

Review

Antimicrobial activity inactivation and toxic immune reactions induce Epilepsy in humans

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The calorie sensitive gene Sirtuin 1 (Sirt 1) determines nitric oxide (NO) homeostasis and immunosenescence relevant to the induction of various chronic diseases in human and other species. Appetite control is essential to Sirt 1 function for preventing adipose tissue transformation (adipocytokine release), non alcoholic fatty liver disease (NAFLD) and the development of epilepsy. Sirt 1 repression by bacterial lipopolysaccharides (LPS) leads to delayed hepatic clearance of anti-microbial drugs with relevance to mitophagy, neuron apoptosis and interference with antimicrobial/antiepileptic drug therapy. Increased absorption of LPS from food/water induces magnesium deficiency with inactivation of antimicrobial/antiepileptic drug therapy. Heat and cold stress alters Sirt 1's role in cell cholesterol dyshomeostasis associated with increased heat shock proteins (HSP) involved with inactivation of antimicrobial proteins and promotion of the cytotoxic immune response. The genetics of immunity that determines immune competence changes over a human's life span and involves the gene Sirt 1 that has antimicrobial properties by its regulation of NO metabolism connected to the immune system, mitophagy and epilepsy.

Keywords: Antimicrobial; Sirtuin 1; immunosenescence; immune; epilepsy; global; mitophagy; heat shock protein; nitric oxide; bacterial lipopolysaccharides; antiepileptic; drug; NAFLD; heat shock gene.

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Introduction

The genetics of immunity have been studied in plants and various species such as *Drosophila* and humans [1, 2]. Immune competence changes over human's life span, which is known as immunosenescence [3]. Aging and defects in the function of the immune system range from defects in the haematopoietic bone marrow to defects in peripheral lymphocyte migration, maturation and function. Human aging and adipose tissue transformation now involve the increased release of adipocytokines [4, 5] that is linked to the global non alcoholic fatty liver disease (NAFLD) epidemic [6, 7] and epilepsy [8-11]. The gene that involves immunosenescence is Sirtuin 1 (Sirt 1) and

determines adipose tissue transformation and liver inflammation [5]. Sirt 1 is a nicotinamide adenine dinucleotide (NAD⁺) dependent class III histone deacetylase (HDAC) that targets transcription factors to adapt gene expression to metabolic activity and the deacetylation of nuclear receptors indicating its critical role in insulin resistance in rodents and man [12].

Sirt 1 is a calorie sensitive gene that is important to the nuclear-mitochondria interaction with deacetylation of transcription factor p53 which is important for the adipose tissue and liver fat metabolism [5]. The p53 transcription factor is involved in immune responses and mitochondrial apoptosis [4] that is critical to the regulation of Sirt 1/p53 immunometabolism and induction of global

NAFLD [5]. Sirt 1 plays an important role in B cell antibody response and T cell tolerance with relevance to autoimmune and chronic disease [13-16]. Sirt 1 is now one of the major genes involved in immunosenescence and global chronic disease in human [17, 18] and various species [18]. Sirt 1 has antimicrobial properties by its regulation of nitric oxide (NO) metabolism [19] that is now connected to the immune regulation of the mammalian immune system [18]. The global antimicrobial and epileptic drug market is expected to cost 80 billion dollars [20, 21] by the year 2020 with the critical role of Sirt 1 in the maintenance of immunocompetence.

Sirt 1 repression with relevance to Antimicrobial Activity

Repression of Sirt 1 has become of major concern with plasma bacterial lipopolysaccharides (LPS) involved in Sirt 1 repression [22] with

interference with NO related immune regulation and global chronic disease [20, 21]. Sirt 1 is essential to antimicrobial drug metabolism [23], caffeine metabolism [24] and xenobiotic metabolism [7] with relevance to its antimicrobial activity (Figure 1). Sirt 1 repression leads to delayed clearance (pharmacokinetic/pharmacodynamics) of antimicrobial drugs with relevance to core body temperature and mitophagy [25-27]. LPS is an inhibitor of the apolipoprotein E (apo E) and its neutralization of apo E is involved in the promotion of amyloid beta aggregation [28-30]. LPS interference of apo E and amyloid beta proteins neutralize their role as antimicrobial proteins [31-34]. Elevated plasma LPS levels lead to magnesium deficiency [35, 36] that is now one of major relevance to antimicrobial/antiepileptic drug treatment [37, 38] in various global communities (Figure 1).

