

Novel Biotechnological Products from Natural Sources: Nutri/Pharmacogenomic Component

Ramón Cacabelos*

EuroEspes Biomedical Research Center, Institute of Medical Science and Genomic Medicine, Spain

*Corresponding author: Ramón Cacabelos, EuroEspes Biomedical Research Center, Institute of Medical Science and Genomic Medicine, 15165-Corunna, Spain, Tel: 34981780505; Fax: 34981780511; E-mail: rcacabelos@euroespes.com

Received date: October 31, 2016; Accepted date: November 1, 2016; Published date: November 7, 2016

Copyright: © 2016 Ramón Cacabelos. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Editorial

A series of novel bioproducts obtained from natural sources (marine, animal, vegetal) have been discovered and characterized for the prevention and treatment of Neuro Degenerative Disorders (NDDs) and vascular pathology. Lipofuscins (LFs) are a new class of lipoproteins derived from the muscle of different fish species. Examples of LPs obtained from biomarine sources by means of non-denaturing biotechnological procedures include the following: E-JUR-94013 (DefenVid[®]), E-CAB-94011 (CabyMar[®]), E-Congerine-10423 (AntiGan[®]), E-SAR-94010 (LipoEsar[®]), and E-MHK-0103 (MineraXin[®]) [1-6]. Most effects of these novel bio products are genotype-dependent, showing specific nutrigenomic and pharmacogenomic profiles [7-10].

E-CAB-94011 is an LF obtained from the muscle of the species *Scombrus scombrus*, with anti-oxidant, anti-inflammatory, and bio-energizing properties, with potential utility in several medical conditions (anemia, debilitating disorders, alterations in growth and development, ROS generation, NDDs) [3].

E-Congerine-10423 is an LP extracted from muscular structures of the species *Conger conger*. This compound displays a powerful anti-tumoral effect in many different tumor cell-lines, with specific effects in colon cancer, ulcerative colitis, and Crohn's disease [6].

E-MHK-0103 is an atypical LP derived from the Atlantic mollusc *Mytilus galloprovincialis* cultivated on the Atlantic coast of Galicia (Spain). This bioproduct regulates hypothalamus-pituitary hormones, influences growth and development, protects against menopause-related biological decline, and modulates bone metabolism, acting as a powerful anti-osteoporotic agent [10,11].

E-SAR-94010 (Sardilipin, LipoEsar[®], LipoSea[®]) is an LP obtained from the species *Sardina pilchardus* [1]. The main chemical compounds of LipoEsar[®] are lipoproteins (60-80%) whose micelle structure probably mimics that of physiological lipoproteins involved in lipid metabolism. In preclinical studies, sardilipin has been shown to be effective in (i) reducing blood cholesterol, triglyceride, uric acid, and glucose levels, as well as liver alanine aminotransferase, and aspartate aminotransferase activity; (ii) enhancing immunological function by regulating both lymphocyte and microglia activity; (iii) inducing antioxidant effects mediated by superoxide dismutase activity; and (iv) improving cognitive function [2]. This LP shows a powerful effect in the regulation of lipid metabolism, especially by reducing total-cholesterol and LDL-cholesterol levels in cases of dyslipidemia or hypercholesterolemia, and also acting as an effective co-adjuvant of statins. E-SAR is effective in liver steatosis and in cases of primary or secondary transaminitis. It is also a strong anti-atherogenic agent, reducing the size of atheroma plaques in systemic

atherosclerosis. E-SAR has shown cognitive-enhancing properties in hypercholesterolemic patients with Alzheimer's disease. The therapeutic response of patients with dyslipidemia to sardilipin is APOE-related. The best responders are patients with the APOE-3/3>APOE-3/4>APOE-4/4 genotypes. Patients with the other APOE genotypes (2/2, 2/3, 2/4) do not show any hypolipemic response to this novel compound. In patients with dementia, the effects of sardilipin are very similar to those observed in patients with chronic dyslipidemia, suggesting that the lipid-lowering properties of sardilipin are APOE-dependent [2,7-9,12,13].

