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Integrative Bioinformatic Analysis Reveals Potential Targets and Mechanisms Of Epigallocatechin Gallate In Preventing Cellular Senescence

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ABSTRACT

Background: Age-related diseases account for 51.3% of the leading causes of degenerative disease and mortality worldwide. A major contributor to death in age-related disease is the accumulation of senescent cells resulting from elevated reactive oxygen species (ROS) levels, which impair cell proliferation. Antioxidant compounds such as epigallocatechin gallate (EGCG), a constituent of banana peel, have been shown to reduce ROS levels and are correlated with the inhibition of cellular senescence. **Aim:** This study comprehensively investigates the potential targets and molecular mechanisms of EGCG in preventing cellular senescence through a bioinformatics approach coupled with in silico molecular docking. **Methods :** This study employed a bioinformatics approach, combined with in silico molecular docking, to elucidate the molecular mechanism by which EGCG inhibits cellular senescence and to characterize the strength of the interactions between EGCG and several candidate target proteins. The analysis identified 11 proteins that interact with EGCG derived from banana peel within the cellular senescence pathway. **Results:** Among these, Serpine1, MAPK14, TP53, and TERT exhibited the strongest binding interactions with EGCG relative to their native ligands. Molecular docking results demonstrated that all evaluated proteins formed stronger interactions with EGCG than with their respective native ligands. **Conclusion:** Collectively, these findings indicate that EGCG has the potential to prevent cellular senescence through a multi-target therapeutic mechanism associated with ROS regulation.

Keywords: *Age-related disease, Banana Peel, Cellular Senescence, EGCG, ROS*

INTRODUCTION

Age-related disease represents a complex category of conditions accounting for 51.3% of the leading causes of degenerative disease, including heart failure, diabetes, renal failure, and cancer, and is a major contributor to mortality.[1–3] Age-related disease is characterized by a progressive physiological decline in biological activity across organs, driven by the accumulation of DNA damage, which reduces cellular regenerative capacity and ultimately induces cellular senescence.[4,5] Senescence refers to an irreversible arrest of cell growth and replication that results in failure of cell proliferation.[6] Oxidative stress (ROS) induced by chemical exposure and ultraviolet radiation is a principal trigger of cellular senescence, leading to permanent cell-cycle arrest and apoptosis.[7–10] The senescence pathway

is critically dependent on the tumor suppressor protein TP53, which regulates the expression of senescence-associated target genes.[11] Previous studies have demonstrated that TP53 plays a central role in the DNA damage response induced by excessive ROS in senescent cells.[12–14] TP53 also modulates the expression of several downstream proteins, including Serpine1, MAPK14, and TERT, each of which plays an important role in cellular senescence.[15,16] Targeting the p53–ROS axis to regulate cellular senescence represents a promising strategy for developing novel therapeutics.

The use of antioxidant compounds has been shown to reduce ROS levels, enhance immune function, and prevent DNA damage, thereby limiting the accumulation of senescent cells.[17–20] However, synthetic antioxidant compounds are increasingly associated with adverse effects compared with natural antioxidants. One promising natural antioxidant is epigallocatechin gallate (EGCG), derived from banana peel. Banana peels remain an underutilized, readily available organic waste product.[21,22] EGCG isolated from banana peel has been reported to possess strong antioxidant capacity capable of lowering ROS levels and preventing cellular apoptosis, thereby exerting protective effects against diseases such as cancer and age-related disease.[23–25] Based on this evidence, EGCG holds considerable potential to prevent cellular senescence; however, the underlying mechanism through which its anti-senescence activity targets TP53-related proteins remains poorly characterized. Therefore, this study comprehensively investigates the potential targets and molecular mechanisms of EGCG in preventing cellular senescence through a bioinformatics approach coupled with in silico molecular docking.

