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Human Pancreatic β Cell Regenerative Therapy: Exploring the Role of Chicoric Acid as a Phytochemical Candidate

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ABSTRACT

Diabetes is a global health issue, impacting life expectancy and productivity. Pathogenesis of diabetes mellitus involves decreased functional beta cells, making beta cell replacement and regeneration a crucial area of research. However, current methods like whole pancreas transplant or stem cell-derived beta cells have limitations for diabetic patients. Exploring pharmacological approaches to stimulate regeneration of residual beta cells is valuable, as many diabetic patients retain some beta cells. Finding drugs that target and regenerate these cells effectively is a challenge, with no approved options available currently. Nature provides several therapeutic agents, and chicoric acid (CA) found in medicinal plants like *Cichorium intybus*, and shows potential for beta cell regeneration. *Cichorium intybus* possesses antioxidants, phenolics, and flavonoids, aiding its antidiabetic activity by targeting hyperglycemia, oxidative stress, inflammation, and hyperlipidemia. CA's multifaceted effects on glucose homeostasis are attributed to its involvement in various interconnected processes and pathways. This comprehensive review explores the molecular-level mechanisms through which chicoric acid facilitates beta cell regeneration, insulin release, and glucose uptake. The findings suggest that chicoric acid holds promise as a phytochemical agent for diabetes prevention and treatment. Its natural origin, antidiabetic properties, and multi-dimensional effects make it a potential candidate. Hence, further research to fully elucidate the efficacy and safety of chicoric acid for β cell regeneration as an antidiabetic agent is essential. In summary, this extensive review at the molecular level, concludes that chicoric acid is a phytochemical with great antidiabetic potential and may be indicated both as a preventive and therapeutic agent.

Keywords: β cell regeneration, Diabetes mellitus, Chicoric acid, Phytochemicals, Insulin release, Glucose uptake.

INTRODUCTION

Hyperglycaemia is a major characteristic of diabetes mellitus caused due to impairment in carbohydrate metabolism, either because the pancreas cannot secrete adequate insulin (type 1 diabetes mellitus, T1DM) or the insulin cannot be utilised properly by the body (type 2 diabetes mellitus, T2DM)). Insulin secreted by pancreatic β-cells is an anabolic hormone that is vital in controlling the blood sugar levels. T2DM is commonly referred to as non-insulin dependent diabetes mellitus, or adult-onset diabetes, that includes people with insulin resistance and relative insulin deficiency. However, these patients do not need insulin administration for treatment and survival. Decreased functional beta-cells being the basic abnormality in both type 1 and type 2 diabetes mellitus, their replacement and regeneration is currently the key potential area where scientific community is focusing for the management of diabetes mellitus. Many patients with T2DM suffer from obesity which is also associated with insulin resistance. Moreover, non-obese T2DM patients present with central obesity comprising of high body fat distribution in the abdominal region [1]. This category of patients accounts for 90-95 % of all diabetic patients [2]. Diabetes is a global problem which kills and disables people at their most productive age, reducing the life expectancy. Diabetes is a common threat with no country immune to it. It has an epidemic prevalence which is expected to continue. It is among the top 10 causes of death globally. The current guideline for medical management of T2DM comprises of pharmacological treatment with nine classes of antidiabetic drugs.

Natural products of plant origin have been used for therapeutic and preventive purpose since times immemorial. Natural products are the cornerstone of ancient medicine systems such as; Ayurveda, Unani, Egyptian and Chinese. These traditional medicine systems are even currently being practised as Alternative & Complimentary Medicine (ACM). According to World Health Organization, the primary health care needs of 75% of the world population are still met by the plant-based traditional medicine. Nature has been a rich source of products with medicinal value.

Many essential modern medications have been obtained from natural sources such as; morphine from *Atropine* from *Atropa belladonna*, *Papaver somniferum*, vincristine from *Vinca rosea*, Taxol from *Taxol brevifolia*, etc. [3]. In recent times the researchers across the globe have again shifted focus on the natural products for management of chronic and refractory health issues. Lot of research is being conducted to generate evidence and validate the claim of these natural products possessing antidiabetic, anti-inflammatory and antioxidative activities.

