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Review

A Review of the Effects of Policosanol on Metabolic Syndrome

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ABSTRACT

Background: Cardiovascular disease is the world's number one killer disease and the leading non-communicable disease in terms of causing premature deaths. Overwhelming evidence suggest that effective management of metabolic syndrome will markedly reduce morbidity and premature deaths from cardiovascular disease. Although many therapies exist, most of them are ineffective due to decreased effectiveness and/or side effects following prolonged usage. Policosanol, a well-tolerated long-chain aliphatic alcohol has been proven to be effective against the components of metabolic syndrome (namely dyslipidemia, diabetes, hypertension, and obesity) even when used for a long period with minimal or no adverse effects.

Objective: This study intends to explore the potential benefits of Policosanol in the management of metabolic syndrome.

Methods: PubMed, Google Scholar, and Science Direct were used as the search engines to retrieve articles related to Policosanol and metabolic syndrome from 2010 to 2021.

Results: The results from the three search engines were scrutinized and merged. Duplicate publications were excluded. Similarly, four articles from the WHO website (*www.who.int/publications*) were included making a total of 63 articles used in this review. Most of the reviewed articles show Policosanol to be effective in reducing systolic and diastolic blood pressure, blood glucose level, body weight, total cholesterol level, triglyceride level, low density lipoprotein and increasing high density lipoprotein levels. There are few conflicting articles that reported Policosanol to have no effect on lipid parameters.

Conclusion: Policosanol was shown to be a safe and well-tolerated natural product that is effective against all the components of metabolic syndrome. Thus, using this natural product will go a long way in reducing the burden and economic consequences of the syndrome.

1. Introduction

Non-communicable diseases (NCDs) pose great global public health concerns as the leading causes of morbidity and mortality globally. The burden of these diseases is rapidly increasing especially in the middle and low-income countries causing significant health, social, and economic consequences. Risk factors contributing to the development of NCDs are mainly physical inactivity, unhealthy diets, harmful use of alcohol, and exposure to tobacco smoke compounded by the globalization of unhealthy lifestyles, population aging, and rapid unplanned urbanization. Lack of physical activity and unhealthy diets may present as raised blood pressure (BP), elevated blood lipids, increased blood glucose levels, and obesity. These are referred to as metabolic risk factors of NCDs and can lead to cardiovascular disease (CVD), which is the world's number one killer disease and the leading NCD in terms of causing premature deaths (WHO, 2018a, 2020).

These risk factors constitute metabolic syndrome and affect about one fifth of most countries' population including about 25% of the adult population worldwide (Nolan et al., 2017; Ranasinghe et al., 2017). Although many therapies are available for each component of the metabolic syndrome, no known single therapy exists for the whole risk factors combined (Nolan et al., 2017; Grabia et al., 2021). Moreover, therapies for the individual components often fail to produce desired results. For example, Statins have been used effectively for the treatment of dyslipidemia, but their side effects often cause withdrawal and discontinuation by individuals with dyslipidemia (Scarpini et al., 2012; Ward et al., 2019). Similarly, optimal Low-Density Lipoproteins (LDL) blood level was not achieved in over 50% of individuals initiated on statin therapy (dyslipidemia treatment). Two years after the commencement of this therapy, the patients may experience a significantly increased risk of cardiovascular events (Akyea et al., 2019).

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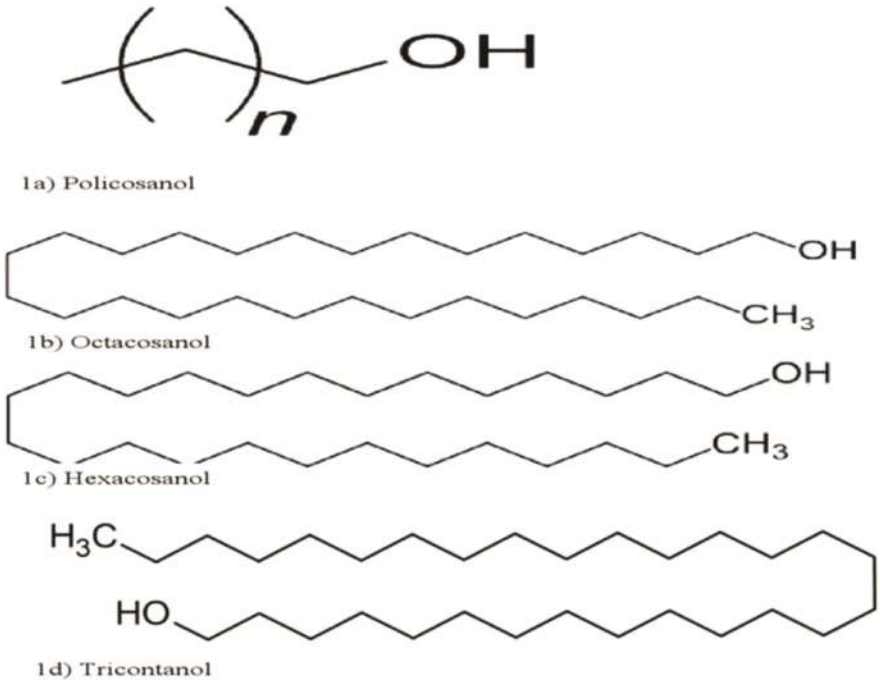

Fig. 1. Chemical structure of Policosanol. (a) General chemical structure for long chain aliphatic alcohol (where n = 22–34 carbon atom); (b) Chemical structure for Octacosanol; (c) Chemical structure for Hexacosanol; (d) Chemical structure for Triacontanol.

1.1. Chemistry of Policosanol

Policosanol exists in nature as a white crystal or powder that contains a mixture of alcohol esters with carbon chains ranging from 22 to 34 in length (Fig. 1a). These alcohols include docosanol (C-22), tetracosanol (C-24), hexacosanol (C-26), octacosanol (C-28), nonacosanol (C-29), triacontanol (C-30), dotriacontanol (C-32), and tetratriacontanol (C-34), which are only stable in nature as a mixture (Policosanol). Three most prevalent aliphatic alcohols in Policosanol are octacosanol (Fig. 1b), hexacosanol (Fig. 1c) and triacontanol (Fig. 1d). The quality of this natural product depends on its source and composition (Harrabi et al., 2018). Octacosanol has been shown to have anti-inflammatory effects while triacontanol can prevent oxidative stress, induce anti-inflammatory responses and inhibit lipid peroxidation. On the other hand, hexacosanol has been demonstrated an ability to reduce hepatic and plasma cholesterol through the AMPK pathway and suppression of SREBP2 in HepG2 and C57BL/6 J mice (Hae et al., 2015; Lee et al., 2016b; Kim et al., 2017; Harrabi et al., 2018; Sharma et al., 2019).

The bioavailability of Policosanol is less than 10% when taken orally (the only route of administration), but tends to be improved either by nanoemulsification (Ishaka et al., 2014) or by esterification with oleic acid (Haim et al., 2012). Policosanol is metabolized by the liver and excreted through the kidney.