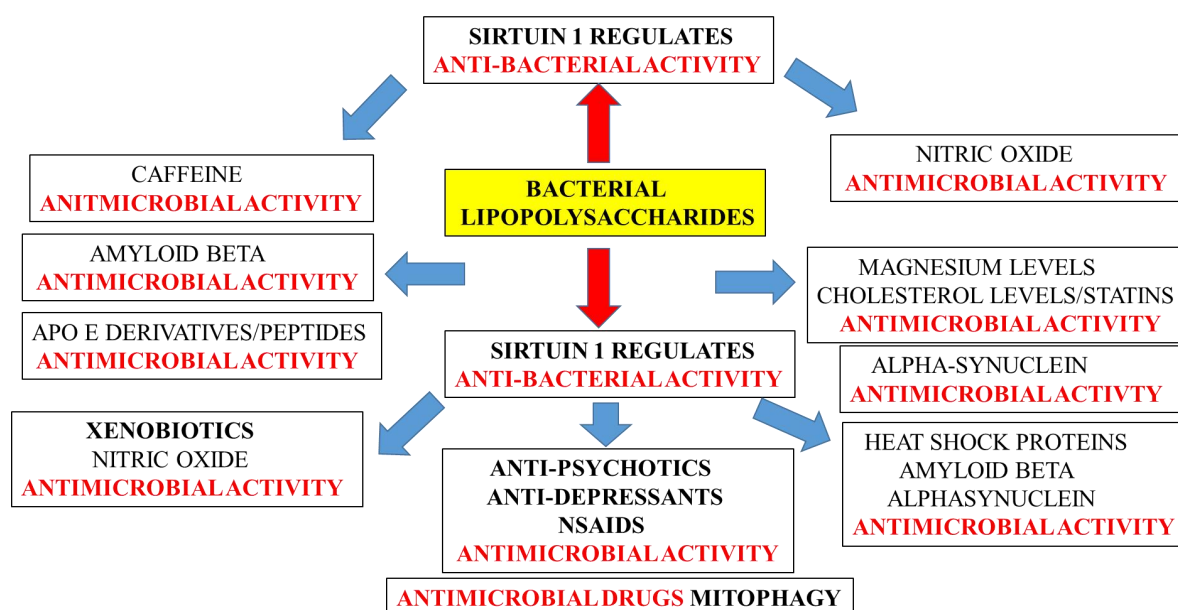


Figure 1. Sirt 1 regulates antimicrobial activity by regulation of nitric oxide homeostasis, antimicrobial proteins, heat shock proteins and hepatic caffeine/xenobiotic metabolism. LPS represses Sirt 1 (hepatic drug metabolism) and apo E/amyloid beta interactions (antimicrobial proteins) and induces magnesium deficiency with relevance to antimicrobial activity.

Heat shock proteins (HSP) induce cytotoxic immune response and override antimicrobial drug activity

Sirt 1 is essential to maintain cell cholesterol homeostasis (Figure 2), such as cholesterol efflux [39], which is important for the binding of

antidepressant drugs (antimicrobial activity) [40], antipsychotic drugs (antimicrobial activity) [41], NSAIDs and LPS (sphingomyelin/cholesterol domain) to mammalian cell membranes (Figure 2). Sirt 1 is involved in the metabolism of antimicrobial proteins such as amyloid beta and

alpha synuclein with relevance to cell cholesterol homeostasis [42]. Sirt 1 is now referred to as a heat shock gene and its deacetylation of heat shock factor 1 (Figure 2) is involved with regulation of heat shock protein (HSP) metabolism [43, 44]. HSPs role in alpha synuclein and amyloid beta aggregation is important to antimicrobial activity and mammalian cell immune regulation [45-48]. Elevated HSP levels have been reported in natural killer cell activation with uncontrolled toxic