Cichorium intybus L. is a perennial plant which grows easily in different cultivation conditions, in North West India (Kashmir, Punjab, Andhra Pradesh, Gujarat, Maharashtra and Karnataka), and in other countries such as Persia, Baluchistan, Waziristan, West Asia, France, Belgium, Germany, Netherlands, Switzerland, the United Kingdom and South Africa [4]. The blue or white flowered plant has been used in Unani, Ayurveda and Siddha systems of medicine due to its huge medicinal potential in treatment of renal and hepatobiliary disorders [5]. This medicinal herb has shown anti-diabetic [6–8], anti-inflammatory [9], antioxidant [10], and antihepatotoxic activities [11]. The phytochemicals analysis of *Cichorium intybus* seeds using the ultra-performance liquid chromatography-mass spectrometry has interestingly revealed that chicoric acid is the one of the major metabolites present in the aqueous extract of *Cichorium intybus* [12]. We have carried out the docking analysis of the phytochemicals present in *Cichorium intybus* with the GLUT 4 receptor and detail is as follows:

1. Docking analysis of phytochemicals present in *Cichorium intybus* with GLUT 4 receptor:

Chicoric acid, quercetin, oleic acid, 2,6-dihydroxyflavone, margaric acid, 11,13-dihydroxy lactucin, linoleic acid, palmitic acid and coumarin are the major phytochemicals present in *Cichorium intybus* seeds [13].Docking strategies are pivotal and effective tools in the design and development of molecules, aiding in the estimation of interactions between natural ligands and receptors to predict affinity and biological activity. In this study, molecular docking was conducted on naturally active molecules (phytochemicals) with diverse scaffolds against the GLUT-4 (Glucose transporter 4) target, a key player in the diabetes process. The Glide Extra Precision (XP) Maestro 10.1 Schrodinger software, operating on a Linux 64 operating system, was employed for the docking simulations. The 2D structures of the natural compounds were initially generated and then converted into their corresponding 3D structures using LigPrep. The X-ray crystal structure of GLUT-4 bound to an inducer (PDB ID: 3PCU, Resolution: 2.0 Å) was obtained from the RCSB Protein Data Bank (www.rcsb.org). The protein underwent processing through the Protein Preparation Wizard, and a grid was established for the co-crystal ligand by adopting receptor grid generation. Water residues beyond 5 Å were eliminated to refine the system. Subsequently, the target protein underwent optimization through the assignment of hydrogen bonds and energy minimization using the OPLS 2005 force field. The docking poses of the natural ligands (phytochemicals), specifically the inducer of GLUT-4, were rigorously examined along with their binding interactions and summarized in Table 1. The estimated free energy of ligand–protein interaction (phytochemicals vs GLUT4) was found <−5.0 that revealed a significant interaction. The docking score of chicoric acid with GLUT 4 was found -10.013 and it showed the antidiabetic potential of chicoric acid. Docked Pose of chicoric acid (A), palmitic acid (B), quercetin (C), oleic acid (D), coumarin (E), margaric acid (F), 2,6-dihydroxyflavone (G), 11,13-dihydroxy lactucin (H), linoleic acid (I) and co-crystal (J) represented as turquoise ball and stick in the binding site of GLUT-4 showing hydrogen bond interaction with amino acid (Figure 1). With all the traditional and scientific claim regarding the use of *Cichorium intybus* in diabetes mellitus and the promising antidiabetic evidences of Chicoric acid, we have compiled a comprehensive review discussing the various mechanisms for beta cell regeneration, insulin release and glucose uptake by Chicoric acid.

Table 1: The interaction of phytochemicals of *Cichorium intybus* seeds with GLUT 4 receptor

S. No	Ligands	Docking scores	Interacting amino acids
1	Chicoric acid	-10.013	Asn 306, Ala 271, Ala 327, Arg 316 Leu 325, Phe 346 and Ile 345
2	Quercetin	-10.924	Cys 432, Leu 309, Ala 327, Arg 316, Phe 313 and Val 342.
3	Oleic acid	-10.239	Ala 327 and Thr 328
4	2,6-dihydroxyflavone	-9.518	Leu 309, Arg 316, Ala 327 and Phe 313
5	Margaric acid	-8.949	Arg 316, Ala 327 and Thr 328
6	11,13-dihydroxy	-8.840	Ile 310 and Ile 268
7	Linoleic acid	-8.595	Arg 316, Ala 327 and Thr 328
8	Palmatic acid	-8.192	Arg 316, Ala 327 and Thr 328
9	Coumarin	-7.584	Arg 316, Ala 327 and Phe 313
10	Co-crystal	-8.831	Leu 309, Ala 327 and Arg 316

Docking score <-5.0 is the significant interaction between phytochemicals and GLUT 4.

