

Baicalin Promotes Pancreatic β -cell Proliferation through NF- κ B Modulation: An *In-silico* and *In-vitro* Approaches

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ABSTRACT

Type 2 diabetes mellitus (T2DM) is a chronic disorder associated with pancreatic β -cell dysfunction and their loss, eventually requiring insulin supplementation. Strategies targeting β -cell loss and their proliferation may offer a promising approach towards β -cell preservation, thus delaying progression of T2DM. Baicalin is a phytoconstituent with anti-oxidant and anti-inflammatory properties. Due to its therapeutic properties baicalin has an advantage to modulate pathways involved in T2DM progression. Histone Deacetylase (HDAC) and Nuclear Factor Kappa B (NF- κ B) are key pathways that are involved directly or indirectly in the β -cell dysfunction and their loss. Further, studies have reported that baicalin has the ability to modulate HDAC and NF- κ B. In present study, molecular docking was carried using Maestro version 9.6 within the Schrodinger software suite to investigate the interaction of baicalin with HDAC and NF- κ B. The three-dimensional structures of proteins were obtained from the protein data bank (PDB). Prior to docking, protein preparation was carried out by removing solvent molecules and adding hydrogen atoms. Furthermore, the protective and functional effect of baicalin was assessed in pancreatic β -cell lines, RIN-5F and MIN6 cell lines. MTT, CCK-8, BrdU incorporation and insulin secretion assays were performed to evaluate cytotoxicity, cell viability, cell proliferation and β -cell function. The results of molecular docking revealed that baicalin has strong binding affinity towards NF- κ B than HDAC. In *In-vitro* study, it was observed that baicalin has significantly reduced cytotoxicity, enhanced cell viability, cell proliferation and insulin secretion. Collectively these findings indicate that baicalin has a potential to protect β -cell against their loss and preserve their function probably through NF- κ B modulation.

Keywords: Baicalin, pancreatic cells, cytotoxicity, insulin.

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1. Introduction

Diabetes mellitus is one of the most prevalent metabolic disorders that has emerged as a major health concern globally. Type 2 diabetes mellitus (T2DM) is a progressive disease that worsens in most patients thus ultimately requiring insulin supplementation¹. Therefore, strategies aimed at pancreatic β -cell protection, providing favorable environment for their proliferation and preservation of their functionality are of great importance. Several studies have reported the association between Histone deacetylases (HDACs) and diabetes progression. Multiple HDACs are expressed in the pancreatic β -cells, and their expressions are affected by the cytokines. Previous studies have observed that inhibition of HDAC may exert protective action on pancreatic islets against cytokine induced apoptosis and may promote β -cell proliferation and insulin secretion²⁻⁵. Nuclear Factor Kappa B (NF- κ B) is also found as a potential target to attenuate β -cell loss. NF- κ B is a key transcription factor involved in the immune and inflammatory responses that may contribute to inflammation mediated β -cell loss. Previous studies showed that pharmacological inhibition of NF- κ B could protect β -cell and prevent apoptosis in pancreatic islets. Therefore, suggesting modulation of NF- κ B could have a protective effect on β -cells thus preserving β -cell mass and their functionality⁶⁻⁷. Under normal conditions, NF- κ B remain in an inactive form in cytoplasm through its association with the inhibitor of κ B (I κ B). Under stressed cellular responses, I κ B undergoes phosphorylation

resulting in the breakdown of NF- κ B- I κ B complex. Free NF- κ B translocated to the nucleus, there it binds to the specific DNA sequence that leads to the transcription of target gene resulting in the apoptosis of β -cell⁶. Therefore, pharmacological inhibition of NF- κ B may prevent the β -cell apoptosis thus providing favorable environment for the β -cell proliferation. Thus, targeting modulation of HDAC and NF- κ B could reduce the pancreatic β -cell loss and preserve its functionality.

