Rev. CENIC Cienc. Biol.; vol. 51. (3):222-229. Año. 2020. e-ISSN: 2221-2450.

ARTICULO DE REVISION

Dementia post ictus: Is policosanol a prevention therapy?

Demencia post ictus: ¿Es útil el policosanol como terapia preventiva?

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Recibido: 17 de febrero de 2020; **Aceptado:** 8 de julio de 2020;

ABSTRACT

Stroke is a global health problem related to various risk factors. Although its frequency is increasing with age, it can also appear in young people. The sequelae observed, after the event, include the presence of motor and cognitive disabling effects, including appearance of dementia, Alzheimer disease and, conditioning the recurrence of stroke episodes, all together constituting a serious socioeconomic problem. Taking into account, on one side, the relationship between lipid metabolism disorders, atherosclerosis, the age of onset of stroke and the development of cognitive decline after the event and on the other, that policosanol, a drug of natural origin, has demonstrated efficacy in the treatment of dyslipidemia (a risk factor commonly present in patients suffering a stroke), as well as on their motor and functional recovery, without showing evidences of cognitive decline during a long period of time after occurring the event, then this paper is aimed to assess a putative role of policosanol in preventing cognitive decline or at least decrease the prevalence of its appearing in such patients. A brief analysis on the molecular basis that would support this hypothesis, is done and is concluded that conducting of appropriates clinical assays is needed to prove the presented hypothesis.

Keywords: Dementia; Policosanol; Stroke; Alzheimer Disease; Central Nervous System.

RESUMEN

El ictus es un problema de salud global relacionado con varios factores de riesgo. Aunque su frecuencia aumenta con la edad, también puede aparecer en personas jóvenes. Las secuelas observadas, después del evento, incluyen la presencia de efectos de discapacidad motora y cognitiva, incluida la aparición de demencia, enfermedad de Alzheimer y, condicionando la recurrencia de episodios de ictus, todo lo cual constituye un grave problema socioeconómico. Teniendo en cuenta, por un lado, la relación entre los trastornos del metabolismo de los lípidos, la aterosclerosis, la edad del paciente en que se produce el ictus y el desarrollo del deterioro cognitivo después del evento y, por el otro, que el policosanol, un medicamento de origen natural, ha demostrado eficacia en el tratamiento de la dislipidemia (un factor de riesgo comúnmente presente en pacientes que sufren un ictus), así como en su recuperación motora y funcional, sin mostrar evidencias de deterioro cognitivo durante un largo período de tiempo después de su recuperación, el objetivo de este trabajo es analizar el papel ue pudiese desempeñar el policosanol en la prevención del deterioro cognitivo o al menos en la disminución de la prevalencia de su aparición en dichos pacientes. Se realiza un breve análisis sobre la base molecular que respaldaría esta hipótesis, y se concluye que se necesita realizar ensayos clínicos apropiados para probar la hipótesis presentada.

Palabras clave: Demencia; Policosanol; Ictus; Enfermedad de Alzheimer; Sistema Nervioso Central.

INTRODUCTION

Stroke is, the third cause of death in Cuba, but in addition, almost 85 % of deaths, because of cerebrovascular events, occur in elderly, older than 60 years (Anuario Estadístico de Salud, Ministerio de Salud Pública de Cuba, 2018). There are three types of strokes: ischemic and hemorrhagic strokes and Transient ischemic attack, also named "mini-stroke", being ischemic strokes, the most frequent, about 87 %. Every stroke is different. Each person affected by stroke will have different problems and different needs. Several factors determine the effects of stroke and impact recovery. Among the most common co-morbidities, after the episode, are falling because of motor deficits or gait disturbances, urinary incontinence, sleep disturbances, depression and cognitive and emotional dysfunction. All together contribute to diminish the Quality of Life (QoL) in elderly, its third cause after depression and heart attack (Katan & Luft, 2018). We will focus the attention on management of several types of cognitive disorders after ischemic strokes.

Policosanol is a mixture of higher aliphatic alcohols obtained from sugar cane wax (Saccharum oficinarum). It is a cholesterol-lowering product, decreasing serum total cholesterol and LDL-c, increasing serum HDL-c and its functionality. Likewise, Policosanol is an antiplatelet agent. All these actions have been demonstrated in preclinical and clinical studies (Mas, 2000).