1.2. Extraction and purification of Policosanol

Policosanol was first isolated from sugarcane by Cuban scientists in 1991. Other rich sources of Policosanol are rice bran, grapes, germ, apples, maize, beeswax, tomato seed, peanuts, ginseng, and others (Asikin et al., 2012; Ishaka et al., 2014; Giuffrè and Capocasale, 2015; Ji et al., 2016; Hunter and Hegele, 2017; Shen et al., 2019). There are many methods of Policosanol extraction (Asikin et al., 2012; Ji et al., 2016; Shen et al., 2019). For example, saponification involves alkaline digestion of the sample and has been used extensively in the extraction of rice bran wax Policosanol (Ishaka et al., 2014; Shen et al., 2019). Solvent extraction is another method that utilizes ethanol or hexane to extract Policosanol (Shen et al., 2019). These two methods experience a long time for sample preparation and yield a low amount of end-product.

Nanoemulsified Policosanol may be extracted using a low-intensity ultrasound, and high-pressure homogenization. This method is relatively simple and effective (Ishaka et al., 2014). Microwave-assisted technology as a method for Policosanol extraction was first used by Venturelli and his team (Venturelli et al., 2019).This method involves mixing the beeswax with ethanol and potassium hydroxide in a microwave vessel and stirring with a magnetic stirrer at a temperature of 120°C for 5 min. The mixture is then allowed to dry after filtering and washing with 600 mL of distilled water (microwave-assisted trans-esterification). Thereafter, the dry powder is then mixed with ethanol and sodium hydroxide in a microwave vessel and stirred using a magnetic stirrer at a temperature of 120°C for 30 min and allowed to dry after another round of filtration and washing (microwave-assisted hydrolysis). Finally, the hydrolyzed mixture is purified with liquid chromatography.

Although this method is expensive, it reduces sample preparation time and increases end-product yield (Venturelli et al., 2019). Furthermore, beeswax Policosanol can also be isolated using supercritical carbondioxide extraction, and although, this method produces high yield, which is not feasible on a large scale due to its high production cost (Asikin et al., 2012; Shen et al., 2019). Furthermore, to separate Policosanol into its individual components, thin-layer chromatography (TLC), gas chromatography-mass spectrometry (GC–MS), high-performance liquid chromatography (HPLC), and high-performance thin-layer chromatography (HPTLC) have been used (Shen et al., 2019).

1.3. Uses of Policosanol

Policosanol has numerous uses in the field of medicine including its use as an organogel for nutraceutical and drug delivery purposes (Lupi et al., 2013; Tian and Acevedo, 2018, 2020), as platelet anti-aggregation, an agent to relieve intermittent claudication and to prevent other cardiovascular risks (Guo et al., 2014; Purohit et al., 2015; Elseweidy et al., 2016, 2018; Wong et al., 2016; Jang et al., 2019), and as an agent for the enhancement of neurological function in patients with ischemic stroke (Sánchez et al., 2010, 2016; Sánchez-López et al., 2018; Fernández-travieso et al., 2020). Policosanol from milk thistle oil exhibits a potential anti-arthritic, thus may be used for the treatment of diseases like rheumatoid arthritis (Harrabi et al., 2018), while which

has also been shown to reduce serum uric acid levels and as such is very useful in the management of patients with gout (Kim et al., 2017).

Other properties of Policosanol include lipid-lowering (Wang et al., 2018; Arteche-Hidalgo et al., 2020), and prevention of androgenetic alopecia (Wang et al., 2021). It has also been shown to prevent and alleviate symptoms associated with neurodegenerative disorders, such as Alzheimer's disease and Parkinson's disease (Zhang et al., 2021).

1.4. Molecular mechanism of action of Policosanol

The proposed mechanisms of action of Policosanol are multiple, it binds to the β-subunit of adenosine 5′-monophosphate (AMP)-activated protein kinase and activates the AMPK pathway which suppresses the activity of 3-hydroxy-3-methyl glutaryl coenzyme A (HMGCS2) reductase enzyme which results to an increased receptor-mediated uptake of LDL in the liver via increasing hepatic LDL receptors (Li et al., 2020). Similarly, AMPK activation leads to the inhibition of cholesteryl ester transfer protein (CETP), thus preventing the binding of HDL and LDL to CETP with resultant increase in LDL catabolism and a decrease in the metabolism of triglycerides (TGs). Inhibition of CETP activity may also lead to anti-inflammation and anti-aging effects resulting in tissue regeneration and cellular replication (Shen et al., 2019; Li et al., 2020). Through AMPK activation, Policosanol may also suppress the activity of sterol regulatory element-binding protein-2 (SREBP2) by inhibiting its nuclear translocation leading to reduced cholesterol biosynthesis (Lee et al., 2016a; Li et al., 2020; Ra et al., 2020). The glucose-lowering effect of Policosanol may also be associated with the activation of AMPK (Lee et al., 2016a).

Furthermore, Policosanol inhibits the phosphorylation of p38 mitogen-activated protein kinase (p38MAPK), thus suppressing the effects of the p38MAPK pathway (Shen et al., 2019). There are four p38MAPKs namely p38α (expressed in most cell types), p38β (expressed in the brain), p38γ (expressed in skeletal muscle), and p38δ (expressed in endocrine glands). Inhibition of these kinases suppresses the p38MAPK pathway, leading to directly reduced expression of apoptotic and atherosclerotic genes. The p38MAPK suppression also causes a reduction in the levels of C-reactive protein, homocysteine, and other inflammatory factors which in turns reduces endothelial injury and promotes an anti-inflammatory effect that results in tissue regeneration and reduced atherosclerosis (Cuadrado and Nebreda, 2010; Shen et al., 2019). p38δ helps regulate pancreatic β-cells survival as well as insulin secretion. Policosanol enhances the growth of human dermal and brain glial cells via p38α and p38β MAPK dependent inhibition of apoptosis. This is associated with increased cell number and reduced production of reactive oxygen species. Policosanol also reduces the accumulation of fats in hepatic tissue (Cuadrado and Nebreda, 2010; Lee et al., 2016a).

Additionally, Policosanol stimulates the phosphatidylinositol 3 kinases (PI3K)/Protein kinase B (AKT) pathway. This pathway promotes cell growth, survival, proliferation, and is involved in metabolism and angiogenesis (Xu et al., 2020). There are 3 AKT types, AKT1 (expressed in various tissues), AKT2 (expressed mainly in insulin- sensitive tissues), and AKT3 (expressed only in the brain and testis). Similarly, the PI3K proteins have three subtypes; class-I, class-II and class-III kinases. There are two prototypes of class I, class-Ia PI3K which is involved in phosphorylation of insulin receptor substrate, and class-Ib PI3K which activates the MAPK signaling cascade. There is a relationship between the MAPK and PI3K/AKT3 pathways. PI3K/AKT3 pathways are more involved in apoptosis regulation and cell survival while the MAPK pathway is more involved in cellular proliferation (Madhunapantula et al., 2011; Xu et al., 2020). When Policosanol is being esterified to improve its bioavailability, its acts to enhance bile acid excretions as a result of 7-a-hydroxylase up-regulation and clearance of LDL due to increased in cell membrane LDL receptors (Haim et al., 2012).

