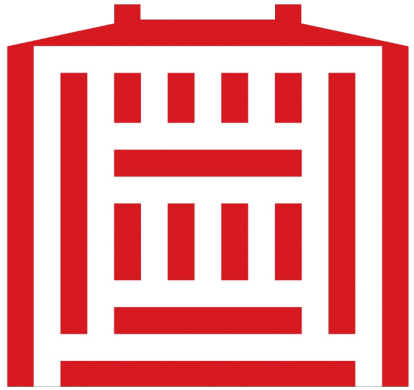

MAAA
MACEDONIAN AMERICAN ALUMNI ASSOCIATION

„Alumni encouraging community services and extracurricular activities“

ФАКУЛТЕТСКО СТУДЕНТСКО СОБРАНИЕ
ФАКУЛТЕТ ЗА МЕДИЦИНСКИ НАУКИ
УНИВЕРЗИТЕТ „ГОЦЕ ДЕЛЧЕВ“ - ШТИП
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СЕМИНАР

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Молекуларни аспекти на исхраната

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- Полот како фактор за интер-индивидуални разлики во однос на исхраната
  - Ангела Кочоска, Ванеса Крстева и Ирена Жежова
- Исхрана и хипертензија
  - Анастасија Атанасоска, Љубенка Ордева, Ирина Селвиевска, Сашка Јованчевска и Мартина Јовевска
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  - Сара Николова и Филип Постолов
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  - Ивона Џамбазова и Методи Речаноски

Молекуларни аспекти на исхраната – научни достигнувања и перспективи

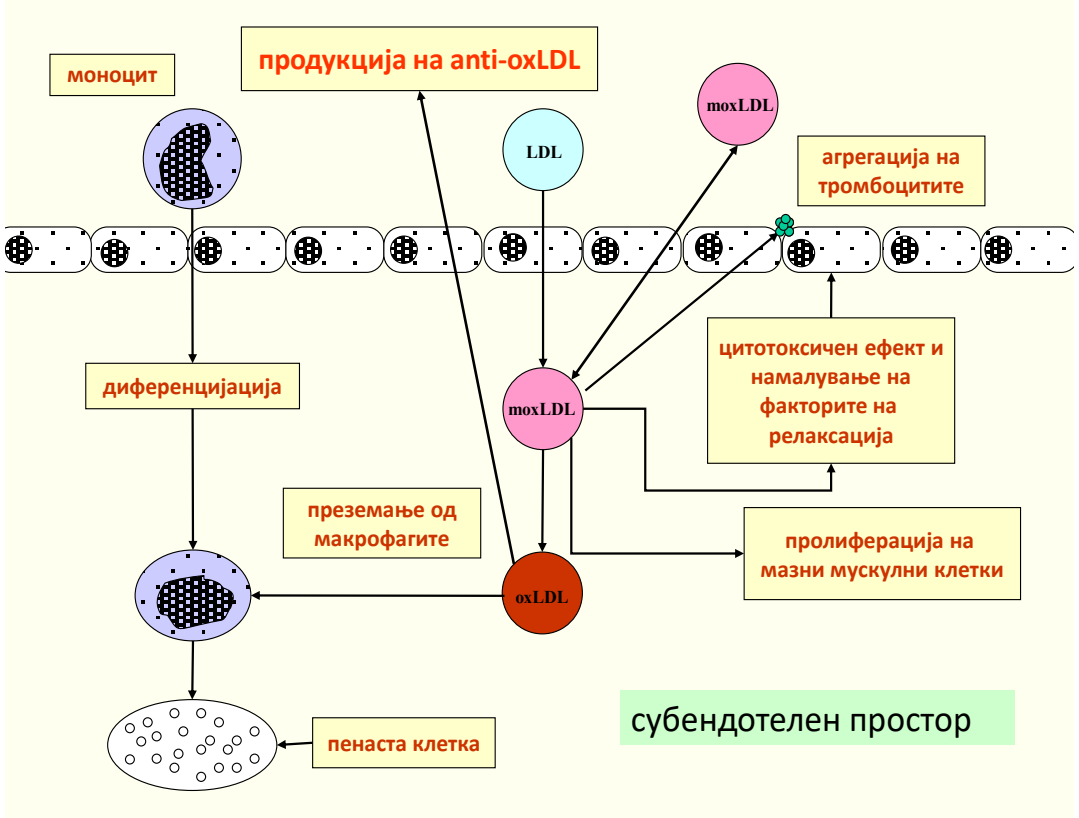
Проф. д-р Татјана Рушковска

Од каде интересот?