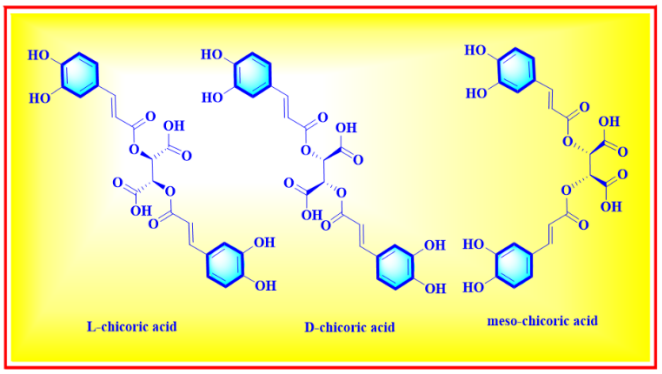

Figure 1: Optical structure of Chicoric acid

3. Chicoric Acid; structure, chemistry, and isomers

Chicoric acid is a caffeic acid derivative, soluble in methanol, ethanol, dioxane, acetone, and hot water. It is slightly soluble in ether and ethyl acetate, and completely insoluble in benzene, ligroin and chloroform [14]. The molecular formula of Chicoric acid is C22H18O12 and with presence of two chiral carbon atoms it is geometrically found in three confirmations i.e. dextrorotatory-chicoric acid (D-chicoric acid), laevorotatory-chicoric acid (L-chicoric acid) and meso-chicoric acid (meso-chicoric acid) [Figure 2] [15]. L-chicoric acid [i.e., (-)-chicoric acid, 2,3-dicaffeoyl-L-tartaric acid, 2,3-O-dicaffeoyltartaric acid, 2R,3R-O-dicaffeoyltartaric] is the most abundant, widely distributed and present in many plant species

[16]. These chicoric acid molecules occur either as the naturally prevalent *RR*-chicoric acid, or the less prevalent *RS*-chicoric acid (*RS*-CA), also known as *meso*-chicoric acid i.e., Di caffeoyl-meso-tartaric acid or di-E-caffeoyl-(2R-3S) -(-)-tartaric acid)[17].

