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Baicalein-Driven Activation of the Hypothetical REME1 Gene: A immunoinformatic Approach to Mitigate and Treat Ageing and Pancreatic Cancer

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Abstract

Ageing and age-related diseases, including pancreatic cancer, are intricately linked to molecular disruptions that compromise cellular integrity and homeostasis. The REME1 gene, a novel hypothetical anti-ageing gene, is believed to be critical in mitigating these age-related processes. Mutations in REME1 critical binding pockets reduce expression, resulting in increased redox stress, telomere shortening, and impaired cellular repair mechanisms hallmarks of ageing that contribute to the onset of age-related diseases, particularly pancreatic cancer. This research explores the potential of Baicalein, a natural compound, as a therapeutic ligand to restore REME1 expression. In silicon docking studies show that Baicalein binds effectively to the mutated REME1 binding pockets, stabilizing its structure, and enhancing gene expression. This work seeks to assess the probability of Baicalein, which is a flavonoid obtained from natural products, acting as a therapeutic ligand for the replacement of REME1. Baicalein shows promising binding characteristics with REME1 binding domains which were PDB-transformed sites thus implying good affinity. In alleviating these alterations, REME1 is fully restored and therefore possesses its three essential functions; compromising oxidative stress, maintaining the integrity of the telomeres, and aiding cellular repair mechanisms which in elevated levels may offer treatment for old age and other related disorders such as Pancreatic cancer. Upregulation of REME1 is further supported through key molecular pathways, including AMPK, Akt, NF-κB, TGF-β, LXRα, SREBP1, and the Warburg effect. It is observed that these pathways uniformly reduce oxidative stress, and NEFA metabolism, and enhance cellular operation. More importantly, when inflammation is modulated and mitochondria bioenergetics are altered, a most favourable outcome for energy intake and utilization appears by the upregulation of REME1. Thus, this upregulation targets ageing and age-related diseases including pancreatic cancer. In general, this type of research underscores the utility of REME1 in cancer and ageing therapies and its importance resulting from novel cancer strategies which are computational and thus grant grounds for possible further laboratory exploration.

Keywords: REME1 Gene, Baicalein, Pancreatic Cancer, Oxidative Stress, Telomere Integrity and Mitochondrial Bioenergetics.

Introduction:

Ageing can be seen as a complex, multiphase biological process that seeks to describe the gradual functional decline of biological systems and increased vulnerability to mild environmental inconveniences or diseases(Braun et al., 2014). One of the defining characteristics of a cellular ageing phenomenon is a shortening of the telomeres, which are the protective ends of chromosomes. Telomeres are shortened with each duplication of DNA, which triggers senescence or cell death. These cellular ageing processes are a major factor in the deterioration of tissues and organ systems as well as the more common diseases among people of advanced ages(Budar et al., 2018). Cancer, especially pancreatic cancer, is one of the diseases related to ageing. Although it can happen at any age, pancreatic cancer is well known to be more prevalent in the aged population. The regulation of ageing and protection of cell integrity are areas within ontology influenced by the REME1 gene(Fields, 1984). This gene may produce a protein crucial in ageing processes such as DNA damage repair, cellular senescence, and autophagy. This, in turn, might allow REME1 to regulate the rate at which cells age and the inception of age-related pathologies. For example, it could enhance the efficiency of cells' DNA repair mechanisms, reducing the accumulation of DNA lesions with age. In addition, cellular senescence may be partially controlled through REME1 to limit the number of senescent cells which negatively affect tissues. Autophagy, the process of degradation and recycling of damaged parts of a cell, could also increase(Munshi et al.). By tackling the traits of cellular agedness, the REME1 gene may be regarded as a worthwhile one to work with to develop therapies targeting elderly people to prolong their lives. It is necessary to stress that this is merely an assumption and exists in theory, and a more in-depth investigation to prove the existence and function of such a type of gene is warranted(Ramallo et al., 2008). The ageing process and cellular health are two areas where genetic changes in the REME1 gene might have detrimental effects(Sandin et al., 2023). When the REME1 protein malfunctions, the balance of reactive oxygen species, a crucial metabolite in cells, is upset, which results in severe oxidative stress. In addition to affecting the cellular components of DNA, proteins, and lipids this redox imbalance accelerates ageing and significantly increases the risk of developing age-related illnesses like cancer(Schulman & Wicker, 2013). The enzyme telomerase, which maintains the length of the telomere, may not work properly if the REME1 gene is altered genetically. Apoptosis and senescence of the cells may ensue from excessive telomere shortening caused by decreased telomerase levels(Sunde, 2024). This may result in organ dysfunction and tissue deterioration. Furthermore, a malfunctioning REME1 protein may impact DNA repair mechanisms, thereby speeding up the development of genetic abnormalities. This circumstance may increase the risk of developing cancer and result in a condition of genetic instability(Weber et al., 2009). Computational techniques are necessary to find therapeutic targets and ligands, which significantly improves the drug discovery process. The structure, role, and interaction processes of the REME1 protein can be clarified using methods like as molecular docking, bioinformatics, and molecular dynamics simulations(Weber et al., 2010). Finding potential binding sites and predicting the atomic-level interactions between various substances, like baicalein, and the protein are made simpler by these techniques. Baicalein, a flavonoid compound derived from the roots of the Scutellaria baicalensis plant, has long been recognized in traditional Chinese medicine for its many medicinal advantages(Munir et al., 2025). Recent scientific research has further demonstrated its potential as a natural chemical that may target and repair damaged proteins, including the putative REME1 protein. Baicalein has demonstrated strong antioxidant, anti-inflammatory, and neuroprotective qualities, suggesting that it may be able to mitigate the detrimental effects of oxidative stress and cellular damage associated with ageing and disease. The computational study can speed up the assessment of baicalein as a ligand for REME1 by determining its binding affinity, stability, and potential effectiveness in altering the protein's function. Additionally, by

optimizing baicalein's structure to enhance binding, these computational methods cut down on the time and cost of experimental drug discovery.

Material and Method

This research employed various tools and resources, including bioinformatics approaches, to conduct comprehensive analyses and investigations.

