Research Article

Multi-target effects of flavonoids as PPARG agonists in TCGA cancers

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PPARG (peroxisome proliferator-activated receptors gamma) is a nuclear receptor protein superfamily member, PPARG agonists have been proven to have broad anticancer properties in experimental studies. Associated clinical oncology investigations have been widely conducted, but no good relevant findings have been reported thus far. This might be caused by the limitations of a few cancer types of clinical studies. Simultaneously, screening natural products of PPARG agonists with minimal toxicity and side effects may aid in the clinical translation of PPARG agonists into the field of cancer. To that purpose, we investigated the association between PPARG gene expression and prognosis in 34 TCGA cancers and discovered that high PPARG gene expression was only a significant correlation ($p < 0.05$) with overall survival and progression-free survival in KIRP and UVM patients. An up-regulated PPARG expression with down-regulated ATP8B3 expression had the best prognosis in KIRP and UVM patients revealed by differential expression analysis, KEGG enrichment analysis, and tumor single-cell sequencing analysis. Flavonoids in yellow tea were demonstrated may both activate PPARG and inhibit the action of ATP8B3 using quantitative structure-activity relationships and molecular docking. As natural PPARG agonists, tea flavonoids are worth additional investigation in the field of clinical cancer research, especially in KIRP and UVM.

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1. Introduction

PPARG (peroxisome proliferator-activated receptors gamma) is a nuclear receptor protein superfamily member that regulates the transcription of fatty acid peroxisomal-oxidation pathway-

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related enzymes like acyl-CoA oxidase, as well as adipocyte differentiation, glucose metabolism, and other biological processes [1][2][3]. PPARG agonists can induce terminal differentiation of tumor cells, reduce cell proliferation, increase cell death, suppress innate inflammation, and regulate several cancer models in many cancer types[4]. Several demographic surveys and cancer clinical investigations in recent years have revealed that PPARG agonists may have therapeutic relevance[5].

In a phase 1 clinical study of Japanese mCRC (Metastatic Colorectal Cancer) patients, the PPARG agonist Efatutazone coupled with FOLFIRI demonstrated adequate safety and effectiveness (DCR=57.1%)[6]. Acceptable safety and efficacy have also been demonstrated in phase 1 clinical studies in cancer patients, including a phase 1/2 clinical study (NCT00603941) of Etanerone combined with paclitaxel in patients with ATC (Anaplastic Thyroid Cancer), but the study was not continued due to the small number of patients included (n=15)[7]. A phase 1 clinical trial of Etabonone monotherapy in myxoid liposarcoma (NCT02249949) is now underway. A phase 2 clinical trial (NCT02888964) of the PPARG agonist pioglitazone in combination with imatinib demonstrated safety in patients with chronic myelogenous leukemia (CML). The results of a phase 2 clinical investigation of the PPARG agonist Rosiglitazone as a monotherapy in liposarcoma (NCT00004180) have not yet been published. Because PPARG agonists are extensively used in the treatment of type 2 diabetes, most research on PPARG agonists in cancer treatment begins with patients with type 2 diabetes who take PPARG agonists. Although Daiichi Sankyo's new generation of high-efficiency PPARG agonist Efathrone has entered Phase II clinical studies in the treatment of mCRC and other malignancies. At the moment, the vast majority of tumor clinical studies targeting PPARG agonists are limited to a few cancer types, and understanding the specific effects of PPARG agonists in different tumors is critical for the clinical translation of such drugs.

TZDs (Thiazolidinediones, a type of PPARG agonist that includes Rosiglitazone) have certain applications in diabetes and potential applications in tumor, but a large number of studies have shown that using TZD-type PPARG agonists increases the risk of liver toxicity, edema, myocardial ischemia, heart failure, and fractures[8][9][10][11], It is advantageous to discover natural substances with minimal toxicity and PPARG agonist activity[12]. Flavonoids, which are essential physiologically active chemicals found in a wide range of plants, have the potential to become a new generation of natural PPARG agonists and to be used in cancer treatment. Yellow tea, on the other hand, made from the Camellia sinensis leaf, has been demonstrated to be high in Flavonoids[13][14][15].

In this study, we will examine the PPARG gene expression and prognosis data from 34 cancers in The Cancer Genome Atlas (TCGA), identify specific tumor types whose prognosis can benefit significantly from PPARG gene expression upregulation, and compare the gene expression profiles of these patients to those who cannot benefit from PPARG upregulation. Then, in our other study, we will see if the flavonoids found in yellow tea using liquid chromatography-tandem mass spectrometry (LC-MS/MS) may act as natural PPARG agonists and assist cancer patients[15].