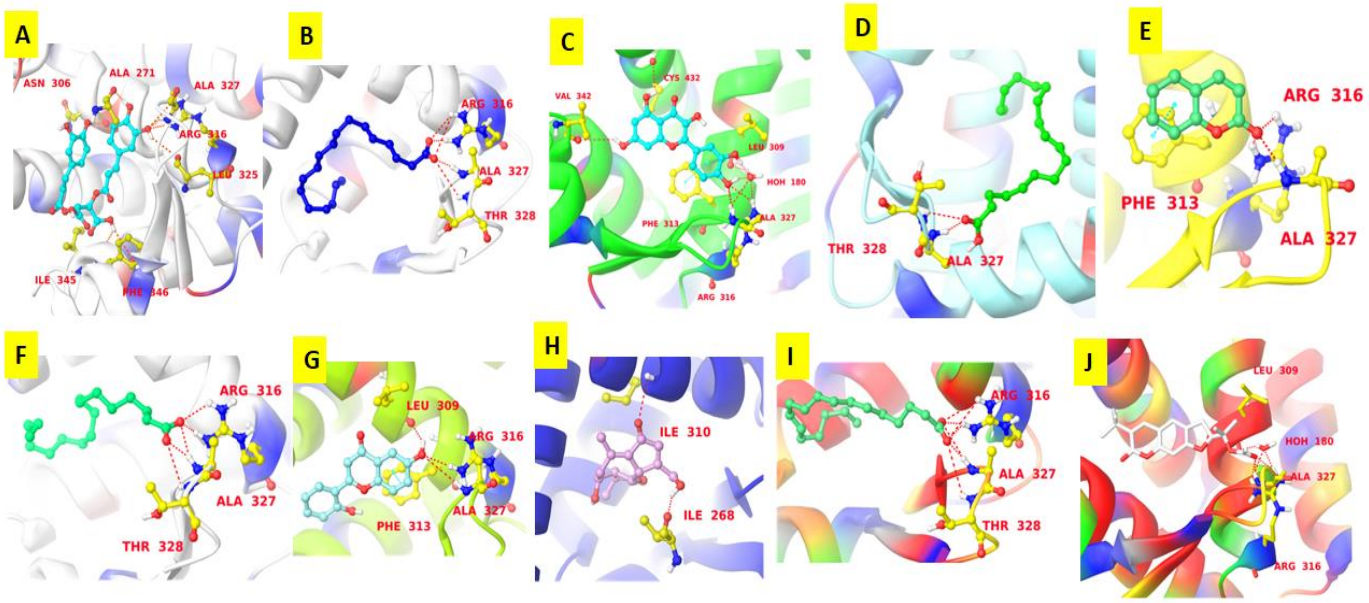

Figure 2: Docked Pose of chicoric acid (A), palmitic acid (B), quercetin (C), oleic acid (D), coumarin (E), margaric acid (F), 2,6-dihydroxyflavone (G), 11,13-dihydroxy lactucin (H), linoleic acid (I) and co-crystal (J) represented as turquoise ball and stick in the binding site of GLUT-4 showing hydrogen bond interaction with amino acids. The red dash lines denote the hydrogen bonds and the amino acids are represented as yellow ball and stick.

4. Beta cells regeneration and potential application in management of diabetes mellitus

The decreased functionality of beta-cells is now considered to be the most significant pathology in both type 1 and type 2 diabetes. In type 1 diabetes the reduction of beta cell mass due to autoimmune destruction as well as de-differentiation is an established fact [18]. However, in type 2 diabetes mellitus (T2DM), many evidences reflect that the decrease beta cell mass is due to the prolonged insulin resistance and/or impaired beta cell function [19]. Hence, both the diabetic conditions (T1 and T2DM) may have absolute or relative insulin insufficiency. The lipotoxicity, glucotoxicity and/or endoplasmic reticulum (ER) stress induced beta cell de-differentiation [20] and genetic predisposition to reduced level of beta cell population and/or diminished beta cell function [21] are the two possible reasons for relatively reduced beta cells in T2DM patients. With this background, beta cell replacement/regeneration is the future area of research and therapy for diabetes mellitus. The beta cells can be replaced either by transplant of pancreas or isolated human islets [22] or by stem cell-derived beta cells [23]. However, this process has a huge limitation (i.e. cost, donor, practical feasibility) for its use in diabetic patients. Presence of residual beta cells has been found in many diabetic patients, it will be interesting to explore alternate pharmacological strategies to target these residual beta cells for regeneration and normal functioning. Currently, none of the drugs is approved yet for the regeneration/expansion of these residual beta cells. In the present review we are elucidating the potential gene/protein targets for beta cells regeneration/replication and discussing the possible affinity of chicoric acid with these target (s).

5. Dual-specificity tyrosine-regulated kinases (DYRK1A) induced beta cell replication

DYRK1A is a member of protein kinases that belongs to the CMGC (MAP kinases, CDKs, CDK-like kinases and GSKs,) class of kinases. Its gene is found at the 21q22.2 region of human chromosome and has attracted attention due to its association with various type of clinical disorders [24]. Annes et al, in 2012 reported for the first time that DYRK1A inhibitor caused induction of beta cell proliferation and 5-iodotubericidin replication of rodent and porcine beta cells [25]. Various research groups have demonstrated that multiple DYRK1A inhibitors such as leucettine- 41, harmine, etc., induce the replication of human beta cells at rates of 2-3%. It is also validated that proliferation of human beta cell can be stimulated by silencing the DYRK1A gene expression directly in human islets [26–32]. The transcription factors of Nuclear Factor activated in T-cells (NFaT) family commonly residing in cytoplasm are also vital in beta cell proliferation [33]. Subsequent to presence of glucose, GLP1 receptor agonists or sulfonylureas, calcium enters in to beta cells and activates the calmodulin protein and thereafter the phosphatase calcineurin. The activated calcineurin dephosphorylates the NFaTs that allows their entry in the nucleus and binding with their target genes such as cyclins and cyclin dependent kinases (e.g., cyclin A, cdk1, cyclin E). Thus, preventing the cell cycle inhibitors genes such as p57KIP2, p15INK4, etc from being expressed. The overall cascade of this gene pathway leads to increased proliferation of beta cells. Interestingly, DYRK1A in this process rephosphorylates the nuclear NFaTs forcing their exit from the nucleus, thus terminating their mitogenic signalling [32,34,35]. Hence, it can be inferred that DYRK1A suppresses the beta cell proliferation and its inhibitor may be a potential candidate for beta cell regeneration. In a study by Zhu et.al., chicoric acid was documented to play a vital role in β-cell protection, which was correlated with its role in modulation of apoptosis related-genes, such as; pancreatic duodenal homeobox 1 (PDX-1), B-cell lymphoma 2-associated X/B-cell lymphoma 2 (Bax/Bcl-2) ratio, and c-Jun N-terminal kinase (JNK) [36]. Further, the transforming growth factor (TGF) beta superfamily, comprising of over 30 members including Activins, Nodals, etc., has also been found to be involved in beta cell replication [37]. It is reported that inhibition of only TGF beta has little or no effect on proliferation of human beta cells, whereas the

inhibition of both TGF beta and DYRK1A in combination leads to significant increase in proliferation of adult human beta cells [38].

