

D-003 (*Saccharum officinarum*):

THE FORGOTTEN LIPID-LOWERING AGENT

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ABSTRACT:

Reduction of elevated cholesterol levels, particularly low-density lipoprotein cholesterol (LDL-C), is essential in primary and secondary prevention of cardiovascular disease (CVD). Therefore there is still a large need for new effective drugs, which would be able to essentially reduce LDL-C and in the consequence CV residual risk.

D-003 is a mixture of high aliphatic primary acids purified from sugarcane (*Saccharum officinarum*) wax. It showed promising hypocholesterolemic effects in both animal and human studies; it significantly lowers both serum total cholesterol (TC) and LDL-C, and increases high-density lipoprotein cholesterol (HDL-C). In addition, it showed a favorable safety profile. In this review, we evaluated the profile of D-003 as a lipid-lowering agent based on data from available preclinical and clinical studies.

Keywords: Hypercholesterolemia, Cardiovascular Diseases, Cholesterol, LDL, Fatty Acids, Saccharum.

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1. INTRODUCTION

Despite the recent medical improvements in cholesterol management, coronary heart disease (CHD) is still the leading cause of mortality and morbidity worldwide [1]. Elevated total cholesterol (TC) and especially low density lipoprotein cholesterol (LDL-C) are major risk factors for the development of atherosclerosis and subsequently CHD [2–4]. It is now well-established that LDL-C lowering significantly decreases the incidence of atherosclerotic cardiovascular disease (ASCVD) [5–7]. Available data revealed that there is a corresponding 20-25% reduction in cardiovascular disease mortality for every 1.0 mmol/l reduction in LDL-C [8].

D-003 is a mixture of high aliphatic primary acids isolated from sugarcane (*Saccharum officinarum*) wax [9,10]. Its main component is octacosanoic acid, followed by triacontanoic, dotriacontanoic and tetracontanoic acids. There are also some other acids (hexacosanoic, heptacosanoic, nonacosanoic, hentriacontanoic, tritriacontanoic, pentatriacontanoic and hexacotriacontanoic) as minor components of this mixture [11].

D-003 showed very promising results as a lipid-lowering agent in both animal and clinical studies. All published studies about this compound recommended conducting well-designed, large-scale clinical studies to confirm its efficacy as a lipid-lowering agent. However, surprisingly since 2008, there have been no reports of completed or ongoing investigations into the lipid-lowering properties of D-003. Therefore, we have decided to remind this agent and comprehensively reviewed published reports about the lipid lowering effect of D-003 with regard to its promising results.

2. MECHANISM OF ACTION

In fibroblasts cultured in a lipid-deficient medium (LDM), D-003 showed a dose-dependent inhibition of cholesterol biosynthesis from ^{14}C -labelled acetate but not from ^{14}C -labelled mevalonate [12]. This revealed that D-003 inhibits cholesterol biosynthesis at a step between acetate consumption and mevalonate generation. In addition, D-003 did not show any direct effect on the activity of 3-hydroxy-3-methyl glutaryl coenzyme A (HMG-CoA) reductase when added to the incubation mixture [12]. However, when it was added to the cultured cells, it suppressed the enzyme activity. This inhibitory effect could be explained by: (i) suppression of *de novo* synthesis of the enzyme; (ii) enhancement of the enzyme degradation; or (iii) the effect of the drug on the physico-chemical properties of the endoplasmic reticulum based on the suggestion of some studies that presence of fatty acids with the incubated cultured cells can affect the composition of the membrane and this modulates the activity of HMG-CoA reductase (**Figure 1**) [13–17]. Also, Menendez *et al.* [12] hypothesized that D-003 may have an effect on HMG-CoA synthase up-regulation based on the fact that this enzyme is a key enzyme in the regulation of cholesterol biosynthesis pathway [18], but this action was not investigated in their experiment.

Results from an experimental study on casein-induced hypercholesterolemia in rabbits revealed that D-003 also increases the clearance of LDL-C from serum by increasing the number of LDL receptors in the liver, in addition to its inhibitory effect on *de novo* synthesis of cholesterol [19].

Finally, future studies are recommended to investigate the effect of D-003 on HMG-CoA synthase activity, cholesterol absorption and fecal excretion of bile acids to specify the precise actions of this compound.