2. Materials and methods

2.1. PPARG gene expression and prognosis

"Survival map" and "Survival analysis" in "GEPIA2"16 (Gene Expression Profiling Interactive Analysis 2) were used to analyze the survival, including OS (Overall survival) and DFS (Disease-free survival), of patients with different PPARG expression in TCGA tumors, "Group Cutoff" is "Median", "Cutoff-High /Low (%) " is 50, and the hazard ratio according to the Cox PH model was[16].

2.2. Differentially expressed genes analysis

The R tool "TCGA2STAT" was used to download the detected cancer patient transcriptome sequencing data in TCGA, and the patients were divided into two groups based on their individual PPARG gene expression levels: high PPARG expression and low PPARG expression. To visualize the gene differential expression pattern and co-differentially gene expression (up-regulation gene in all PPARG benefits patients) in malignancies, volcano and Venn maps were created. To illustrate differentially expressed genes and expression changes in each PPARG expression group, a heat map was created[17].

2.3. Gene enrichment and tumor single-cell analysis

"Metascape" was utilized to do a KEGG enrichment analysis on the differentially expressed genes in cancer patients who had a PPARG benefit predictive. A heat map was created based on the tumor single-cell atlas data (CancerSEA) to illustrate the discovered gene expression change of PPARG up-regulation patients and the biology process effect of these gene expression changes in cancer cells. Patients were separated into four groups based on the expression differences of two genes, and survival curves were created to represent the overall survival of the patients [18][19].

2.4. *Probing the PPARG agonist activity of Flavone via QSAR modeling*

Figure 1 depicts a summary of the process for this section of the investigation. In brief, this comprised developing a large-scale QSAR (quantitative structure-activity relationship) model for predicting and assessing PPARG activation in compliance with OECD norms, as follows: I a data set with a specified endpoint; (ii) an unambiguous learning method; (iii) the QSAR model's application area; and (iv) the use of acceptable goodness-of-fit, robustness, and predictivity metrics. The molecular PubChem fingerprints were retrieved and annotated using PaDEL-Descriptor 2.21, and the model was trained using a random forest model[20][21][22].