MATERIALS AND METHODS

Secondary Data Collection for Bioinformatics Analysis

Secondary data for the bioinformatics analysis were collected from protein expression datasets relevant to senescence regulation, retrieved from PubMed NCBI-Gene using the keyword "cellular senescence." The chemical characteristics of EGCG were obtained from PubChem (https://pubchem.ncbi.nlm.nih.gov/). The Canonical SMILES notation obtained from PubChem was used to predict the cytotoxic activity of the compound against various cell lines using the CLC-Pred (Cell Line Cytotoxicity Predictor) web server (http://way2drug.com/Cell-line/). Direct protein targets (DPTs) of EGCG were retrieved using the Similarity Ensemble Approach (SEA) database (http://sea.bkslab.org/), the DrugBank protein target database (https://go.drugbank.com/), and SwissTargetPrediction. The overlap between the protein targets obtained from PubMed NCBI-Gene and the DPT datasets was analyzed using Venny (https://bioinfogp.cnb.csic.es/tools/venny/). Gene ontology (GO) analysis was performed using over-representation enrichment analysis (ORA) in WebGestalt, applying a false discovery rate (FDR) cutoff of <0.05. Protein–protein interaction (PPI) networks were constructed and analyzed using STRING-DB v11.0 (https://string-db.org/) to delineate the senescence-associated pathway. The strength of protein–protein interactions was further evaluated using Cytoscape-cytoHubba to identify the hub proteins within the network.

Identification of Target Protein Expression Using UALCAN

UALCAN was used to evaluate the expression levels of the eight target proteins across various cancer cell types relative to normal cells. This analysis was performed to confirm the elevated expression of the eight target proteins in abnormal (malignant) cells.

In Silico Molecular Docking Study

The three-dimensional structures of the 11 primary target proteins were obtained from the Protein Data Bank (PDB) (https://www.rcsb.org/), and the Canonical SMILES structure of EGCG

was retrieved from PubChem. Molecular docking was performed to determine the binding affinity between the ligand and each target protein, followed by visualization of the macromolecule–ligand interaction to identify the amino acid residues and chemical bonds forming the binding site of each direct protein target, using Molecular Operating Environment (MOE) software licensed to Universitas Gadjah Mada (UGM). This process was conducted to compare the docking scores between each protein and its native ligand versus EGCG. The molecular docking results yielded binding affinity values (kcal/mol; docking score), reflecting the strength of the interaction between the ligand and the receptor.

RESULTS

Bioinformatic Profile of EGCG in Relation to Cellular Senescence

A bioinformatics approach using publicly available databases was employed to predict proteins involved in cellular senescence that are influenced by EGCG. Based on bioinformatics analysis, 38 target proteins were identified as direct targets of EGCG using data from the SEA, DrugBank protein targets, and SwissTargetPrediction databases. Analysis of NCBI-Gene using the keyword “cellular senescence” yielded 355 target proteins associated with the cellular senescence mechanism. Cross-referencing these two datasets revealed 11 proteins that are direct targets of EGCG and are also implicated in the cellular senescence mechanism (Figure 1A). These proteins include TERT, AKT1, HIF1A, TP53, MAPK14, MET, MAPK8, PRKCD, MAPKAPK5, SERPINE1, and PRKCH. These 11 proteins were further analyzed using STRING-DB to determine the strength of their protein–protein interactions, yielding a network of 11 nodes and 15 edges with an average node degree of 2.73. The results further revealed that nine of the eleven proteins interact with one another, whereas two proteins, PRKCH and SERPINE1, showed no interaction with the other proteins in the network (Figure 1B). This finding suggests that EGCG exerts its anti-senescence effects through multiple pathways.

The 11 proteins were subsequently classified according to functional gene ontology using ORA in WebGestalt, which revealed that the therapeutic targets of EGCG (TTE) exert a strong influence on the senescence process through mechanisms including self-induced premature senescence, replicative senescence, and cellular senescence, as determined by biological process analysis (Figure 1C). These findings guided this study's subsequent focus on exploring the primary proteins involved in regulating cellular senescence. Node analysis revealed that the three proteins with the highest degree scores were TP53, HIF1A, and AKT1 (Figure 1D).