In connection with these results, Policosanol (20 mg) has been evaluated in patients after being affected by ischemic strokes. The results evidenced a best neurological recovery (Sánchez et al., 2010; Sánchez et al., 2013; Sánchez et al., 2017; Sánchez et al., 2018). On this basis, this article is aimed to analyze the convenience of conducting clinical trials to test the hypothesis about Policosanol usefulness to manage of occurrence post-stroke cognitive impairment.

Epidemiology

Disease. Stroke is, in general, the second leading cause of death (the position is depending on income groups and definitions of pathologies causing mortality) and a major cause of disability worldwide. Stroke incidence is increasing because the population ages. In addition, the increase has been also observed in younger patients, in low- and middle-income. On the contrary, stroke incidence decreases in countries with better economic resources. The incidence of stroke not only differs depending on the country, there are also others influencing factors, such as geographic region and ethnicity. The prevalence of ischemic stroke is greater than that of hemorrhagic stroke, but the later cause greater disability and mortality (Katan & Luft, 2018).

Prevalence of post-stroke cognitive impairment, including mild cognitive decline, vascular dementia and Alzheimer Disease (AD): Stroke is considered a risk factor for the development of cognitive decline and dementia, including Alzheimer Disease, in a third of the cases (33 %) (Desmond et al., 2000). The prevalence of post stroke dementia ranges from 7 % to 41 % (± 24 %), increasing by 3 % each year (Pendlebury & Rothwell, 2009). In a population-based follow-up study, conducted through the use of periodic interviews for 5 years, participating 92,728 subjects, were recruited 2305 patients with a history of cerebrovascular events, between years 2002 and 2012, 20 % of the patients admitted by Stroke (461 patients) developed dementia within the first year after the event, with the highest incidence in cases that presented recurrent stroke (Hillen et al., 2019).

Another study identifies factors such as age, low educational level, stroke severity, dysphasia, diabetes, atrial fibrillation and leukoaraiosis in brain imaging among predictors of post-stroke dementia (Lai et al., 2009). In the elderly, dementia coincided with Alzheimer Disease, this association being high morbidity and mortality, which is devastating for the patient and for caregivers (Couillard et al., 2009).

In Cuba, after the implementation of the National Program for the Prevention and Control of Cerebrovascular Disease, it has been possible to reduce stroke intra-hospital mortality (Zuaznábar et al., 2008). However, it is noteworthy a tendency to increase the frequency of deaths in Alzheimer Disease and dementia, in patients between the years 2015-2018 (Anuarios Estadísticos de Salud, 2015-2018) (Figure 1) in the general population, which, in a number of cases, could be supposed to be occurred (or not) later at patient discharge from the hospital. In this regard, it is necessary to promote prevention measures related to this risk before discharge.

Associated risk factors for stroke recurrence

There is the opinion that in response to conventional risk factors, most recurrences have no explanation (Lovett et al., 2004). However, arterial hypertension, myocardial infarction, cardiac arrhythmia, diabetes mellitus and Transient Ischemia Attack are considered to be the 5 most important risk factors for the occurrence of a second stroke. It is considered that the control of arterial hypertension and atrial fibrillation could be the factors most likely to reduce the risk of stroke recurrence (Ankolekar et al., 2010). The risk of stroke after having suffered a transient ischemic attack or a minor stroke is approximately 10 % within the following 90 days (Couillard et al.,

2009). There are several criteria to define what time after the first stroke would be adequate to consider as recurrent a second stroke, but it is estimated that between 15 % and 20 % of patients with a first stroke may have recurrence before 90 days (Dichgans et al., 2019).
Only 14 % of the first stroke is associated with atherosclerosis in the great arteries. However, the risk of recurrent stroke rises to 37 % in those patients, associated with a risk of recurrence within 7 days after the event, which supports the need to examine the images of the carotids and recommend endarterectomy if required (Coull & Rothwell, 2004; Liu et al., 2019; Lovett, et al., 2004).

Role of lipids in these co-morbidities.