Policosanol may suppress1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) which induces the phosphorylation of c-Jun-N-terminal kinase (JNK) that has been implicated in Parkinsonism. Furthermore, the ProNGF and NGF signaling pathways are also stimulated by Policosanol as part of its anti-parkinsonian effects (Guo et al., 2014; Shen et al., 2019) (Fig. 2).

1.5. Toxicity of Policosanol

The safety profile of Policosanol has been well established. Policosanol is safe both in animal and human models with tremendous health benefits (Cicero et al., 2012; Pérez et al., 2013; Purohit et al., 2015; Barrios et al., 2016; Xu et al., 2016; Al-Miahy and Alkalby, 2018; Wang et al., 2018). In rabbits and humans, Policosanol has been found not to affect hematological and biochemical parameters of the blood such as blood hemoglobin concentration, whiteblood cells, red blood cells, total blood protein, MCV, MCH, MCHC, lymphocytes, monocytes, granulocytes, RDW, PCT, MPV, PDW, hematocrit, blood urea, blood sugar, blood creatinine, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) (Guo et al., 2014; Purohit et al., 2015). However, the experiment conducted by Purohit et al., suggests that Policosanol may reduce the platelet count of humans in a similar fashion as statins (Purohit et al., 2015; Elseweidy et al., 2016, 2018; Jang et al., 2019).

Policosanol shows some level of protection on hepatocytes, assisting in cell replication and tissue regeneration (Al-Miahy and Alkalby, 2018). Furthermore, when Policosanol is used in combination with the statins *e.g.* atorvastatin, simvastatin, or other lipid-lowering agents, it helps to attenuate or neutralize the toxic effect of these agents (Guo et al., 2014; Al-Miahy and Alkalby, 2018; Wang et al., 2018). Arteche-Hidalgo et al. show Policosanol to be a safe and well-tolerated agent that does not affect any biochemical or physical parameters but with tremendous health benefits in a patient with metabolic syndrome (Arteche-Hidalgo et al., 2020). Policosanol is mostly safe when taken between doses of 5 mg to 80 mg orally for duration of up to 3 years. The side effects encountered are often mild and relatively uncommon. They include mild headache, dizziness, redness of the skin, weight loss, and stomach upset.

Several literatures have reported that Policosanol shows safe and very useful in the management of metabolic risk factors or metabolic syndrome such as raised blood pressure (hypertension), elevated blood lipids levels (dyslipidemia), increased blood glucose levels (diabetes), and obesity (Lee et al., 2016a; Pirro et al., 2016; Cho et al., 2018b; Kim et al., 2018; Sharma et al., 2019; Fernández-travieso et al., 2020; Li et al., 2020). Controlling/managing these risk factors will go a long way in curtailing the burden of NCDs both in terms of mortality and economic consequences. Thus, we performed a review of previous literature on the effects of Policosanol on these metabolic risk factors.

2. Material and Methods

Data bases searched include PubMed, Google Scholar, and Science Direct. The MeSH terms were search in title and include: "Policosanol", "metabolic syndrome", "hypertension", "hypertensive", "antihypertensive", "diabetic", "diabetes", "hyperglycaemia" "hyperglycemia", "hyperlipidemia", "hyperlipidaemia", "dyslipidemia", "dyslipidaemia", "hypercholesterolaemia", "hypercholesterolemia", "hyperlipidemic", "obesity". The Boolean operator "AND" was used between "Policosanol" and "metabolic syndrome" while the Boolean operator "OR" was used between "metabolic syndrome" and its components. Searches were conducted on 1st August 2021 and limited to studies published after 31st December 2009. Titles and abstracts of studies were reviewed, and full-texts of relevant studies were also accessed. Only articles that present Policosanol separately were included in the study while those that present its functions as part of a dietary supplement or nutraceutical were excluded. References of the accessed full-texts were further manually searched to obtain additional studies. The article was reviewed by three independent reviewers.

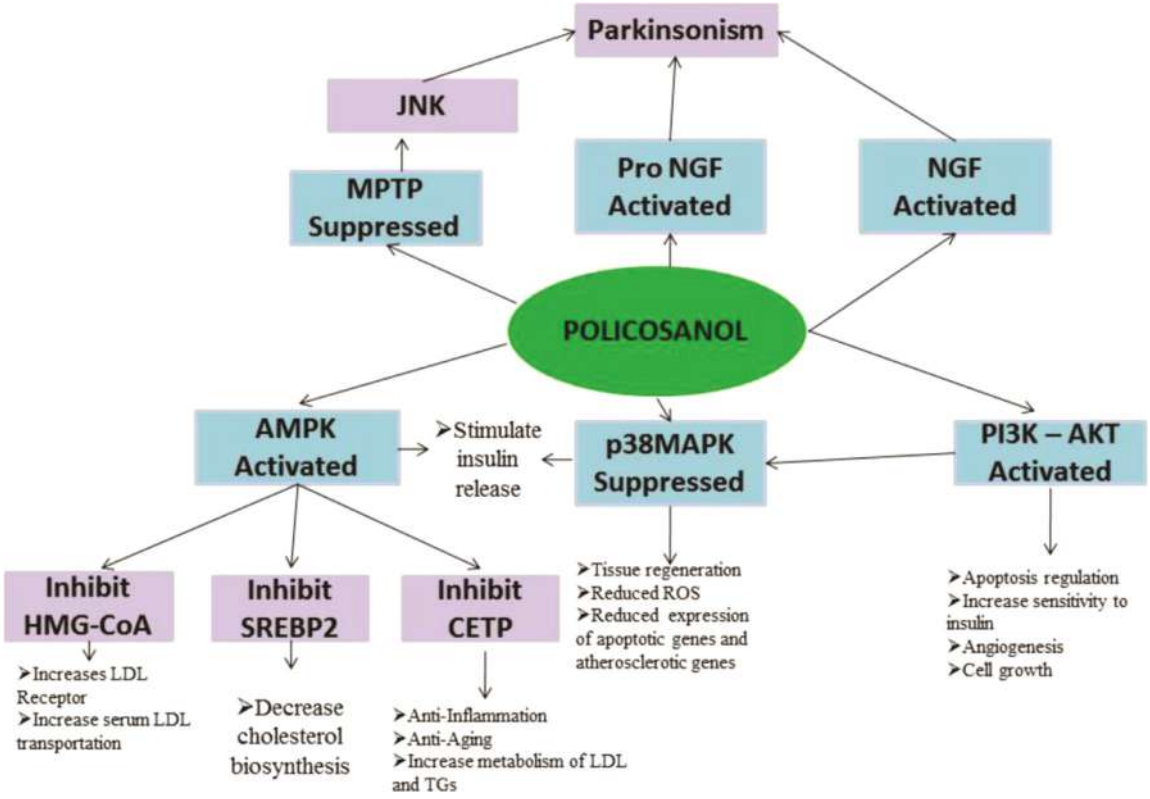

Fig. 2. Molecular pathway of the mechanism of action of Policosanol.

