2nd UNIFood International Conference – UNIFood 2021
September 24th-25th 2021 University of Belgrade

BILE ACIDS – A PHARMACO-NUTRACEUTICAL APPROACH

Bojan Stanimirov[1]*, Karmen Stankov[1], Nebojša Pavlović[2], Maja Đanić[3], Momir Mikov[3]

[1]*University of Novi Sad, Faculty of Medicine, Department of Biochemistry, Novi Sad, Serbia*
[2] *University of Novi Sad, Faculty of Medicine, Department of Pharmacy, Novi Sad, Serbia*
[3] *University of Novi Sad, Faculty of Medicine, Department of Pharmacology, Toxicology and Clinical Pharmacology, Novi Sad, Serbia*
Corresponding author: bojan.stanimirov@mf.uns.ac.rs

Introduction

Due to amphipathic properties, bile acids (BAs) a major constituent of the bile, have several physiological functions including solubilization and absorption od dietary lipids and lipophilic xenobiotics, solubilization of cholesterol in bile, stimulation of bile flow and biliary phospholipid secretion and cholesterol excretion. BAs have also antibacterial properties, significantly influencing the composition of intestinal bacterial flora and maintaining the sterility of biliary tree.

Aim

The aim of this study was to summarize the present knowledge in the innovative field of BAs pharmacology, to reveal novel mechanisms of their action, focusing on clinically-relevant aspects.

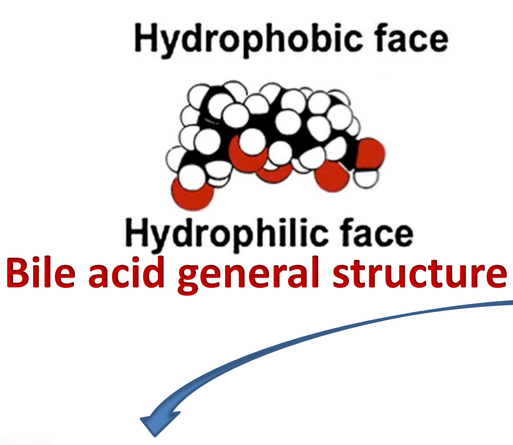
Material and methods

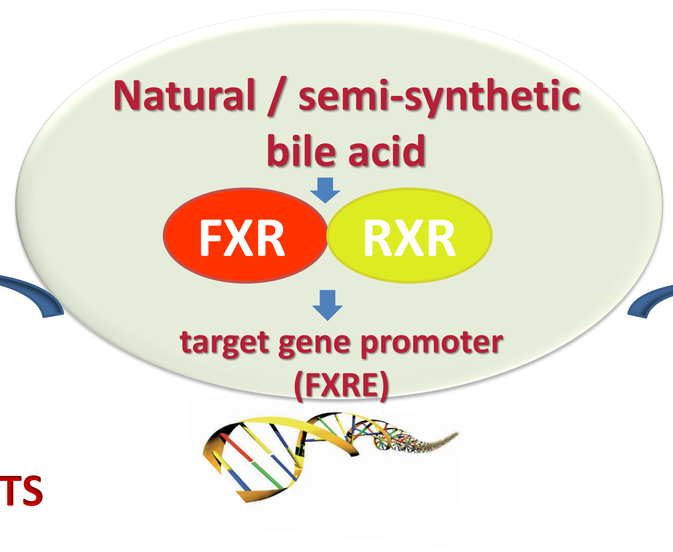
Detailed and comprehensive analisys of original and review articles published on PubMed and Scopus databases in the period 1999-2020.

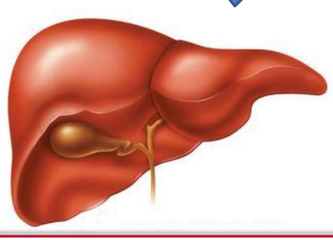
Results and Conclusion

Initial mainly mechanistic function of BAs has been expanded to diverse and versatile regulatory functions involving cell homeostasis, hepatic and extra-hepatic metabolic processes, regulation of cell proliferation and death, and carcinogenesis. BAs are now recognized as signaling molecules capable to activate specific nuclear and membrane receptors, multiple cellular kinase signaling pathways. BAs can directly and through epigenetic mechanisms regulate the expression of genes involved in integrative metabolism and homeostasis. Disturbances in BA homeostasis contribute to the development of intestinal dysbiosis, dyslipidemia, obesity, inflammatory diseases, common metabolic diseases such as diabetes, non-alcoholic fatty liver disease, liver cirrhosis, hepatobiliary and intestinal disorders, carcinogenesis, even the disorders of central nervous system. The field of research of natural and semisynthetic derivatives of BAs and BA-receptors ligands has been extensively expanding and several BA-based therapeutics have been approved for the treatment liver and intestinal diseases. These biomolecules may also influence the drug bioavailability and metabolism, by interacting with nuclear receptor-transcriptional networks, the expression of membrane transport proteins and drug-metabolizing enzymes. Bile acids can be utilized in the formulation of conventional dosage forms, but also of novel micellar, vesicular and polymer-based therapeutic systems.

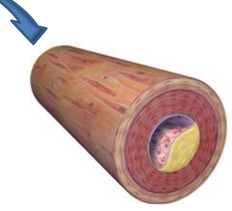
Metabolic effects of bile acids mediated by the farnesoid X receptor (FXR)







METABOLIC EFFECTS



MODULATION OF LIPID METABOLISM

Decreased intestinal cholesterol absorption

Decreased level of HDL cholesterol
- Reduction of ApoA1 expression
- Increased clearance via hepatic SR-BI

Increased clearance of LDL
- Increased LDL-receptor activity

Increased clearance of VLDL
- Enhanced activity of lipoprotein lipase
- Increased VLDL-receptor activity
- Induction of syndecan-1

Promotion of fatty acid oxidation
- Induction of PPARα

MODULATION OF GLUCOSE METABOLISM

Decreased gluconeogenesis
- Repression of hepatic PEPCK and G6Pase expression

Increased hepatic glycogen synthesis
- Increased phosphorylation of GSK3β

Improved insulin transcription and secretion

Improved hepatic insulin sensitivity
- Induction of GLUT4 expression

Decreased peripheral insulin resistance
- Induction of GLUT4 expression in white adipose tissue
- Reduction of FFA contribute to restoration of insulin signaling in muscle

VASCULAR EFFECTS

Endothelial cells:
Anti-hypertension phenotype
- Increased NO release
- Decreased ET-1 release

Smooth muscle cells:
Anti-atherogenic phenotype
- Inhibition of proliferation
- Inhibition of migration
- Inhibition of inflammatory IL-1β phenotype
- Increased PLTP expression
- Increased ATR-2 expression

Macrophages:
Supression of inlflammatory cascade
- Decreased IL-1β, IL-6 and TNF-α release

ABBREVIATIONS: **FXR** Farnesoid X Receptor, **BA** Bile Acid, **FXRE** FXR-Response Element, **ApoA1** Apolipoprotein-A1, **SR-B1** Scavenger Receptor Class B Member 1, **PPARα** Peroxisome Proliferator-Activated Receptor α, **PECPK** Phosphoenolpyruvate Carboxykinase, **G6Pase** Glucose-6-Phosphatase, **GLUT4** Glucose Transporter Type 4, **FFA** Free Fatty Acid, **NO** Nitric Oxide, **ET-1** Endothelin-1, **IL-1β** Interleukin-1β, **PLPT** Phospholipid Transfer Protein, **ATR-2** Angiotensin Type 2 Receptor

Funded by the Ministry of Education, Science and Technological Development, the Republic of Serbia, project No. III 41012