Blood Lipids and Central Nervous System function

Dyslipidemia is not only considered a risk factor involved in the occurrence of stroke, but is also related to the further evolution towards cognitive decline. For this reason, according with a limited number of clinical trials, treatments have been suggested to reduce the development of cognitive decline by decreasing dyslipidemia and also blood pressure, using choline stearase inhibitors, lipid lowering agents, antiplatelet agents, and serotonin reuptake (Liu et al., 2019).
However, despite these treatments, the prevention of cognitive decline after stroke remains a critical need. In this sense, stronger clinical trials are required, capable of demonstrating the effectiveness of new and more effective treatments (Ginneken, et al., 2017) Blood plasma lipids and the quantitative relationships between them have been considered indicators that are very associated with atherosclerosis and cardiovascular disease. However, these indicators have not been sufficiently studied in their relationship with stroke and with the subtypes of the stroke. In order to confirm the existence of some relationship between these indicators and the stroke, a prospective study was carried out in China where 42,005 individuals between 20 and 80 years of age participated, which lasted 3.8 years on average, during which time 623 ischemic strokes occurred (1.48 % of the total participants) and 158 hemorrhagic strokes (0.57 %). In this study, it was found that the highest quintile of the quotient: Total Cholesterol/Cholesterol linked to High Density Lipoprotein, was associated with ischemic stroke in men, while the highest quintile of triglycerides was associated with ischemic stroke in women. These data could be taken into consideration in the design of clinical trials and in medical practice for the evaluation of risk and the effectiveness of the therapy used (Liu et al., 2019).

Lipids in the Central Nervous System

Lipids have a unique importance in the molecular composition, anatomy and functionality of the central nervous system. In this sense, it should be taken into consideration that the ratio between brain mass and body mass is only 1:40, however, lipids constitute 60 % of the dry matter of the human brain, thus being the tissue with the greatest proportion of lipids in the body after adipose tissue. With regard to cholesterol, it is known that a quarter of all the cholesterol in the body is in the brain and in terms of triacylglycerides, it has been speculated about its importance in brain growth and as a trigger in human evolution to encephalization. (Zarrouk et al., 2017).
The importance of lipids in the central nervous system is not only based on their quantitative proportion in brain tissue, but also because, they participate in key functions of the central nervous system, such as cell signaling and nerve impulse conduction (Fidaleo et al., 2014). Some lipids are able to launch some physiological responses, control inflammatory reactions and regulate several cellular processes, including: cell proliferation, survival, apoptosis, migration and energy metabolism. In addition, lipids contribute to the growth and renewal of cell membranes as well as the synthesis and replacement of the myelin sheaths that line the axons. The relevance of lipids in the structure and functioning of the central nervous system justifies a drug intervention that could contribute to improve their function in the brain in the case of stroke patients.
Particularly, plasmalogen, which are synthesized from very long chain fatty alcohols with the participation of peroxisomes and endothelial reticulum, participate in neuronal excitability, but also, they are related to the fluidity of the membranes and the neuroprotection, due to its antioxidant capacity. Thus, when peroxisomes are not able to synthesize plasmalogens, as a result of some genetic disorder that disturb the metabolism of very long chain fatty alcohols, neuronal degeneration occurs (Fidaleo et al., 2014).
Given the dramatic decline of brain plasmalogen levels with aging and the critical roles played by these lipids in the central nervous system, it is not surprising that serum and brain plasmalogen deficits are closely associated with disease progression for aging-related neurodegenerative disorders such as Alzheimer Disease and Parkinson Disease (Senanayake & Goodenave, 2019).

The role of plasmalogens is further evidenced, because its concentration is markedly decreased in white matter both in the brain of patients affected with Alzheimer Disease and in cases of dementia, which has also been confirmed in experimental animals (Han et al., 2001).
Growing evidence suggests that ethanolamine plasmalogens (PlsEtns), a subtype of phospholipids, have a close association with Alzheimer Disease. Decreased levels of PlsEtns have been commonly found in Alzheimer Disease patients, and were correlated with cognition deficit and severity of disease (Su et al., 2019).