Acquisition of the sequence of REME1 gene

The whole sequence of the mutant REME1 gene, which is required to encode the primary structure of the protein, is available through the University of California, Santa Cruz (UCSC) Genome Browser (https://genome.ucsc.edu/). The UCSC Genome Browser is a versatile computer tool that is widely used in bioinformatics to view genetic data. It enables researchers to access, inspect, and analyze the complete genetic sequences of many species, including humans, mice, and other model organisms. By integrating gene annotations, mutations, and regulatory regions, the UCSC Genome Browser offers a comprehensive platform for investigating gene structure and function. The UCSC Genome Browser played a significant role in this study's prediction of the complete sequence of the REME1 gene, including mutations that could impact the protein's function.

Prediction of REME1 primary structure

The EXPASY Translate online tool is a helpful bioinformatics tool for figuring out the basic structure of proteins by converting nucleotide sequences into corresponding amino acid sequences. In the context of studying the unstable REME1 protein, this method is crucial for comprehending how specific gene sequences translate into protein structures. This knowledge will aid in clarifying the gradual decrease in gene expression. By scientifically examining the exact arrangement of amino acids, researchers may investigate factors such as the existence of destabilizing residues or regions susceptible to degradation, which may help explain why REME1 is unstable. In addition to its ability to predict protein structure, the EXPASY Translate program is widely used in genome analysis, protein engineering, and functional prediction of unknown genes (https://www.expasy.org/).

Identification of mutations in the REME1 gene

The complete coding sequence of the target gene, REME1, was aligned with sequence homologous from other species using the protein search tool BLASTx from the NCBI database. The BLASTx program enables an established protein database to be compared with a gene's nucleotide sequence translated into amino acids. This allows us to identify conserved regions and specific mutations that may alter gene expression with age. BLASTx is a powerful tool able to perform gene annotation, gene ortholog identification and identification of functional domains. We verified the detected mutations through a combination of approaches (https://blast.ncbi.nlm.nih.gov/Blast.cgi).

- **PolyPhen-2**, Then the full coding sequence of target gene REME1 was aligned with similar sequences in other species and polypeptide mutations of amino acid changes on the structure and function of protein were the result of evolutionary conservation of amino acid done by using Polymorphism Phenotyping v2. The method considers structural changes and sequence conservation to assess if a mutation is benign, mildly deleterious, or strongly harmful. PolyPhen-2 is widely used in disease research to assess the potential toxicity of genetic variants (http://genetics.bwh.harvard.edu/pph2/).
- **MuPro** assesses how single amino acid changes impact protein stability. Key to understanding the metabolic effects of age-related mutations is the ability to predict, from

sequence information alone, whether a mutation increases or decreases the stability of a protein (https://mupro.proteomics.ics.uci.edu/).

- **I-Mutant** is an automated tool that predicts how mutations affect the stability of proteins. This method uses machine-learning approaches to predict how point mutations will impact protein folding, function, and lifespan, thus offering useful information about the effect of mutations on protein stability (https://folding.biofold.org/i-mutant/i-mutant2.0.html).
- **PROVEAN** (Protein Variation Effect Analyzer) to predict whether an observed alteration to a protein sequence affects its biological function. Its scoring system allows us to assess the potential implications of mutations in protein function, thus providing insight into whether mutations that occur during ageing increase or decrease protein activity (https://provean.jcvi.org/).

Prediction of the secondary structure of the REME1 protein

Secondary structure models for the REME1 protein were generated using PsiPred. It is an excellent and beneficial tool for structural bioinformatics provided it gives a precise and consistent prediction of protein secondary structural features. PsiPred makes use of the PSiBLAST-derived position-specific scoring matrix (PSMSM) and a neural network approach to predict α-helices, β-strands, and random coils in protein sequences. Incorporating information from similar sequences significantly improves the precision of its predictions of secondary structures. PsiPred is well known for its accuracy rate, which is about 80%, and it has earned a pretty solid reputation in this field. For our analysis of predicted secondary structures, we used a confidence score of 0–9, which PsiPred considers >5 as acceptable. Research identifying the predicted protein folding patterns producing confidence levels for using this score to investigate — Residue site. Moreover, PsiPred can provide predictions not only about the secondary structure of proteins but also about transmembrane regions, the boundaries of protein domains, and structural annotations in the absence of experimental data. It is also used in pipelines for homology modelling and tertiary structure prediction, highlighting the importance of this analytical protein computational task. The structure of REME1 protein was determined by PsiPred analysis in this study, which was quite critical for directional docking and functional annotation (http://bioinf.cs.ucl.ac.uk/psipred).

Anticipation of the Tertiary structure of the REME1 protein

Swiss Model (https://swissmodel.expasy.org/interactive) is an established online tool that predicts the three-dimensional structures of proteins by utilizing amino acid sequences along with known structures of homologous proteins. This program identifies suitable templates from the Protein Data Bank (PDB), aligns the target sequence with these templates, and creates a protein structure model. One of its key benefits is the application of precise quality standards to assess the reliability of the generated models. Two important metrics provided by the Swiss Model are the Global Model Quality Estimation (GMQE) and qualitative model energy analysis (QMEAN). GMQE evaluates the model's quality based on sequence alignment coverage and template quality, yielding values between 0 and 1, where higher numbers indicate better models. Conversely, QMEAN assesses the overall accuracy of the model based solely on statistical potentials, without considering the sequence coverage, thus reflecting structural correctness. These scores determine the reliability of the predicted structure and can be used for further functional analysis, drug design, or investigating protein-protein interactions. In addition to homology modelling, In the fields of structural biology, bioinformatics, and molecular modelling, the user-friendly interface and reliable computational capabilities of this tool make it highly advantageous. The precise protein structures produced by the tool enable various applications, including the analysis of disease-related mutations, the exploration of protein functions, and the development of therapeutic drugs.

The Swiss Model is also employed for structural comparisons, refining predicted models, and visualizing protein architectures.

Verification of the suggested model for the REME1 protein

Errat and Ramachandran's plots are essential tools for assessing the accuracy of protein structures available in databases (https://www.doe-mbi.ucla.edu/errat/)Errat plots illustrate discrepancies between predicted values and experimental results. Concentrating on geometric parameters such as bond lengths and angles. Ramachandran plots illustrate the distribution of phi (ϕ) and psi (ψ) dihedral angles, offering valuable insights into stereochemical quality. These plots are instrumental in evaluating the accuracy and reliability of computational protein models, which is essential for their refinement and validation.

Molecular docking of REME1

Baicalein shows strong docking strength with the REME1 protein structure as indicated by analysis of the docking data performed with PyrX and Autodock Vina. Specifically, it shows tight binding within the protein's binding pocket, tuned to accommodate the altered amino acid sequence. This discovery makes Baicalein an important candidate to impact REME1 function and offers insight into the roles of Baicalein in its mechanism of action and possible therapeutic application to combat age-related metabolic disorders.