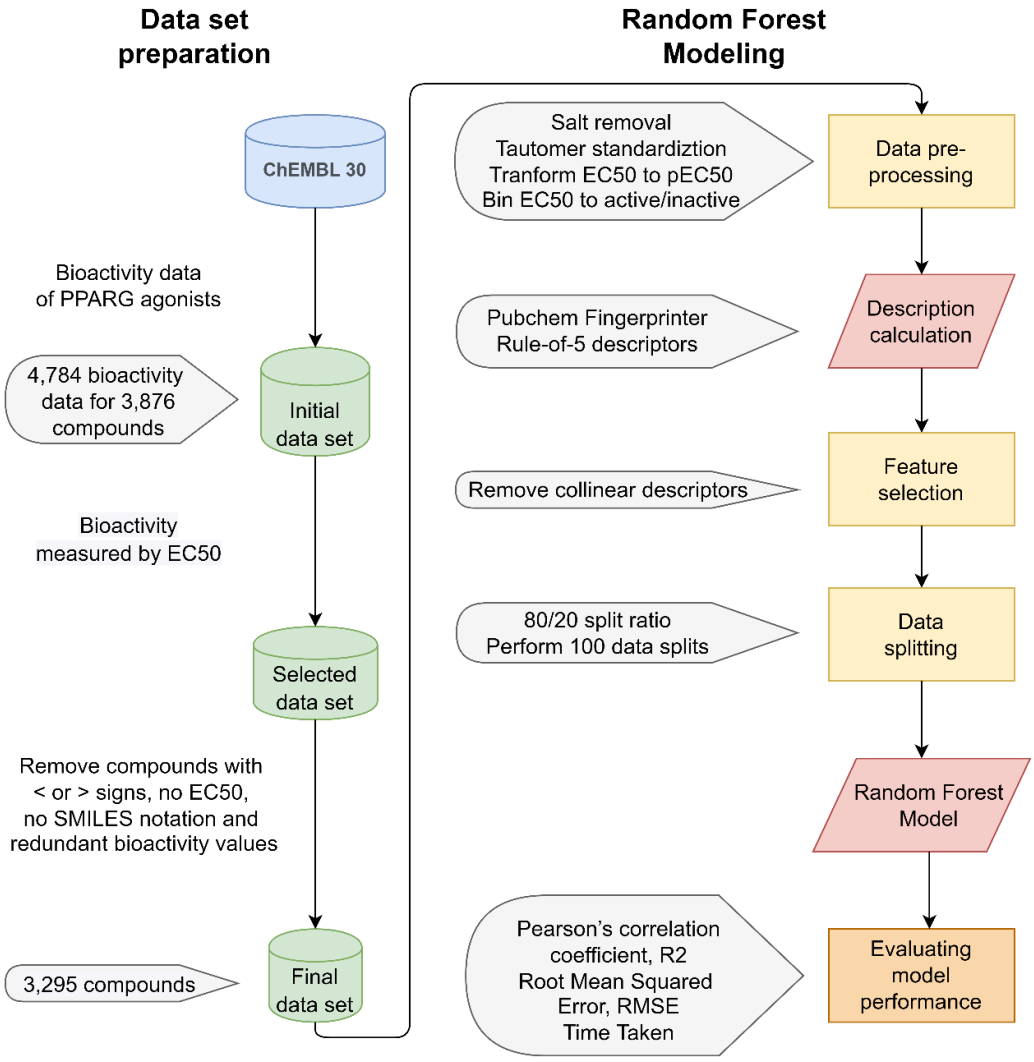

Fig. 1. Workflow of random forests modeling for investigating PPARG agonists activity.

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2.5. Molecular docking

Molsoft (molsoft.com/mprop) and SwissADME were used to determine parameters throughout the molecular docking procedure (swissdock.ch). All small molecule compounds' structures were generated in ChemDraw 8.0 and converted to 3D structures. To optimize the structure, all small molecule compounds were subjected to energy minimization using the AMBER10 force field in MOE (Molecular Operating Environment) and stored in pdb format for future molecular docking investigations. The target protein's crystal structure is retrieved from the protein database (www.rcsb.org/pdb). The molecular docking program MOE is utilized, and the binding site is identified by the binding ligand in the protein's crystal structure. Each docking produces a docking conformation that may bind freely. The assessment benchmark is an absolute value of DS (Docking score) greater than 6, and the complex of small molecule ligand and receptor protein is screened and the structural diagram is created[23][24][25].

3. Results

3.1. Prognostic impact of PPARG expression

Figure 2 depicted the findings of an analysis of PPARG gene expression and prognosis data from 34 cancers in the TCGA database. High PPARG expression is associated with a better overall survival (OS) of Bladder Urothelial Carcinoma (BLCA), Kidney Renal Clear Cell Carcinoma (KIRC), Rectum adenocarcinoma (READ), and uveal melanoma (Uveal Melanoma, UVM), as well as a better progression-free survival (DFS) of KIRC, Kidney Renal Papillary Cell Carcinoma Meanwhile, increased PPARG expression was linked to a poor prognosis in patients with liver hepatocellular carcinoma (LIHC) and glioblastoma multiforme (GBM).

