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RESEARCH ARTICLE

# Exploring the Anti-Diabetic Potential of *Cichorium intybus* through Integrated Network Pharmacology Analysis and Molecular Docking Validation

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## Abstract

**Background:** The major global health concern known as Type 2 Diabetes Mellitus (T2DM) ischaracterized by increased blood sugar level and insulin resistance. It is a common and complicated metabolic illness that needs to be understood from many angles in order to be predicted and treated effectively. **Aim:** Therefore, in his study, we aim to reveal the accurate and in-depth roots to predict the progression of diabetes and its management. **Methods:** A workable compound-target-pathway network pharmacology model and molecular docking studies were created by combining compound screening and target prediction. This model enabled researchers to systematically anticipate potential compounds and the mechanisms of *Cichorium intybus* anti-diabetic actions. **Results:** The results of the network pharmacology study were subsequently verified by using molecular docking, which effectively identified several active compounds of *C. intybus* and several targets that support anti-diabetes. For analytical purposes, four primary active chemicals are considered here: myricetin, cyanidin, quercitrin, and chicoric acid. These compounds act on targets such as alpha-amylase (1B2Y) and alpha-glucosidase (3W37). Here network pharmacology is used to build an interactive, complete network of genes relevant to diabetes, proteins, and pathways then validation is done through docking. Docking score of all 5 active compounds for both the targets alpha-glucosidase (PDB:3W37) and alpha-amylase (PDB:1B2Y) are considered. So, compound quercetin and cyanidin with both targets show the strongest binding affinities and interactions. **Conclusion:** Thus, this research successfully concludes the prediction of the active chemicals and targets of *C. intybus* for the treatment of diabetes. It offers fresh perspectives on the pharmacological and molecular foundations of *C. intybus*.

**Keywords:** Antidiabetic, *Cichorium intybus*, Molecular Docking, Network Pharmacology, Type 2 Diabetes

## 1. Introduction

Type 2 diabetes is a chronic illness that a chronic illness called type 2 diabetes affects how our bodies metabolize sugar, or glucose, an essential source of energy for our bodies. When you have type 2 diabetes, your body either doesn't create levels or doesn't respond well to the hormone insulin, which regulates the amount of sugar that enters your cells. With an increasing incidence brought on by various causes including obesity, bad diets, and sedentary lifestyles, it is a serious global health concern. Serious side effects from type 2 diabetes include nerve damage, heart disease, stroke, renal disease, and eye impairment[1]. It can also negatively impact quality of life, leading to decreased productivity and increased healthcare costs. The International Diabetes Federation (IDF) estimates that 537 million people worldwide will have diabetes in 2021; if effective preventive measures are not taken, this number is expected to rise to 643 million by 2030. Over 541 million people are at an elevated risk of developing diabetes. India has the second-highest number of diabetic patients in the world, with 74.9 million people in the 2021 age group projected to increase to 124.9

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million by 2045. One in every seven adult diabetics worldwide lives in India, and one in every third household has some diabetic members[2]. Nowadays, the use of natural products for treatment is gaining huge popularity due to their various benefits, such as safety, being very economical, and having minimal side effects. So here, we discuss the treatment of diabetes by natural products known as *C. intybus*.

Chicory, also called *C. intybus*, is a perennial herbaceous plant that is woody and a member of the Asteraceae family. It is widely cultivated for its leaves, roots, and seeds, which have been traditionally used for culinary, medicinal, and commercial purposes. While various parts of chicory, including the leaves and seeds, may have nutritional value and potential health benefits, it is primarily the root, particularly its inulin content, that has been studied for its potential role in diabetes management. The use of chicory root extract, inulin supplements, or incorporating chicory root as a dietary component are avenues that have been explored in research focused on diabetes management[3]. Chicory (*C. intybus*) is a plant that has various parts like roots, leaves or seeds, each containing different phytochemicals. Some of them are inulin, flavonoids, chicoric acid, vitamins, etc, these components show many potent bioactivities. These phytochemicals collectively possess properties that are relevant to diabetes management, including antioxidant, anti-inflammatory, and potential glucose-regulating effects. The pharmacological properties of the phytochemicals found in chicory are quite diverse. They collectively possess properties that are relevant to diabetes management, including antioxidant, anti-inflammatory, and potential glucose-regulating effects. The extract of *C. intybus* roots has been used for diabetes control.

Traditional medicines, often known as compounded drugs, operate on several targets simultaneously, contradicting the accepted view that "one drug corresponds to one target, one target corresponds to one disease". Usually, complex active ingredients or a combination of medicines make up traditional remedies. It can be difficult to understand how multi-component and multi-targeted medications work. Network pharmacology is the study of biological networks, such as metabolic, signaling, and protein-protein interaction networks, to understand the connections between medications, genes, proteins, and illnesses on a systemic level[4]. Overall, network pharmacology provides a framework for understanding the complex relationships between drugs, targets, and diseases within biological systems, with the potential to aid in the discovery of new medication targets, optimization of drug combinations, and personalized medicine approaches.