Targeted Classes that Release Baicalein from its Burden

Swiss Target Prediction: a ligand-based approach to predicting small molecule targets; that integrates both ligand-based similarity approaches and machine learning algorithms. In this approach, which involves comparing a compound against known ligands with their respective targets in an extensive database, the activity of a compound is predicted based on the structural and chemical similarities between the query molecules and previously characterized compounds. The technology has enhanced the objectivity of these predictions using methods such as structural similarity searches, pharmacophore modelling, and interaction fingerprinting. It also enables comparison of the chemical structure of the target molecule with known ligands, to select promising proteins with potential to interact with the target. The unparalleled accuracy in predicting targets from this machine-learning and ligand-based methodology provides invaluable insight into drug activity, and potential off-target effects and can be used to identify adverse reactions and other potential therapeutic targets (http://www.swisstargetprediction.ch/).

ADME analysis of Baicalein

The compounds' diverse pharmacokinetic and pharmacodynamic characteristics such as water solubility, ability to penetrate the blood-brain barrier, hepatotoxicity, absorption in the human intestine, physicochemical properties, pharmaceutical kinetics, drug-likeness, and suitability in medicinal chemistry were thoroughly evaluated using Swiss-ADME. The findings outlined in the referenced study included the ADME (Absorption, Distribution, Metabolism, and Excretion) properties of three compounds that showed favourable docking outcomes. Understanding the chemical ADME characteristics is essential in drug research and development, as these properties determine how a compound is absorbed, distributed, metabolized, and excreted, all of which influence its effectiveness and safety profile. Therefore, in silico models are often used to predict these vital ADME properties, ensuring that potential drug candidates not only exhibit effective action against their intended targets but also possess advantageous ADME attributes when administered at therapeutic doses (http://www.swissadme.ch/).

Molecular Dynamics Modeling

Several key structural and functional characteristics of the REME1 protein were forecasted using molecular dynamics simulations with the iMODS methodology (https://imods.iqf.csic.es/) Key parameters include the B-factor, which provides insights into the flexibility of different regions of the protein; deformability, which highlights specific areas that may undergo structural alterations; and the eigenvalue, which indicates the stiffness of the protein and the energy required for conformational changes. Additionally, variance calculations were performed to assess the overall mobility within the protein and residue and atom indices were analyzed to pinpoint the exact locations and atoms involved in these dynamics. These simulations improve our understanding of the protein's stability, particularly when associated with ligands such as.

RESULTS

Determination of REME1 Nucleotide Sequence

To ascertain the complete sequence of the altered REME1 quality, an analysis is conducted. This investigation is very crucial for determining the protein's fundamental structure. **Table 1** displays the gene sequence that was obtained from UC Santa Cruz's genome browser.

Table 1: A database called UCSC is used to anticipate the whole sequence of the altered REME1 gene, which codes for the protein's basic structure.

The nucleotide sequence of the coding region	GAGTGATTTGAAATTTTTGAAGTTGTTTCCATAGTTTTAGTGGAGA CGATGAAGTCAGTAATGTCAAAGATCAAACTTTTTAGACCAGTCG TCACGTTACGTTGTTCTTACAGCTCCACAGATCAAACTCTTCTTCT TAGCGAATTTACCAGACTCTGTTACCAGAGAGACCTTCCCAGAGC TATGAAAGCAATGGATTCATTGCAAAGTCATGGTCTTTGGGCAGA CTCTGCAACTTATTCTGAGCTTATCAAGTGTTGTATATCTAATAGA GCTGTTCATGAAGGGAATCTCATTTGTCGTCATTTATACTTCAATG GTCATCGACCAATGATGTTTCTGGTTAATGTTCTGATCAATATGTA TGTAAAATTCAATCTTTTGAATGATGCTCACCAACTGTTCGATCAA ATGCCTCAAAGGAATGTTATTTCTTGGACTACGATGATTTCTGCTT ATTCTAAGTGTAAGATTCATCAAAAGGCTTTGGAGCTTTTGGTTTT GATGTTGAGAGATAATGTGAGGCCTAATGTGTATACTTACTCTTC TGTTTTGAGATC

EXPASY Translation Analysis

Utilizing the EXPASY technique, one can predict the fundamental structure of a challenging REME1 protein. As indicated in **Table 2**, this will lead to the prediction of the protein's main structure, which in turn will cause gene expression to gradually decline.

Table 2: The EXPASY tool predicts the primary structure of a REME1 protein

Primary Sequence of the mutated protein	MKSVMSKIKLFRPVVTLRCSYSSTDQTLLLSEFTRLCYQRDLPRA MKAMDSLQSHGLWADSATYSELIKCCISNRAVHEGNLICRHLYFN GHRPMMFLVNVLINMYVKFNLLNDAHQLFDQMPQRNVISWTTM ISAYSKCKIHQKALELLVLMLRDNVRPNVYTYSSVLRSCNGMSD VRMLHCGIIKEGLESDVFVRSALIDVFAKLGEPEDALSVFDEMVT GDAIVWNSIIGGFAQNSRSDVALELFKRMKRAGFIAEQATLTSVLR ACTGLALLELGMQAHVHIVKYDQDLILNNAL

Identification of mutations in the REME1 gene

Two important causes that contribute to the decrease in REME1 protein expression are changes to the protein sequences V13L and T351. It is a significant phenomenon that these mutations are found inside the protein binding pocket. A range of analytical techniques were used to produce the mutation list listed in Table 3.

Table 3; List of mutations identified with various techniques

Mutation	Polyphen 2	Mupro	I-mutant	PHDsp	PROVEAN
V15L	PROBABLY Damaging	Decrease	Decrease	Decrease	Deleterious
T35I	PROBABLY Damaging	Decrease	Decrease	Decrease	Deleterious

Prediction of REME1 protein secondary structure

In structural bioinformatics, the popular PSIPRED tool is used to forecast the secondary structure of proteins, especially those having erratic structures. The sequence is produced by this predictive model. Plots illuminate the structural organization of the protein by displaying strand, helix, and coil forms. Furthermore, PSIPRED highlights the precise locations where this full-blown structure is optional by providing an animation representation of the confidence score corresponding to such a forecast model. An additional useful memset sequence plot that defines the protein's transmembrane region and schematically shows the membrane-associated protein segments supports this plot. These instruments are essential for characterizing protein structures and for directing the subsequent experimental procedures, as results shown in **Figures 1** .