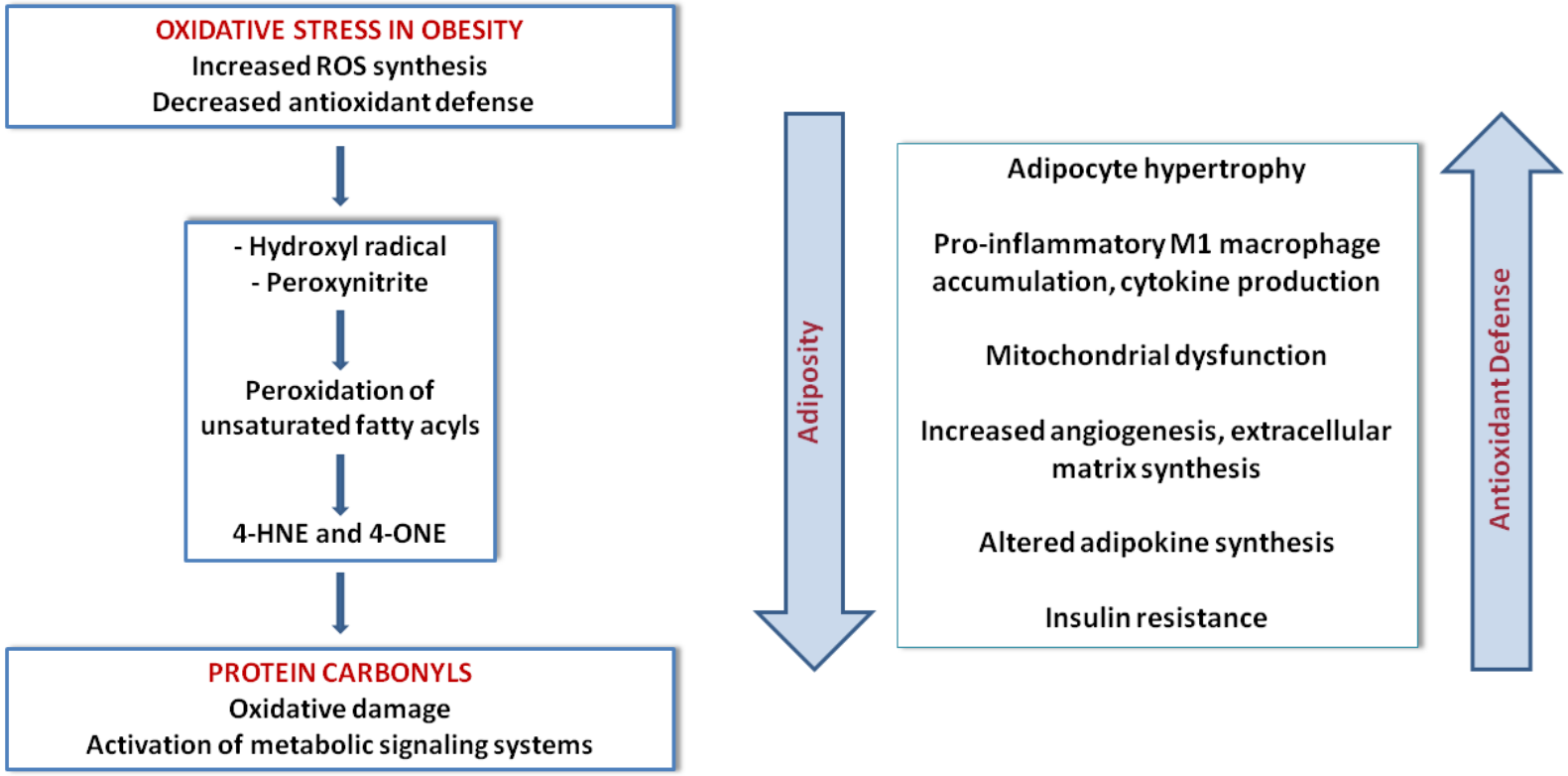
- Ruskovska, Tatjana (2002)

Influence of lovastatin on the oxidative stress and on the IgG autoantibodies against MDA-modified LDL particles in patients with dyslipidemia.

PhD thesis, Ss. Cyril and Methodius University.