Dementia-atherosclerosis relationship

The increasing prevalence of dementia makes it necessary to develop new contributions to mitigate its enormous socioeconomic impact. In this sense, the detection and control of several risk factors associated with its development have been proposed. Cardiovascular risk factors are common to atherosclerosis and dementia. Although it is on discussion whether or not there is any interrelation between atherosclerosis and Alzheimer Disease. In this sense, the existence of underlying processes common to both pathologies such as inflammation, macrophage infiltration, blood vessel occlusion, amyloid accumulation and allelic common genes that include Apo E variants is demonstrated (Xianlin et al., 2001).
The results of the Framingham study suggest that both, dementia and Alzheimer Disease, could be related to atherosclerosis (Zachacharopoulou et al., 2018). In fact, stroke can occur due to fractures of atheromatous lesions in the carotid, where clots occur and then migrate to the brain through the bloodstream and obstruct intracerebral arteries of smaller diameter. One study showed that the number of plaques in the external carotid is strongly correlated with the presence of lacunar stroke (Chambliss et al., 2018). On the other hand, a relationship has also been found between the degree of carotid stenosis and the frequency of the stroke. According to this study, a carotid stenosis less than 75 % is more related to a relatively higher annual probability of cardiac ischemia (9.9 %) than stroke (1.3 %) (Ionescu et al., 2017). However, when the level of stenosis exceeds 75 % the probability of combined coronary infarction and stroke increases to 10.5 % (Norris et al., 1991).
Considering these associations between the stroke and atherosclerosis, it has been suggested that lipid-lowering agents such as statins could prevent dementia, due to their effect on blood cholesterol concentration reduction and on the lesions size reduction of athermanous lesions, which would seem promising according to observational study results which indicate that, regardless of the traditional risk factors, there has been a decrease in the diagnosis of new cases of dementia in the elderly who had been treated with high doses of statins such as atorvastatin and rosuvastatin (Wu et al., 2015). However, there are also evidences that statins, indicated at the end of life to people at risk of vascular disease, do not prevent cognitive decline or dementia, although it is considered the possibility that biases derived from different types of statins and doses used could be factors that have influenced these controversial results (Grilli et al., 2002). It is necessary to hold in mind that in the case of stroke patients who are already on statins, is risky to withdraw the statin treatment upon admission, since according to studies, this is associated with the increased risk of death 4.7 times after three months or risk of early neurological deterioration in 8.7 times, among other undesirable effects, in comparison with those patients who continued the treatment, so in patients with ischemic stroke it is recommended to maintain treatment with statin at least during the acute phase of the stroke due to the possible “rebound effect” of those products (Blanco et al., 2007).

Hypothesis Rationality

The proposal of the use of Cuban Policosanol in the prevention of ictus recuperation and post stroke cognitive decline has its preclinical basis in studies conducted with a Mongolian gerbil model. A positive effect of Policosanol was shown in the recovery of the induced ischemic stroke (Molina et al., 1999).
Policosanol had also been tested in a large number of elderly people in different clinical trials, for long periods of time, in order to assess its effect on hypercholesterolemia. In those trials no side effects related to cognitive decline were reported in treated individuals, suggesting a possible positive effect on this condition (Illnait et al., 2019).
Moreover, several clinical trials indicate that Policosanol shortened the time of recovery in patients who have suffered ischemic stroke, decreasing the frequency of recurrences, which is also a dementia prevention factor (Fernández et al., 2019). In those studies, there were no reports on cognitive decline manifestations, even in those patients who maintained treatment with policosanol for 5 years or more, after stroke (Sánchez et al., 2010; Sánchez et al., 2013; Sánchez et al., 2017; Sánchez et al., 2018). However, no specifically aimed study to demonstrate this effect has been carried out.

A possible effect of Policosanol on reduction of dementia incidence in patients with previous ischemic stroke could be associated with the increase of oxidative protection capacity of LDL. The resistance to oxidation of LDL, induced by Policosanol, observed in experimental models and humans (Menendez et al., 2000; Fraga et al., 1997), is probably due to the increased content of plasmalogen in its lipidome (Vance, 1990).

Results on the molecular and physiological field supports the hypothesis of a positive effect of Policosanol treatment on the reduction of cognitive decline in post stroke events patients:

1. The increase of plasmalogen in the HDL lipidome (Vance, 1990).

Evidences have been accumulated indicating that low plasma levels of plasmalogen are closely associated to cognitive deficit and severity of Alzheimer Disease, and several clinical studies had been shown a positive result of plasmalogen treatment in patients with adverse events and also in rodents. It is assumed that these results could be related to the reduction of the gamma secretase activity, which is the enzyme that catalyzes the synthesis of beta amyloid, a key molecule in the etiology of adverse events. On the other hand, in vitro evidence indicates that plasmalogen prevent neuronal death in both humans and rodents (Wang & Sinclair, 2019).