Figure 1: illustrates the psipred sequence plot, which indicates the sequence's helix, coil, and strand forms.

The REME1 protein's tertiary structure prediction using SWISS-MODEL

A popular computational biology toolbox has seen notable success. Created specifically to forecast the tertiary structures of proteins. SWISS-MODEL can independently predict protein structures from public datasets by using homology modelling techniques, such as independent and dependent approaches, producing incredibly accurate three-dimensional models. Researchers may examine the activities, interactions, and dynamics of proteins because of this prediction capability, which provides a thorough understanding of the spatial arrangement of amino acid residues. Additionally, additional tools like I-TASSER are used to validate the predictions generated by SWISSMODEL. To increase the protein model's accuracy, I-TASSER incorporates iterative structural assembly simulations and numerous threading alignments. Additionally, carrying out this extra validation improves the model's dependability. Figure. 2 and Figure 3 display the SWISS model's findings.

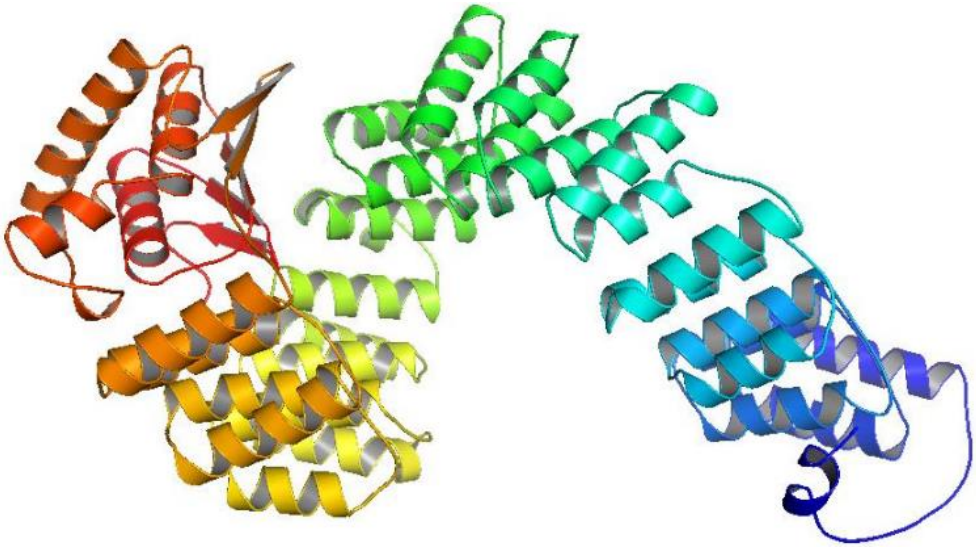

Figure 2: prediction of REME1 protein tertiary structure by SWISS model

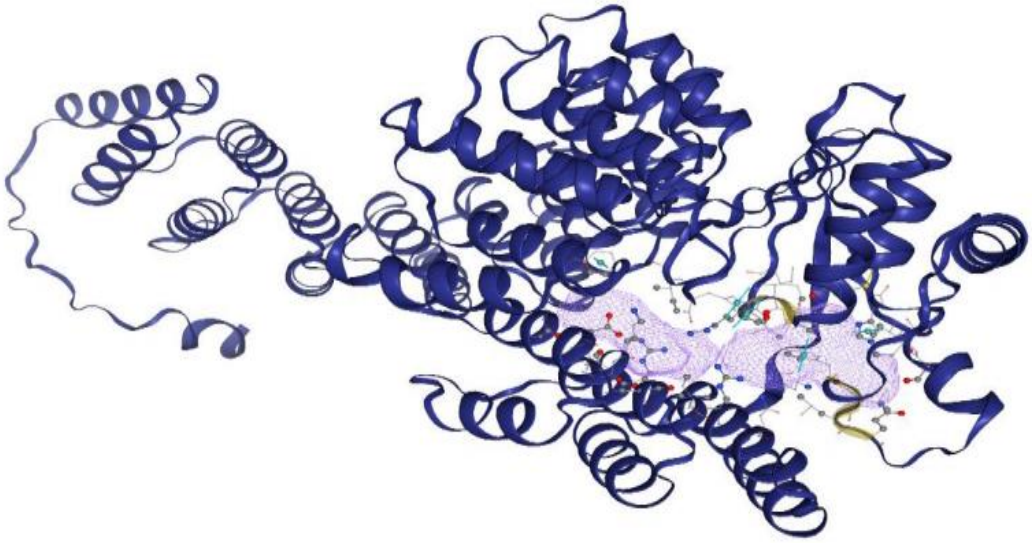

Figure 3: We have identified binding sites in the REME1 gene using protein plus that ligands will bind to and stabilize, reinforcing a whole pathway.

Verification of the suggested REME1 protein model

The results are enhanced by the use of Errat and Ramachandran plots for secondary structure verification. However, what was taught is validated by the data that Errat and Ramachandran's

plots provide for insilico-enhanced secondary structure predictions. Furthermore, the accompanying photos' graphical portrayal confirms the secondary structure predictions and lends credence to their legitimacy. **Figure 4** displays evidence of the Errat and Ramachandran plot.

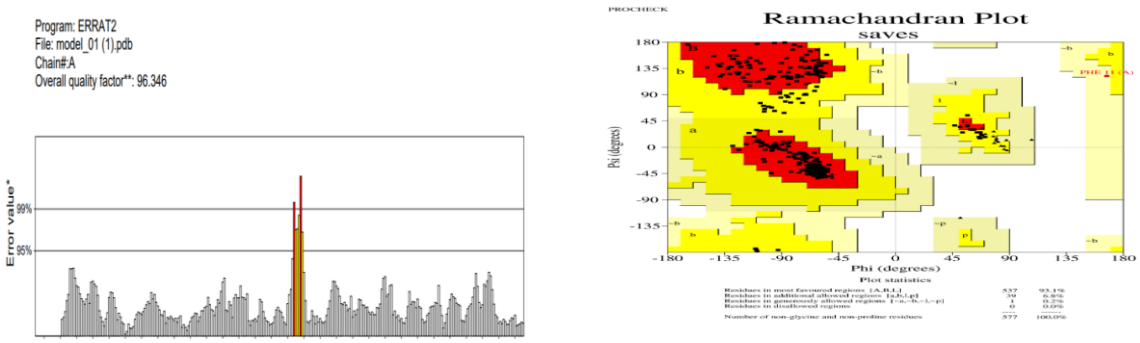

Figure 4: Errat's quality factor score of 90 and the Ramachandran plot's value of 94.9 are used to validate the secondary structure, confirming the significance of your research.

