SYNOPSIS

SYNOPSIS OF THE THESIS

On

"Exploring Metabolically Compromised Secretome and Bioactives on Islet Differentiation and Function for Effective Diabetic Therapy"

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Doctor of Philosophy in Biochemistry

By

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INTRODUCTION

Hyperglycaemia is a hallmark characteristic of diabetes mellitus which when left unmanaged cause glucose toxicity which ultimately affects other vital organs of the body and hence progresses towards more severe micro and macro-complications of diabetes. Thus, maintaining a good glycemic control is a pre-requisite of any effective diabetes therapy [1]. Failing pancreas and subsequent loss of pancreatic β cells worsen diabetic conditions which are further alleviated by the mounting up of glucose levels. Current commercial class of anti-diabetic drugs targets a potentially limited subset of druggable targets in managing diabetes with their own limitations [2]. Maintaining normoglycemia requires complex integration of pancreas, muscle, adipocyte and neuroendocrine system [3]. Reports have demonstrated that kidney also plays a key role in maintaining normoglycemia in blood. [4] [5].90 % of reabsorption of glucose occurs via Sodium glucose co-transporter 2 (SGLT2) which is a high-capacity, low-affinity glucose transporter located in the early convoluted segment (S1) of the proximal tubule and 10 % by SGLT1,a low capacity high affinity sodium glucose co-transporter[6]. This mechanism becomes malabsorptive in diabetes and hence hyperglycaemia persists [7]. SGLT2 inhibitors or gliflozins like canagliflozin, dapagliflozin, empagliflozin promotes glucosuria by inhibiting glucose reabsorption in the kidney [8]. The important role of the natural compound phlorizin in the development of SGLT2-inhibitors has been extensively reported [9]. Other than phlorizin, various flavonoids and flavonoid enriched plant extracts have been explored for their glucose lowering effect [10]. One such C-glucosyl flavone, swertisin, from a medicinal plant *Enicostemma Littorale* (EL) has been explored as a potent islet neogenic agent by our group [11] [12] [13]. The Aqueous extract of EL has shown glucose lowering effect in diabetic mice model [14]. Srivastava et al. demonstrated that swertisin treated diabetic BALB/c mice showed improvement of diabetic condition by triggering pancreatic progenitors for islet neogenesis. Swertisin besides being a potent islet neogenic agent has the potential to early glucose lowering response in blood upon administration [15]. Thus, it not only helps in increasing the insulin producing islet clusters within the diabetic pancreas but swiftly controls blood glucose levels also. Some recent emerging research

on gliflozins suggested that they have pleiotropic roles beyond glycaemic control [16]. SGLT inhibitors have demonstrated protection against failing pancreas [17]. Thus, we explored swift glucose lowering action of swertisin in the direction of SGLT activity along with various metabolic alterations. Further, we mechanistically dissected glucose lowering property of bioactive swertisin by *in silico, in vitro,* and *in vivo* studies. The potential property of swertisin as a glucose-lowering agent is remarkable which points towards the likelihood of a wider avenue of diabetes therapy.

Another major cause of hyperglycemia is insulin resistance, caused by the unresponsiveness of insulin in target tissues like skeletal muscle and adipose tissue which further results in multiple metabolic etiology including Type 2 Diabetes Mellitus [18]. In insulin resistant condition, lipid storage capacity of subcutaneous and visceral adipose tissue decreases which elevates levels of free fatty acid in systemic and portal circulation increasing intramyocellar fat content in muscle cell. Insulin stimulated glucose disposal in skeletal muscle is markedly impaired due to multiple defects in insulin signalling pathway as well as defective mitochondrial oxidative phosphorylation [19].

Skeletal muscle and adipose tissue have been identified as a secretory organ. A different panel of Myokines is secreted by insulin sensitive and insulin-resistant myotubes with beneficial or detrimental impact on β -cell function, proliferation, and survival [20]. IL-6 mediates cross talk between intestinal L cells and pancreatic islets [21]. Fractalkine (CX3CL1) protects β-cells against TNF- α (Tumor necrosis factor-α) [22]. Thus, noticing the pleiotropic effects of Myokines on other tissues it is believed that the trophic effects of these Myokines exerts regulatory effects in maintaining healthy cellular environment, low grade inflammation and thereby preventing metabolic related diseases like insulin resistance [23].