E-JUR-94013 (DefenVid[®]) is an LF derived from the fish *Trachurus trachurus*, with anti-inflammatory activity and powerful immune-enhancing properties in cases of immunodeficiency, microbial infections and/or diseases in which there is a functional compromise of the immune system [3-5]. DefenVid significantly modifies White Blood Cell (WBC) numbers in a differential fashion, decreasing neutrophils, increasing lymphocytes, monocytes, and eosinophils, and not affecting basophils. The effect of DefenVid is immunomodulatory due to the fact that in cases with high WBC numbers the general tendency is to reduce the excess of WBC, whereas in cases with low levels of WBC DefenVid tends to increase WBC, approaching normal levels. This immunomodulatory effect of DefenVid is influenced, in part, by Single-Nucleotide Polymorphism (SNP) variation associated at least with the IL1B, IL6, and TNF genes, classically involved in neuroimmune regulation and inflammatory reactions. In patients with immunodeficient phenotypes, DefenVid reduces blood cholesterol levels in over 60% of the cases, similarly to LipoEsar in dyslipidemic patients. A differential pattern of cholesterol response to DefenVid was also associated with the IL1B-T3954C, IL6-G174C, IL6R-A1510C, and TNFA-G308A variants, which are involved in inflammatory reactions associated with atherogenesis [14]. These data, together with those reported on the APOE-dependent anti-atherogenic effect of LipoEsar [9], suggest that this class of LFs might be useful to prevent arteriosclerosis and vascular risk, either peripheral or central, in the hypercholesterolemic population and in NDDs [7,8,14].

E-PodoFavalin-15999 (Atremorine[®]) is a novel biopharmaceutical compound, obtained from structural components of *Vicia faba* L. by means of non-denaturing biotechnological processes, for the prevention and treatment of Parkinson's Disease (PD) [15,16]. In vitro studies revealed that Atremorine is a powerful neuroprotectant in (i) cell cultures of human neuroblastoma SH-SY5Y cells; (ii) hippocampal slices in conditions of oxygen and glucose deprivation; and (iii) striatal slices under conditions of neurotoxicity induced by 6-OHDA. In vivo studies showed that Atremorine (i) protects against 1-Methyl-4-Phenyl-1,2,3,6-Tetrahydropyridine (MPTP)-induced dopaminergic neurodegeneration; (ii) inhibits MPTP-induced microglia activation

and neurotoxicity in substantia nigra; and (iii) improves motor function in mice with MPTP-induced neurodegeneration [16].

Clinical studies have been performed in 3 groups of patients: (i) NP: drug-free patients with PD; (ii) AP: Parkinsonian patients chronically treated with L-Dopa; and (iii) MX: a heterogeneous sample of patients with Parkinsonian disorders. One hour after a single dose (5 g) of Atremorine, plasma levels of dopamine increased from 16.71 ± 14.38 pg/mL to $2,286 \pm 4,218$ pg/mL ($p < 0.001$) in NP, from $4,149 \pm 7,062$ pg/mL to $13,539 \pm 12,408$ pg/mL ($p < 0.001$) in AP, and from $860 \pm 3,445$ pg/mL to $4,583 \pm 8,084$ pg/mL ($p < 0.001$) in MX patients, with a parallel clinical improvement lasting for 3-6 h. Atremorine administration also increased the plasma levels of noradrenaline in NP and MX. Atremorine decreased prolactin levels in NP and MX, and Growth Hormone (GH) levels in NP and MX. Pharmacogenetic studies indicate that the therapeutic response induced by Atremorine in PD is associated with the pharmacogenetic profile of each patient.

LFs and Favalins are clear examples of novel bioproducts with genotype-dependent beneficial effects in complex disorders such as cardiovascular, oncological and brain diseases.