Фулбрајт стипендија



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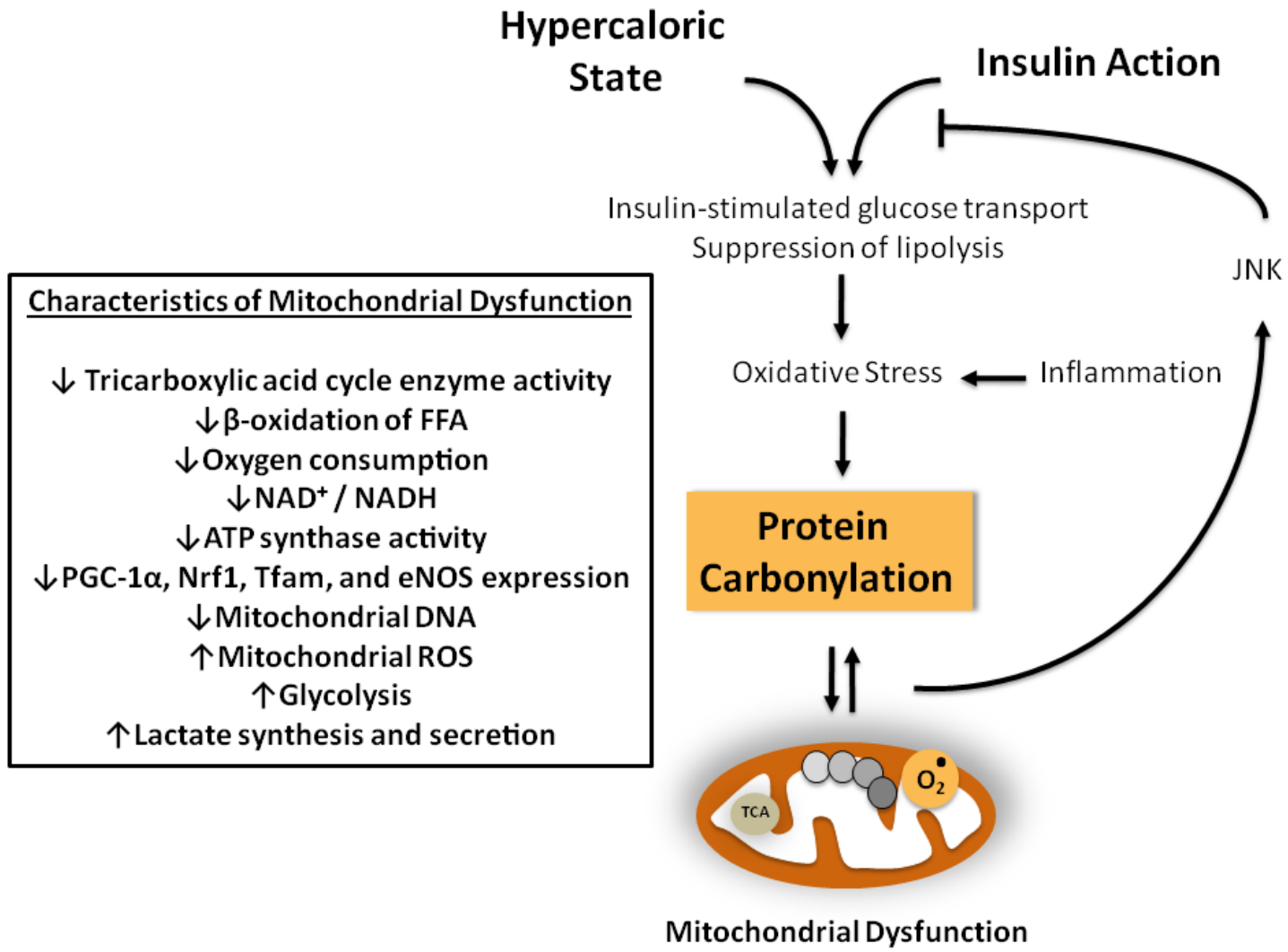
FULBRIGHT

Фулбрајт стипендија



Characteristics of Mitochondrial Dysfunction

↓ Tricarboxylic acid cycle enzyme activity
↓β-oxidation of FFA
↓Oxygen consumption
↓NAD^+ / NADH
↓ATP synthase activity
↓PGC-1α, Nrf1, Tfam, and eNOS expression
↓Mitochondrial DNA
↑Mitochondrial ROS
↑Glycolysis
↑Lactate synthesis and secretion