In this study, firstly the effect of *C. intybus* (chicory) on diabetic patients is evaluated and determines the active compound of chicory. Moreover, the network pharmacology approach used here includes the evaluation of drug-likeness, component target prediction, target collecting linked to diabetes, network creation, and network analysis. In the end, the outcomes of the network analysis are confirmed using molecular docking.

## 2. Materials and Methods

### 2.1 Building a Chemical Constituents Dataset

The following electronic literature databases were used to gather all the chemical components of *Cichorium intybus*: Sci Finder[22], PubMed[23], and the China National Knowledge Infrastructure (CNKI)[24] 159 chemical components in all were gathered. Screening of active compound Chicory is known for containing various bioactive compounds such as inulin, flavonoids, sesquiterpene lactones, and polyphenols. These compounds have been attributed to potential health benefits, including anti-inflammatory, antioxidant, hepatoprotective, and prebiotic properties[5,6]. For screening of active compounds, the drug-likeness is evaluated by using Lipinski's rule of five, it states that Drug-Likeness (DL) is an essential measure of a compound's chemical compatibility because The octanol-water partition coefficient log P (AlogP), rotatable bonds, molecular weight, hydrogen bond donors, hydrogen bond acceptors, and other pharmacokinetic and pharmacological features are described[7]. Therefore, from this study screening of active compounds is done. Significant pharmacological efficacy of chicory's inulin and flavonoids has been demonstrated to improve diabetes. Therefore, regardless of whether these chemicals satisfied the requirements,

all flavonoids and inulin were chosen for additional research.

## 2.2 Constructing a Protein Target Database

Target and active chemical prediction Predicting interactions between bioactive chemicals and target proteins, which may be useful in understanding the underlying biological mechanisms, is one of the most critical aspects in the drug development process. A bioactive compound can interact with several target proteins. The canonical structure of all the bioactive compounds from chicory was obtained through PubChem[25]. Bioactive compounds screed from ADME analysis were used for the protein target interaction study[8]. The target for the bioactive compounds was retrieved from the binding BD (https://www.bindingdb.org/rwd/bind/index.jsp) server. The canonical structure was subjected in the server to find bioactive targets, using similarity search >0.07. UniProt ID were collected for all the bioactive targets, these UniProt were used to find the Kegg pathway and disease involved in the Kegg Gen were collected using KEGG Mapper[26].

## 2.3 Network Construction and Kyoto Encyclopedia of Genes and Genomes (KEGG) Pathway Analysis

Protein-protein interaction is a very important process for various cellular methods[10]. The network was constructed by subjecting the prepared compound target dataset to the Cytoscape 3.7.0 software. To find out interactions between proteins. Networks of compound-target pathways were built with Cytoscape 3.7.0. Compounds, targets, and pathways were shown as nodes in graphical representations of the networks, and interactions were shown as edges[11].

After removing the targets that did not exhibit any interactions, the protein-protein interactions underwent additional filtering with a minimum combined score of 0.7 (high confidence)[12,13] to increase the data's dependability. The building and analysis of networks were done with the remaining PPIs. For GO enrichment analysis and KEGG pathway analysis, the DAVID[27] (functional annotation result summary) website was utilized. KEGG and GO enrichment pathways with P-values less than 0.05 were chosen, but pathways unrelated to diabetes were not selected[10].

## 2.4 Molecular Docking by Schrodinger

In addition to virtual screening to find new ligands, the Schrodinger (version 2018) tool is used to estimate the binding mode of a known active ligand and the binding affinities of comparable compounds from a known active series. The candidate compounds were drawn in the SDF format using chem draw. Protein data bank downloads[28] were made available for protein crystal structures. The schrodinger software was used to enter the candidate compounds and the associated targets to obtain docking scores (S values). The binding energy (docking score, S) ≤− 5.0 kJ/mol was utilized since it is generally acknowledged that the chance of interaction increases with decreasing the energy at which the ligand-receptor combination is stable[14].

# 3. Results and Discussions

## 3.1 Database Construction

### *3.1.1 Compound Database Construction and Target Prediction*

There are several chemical constituents of *C. intybus* which were identified by several datasets and consisting of several properties like anti-inflammatory, antioxidant, hepatoprotective, and prebiotic properties. Inulin and flavonoids are selected and known to produce anti-diabetic effects[15]. Hence these active compounds are selected for the next step in analysis. Figure 1 represents the most effective compounds in chicory.