Molecular docking of REME1 for virtual screening

This depiction presents the novel pharmaceutical substance baicalein, which interacts with the REME1 protein to stabilize its structure and increase the expression of the REME1 gene. According to the data shown in the following graphics, the representation of this unique medication highlights its potential therapeutic efficacy in modifying REME1 activity. The binding location and bond distance between the ligand and REME1 protein are displayed in **Figures 5** and **Figure 6.**

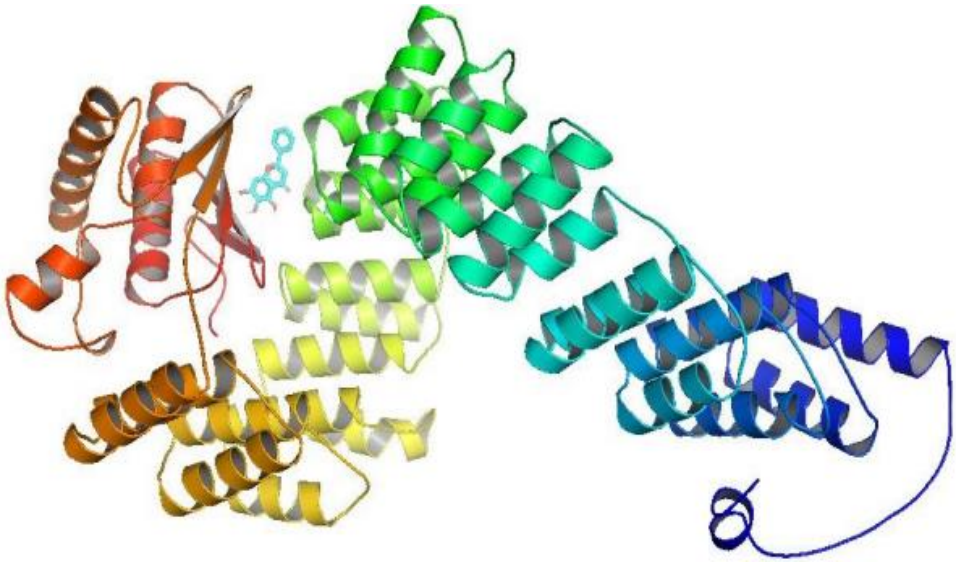

Figure 5: This figure illustrates where the baicalein binds to the REME1 protein.

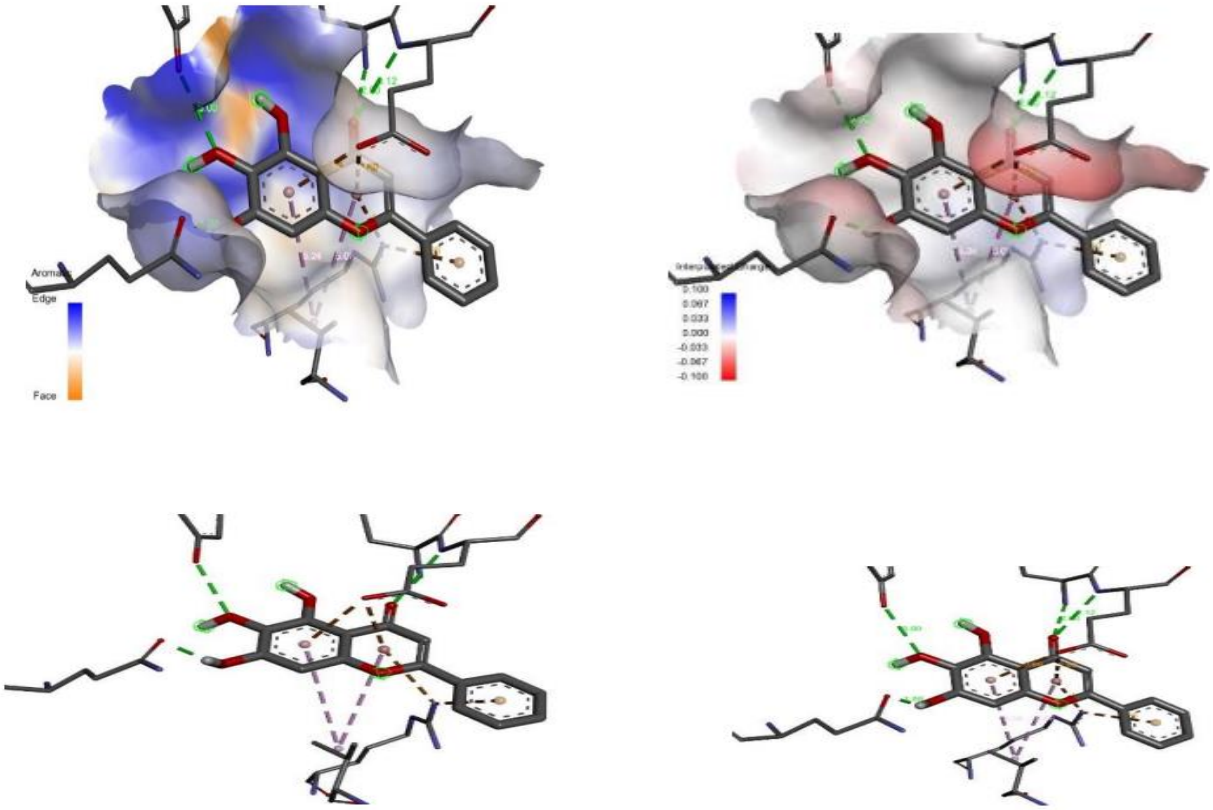

Figure 6: This demonstrates the bonding distance. The medication baicalein binds to the REME1 protein through a variety of bond types, including H bonds.