3. EVIDENCE FROM ANIMAL STUDIES

In an experiment on normocholesterolemic rabbits, D-003 (5 to 200 mg/kg/day) for 30 days showed a reversible and dose-dependent decrease in circulating concentrations of TC and LDL-C [20]. Additionally, HDL-C concentrations were increased, but not in a dose-dependent manner. However, no effect on TG was observed. There was no evidence of drug-related toxicity. In 2004, Menedez *et al.* [19] investigated the effect of D-003 (5, 50 and 100 mg/kg/day) for 30 days on casein-induced hypercholesterolemia in rabbits, and they observed similar results.

A comparison was made between the lipid-lowering effects and toxicity profile of D-003 (5 mg/kg/day) and lovastatin (10 mg/kg/day) administered for 30 days in normocholesterolemic rabbits. D-003 and lovastatin showed similar reductions in LDL-C concentrations, while lovastatin was slightly superior to D-003 in lowering TC [21]. Additionally, D-003 increased HDL-C and did not affect TG, while lovastatin did not increase HDL-C but decreased TG levels. When administered in these small doses, no safety indicators were affected. On the other hand when D-003 (200 and 400 mg/kg/day) was compared against lovastatin (100 mg/kg/day) for 10 days, the two drugs showed similar reductions in LDL-C and TC levels. In addition, D-003 increased HDL-C, but lovastatin did not. Neither drug altered plasma concentrations of TG. Lovastatin (100

mg/kg) but not D-003 (200 or 400 mg/kg) impaired bodyweight gain and food consumption, increased aspartate aminotransferase (AST), alanine aminotransferase (ALT) and liver weight, and induced hepatocellular and renal tubular necrosis. These data suggest a promising safety profile of D-003.

Another study compared the cholesterol-lowering effects of D-003 (5 mg/kg/day), fluvastatin (5 mg/kg/day) and their combination in normocholesterolemic rabbits for 30 days [22]. It demonstrated that D-003 and fluvastatin alone both significantly decreased LDL-C and TC. D-003 alone, but not fluvastatin alone, increased HDL-C. Fluvastatin, but not D-003 alone, was effective in decreasing TG. The combination therapy induced better therapeutic responses in case of HDL-C and TG than monotherapy but the reverse occurred in case of LDL-C and TC. Both treatments were well tolerated.

In an experimental study, Mendoza *et al.* [23] compared the cholesterol-lowering effects of D-003 and policosanol, a mixture of higher aliphatic alcohols that also purified from sugarcane, in normocholesterolemic New Zealand rabbits. Animals were randomly allocated to three groups: (i) D-003 (5 mg/kg/day), (ii) policosanol (5 mg/kg/day) or (iii) control group, for 30 days. Both treatments significantly reduced serum TC and LDL-C, compared to baseline and control group. The reductions in TC were similar in the two treatments. However, the percentage reductions in LDL-C were significantly greater in D-003 group than in policosanol group. Additionally, both treatment significantly increased serum concentrations of HDL-C but the percentage increases were significantly greater in D-003 group. Neither of the two treatments affected TG values but both were well-tolerated.

4. EVIDENCE FROM CLINICAL STUDIES

Castano *et al.* [24,25] investigated the cholesterol-lowering effects of D-003 in healthy volunteers in two trials. The first was a single-blind, randomized, placebo-controlled, parallel trial conducted in 2002 and included 38 subjects [24]. D-003 (5, 25 and 50 mg/day) for 30 days significantly and dose-dependently reduced serum LDL-C (by 11.6 to 22.6%) and TC (by 13.3 to 17.4%). In addition, it increased HDL-C (by 14.6 to 29.7%). However, TG levels were not altered. These effects were reversed after stopping the treatment except for its effects on LDL-C and HDL-C that persisted for some time. The effect of D-003 on HDL-C was observed after 14 days of its administration, representing the first response to the treatment. D-003 was well tolerated and no drug-related adverse events were observed. Additionally, this trial confirmed the antiplatelet effects of D-003 that were investigated in other animal and clinical studies [26–31].

The second study was a double-blind, randomized, placebo-controlled trial in 46 healthy volunteers [25]. D-003 (5 and 10 mg/day) for 8 weeks led to results similar to the first trial. In addition, this trial revealed that D-003 also inhibits the susceptibility of LDL-C to lipid peroxidation, as demonstrated previously in experimental studies [32,33].

In another similar trial lasting only 30 days, D-003 (5 and 10 mg/day) similar results were seen, however in this case, D-003 (5 mg/day) failed to increase HDL-C [27]. This could be due to the short duration of treatment.