6. Modulation of glucose metabolism by chicoric acid

Chicoric acid, a caffeoyl derivative is also recognized as a modulator of cellular processes involved in glucose metabolism. CA is reported to critically facilitate in overcoming insulin resistance by increasing basal glucose uptake and secretion of insulin[39].

6.1. Role of chicoric acid in insulin resistance

Insulin resistance is marked by the inability of insulin to adequately regulate the glucose and lipid metabolism [40]. Insulin maintains glucose homeostasis by facilitating glucose uptake in skeletal muscles and inhibiting production of glucose in liver [41]. At the molecular level, insulin resistance is characterized by mitochondrial dysfunction in skeletal muscle and liver [41]. Mitochondria are cellular organelles associated with regulation of cellular respiration and adenosine triphosphate (ATP) generation through concurrent energy pathways such as oxidative phosphorylation (OXPHOS), β-oxidation of fatty acids and tricarboxylic acid (TCA) cycle [40,42]. Insulin resistance has also been correlated with decreased mitochondrial size and density [43], decreased mitochondrial number and function [41] decreased expression of mitochondrial genes and lower levels of mitochondrial DNA (mtDNA), in the skeletal muscles and liver of patients with T2DM. Severe insulin resistance is reported to be associated with decreased mitochondrial oxidative activity and ATP synthesis [44]. Mitochondrial dysfunction is proposed to be mediated by various regulators of mtDNA, such as decreased expression of nuclear respiratory factor (NRF), peroxisome proliferator-activated receptor gamma coactivator 1α (PGC-1α), and mitochondrial transcription factor A (TFAM) [45]. It is postulated that interventions that amend the mitochondrial dysfunction will help overcome the insulin resistance [40]. CA has been documented to ameliorate obesity-induced insulin resistance, both in vitro and in vivo, by enhancing mitochondrial function and biogenesis [46]. Furthermore, CA supplementation is found to significantly increase the mitochondrial content through the increased expression of TFAM, NRF-1, PGC-1α and NRF-2; as well as increase the mitochondrial enzyme actions such as Complex I from OXPHOS and citrate synthase from TCA cycle [46,47]. As already elucidated, PGC-1a enhances the expression of genes for antioxidant enzymes, hence the effect of CA on SOD and GPx activities and/or expression may be attributed to its effect on expression of PGC-1a [48].

6.2. Role of chicoric acid in insulin signalling cascade

Insulin receptor substrate (IRS)/PI3K/ AKT signaling cascade, is reported to regulate the nutrient and metabolic homeostasis. It is documented that activated AKT induces protein and glycogen synthesis through mammalian target of rapamycin (mTOR) and its various downstream effectors. In skeletal muscle and adipocytes, which have cells expressing GLUT4, activation of AKT and AMPK has been associated with increased glucose uptake [47].Further, PI3K/AKT signal activation is found to be critical for insulin-induced GLUT4 translocation which results in glucose uptake in the skeletal muscles [49]. However, molecular studies have established that CA increases the activation of AKT and mTOR phosphorylation by insulin [50]. It is noteworthy that fatty acids have been associated with decreased IRS-PI3K, inhibiting the glucose transport which translates into insulin resistance [51]. CA has also been documented to significantly improve glucose uptake and increase expression of p-AKT, PI3K and p-p70S6K in C2C12 myoblasts having fatty acid induced insulin resistance [50]. Yet another study has revealed that CA ameliorates hyperglycemia and dyslipidemia in high-fat diet (HF)-fed mice as well as lowers their homeostatic assessment of insulin resistance (HOMA-IR) [52]. Ghamarian et al. have revealed in their study that chicory seeds are significantly decrease fasting blood glucose (FBS) and prevent the weight loss [53]. They further demonstrated other beneficial effects such as; decrease triacylglycerol (TG), total cholesterol (TC), aminotransferase (ALT), glycosylated hemoglobin (HbA1c), as well as increase NO concentration. The study results imply that chicory seeds have both short-term effects (2 h glucose tolerance test), ability to slow down the progression of diabetes; as well as long-term effects, delay the occurrence of complications [53]. Recently, protein tyrosine phosphatase 1B (PTP1B) has been studied for its negative regulation of insulin signalling pathway through insulin receptor kinase inhibition. Molecular docking studies have revealed existence of interactions between chicoric acid and the allosteric site of PTP1B, suggesting inhibition of PTP1B by chicoric acid and amplifying the activation of insulin signalling pathway*.