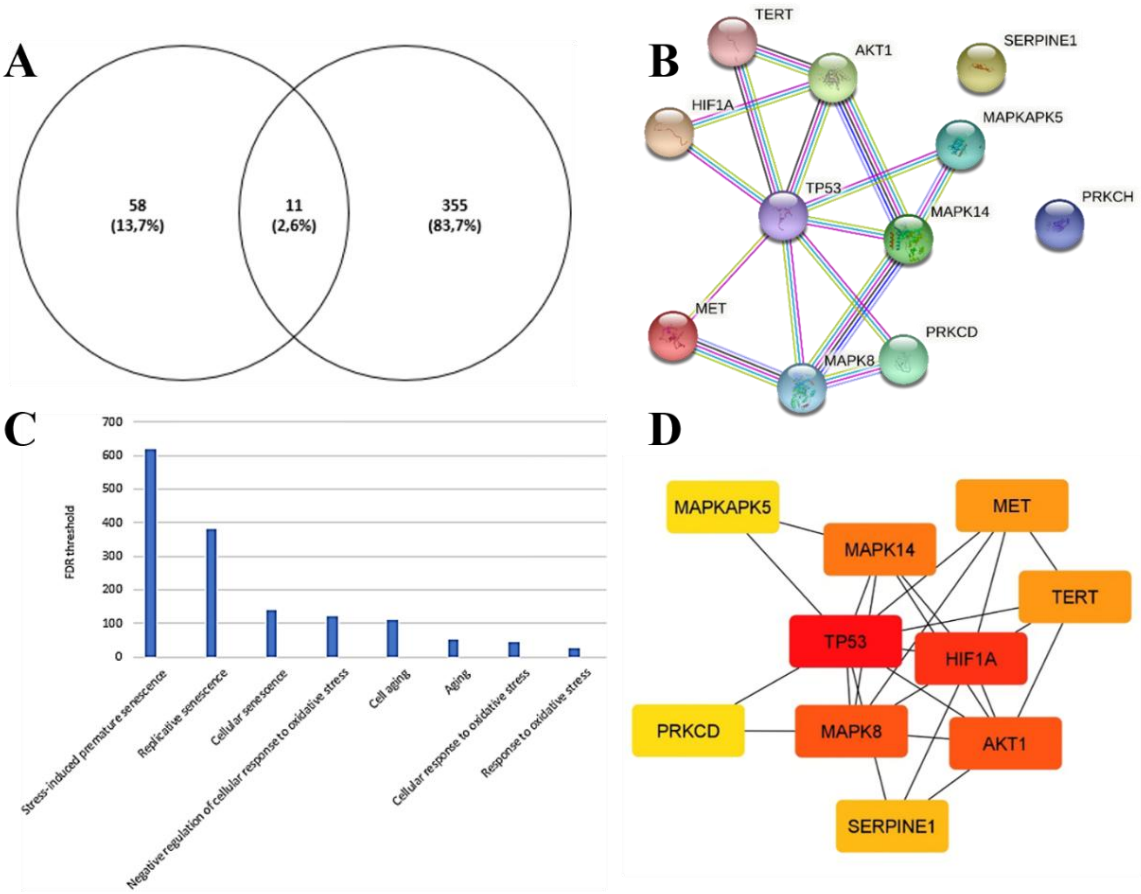


Figure 1. Bioinformatic analysis of EGCG in relation to cellular senescence. (A) EGCG target proteins associated with senescence markers. (B) Protein–protein interactions among the therapeutic target proteins of EGCG (TTE) determined via STRING. (C) Involvement of TTE proteins in biological processes, molecular function, and cellular components. (D) The 11 TTE genes selected based on the highest degree scores, visualized using Cytoscape.

Analysis of Target Protein Expression Levels Using UALCAN

The TCGA database is the largest and most comprehensive gene-chip database for predicting protein expression across multiple cell types.[26,27] UALCAN is a data-extraction platform built upon the TCGA database and provides in-depth analysis of TCGA gene expression profiling data.[28,29] In this study, we performed an in-depth investigation of the expression profiles of the eight proteins with the most substantial roles in the cellular senescence process and found that the expression of all eight proteins, including TP53, SERPINE1, AKT1, TERT, PRKCD, MET, MAPK8, and MAPK14, was significantly elevated in skin cutaneous melanoma (SKCM) relative to normal cells. Overall, expression of these proteins was elevated across several cancer cell types, indicating a senescence-associated cellular state. This analysis confirms that the elevated expression of these eight proteins across multiple cancer types reflects their substantial involvement in the cellular senescence process (Figure 2).