Forty one healthy volunteers were randomly allocated to either D-003 (5, 10 or 20 mg/day) or placebo for 10 days, to investigate the effects of D-003 on their lipid profile

and platelet aggregation [34]. Only D-003 (20 mg/day) could significantly lower serum LDL-C (by 13.9%, $p < 0.05$ versus placebo). D-003 (10 and 20 mg/day) significantly, not in a dose-dependent manner, increased HDL-C (by 20% and 21% respectively, $p < 0.05$ versus placebo). TC and TG concentrations were not affected, and this was expected due to the short duration of the treatment. In addition, D-003 significantly inhibited the platelet aggregation and did not affect any safety indicator.

A double-blind, randomized, placebo-controlled trial assessed the safety and efficacy of D-003 (5 and 10 mg/day) versus placebo in 51 patients aged > 60 years with TC concentrations of < 6.1 mmol/l [35]. The duration of the treatment was 8 weeks. D-003 at both doses (5 and 10 mg/day) significantly decreased serum LDL-C levels (by 15.8% and 23.8% respectively, $p < 0.001$) and also TC levels (by 13% and 16.8% respectively, $p < 0.05$) compared with placebo. HDL-C was significantly increased, compared with placebo, after treatment with each dose of D-003 (5 and 10 mg/day) by 5.7% and 18.2% respectively, $p < 0.05$ and $p < 0.001$ respectively. In subjects treated with D-003, there was a slight decrease in TG levels. However, this reduction (by 10.9%, $p < 0.05$ versus placebo) was only statistically significant with the higher dose of D-003 (10 mg/day). D-003 in both doses was well tolerated and also inhibited lipid peroxidation of LDL-C.

In a double-blind, parallel group clinical trial, 55 patients with type II hypercholesterolemia were randomly allocated to either D-003 (5, 10, 20 or 40 mg/day) or placebo for 8 weeks [36]. D-003 significantly lowered, in a dose-dependent manner, both serum LDL-C and TC (by 20.5 to 26.1% and 13 to 17.9% respectively, $p < 0.0001$ versus baseline and placebo). Additionally, it significantly increased serum HDL-C (by 11.7 to 16.7%, $p < 0.01$ versus placebo), but not in a dose-dependent manner. TG

concentrations were not altered and the drug well-tolerated. This study also showed that 68.2% of patients received D-003 achieved their LDL-C targets according to their individual global risk status.

In 2008, Arruzazabala *et al.* [37] conducted a double-blind, placebo-controlled trial in which 56 hypercholesterolemic patients were randomized to titrated doses of D-003 (5-20 mg) or placebo for 45 days. In the D-003 group, LDL-C and TC were significantly decreased (by 22% and 14.7% respectively) compared with the placebo group ($p < 0.0001$ and $p < 0.05$ respectively). In addition, D-003 significantly increased HDL-C levels (by 10.9%) compared with placebo ($p < 0.05$). However, there were no differences in post-treatment values of TG in D-003 and placebo groups. D-003 did not affect any of the safety indicators and its antiplatelet effect was also confirmed in this study.

One hundred patients with type II hypercholesterolemia were randomized, in a double-blind manner, to D-003 or policosanol [38]. Both preparations were tested at doses of 5 mg/day and 10 mg/day. The duration of the treatment was 8 weeks. In both doses, D-003 was more effective than policosanol in decreasing LDL-C and TC ($p > 0.05$), and also at increasing HDL-C. Neither of the two treatments altered TG levels but both were well tolerated. Clinical studies are summarized in **Table 1**.

5. FUTURE PERSPECTIVES AND CONCLUSIONS

D-003 is very effective agent in lowering both serum LDL-C (up to 35%) and TC (up to 21%), and increasing HDL-C (up to 30%). It does not affect TG values. However, when combined with statins, TG were significantly lowered. Additionally, it showed a

favorable safety profile and did not affect any safety indicator. From the currently available data, we could not specify the most effective dose of this agent but 5 mg/day seems to be the minimal effective dose.

Future, large-scale RCTs are recommended to: (i) specify the most effective dose of D-003, (ii) compare it with more other lipid lowering agents, (iii) investigate its effect when combined with other lipid lowering drugs, (iv) investigate its long term effect on TG due to relatively short duration of available studies, and (v) investigate its effects on other lipid parameters (e.g.: lipoprotein (a), apolipoprotein B and apolipoprotein A-1). The precise mechanism of action of D-003 has not been also completely investigated. Therefore, more experimental studies are still required to specify it. Finally, hypocholesterolemic effects of D-003 beside its possible antiplatelet, antithrombotic and antioxidant effects may have a promising potential in preventing the pathogenesis of atherosclerosis.