ORIGINAL ARTICLE

Flavonoid Apigenin Is an Inhibitor of the NAD$^+$ase CD38

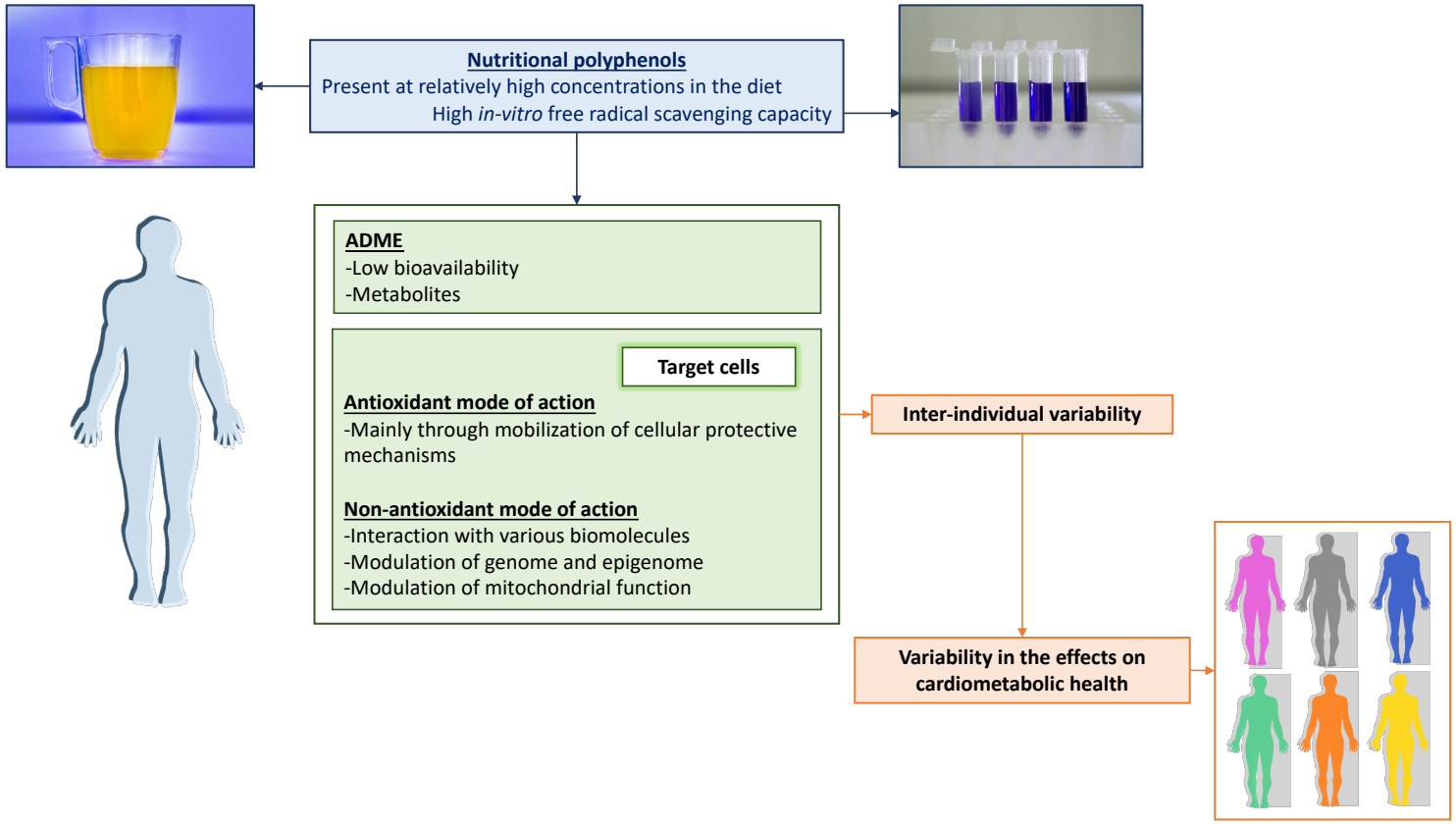
Implications for Cellular NAD$^+$ Metabolism, Protein Acetylation, and Treatment of Metabolic Syndrome

Carlos Escande,[1] Veronica Nin,[1] Nathan L. Price,[2] Verena Capellini,[1] Ana P. Gomes,[2] Maria Thereza Barbosa,[1] Luke O'Neil,[1] Thomas A. White,[1] David A. Sinclair,[2] and Eduardo N. Chini[1]