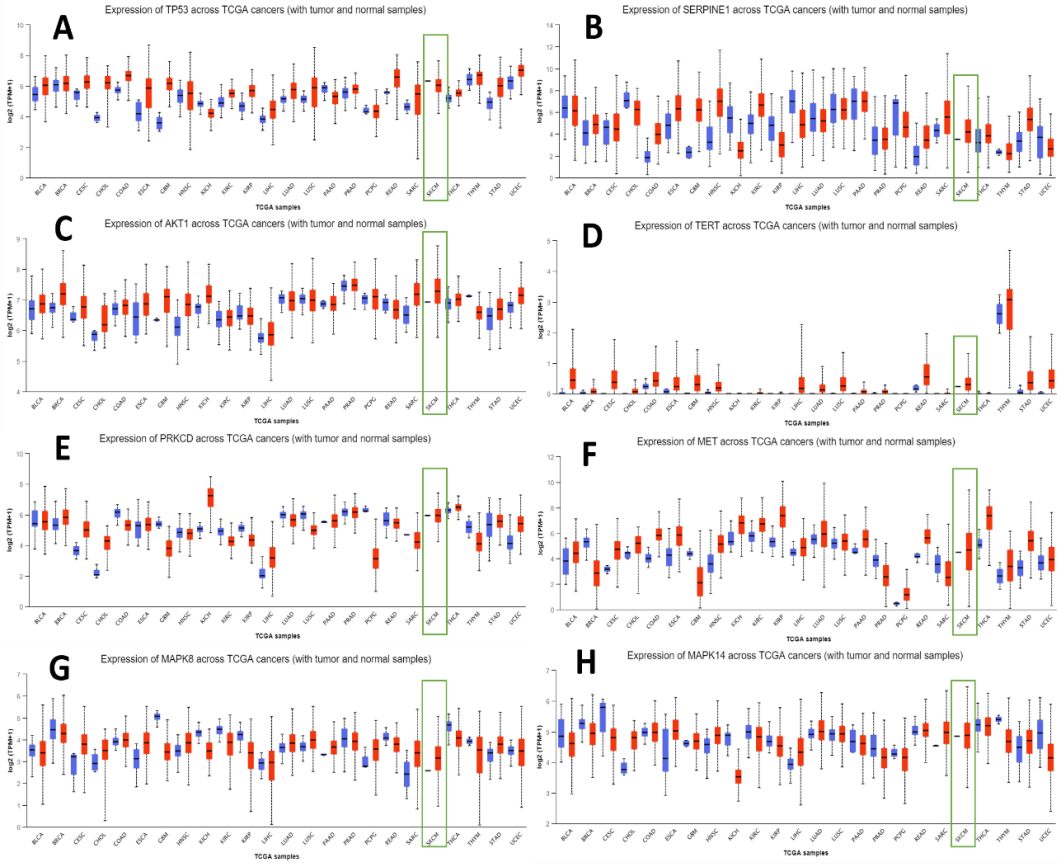


Figure 2. Expression levels of (A) TP53, (B) SERPINE1, (C) AKT1, (D) TERT, (E) PRKCD, (F) MET, (G) MAPK8, and (H) MAPK14 across several cancer cell types compared with normal cells.

Table 1. Docking scores of EGCG against the eight target proteins

Ligand	**Binding Affinity (kcal/mol)**	**RMSD (Å)**
TERT	-12.8	1.87
TP53	-16.2	1.39
MAPK14	-22.7	1.16
MET	-3.7	1.25
MAPK8	-0.3	1.55
AKT1	-10.3	1.89
SERPINE1	-23.8	1.23
PRKCD	-7.5	1.65

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Molecular Interaction of EGCG Revealed by In Silico Molecular Docking

An in silico molecular docking study was conducted for eight target proteins TERT, TP53, MAPK14, MET, MAPK8, AKT1, Serpine1, and PRKCD, which play the most substantial roles in the cellular senescence process. The results demonstrated that several compounds bound the target receptors at the desired active sites. Docking scores were evaluated based on the root-mean-square deviation (RMSD) of each binding pose. EGCG exhibited stronger interactions with Serpine1, MAPK14, TP53, and TERT than their respective native ligands (Table 1), with several involving hydrogen and covalent bonds (Figure 3). These findings indicate that EGCG has the potential to act as a multi-target therapeutic agent against Serpine1, MAPK14, TP53, and TERT, proteins associated with the inhibition of oxidative-stress-induced cellular senescence.