REFERENCES

- [1] S. Barquera, A. Pedroza-Tobías, C. Medina, L. Hernández-Barrera, K. Bibbins-Domingo, R. Lozano, A.E. Moran, Global Overview of the Epidemiology of Atherosclerotic Cardiovascular Disease., *Arch. Med. Res.* 46 (2015) 328–38. doi:10.1016/j.arcmed.2015.06.006.
- [2] Colantonio LD, Bittner V, Reynolds K, Levitan EB, Rosenson RS, Banach M, Kent ST, Derose SF, Zhou H, Safford MM, Muntner P. Association of Serum Lipids and Coronary Heart Disease in Contemporary Observational Studies. *Circulation.* 2016 Jan 19;133(3):256-64.
- [3] Banach M, Serban C, Sahebkar A, Mikhailidis DP, Ursoniu S, Ray KK, Rysz J, Toth PP, Muntner P, Mosteoru S, García-García HM, Hovingh GK, Kastelein JJ, Serruys PW; Lipid and Blood Pressure Meta-analysis Collaboration (LBPMC) Group. Impact of statin therapy on coronary plaque composition: a systematic review and meta-analysis of virtual histology intravascular ultrasound studies. *BMC Med.* 2015 Sep 18;13:229.
- [4] Hobbs FD, Banach M, Mikhailidis DP, Malhotra A, Capewell S. Is statin-modified reduction in lipids the most important preventive therapy for cardiovascular disease? A pro/con debate. *BMC Med.* 2016 Jan 14;14:4.
- [5] F.M. Sacks, M.A. Pfeffer, L.A. Moye, J.L. Rouleau, J.D. Rutherford, T.G. Cole, L. Brown, J.W. Warnica, J.M.O. Arnold, C.-C. Wun, B.R. Davis, E. Braunwald, The Effect of Pravastatin on Coronary Events after Myocardial Infarction in Patients with Average Cholesterol Levels, *N. Engl. J. Med.* 335 (1996) 1001–1009. doi:10.1056/NEJM199610033351401.
- [6] T.R. Pedersen, A.G. Olsson, O. Faergeman, J. Kjekshus, H. Wedel, K. Berg, L. Wilhelmsen, T. Haghfelt, G. Thorgeirsson, K. Pyörälä, T. Miettinen, B. Christophersen, J.A. Tobert, T.A. Musliner, T.J. Cook, Lipoprotein changes and reduction in the incidence of major coronary heart disease events in the Scandinavian Simvastatin Survival Study (4S), *Circulation.* 97 (1998) 1453–60.

- [7] Lowering Blood Cholesterol to Prevent Heart Disease, JAMA J. Am. Med. Assoc. 253 (1985) 2080. doi:10.1001/jama.1985.03350380096029.
- [8] Cholesterol Treatment Trialists' (CTT) Collaboration, C. Baigent, L. Blackwell, J. Emberson, L.E. Holland, C. Reith, N. Bhala, R. Peto, E.H. Barnes, A. Keech, J. Simes, R. Collins, Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials., Lancet (London, England). 376 (2010) 1670–81. doi:10.1016/S0140-6736(10)61350-5.
- [9] R. Gnanaraj, Applications of sugarcane wax and its products: a review, Int J Chemtech Res. (2012).
- [10] E.M. Antolín, D. Marrero Delange, V. González Canavaciolo, Y. Tejada Díaz, R. Sierra Pérez, M. Cora Medina, Validation of a gas chromatographic method for determining fatty acids that compose D003 in 10 mg film-coated tablets., Farm. (Società Chim. Ital. 1989). 59 (2004) 543–7. doi:10.1016/j.farmac.2003.11.020.
- [11] D-003., Drugs R. D. 3 (2002) 349.
- [12] [R. Menéndez, R. Más, A.M. Amor, I. Rodeiros, R.M. Gonzalez, J.L. Alfonso, Inhibition of cholesterol biosynthesis in cultured fibroblasts by D003, a mixture of very long chain saturated fatty acids., Pharmacol. Res. 44 \(2001\) 299–304. doi:10.1006/phrs.2001.0851.](#)
- [13] [H. Alexandre, B. Mathieu, C. Charpentier, Alteration in membrane fluidity and lipid composition, and modulation of H\(+\)-ATPase activity in Saccharomyces cerevisiae caused by decanoic acid., Microbiology. \(1996\) 469–75. doi:10.1099/13500872-142-3-469.](#)
- [14] [W.F. Lau, N.P. Das, In vitro modulation of rat adipocyte ghost membrane fluidity by cholesterol oxysterols., Experientia. 51 \(1995\) 731–7.](#)
- [15] [R.W. Whitcomb, W.M. Linehan, R.A. Knazek, Effects of long-chain, saturated fatty acids on membrane microviscosity and adrenocorticotropin responsiveness of human adrenocortical cells in vitro., J. Clin. Invest. 81 \(1988\) 185–8.](#)