Metabolic syndrome is a growing health problem worldwide. It is therefore imperative to develop new strategies to treat this pathology. In the past years, the manipulation of NAD$^+$ metabolism has emerged as a plausible strategy to ameliorate metabolic syndrome. In particular, an increase in cellular NAD$^+$ levels has beneficial effects, likely because of the activation of sirtuins. Previously, we reported that CD38 is the primary NAD$^+$ase in mammals. Moreover, CD38 knockout mice have higher NAD$^+$ levels and are protected against obesity and metabolic syndrome. Here, we show that CD38 regulates global protein acetylation through changes in NAD$^+$ levels and sirtuin activity. In addition, we characterize two CD38 inhibitors: quercetin and apigenin. We show that pharmacological inhibition of CD38 results in higher intracellular NAD$^+$ levels and that treatment of cell cultures with apigenin decreases global acetylation as well as the acetylation of p53 and RelA-p65. Finally, apigenin administration to obese mice increases NAD$^+$ levels, decreases global protein acetylation, and improves several aspects of glucose and lipid homeostasis. Our results show that CD38 is a novel pharmacological target to treat metabolic diseases via NAD$^+$-dependent pathways. ***Diabetes* 62:1084–1093, 2013**

syndrome (5). This concept was later expanded by others using different approaches, including inhibition of poly-ADP-ribose polymerase (PARP)1 (6) and stimulation of NAD$^+$ synthesis (7).

The ability of NAD$^+$ to affect metabolic diseases seems to be mediated by sirtuins (8). This family of seven NAD$^+$-dependent protein deacetylases, particularly SIRT1, SIRT3, and SIRT6, has gained significant attention as candidates to treat metabolic syndrome and obesity (9). Sirtuins use and degrade NAD$^+$ as part of their enzymatic reaction (8), which makes NAD$^+$ a limiting factor for sirtuin activity (9). In particular, silent mating information regulation 2 homolog 1 (SIRT1) has been shown to deacetylate several proteins, including p53 (10), RelA/p65 (11), PGC1-α (12), and histones (13), among others. In addition, increased expression of SIRT1 (14), increased SIRT1 activity (15), and pharmacological activation of SIRT1 (16) protect mice against liver steatosis and other features of metabolic syndrome when mice are fed a high-fat diet. Given the beneficial consequences of increased SIRT1 activity, great



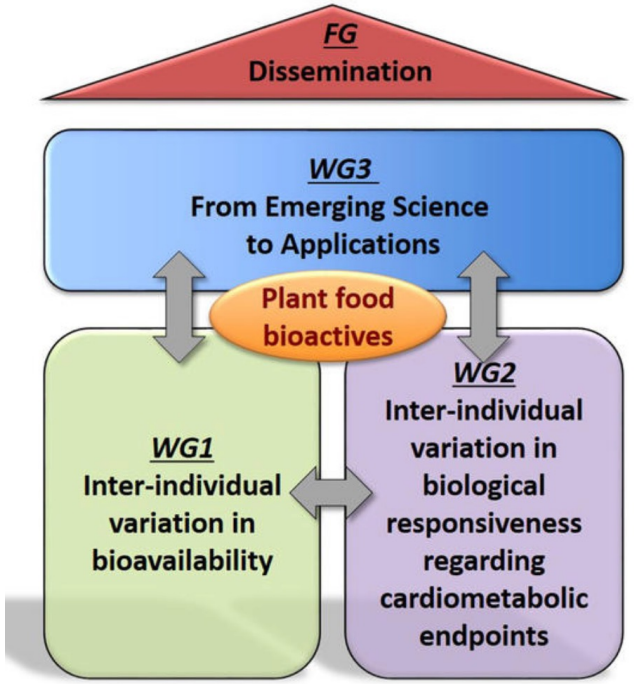
COST POSITIVe – Interindividual variation in response to consumption of plant food bioactives and determinants involved

COST POSITIVe

- Menezes, Regina and Rodriguez-Mateos, Ana …Ruskovska, Tatjana and Maksimova, Viktorija and Combet, Emilie and Pinto, Paula (2017)

Impact of flavonols on cardiometabolic biomarkers: A meta-analysis of randomized controlled human trials to explore the role of inter-individual variability.

Nutrients, 9 (2).