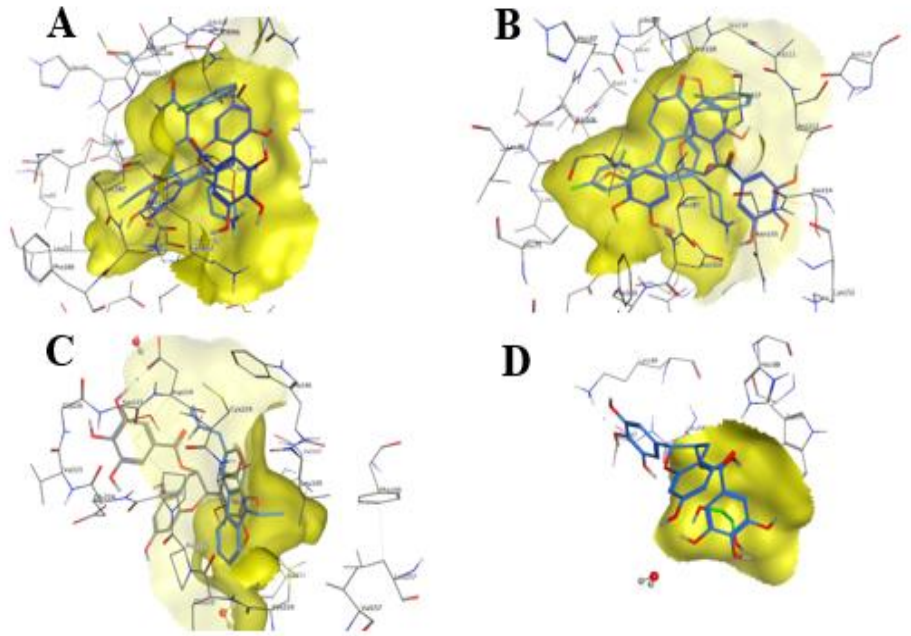


Figure 3. Visualization of the strongest interactions between EGCG and (A) Serpine1, (B) MAPK14, (C) TP53, and (D) TERT.

DISCUSSION

The transcription factor p53 plays a critical role in the mechanism of cellular senescence. One of the key functions of TP53 is mediating the cellular response to stress.[11,30] Activation of TP53 occurs in response to DNA damage, leading to cell-cycle arrest that allows the cell to undergo DNA repair, enter cellular senescence, or undergo apoptosis. This mechanism enables the cell to preserve genomic integrity, which underlies the role of TP53 in suppressing cancer cell growth.[31] Interestingly, recent studies have reported that TP53 overexpression together with its regulator ARF (P19) not only suppresses cancer growth but also significantly extends the lifespan of mice.[32,33] Previous study has shown that EGCG can extend cellular lifespan by suppressing TP53 expression.[23,24] In addition, the interaction between EGCG and HIF-1A has been implicated in delaying premature cellular senescence through activation of macrophage migration inhibitory factor (MIF).[34,35] Other studies have reported that EGCG inhibits the synthesis of MAPK14 protein, suggesting a potential role in suppressing the cellular senescence process.[36,37] Together, these findings support that EGCG exerts its anti-senescence effects through multiple, interconnected pathways rather than through a single target.

This study showed the significantly elevated expression of TP53, SERPINE1, AKT1, TERT, PRKCD, MET, MAPK8, and MAPK14 across several cancer cell types, particularly SKCM, relative to normal cells indicates a senescence-associated cellular state and confirms the substantial involvement of these eight proteins in the cellular senescence process. This expression pattern lends further support to their selection as priority targets for the subsequent molecular docking analysis. In the molecular docking analysis, the RMSD values obtained for all complexes were below 2 Å, confirming that the protein structures used for docking were appropriately validated. A more negative binding affinity value indicates a stronger interaction and thus a more substantial inhibitory effect on the corresponding signaling pathway.[38] The stronger binding of EGCG to Serpine1, MAPK14, TP53, and TERT compared with their native ligands, mediated in part by hydrogen and covalent bonds, indicates that EGCG has the potential to act as a multi-target therapeutic agent against proteins associated with the inhibition of oxidative-stress-induced cellular senescence.

CONCLUSION

TP53 is a protein that plays a key role in regulating intracellular ROS levels in the context of cellular senescence. Elevated ROS levels are a hazardous driver of degenerative disease and mortality. TP53 is therefore considered to play a critical protective role in preventing senescence. The findings of this study demonstrate that TP53 is overexpressed across multiple cancer cell types, consistent with a supportive role in the senescence process. EGCG was found to selectively compete with TP53, indicating strong promise for its development as an anti-senescence agent. Nevertheless, further research is required to directly evaluate its activity in senescent cells.

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Authors' contributions

All authors contributed to the discussion of results, reviewed the final manuscript, and approved the submitted version.

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None.

Conflict of interest

The authors declare that there are no conflicts of interest related to this work.

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