doi:10.1172/JCI113292.

- [16] [H. Borochoy, P. Zahler, W. Wilbrandt, M. Shinitzky, The effect of phosphatidylcholine to sphingomyelin mole ratio on the dynamic properties of sheep erythrocyte membrane, *Biochim. Biophys. Acta - Biomembr.* 470 \(1977\) 382–388. doi:10.1016/0005-2736\(77\)90129-8.](#)
- [17] [P.J. Davis, M.J. Poznansky, Modulation of 3-hydroxy-3-methylglutaryl-CoA reductase by changes in microsomal cholesterol content or phospholipid composition., *Proc. Natl. Acad. Sci. U. S. A.* 84 \(1987\) 118–21.](#)
- [18] [J.L. Goldstein, M.S. Brown, Regulation of the mevalonate pathway., *Nature.* 343 \(1990\) 425–30. doi:10.1038/343425a0.](#)
- [19] [R. Menéndez, R. Más, J. Pérez, R.M. González, S. Jiménez, Oral administration of D-003, a mixture of very long chain fatty acids prevents casein-induced endogenous hypercholesterolemia in rabbits., *Can. J. Physiol. Pharmacol.* 82 \(2004\) 22–9. doi:10.1139/y03-123.](#)
- [20] [R. Gámez, S. Mendoza, R. Mas, R. Mesa, G. Castano, B. Rodriguez, D. Marrero, Dose-dependent cholesterol-lowering effects of d-003 on normocholesterolemic rabbits, *Curr. Ther. Res.* 61 \(2000\) 460–468. doi:10.1016/S0011-393X\(00\)80029-6.](#)
- [21] [R. Gámez, S. Mendoza, R. Mas, M. Noa, L. Arruzazabala, D. Carbajal, G. Castaño, E. Goicochea, M. Mesa, N. Mendoza, Comparison of the cholesterol-lowering effects and toxicity of D-003 and lovastatin in normocholesterolaemic rabbits., *Drugs R. D.* 4 \(2003\) 219–29.](#)
- [22] [S. Mendoza, R. Gamez, R. Mas, E. Goicochea, Effects of D-003, a mixture of long-chain aliphatic primary acids, fluvastatin and the combined therapy of D-003 plus fluvastatin on the lipid profile of normocholesterolemic rabbits., *Int. J. Tissue React.* 25 \(2003\) 81–9.](#)
- [23] [S. Mendoza, R. Gámez, M. Noa, R. Más, Comparison of the effects of D-003 and policosanol on lipid profile and endothelial cells in normocholesterolemic rabbits,](#)

Curr. Ther. (2001).