Baicalein's target classes

The categories of pharmacological targets that the chemical affects are depicted visually. The drug's target classes are displayed in **Figure 7.**

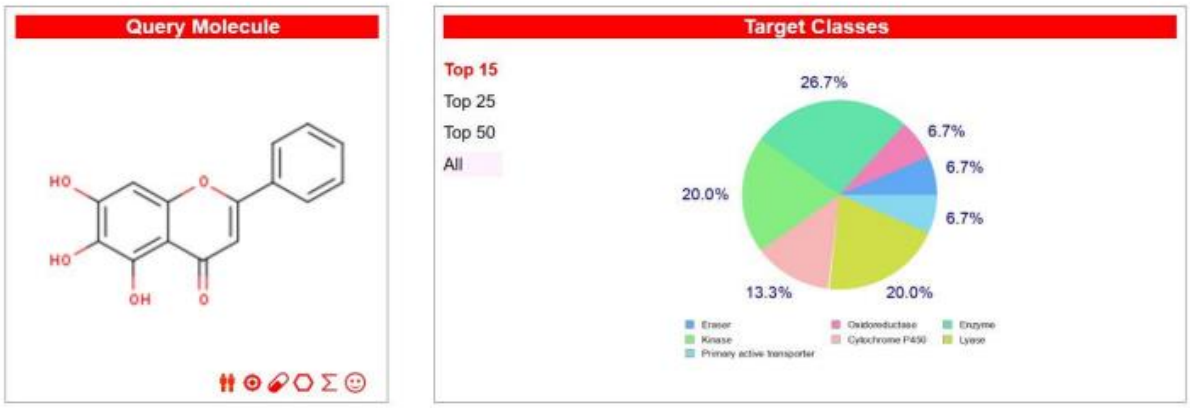

Figure 7: This image serves as an illustration of these pharmacological target classes. The method of drug attachment to the protein within the binding pockets has proven the effectiveness of this study. Addressing mitochondrial failure, autophagy, cell death, disrupted proteostasis, changed nutrition sensing, and impaired intercellular communication produces an elevated degree of oxidative stress, which results in improved cell expression and stability of the REME1 gene.

ADME analysis of Baicaleins

The boiled egg model's visual representation effectively illustrates the remarkable absorption capabilities of baicalein its absorption within the human gastrointestinal tract (HIA) and its capacity to pass through the blood-brain barrier (BBB). The pharmacokinetic characteristics of baicalein and its possible clinical uses are described in Figure 8 and Table 4.

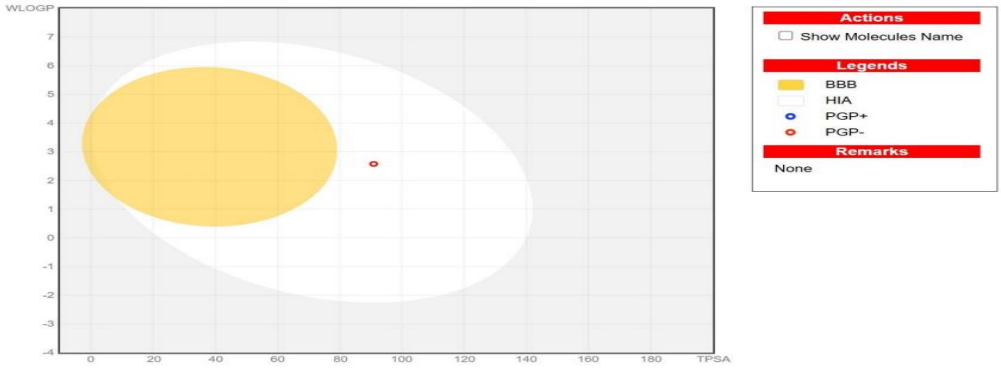

Figure 8: The blood-brain barrier can be readily crossed by *Baicaleins*, as demonstrated by the cooked egg model.

Table 4: This finding strengthens the invention's confidence that the medication *Baicaleins* is water soluble, has strong absorption by the blood-brain barrier, and does not break the Lipinski rule.

Physiochemical Properties	
Formula	C15H10O5
Mol. Weight	270.24 g/mol
Num, from, heavy atoms	20
Num, H-bond acceptors	5
Num, H bond donors	3
Molar Refractivity	73.99
TPSA	90.90 A
Drug likeness	
Lipinski	0 violation
Pharmacokinetics	
GI absorption	High
BBB permeant	NO
P-gp substrate	NO
CYP1A2 inhibitor	YES
CYP2C19 inhibitor	NO
CYP2D6 inhibitor	NO
CYP3A4 inhibitor	NO

Summary of Docking Results

The affinity of Baicaleins for the REME1 protein structure has been identified by docking studies conducted using PyrX as shown in Table 5.

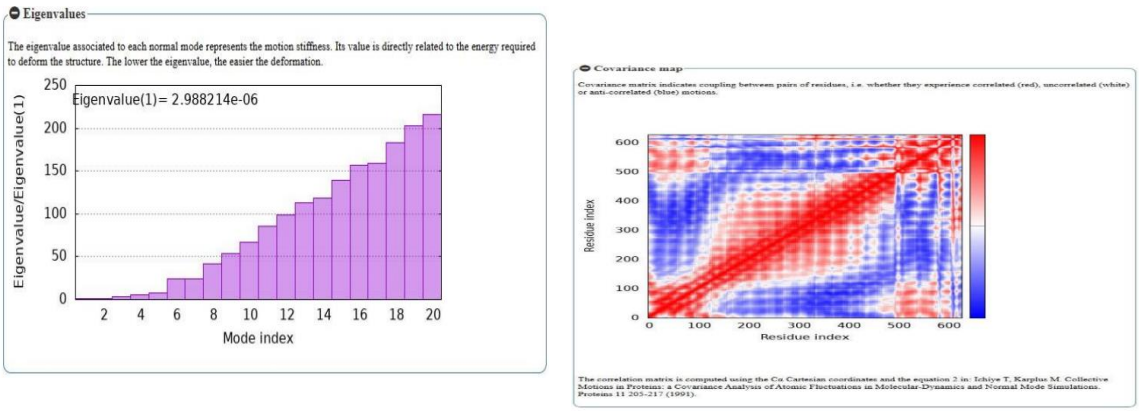

Table 5: The docking analysis's findings show that there is a 6.7 kcal/mol binding affinity between Baicaleins and the REME1 protein. To ensure accuracy and consistency, this conclusion was validated using a few docking applications, including AutoDock Vina, SwissDock, and PyRx. These additional technologies increase the confidence in the docking analysis, confirming the strong interaction between the ligand and REME1 protein.

model_01_(1)_5281605_uff_E=197.50	-7	0	0
model_01_(1)_5281605_uff_E=197.50	-6.7	7.079	3.983
model_01_(1)_5281605_uff_E=197.50	-6.5	8.327	5.021
model_01_(1)_5281605_uff_E=197.50	-6.4	22.197	20.385
model_01_(1)_5281605_uff_E=197.50	-6.3	24.114	22.011
model_01_(1)_5281605_uff_E=197.50	-6.2	22.659	20.945
model_01_(1)_5281605_uff_E=197.50	-6.1	40.921	39.258
model_01_(1)_5281605_uff_E=197.50	-6	14.398	12.336
model_01_(1)_5281605_uff_E=197.50	-6	34.339	32.738

Molecular Simulation: Dynamics

The structural and functional characteristics of the REME1 protein were anticipated by molecular dynamics simulations conducted via the iMODS as shown in Figure 9.