By looking through the databases of the swiss target prediction, similarity ensemble approach, and pharm mapper server, a total of 56 targets for possible active molecules were discovered. Among these targets were those connected to mitogen-activated protein kinase, insulin-like growth factor-binding proteins, tyrosine-protein phosphatase, and other anti-inflammatory targets.

## 3.2 Target Protein Dataset Construction

As seen in Table 1, a total of 56 targets are screened to create the protein target dataset. These targets, which included 3W37, 1B2Y, IGF1R, PIK3R1, and others, were mostly associated with inflammation or anti-diabetes action.

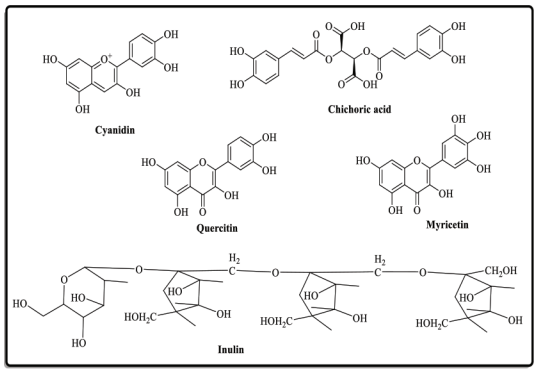



**Figure 1.** Structure of potentially active compounds.

**Table 1.** Insulin resistance-related targets of *Cichorium intybus* information

| Sr. No. | Target Name | Uniprot ID | Gene Name |
|---|---|---|---|
| 1 | NADPH oxidase 4 | Q9NPH5 | NOX4 |
| 2 | Vasopressin V2 receptor | P30518 | AVPR2 |
| 3 | Aldose reductase | P1512 | AKR1B1 |
| 4 | Xanthine dehydrogenase | P47989 | XDH |
| 5 | Monoamine oxidase A | P21397 | MAOA |
| 6 | Insulin-like growth factor I receptor | P08069 | IGF1R |
| 7 | Tyrosine-protein kinase receptor FLT3 | P36888 | FLT3 |
| 8 | Cytochrome P450 19A1 | P11511 | CYP19A1 |
| 9 | Epidermal growth factor receptor erbB1 | P00533 | EGFR |
| 10 | Thrombin | P00734 | F2 |
| 11 | Carbonic anhydrase II | P00918 | CA2 |
| 12 | Serine/threonine-protein kinase PIM1 | P11309 | PIM1 |
| 13 | Arachidonate 5-lipoxygenase | P09917 | ALOX5 |
| 14 | Serine/threonine-protein kinase Aurora-B | Q96GD4 | AURKB |
| 15 | Dopamine D4 receptor | P21917 | DRD4 |
| 16 | Microtubule-associated protein tau | P10636 | MAPT |
| 17 | Lysine-specific demethylase 4D-like | B2RXH2 | KDM4E |
| 18 | G-protein coupled receptor 35 | Q9HC97 | GPR35 |
| 19 | DNA topoisomerase II alpha | P11388 | TOP2A |
| 20 | Xanthine dehydrogenase | P47989 | XDH |
| 21 | Tyrosine-protein kinase receptor FLT3 | P36888 | FLT3 |
| 22 | Insulin receptor | P06213 | INSR |

**Table 1.** Continued...

| Sr. No. | Target Name | Uniprot ID | Gene Name |
|---|---|---|---|
| 23 | Acetylcholinesterase | P22303 | ACHE |
| 24 | Glyoxalase I | Q04760 | GLO1 |
| 25 | Myosin light chain kinase, smooth muscle | Q15746 | MYLK |
| 26 | Tyrosine-protein kinase SYK | P43405 | SYK |
| 27 | Multidrug resistance-associated protein 1 | P33527 | ABCC1 |
| 28 | PI3-kinase p110-gamma subunit | P48736 | PIK3CG |
| 29 | Beta-secretase 1 | P56817 | BACE1 |
| 30 | DNA-(apurinic or apyrimidinic site) lyase | P27695 | APEX1 |
| 31 | Thrombin | P00734 | F2 |
| 32 | LXR-alpha | Q13133 | NR1H3 |
| 33 | Glyoxalase I | Q04760 | GLO1 |
| 34 | Lymphocyte differentiation antigen CD38 | P28907 | CD38 |
| 35 | NADPH oxidase 4 | Q9NPH5 | NOX4 |
| 36 | Microtubule-associated protein tau | P10636 | MAPT |
| 37 | Lysine-specific demethylase 4D-like | B2RXH2 | KDM4E |
| 38 | G-protein coupled receptor 35 | Q9HC97 | GPR35 |
| 39 | Vasopressin V2 receptor | P30518 | AVPR2 |
| 40 | DNA topoisomerase II alpha | P11388 | TOP2A |
| 41 | Aldose reductase | P15121 | AKR1B1 |
| 42 | Xanthine dehydrogenase | P47989 | XDH |
| 43 | Monoamine oxidase A | P21397 | MAOA |
| 44 | Insulin-like growth factor I receptor | P08069 | IGF1R |
| 45 | Tyrosine-protein kinase receptor FLT3 | P36888 | FLT3 |
| 46 | Aldo-keto reductase family 1 member B1 | P15121 | AKR1B1 |
| 47 | Aldo-keto reductase family 1 member B10 | O60218 | AKR1B10 |
| 48 | Alpha-synuclein | P37840 | SNCA |
| 49 | Amyloid-beta precursor protein | P05067 | APP |
| 50 | Histone deacetylase | Q13547 | HDAC1 |
| 51 | Histone deacetylase | O15379 | HDAC3 |
| 52 | Histone deacetylase | P56524 | HDAC4 |
| 53 | Matrix metalloproteinase-9 | P14780 | MMP9 |