Baicalin is a flavonoid isolated from the roots of *Scutellaria baicalensis*, also known as Baikal Skullcap. It is a medicinal plant found in China. For centuries it is used in several Chinese medicines in the management of various conditions due to its several therapeutic properties. It is administered in infections, inflammatory disorders, and some of the neurological conditions. Previous studies have demonstrated several pharmacological activities of baicalin including anti-infective, anti-oxidant and anti-inflammatory⁸⁻⁹. Researchers have reported that baicalin has potential to modulate HDAC and reduce inflammatory responses⁹⁻¹⁰. Baicalin is also found to inhibit the activation of NF- κ B thereby contributing to the reduction of oxidative stress and inflammation¹¹⁻¹². Targeting β -cell proliferation is a novel approach and underexplored therapeutic strategies for the management of T2DM thus needs to be investigated. In the current study, we aim to identify the target among the HDAC and NF- κ B towards which baicalin has highest binding affinity based on docking score and protein-ligand interactions.

Additionally, effect of baicalin on cytotoxicity, cell viability, cell proliferation and insulin secretion was assessed in the pancreatic cell lines, Mouse Insulinoma Cell Line (MIN6) and rat insulinoma cell line (RIN-5F).

2. Material and method

2.1 Chemicals and Kits

Roswell Park Memorial Institute (RPMI-1640) and Dulbecco's modified Eagle's medium (DMEM) were purchased from HiMedia. Antibiotic solution (penicillin and streptomycin) was procured from Gibco (USA); STZ and baicalin (batch no. MKCT4279) were obtained from Sigma-Aldrich (USA); Bromodeoxyuridine (BrdU) cell proliferation assay kit was purchased from MyBioSource, enhanced cell counting kit 8 (WST-8/CCK8) was purchased from Elabscience. Inc.

2.2 Molecular Docking

Molecular docking was performed to investigate the potential interactions of baicalin with HDAC and NF- κ B. Molecular docking was conducted with the help of Maestro version 9.6 within the Schrodinger software suite. Structure of baicalin was obtained from PubChem and three-dimensional structure were generated by build panel and further prepared for docking using LigPrep application. The three-dimensional crystal structure of HDAC and NF- κ B were downloaded from RCSB Protein Data Bank (PDB) using PDB ID's 7JS8 and 1VKX, respectively. Protein structures were prepared using Protein Preparation Wizard by removing solvent molecules, adding hydrogen atoms and carrying out energy minimization. The docking grids were generated based on binding site of co-crystallized ligand to facilitate the validation of docking parameters. Baicalin was docked using Glide extra-precision (XP) mode. Reference ligands used for NF- κ B and HDAC inhibition are edasalonexent and vorinostat, respectively.

2.3 Cell culture

MIN6 and RIN-5F were purchased from the National Centre for Cell Science (NCCS), Pune, India. MIN6 and RIN-5F were cultured in DMEM (25 mmol/L glucose) and RPMI-1640 (25 mmol/L glucose), respectively, in a humidified atmosphere at 37 °C and 5% CO₂ (carbon dioxide). Both culture media were supplemented with 10% fetal bovine serum (FBS) and 100 U/ml penicillin and 100 µg/ml streptomycin. All the experiments were performed when cells achieved 80% confluency.

2.3.1 Methyl thiazolyl tetrazolium (MTT) assay

RIN-5F were seeded in a 96 well plate at a density of 2×10^4 cells/well and incubated for 72 h to promote cell attachment. MIN6 were seeded in a 96 well plate at a density of 1×10^4 cells/well and incubated for 24 h to facilitate cell attachment. RIN-5F and MIN6 were treated with different concentrations of baicalin (5, 10, 15, 20, and 25 µg/mL) and STZ (2.5mM) followed by 24 h incubation. MTT reagent was added to each well and incubated for 4 h to allow the formazan crystals formation. After incubation, supernatant was removed carefully followed by addition of 150 µL of dimethyl sulfoxide (DMSO) to each well to dissolve the formazan crystals. The absorbance was measured at 570 nm with the help of multimode microplate reader (Guan et al. 2014; Kimani et al. 2024).

2.3.2 Cell Counting Kit-8 (CCK-8)

The experiment was carried out using enhanced cell counting kit-8 (WST-8/CCK8) by following the manufacturer's instructions. In short, RIN-5F cells were seeded in a 96 well plate at a density of 2×10^3 cells/well and incubated for 72 h. After incubation, the cells were administered with baicalin (20 and 25 µg/ml in RIN-5F) and STZ (2.5mM) and incubated for 24 h. MIN6 cells were seeded in a 96 well plate at a density of 2×10^3 cells/well followed by incubation of 24 h. After incubation, the cells were exposed to baicalin (15 and 20 µg/ml), and STZ (2.5mM) according to the respective groups, and incubated for 24 h. After incubation, CCK-8 buffer was added to each well followed by incubation of 3 h. Optical density was determined at 450nm with the aid of multimode reader.