immune reactions [4, 49] and stress responses in epilepsy [50]. Sirt 1 is now connected to epilepsy in man with the Sirt 1 activator resveratrol essential to stabilize epilepticus and epilepsy [51, 52]. Cholesterol lowering agents such as statins have antimicrobial properties with Sirt 1 repression associated with increased cell cholesterol (Figure 2) that may interfere with statins' antimicrobial properties [53].

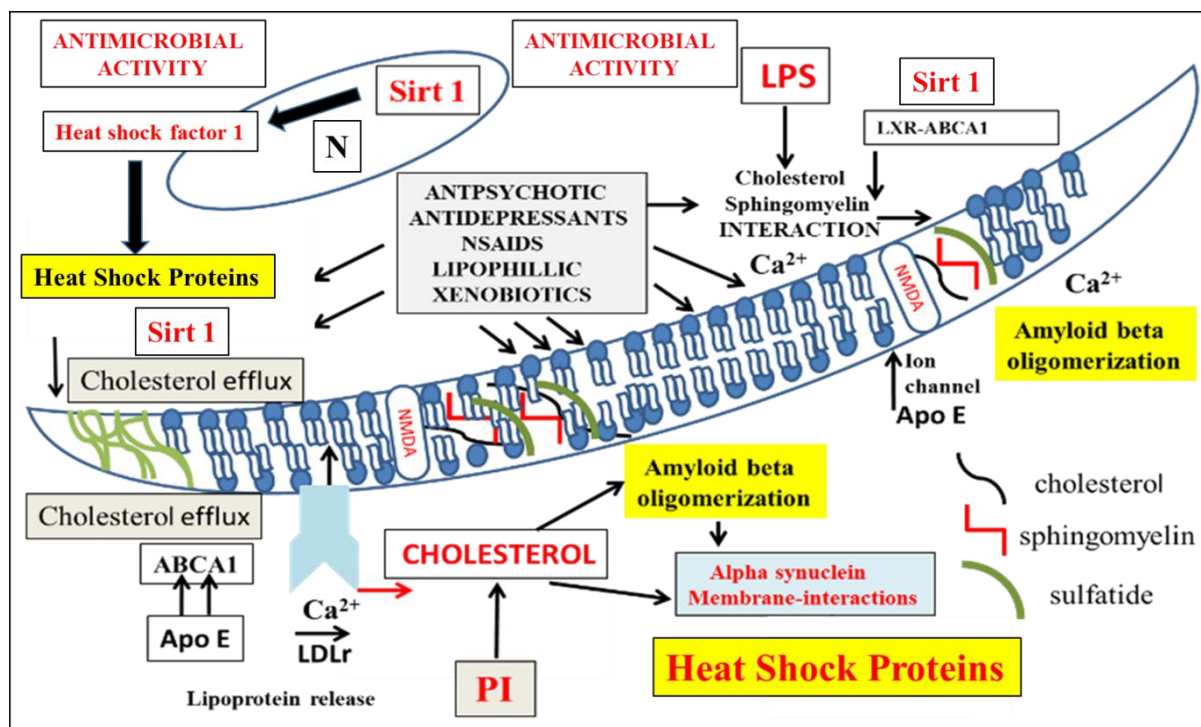


Figure 2. Antimicrobial drugs, antimicrobial proteins (amyloid beta, apo E, alpha synuclein) and heat shock proteins are connected to cell cholesterol levels. Sirt 1 is critical to cell cholesterol efflux with its repression controlled by LPS that is involved in binding to cholesterol:sphingomyelin domains relevant to amyloid beta and alpha synuclein oligomerization. Sirt 1 is important to deacetylation of heat shock factor 1 with relevance to heat shock protein metabolism and antimicrobial activity in neurons and hepatocytes.

