# Inactivation of Drug Metabolism and Therapy with connections to Mitochondrial Toxicity in Global Chronic Diseases

Euro Neuropharmacology 2018

Ian James Martins

Centre of Excellence for Alzheimer's Disease Research and Care, Edith Cowan University, PERTH, Sarich Neuroscience Research Institute, Edith Cowan University, Verdun Street, Nedlands, 6009, Australia

## INTRODUCTION

Various factors such as diet, environment, stress and lifestyle as important factors that regulate drug safety and therapy to stabilize insulin resistance are now relevant to various chronic diseases. The need to optimize drug therapy and improve therapeutic outcomes has become of major concern with relevance to alarming reports of drug-drug interactions or drug-protein interactions. Anti-aging genes such as Sirtuin 1 (Sirt 1) are important to hepatic drug metabolism with its pregnane X receptor inactivation (**REF 1, REF 2**) associated with the defective hepatic clearance of drugs with inactivation of drug therapy. Pharmacological management that includes the use of antimicrobial drugs (**REF 3**) statin and anti-epileptic drug use can be inactivated with Sirt 1 repression associated with drug induced mitochondrial apoptosis. Defective heat shock response regulation (**REF 4**) can induce protein aggregation and inactivate drug metabolism with relevance to neuronal mitophagy and epilepsy induced stroke. In global chronic diseases the disturbed xenobiotic metabolism (**REF1**) will inactivate drug therapy with relevance to the induction of insulin resistance and neurodegenerative diseases.

## METHODS AND RESULTS

Research trends now indicate that the anti-microbial drug market will cost the global population approx. 36 billion dollars by the year 2022. The understanding of nutritional therapy to activate the antimicrobial drug therapy has become important to antimicrobial resistance and mitophagy (**REF5**) (**Figure 1**). In recent studies protein biomarker investigation is now critical to activation of drug metabolism. Gene expression and plasma heat shock protein analysis identify Sirt 1 linked to be defective in Type 3 diabetes and chronic disease. In vivo and in vitro studies have indicated that immunogenic proteins such as heat shock proteins and amyloid beta oligomers are important to drug metabolism (**REF2,REF4**) Unhealthy diets can repress Sirtuin 1 and promote immunogenic protein formation with the induction of mitophagy and programmed cell death.

**REF1:** Martins IJ. Chapter 01. Increased Risk for Obesity and Diabetes with Neurodegeneration in Developing Countries. Top 10 Contribution on Genetics. Book Chapter. 2018. www.avid.science.com

**REF 2**: Martins IJ. Sirtuin 1, a Diagnostic Protein Marker and its Relevance to Chronic Disease and Therapeutic Drug Interventions. EC Pharmacology and Toxicology 6.4 (2018): 209-215. **REF 3:** Martins IJ. Food Quality and Advances in Pharmacological Management Prevent Mitochondrial Apoptosis and Epilepsy Induced Stroke. Research and Reveiws: Neuroscience. 2018;2:7-9. **REF 4**: Martins IJ. Heat Shock Gene Inactivation and Protein Aggregation with Links to Chronic Diseases. Diseases. 2018, 6;39:1-5. **REF 5**: Martins IJ. Antibiotic Resistance Involves Antimicrobial Inactivation in Global Communities. SAJ Pharma Pharmacol 2017;2: 102.

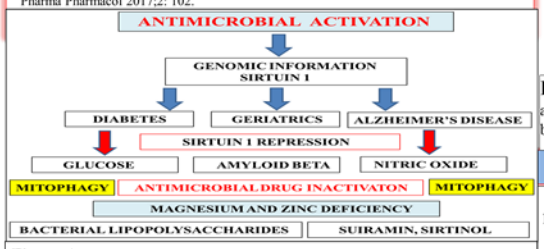


**Figure 1.** Nutritional therapy is essential for maintenance of Sirtuin 1 (Sirt 1) with Sirt 1 inactivation associated with mitophagy and inactivation of hepatic antimicrobial drug metabolism connected to Sirt 1 inhibitors and magnesium deficiency. (**REF 5**)

## METHODS AND RESULTS

Editorials published in various journals have indicated the need to optimize drug therapy and improve therapeutic outcomes with relevance to alarming reports of drug-drug interactions (**REF6**). Individuals with NAFLD, diabetes and neurodegenerative diseases that consume caffeine [**REF7**] or Indian spices [**REF8,9**] need to be carefully evaluated with relevance to interference with drug therapy (**Figure 2**). In the developing world plasma bacterial lipopolysaccharides (LPS) levels need to be carefully assessed to prevent Sirt 1 repression and antimicrobial drug use monitored with relevance to the release from gram negative bacteria of bacterial amyloid peptide and induction of toxic amyloid beta oligomers (**REF10**). Heat shock gene inactivation may lead to complete heat shock factor 1 inactivation (**Figure 3**) associated with protein aggregation and inactivation of drug metabolism (**REF11**).

**REF6:**Drug-Drug Interactions with Relevance to Drug Induced Mitochondrial Toxicity and Accelerated Global Chronic Diseases. EC Pharmacology and Toxicology 3.1 (2017):18-22. **REF7**: Caffeine with Links to NAFLD and Accelerated Brain Aging. Chapter: Non-Alcoholic Fatty Liver Disease - Molecular Bases, Prevention and Treatment. InTech - Open Science Open Minds | InTechOpen. 2017. **REF8:** Indian Spices and Unhealthy Diets interfere with Drug Therapy in Diabetes and Neurodegenerative Diseases. NAPDD. 2018. **REF9**: Indian Spices and Biotherapeutics in Health and Chronic Disease. Health, 2018.**REF10**: Antimicrobial Drugs and Bacterial Amyloid Peptide Induce Toxic Manifestations in Chronic Diseases. EC Pharmacology and Toxicology 6.1 (2018): 01-04. **REF11**: Heat Shock Gene Dysregulation and Inactivation of Drug Therapy. EC Pharmacology and Toxicology. ECO.01 (2017): 13-15.

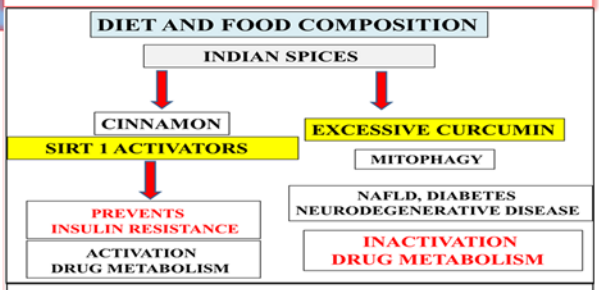


**Figure 2.** Excessive Indian spice intake such as curcumin may induce mitophagy with relevance to NAFLD, chronic disease with inactivation of hepatic drug metabolism.

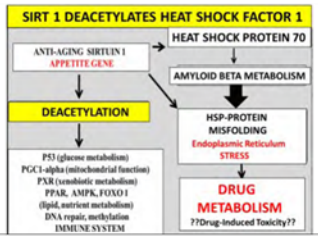


**Figure 3.** Overnutrition inactivates Sirt 1-HSF-1 interactions with interference of brain and liver drug pharmacokinetics. Sirt 1 repression is involved with primary HSP-amyloid beta misfolding and intersects with defective drug metabolism and drug toxicity.

## CONCLUSIONS

**1. Analysis of plasma Sirtuin 1 is essential to determine defective Sirt 1 expression with relevance to antimicrobial activation and hepatic drug metabolism.**

**2. Food quality and healthy diets are essential to maintain hepatic drug metabolism with relevance to mitophagy in NAFLD, diabetes and neurodegenerative diseases.**