3. Results

Using the above search strategies, 154 articles were retrieved from PubMed, 849 from Google Scholar, and 478 from Science Direct. These articles were further filtered by applying a customized date search from 2010 to 2021 and selecting English as the language, to give 75 articles from PubMed, 665 articles from Google Scholar, and 242 articles from Science Direct. These articles were then scrutinized by screening the titles and abstracts to obtain 25 articles from PubMed, 56 articles from Google Scholar, and 14 articles from Science Direct. The results from the three search engines *i.e.* PubMed, Google Scholar, and Science Direct were merged, excluding duplications and including four articles from the WHO website (*www.who.int/publications*) to obtain a total of 72 articles. After full-text reading, nine articles were excluded as they present the effect of Policosanol in combination with other nutraceuticals or as part of a dietary supplement. Thus only 63 articles were included for the study (Fig. 3)

4. Discussion

4.1. Policosanol and metabolic syndrome

The components of metabolic syndrome are also referred to as the major metabolic risk factors for NCDs and include raised blood pressure (hypertension), elevated blood lipids (dyslipidemia), increased blood glucose (diabetes), and obesity.

4.2. Policosanol and dyslipidemia

Abnormal blood lipid level (dyslipidemia) is a state that exhibits an increased blood plasma level of triglycerides and/or cholesterol, or a low level of high-density lipoprotein (HDL) which may eventually lead to the development of atherosclerosis (Al-Miahy and Alkalby, 2018). Abnormal blood lipid level has been implicated in many cardiovascular events either singly or in combination with other metabolic risk factors. Without timely, effective, and efficient control of dyslipidemia, the trend will continue, leading to a higher burden of CVDs (Xi et al., 2020). Overwhelming evidence suggests that effective treatment of dyslipidemia will markedly reduce the morbidity and premature deaths associated with CVDs (Noubiap et al., 2018).

The lipid-lowering effects of Policosanol have been an area of discussion by researchers. In a review paper entitled “Policosanols as Nutraceuticals: Fact or Fiction”, Marinangeli et al. show that predominant research on the lipid-lowering effects of Policosanol at the time of their publication was from a single research group of Dalmer Laboratories in La Habana, Cuba. They consequently highlighted the need for other independent and external experiments to confirm the effects (Marinangeli et al., 2010). Since then, Guo and coworkers have shown that Policosanol does not affect lipid parameters in 16 healthy volunteers from China. However, the source and characteristic of Policosanol used in this randomized trial was not mentioned (Guo et al., 2014). Later on (Elseweidy et al., 2016) demonstrated that Policosanol from local sugar cane in Egypt effectively reduce serum cholesterol, LDL, and increase HDL in adult male Wister rats .

Similarly, Lee et al. found that Policosanol significantly reduce the levels of total cholesterol and LDL while increasing the HDL levels in Zebrafish fed with high cholesterol diet for 9 weeks at the Yeungnam University, Gyeongsan, Korea (Lee et al., 2016a). A further experiment was held in Iraq, to determine the effect of Policosanol both in standard dosage purified form and in crude extract form from sugarcane. This study was conducted by Al-miahy and Alkalby on hypercholesterolemic female rats during lactation. Their findings suggest that both forms of Policosanol significantly reduce the total cholesterol and LDL levels. Also, there was an increase in the level of HDL only after standard dosage

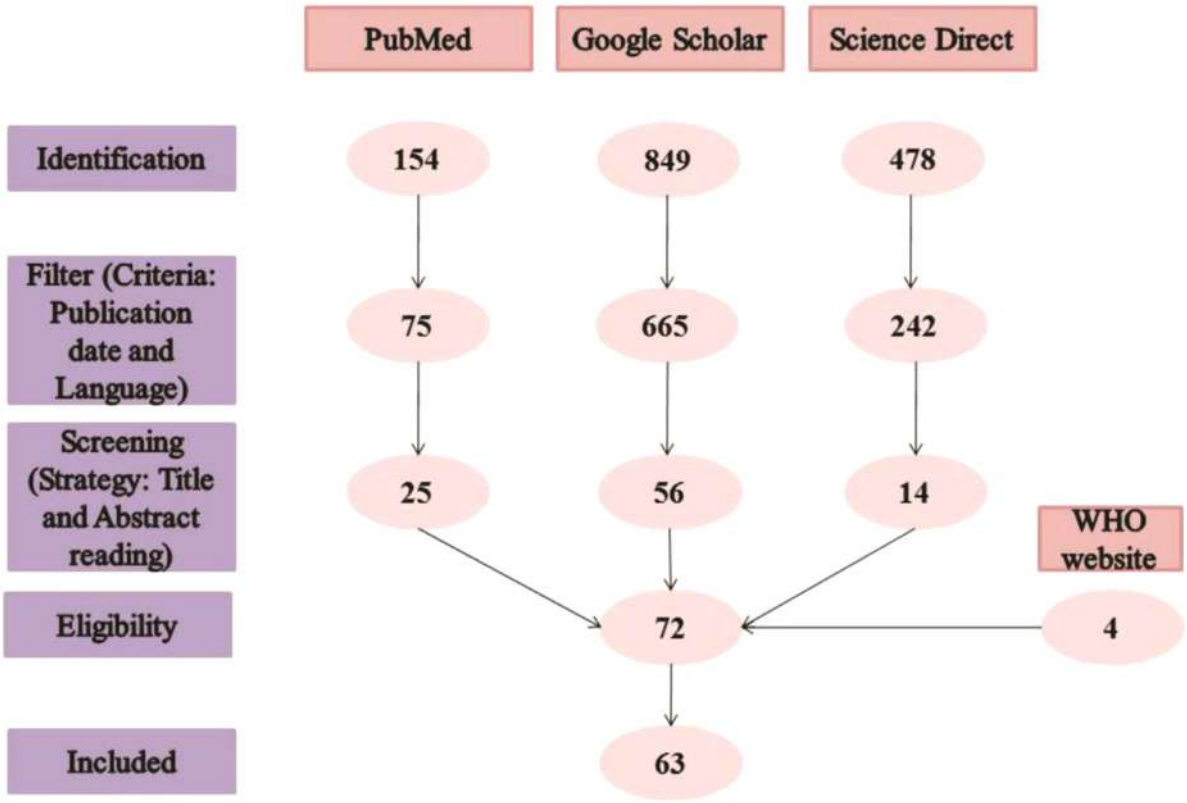

Fig. 3. Search methodology and results.

of purified Policosanol but not after crude extract sugar cane form. Possibly the crude extract form contains phytochemicals that may be antagonistic to the HDL increasing effect of Policosanol (Al-Miahy and Al-kalby, 2018).