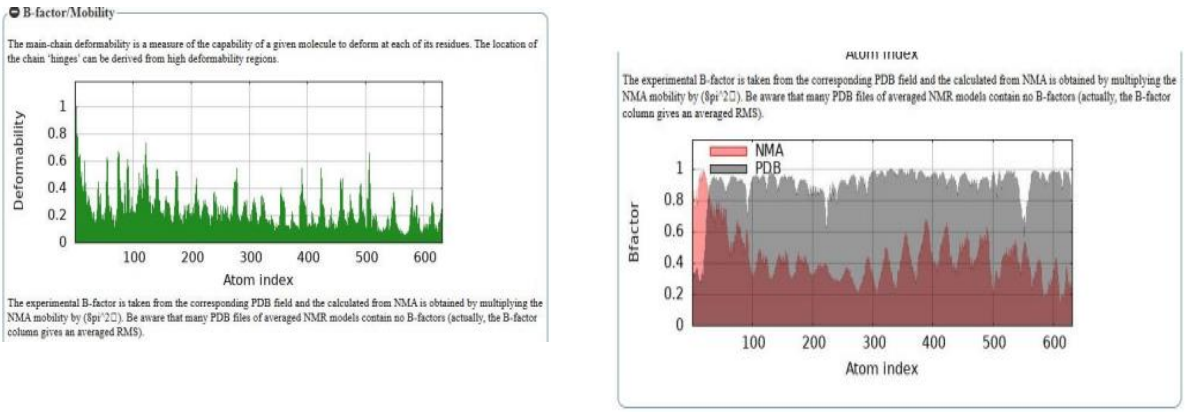

Figure 9: This figure shows that the B-factor, which provides information about the flexibility of various protein regions, yields excellent results, indicating that the relevant regions have optimal flexibility. Particularly satisfactory results are also shown by the deformability index, which identifies specific protein areas that may undergo structural changes. Furthermore, consistently strong results are obtained using the eigenvalue, which measures the protein's stiffness and represents the energy required for conformational changes. Additionally, the residue and atom indices were analyzed to specifically identify the specific sites and atoms implicated in these

dynamics, and the variance was computed to assess the overall mobility throughout the protein. Both analyses produced excellent findings. Our understanding of the protein's stability is enhanced by computer simulations, particularly when it is coupled to ligands such as baicaleins. The results unequivocally demonstrate that the anticipated structural and functional dynamics are optimal, hence validating the stability and efficacy of the ligand-protein interaction. These investigations show great promise for therapeutic uses in averting metabolic dysfunction and age-related diseases.

Navigating the PATHWAY

The PATHWAY provides an in-depth understanding of molecular interactions throughout biological systems, accompanied by detailed visual representations as shown in Table 6. The table shows that the upregulation of REME1 is proposed to enhance mitochondrial stability by regulating the assembly or processing of respiratory complexes, which plays a crucial role in improving mitochondrial bioenergetics. This improvement is instrumental in reducing oxidative stress, a significant contributor to ageing and the progression of pancreatic cancer. By decreasing the production of reactive oxygen species (ROS), REME1 helps to mitigate DNA damage and genomic instability, thus slowing down the initiation and progression of cancer. Additionally, REME1 activation is hypothesized to impact the AMPK pathway, which is central to metabolic regulation. AMPK activation enhances glucose metabolism and reduces lipogenesis, while simultaneously stimulating the Akt pathway. This dual-pathway modulation not only promotes cell survival and metabolic homeostasis but also protects pancreatic β-cells from apoptosis. Such protective effects preserve β-cell integrity, alleviating age-related metabolic dysfunctions and reducing the risk of pancreatic cancer. In the pancreatic microenvironment, chronic inflammation is a defining characteristic of cancer development. REME1 upregulation could counteract this by suppressing the production of inflammatory cytokines and inhibiting fibrotic signalling. Mechanistically, this involves the downregulation of the NF-κB signalling pathway and TGF-β pathways, which are key drivers of pro-inflammatory and fibrotic responses. By mitigating these processes, REME1 protects pancreatic tissue from damage associated with inflammation and fibrosis. Moreover, REME1 may play a role in maintaining telomere stability by reducing oxidative damage and facilitating the repair of telomeric DNA. This preservation of telomeres delays replicative senescence, which is often a precursor to cancer development. By preventing senescence-induced secretory phenotypes (SASP), REME1 inhibits the pro-tumorigenic effects of cellular ageing, thereby contributing to the prevention of cancer. Beyond these protective mechanisms, REME1 is implicated in the regulation of lipid metabolism. Its modulation of the LXRα and SREBP1 pathways helps reduce lipid accumulation and foam cell formation, alleviating metabolic stress linked to cancer progression. This lipid metabolism regulation is critical for maintaining pancreatic health and preventing the metabolic dysregulation that supports tumour growth and at last REME1 activation may reverse the Warburg effect commonly observed in pancreatic cancer cells, which favours glycolysis over oxidative phosphorylation for energy production. By restoring oxidative phosphorylation, REME1 normalizes energy metabolism, creating an environment less conducive to tumour proliferation and progression. These multifaceted mechanisms highlight the potential of REME1 as a therapeutic target for improving mitochondrial function and combating pancreatic cancer.

