus should possess similar cholesterol lowering properties. Furthermore, Dullens *et al.* (2008) recently investigated the effects of emulsified policosanols with different chain lengths on cholesterol metabolism in LDL receptor-deficient mice. They showed that neither the individual policosanol components [tetracosanol (C24), hexacosanol (C26), octacosanol (C28) or triacosanol (C30)] nor the natural policosanol mixture (all 30 mg/100 g diet) lowered serum cholesterol in this

animal model. From the results they concluded that the evaluated individual policosanols as well as the natural policosanols mixture, have no potential for reducing coronary heart disease risk through effects on serum lipid concentrations. These results support those of Kassis *et al.* (2007) in hamsters, another animal model. With regard to humans, Francini-Pesenti *et al.* (2007) reasoned that ethnic and environmental factors cannot explain differences in Cuban and other studies, when considering the fact that diet and other lipid lowering agents, such as statins, have been shown to have similar effects in different populations (Howard *et al.*, 1995; Tan *et al.*, 2003).

From **Table 4.1** it is possible to see that most of the studies used the same policosanols extract and were performed in the same areas by the same research group on the surrounding population. It is also of importance to note that Cuba has been the leading supplier of sugar cane for almost a decade, thus sugar is an excellent source of revenue for the country. The studies that were performed elsewhere did not uncover the same positive and outstanding results and thus a question is raised regarding the studies that were performed in Cuba. It was suggested that the absorption and metabolism of policosanols might have been different when various different sources of policosanols were used, but the study performed by Marinangeli *et al.* (2007) found that the amount of the octacosanol in the different supplements of policosanols is almost the same and it was suggested that further studies are required where the absorption is concerned. Therefore, Kassis and Jones (2008) recently determined cholesterol absorption and synthesis in humans by measuring red cell cholesterol ^{13}C and deuterium enrichment, respectively. Policosanols derived from sugar cane wax from Havana, Cuba, and provided in dosages of 10 mg/day mixed with 10 g of margarine, reduced cholesterol absorption (7.2%) non-significantly ($p=0.10$) compared to the control group, with no difference between cholesterol fractional rate of synthesis in the experimental and control groups (Kassis & Jones, 2008).

Francini-Pesenti *et al.* (2007) also reasoned that ethnic and environmental factors cannot explain differences in Cuban and other studies, when considering the fact that diet and other lipid lowering agents, such as statins, have been shown to have similar effects in different populations (Howard *et al.*, 1995; Tan *et al.*, 2003). Therefore, in order to be confident and convinced of the possible lipid lowering properties that policosanols may hold, further studies elsewhere in the world are required using both the original as well as alternative sources of policosanols in different population groups,

preferably in a double blind manner in an interlaboratory study involving experienced researchers.

Table 4.1 Centres where studies were performed

Author	Centre	Type of policosanol
Aneiros <i>et al.</i> , 1993 Aneiros <i>et al.</i> , 1995 Arruzazabala <i>et al.</i> , 2002 Batista <i>et al.</i> , 1995 Batista <i>et al.</i> , 1996a Batista <i>et al.</i> , 1996b Canetti <i>et al.</i> , 1995a Canetti <i>et al.</i> , 1995a Castano <i>et al.</i> , 1995a Castano <i>et al.</i> , 1995b Castano <i>et al.</i> , 1996 Castano <i>et al.</i> , 1997 Castano <i>et al.</i> , 1998 Castano <i>et al.</i> , 1999 Castano <i>et al.</i> , 2000 Castano <i>et al.</i> , 2001a Castano <i>et al.</i> , 2001b Castano <i>et al.</i> , 2001c Castano <i>et al.</i> , 2002 Castano <i>et al.</i> , 2003 Crespo <i>et al.</i> , 1997 Hernandez <i>et al.</i> , 1992 Mas <i>et al.</i> , 1999 Mas <i>et al.</i> , 2001 Menendez <i>et al.</i> , 2000a Menendez <i>et al.</i> , 2000b Mirkin <i>et al.</i> , 2001 Pons <i>et al.</i> , 1992 Pons <i>et al.</i> , 1993 Pons <i>et al.</i> , 1994a Pons <i>et al.</i> , 1994b Torres <i>et al.</i> , 1995	Havana, Cuba	Original sugar cane policosanol
Reiner <i>et al.</i> , 2005	Zagreb, Croatia	Rice policosanol (<i>Oryza. Sp</i>)
Dulin <i>et al.</i> , 2006	Charlotte, NC, USA	Sugar cane policosanol
Francini-Pesenti <i>et al.</i> , 2007	Padua, Italy	Original sugar cane policosanol
Greyling <i>et al.</i> , 2006	Potchefstroom, South Africa	Lesstanol Octa-60 sugar cane policosanol
Kassis & Jones, 2006	Quebec, Canada	Original sugar cane policosanol
Lin <i>et al.</i> , 2004	Vlaardingen, The Netherlands	Wheat germ chocolate pellet policosanol
Berthold <i>et al.</i> , 2006	Cologne, Germany	Original sugar cane policosanol

4.2.2 Compliance

In the general population it is essential to be attentive to the fact that in order to benefit from the possible effects that policosanol may hold, daily intake of one to two tablets is required, thus when recommending the intake of this supplement it is important to consider the compliance of the subject. In the studies reviewed in Chapter 3

compliance was found to be at a very high level, especially in those trials where regular interviews and tablet or pill counts were performed. Most of the trials were performed on women who were noted to be more diligent with compliance. Therefore, when considering the use of policosanol it is recommended that regular follow-ups and interviews be undertaken to ensure compliance of the patient/client and intake be only once a day, preferably in the evening.