References

1. Lombardi VRM, Cacabelos R (1999) E-SAR-94010: A marine fish extract obtained by advanced biotechnological methods. *Drugs Fut* 24: 167-176.
2. Cacabelos R, Vallejo AI, Lombardi V, Fernández-Novoa L, Pichel V (2004) E-SAR-94010 (LipoEsar®): A pleiotropic lipoprotein compound with powerful anti-atheromatous and lipid lowering effects. *CNS Drug Rev* 10: 200-201.
3. Lombardi VRM, Cagiao A, Fernández-Novoa L, Álvarez XA, Corzo MD, et al. (2001) Short term food supplementation effects of a fish derived extract on the immunological status of pregnant rats and their sucking pups. *Nutrition Res* 21: 1425-1434.
4. Lombardi VR, Fernández-Novoa L, Corzo D, Zas R, Cacabelos R (2002) Enhancement in immune function and growth using E-JUR-94013 supplementation. *Methods Find Exp Clin Pharmacol* 24: 573-578.
5. Lombardi VRM, Fernández-Novoa L, Etcheverría I, Seoane S, Cacabelos R (2005) Effects of fish-derived lipoprotein extracts on activation markers, Fas expression and apoptosis in peripheral blood lymphocytes. *Int Immunopharmacol* 5: 253-262.
6. Lombardi VRM, Pereira J, Etcheverría I, Fernández-Novoa L, Seoane S, et al. (2006) Improvement of immune function by means of Conger conger extract in an in vivo model of cold stress. *Food Agric Immunol* 17: 115-127.
7. Cacabelos R (2008) Pharmacogenomics in Alzheimer's disease. *Methods Mol Biol* 448: 213-357.
8. Cacabelos R, Cacabelos P, Torrellas C, Tellado I, Carril JC (2014) Pharmacogenomics of Alzheimer's disease: novel therapeutic strategies for drug development. *Methods Mol Biol* 1175: 323-556.
9. Cacabelos R, Takeda M (2006) Pharmacogenomics, nutrigenomics and future therapeutics in Alzheimer's disease. *Drugs Fut* 31: 5-146.
10. Corzo L, Rodríguez S, Lombardi V, Alejo R, Cacabelos R (2013) Biological properties of Mineraxin. *EuroEspes J (Gen-T)* 9: 31-40.
11. Corzo L, Rodríguez S, Alejo R, Fernández-Novoa L, Aliev G, et al. (2016) E-MHK-0103 (Mineraxin c): A Novel Nutraceutical with Biological Properties in Menopausal Conditions. *Curr Drug Metab*.
12. Cacabelos R (2007) Molecular pathology and pharmacogenomics in Alzheimer's disease: Polygenic-related effects of multifactorial treatments on cognition, anxiety, and depression. *Meth Find Exp Clin Pharmacol* 29: 1-91.
13. Cacabelos R (2012) World Guide for Drug Use and Pharmacogenomics. (1st edn). EuroEspes Publishing, Corunna.
14. Cacabelos R, Carril JC, Tejjido O (2016) Pharmacogenomics and epigenomics of age-related neurodegenerative disorders: Strategies for drug development. In: *Anti-Aging Drugs: From Basic Research to Clinical Practice*, Vaiserman A (ed). RSC Publishing, Royal Society of Chemistry, Cambridge.
15. Cacabelos R, Fernández-Novoa L, Alejo R, Corzo L, Alcaraz M, et al. (2016) E-PodoFavalin-15999 (Atremorine®)-induced dopamine response in Parkinson's Disease: Pharmacogenetics-related effects. *J Genomic Med Pharmacogenomics* 1: 1-26.
16. Carrera I, Fernández-Novoa L, Sampedro C, Aliev G, Cacabelos R (2016) Dopaminergic neuroprotection with atremorine in Parkinson's disease. *Cur Med Chem*.