- [24] [G. Castaño, R. Más, L. Fernández, E. López, J.A. Gutiérrez, J. Illnait, J.C. Fernández, R. Gámez, E. Alvarez, Assessment of the effects of D-003, a new antiplatelet and lipid-lowering compound, in healthy volunteers. A phase I clinical study., *Drugs R. D.* 3 \(2002\) 337–48.](#)
- [25] [G. Castaño, R. Menéndez, R. Más, N. Ledón, Effects of D-003, a new hypocholesterolaemic and antiplatelet compound, on lipid profile and lipid peroxidation in healthy volunteers, *Clin. Drug.* \(2003\).](#)
- [26] [V. Molina, D. Carbajal, L. Arruzazabala, R. Más, Effect of D-003 on intravascular platelet aggregation induced with collagen in rats., *J. Med. Food.* 8 \(2005\) 232–6. doi:10.1089/jmf.2005.8.232.](#)
- [27] [M.L. Arruzazabala, V. Molina, D. Carbajal, L. Fernández, R. Mas, G. Castaño, J. Illnait, S. Mendoza, J. Fernández, Effects of D-003, a mixture of very long chain fatty acids purified from sugar cane wax, at 5 and 10 mg/day on platelet aggregation in healthy volunteers., *Int. J. Clin. Pharmacol. Res.* 25 \(2005\) 29–39.](#)
- [28] [M.L. Arruzazabala, R. Mas, V. Molina, D. Carbajal, L. Fernández, J. Illnait, G. Castaño, J. Fernández, S. Mendoza, Effects of d-003, a new substance purified from sugar cane wax, on platelet aggregation and plasma levels of arachidonic acid metabolites in healthy volunteers., *Int. J. Clin. Pharmacol. Res.* 24 \(2004\) 55–63.](#)
- [29] [M.L. Arruzazabala, V. Molina, D. Carbajal, R. Más, D-003 and warfarin interaction on the bleeding time and venous thrombosis experimentally induced in rats., *J. Med. Food.* 7 \(2004\) 260–3. doi:10.1089/1096620041224003.](#)
- [30] [V. Molina, M.L. Arruzazabala, D. Carbajal, R. Más, D-003, a potential antithrombotic compound isolated from sugar cane wax with effects on arachidonic acid metabolites., *Prostaglandins. Leukot. Essent. Fatty Acids.* 67 \(2002\) 19–24.](#)
- [31] [V. Molina, M.L. Arruzazabala, D. Carbajal, R. Más, S. Valdés, Antiplatelet and antithrombotic effect of D-003., *Pharmacol. Res.* 42 \(2000\) 137–43.](#)

doi:10.1006/phrs.2000.0664.

- [32] [R. Menéndez, R. Más, A.M. Amor, N. Ledón, J. Pérez, R.M. González, I. Rodeiro, M. Zayas, S. Jiménez, Inhibition of rat lipoprotein lipid peroxidation by the oral administration of D003, a mixture of very long-chain saturated fatty acids., *Can. J. Physiol. Pharmacol.* 80 \(2002\) 13–21.](#)
- [33] [Y. Pérez, R. Más, R.M. González, S. Jiménez, V. Molina, Effects of D-003, a mixture of very long chain saturated fatty acids, and policosanol on in vivo lipid peroxidation in rats., *Arzneimittelforschung.* 58 \(2008\) 126–30. doi:10.1055/s-0031-1296481.](#)
- [34] M. de L. Arruzazabala, D. Carbajal, R. Mas, Effects of D-003, a New Compound Purified from Sugarcane Wax, on Platelet Aggregation in Healthy Volunteers, *Clin. Drug.* (2003).
- [35] [Y. Pérez, R. Menéndez, J.I. Ferrer, E. Lopez, G. Castaño, J. Fernández, R.M. Ferreiro, L. Fernández, S. Mendoza, R. González, M. Mesa, Effects of D-003, a mixture of high-molecular-weight sugar cane wax acids, on lipid peroxidation markers in older individuals: A randomized, double-blind, placebo-controlled study., *Curr. Ther. Res. Clin. Exp.* 69 \(2008\) 36–48. doi:10.1016/j.curtheres.2008.01.001.](#)
- [36] G. Castaño, R. Mas, L. Fernández, J. Illnait, Effects of D-003 on the Lipid Profile of Patients with Type II Hypercholesterolaemia, *Clin. Drug.* (2003).
- [37] M. de L. Arruzazabala, V. Molina, E. López, G. Castaño, L. Fernández, D. Carbajal, R. Mas, J.I. Ferrer, S. Mendoza, Y. Ramírez, Effects of D-003, a mixture of sugarcane wax acids, on platelet aggregation in hypercholesterolemic patients. A dose-titration, randomised, placebo-controlled trial., *Arzneimittelforschung.* 58 (2008) 376–84.
- [38] G. Castaño, R. Más, L. Fernández, J. Illnait, S. Mendoza, R. Gámez, J. Fernández, M. Mesa, A comparison of the effects of D-003 and policosanol (5 and 10 mg/day) in patients with type II hypercholesterolemia: a randomized, double-blinded study.,

FIGURE LEGEND:

Figure 1. D-003 mechanism of action.

The inhibitory effect of D-003 on cholesterol biosynthesis could be explained by: (I) suppression of *de novo* synthesis of the enzyme; (II) enhancement of the enzyme degradation; (III) the effect on the physico-chemical properties of the endoplasmic reticulum; and (IV) increasing the clearance of LDL-C from serum by increasing the number of LDL receptors in the liver.