2.3.3 5-Bromo-2'-deoxyuridine (BrdU) incorporation assay

The experiment was carried out using a BrdU cell proliferation assay kit with the help of manufacturer's instructions. Briefly, RIN-5F cells were seeded in a 96 well plate at a density of 2×10^3 cells/well in a 96-well plate and incubated for 72 h followed by the treatment with baicalin (20 and 25 µg/ml) and STZ (2.5mM), and incubation of 24 h. MIN6 cells were seeded in a 96 well plate at a density of 2×10^4 cells/well in a 96-well plate and incubated for 24 h followed by the treatment with baicalin (15 and 20 µg/ml) and STZ (2.5mM) and incubation for further 24 h. After 5 h of treatment, BrdU reagent was added to each well and incubated for 19 h. Followed by the addition of fixative solution to each well and incubation of 30 mins at room temperature. All the wells were washed three times with Tris/Tween plate wash followed by the addition of prediluted anti-BrdU detector antibody and incubation of 1 h at room temperature. All the wells were washed again three times with Tris/Tween plate wash. Peroxidase Goat anti-Mouse IgG was added to every well and incubated for 30 mins at room temperature and final wash was carried out as described above. Stop solution was added to all the wells to stop the reaction, and optical density was measured at 450nm with the help of multimode reader.

2.3.4 Insulin Secretion Assay

RIN-5F cells were seeded in a 96 well plate at a density of 2×10^5 cells/well in a 24-well plate, incubated for 72 h followed by the treatment with baicalin (20 and 25 µg/ml in RIN-5F) and streptozotocin (2.5mM), and incubation of 24 h. MIN6 cells were seeded in a 96 well plate at a density of 2×10^5 cells/well in a 24-well plate and followed by incubation of 24 h to and notably, both the cell lines were cultured in high glucose media. MIN6 were Treated with baicalin (15 and 20 µg/ml), and STZ (2.5mM) and incubated for further 24 h. Further, supernatant was collected from each well to assess the insulin level. Insulin secretion was evaluated using an insulin ELISA kit according to the manufacturer's protocol.

2.4 Statistical Analysis

The results were assessed using one-way ANOVA with post hoc Tukey's multiple comparison test. P values <0.05 were considered statistically significant. The data are represented as Mean $\pm$ SD.

3. Results

3.1 In silico study for the identification of respective targets

To identify the target towards which baicalin have the highest binding affinity, molecular docking was performed using GLIDE, within the Schrödinger software suite.

3.1.1 Interaction of ligands with NF- κ B

Docking results revealed that baicalin strongly bind to the active site of NF- κ B with binding affinities of -5.8

Table 1: Docking score and amino acid interaction of baicalin with NF- κ B

S. No.	Ligand	Docking Score	Protein	H-bond Interaction
1	Baicalin	-5.881	NF- κ B	Glu 89, Gln 132, Gln 119, Lys 37
2	Edasalonexent (standard)	-4.891	NF- κ B	Glu 89, Asp 97

3.1.2 Interaction of ligands with HDAC

Docking scores suggested that baicalin bind to the active site of HDAC with binding affinities of -6.4 kcal/mol. Moreover, the re-docking of the protein (HDAC) with the reference ligand (vorinostat) in the active site reveals that

Table 2: Docking score and amino acid interaction of baicalin with HDAC

S. No.	Ligand	Docking Score	Protein	H-bond interaction
1	Baicalin	-5.881	HDAC	-
2	Vorinostat (standard)	-4.891	HDAC	Asp 100

3.2 The effect of baicalin on STZ-induced cytotoxicity

To mimic the effects of diabetes, oxidative stress and apoptosis were triggered by STZ in RIN-5F and MIN6. The effect of baicalin on cytotoxicity was evaluated using MTT assay and results represented as cell viability. Baicalin has significantly augmented the cell viability as compared to STZ alone as shown in Figure 3. Baicalin