COST POSITIVe

- Ruskovska, Tatjana and Budic-Leto, Irena and … Morand, Christine and Scoditti, Egeria and Suárez, Manuel and Vazour, David and Milenkovic, Dragan (2021)

Systematic bioinformatic analyses of nutrigenomic modifications by polyphenols associated with cardiometabolic health in humans—Evidence from targeted nutrigenomic studies.

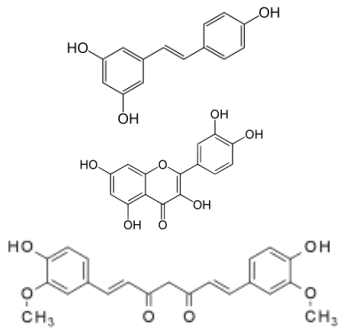
Nutrients, 2021 (13). p. 2326.

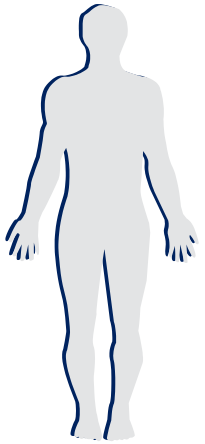
SYSTEMATIC LITERATURE SEARCH
Human intervention studies

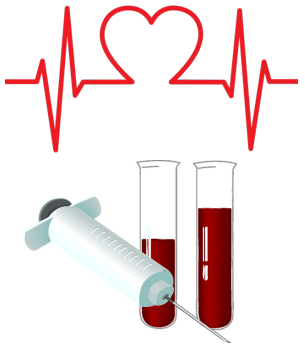
Dietary polyphenols
- Olive oil polyphenols
- Resveratrol
- Quercetin
- Curcumin
- Grape extract

Effects on cardiometabolic risk factors
- Decreased blood pressure
- Improved blood lipids
- Decreased blood glucose and HbA1c
- Decreased oxidative stress

Nutrigenomic effects – targeted approach
- 58 mRNAs
- 5 miRNAs





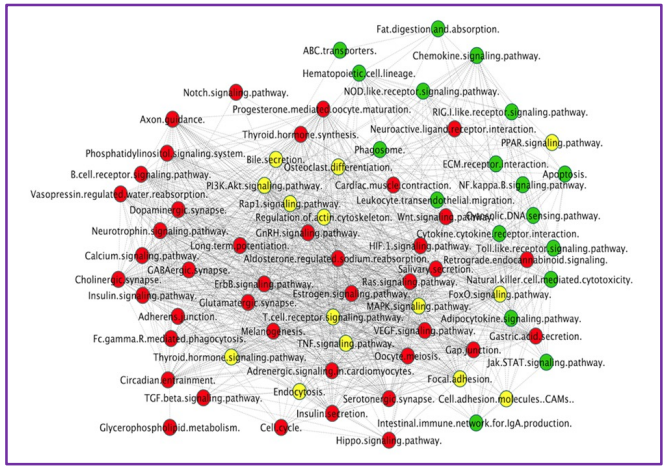


INTEGRATIVE BIOINFORMATIC ANALYSES

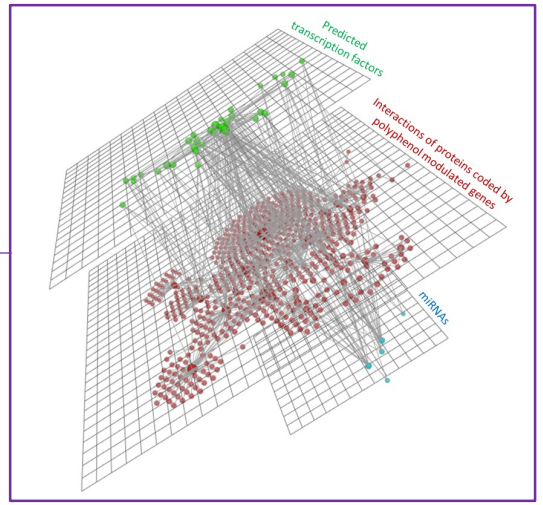
mRNAs
- Pathways analyses
- Interactions between functional groups of genes
- Protein-protein interactions
- Predicted transcription factors

miRNAs
- miRNA targets
- Pathways analyses

Pathways integration analysis



Multi-layer molecular mode of action of polyphenols



TOWARDS FUTURE NUTRIGENETIC STUDIES

ПЕРСПЕКТИВИ

ARTICLE IN PRESS

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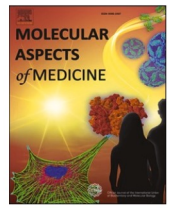