6.3. Role of chicoric acid in energy metabolism

AMPK is a heterotrimeric Ser/Thr kinase, which is also called the ‘‘metabolic master switch’’ because it acts as a cellular energy sensor [54]. The activation of AMPK is induced through Thr172 phosphorylation, which in turn is mediated by two upstream kinases; the AMPK kinases liver kinase B1 (LKB1) and the calcium/ calmodulin-dependent protein kinase kinase (CaMKK). LKB1 is stimulated by rise in AMP/ATP ratio while CaMKKb is activated by a rise in Ca2+ level within the cells. The major metabolic effects of activated AMPK are: (a) glycemic regulation by stimulation of glucose uptake and inhibition of hepatic glucose production [55]; (b) enhanced fatty acid b-oxidation by inhibition of acetyl-CoA carboxylase (ACC) which inturn depends on Ser-79 phosphorylation, resulting in decreased malonyl-CoA levels and stimulation of carnitine palmitoyl transferase I (CPT1) [56]; (c) improved mitochondrial function by stimulation of mitochondrial synthesis and prevention of oxidative stress [57]and (d) inhibition of mammalian target of rapamycin (mTOR) pathway [58]. AMPK pathway dysfunction is known to be a major factor related to metabolic disorders especially type 2 diabetes and metabolic syndrome, involving lipid accumulation and resistance to insulin [59]. Hence, AMPK is one of the most studied therapeutic targets for metabolic syndrome and type 2 diabetes mellitus [59]. It is documented to be activated by metformin, a major antidiabetic agent, as well as by antidiabetic polyphenols such as resveratrol [60] or epigallocatechinegallate (EGCG) [61]. CA is also reported to regulate the response to hepatocyte injury response and the glucose levels in diabetic mice through AMPK pathways [62]. Interestingly, CA is also found to increase PGC-1a mRNA expression, which is attributed to activation of AMPK pathway by AICAR which in turn leads to high PGC-1a expression [5]. In a study by Schlernitzauer et.al. CA was reported to activate the AMPK pathway that further resulted in (a) enhanced superoxide dismutase (SOD) and glutathion peroxidase (GPx) activity, resulting in improved oxidative enzymatic defence, (b) augmentd MnSOD protein expression, providing mitochondria protection against oxidative damage, (c) increase in complex II and citrate synthase activity, and up-regulation of PGC-1a mRNA expression, culminating to increased mitochondrial biogenesis and (d) inhibition of insulin/Akt/mTOR pathway [47]. However, conflicting effects on glucose uptake have been reported with polyphenolic compounds. On one hand, Minakawa et. al.,[63] have reported

increased AKT and AMPK phosphorylation and glucose uptake in the absence of insulin, in L6 myotubes by resveratrol. Whereas, in a study by Robb et.al., caffeic acid phenethyl ester (CAPE) was found to increase AKT activation and glucose uptake in the presence of insulin, in L6 muscle cells, through the AMPK pathway [64].

In addition, literature review also reveals that CA treatment in mice enhances the expression of hepatic glycolytic (glucokinase, GK and phosphofructokinase, PFK) and gluconeogenic (glucose 6 phosphotase, G6Pase and phosphoenolpyruate carboxykinase, PEPCK) genes which regulate the glucose homeostasis [65]. GK is the key enzyme in regulation of glucose uptake in hepatocytes which is sensitive to glucose concentration. Whereas, G6Pase de-phosphorylates glucose 6-phosphate in the last step of gluconeogenesis and glycogenolysis [65]. Thus, in CA-treated mice, decreased liver G6Pase and PEPCK, resulting in suppression of gluconeogenesis, and increased liver GK and PFK, thereby facilitating glucose usage, are expected to improve hepatic insulin sensitivity. Azay-Milhau et.al., reported that chicoric acid (leafy extracts of basil or echinacea) decreased the streptozotocin induced-hyperglycemia in a landmark in- vivo study in mice [66]. Further, another study revealed that chicory extract decreased the glucose-6-phosphatase levels, both in early or late phase of diabetes, in contrast to the control group [67]. It is thus postulated that decreased liver G6Pase activity may control the glucose synthesis resulting in decreased glucose levels in chicory extract fed rats.