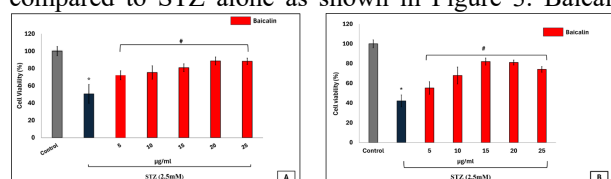


Figure 3. The effect of baicalin on STZ-induced cytotoxicity in RIN-5F (A) and MIN6 (B). The results

3.3 The effect of baicalin on cell viability

The effect of baicalin on cell viability was evaluated with the help of CCK-8 assay. STZ (2.5 mM) significantly reduces the cell viability in RIN-5F and MIN6 in comparison to the control. It is to be noted that baicalin

kcal/mol, which is comparable to that of edasalonexent (-4.8 kcal/mol). Moreover, baicalin formed a hydrogen bond with Glu 89, Gln 119, Lys 37, Gln 132 with the active site of NF- κ B, as shown in Table 1. The reference ligand edasalonexent was re-docked into the active site of NF- κ B and found to occupy the same binding pocket as baicalin, as shown in Figure 1.

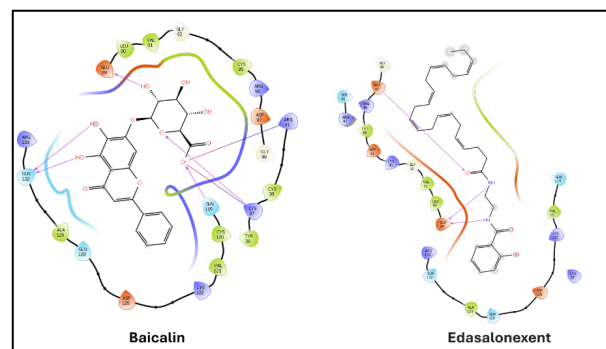


Figure 1: Ligplot of baicalin and edasalonexent with the binding site of NF- κ B. (Docking results revealed that baicalin strongly bind to the active site of NF- κ B and forms a hydrogen bond with Glu 89, Gln 132, Gln 119, Lys 37).

the binding pocket for vorinostat is the same as for baicalin as shown in Figure 2. However, the interaction of the protein with baicalin is not as strong as compared to vorinostat, as shown in Table 2. Thus, we concluded that baicalin has strong binding affinity for NF- κ B inhibition.

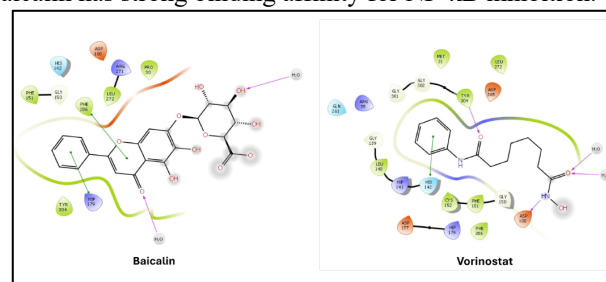


Figure 2 Ligplot of baicalin and vorinostat with binding site of HDAC.

increased cell viability to 88% in STZ exposed cells. Moreover, in MIN6, baicalin significantly increased the cell viability to 82% in STZ exposed cells. In RIN-5F, baicalin exhibits highest cell viability at two concentrations, 20 and 25 μ g/ml. In MIN6, baicalin exhibits highest cell viability at 15 and 20 μ g/ml. Further assays were performed at these doses.

are presented as cell viability expressed as a percentage. Statistical differences between groups were analyzed by one-way ANOVA and Tukey's multiple comparison test. Data is expressed as mean $\pm$ SD for 3 independent experiments, whereas * p <0.05 as compared with control, p <0.05 as compared to STZ alone.

significantly improved cell viability as compared to STZ alone, as shown in Figure 4.

3.4 The effect of baicalin on β -cell proliferation

Effect of baicalin on β -cell proliferation was carried out by BrdU incorporation assay. BrdU is inserted into the newly

synthesized DNA instead of thymidine thus it is an indicator of actively proliferating cells. It was detected immunochemically and used to analyze the percentage of cells that are actively proliferating. STZ-induced cytotoxicity significantly reduced the cell proliferation rate as compared to the control. Baicalin has significantly increased the percentage of dividing cells as compared to STZ alone in both the cell lines (Figure 5).