An experiment carried out by Banerjee in Kentucky, USA shows that Policosanol reduces the cholesterol biosynthesis of female C57BL/6 J mice in a dose-dependent manner (Banerjee et al., 2011). More recent study by Nam et al. indicates that Policosanol inhibits the biosynthesis of cholesterol through AMPK pathway activation. This results in reduced levels of total cholesterol and LDL (Nam et al., 2019). Furthermore, a clinical trial of 100 patients with metabolic syndrome demonstrates the ability of Policosanol to increase the levels of HDL while to decrease the blood levels of LDL and cholesterol (Arteche-Hidalgo et al., 2020). The effects of Policosanol on lipid profile have been conflicting, while some experiments show that Policosanol reduce cholesterol, LDL and increase HDL, others demonstrate the opposite. Several questions remain unanswered (Table 1).

What can cause this disparity? Could it be due to genetic differences between the study participants? Could it be due to differences in the nature of the Policosanol source? Could it be due to the nature of the area where the Policosanol was cultivated? Or perhaps the dietary pattern of the population where the trial was carried out?

4.3. Policosanol and hypertension

Hypertension, also known as high or raised blood pressure, is defined by record of a systolic blood pressure ≥140 mmHg or a diastolic blood pressure ≥90 mmHg on two different days. Hypertension affects more than 1.13 billion people globally with greater prevalence in women than men (WHO, 2020). It is also a major cause of premature death globally. Despite its high prevalence and mortality in terms of premature death, only about 20% of individuals with hypertension have it under control (WHO, 2020). In a systematic review and meta-analysis, it was shown that Policosanol significantly decreases both systolic and diastolic blood pressure (Askarpour et al., 2019) . Another study suggests that the prolonged consumption of Policosanol significantly reduces peripheral blood pressure as well as aortic blood pressure in healthy Korean subjects in a dose-dependent manner (Kim et al., 2018). Similarly, Park and coworkers show that a short term consumption of Policosanol significantly reduces both systolic and diastolic peripheral blood pressure as well as systolic and diastolic aortic blood pressure and mean arterial pressure in healthy Korean subjects with pre-hypertension in a dose-dependent manner (Park et al., 2019). Furthermore, Policosanol was found to significantly reduce the average systolic blood pressure level by 10% and the average diastolic blood pressure level by 14% in healthy women (Cho et al., 2018a). Notably, Policosanol reduces both systolic and diastolic blood pressure in type II diabetic patients with dyslipidemia (Fernández-travieso et al., 2020). By and large, Policosanol have good antihypertensive properties; significantly reducing both systolic and diastolic blood pressure in many clinical trials from Cuba and other parts of the world.

4.4. Policosanol and diabetes

Diabetes is a chronic metabolic disease that is characterized by high blood glucose as a result of either an in ability of the pancreas to produce sufficient insulin (a hormone that regulates body glucose level) or the body's inability to effectively utilize the insulin produced. Diabetes is a major cause of limb amputation, blindness, stroke, kidney failure, and premature death. The prevalence of diabetes is rapidly increasing especially in low and middle-income countries (WHO, 2020). Several studies have confirmed the anti-diabetic effects of Policosanol. The hypoglycemic effect of Policosanol has mainly been attributed to signaling pathways which increase glucose uptake by the skeletal muscle and inhibit hepatic gluconeogenesis (Hae et al., 2015; Elseweidy et al., 2016; Jang et al., 2019; Shen et al., 2019). Several effects of Policosanol on glucose metabolism have been reported in both human and animal studies. Cho et al. reported that at basal glucose level, Policosanol causes

Table 1
Relationship between Policosanol and components of metabolic syndrome.

S/N	Refs. (Country)	Study Subjects	Metabolic Syndrome Components			
			Lipid Profile	Glucose Level (GL)	Blood Pressure	Body Weight (BW)
1.	(Arteche-Hidalgo et al., 2020) (Cuba)	Human	↓TC, ↓LDL, ↑HDL	N/E	N/R	N/E
2.	(Nam et al., 2019) (Korea)	Rat	↓TC, ↓LDL, N/E HDL	N/R	N/R	N/R
3.	(Banerjee et al., 2011) (USA)	Rat	↓TC, N/R LDL, N/R HDL	N/R	N/R	N/R
4.	(Lee et al., 2016a) (Korea)	Zebra fish	↓TC, ↓TGs, ↑HDL	↓GL	N/R	N/R
5.	(Al-miahy and Alkalby 2018) (Iraq)	Rat	↓TC, ↓LDL, ↑HDL	N/R	N/R	N/R
6.	(Elseweidy et al., 2016) (Egypt)	Rat	↓TC, ↓LDL, ↑HDL	↓GL	N/R	N/R
7.	(Guo et al., 2014) (China)	Human	N/E on TC, TGs, LDL, HDL	N/R	N/R	N/R
8.	(Sharma et al., 2019) (Japan)	Mice	N/R	N/R	N/R	↓BW
9.	(Hae et al., 2015) (Korea)	Mice	↓TC,↓TGs, N/E LDL, N/E HDL,	↓GL	N/R	↓BW
10.	(Askarpour et al., 2019) (Iran)	Human	N/R	N/R	↓SBP, ↓DBP	N/R
11.	(Park et al., 2019) (Korea)	Human	↓TC, ↓LDL, ↑HDL	N/E	↓SBP, ↓DBP	N/E
12.	(Cho et al., 2018a) (Korea)	Human	↓TC, ↓LDL, ↑HDL	↓GL	↓SBP, ↓DBP	↓BW
13.	(Cho et al., 2018b) (Korea)	Rat	N/E TC,↑HDL, ↓TGs	N/R	↓SBP, ↓DBP	N/R
14.	(Fernández-travieso et al., 2020) (Cuba)	Human	↓TC, ↓LDL, ↑HDL, ↓TGs	N/E	↓SBP, ↓DBP	N/R
15.	(Kim et al., 2018) (Korea)	Human	↓TC, ↑HDL, ↓TGs	N/R	↓SBP, ↓DBP	N/E
16.	(Kim et al., 2017) (Korea)	Human	N/E TC, N/E TGs,	N/E	↓SBP, ↓DBP	N/E
18.	(Lee et al., 2016b) (Korea)	Rat	↓TC, ↓LDL, ↓TGs	↓GL	N/R	↓BW

N/R, Not recorded; N/E, No effect; DBP, Diastolic blood pressure; SBP, Systolic blood pressure; ↓, Decrease; ↑, Increase.

a 5% increase in insulin secretion while at high blood glucose levels it causes a 14% increase in insulin secretion (Cho et al., 2018a). Elseweidy et al. reported that Policosanol have a hypoglycemic effect which is more pronounced as compared to other dyslipidemic drugs (*e.g.* Atorvastatin) or natural products (*e.g.* omega-3 fatty acids) (Elseweidy et al., 2016). Similarly, Policosanol enhances the metabolism of dietary fat and glucose leading to desirable reduction of blood glucose and cholesterol levels (Lee et al., 2016b). Hae et al. also demonstrates that Policosanol could reduce fasting glucose level, and improve tissue insulin sensitivity (Hae et al., 2015). Lee et al. found that Policosanol could significantly reduce the level of glucose in an experiment on Zebra fish (Lee et al., 2016a). Conclusively on Policosanol and diabetes, it has been shown Policosanol possesses an excellent anti-diabetic effect both in human and animal experiments.