7. Antioxidant and anti-inflammatory effect of chicoric acid

Chicoric acid is also a documented potent antioxidant exhibiting its action by restricting the collection of reactive oxygen species as well as production of metabolic cytokines, such as interleukin 6, tumor necrosis factor-α and nitrogen oxide [68]. Chicoric acid has been found to modulate the pro-inflammatory cytokines known to be associated with impairment of glucose homeostasis [69], proposing yet another mechanism for regulating glucose levels. The mechanisms involved in regulation of inflammatory responses also include regulation of mitogen-activated protein kinase (MAPK), COX-2, NF-κB and cAMP response element binding protein (CREB) [68].

Multiple inter-connected processes and pathways complimentary to each other are involved in regulation of glucose homeostasis, which may explain the multi-dimensional effects of CA as an anti-diabetic agent. This extensive review at the molecular level recognises the potential of chicoric acid as an antidiabetic-phytochemical which may be proposed both as a preventive and therapeutic agent.

8. Elucidation of positive effects of chicoric acid in pancreatic β Cell Regeneration

The proposed targets of chicoric acid are illustrated in figure 3 (A) in which we have hypothesized that these factors/genes are the probable targets of the chicoric acid in modulating beta cell regeneration. DYRK1A is a member of protein kinases and may be targeted by chicoric acid for beta cell regeneration. There are reports that inhibition of DYRK1A gene/protein induces the beta cell replication [25] [26–32]. The factors associated with transcription of Nuclear Factor activated in T-cells (NFaT), commonly residing in cytoplasm in phosphorylated form, get dephosphorylated in response to their activators and then translocated to the nucleus for the synthesis of cyclin and their dependent kinases leading to beta cell replications [33]. Further, DYRK1A also rephosphorylates the NFaTs residing in the nucleus, which results in driving them out of the nucleus and abolishing their mitogenic signalling [32,34,35]. It is noteworthy that chicoric acid might play a role in the inhibition of DYRK1A which needs to be established scientifically. Chicoric acid may also induce human β-cell proliferation by suppressing the inhibitor of nuclear factor kappa-B kinase subunit epsilon (IKK-ε), translating into inhibition of nuclear factor kappa-B (NFκB). Additionally, it modulates the ErbB3-binding protein 1 (EBP1) which is an inhibitor of cellular replication leading to augmentation of E2F1-mediated cell proliferation. There are reports that β-cell replication is augmented by the inhibition of TGF-β. The signal transduction by TGF-β receptor is possible through stimulation of SMAD proteins which migrate into the nucleus leading to attenuation of genetic expression and activation of non-canonical agents like p38, ERK, AKT and JNK [70,71]. It is also proved that the proliferation of β-cells can be increased by 5-8 % through blocking of DYRK1A and TGF-β associated processess. The activation of MAPK signalling pathway by the activation of insulin/IGF-1 receptor, PI3K-AKT and inhibition of GSK3β activity and receptor to activated nuclear factor kappa-B ligand (RANKL) revealed β-cell proliferation in rodents [72–74]and human islets (H. Liu et al., 2009). In addition to this, chicoric acid might also have role in the inhibition of transcription factors like pax 1 and pax 2 that have a potential for trans-differentiation of pancreatic α and δ cells to β cells. The above-mentioned molecular switches/genes are the possible targets of chicoric acid and its action on beta cell regeneration needs to be explored further.