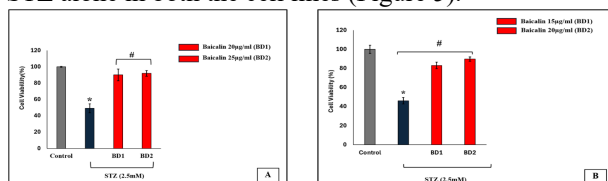
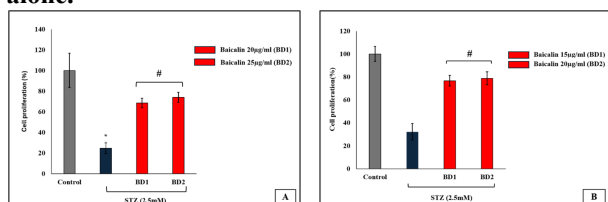


Figure 4. The effect of baicalin on cell viability in RIN-5F (A) and MIN6 (B). The results are presented as cell viability expressed as a percentage. Statistical differences between groups were analyzed using one-way ANOVA and post hoc Tukey's multiple comparison test. Data is expressed as mean $\pm$ SD for 3 independent experiments, whereas * p <0.05 as compared with control, p <0.05 as compared to STZ alone.



4. Discussion

T2DM is one of the prevalent disease and currently available treatments for the management of T2DM are associated with adverse effects and mostly fail to provide adequate glycemic control in all patients. However, despite the therapies, T2DM continues to progress leading to substantial loss of pancreatic β -cells and their function eventually requiring supplementation with insulin. According to previous studies, HDAC inhibition results in the enhanced proliferation of pancreatic β -cell and insulin secretion. Moreover, there is evidence that HDAC inhibition can also reduce cytokine associated apoptosis in pancreatic islets^{2-5,12}. NF- κ B is a key transcription factor involved in inflammatory signaling and associated with inflammation induced β -cell destruction. Previous studies have shown that inhibition of NF- κ B pathway may result in the protection of β -cell and reduction in their apoptosis, highlighting its potential as a target for preserving β -cell mass and providing favorable condition for their proliferation⁶⁻⁷. Moreover, there are reports revealing the potential role of baicalin in the inhibition of HDAC and NF- κ B, indicating their significance in β -cell survival and function⁶⁻⁷. Based on these evidences, baicalin was further evaluated for its role in the β -cell survival, proliferation and function.

The present study assessed the binding affinity of baicalin towards HDAC and NF- κ B and explored their effects on β -cell protection, proliferation and function in pancreatic cell lines, RIN-5F and MIN6. Molecular docking reveals that baicalin binds strongly to the active site of NF- κ B with the

3.5 The effect of baicalin on insulin secretion

The effect of baicalin on insulin was evaluated in RIN-5F and MIN6. Treatment with reduced insulin secretion in comparison to control. Notably, that baicalin (20 and 25 μ g/ml) significantly enhanced insulin secretion in RIN-5F in comparison to STZ alone. Similarly, baicalin (15 and 20 μ g/ml) has augmented the insulin secretion in MIN6 as shown in Figure 6.

Figure 5. The effect of baicalin on cell proliferation rate in RIN-5f (A) and MIN6 (B). The results are presented as cell proliferation rate expressed as percentage. Statistical differences between groups were analyzed using one-way ANOVA and Tukey's multiple comparison test. Data is expressed as mean $\pm$ SD for three independent experiments whereas * p <0.05 as compared with control, p <0.05 as compared to STZ alone.