4.5. Policosanol and obesity

Obesity results from a chronic imbalance between energy/carbohydrate intake and expenditure (Sharma et al., 2019). There is a high prevalence of obesity, especially among children and youth. An unhealthy diet and reduced physical activity may contribute to the development of obesity (WHO, 2018b, 2018c). Obesity is a strong risk factor for metabolic diseases such as type 2 diabetes mellitus, atherosclerosis, hyperlipidemia, and non alcoholic fatty liver disease (Forouzanfar et al., 2016; Sharma et al., 2019). A study has shown that Policosanol can increase the energy expenditure of adipose tissue, thus standing as a promising therapeutic target for the control of obesity and obesity-associated metabolic disorders (Sharma et al., 2019). Sharma et al. also demonstrates that Policosanol can alleviate diet-induced obesity and other obesity-associated metabolic disorders by improving hepatic lipid metabolism and increasing brown adipose tissue activity (Sharma et al., 2019). Similarly, Hae et al. showed that the consumption of Policosanol derived from barley sprout extracts significantly reduces the weight of the experimental animals (Hae et al., 2015). Further research by Lee et al. suggests that Policosanol can reduce energy intake (decreasing feeding) while increasing energy expenditure, resulting in significant weight loss (Lee et al., 2016b). Similarly, about 12% of total body fat mass is lost in healthy female subjects following 8 weeks of Policosanol intake (Cho et al., 2018a).

5. Conclusion

The effect of Policosanol on hypertension is well supported by clinical and experimental reports on decreasing both systolic and diastolic blood pressure. Other components of metabolic syndrome, such as blood glucose level and obesity also respond to Policosanol therapy. However, its conflicting impacts on lipid profile demand further research particularly in Europe and Africa where there is minimal or no research about Policosanol. Nevertheless, Policosanol is shown to be a safe, well-tolerated and effective against most components of metabolic syndrome. Thus, using this natural product will go a long way in reducing the burden and economic consequences of the syndrome.

Ethical Approval

Not applicable.

Data Availability

Nil.

Funding

Nil.

Declaration of Competing Interest

The authors declare that they have no known competing interest with regard to this research article.

CRediT authorship contribution statement

Lawal Kayode Olatunji: Conceptualization, Writing – Original draft preparation, Methodology, Formal Analysis. **Abdulgafar O. Jimoh:** Validation, Writing – Reviewing and Editing, Supervision. **Umar Muhammad Tukur:** Visualization, Investigation. **Mustapha Umar Imam:** Validation, Writing – Reviewing and Editing. All authors fully contributed in all aspect of the manuscript writing.

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Supplementary Materials

Nil.

References

Akyea, R.K., Kai, J., Qureshi, N., Iyen, B., Weng, S.F., 2019. Sub-optimal cholesterol response to initiation of statins and future risk of cardiovascular disease. Heart 105, 975–981.

Al-Miahy, A., Alkalby, J, 2018. Effect of policosanol extract and simvastatin on some liver enzymes and histopathology in hypercholesterolemic female rats during lactation. J. Coll. Educ. Pure Sci. 8, 43–56.

Asikin, Y., Takahashi, M., Hirose, N., Hou, D.-X., Takara, K., Wada, K., 2012. Wax, policosanol, and long-chain aldehydes of different sugarcane (*Saccharum officinarum* L.) cultivars. Eur. J. Lipid Sci. Technol. 114, 583–591. doi:10.1002/ejlt.201100300.

Arteche-Hidalgo, L., Fernandez-Travieso, J., Suarez-Camejo, N., Marin-Preval, J., Alvarez-Acosta, V., Chaviano-Pereira, J., Garcia-Sanchez, M., Esquivel-Moinelo, I., Diaz-Gonzalez, M., Matos-Reyes, O., Fernandez-Dorta, L., Illnait-Ferrer, J., Mendoza–Castano, S., Monzon-Perez, M., Sanchez Pedroso, V., 2020. Effects of Policosanol in Patients With Metabolic Syndrome: A Six-Month Study. Journal Of Endocrinology And Metabolism 10 (2), 36–44.

Askarpour, M., Ghaedi, E., Roshanravan, N., Hadi, A., Mohammadi, H., 2019. Complementary therapies in medicine policosanol supplementation significantly improves blood pressure among adults: a systematic review and meta-analysis of randomized controlled trials. Complement. Ther. Med. 45, 89–97.

Banerjee, S., Ghoshal, S., Porter, T.D., 2011. Activation of AMP-kinase by Policosanol requires peroxisomal metabolism. Lipids 46, 311–321.

Barrios, V., Escobar, C., Francesco, A., Cicero, G., Burke, D., Fasching, P., et al., 2016. A nutraceutical approach (Armolipid Plus) to reduce total and LDL cholesterol in individuals with mild to moderate dyslipidemia: review of the clinical evidence. Atheroscler. Suppl. 24, 1–15. doi:10.1016/j.atherosclerosissup.2016.10.003, 2017 FebEpub 2016 Dec 18.

Cho, K.H., Kim, S.J., Yadav, D., Kim, J.Y., Kim, J.R., 2018a. Consumption of Cuban Policosanol improves blood pressure and lipid profile via enhancement of HDL functionality in healthy women subjects: randomized, double-blinded, and placebo-controlled study. Oxid. Med. Cell. Longev. 2018. doi:10.1155/2018/4809525, Article ID 4809525, 15 pages, 2018.

Cho, K.H., Yadav, D., Kim, S.J., Kim, J.R., 2018b. Blood pressure-lowering effect of Cuban Policosanol is accompanied by improvement of hepatic inflammation, lipoprotein profile, and HDL quality in spontaneously hypertensive rats. Molecules 23, 1–16.

Cicero AF, Ferroni A, Ertek S. Tolerability and safety of commonly used dietary supplements and nutraceuticals with lipid-lowering effects. Expert Opin Drug Saf. 2012 Sep;11(5):753-66. doi:10.1517/14740338.2012.705827. Epub 2012 Jul 13. PMID: 22788832.

Cuadrado A, Nebreda AR. Mechanisms and functions of p38 MAPK signalling. Biochem J. 2010 Aug 1;429(3):403-17. doi:10.1042/BJ20100323. PMID: 20626350.