Besides that, Plasmalogen phospholipids are also involved in HDL mediated cholesterol efflux (Mandel et al., 1998). Moreover, the improvement of HDL functionality promote cardiovascular protection (Kontush et al., 2014), by the increase of reverse cholesterol efflux efficiency (Mandel et al., 1998), and the stimulation of nitric oxide synthesis, which in turn produces vascular dilatation and a blood pressure improvement (Askarpour et al., 2019). Beside antioxidant protection to endothelial cells, macrophages, and antithrombotic activity (Wang & Sinclair, 2019) Policosanol is also involved in the modulation of glucose metabolism as well as in the management of cholesterol and activation of AMPK in the brain (Drew et al., 2009; Mortensen & Bousel, 2013).

2. The increase of Paraoxonase activity in the HDL proteome (Kim et al., 2017).

Paraoxonase could be the link between lipid metabolism and cognitive disturbances. In these sense, Paraoxonase is considered to participate in mild cognitive prevention (Cervellati et al., 2015).

The enzyme Paraoxonase 1, is part of the HDL proteome, and contributes as antioxidant to this lipoprotein functionality. It was found decreased in subjects with mild cognitive impairment, and two years later in developed dementia (Paragh et al., 2002). Paraoxonase activity was also decreased both in patients with Alzheimer Disease, as well as with dementia compared to normal controls, suggesting that a defect in the antioxidant capacity of paraoxonase in HDLs could be related to the development of these pathologies. For this reason, the knowledge that Policosanol was able to raise paraoxonase activity by 17 % in the HDL fraction in the Policosanol treated subjects (Kim et al., 2017), gives Policosanol a paramount importance for its indication in the prevention of dementia in the patients who have had cerebral ischemic events.