**Table 1.** Continued...

| Sr. No. | Target Name | Uniprot ID | Gene Name |
|---|---|---|---|
| 54 | PC4 and SFRS1-interacting protein | O75475 | PSIP1 |
| 55 | Tyrosine-protein phosphatase non-receptor type 1 | P18031 | PTPN1 |
| 56 | Tyrosine-protein phosphatase non-receptor type 1 | P18031 | PTPN1 |

## 3.3 Bioinformatics Analysis

### *3.3.1 Gene Ontology and KEGG Pathway Enrichment Analysis*

Using DAVID bioinformatics tools (version 6.8), GO enrichment analysis was then carried out to further study the biological process, molecular function, and cellular component of the component's targets. Figure 3 displays the route enrichment categories (P<0.01), whereas the top six GO enrichment terms are shown in Figure 2. The target proteins' anti-diabetic and inflammatory response functions were separated into two categories by the GO enrichment analysis. The top three terms in the GO biological processes, as shown in the figure below, were as follows: control of the JNK cascade, the metabolism of carbohydrates, and the equilibrium of glucose. In Figure 3 after excluding broad-spectrum pathways that were not relevant[16], possible pathways with a 0.01 cut-off P-value were found using the KEGG enrichment analysis. The three most enriched routes in order of decreasing P-values. Consequently, the paths that were deemed to be the most significant (Figure 3) were: Steroid hormone biosynthesis, nitrogen metabolism, and oxytocin signaling pathway. These pathways are crucial for insulin signaling and are strongly linked to type 2 diabetes[17].

*Cichorium intybus* capacity to control inflammatory responses and enhance anti-diabetic effects mediates its two primary therapeutic benefits. Chicory can reduce diabetes through the synergistic impact of these two systems. Therefore, the idea behind treating *Cichorium intybus* is that it can control the release of inflammatory factors that obstruct diabetic activity.

## 3.4 Network Analysis

The interaction between pathways and multiple diseases is represented in Figure 4. It shows how a target pathway is related to multiple diseases.