Elseweidy, M.M., Amin, R.S., Atteia, H.H., El-Zeiky, R.R., Al-Gabri, N.A, 2018. New insight on a combination of policosanol and 10-dehydrogingerdione phytochemicals as inhibitors for platelet activation biomarkers and atherogenicity risk in dyslipidemic rabbits: role of CETP and PCSK9 inhibition. Appl. Biochem. Biotechnol. 186, 805–815.

Elseweidy, M.M., Zein, N., Aldhamy, S.E., Elsawy, M.M., Saeid, S.A., 2016. Policosanol is a new inhibitor candidate for vascular calcification in diabetic hyperlipidemic rats. Exp. Biol. Med. 241, 1943–1949.

Fernández-travieso, J.C., Illnait-ferrer, J., Fernández-dorta, L., Gámez-menéndez, R., Mendoza-castaño, S., Alvarez-varela, E., et al., 2020. Long-Term Therapy with Cuban Policosanol on Hypercholesterolemic Elder Patients: Analysis by Gender. International Research Journal of Pharmacy and Medical Sciences 3 (5), 11–17.

Forouzanfar, M.H., Afshin, A., Alexander, L.T., Biryukov, S., Brauer, M., Cercy, K., et al., 2016. Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet 388, 1659–1724.

Giuffrè, A.M., Capocasale, M, 2015. Policosanol in tomato (Solanum lycopersicum l.) seed oil: the effect of cultivar. J. Oleo Sci. 64, 625–631.

Grabia, M., Markiewicz-Żukowska, R., Socha, K., 2021. Prevalence of metabolic syndrome in children and adolescents with type 1 diabetes mellitus and possibilities of prevention and treatment: a systematic review. Nutrients 13, 1–15.

Guo, Y., Xu, R., Zhu, C., Wu, N., Cui, Z., Li, J., 2014. Policosanol attenuates statin-induced increases in serum proprotein convertase subtilisin /Kexin type 9 when combined with atorvastatin. Evid. Based Complement Alternat. Med. 2014 (2014), 926087. doi:10.1155/2014/926087, Epub 2014 Nov 16.

Hae, J., Young, S., Kim, B., Duck, W., Jia, Y., Wu, C., et al., 2015. Barley sprout extract containing policosanols and polyphenols regulates AMPK, SREBP2, and ACAT2 activity and cholesterol and glucose metabolism *in vitro* and *in vivo*. FRIN 72, 174–183.

Haim, D., Valenzuela, A., Brañes, M. C., Fuenzalida, M., Videla, L. A., 2012. The oleic acid esterification of policosanol increases its bioavailability and hypocholesterolemic action in rats. Grasas y Aceites 63 (4).

Harrabi, S., Ferchichi, A., Bacheli, A., Fellah, H., 2018. Policosanol composition, antioxidant and anti-arthritic activities of milk thistle (Silybum marianum L.) oil at different seed maturity stages. Lipids Health Dis. 17, 1–7.

Hunter, P.M., Hegele, R.A., 2017. Functional foods and dietary supplements for the management of dyslipidemia. Nat. Rev. Endocrinol. 13, 278–288.

Ishaka, A., Imam, M.U., Mahamud, R., Zuki, A.B.Z., Maznah, I., 2014. Characterization of rice bran wax policosanol and its nanoemulsion formulation. Int. J. Nanomedicine 9, 2261–2269.

Jang, Y.S., Kim, D.E., Han, E., Jung, J, 2019. Physiological activities of Policosanol extracted from sugarcane wax. Nat. Prod. Sci. 25, 293–297.

Ji, S., Yeon, S., Su, J., Park, S., Yhung, M, 2016. Contents and compositions of policosanols in green tea (Camellia sinensis) leaves. FOOD Chem. 204, 94–101.

Kim, J.Y., Kim, S.M., Kim, S.J., Lee, E.Y., Kim, J.R., Cho, K.H., 2017. Consumption of Policosanol enhances HDL functionality via CETP inhibition and reduces blood pressure and visceral fat in young and middle-aged subjects. Int. J. Mol. Med. 39, 889–899.

Kim, S.J., Yadav, D., Park, H.J., Kim, J.R., Cho, K.H., 2018. Long-term consumption of Cuban Policosanol lowers central and brachial blood pressure and improves lipid profile with an enhancement of lipoprotein properties in healthy Korean Participants. Front. Physiol. 9, 1–11.

Lee, E.Y., Yoo, J.A., Lim, S.M., Cho, K.H., 2016a. Anti-aging and tissue regeneration ability of Policosanol along with lipid-lowering effect in hyperlipidemic zebrafish via enhancement of high-density lipoprotein functionality. Rejuvenation Res. 19, 149–158.

Lee, J.Y., Choi, H.Y., Kang, Y.R., Chang, H.B., Chun, H.S., Lee, M.S., Kwon, Y.I., 2016b. Effects of long-term supplementation of policosanol on blood cholesterol/glucose levels and 3-hydroxy-3-methylglutaryl coenzyme a reductase activity in a rat model fed high cholesterol diets. Food science and biotechnology, 25(3), 899–904. doi:10.1007/s10068-016-0147-y.

Li, C., Ding, Y., Si, Q., Li, K., Xu, K., 2020. Multiple functions of Policosanol in elderly patients with dyslipidemia. J. Int. Med. Res. 48 (7), 300060520936082. doi:10.1177/0300060520936082, 2020 Jul.

Lupi, F.R., Gabriele, D., Baldino, N., Mijovic, P., Parisi, O.I., Puoci, F., 2013. Olive oil/policosanol organogels for nutraceutical and drug delivery purposes. Food Funct. 4, 1512–1520.

Madhunapantula, S. V., Mosca, P. J., Robertson, G. P., 2011. The Akt signaling pathway: an emerging therapeutic target in malignant melanoma. Cancer biology & therapy 12 (12), 1032–1049. doi:10.4161/cbt.12.12.18442.

Marinangeli, C.P.F., Jones, P.J.H., Kassis, A.N., Eskin, M.N.A., 2010. Policosanols as nutraceuticals: fact or fiction. Crit. Rev. Food Sci. Nutr. 50, 259–267.

Nam, D.E., Yun, J.M., Kim, D., Kim, O.K, 2019. Policosanol attenuates cholesterol synthesis via AMPK activation in hypercholesterolemic rats. J. Med. Food 22, 1110–1117.

Nolan, P.B., Carrick-Ranson, G., Stinear, J.W., Reading, S.A., Dalleck, L.C., 2017. Prevalence of metabolic syndrome and metabolic syndrome components in young adults: a pooled analysis. Prev. Med. Rep. 7, 211–215.

Noubiap, J.J., Bigna, J.J., Nansseu, J.R., Nyaga, U.F., Balti, E.V., Echouffo-Tcheugui, J.B., et al., 2018. Prevalence of dyslipidemia among adults in Africa: a systematic review and meta-analysis. Lancet Glob. Health 6, e998–e1007.

