Multi-regulator of EZH2-PPARs Therapeutic Targets: A Hallmark for Prospective Restoration of Pancreatic Insulin Production and Cancer Dysregulation

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Research Summary

Cancer and diabetes pose significant global challenges, and research is focused on identifying biomarkers for innovative therapeutic targets. The regulatory role of EZH2-PPARs in these diseases has been discovered, with GSK-126 and bezafibrate as effective inhibitors. This study identified gene-disease associations, protein interactions, and potential natural products for drug development. Obesity and hypertension were linked to the investigated biomarkers, validating their connection to cancer and diabetes. Nine natural products showed strong binding capacity, particularly phytocassane A, surpassing standard drugs. Experimental screening is recommended to further explore their potential in diabetes and cancer therapy targeting EZH2-PPARs.

Keywords: EZH2-PPARs · Diabetes mellitus · Natural products · Pancreatic cancer ·Protein-protein network · In silico profiling

Introduction

- Diabetes mellitus (DM) is a prevalent chronic disease caused by insulin-related changes
- Type 1 diabetes (T1DM) is an autoimmune disorder that destroys beta cells, while type 2 diabetes (T2DM) involves beta cell dysfunction or insulin resistance.
- Pancreatic cancer (PC) is a lethal disease originating from exocrine cells, primarily pancreatic ductal adenocarcinoma (PDAC).
- PDAC, the fourth leading cause of cancer-related death), causes 90% of pancreatic malignancies.
- Diabetic patients have a twofold increased risk of pancreatic cancer compared to non-diabetic individuals.
- Pancreatic duct cells have been identified as potential progenitors for cell regeneration in pancreatic cancer and diabetes.
- The genes EZH2 and PPARs (pan-peroxisome proliferator-activated receptors) have therapeutic potential in treating both cancer and diabetes.
- Natural products from plants and biological materials are being investigated for their inhibitory effects on therapeutic target enzymes.

Research Questions

- What are the proteins existing between diabetes and pancreatic cancer?
- What are the gene-disease association between the disease subtypes?
- Which available natural products are suitable for the therapeutics of EZH2-PPARs?

Methodology

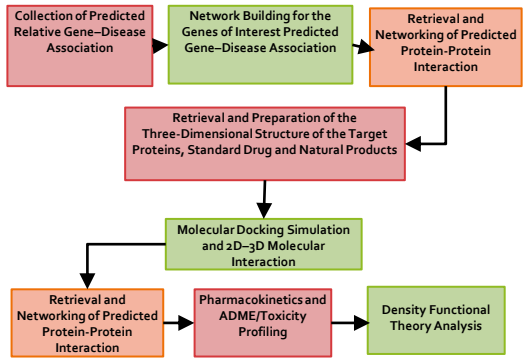

Fig. 1. Predicted gene-disease association network of the EZH2-PPAR

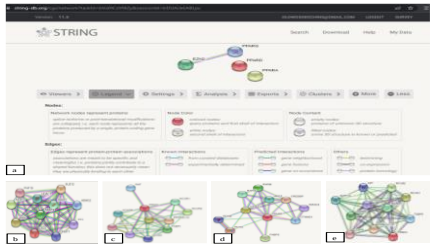

Fig 2. Predicted gene-disease association network of the EZH2-PPAR Legend: a; EZH2-PPAR analogues interaction, b; EZH2-Other genes interaction, c; PPARAlpha-Other genes interaction, d; PPARDelta-Other genes interaction, e; PPARGamma-Other genes interaction.

Results

- The top 15 disease associations revealed standard connections between PPARs (Alpha, Delta, and Gamma), but not directly to EZH2 for the selected diseases.
- The protein-protein interaction network confirmed the interaction between EZH2 and PPAR Gamma.

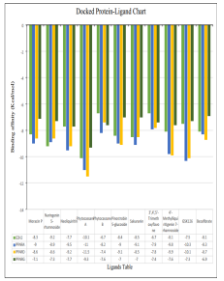

Fig. 3 Graphical representation of lead hit compounds with EZH2-PPARs target binding affinity

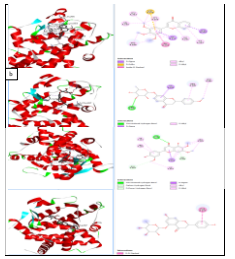

Fig 4. 2/3D Interaction profile of PPARGamma-Ligand complex. Bonding are shown in dotted lines: a; PPARG-3',4',5'-Trimethoxyflavone, b; PPARG-4'-Methylliquiritigenin 7-Rhamnoside, c; PPARG-Cirsilineol, d; PPARG-Naringenin 5-Rhamnoside.

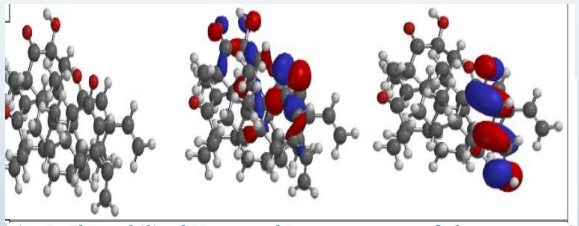

Fig. 5. The stabilised Homo and Lumo structure of phytocassane A

Conclusion

- Phytocassane A exhibit good drug property
- Further in vitro and in vivo investigations are needed to validate the potential of these natural compounds for drug development targeting EZH2-PPARs.

Recommendations

- Investigate the safety and toxicity profiles of the selected natural compounds to ensure their suitability for clinical use.
- Explore the potential synergistic effects of combining the identified natural compounds with existing standard drugs for enhanced therapeutic outcomes.

For more Details/References, please scan the code