Mechanistic insights into dietary (poly)phenols and vascular dysfunction-related diseases using multi-omics and integrative approaches: Machine learning as a next challenge in nutrition research

Dragan Milenkovic [a,*], Tatjana Ruskovska [b]

[a] Department of Nutrition, University of California Davis, Davis, CA, USA
[b] Faculty of Medical Sciences, Goce Delcev University, 2000 Stip, North Macedonia

ARTICLE INFO

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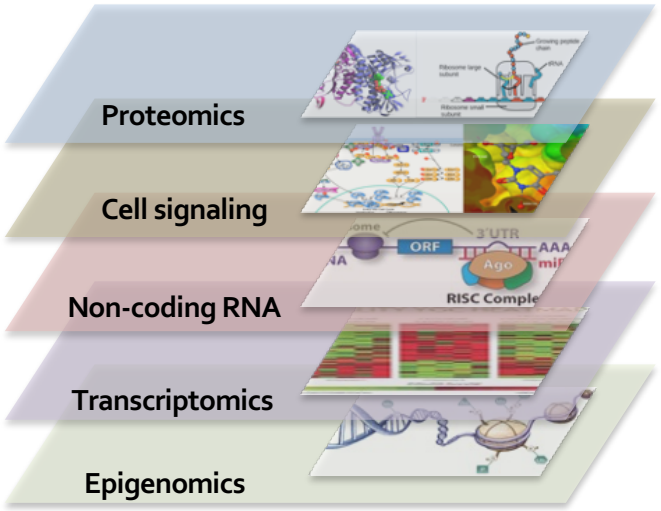
Cardiometabolic disease
Neurodegenerative diseases
Bioinformatics
Mechanisms of action
Artificial intelligence

ABSTRACT

Dietary (poly)phenols have been extensively studied for their vasculoprotective effects and consequently their role in preventing or delaying onsets of cardiovascular and metabolic diseases. Even though early studies have ascribed the vasculoprotective properties of (poly)phenols primarily on their putative free radical scavenging properties, recent data indicate that in biological systems, (poly)phenols act primarily through genomic and epigenomic mechanisms. The molecular mechanisms underlying their health properties are still not well identified, mainly due to the use of physiologically non-relevant conditions (native molecules or extracts at high concentrations, rather than circulating metabolites), but also due to the use of targeted genomic approaches aiming to evaluate the effect only on few specific genes, thus preventing to decipher detailed molecular mechanisms involved. The use of state-of-the-art untargeted analytical methods represents a significant breakthrough in nutrigenomics, as these methods enable detailed insights into the effects at each specific omics level. Moreover, the implementation of multi-omics approaches allows integration of different levels of regulation of cellular functions, to obtain a comprehensive picture of the molecular mechanisms of action of (poly)phenols. In combination with bioinformatics and the methods of machine learning, multi-omics has potential to make a huge contribution to the nutrition science. The aim of this review is to provide an overview of the use of the omics, multi-omics, and integrative approaches in studying the vasculoprotective properties of dietary (poly)phenols and address the potentials for use of the machine learning in nutrigenomics.

Multigenomics data

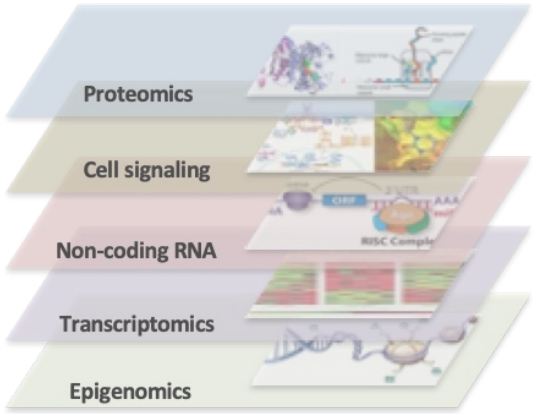


Bioinformatics

- *Gene networks*
- *Cellular pathways*
- *Cellular processes*
- *Transcription factors*
- *Interactome*

Molecular mechanisms underlying health properties of bioactives

Bioactives



Genomic databases

Machine learning – multi-omics integration

Supervised learning → *Classification*, *Regression*

Unsupervised learning → *Clustering*

- Prediction of health effects
- Identification of variability in effects
- Major genes of the health effects

Precision nutrition

Ви благодарам за вниманието