Secretome of Adipose derived stem cells secretes large array of factors in the extracellular milieu that exhibit regulatory effects on other tissues [24].Hyperglycemic condition metabolically compromises biological function of ADSCs [25]and thus may impact its secretome under hyperglycemic condition.

hADSCs (human ADSCs) conditioned medium under hypoxic condition cause apoptotic activity of islet with decreased anti-apoptotic factors, VEGF(Vascular Endothelial growth factor), and insulin secretion was increased compared to those islets cultured with FGF2(Fibroblast Growth Factor 2) supplement [26, 27] suggesting paracrine signalling of trophic factors, particularly VEGF, secreted by human ADSCs enhanced the survival and function of porcine islet cells in vitro. Expression levels of the islet-specific genes (insulin, PDX1, and GLUT2) and Bcl-2 (an anti-apoptotic gene) were consistently higher in hADSC co-culture islets than in mono-cultured islets [28].Hence, we also investigated the effect of the altered secretome of Adipose derived stem cell and skeletal muscle on Islet differentiation and functionality.

SPECIFIC OBJECTIVES:

Objective-1: Identification of molecular targets of swertisin in glucose homeostasis and islet differentiation & functionality

Objective-2: Effect of secretome of skeletal Muscle on islet differentiation & functionality

Objective-3: Effect of secretome of Adipose derived Stem cells on islet differentiation & functionality

Objective-1: Identification of molecular targets of swertisin in glucose homeostasis and islet differentiation & functionality

a) *In silico* Identification of molecular targets

In silico analysis showed Sodium glucose co transporters as possible targets of swertisin in case of glucose lowering effect (Software used: Swiss target prediction software, ZINC software, PASS online software). Due to non-availability of human SGLT2 structure in PDB, hSGLT2 structure was modelled by homology modelling. C-score = - 0.68 (estimated) (Software used: ITASSER). Successful hSGLT2 model was generated and energy minimized (Software used: RAMPAGE) and

structure validated by Ramchandran plot analysis.97.6 % residues of hSGLT2 model were in favourable region. (Software used: PROCHECK). Effective molecular docking of swertisin and canagliflozin with hSGLT2 structure was done and important molecular interaction with Asp 294 was observed within ligand binding active site of hSGLT2 which is crucial interaction for SGLT2 inhibition. The docking score for the Swertisin-hSGLT2-interaction and Canagliflozin-hSGLT2-interaction were determined to be -8.5 and -8.7 kcal/mol respectively (Software used: Autodock vina). The overall interaction pattern of canagliflozin and swertisin is quite similar indicating a stable interaction of swertisin with hSGLT2. Molecular docking occurs in a static condition and SGLT2 is a membrane bound transporter protein, with some of its domains embedded in the lipid bilayer; molecular dynamic simulation was performed to mimic dynamic membrane condition. GROMACS software was used to carry out MD Simulation. A simple simulation was run of SGLT2 in an aqueous system to check whether the stability of modelled structure at 300K temperature and 1.0 bar pressure, the same conditions at which the living – systems operate. Pharmacokinetic properties of Swertisin were studied in *in silico* human system. A comparative study was done of Swertisin with its natural precursors and commercially available SGLT-inhibitors. Drug-likeliness studies showed that compared to the natural precursors, Swertisin follows Lipinski's rules and can be recommended for a daily dosage.

b) *In vitro* identification of molecular targets of swertisin

In vitro investigation was performed to assess the sodium dependent and independent 2-NBDG uptake by swertisin in the HEK293 cell line. These tests revealed that 7.5 µg/ml concentration of swertisin strongly inhibited sodium dependent glucose uptake, reducing 2-NBDG from 100% to 51.4% and 30.4% in the absence or presence of cytochalasin B respectively compared to control. Live imaging Fluorescence microscopy analysis demonstrated time-dependent intracellular accumulation of 2- NBDG FITC in HEK293 cells in control while swertisin treated cells observed no transport of 2- NBDG inside the cell. Sodium dependent and independent 2-NBDG uptake in Caco2 cell line was performed and we observed unaltered and non-significant inhibition of glucose

uptake even at a higher concentration of swertisin. Thus, swertisin displayed higher selectivity of SGLT2 in HEK293 (kidney) cell line. To determine whether swertisin contributed to the regulation of SGLT2 expression, we examined the time-dependent expression of SGLT2 in presence of 7.5 µg/ml of swertisin. Incubation of the HEK293 cell line with swertisin abolished the induction of SGLT2 expression in a time dependent manner. Previous reports have demonstrated the role of PKC, pp38 MAPK, and Erk1/2 as a few of the factors regulating the expression of the SGLT2. Temporal analysis of SGLT2 levels with swertisin treatment demonstrated overall downregulation of SGLT2 with differential regulation of regulating proteins.