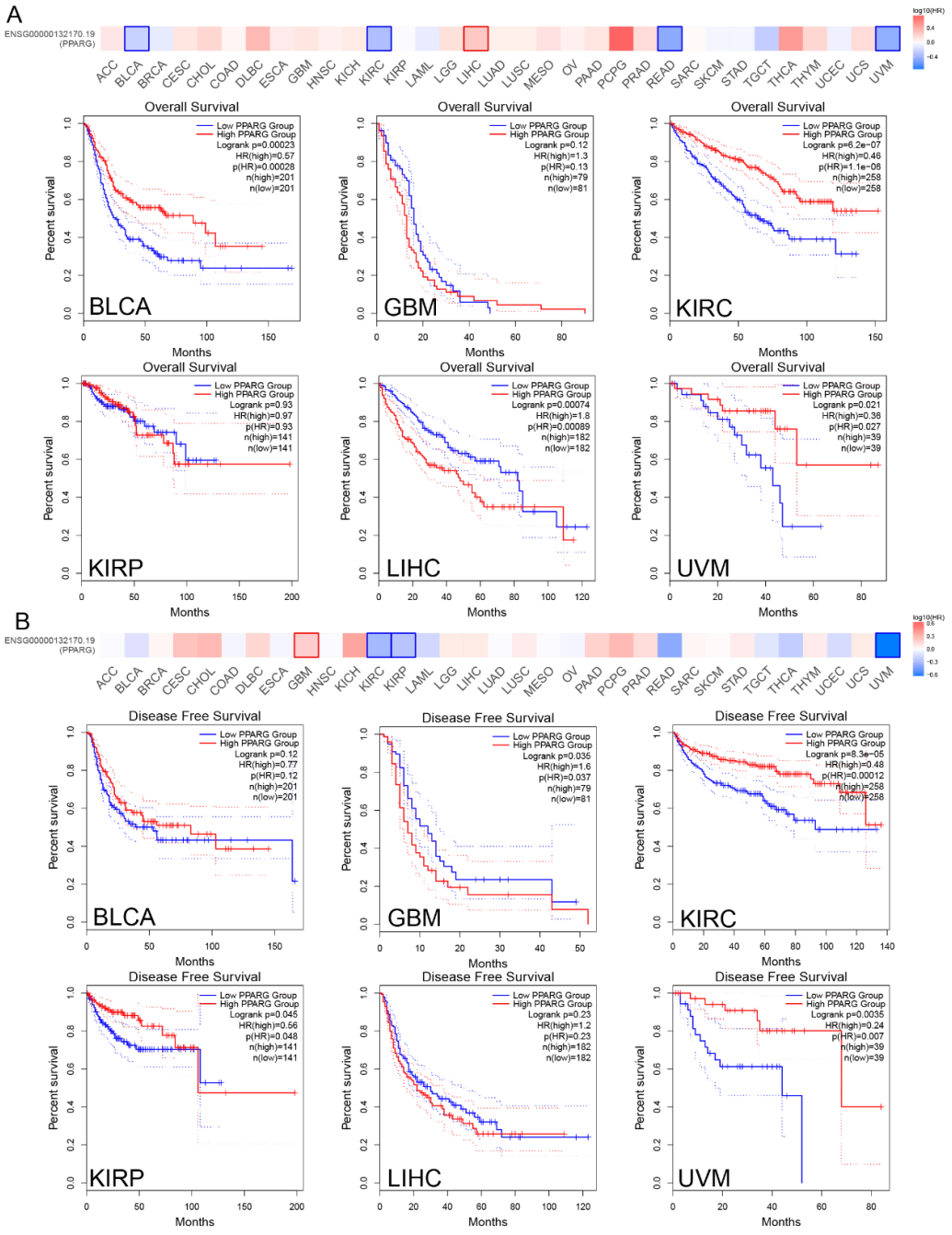

Fig. 2. Correlation between PPARG gene expression and survival prognosis of different cancers. The GEPIA2 tool was used to perform OS (A) and DFS (B) analyses of different tumors in TCGA. The survival map and the Kaplan–Meier curves were shown, respectively.

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3.2. Differentially expressed genes analysis

The volcano map of differentially expressed genes in KIRC, UVM, and GBM patients with PPARG up-regulation (red points) and PPARG down-regulation (blue points) was shown in Figure 3A. (green points). Amnion Associated Transmembrane Protein (AMN), ATPase Phospholipid Transporting 8B3 (ATP8B3), myeloma overexpressed gene (MYEVO), Solute Carrier Family 27 Member 2 (SLC27A2), metalloreductase STEAP3 (STEAP3), and transmembrane protein 171 (TMEM171) have significant expression changes in both cancer patients (Figure 3B). Figure 3C depicted a heat map of gene expression changes in KIRC, UVM, and GBM, with only ATP8B3, MYEOV, and STEAP3 showing consistent expression changes in KIRC and UVM. All of the genes discussed above show no change in expression in GBM.