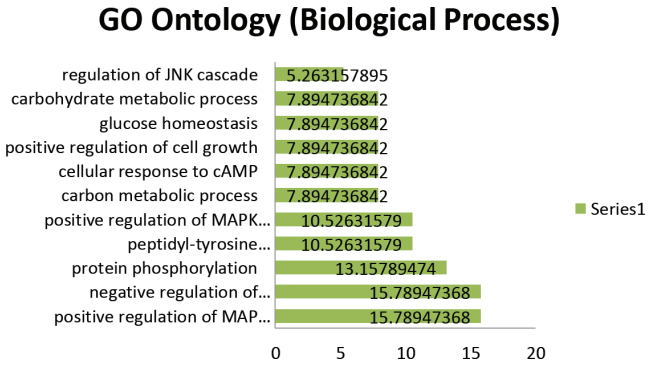



**Figure 2.** GO ontology biological process analysis.

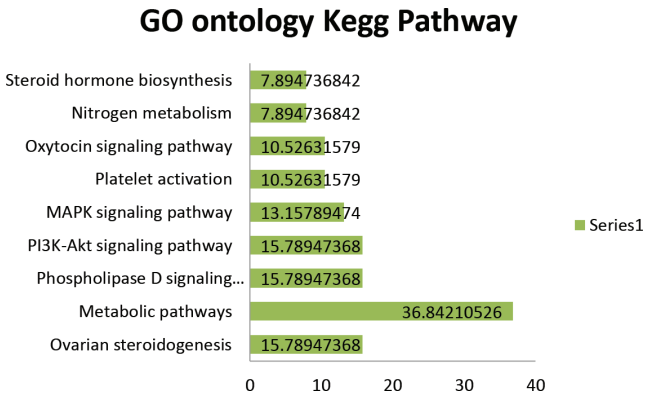



**Figure 3.** KEGG pathway enrichment analysis.

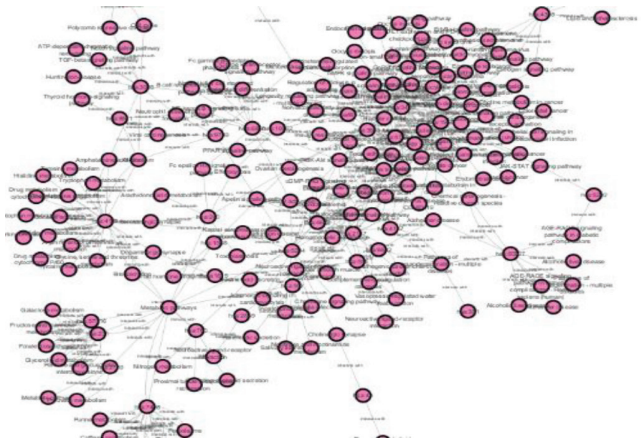


**Figure 4.** Pathway and diseases interaction of *Cichorium intybus*.

In Figure 5, the compound-target-pathway network, which has 361 edges and 95 nodes and is shown from a global perspective, was built to learn more about the molecular mechanism underlying *C. intybus* improved anti-diabetic effects. The above image is the networking of active compounds and

pathways along with their UniProt ID. A protein entry in the UniProt database is uniquely identified by its UniProt ID, also known as its UniProt accession number[18]. An extensive resource that offers details on the characteristics, structure, and function of proteins is the Uniprot database. This network offered a good knowledge of the complex connections in and among various compounds and targets, and it showed the possibility of complicated correlations in terms of the "one target-multiple ingredient" and "one ingredient-multiple targets" models[19]. The two target nodes that were most strongly associated with the number of compound nodes were alpha-glucosidase (PDB:1B2Y) and alpha-analyse (PDB:3W37). Numerous significant pathways, including the insulin signalling system, the anti-diabetic, and focal adhesion, are impacted by these targets. These findings suggest that chicory has a multi-target, multi-pathway, and synergistic beneficial effect on diabetes.

## 3.5 Validation of Targets via Molecular Docking Analysis

As per the analysis done above it shows antidiabetic receptor glucosidase (PDB:1B2Y) and amylase (PDB:3W37) linked with maximum numbers of compound nodes. The top two targets associated with the greatest quantity of Inulin and flavonoids were 3W37 and 1B2Y. The primary active ingredients that show anti-diabetic properties are Inulin and flavonoids, which is why 3W37 and 1B2Y. were chosen as docking targets. Schrodinger computed docking scores (S values) between drugs and targets. The findings of building two pairs of compound-target docking connections are displayed in Figure 6. For the vast majority of compounds, the S values were below −5.0.

However, the docking score of inulin is greater than -5.0 for the target alpha-glucosidase (PDB:1B2Y). Among all the active compounds with both the targets like alpha-glucosidase (PDB:1B2Y) and alpha-amylase (PDB:3W37). quercetin and cyanidin show the most effective binding. These findings offered significant proof in favour of the identification of potentially useful compounds, as seen in Figure 4. quercetin and cyanidin together are the main and potent components that mediate *Cichorium intybus* anti-diabetic actions.

A superimpose of the docked pose of quercetin and cyanidin with acarbose at the binding site of alpha-amylase and alpha-glucosidase is given in Figure 7 and Figure 8 respectively. Quercetin interacts with alpha-amylase (PDB: 3W37) receptors using interactive residue ASP630 and ASP568 through hydrogen bonding (Figure 7a) also in Figure 7b cyaniding interacts with alpha-amylase (PDB: 3W37) receptors using interactive residue ASP630 and ASP568 through hydrogen bonding. For Figure 8a Quercetin interact with alpha-glucosidase (PDB: 1B2Y) receptor using intractive residue UNK900, TRP 59, and ASP300 through hydrogen bonding. However, cyaniding interacts with alpha-glucosidase (PDB: 1B2Y) receptors using intractive residue HIP305 through hydrogen bonding (Figure 8b).