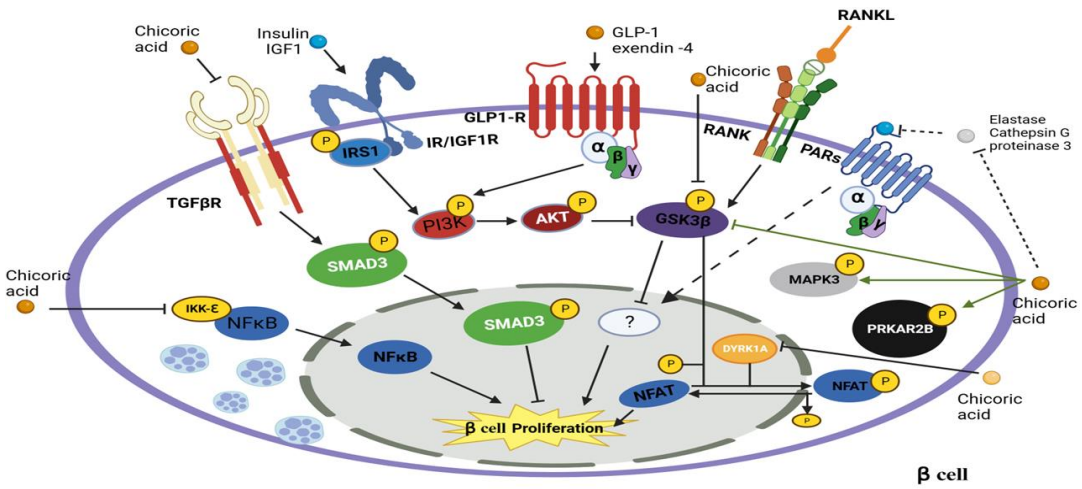

Figure 3A: Potential targets of chicoric acid in modulation of pancreatic β cell regeneration

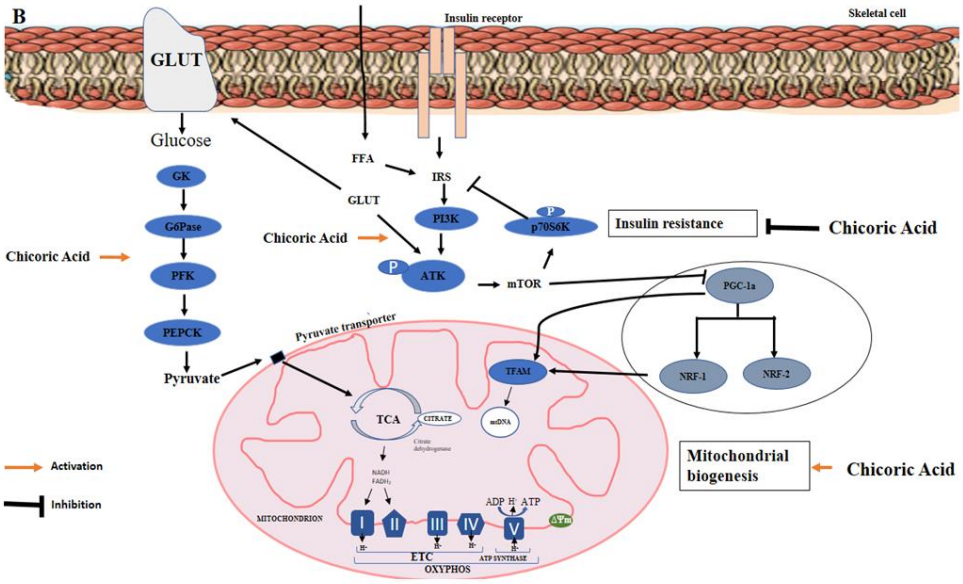

Figure 3B: Potential targets of chicoric acid in modulation of glucose homeostasis

The anti-diabetic potential of chicoric acid is further elucidated in figure 3 B. Abundant evidences are available establishing the efficacy of chicoric acid on insulin secretion and uptake of glucose. After reviewing the literature, we summarize that chicoric acid has an anti-diabetic activity by targeting glucose metabolic pathway, oxidative phosphorylation and insulin signalling cascades.

CONCLUSION AND PERSPECTIVES

Chicoric acid is a polyphenol compound found in various plants, including *Cichorium intybus*, and other anti-diabetic medicinal plants. Several studies have evaluated the potential of chicoric acid as a modulator of insulin release and glucose uptake. Beta cells are the specialized pancreatic cells that produce insulin and their regeneration is critical for the management of diabetes mellitus, as the loss of these cells contributes to the development or worsening of the disease. Insulin release is necessary for the uptake of glucose by cells in the body and there are reports that chicoric acid has a significant role on the insulin secretion and its action. Overall, studies suggest that chicoric acid has therapeutic applications for diabetic patients by promoting beta cell regeneration, stimulating insulin release, and enhancing glucose uptake. However, targeted research is highly recommended to establish the safety and efficacy of chicoric acid as a therapeutic agent primarily targeting beta cell regeneration.

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Conflict of interest

The authors declare that they have no conflict of interest.

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