c) *In vivo* identification of molecular targets of swertisin

STZ treated diabetic BALB/c mice were treated with swertisin and analysed for amelioration for their diabetic condition. Treatment of swertisin reduced hyperglycemia which was observed till the duration of swertisin treatment. An oral glucose tolerance test was performed on Day 15th on overnight fasted mice which demonstrated controlled glycemia over the period of 2H. To understand the implications of swertisin on metabolic factors, we then examined several physiological parameters in the treatment groups of mice. Weight loss was persistently detected in swertisin and canagliflozin treated mice. Chow intake, water intake, Urine output, Glucosuria and proteinuria along with serum and urine urea and creatinine were evaluated for all treatment groups. Protein expression by western blotting and Immunohistochemistry of kidney tissues of swertisin treated diabetic mice showed remarkable reduction in expression of SGLT2 along with differential expression of regulating proteins.

Objective-2: Effect of Secretome from skeletal Muscle on islet differentiation & functionality

C2C12 is a myoblast cell line, which differentiates rapidly, forming contractile myotubes, served as *in vitro* model for skeletal muscle. Confirmation of myotube was done by expression of desmin, myogenin and αSMA. Insulin resistance was developed by inflammatory mediatory cytokine TNF-α in differentiated C2C12 myotubes and confirmed gene expression of insulin signalling proteins. We

found a significantly lower gene levels of insulin receptor, IRS1 and GLUT4 in TNF-α treated myotubes. We also found significantly lower protein levels of phosphorylated Akt in TNF-α treated cells as compared to control groups. Gene profiling of various Myokines such as IL-6, IL-13, IL-15, CXCL1,CCL3 etc. In conditioned media (secretome) from control and insulin resistant myotube groups which were subjected to pancreatic progenitor cells during islet differentiation. Protein expression studies for differentiation parameters Nestin, Pdx-1, Ngn-3 and Neuro-D showed differential regulation in islet treated with IR muscle secretome compared to control speculating differentiation was hampered when progenitors were treated with altered panel of myokines. Newly formed islets from pancreatic Progenitor cells which had been subjected to IR Muscle secretome compared to IS (insulin sensitive) had lesser yield and were morphometrically compromised. ILCCs along with lesser expression of C peptide and glucagon. Temporal profiling of differentiation markers and secretome profiling by ELISA /LCMS/HPLC is in progress. ILCCs with IR Muscle secretome demonstrated compromised islet neogenesis and islet functionality with higher ROS, low C peptide, Glucagon and more Annexin PI and cleaved PARP.

Objective-3: Effect of secretome of Adipose derived Stem cells on islet differentiation & functionality

The secretome from metabolically compromised hADSCs in which insulin signalling was hampered; was collected and added to PREPs along with differentiation media, till Islet like Cell Clusters (ILCCs) were obtained. To analyse the secretory specific secreted factors, the conditioned media was assessed using HPLC which showed differential peptide peaks between 35-47 mins in both lean and obese hADSC secretome. The results showed the elusion of a distinct peak at 41 min interval, which was found in lean secretome but not obese secretome. Similarly, expression of genes regulating the insulin – sensitivity and differentiation of pre-adipocytes to adipocytes such as CEBPA, CEBPB, CEBPD, PPAARG, SIRT1, PREF1 and SREBF1 were also reduced in obese ADSC's compared to the lean one. Thus, explaining differential status of key metabolic genes in wake of metabolic compromised state. Functionality was hampered in obese ADSC secretome treated ILCCs as they

had lower expression of C-peptide and Glucagon as well as higher ROS activity. Expression of key transcription factors involved in development was differentially regulated as compared to lean ADSC secretome treated ILCCs; HNF-3β, NGN-3 and Glut-2 showed lower levels of expression on Day 4 in obese ADSC secretome treated ILCCs as compared to lean ADSC secretome treated ILCCs; conversely NeuroD, Pdx- 1 and MafA showed higher levels of expression in comparison, MafA showing significantly higher expression from Day 2 of differentiation itself. Thus, Obese ADSC secretome hampered or delayed differentiation of ILCCs causing delay in functional maturity of islet.