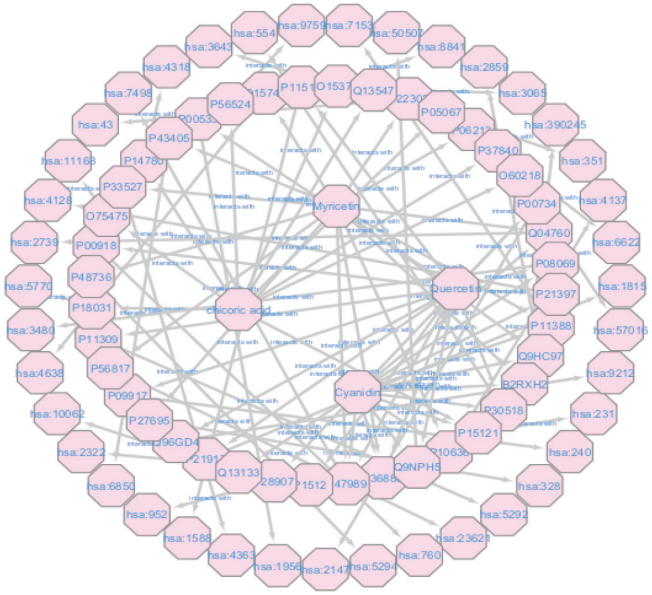



**Figure 5.** The *Cichorium intybus* compound-target-pathway network. Several active ingredients are shown in the center.

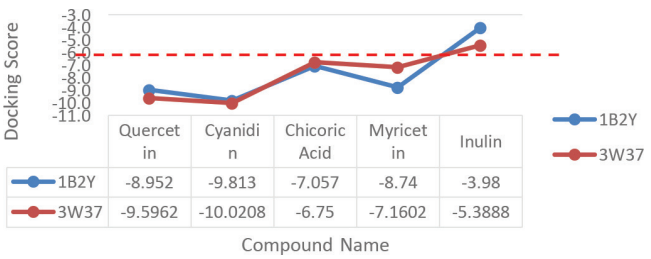



**Figure 6.** Molecular docking data (S values) of molecules linked to 3W37 and 1B2Y that may be active are shown in a line chart.

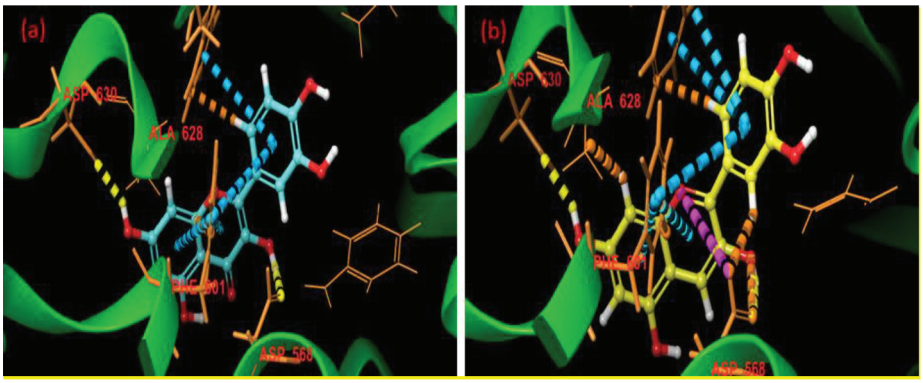



**Figure 7.** **(a).** Docked pose of Quercetin (turquoise color, stick model) at the binding site of alpha-amylase (PDB: 3W37) **(b).** Docked pose of Cyanidin (turquoise color, stick model) at the binding site of alpha-amylase (PDB: 3W37). Hydrogen bonds are shown as yellow dashed lines.

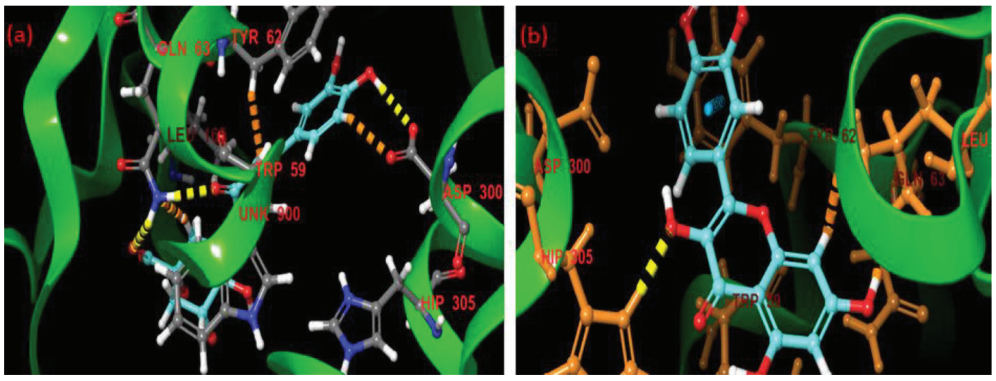



**Figure 8.** **(a).** Docked pose of Quercetin (turquoise color, stick model) at the binding site of alpha-glucosidase (PDB: 1B2Y); **(b).** Docked pose of Cyanidin (turquoise color, stick model) at the binding site of alpha-glucosidase (PDB: 1B2Y). Hydrogen bonds are shown as yellow dashed lines.