Nutrition determines mitochondrial disease, drug therapy and induction of Epilepsy

Appetite control is essential to maintain Sirt 1 regulation of the suprachiasmatic nucleus (SCN) and the circadian rhythm that is defective in NAFLD, obesity and diabetes [54, 55]. Sirt 1 is critical to maintain mitochondrial survival with food restriction essential to maintain mitochondrial biogenesis and reverse NAFLD and diabetes. Appetite regulation and its relevance to various chronic disease is now critical to Sirt 1' role in antimicrobial activity and immune regulation in

mammalian cells. Overnutrition overrides appetite control with antimicrobial activity dysregulation now connected to insulin resistance and neurodegenerative diseases in global populations [56].

Food restriction reduces the absorption of LPS that may enter after ingestion of contaminated food and water with relevance to diabetes and neurodegenerative diseases [56-58]. Nutritional diets that contain Sirt 1 activators [24] may reverse NAFLD and epilepsy with relevance cholesterol and HSP metabolism. Consumption of Sirt 1

inhibitors [24] should be avoided that induce NAFLD and inactivate consumption of essential nutrients with relevance to the prevention of NAFLD and epilepsy. Contaminants such as xenobiotics, mycotoxins (patulin) and caffeine may induce mitophagy and impair various therapeutic drugs [25-27] that are essential for treatment of epilepsy.

Epilepsy is a group of neurological disorders with episodes of epileptic seizures (provoked/unprovoked) that involve undetectable periods to long periods of vigorous shaking. Provoked epilepsy with CNS infections [59] involve mitochondrial disease that lead to

mitochondrial epilepsy [60] that may be irreversible and connected to the global stroke epidemic [61, 62]. Appetite dysregulation [19] and Sirt 1 dysregulation indicate NO defects and the induction of provoked epilepsy and seizures [63, 64] now relevant to millions of patients in the world (Figure 3) with billion dollar costs to the global community [20, 21]. Sirt 1 repression and its connections to NAFLD and diabetes [5, 7, 12, 24, 35, 36, 39, 44, 58] now implicate between 20-40% of individuals with provoked epilepsy with Sirt 1 inactivation influenced by Western diets and sedentary lifestyles.

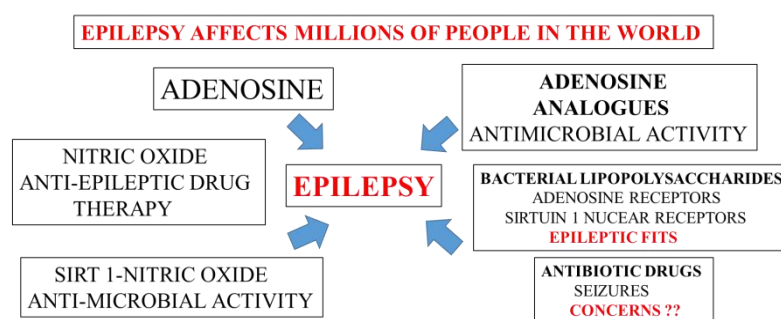


Figure 3. Nutrition is essential to prevent epilepsy that effects millions of individuals in the world. The calorie sensitive gene Sirt 1 regulates NO metabolism with relevance to adenosine treatment and anti-epileptic drug therapy. Overnutrition with Sirt 1 repression (NAFLD) delays hepatic antibiotic drug metabolism such as adenosine analogues, unsubstituted penicillins, fourth-generation cephalosporins, imipenem, and ciprofloxacin with the induction of seizures.

Sirt 1 is now critical to anti-epileptic drug therapy/anticonvulsive actions (Figure 3) and regulation of NO homeostasis [19] control mitochondrial function [54], neuromodulation and neurotransmitter release [65, 66]. Sirt 1 is essential for the prevention of mitochondrial apoptosis and epileptic fits but with increased plasma LPS levels (Sirt 1 repression) in the developing world concerns for decreased antibiotic metabolism may associated with epileptic fits and seizures [67-71]. Adenosine has been used to maintain NO levels and mitochondrial function with relevance to neuromodulation and NO homeostasis (Figure 3) in epileptic conditions [67]. Adenosine analogues [72] have now been shown to have antibacterial activity but increased LPS levels that enter the CSF/ brain [59] may interfere with antibiotic adenosine analogue therapy. LPS binding agents [39] may assist with neutralization of LPS with the

prevention of increased transport to the brain and the induction of epilepsy.