Conclusion

Diabetes Mellitus, one of the leading metabolic syndromes in the world, has claimed much burden on healthcare system in terms of effective treatment which should be safe and cost effective bringing focus to herbal and natural repertoire. Bioactive Swertisin, a C-glucosyl flavone has been well explored and mapped for controlling hyperglycaemia. This study helped in identification of molecular targets and mechanistic approach of swertisin having a potent glucose lowering activity as a potent SGLT2 inhibitor. Based on *in silico, in vitro,* and *in vivo* studies our work has led to conclude swertisin as a promising candidate ameliorating diabetic impediment by SGLT2 inhibition. Our research has highlighted the importance of SGLT2 inhibition and its reduced expression by swertisin. Direct role of swertisin in controlling hyperglycemia makes it an excellent pharmacophore agent that can ease the burden of diabetes healthcare management by providing holistic treatment and a foremost candidate for a new class of anti-diabetic drugs SGLT2 inhibitors.

Moreover, Diabetes Mellitus is attributed by insulin resistance and pancreatic beta cell dysfunction. In this study, we have also studied crosstalk between Skeletal Muscle and hADSC with Pancreatic Islet respectively in terms of Trophic effects (via Secretome). The secretome of muscle and hADSC gets altered in insulin resistant condition thereby affecting islet functionality but this study also provide insights on effect of altered secretome on islet differentiation as well. This study adds to the knowledge on effect of altered secretome on islet functionality and differentiation which will

provide greater understanding of cross talk between skeletal muscle and pancreatic islets in terms of secretome. An alternative secretome administration for treating diabetes would be an effective therapeutic approach. Therefore the present study aids in array of knowledge on how muscle and hADSC secretome can be a potent therapy for diabetes.

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Achievements

Publications

- "A perspective on regenerative potentials of herbs for diabetes therapeutics" Abhay Srivastava, Mitul Vakani, Gurprit Bhardwaj and Sarita Gupta **(Communicated)**
- "Swertisin, a novel SGLT2 inhibitor, with improved glucose homeostasis for effective diabetes therapy" Gurprit Bhardwaj, Mitul Vakani, Abhay Srivastava, Dhaval Patel, Anju Pappachan, Prashant Murumkar, Hemal Shah, Rushabh Shah, Sarita Gupta **(Communicated)**

Oral presentation

- Gurprit Bhardwaj, Komal Rawal, Kishan Purohit ,Mitul Vakani, Abhay Srivastava,Sarita Gupta* "Effect of metabolically compromised human Adipose derived stem cell secretome on islet neogenesis: an vitro study" Oral and Poster presentation at 9th International conference NGBT Nextgen Genomics, Biology, Bioinformatics and Technologies

Conference organized by SciGenom Research Foundation (SGRF) at MUMBAI, INDIA Sep 30th to Oct 2nd, 2019.

- Gurprit Bhardwaj, Mitul Vakani, Abhay Srivastava, Ruchika Agarwal and Sarita Gupta* 'Abatement of islet neogenesis by altered muscle-pancreatic crosstalk in insulin resistant condition" Oral presentation at 4th International Conference on Translational Research: Recent Developments and Innovations in Human Health and Agricultural Research, Bogmallo Beach Resort, Goa, India,11th-13th October,2018.
- Oral presentation on "Impact of metabolically compromised muscle secretome on islet functionality and differentiation" in UGC National Conference ON Current Trends in Biological Sciences-II(CTBS-2018) on 9th Feb 2018 at Anand, Gujarat.
- Oral presentation on' Exploring Islet Neogenesis with Stem cells & Bioactives: A Novel perspective approach in Diabetic Therapeutics' in Science Conclave 2017 at Faculty of Science The Maharaja Sayajirao University of Baroda 28th February 2017.