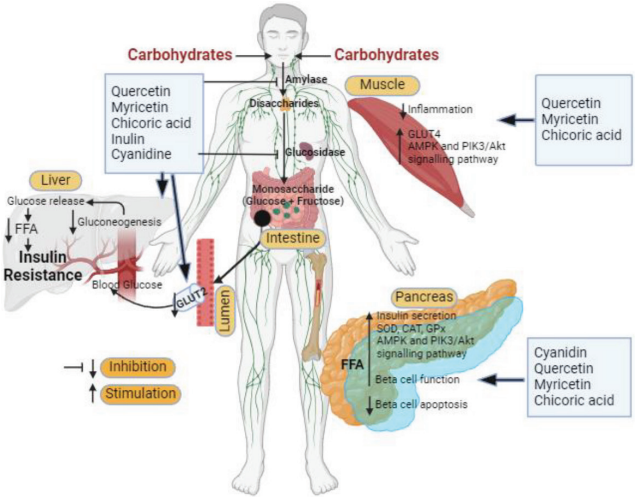



**Figure 9.** Proposed action mechanism of all the compounds of chicory based on the current findings and literature.

## 4. Discussion

It is recognized that *C. intybus* has anti-diabetic properties, through ameliorating diabetes; however, the specific active ingredients and how they work remain unknown. The network pharmacology method was employed in this work to forecast the components that may be active as well as their mechanisms of action. Inulin and flavonoids were the main active ingredients that improved diabetes, according to our network pharmacology research. Due to these compounds' documented antidiabetic benefits, they are incorporated into the network architecture. Prostate, breast, and prostate cancer pathways were among the pathways associated with cancer in the preliminary KEGG pathway analysis results because many targets, including 3W37, 1B2Y, and IGF1R, were either

implicated in multiple cancer pathways or anti-diabetic pathways. The purpose of this work was to elucidate the underlying mechanisms of anti-diabetes rather than cancer, even though anti-diabetes is implicated in the pathogenesis of cancers[20]. Therefore, we eliminated broad-spectrum pathways that are not relevant, such those linked to cancer, in order to create an efficient network pharmacology model. Following this, it was discovered that the PI3K/Akt signalling pathway, insulin resistance, and focal adhesion were the main pathways linked to both the inflammatory response and anti-diabetes. An increasing amount of data points to the mechanism of anti-diabetes being influenced by the persistent low-grade inflammatory response. The pattern of binding ability between two targets and the majority of immensely powerful active compounds through molecular docking is depicted in Figure 5. Apart from the outcomes of the Western blot examination, the molecular docking analysis showed clearly that 3W37 and 1B2Y were the primary mechanisms through which *C. intybus* exhibited its anti-diabetic benefits. According to KEGG pathway analysis, 1B2Y was engaged in the insulin signalling pathway and anti-diabetic mechanisms, whereas 3W37 was implicated in processes including prolactin signalling, VEGF signalling, and focal adhesion[21]. Despite 1B2Y's involvement it was found to be a major target connected to many different chemicals in just two pathways, ranking among the top two targets in those pathways. The specifications for a network pharmacology approach are still unknown as of right now. There are significant differences between studies in the databases for chemical components, active compound screening criteria, protein target databases, PPI screening scores, and molecular docking software. Thus, there is a chance that the same study's findings will vary. Thus, to guarantee the accuracy and consistency of results, thorough and practical design guidelines are needed for upcoming network pharmacology investigations. Overall, the proposed action mechanism of the screen compounds is presented in Figure 9.

## 5. Conclusion

In this paper, we investigated the anti-diabetic properties of *C. intybus* using a systematic network pharmacology approach. Furthermore, it has been suggested that the main active compounds quercetin and cyanidin act on significant targets i.e. 3W37 and 1B2Y. Our findings serve as the foundation for more research to completely clarify chicory's anti-diabetic benefits.