Table 6: This table summarizes the relevant metabolic pathways and their relation to the REME1 hypothesis, suggesting how REME1 upregulation is thought to improve mitochondrial functioning and decrease levels of reactive oxygen species

Metabolic Pathway	Mechanism	Connection to REME1 Hypothesis
Amino Acid Metabolism	Glutamate, Glutamine, and Aspartate Metabolism help regulate mitochondrial stability and supply TCA cycle intermediates.	Reduces oxidative stress, supporting REME1 function in combating ROS production.
Valine, Leucine, and Isoleucine Biosynthesis	Involves the regulation of branched-chain amino acids that affect metabolism and mitochondrial function.	REME1 upregulation may modulate BCAA metabolism, improving mitochondrial function and reducing oxidative stress.
Lysine and Arginine Metabolism	This involves arginine joining nitric oxide production and its effect on mitochondrial function.	Finds way with metabolic regulation of REME1, specifically through AMPK and Akt paths for its metabolic homeostasis
Methionine and Cysteine Metabolism	Controls the homeostasis of sulfur amino acids, and regulates the cellular redox homeostasis and oxidative stress.	Reduces oxidative stress and production of ROS, preserving antioxidant defences that are vital to cellular health
Lipid Metabolism	It regulates storage and foam cell generation, related to metabolic stress and cancer progression.	REME1 upregulation may help reduce lipid accumulation, thereby alleviating the stress associated with pancreatic health and cancer progression
Glucose Metabolism (AMPK Pathway)	AMPK pathway activation boosts GLU uptake and mitochondrial functions	Effects of REME1 include improved glucose metabolism, reduced lipogenesis and enhanced energy balance at the cellular level.

Discussion

Malfunction of REME1 has been associated with ageing and several cancers, including pancreatic cancer(Bentolila et al., 2012). Cellular pathways such as protein folding, transport, and homeostasis fail with age, commonly leading to increased cellular stress. REME1 is important for maintaining cellular function through the regulation of ER protein quality control(Çiçek et al., 2022). Dysfunctional REME1 hinders this process and causes the accumulation of compromised proteins and over-activating oxidative stress factors responsible for ageing and the progression of diseases such as pancreatic cancer(Jia et al., 2014). These aberrations are often associated with aberrant signalling cascades, inflammatory processes, and disturbed cellular homeostasis in pancreatic cancer, which may promote carcinogenesis(Jiang et al., 2011). The accumulation of cellular damage due to the malfunction of REME1 could potentiate the development of cancer as the organism ages, by establishing a growth-promoting environment for cancerous cells. These

results indicate that the failure of REME1 activity may contribute to the cellular decay seen during ageing in addition to the propensity of pancreatic cancer-associated cells to develop tumours(Liu et al., 2013). Baicalein was found to preserve the structural stability of the mutant protein, which has a profound inhibitory effect against mutations. Mutations in REME1 result in either misfolded or otherwise disordered protein folding, which engenders cellular stress by preventing normal regulation of endoplasmic reticulum (ER) stress responses. Baicalein therefore engages with misfolded REME1 proteins and promotes their correct folding whilst inhibiting aggregation of these proteins, addressing this issue(Lohman, 1982). By stabilizing the tertiary structure of the mutated protein, it can enhance its functional activity and regain its ability to cope with cellular stress. Decreasing oxidative stress and prolonging telomere preservation are some potential treatment options to minimize the effects of REME1 mutations(Ramallo et al., 2008). Oxidative stress, a state characterized by excessive reactive oxygen species (ROS) and insufficient antioxidant defences, is implicated in cellular damage and ageing. Because REME1 mutations compromise protein folding and lead to an overload of misfolded proteins in the endoplasmic reticulum, oxidative stress might be aggravated(Munir et al., 2025). Therapeutic signalling targeting oxidative stress has been implemented to prevent protein aggregation, reduce cellular damage, and improve overall cell function. These might be agents such as Baicalein that exert antioxidant effects (lower oxidative stress, increase protein stability) or possibly even some other antioxidant. So telomere maintenance is another key therapeutic target. With ageing, telomeres the protective caps on chromosomes shorten, a phenomenon known as cellular senescence. Because REME1 mutations influence cellular stress responses and DNA repair pathways, telomere shortening could be accelerated. Methods to preserve telomere length, such as activating telomerase or inhibiting telomere-linked senescence pathways, could extend a healthy cellular lifespan and delay the onset of ageing-related diseases(Weber et al., 2010). It is possible that reducing oxidative stress and protecting telomeres are complementary mechanisms acting to revitalize cellular health, reduce the risk of ageing- and mutation-related diseases, as well as to reverse the damaging effects of REME1 mutations. Focusing on pathways such as telomere-preservation and oxidative-stress-mediated diseases can have a huge advantage in treating age-related illnesses(Weber et al., 2010). This means that oxidative damage will be reduced, allowing the cells to maintain the function of the cell and prevent degenerative diseases such as Parkinsons and Alzheimers. Improving telomere preservation could delay cellular senescence, with ramifications for age-related diseases such as cancer and heart disease. Targeting these mechanisms could promote healthy ageing and improve both longevity and quality of life. Extension of cellular health and mitigation of age-related diseases is the promise of these treatment methods, with all their caveats.

Conclusion

The REME1 gene has been implicated as a putative therapeutic target as a major regulator with antagonistic roles in both ageing and cancer pathways. In silico analysis indicated that baicalein could be a therapeutic ligand that could restore the activity of REME1, consistent with its role in ageing and cancer protection such as pancreatic cancer. Dysfunction of the REME1 gene is a major contributor to ageing and age-related diseases, in particular pancreatic cancer. REME1 dysregulation disrupts the major cellular pathways for protein folding, transport, and homeostasis, resulting in oxidative stress and the accumulation of misfolded proteins and setting the stage for the carcinogenesis process. The management of oxidative stress and stabilization of telomeres are important approaches being utilised to counteract the deleterious effects of REME1 mutations. Strategies that target these mechanisms can promote cellular health, extend a healthy lifespan, and protect against age-related diseases. Together, these pathways alleviate oxidative stress, regulate inflammation, and improve mitochondrial bioenergetics to restore cellular function and energy

use. This re-establishment of the REME1 function provides the possibility of a therapeutic strategy targeting ageing and diseases like pancreatic cancer. Thus, this work establishes a clear relevance of computational methods in cancer- and ageing research and lays a solid foundation for future experimental studies about targeted REME1 therapies. These results underscore the need for follow-up experimental verification of the molecular mechanism of REME1 and the potential relevance of baicalein therapeutics. Future research goals should focus on REME1-targeted treatments, as these may offer new avenues for treating cancer and age-related diseases, which in turn, may increase lifespan.

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All relevant data are within the paper and its supporting information files.

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