Conclusion

Evaluating antimicrobial activity has become important to prevent immune reactions that lead to uncontrolled seizures with emergency and acute stroke. Nutritional regulation of Sirt 1 with relevance to antimicrobial activity in humans has become important to the clinical treatment of epilepsy. Sirt 1 activators need to be consumed to prevent LPS competitive inhibitor effects on Sirt 1 with relevance to the induction of provoked epilepsy. Drug doses of suramin and sirtinol (Sirt 1 inhibitors) should be reduced to stabilize drug treatment of epilepsy. Diets that contain increased palmitic acid and fructose (Sirt 1 inhibitors) induce NAFLD and these nutrients need to be carefully

regulated to maintain antimicrobial activity in man and prevent toxic immune reactions involved in diabetes and provoked epilepsy.

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Conflict of Interest

None

References

1. Lazzaro BP, Schneider DS. The Genetics of Immunity. *Genetics*. 2014; 197: 467–470.
2. www. sciencedaily. com/releases/2017/01/170105082755. htm King's College London. "Genetics play a significant role in immunity." ScienceDaily. ScienceDaily, 5 January 2017.
3. Gruver AL, Hudson LL, Sempowski GD. Immunosenescence of ageing. *J Pathol*. 2007 211:144–156.
4. Martins IJ. Defective Interplay between Adipose Tissue and Immune System Induces Non Alcoholic Fatty Liver Disease. *Updates Nutr Disorders Ther*. 2017; 1: 1-5.
5. Martins IJ. Unhealthy Nutrigenomic Diets Accelerate NAFLD and Adiposity in Global communities. *J Mol Genet Med*. 2015; 9:1-11.
6. Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes. *Hepatology*. 2016;64:73-84.
7. Martins IJ. Single Gene Inactivation with Implications to Diabetes and Multiple Organ Dysfunction Syndrome. *J Clin Epigenet*. 2017;3:1-8.
8. Aksoy D, Solmaz V, Taşkıran D, Erbaş O. The association between seizure predisposition and inflammation in a rat model of fatty liver disease. *Neurol Sci*. 2014 ;35:1441-6.
9. Saleh DA, Ismail MA, Ibrahim AM. Non alcoholic fatty liver disease, insulin resistance, dyslipidemia and atherogenic ratios in epileptic children and adolescents on long term antiepileptic drug therapy. *Pak J Biol Sci*. 2012;15:68-77.
10. Farinelli E, Giampaoli D, Cenciarini A, Cercado E, Verrotti A. Valproic acid and nonalcoholic fatty liver disease: A possible association? *World J Hepatol*. 2015;7: 1251–1257.
11. Luef G, Rauchenzauner M, Waldmann M, Sturm W, Sandhofer A,

Nutritional therapy maintains antimicrobial activity to prevent provoked epilepsy and stroke