## 6. Acknowledgment

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## 7. References

1. Aisa HA, Xin X, Tang D. Chemical constituents and their pharmacological activities of plants from *Cichorium* genus. Chinese Herb Med. 2020; 12(3):224-36. https://doi.org/10.1016/j.chmed.2020.05.001
2. Saeedi P *et al.* Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the international diabetes federation diabetes atlas, 9th edition. Diabetes Res Clin Pract. 2019; 157. https://doi.org/10.1016/j.diabres.2019.107843
3. Luo Z, *et al.* Cichoric acid from witloof inhibits misfolding aggregation and fibrillation of hIAPP. Int J Biol Macromol. 2020; 148:1272-9. https://doi.org/10.1016/j.ijbiomac.2019.10.100
4. Matos MS, *et al.* Assessing the intestinal permeability and anti-inflammatory potential of sesquiterpene lactones from chicory. Nutrients. vol. 2020; (12)11:1-20. https://doi.org/10.3390/nu12113547
5. Sureshbabu P, Bhavya DC, Siddalinga EM. A process of electro homeopathic remedy 'SLASS' Preparation, Compared with krauss method by phytochemical analysis, TLC and FTIR Studies. European J Med Plants. 2021. p. 39-55. https://doi.org/10.9734/ejmp/2021/v32i730404
6. Tao W, *et al.* Network pharmacology-based prediction of the active ingredients and potential targets of chinese herbal *Radix curcumae* formula for application to cardiovascular disease. J Ethno Pharma col. 2013; 145(1):1-10. https://doi.org/10.1016/j.jep.2012.09.051
7. Shi XQ, *et al.* A network pharmacology approach to investigate the blood enriching mechanism of danggui buxue decoction. J Ethno Pharma Col. 2019; 235:227-42. https://doi.org/10.1016/j.jep.2019.01.027
8. Daina A, Michielin O, Zoete V. Swiss target prediction: updated data and new features for efficient prediction of protein targets of small molecules. Nucleic Acids Res. 2019; 47(1):W357-W3664. https://doi.org/10.1093/nar/gkz382
9. Wang X, *et al.* Pharm mapper 2017 update: a web server for potential drug target identification with a comprehensive

target pharmacophore database. Nucleic Acids Res. 2017; 45(1):W356-W60. https://doi.org/10.1093/nar/gkx374
10. Carbon S, *et al*. The gene ontology resource: 20 years and still going strong. Nucleic Acids Res. 2019; 47(1):330-8. https://doi.org/10.1093/nar/gky1055
11. Zhu W, Wang Y, Niu Y, Zhang L, Liu Z. Current trends and challenges in drug-likeness prediction: are they generalizable and interpretable? Heal Data Sci. 2023; 3. https://doi.org/10.34133/hds.0098
12. Zhao Z, *et al.* Prevention and treatment of COVID-19 using traditional chinese medicine: A review, Phytomedicine. 2021; 85:153308. https://doi.org/10.1016/j.phymed.2020.153308
13. Taki GS, Mallick AK, Chakraborty B, Pal P, Biswas C, and Samanta C. Electro-homeopathy based COVID-19 safe-home medical management study. J Nat Remedies. 2022; 22(2):261-7. https://doi.org/10.18311/jnr/2022/28201
14. Liu S, McGree J, Ge Z, Xie Y. Classification methods, computational and statistical methods for analyzing big data with applications. 2016. p. 7-28. https://doi.org/10.1016/B978-0-12-803732-4.00002-7
15. Lightowler H, Thondre S, Holz A, Theis S. Replacement of glycemic carbohydrates by inulin-type fructans from chicory (oligofructose, inulin) reduces the postprandial blood glucose and insulin response to foods: report of two double-blind, randomized, controlled trials. Eur J Nutr. 2018; 57(3):1259-68. https://doi.org/10.1007/s00394-017-1409-z
16. Zhao M, *et al*. Phytochemicals and mitochondria: Therapeutic allies against gastric cancer. Phytomedicine. 2023; 110. https://doi.org/10.1016/j.phymed.2022.154608
17. Chén OY, *et al*. The roles, challenges, and merits of the p value. Patterns. 2023; 4(12):100878. https://doi.org/10.1016/j.patter.2023.100878
18. Bateman A. UniProt: A worldwide hub of protein knowledge. Nucleic Acids Res. 2019; 47(1):506-15. https://doi.org/10.1093/nar/gky1049
19. Huang Q, Liu R, Liu J, Huang Q, Liu S, Jiang Y. Integrated network pharmacology analysis and experimental validation to reveal the mechanism of anti-insulin resistance effects of *Moringa oleifera* Seeds. Drug Des Devel Ther. 2020; 14:4069. https://doi.org/10.2147/DDDT.S265198
20. Li A, Qiu M, Zhou H, Wang T, Guo W. PTEN, insulin resistance and cancer. Curr Pharm Des. 2017; 23:25. https://doi.org/10.2174/1381612823666170704124611
21. Djiogue S, *et al*. Insulin resistance and cancer: the role of insulin and IGFs. Endocr Relat Cancer. 2013; 20:1. https://doi.org/10.1530/ERC-12-0324
22. http:// scifinder.cas.org
23. http://www.ncbi.nlm.nih.gov
24. http://cnki.net/
25. https://pubchem.ncbi.nlm.nih.govr/
26. https://www.genome.jp/kegreg/mapper/
27. https://david.ncifcrf.gov/summary.jsp
28. https://www.rcsb.org/