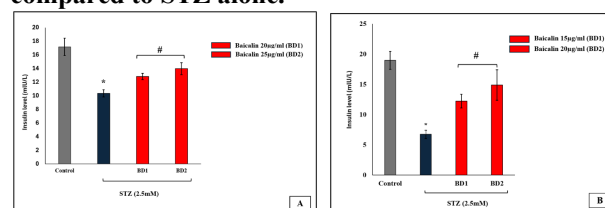


Figure 6. The effect of baicalin on insulin secretion in RIN-5f (A) and MIN6 (B). Statistical differences between groups were analyzed using one-way ANOVA and Tukey's multiple comparison test. Data is expressed as mean $\pm$ SD for 3 independent experiments, whereas * p <0.05 as compared with control, p <0.05 as compared to STZ alone.

binding energy of -5.8kcal/mol which is comparable to its standard (edasalonexent) (-4.8kcal/mol). Redocking with edasalonexent showed that it occupies the same binding pocket as baicalin supporting its significant interaction with NF- κ B. Although baicalin also showed interactions with HDAC, its binding energy was found to be lower than reference standard (vorinostat) suggesting weaker interaction with HDAC because more negative binding energy is a suggestive of stronger interaction with the protein¹⁴. Moreover, two-dimensional interaction showed that baicalin formed a hydrogen bond with Glu 89, Gln 119, Lys 37, Gln 132 of NF- κ B binding pocket. Hydrogen bond is a suggestive of specific positioning of ligand within the active site of ligand and stabilization protein-ligand complex¹⁵. More negative binding energy and hydrogen bond interaction of baicalin with NF- κ B indicates that baicalin has more binding affinity towards NF- κ B than HDAC. These findings suggested that baicalin may have a positive effect on β -cell protection, proliferation and function probably through potential modulation of NF- κ B. Previous studies reported that baicalin is responsible for modulation or inhibition of NF- κ B using experimental methods such as western blotting providing additional support to the docking findings of the present study¹².

Furthermore, the effects of baicalin on β -cell protection, proliferation and function were evaluated in RIN-5F and MIN6. To mimic cellular injury associated with diabetes in β -cell, streptozotocin (STZ) was introduced to induce cytotoxic stress in both the cell lines. STZ is a widely known alkylating agent, specifically toxic to pancreatic β -

cell and can induce oxidative stress, metabolic dysfunction and impaired cellular metabolism eventually resulting in β -cell destruction and loss. Additionally, STZ is approved by FDA to administer as chemotherapeutic agent in metastatic pancreatic carcinoma. Due to its destructive effects on pancreatic β -cell it is widely employed in the induction of diabetes in experimental animals and to induce β -cell injury in cell culture models¹⁶⁻¹⁸. MTT assay was used to study the effect of baicalin on cytotoxicity, STZ successfully induced cytotoxicity in both the cell lines, RIN-5F and MIN6.

According to the MTT results, baicalin was found to protect the β -cell from STZ induced cytotoxicity as compared to cell exposed to STZ alone. These results were supported by CCK-8 findings as the baicalin has significantly improved cell viability. STZ exposure leads to increase in the oxidative stress thereby increasing production of reactive oxygen species (ROS) thus initiating inflammatory signaling and potentially activating NF- κ B directly or indirectly. The anti-inflammatory and NF- κ B modulating properties of baicalin may be associated with the reduced cytotoxicity and improved cell viability¹⁹⁻²⁰. The effect of baicalin on cell proliferation was investigated by BrdU incorporation assay. BrdU is inserted into newly synthesized DNA during S phase of cell cycle instead of thymidine and therefore it acts as an indicator of actively proliferating cells. STZ significantly reduced the cell proliferation because STZ found to be associated with β -cell destruction and thus altering proliferation. However, treatment with baicalin was found to increase the BrdU incorporation in comparison to STZ alone suggesting baicalin is associated with increased cell proliferation rate. Collectively, the results of cytotoxicity, cell viability and proliferation indicate that baicalin fosters the favorable cellular environment for the β -cell survival and proliferation. To confirm that newly proliferated cells are functional or not, insulin secretion assay was carried out. Interestingly, the findings of this assay supported the proliferation results and baicalin was found to increase the insulin secretion as well.

Conclusion

In conclusion, docking analysis provided insights into the probable mechanism responsible for beneficial effects of baicalin on β -cell survival, proliferation and function by showing strong interactions of baicalin with NF- κ B. Cell culture studies demonstrated that baicalin has significantly protected β -cell from STZ induced cytotoxicity and has improved proliferation rate and insulin secretion probably through potential NF- κ B modulation. However, further investigation involving animal diabetic models are warranted to validate these results and confirm underlying mechanism.

Declaration of Competing Interest

The authors declare no competing interests that are relevant to the content of this manuscript.

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