- Seppi K, Trinkla E, et al. Non-alcoholic fatty liver disease (NAFLD), insulin resistance and lipid profile in antiepileptic drug treatment. *Epilepsy Res*. 2009;86:42-7.
12. Martins IJ. Diet and Nutrition reverse Type 3 Diabetes and Accelerated Aging linked to Global chronic diseases. *J Diab Res Ther*. 2016;2:1-6.
13. Gan H, Shen T, Sanchez HN, Vasudev A, Taylor JR, Zan H, et al. Sirt1 modulates immunoglobulin class switch DNA recombination and somatic hypermutation by regulating B lymphocyte Aicda expression through NF-kB deacetylation. *J Immunol*. 2017;98:152. 21.
14. Gao B, Kong Q, Kemp K, Zhao YS, Fang D. Analysis of sirtuin 1 expression reveals a molecular explanation of IL-2-mediated reversal of T-cell tolerance. *Proc Natl Acad Sci U S A*. 2012;109:899-904.
15. Martins IJ. Autoimmune disease and mitochondrial dysfunction in chronic diseases. *Res Chron Dis*. 2017;1:10-12.
16. Kong S, McBurney MW, Fang D. Sirtuin 1 in immune regulation and autoimmunity. *Immunol Cell Biol*. 2012;90:6-13.
17. Chen X, Lu Y, Zhang Z, Wang J, Yang H, Liu G. Intercellular interplay between Sirt1 signalling and cell metabolism in immune cell biology. *Immunology*. 2015;145:455-67.
18. Martins IJ. Regulation of Core Body Temperature and the Immune System Determines Species Longevity. *Curr Updates Gerontol*. 2017;1: 2-6.
19. Martins IJ. Nutritional diets accelerate amyloid beta metabolism and prevent the induction of chronic diseases and Alzheimer's disease. Photon ebooks. The Journal for Endocrinology and Metabolism, Imprint: Photon: Peer Reviewed Indexed International Journal.
20. <http://gbiresearch.com/media-center/press-releases/global-epilepsy-market-value-to-reach-45-billion-by-2019-thanks-to-recent-drug-approvals>.
21. www.prnewswire.com/.../global-antibacterial-drugs-market-to-2022-antibacterial-dru... Global Antibacterial Drugs Market to 2022 - PR Newswire
22. Martins IJ. The Future of Genomic Medicine Involves the Maintenance of Sirtuin 1 in Global Populations. *Int J Mol Biol*. 2017;2:1-4.
23. Schairer DO, Chouake JS, Nosanchuk JD, Friedman AJ. The potential of nitric oxide releasing therapies as antimicrobial agents. *Virulence*. 2012;3:271–279.
24. Martins IJ. Nutrition Therapy Regulates Caffeine Metabolism with Relevance to NAFLD and Induction of Type 3 Diabetes. *J Diabetes Metab Disord*. 2017; 4:1-9.
25. Martins IJ. Heat Shock Gene Dysregulation and Inactivation of Drug Therapy. *EC Pharmacology and Toxicology*. 2017; ECO.

01:13-15.

26. Kalghatgi S, Spina CS, Costello JC, et al. Bactericidal Antibiotics Induce Mitochondrial Dysfunction and Oxidative Damage in Mammalian Cells. *Sci Transl Med*. 2013 ;5:192ra85.
27. Barnhill AE, Brewer MT, Carlson SA. Adverse effects of antimicrobials via predictable or idiosyncratic inhibition of host mitochondrial components. *Antimicrob Agents Chemother*. 2012;56:4046-51.
28. Martins IJ. LPS Regulates Apolipoprotein E and A β Interactions with Effects on Acute Phase Proteins and Amyloidosis. *AAR*. 2015; 4:69-77.
29. Martins IJ, Gupta V, Wilson AC, Fuller SJ, Martins RN. Interactions Between Apo E and Amyloid Beta and their Relationship to Nutriproteomics and Neurodegeneration. *Current Proteomics*. 2014;11:173-183.
30. Martins IJ. Unhealthy Diets Determine Benign or Toxic Amyloid Beta States and Promote Brain Amyloid Beta Aggregation. *Austin J Clin Neurol*. 2015;2:1060-66.
31. Pane K, Sgambati V, Zanfardino A, et al. A new cryptic cationic antimicrobial peptide from human apolipoprotein E with antibacterial activity and immunomodulatory effects on human cells. *FEBS J*. 2016;283:2115-31.
32. Azuma M, Kojimab T, Yokoyama I, et al. A synthetic peptide of human apoprotein E with antibacterial activity. *Peptides*. 2000;21:327-30.
33. Forbes S, McBain AJ, Felton-Smith S, Jowitt TA, Birchenough HL, Dobson CB. Comparative surface antimicrobial properties of synthetic biocides and novel human apolipoprotein E derived antimicrobial peptides. *Biomaterials*. 2013;34:5453-64.
34. Kagan BL, Jang H, Capone R, et al. Antimicrobial properties of amyloid peptides. *Mol Pharm*. 2012;9:708-17.
35. Martins IJ. Magnesium deficiency and induction of NAFLD and Type 3 diabetes in Australasia. *AMJ*. 2017;10:235-237.
36. Martins IJ. Magnesium Therapy Prevents Senescence with the Reversal of Diabetes and Alzheimer's Disease. *Health*. 2016; 8:694-710.
37. Yuen AW, Sander JW. Can magnesium supplementation reduce seizures in people with epilepsy? A hypothesis. *Epilepsy Res*. 2012;100:152-6.
38. Nuytten D, Van Hees J, Meulemans A, Carton H. Magnesium deficiency as a cause of acute intractable seizures. *J Neurol*. 1991;238:262-4.
39. Martins IJ. Nutrition increases Survival and Reverses NAFLD and Alzheimer's disease Ian J Martins. First Edition edited by Alina Berdos, 01/2015; LAP LAMBERT.
40. Rani Basu L, Mazumdar K, Dutta NK, Karak P, Dastidar SG.