4.2.3 Tolerability

In all of the studies reviewed in Chapter 3 few or no side effects or adverse events were recorded in the policosanol group. The side effects that were noted were mostly mild which included weight loss and headache. Policosanol may, therefore, be regarded as safe and tolerable for use.

4.2.4 Comparison to other lipid lowering products

At present the most common lipid-lowering drugs are statins. These are found to be very effective in the treatment of hypercholesterolaemia. However, there have been studies that exhibit a number of adverse effects including myopathy or rhabdomyolysis (Staffa *et al.*, 2002; Thompson *et al.*, 2003). The use of combination treatment is found to be more beneficial than single administration of one product. Therefore, the possibility of a cholesterol-lowering product with no side effects will be ideal in the treatment of these individuals.

4.3 Availability and price

Policosanol is mostly available in a wide number of health stores but not on offer in pharmacies. It is produced by various companies including *Solal Technologies*, *Pure Encapsulation*, *Douglas Labs*, *Pharma Dynamics* and *Now foods- Sports and Speciality formulas* to name a few. They are marketed as pure policosanol and Cholest-go™ policosanol. These manufacturers provide the capsules in 60, 90 and 120 capsules for every container, encouraging between 1 – 2 capsules of 10 – 20 mg/capsule per day. According to the studies, a dosage of between 5 – 20 mg per day is recommended in order to ensure an effect on lipid levels is noted.

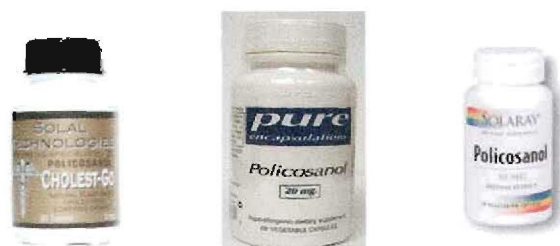


Figure 4.1 Policosanol available at health stores across the country

These products are sold with promises of 'encouraging healthy cardiovascular function', 'supporting healthy lipid metabolism', and 'naturally decreasing cholesterol levels'. The directions for use stated on the packaging include taking tablets with water or other fluids and taking the required dosage preferably in the evenings after the last meal of the day.

Included on some of the packaging are the side effects and special precautions. It is also noted that policosanol is safe and well tolerated in patients with hypercholesterolaemia as well as diabetic and elderly individuals.

The price of a pack varies from between R99 to R256 depending on the company and the amount of capsules and strength. This would provide a month's supply. Most medical aid funds will refuse to reimburse patients for these expenses because the products are viewed as supplements. In comparison, the current available lipid-lowering therapy (simvastatin) costs on average between R140, R155 and R230 (usually covered by medical aid schemes) for strengths of 10, 20 and 40 mg respectively per month, dosages dependent on the individual. The amounts are therefore similar depending on the brands and type of therapy that are chosen. It is, however, to be noted that policosanol is not covered by medical aids and, therefore, may become very expensive for the individual.

4.5 Recommendations

4.5.1 Public

Due to the high prevalence of elevated cholesterol levels and the side effects associated with the use of pharmacological drugs, it is tempting to recommend the use of policosanol among the public. According to the studies performed, there is high

percentage of positive effects that are noted, which largely outweighs the negative, and with no side effects noted. However, as previously explained, most of these studies were performed by the same group of researchers, therefore, before confident recommendations are to be made, further research and studies in other population groups are necessary.

4.5.2 Practitioners

Amongst all practitioners there is a constant need to improve the quality of life of the clients or patients, especially when related to cardiovascular disease. Statins have been proved to be beneficial with lipid-lowering, but with a number of side effects. Thus the possibility of use of policosanol amongst these patients, with its lack of prominent side effects is an option. However, it remains uncertain that policosanol is a lipid-lowering agent as further studies remain to be executed.

4.5.3 Dieticians/Nutrition experts

The first line of defence against hypercholesterolaemia is still suitable and adequate adjustments to the diet and lifestyle of the patients; therefore the role of the dietician or nutritionist is still an essential one. A study that was performed in 1970 known as the classic Seven Countries study was the first to show the strong relationship between a high saturated fat intake and an increase in the cholesterol levels of the population. The countries that reported the highest saturated fat intake were also the ones who had the highest level of cholesterol to report (Keys, 1970). Most patients that suffer from hypercholesterolaemia are encouraged to follow the NCEP cholesterol-lowering diet. However, in some of the studies that were performed with policosanol, the patients remained on their "habitual" diet. With the positive results revealed through the various studies that have been done in Cuba on policosanol, Dieticians or nutrition experts should inform their clients and patients about the possible benefits of policosanol and the improvements they may experience with the daily use of it, but to mention at the same time the concerns that some scientists have expressed about the efficacy of these products for Europeans until positive results are reported.

4.5.4. Researchers

The systematic review performed concluded that further research is required. These investigations should include long-term, controlled, double-blinded trials performed on large population groups from different cultural and ethnic backgrounds. The aims and objectives should include the mechanism of action, amount and rate of absorption as well as the efficacy and required dosage necessary to ensure an adequate effect. The background diet (NCEP step 1 diet) should be carefully monitored to ensure that there are no differences between the diets of the experimental and control groups. Controlled feeding trials may even be considered.

4.6 Conclusions

The results from the systematic review have indicated that policosanol has been shown to benefit Cuban hypercholesterolaemic subjects and is safe and well tolerated. However, studies that have been performed elsewhere in the world up to 2008 showed no lipid-lowering benefits. It is, therefore, necessary for further independent studies to be performed on policosanol to ensure positive results are met with the use of it. It is also essential that further studies be done in different population groups using the same policosanol supplement that has been used in the trials performed in Cuba and that the results of such studies are published as soon as possible.

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