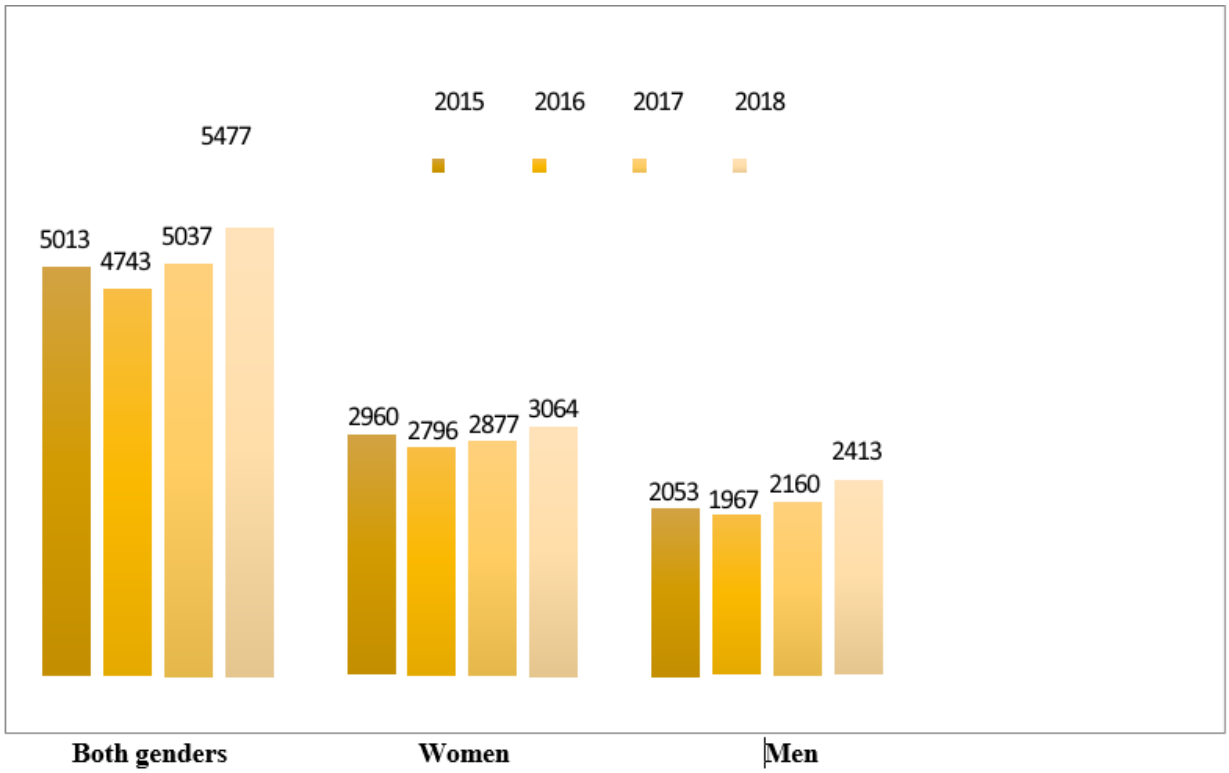

Fig. 1 *Incidence of mortality due to Alzheimer disease and Dementia (2015-2018) in Cuba. Cuban Public Health Statistical Anuary 2015-2018*

CONCLUSION

The development of appropriates clinical assays is recommended to proof the presented hypothesis.

BIBLIOGRAPHIC REFERENCES

Ankolekar S., Geeganage C., Anderton P., Hogg C., Bath P.M.W. (2010). Clinical trials for preventing post stroke cognitive impairment. Journal of the Neurological Sciences, 299, 168-174.

Anuario Estadístico de Salud. Ministerio de Salud Pública de Cuba. Dirección de Registros Médicos y Estadísticas de Salud. La Habana, 2015.

Anuario Estadístico de Salud. Ministerio de Salud Pública de Cuba. Dirección de Registros Médicos y Estadísticas de Salud. La Habana, 2016.

Anuario Estadístico de Salud. Ministerio de Salud Pública de Cuba. Dirección de Registros Médicos y Estadísticas de Salud. La Habana, 2017.

Anuario Estadístico de Salud. Ministerio de Salud Pública de Cuba. Dirección de Registros Médicos y Estadísticas de Salud. La Habana, 2018.

Arruzazabala, M.L., Molina, V., Carbajal, D., Valdés, S., Noa, M., Mas, R., Menéndez,
R. (1999). Effect of policosanol on cerebral ischemia in Mongolian gerbils. Brazilian journal of medical and biological research, 32(10), 1269-1276.

Askarpour, M., Ghaedi, E., Roshanravan, N., Hadi, A., Mohammadi, H., Symonds, M.E., Miraghajani, M. (2019). Policosanol supplementation significantly improves blood pressure among adults: A systematic review and meta-analysis of randomized controlled trials. Complementary Therapies in Medicine, 45, 89-97.

Blanco, M., Nombela, F., Castellanos, M.A., Rodriguez-Yanez, M., Garcia-Gil, M., Leira, R., Davalos, A. (2007). Statin treatment withdrawal in ischemic stroke: a controlled randomized study. Neurology, 69(9), 904-910.

Brian G. (2009) High-Density Lipoprotein Modulates Glucose Metabolism in Patients with Type 2 Diabetes Mellitus. Circulation, 119, 2103-11.

Cervellati, C., Trentini, A., Romani, A., Bellini, T., Bosi, C., Ortolani, B., Zuliani, G.

(2015). Serum paraoxonase and aryl esterase activities of paraoxonase-1 (PON-1), mild cognitive impairment, and 2-year conversion to dementia: A pilot study. Journal of neurochemistry, 135(2), 395-401.

Chambless, L.E., Heiss, G., Shahar, E., Earp, M.J., Toole, J. (2004). Prediction of ischemic stroke risk in the Atherosclerosis Risk in Communities Study. American Journal of Epidemiology, 160(3), 259-269.

Couillard P., Poppe A.Y., Coutts S.B. (2009). Predicting recurrent stroke after minor stroke and transient ischemic attack. Expert Rev Cardiov Ther, 100, 1273-1281.

Coull, A.J., & Rothwell, P.M. (2004). Underestimation of the early risk of recurrent stroke: evidence of the need for a standard definition. Stroke, 35(8), 1925-1929.

Desmond D.W., Maroney J.T, Paik M.C., Sano M, Mohr J.P., Aboumatar S., et al. (2000). Frequency and Clinical determinats of dementia after ischemic Stroke. Neurology, 54, 1124–1131.

Dichgans, M. (2019). Dementia risk after transient ischemic attack and stroke. The Lancet Neurology, 18(3), 223-225.

Drew, B.G., Duffy, S.J., Formosa, M.F., Natoli, A.K., Henstridge, D.C., Penfold, S.A., (2009). High-density lipoprotein modulates glucose metabolism in patients with type 2 diabetes mellitus. Circulation, 119(15), 2103-2111.