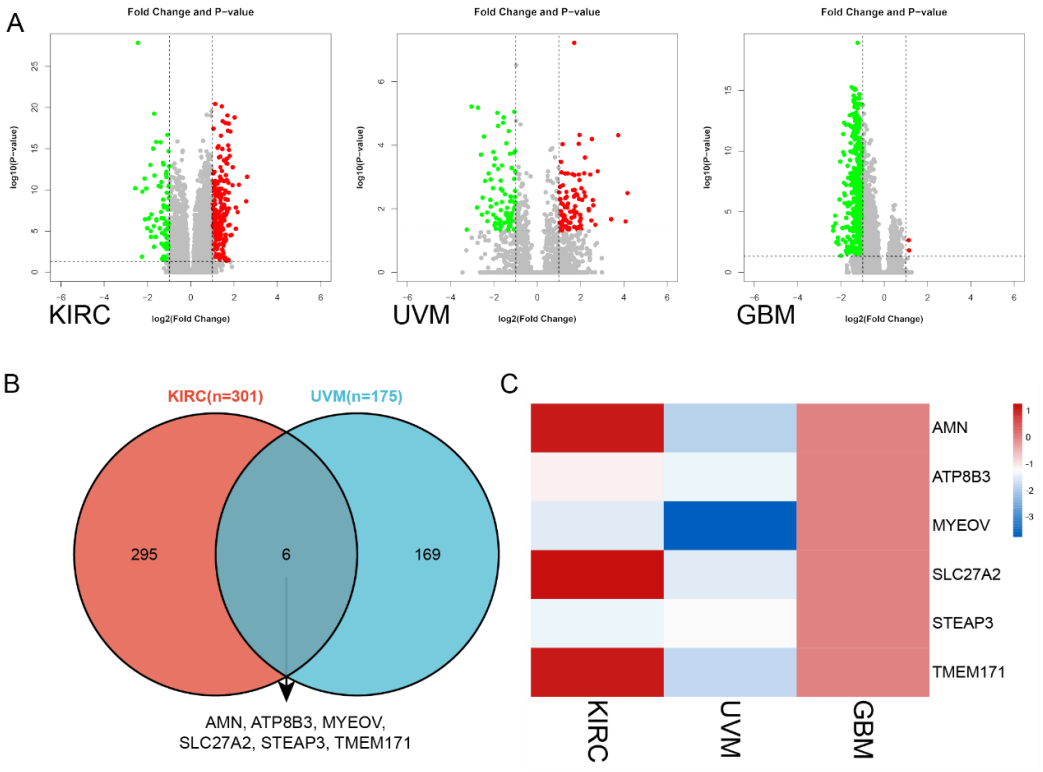

Fig. 3. Different gene expression patterns between high PPARG expression patients and low PPARG expression patients in KIRC, UVM and GBM. The volcano map showed different gene expression changes in high (red) and low (green) PPARG expression groups of KIRC, UVM and GBM patients. The Venn diagram showed two types of crossover different expression genes in KIRC and UVM between PPARG groups, including AMN, ATP8B3, MYEOV, SLC27A2, STEAP3 and TMEM171 (B). Heat map of the change for the six genes expression in KIRC, UVM, BLCA and GBM (red: up expression; blue: down correlation) (C).

3.3. Gene enrichment and single-cell sequencing data analysis

The KEGG enrichment findings of differentially expressed genes in KIRC, UVM, and GBM were shown in Figures 4A-C. UVM, the differentially expressed genes in KIRC, are concentrated in the PPAR pathway. Figure 4 D, F depicted a heat map of the single-cell sequencing data analysis findings of the previously discovered differentially expressed genes. Only the change in ATP8B3 expression caused by PPARG overexpression can considerably help KIRC and UVM patients in single-cell studies (significantly negative correlation with cell hypoxia and stemless in KIRC and significantly positive correlation with DNA damage and DNA repair, significantly negative correlation with angiogenesis in

UVM). The OS curves of the four PPARG and ATP8B3 expression groups in KIRC, UVM, and GBM were shown in Figure 4G-I. PPARG up-regulation and ATP8B3 down-regulation are associated with the best prognosis in KIRC and UVM patients.