Awards

- Awarded YUVA Scholarship for attending 9th International conference NGBT Nextgen Genomics, Biology, Bioinformatics and Technologies Conference organized by SciGenom Research Foundation (SGRF) at MUMBAI, INDIA Sep 30th to Oct 2nd, 2019.
- The M.S University of Baroda, Vadodara, Gujarat funded Travel award under 'Academic activity fees of the faculty of science' for oral presentation on 'Abatement of islet neogenesis by altered muscle-pancreatic crosstalk in insulin resistant condition' at 4th International Conference on Translational Research: Recent Developments and Innovations in Human Health and Agricultural Research, Bogmallo Beach Resort, Goa, India,11th-13th October,2018.

Conference attended

- Science Conclave 2020 for celebration of National Science Day at Faculty of Science, The Maharaja Sayajirao University of Baroda 28th February 2020.

- National Symposium on TRendys IN BIOCHEMISTRY: TURN OF DECADE, TRENDYS 2020 organized by Department of Biochemistry, Faculty of Science, The M S University of Baroda held on 24th and 25th January 2020.
- National Seminar on Human Health: Need of the hour jointly organized by the Indian Science Congress Association and Faculty of Science, The M S University of Baroda with the support of Indian Society of Geomatics and Indian women Scientists' Association held on 24th December 2019.
- Symposium on "Trends in Biochemistry and inauguration of Prof.LJ Parekh Memorial Lecture series" organized by Department of Biochemistry, Faculty of Science The Maharaja Sayajirao University of Baroda, Vadodara, Gujarat, India held on 27th and 28th September 2019.
- 9th International conference NGBT Nextgen Genomics, Biology, Bioinformatics and Technologies Conference organized by SciGenom Research Foundation (SGRF) at MUMBAI, INDIA Sep 30th to Oct 2nd, 2019.
- One day Brain storming Session On 'Opportunities, challenges and Future directions in Life Science Education and research' organized by Dr. Vikram Sarabhai Institute of Cell & Molecular Biology Faculty of Science, The M S University of Baroda, Vadodara, Gujarat, India on 20th January 2019.
- Attended a three-day International Conference on 'Proteins, miRNA and Exosomes in Health and Disease' organized by Department of Biochemistry, Faculty of Science The Maharaja Sayajirao University of Baroda, Vadodara, Gujarat, India from 11th-13th December 2018.
- Attended a Two Days national symposium on "Omics to structural basis of diseases" organized by The department of bio-chemistry Faculty of Science The Maharaja Sayajirao University of Baroda from 30th September 2016 to 1st October 2016.

Webinar

- Understanding and interventions of human diseases on occasion of 9th foundation day organized by Dr. Vikram Sarabhai Institute of Cell and Molecular Biology, Faculty of Science, The M S University of Baroda, Gujarat 30th sep 2020
- "Practical Aspects of Patents and IPR" organized by Dr. Vikram Sarabhai Institute of Cell and Molecular Biology, Faculty of Science, The M S University of Baroda, Gujarat held on 9 sep 2020
- National webinar on "Research and education during Covid-19 pandemic: An opportunity Foretold: Organized by Dr. Vikram Sarabhai Institute of Cell and Molecular Biology, Faculty of Science, The M S University of Baroda, Gujarat June 2020
- International Webinar on "Mitochondrial Copper in Human Disease" organized by Department of Biochemistry, Faculty of Science, The Maharaja Sayajirao University of Baroda, held on 23 May 2020
- National Webinar on "Loss of GSK-3β Kinase Mediated Phosphorylation in an HtrA2 Variant Contributes to Parkinsonian Phenotype" organized by Department of Biochemistry, Faculty of Science, The Maharaja Sayajirao University of Baroda on 22 May 2020.

WORKSHOPS / TRAINING ATTENDED

- Joint workshop on "Basics of Bioinformatics" by Hemchandracharya North Gujarat University and Gujarat Biotechnology Research Centre at Gujarat Biotechnology Research Centre, Gujarat, India on 6th-10th January 2020.
- Workshop on "Empowering women for Entrepreneurship" organized by ENPRENDIA project, Office of International affairs jointly with Management development center and women studies research center, The Maharaja Sayajirao University of Baroda, Vadodara, Gujarat, India held on 7th December 2019.

- Participated in “One day workshop on Biological applications of magnetic nanoparticles’’ at The M.S University of Baroda organized by MagGenome Technologies Pvt.Ltd. and The M.S University of Baroda on 27th march 2019.