Fernández J.C., Sánchez J., Illnait J., Fernández L., Mendoza S. (2019). A preliminary retrospective analysis of the effects of policosanol on ischemic stroke patients. Int Res J Phar Med Sci, 2(3), 28-34.

Fidaleo, M., Fanelli, F., Paola Ceru, M., Moreno, S. (2014). Neuroprotective properties of peroxisome proliferator-activated receptor alpha (PPARα) and its lipid ligands. Current medicinal chemistry, 21(24), 2803-2821.

Fraga, V., Menéndez, R., Amor, A.M., González, R.M., Jiménez, S., Mas, R. (1997). Effect of policosanol on in vitro and in vivo rat liver microsomal lipid peroxidation. Archives of medical research, 28(3), 355-3607.

Ginneken, V.V., Meerveld, A.V., Verheij, E., Greef, J.V.D. (2017). On the Futile Existence of DHA, None of EPA and the Predominant Role of the Triacylglycerols (TGs) in the Post Mortem Human Brain: An LCMS Study with Evolutionary Implications. J Bioanal Biomed, 9, 152-158.

Grilli, R., Ramsay, C., Minozzi, S. (2002). Mass media interventions: effects on health services utilisation. Cochrane database of systematic reviews, 1. Art.No.: CD000389.DOI 10.1002/14651858.CD000389.

Han X., Holtzman D.M., Mc Keel D.W. Jr. (2001). Plasmalogen deficiency in early Alzheimer's disease subjects and in animal models: molecular characterization using electrospray ionization mass spectrometry. Journal of Neurochemistry, 77, 1168-1180.

Hillen T., Coshal C., Tilling K., Rudd G., McGovern R., C.D.A. Wolfe. (2019). Cause of Recurrence is multifactorial patterns, risk factors and outcomes of stroke recurrence in South London Stroke register. Stroke is available at http://www.strokeaha.or Downloaded from http://ahajournals.org by on September 3.

Illnait J., Fernández J. C., Fernández L., Gámez R., Mendoza S., Estrella A., et al. (2019) Benefits of a long-term therapy with policosanol on hypercholesterolemic Elder patients: a controlled study. Int J Med Sci Currt Res, 2(2), 383-395.

Ionescu A M, Carciumaru N, Chirila S, Sîrbu R. (2017) Carotid atherosclerosis and lacunar stroke a possible association. Eur J of Pharm and Med Studies,1(1), 15-23.

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. International journal of molecular medicine, 39(4), 889-899.

Kontush, A. (2014). HDL-mediated mechanisms of protection in cardiovascular disease. Cardiovascular research, 103(3), 341-349.

Lai, S.M., Alter, M., Friday, G., Sobel, E. (1994). A multifactorial analysis of risk factors for recurrence of ischemic stroke. Stroke, 25(5), 958-962.

Liu, X., Yan, L., Xue, F. (2019). The associations of lipids and lipid ratios with stroke: A prospective cohort study. The Journal of Clinical Hypertension, 21(1), 127-135.

Lovett J.K., Coull A.J., Rothwell P.M. (2004). Early risk of recurrence by subtype of ischemic stroke in population-based incidence studies. Neurology, 62(4), 569-573.

Mandel, H., Sharf, R., Berant, M., Wanders, R.J., Vreken, P., Aviram, M. (1998). Plasmalogen phospholipids are involved in HDL-mediated cholesterol efflux: insights from investigations with plasmalogen-deficient cells. Biochemical and biophysical research communications, 250(2), 369-373.

Mas R. (2000). Policosanol. Drugs of the Future; 25, 569-586.

Mc Guinness B, Craig D, Bullock R, Passmore P. (2016). Statins for the prevention of dementia. Cochrane Database of Systematic Reviews, Issue 1. Art. No.: CD003160. doi: 10.1002/14651858.C D003160.pub3.

Menéndez, R., Más, R., Amor, A.M., González, R.M., Fernández, J.C., Rodeiro, I., Jiménez, S. (2000). Effects of policosanol treatment on the susceptibility of low density lipoprotein (LDL) isolated from healthy volunteers to oxidative modification in vitro. British journal of clinical pharmacology, 50(3), 255-262.