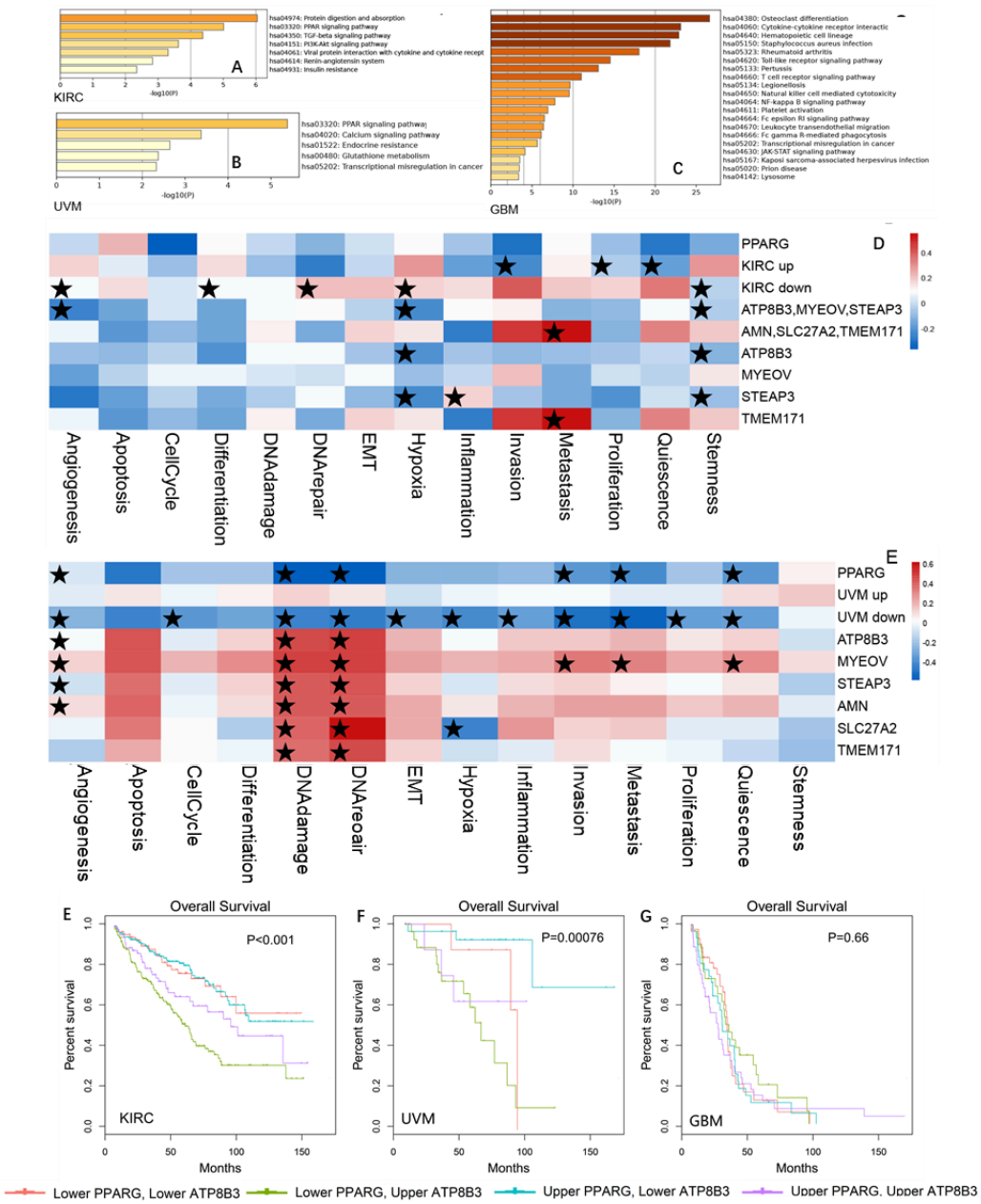

Fig. 4. The influence of different expression genes on the cell function. The KEGG enrichment analysis was performed using the different expression genes between PPARG expression levels in KIRC, UVM and GBM. (A-C) Heat map of the correlation between different gene expression changed by PPARG up-regulation and single cancer cell phenotypes for KIRC (D) and UVM (E) (red: positive correlation; blue: negative correlation). Correlation between PPARG and ATP8B3 expression types and overall survival of KIRC, UVM and GBM (F-H).

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3.4. PPARG agonist activity of Flavone

Figure 5 depicted the agonists' activity and chemical differences in the European Medicinal Chemistry Database (ChEMBL). There are no significant variations in molecular mass (MW), logarithmic coefficient of octanol-water partitioning (ALogP), number of hydrogen bond acceptors (nHBAcc), and number of hydrogen bond donors (nHBDon) between PPARG agonists and inhibitors (Figure 5C-G). Figure 5H depicted the relationship between experimental PPARG pEC50 and molecular PPARG pEC50. The anticipated PPARG pEC50 of the Flavonoids in yellow tea are reported in Table 1.