Nutritional therapy maintains antimicrobial activity to prevent provoked epilepsy and stroke

Antibacterial property of the antipsychotic agent prochlorperazine, and its synergism with methdilazine. *Microbiol Res*. 2005;160:95-100.

41. Macedo D, Filho AJMC, Soares de Sousa CN, et al. Antidepressants, antimicrobials or both? Gut microbiota dysbiosis in depression and possible implications of the antimicrobial effects of antidepressant drugs for antidepressant effectiveness. *J Affect Disord*. 2017;208:22-32.
42. Martins IJ. Diabetes and Cholesterol Dyshomeostasis Involve Abnormal α -Synuclein and Amyloid Beta Transport in Neurodegenerative Diseases. *Austin Alzheimers J Parkinsons Dis*. 2015;2:1020-28.
43. Martins IJ. Heat shock gene Sirtuin 1 regulates post-prandial lipid metabolism with relevance to nutrition and appetite regulation in diabetes. *Int J Diab Clin Diagn*. 2016, 3:20.
44. Martins IJ. Type 3 diabetes with links to NAFLD and Other Chronic Diseases in the Western World. *International Journal of Diabetes*. 2016; 1:1-5.
45. Park SC, Moon JC, Shin SY, et al. Functional characterization of alpha-synuclein protein with antimicrobial activity. *Biochem Biophys Res Commun*. 2016;478:924-8.
46. Jones DR, Moussaud S, McLean P. Targeting heat shock proteins to modulate α -synuclein toxicity. *Ther Adv Neurol Disord*. 2014;7:33–51.
47. Cox D, Selig E, Griffin MD, Carver JA, Ecroyd H. Small Heat-shock Proteins Prevent α -Synuclein Aggregation via Transient Interactions and Their Efficacy Is Affected by the Rate of Aggregation. *J Biol Chem*. 2016;291:22618-22629.
48. Martins IJ. Calorie Sensitive Anti-Aging Gene Regulates Hepatic Amyloid Beta Clearance in Diabetes and Neurodegenerative Diseases. *EC Nutrition*. 2017; ECO. 01:30-32.
49. Multhoff G. Activation of natural killer cells by heat shock protein 70. *Int J Hyperthermia*. 2002;18:576-85.
50. <https://www.ncbi.nlm.nih.gov/books/NBK6614/>Yenari MA. Heat Shock Proteins and Neuroprotection. In: *Madame Curie Bioscience Database [Internet]*. Austin (TX): Landes Bioscience; 2000-2013.
51. Hall AM, Brennan GP, Nguyen TM, Singh-Taylor A, Mun H-Y, Sargious MJ, Baram TZ. The Role of Sirt1 in Epileptogenesis. *eNeuro*. 2017; 4: ENEURO. 0301-16.
52. Shetty AK. Promise of resveratrol for easing status epilepticus and epilepsy. *Pharmacol Ther*. 2011;131:269-86
53. Haeri MZ, White K, Qharebeglou M, Ansar MM. Cholesterol suppresses antimicrobial effect of statins. *Iran J Basic Med Sci*. 2015;18:1253–1256.
54. Martins IJ. Appetite Control with Relevance to Mitochondrial

Biogenesis and Activation of Post- Prandial Lipid Metabolism in Obesity Linked Diabetes. *Ann Obes Disord*. 2016; 1:1012.