Mira Katan, MD, MS Andreas Luft, MD. (2018). Global Burden of Stroke. Semin Neurol; 38, 208–211.

Mortensen, S.P., Boushel, R. (2013). High-density lipoprotein: a new therapeutic target for glucose intolerance. Circulation, 128(22), 2349-2350.

Norris J W, Zhu C Z, Bornstein N M, Chambers, B R. (1991) Vascular risks of asymptomatic carotid stenosis. Stroke. 22(12), 1485-1490. Downloaded from http://stroke.ahajournals.org/ by guest on May 9, 2018.

Paragh, G., Balla, P., Katona, E., Seres, I., Égerházi, A., Degrell, I. (2002). Serum paraoxonase activity changes in patients with Alzheimer's disease and vascular dementia. European archives of psychiatry and clinical neuroscience, 252(2), 63-67.

Pendlebury ST, Rothwell PM. (2009). Prevalence, incidence, and factors associated with pre-stroke and post-stroke dementia: a systematic review and meta-analysis. Lancet Neurol, 8(11), 1006-1018.

Sánchez, J., Illnait, J., Mas, R., Mendoza, S., Fernández, L., Mesa, M., Ruiz, D. (2017). Efecto a largo plazo del policosanol en la recuperación funcional de pacientes con ictus isquémico no cardioembólico: estudio de un año. Revista de Neurología, 64(4), 153-161.

Sánchez, J., Illnait, J., Mas, R., Pérez, Y., Mendoza, S., Cabrera, L., Molina, V. (2013). Effects of policosanol plus aspirin therapy on the neurological recovery and plasma oxidative markers of patients with ischemic stroke. J Pharm, 3, 31-40.

Sánchez, J., Mas, R., Mendoza, S., Fernández, J. C., Ruiz, D. (2010). Effects of policosanol on patients with ischemic stroke with previous transient ischemic attack: a long- term follow-up. Rev CENIC. Cien Biol, 41(1), 23-29.

Sánchez-López, J., Fernández-Travieso, J. C., Illnait-Ferrer, J., Fernández-Dorta, L., Mendoza-Castaño, S., Mas-Ferreiro, R., Reyes-Suarez, P. (2018). Effects of policosanol in the functional recovery of non-cardio embolic ischemic stroke hypertensive patients. Rev de Neurología, 67(9), 331-338.

Senanayake, V. & Goodenave, D.B. (2019). Plasmalogen deficiency and neuropathology in Alzheimer's disease: Causation or coincidence?. Alzheimers Dement, 5, 524- 532.

Su, X.Q., Wang, J. & Sinclair, A.J. (2019). Plasmalogens and Alzheimer's disease: a review. Lipids Health Dis, 18(100). https://doi.org/10.1186/s12944-019-1044-1.

Vance, J. E. (1990). Lipoproteins secreted by cultured rat hepatocytes contain the antioxidant 1-alk-1-enyl-2-acylglycerophosphoethanolamine. Biochimica et Biophysica Acta (BBA)-Lipids and Lipid Metabolism, 1045(2), 128-134.

Wang, J. & Sinclair, A.J. (2019). Plasmalogens and Alzheimer's disease: a review.
Lipids in Health and Disease, 18(1), 100. doi 10.1186/s12944-019-1044-1

Wu C.K., Y H. Yang, T.T. Lin, C.T. Tsai, J.J. Hwang, J.L. Lin et. al. (2015). Statin use reduces the risk of dementia in elderly patients: a nationwide data survey and propensity analysis. Journal of Internal Medicine, 277, 343–352.

Zacharopoulou, V.P., Zacharopoulou, G.P., Karkoulias, K., Tsampalas, E., Lazakidou,
(2018). Atherosclerosis as a Risk Factor for Dementia and Alzheimer's disease. Hellenic Journal of Atherosclerosis, 8(1), 1-2.

Zarrouk, A., Debbabi, M., Bezine, M., Karym, E.M., Badreddine, A., Rouaud, O., & Hammami, M. (2018). Lipid biomarkers in Alzheimer's disease. Current Alzheimer Research, 15(4), 303-312.

Zuaznábar, M.A.B., Fernández Concepción, O., Marre, G.C., Vidal, R.M.T. (2008). Epidemiology of cerebrovascular diseases in Cuba, 1970 to 2006. MEDICC review, 10(2), 33- 38.