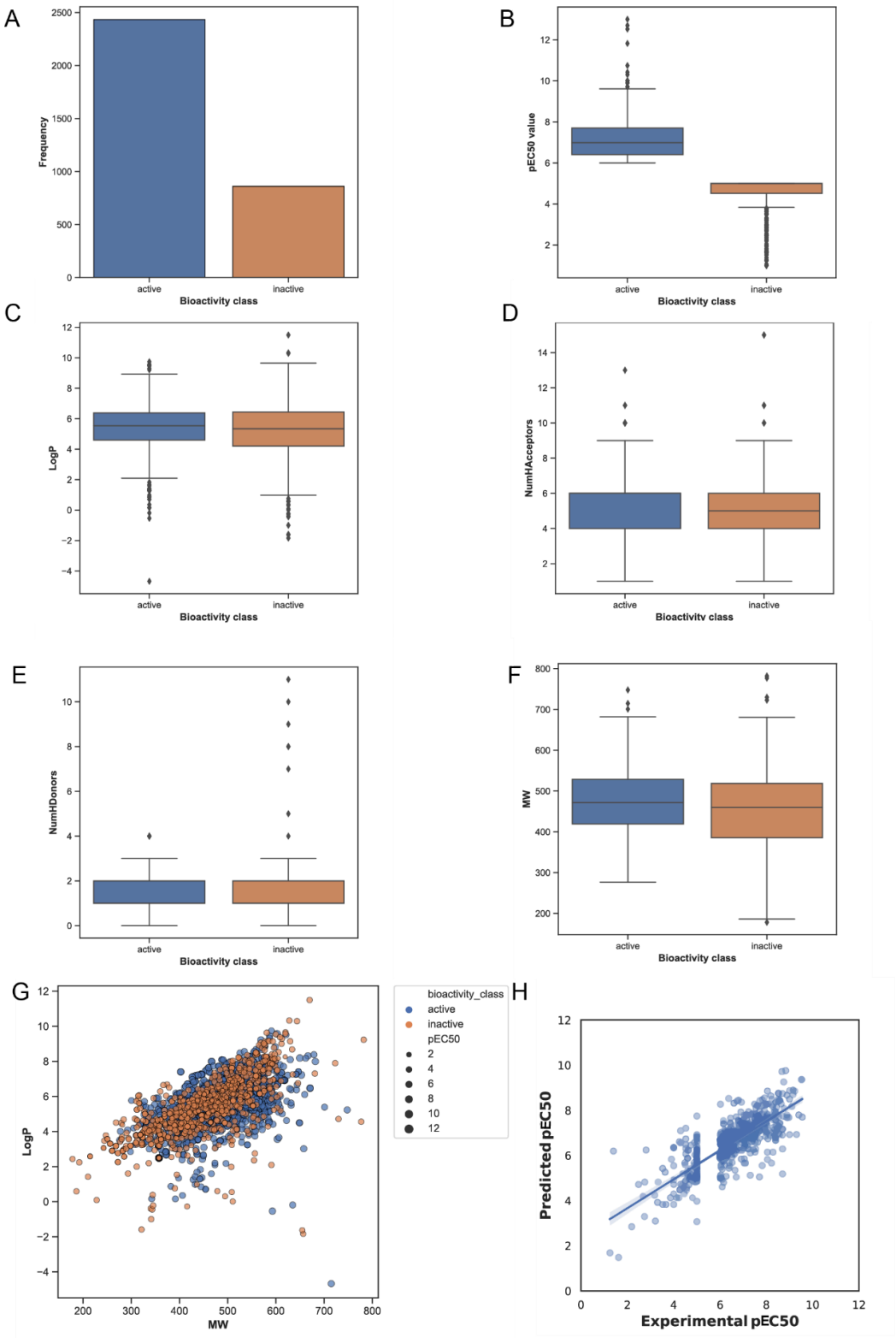

Fig. 5. Frequency of active and inactive PPARG agonists in ChEMBL 30 (A). pEC50 value of active and inactive PPARG agonists in ChEMBL 30 (B). Box plot of PPARG agonists using Lipinski's

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rule-of-five descriptors (C-F). Chemical space of PPARG agonists, actives and inactive are shown in blue and red colors, respectively (G). A plot of experimental versus predicted pEC50 values for models constructed with PubChem fingerprint descriptors (H).

Molecular	CHEMBL ID	pEC50
Rosiglitazone	CHEMBL121	7.12
Chiglitazar	CHEMBL4650349	6.68
Pioglitazone	CHEMBL595	6.60
Isovitexin	CHEMBL465360	6.29
Epigallocatechin gallate	CHEMBL297453	5.60
Baicalin	CHEMBL485818	5.57
Ellagic acid	CHEMBL6246	5.39
Procyanidin B1	CHEMBL504937	5.24
Herbacetin	CHEMBL611029	5.21
Galangin	CHEMBL309490	5.06
Kaempferol	CHEMBL150	5.06
Quercetin	CHEMBL50	5.05
Epicatechin	CHEMBL129482	4.81

Table 1. PPARG pEC50 (log half agonism coefficient) of PPARG agonists and tea flavonoids

3.5. Molecular Docking of ATP8B3 and Flavone

To further investigate the method of action of tiny flavonoids, we created a 3D active pocket and 2D docking interaction map for isovitexin, EGCG, Baicalin, procyanidin b1, quercetin, and ATP8B3 proteins (Figure 6A-E). All five flavonoids may create comparable hydrophobic contacts with amino acids, such as Arg 1320 of the ATP8B3 protein, and can profoundly embed into the ATP8B3 active site. These five tea flavonoids have binding energies that are less than -3 kcal/mol. All of the five

flavonoids that bound to ATP 8B3 had absolute values greater than 6. Baicalin exhibited the lowest binding energy to ATP8B3, and its phenyl ring might make an exposed contact with ATP8B3's amino acid pocket (Figure 6C). Furthermore, ATP8B3 may create arene contacts or arene-hydrogen interactions with isovitexin, EGCG, and quercetin (Figures 6A, B and E).