55. Martins IJ. Appetite dysregulation and obesity in Western Countries Ian J Martins · First edited by Emma Jones, ; LAP LAMBERT Academic Publishing.

56. Martins, IJ. Overnutrition Determines LPS Regulation of Mycotoxin Induced Neurotoxicity in Neurodegenerative Diseases. *Int J Mol Sci*. 2015; 16: 29554–29573.

57. Martins IJ. Dietary Interventions Reverse Insulin and Synaptic Plasticity Defects Linking to Diabetes and Neurodegenerative Diseases. *SL Nutrition and Metabolism*. 2017;1:1-5.

58. Martins IJ. Diabetes and Organ Dysfunction in the Developing and Developed. *World: GJMR F Diseases*. 2015;15:14-21.

59. Singh G, Prabhakar S. The effects of antimicrobial and antiepileptic treatment on the outcome of epilepsy associated with central nervous system (CNS) infections. *Epilepsia*. 2008;49 Suppl 6:42-6.

60. Rahman S. Mitochondrial disease and epilepsy. *Dev Med Child Neurol*. 2012;54(5):397-406.

61. Myint PK, Staufenberg EFA, Sabanathan K. Post-stroke seizure and post-stroke epilepsy. *Postgrad Med J*. 2006; 82(971): 568–572.

62. Martins IJ. The Global Obesity Epidemic is Related to Stroke, Dementia and Alzheimer's disease. *JSM Alzheimer's Dis Related Dementia*. 2014; 1: 1-9.

63. Arhan E, Serdaroglu A, Ozturk B, et al. Effects of epilepsy and antiepileptic drugs on nitric oxide, lipid peroxidation and xanthine oxidase system in children with idiopathic epilepsy. *Seizure*. 2011;20:138-42.

64. Banach M, Piskorska B, Czuczwar SJ, Borowicz KK. Nitric oxide, epileptic seizures, and action of antiepileptic drugs. *CNS*

Neurol Disord Drug Targets. 2011;10:808-19.

65. Zsurka G, Kunz WS. Mitochondrial dysfunction and seizures: the neuronal energy crisis. *Lancet Neurol*. 2015;14:956-66.

66. Folbergrová J, Kunz WS. Mitochondrial dysfunction in epilepsy. *Mitochondrion*. 2012;12:35-40.

67. Martins IJ. Bacterial LPS Overrides Adenosine Treatment of Epileptic Seizures. *EC Microbiology*. 2017;7. 3: 83-86.

68. Irimia A, Van Horn JD. Epileptogenic focus localization in treatment-resistant post-traumatic epilepsy. *J Clin Neurosci*. 2015; 22: 627–631.

69. Grøndahl TO, Langmoen IA. *J Neurosurg*. Epileptogenic effect of antibiotic drugs. 1993;78:938-43.

70. Sutter R, Rüegg S, Tschudin-Sutter S. Seizures as adverse events of antibiotic drugs: A systematic review. *Neurology*. 2015;85:1332-41.

71. Yu N, Liu H, Di Q. Modulation of Immunity and the Inflammatory Response: A New Target for Treating Drug-resistant Epilepsy. *Curr Neuropharmacol*. 2013;11:114–127

72. Vitali LA, Petrelli D, Lambertucci C, Prenna M, Volpini R, Cristalli G. In vitro antibacterial activity of different adenosine analogues. *J Med Microbiol*. 2012;61(Pt 4):525-8.



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