Park, H.J., Yadav, D., Jeong, D.J., Kim, S.J., Bae, M.A., Kim, J.R., et al., 2019. Short-term consumption of Cuban Policosanol lowers aortic and peripheral blood pressure and ameliorates serum lipid parameters in healthy Korean participants: randomized, double-blinded, and placebo-controlled study. Int. J. Environ. Res. Public Health 16 (5), 809. doi:10.3390/ijerph16050809, 2019 Mar 5.

Pérez, Y., Mas, R., Oyarzábal, Á., Jiménez, S., Molina, V., 2013. Effects of policosanol (sugar cane wax alcohols) and D-003 (sugarcane wax acids) on cyclooxygenase (Cox) enzyme activity *in vitro*. Int. J. Pharm. Sci. Rev. Res. 19, 18–23.

Pirro, M., Mannarino, M.R., Bianconi, V., Simental-Mendía, L.E., Bagaglia, F., Mannarino, E., et al., 2016. The effects of a nutraceutical combination on plasma lipids and glucose: a systematic review and meta-analysis of randomized controlled trials. Pharmacol. Res. 110, 76–88.

Purohit, A., Kotru, B., Joshi, K., Kotru, S., 2015. Pharmacology & Toxicology toxicological study of policosanol in experimentally induced hyperlpidemic male albino rabbits. Int. J. Pharmacol. Toxicol. 5, 38–41.

Ra, J., Woo, S., Lee, K., Ja, M., Young, H., Mi, H., et al., 2020. Policosanol profiles and adenosine 5 ′ -monophosphate-activated protein kinase (AMPK) activation potential of Korean wheat seedling extracts according to cultivar and growth time. Food Chem. 317, 126388.

Ranasinghe, P., Mathangasinghe, Y., Jayawardena, R., Hills, A.P., Misra, A., 2017. Prevalence and trends of metabolic syndrome among adults in the Asia-pacific region: a systematic review. BMC Public Health 17, 1–9.

Sánchez-López, J., Fernández-Travieso, J.C., Illnait-Ferrer, J., Fernández-Dorta, L., Mendoza-Castaño, S., Mas-Ferreiro, R., et al., 2018. Effects of policosanol in the functional recovery of non-cardioembolic ischemic stroke hypertensive patients. Rev. Neurol. 67, 331–338.

Sánchez, J., Illnait, J., Mas, R., Mendoza, S., Vega, H., Fernández, L., et al., 2016. Policosanol versus atorvastatin on the functional recovery of patients with ischemic stroke. Int. J. Pharm. Sci. Rev. Res. 37, 7–14.

Sánchez, J., Mas, R., Mendoza, S., César, J., and Ruiz, D. (2010). Effects of Policosanol on patients with ischemic stroke with previous transient ischemic attack: a long-term follow-up. Revista CENIC Ciencias Biológicas, 41 (1): 23–29.

Scarpini, F., Cappellone, R., Auteri, A., Puccetti, L., 2012. Role of genetic factors in statins side-effects. Cardiovasc. Hematol. Disord. Targets 12, 35–43.

Sharma, R., Matsuzaka, T., Kaushik, M.K., Sugasawa, T., Ohno, H., Wang, Y., et al., 2019. Octacosanol and Policosanol prevent high-fat diet-induced obesity and metabolic disorders by activating brown adipose tissue and improving liver metabolism. Sci. Rep. 9, 1–7.

Shen, J., Luo, F., Lin, Q, 2019. Policosanol: extraction and biological functions. J. Funct. Foods 57, 351–360.

Tian, Y., Acevedo, N.C., 2018. Kinetic study on the photostability of retinyl palmitate entrapped in policosanol oleogels. Food Chem. 255, 252–259.

Tian, Y., Acevedo, N.C., 2020. Role of supramolecular policosanol oleogels in the protection of retinyl palmitate against photodegradation. RSC Adv. 10, 2526–2535.

Venturelli, A., Brighenti, V., Mascolo, D., Pellati, F., 2019. A new strategy based on microwave-assisted technology for the extraction and purification of beeswax policosanols for pharmaceutical purposes and beyond. J. Pharm. Biomed. Anal. 172, 200–205.

Wang, H.Ya, Jiao, Q.Ping, Chen, S.Yan, Sheng, J., Jiang, H., Lu, J., et al., 2018. Efficacy and safety of policosanol plus fenofibrate combination therapy in elderly patients with mixed dyslipidemia: a randomized, controlled clinical study. Am. J. Med. Sci. 356, 254–261.

Wang, Z.Di, Feng, Y., Sun, L., Gan, J., Li, X., Ding, W.feng, et al., 2021. Anti-androgenetic alopecia effect of Policosanol from Chinese wax by regulating abnormal hormone levels to suppress premature hair follicle entry into the regression phase. Biomed. Pharmacother. 136, 111241.

Ward, N.C., Watts, G.F., Eckel, R.H., 2019. Statin toxicity: mechanistic insights and clinical implications. Circ. Res. 124, 328–350.

WHO, 2018a. Investing in Noncommunicable Disease Control Generates Major Financial and Health Gains. WHO, pp. 5–7.

WHO (2018b). Key facts; Noncommunicable diseases.

WHO, 2020. The Top 10 Causes of Death - Factsheet. WHO Reports.

WHO, 2018c. Saving lives, Spending less: a Strategic Response to Noncommunicable Diseases 2018 (WHO/NMH/NVI/18.8).

Wong, W.T., Ismail, M., Tohit, E.R.M., Abdullah, R., Zhang, Y.Da, 2016. Attenuation of thrombosis by crude rice (Oryza sativa) bran policosanol extract: *ex vivo* platelet aggregation and serum levels of arachidonic acid metabolites. Evid. Based Complement Alternat. Med. 2016, 7343942. doi:10.1155/2016/7343942, 2016Epub 2016 Oct 5.

Xi, Y., Niu, L., Cao, N., Bao, H., Xu, X., Zhu, H., et al., 2020. Prevalence of dyslipidemia and associated risk factors among adults aged ≥35 years in northern China: a cross–sectional study. BMC Public Health 20, 1–9.

Xu, F., Na, L., Li, Y., Chen, L, 2020. Roles of the PI3K/AKT/mTOR signaling pathways in neurodegenerative diseases and tumours. Cell Biosci. 10, 1–12.

Xu, K., Liu, X., Li, Y., Wang, Y., Zang, H., Guo, L., et al., 2016. Safety and efficacy of Policosanol in patients with high on-treatment platelet reactivity after drug-eluting stent implantation: two-year follow-up results. Cardiovasc. Ther. 34, 337–342.

Zhang, X., Ma, C., Sun, L., He, Z., Feng, Y., Li, X., Gan, J., Chen, X., 2021. Effect of policosanol from insect wax on amyloid β-peptide-induced toxicity in a transgenic Caenorhabditis elegans model of Alzheimer's disease. BMC complementary medicine and therapies 21 (1), 103. doi:10.1186/s12906-021-03278-2.