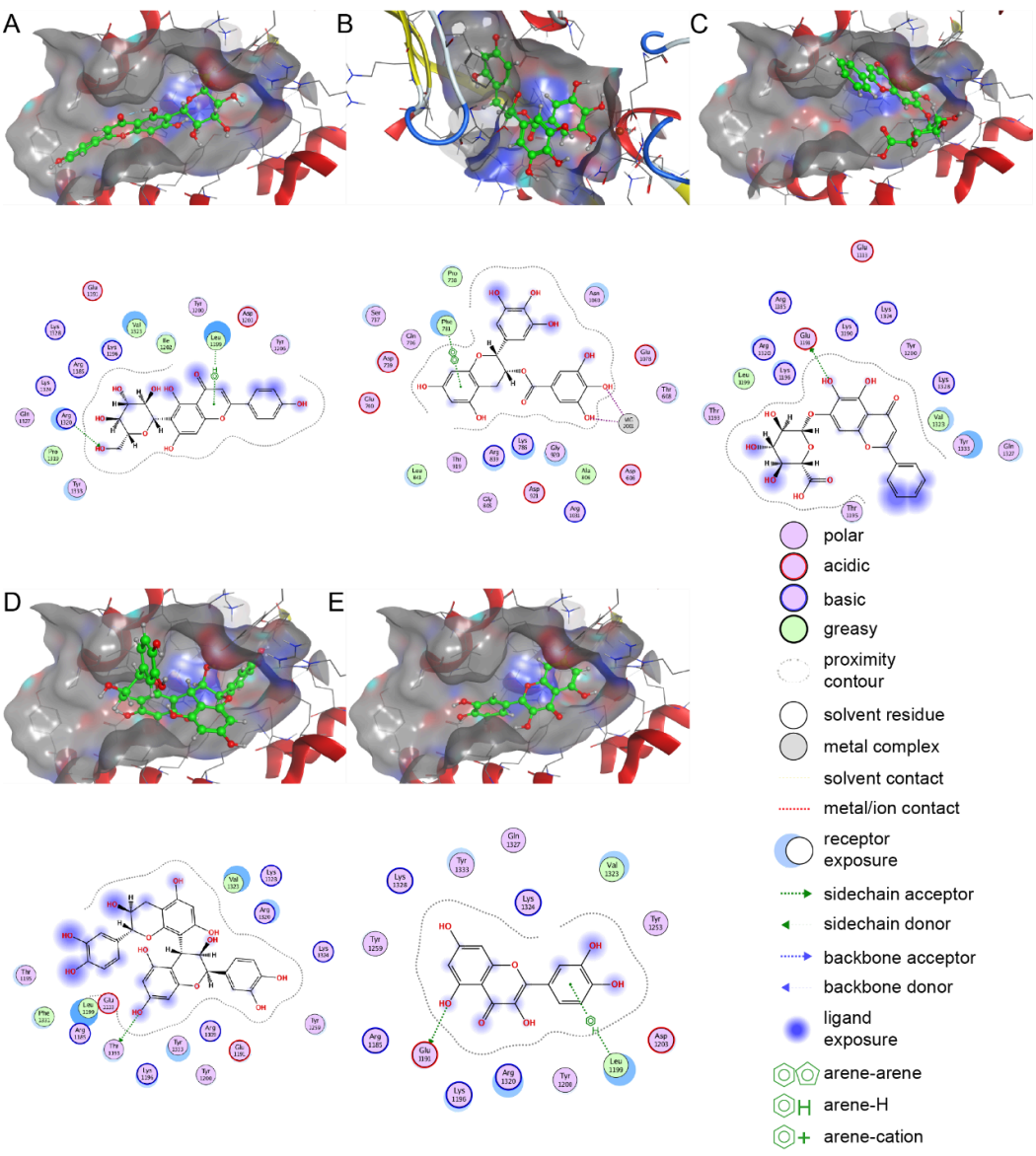

Fig. 6. Molecular docking shown 3D active pocket and 2D interaction of identified natural molecular inhabits ATP8B3 (with an S-score less than -6). Isovitexin (A), EGCG (B), Baicalin (C), procyanidin b1 (D), quercetin (E).

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4. Discussion

Despite the fact that increasing numbers of in vitro studies have shown the tumor suppressor function of PPARG protein, the precise method by which the PPARG gene eventually influences the prognosis of clinical cancer patients remains unknown. Screening for and identifying cancer types that benefit from elevated PPARG gene expression can aid in the clinical transformation efficiency of PPARG agonists. Simultaneously, further screening of differentially expressed genes in these patients suggests that ATP8B3 inhibitors may enhance PPARG agonists for the clinical efficacy of these PPARG agonist-sensitive patients, and further compound validation suggests that flavonoids such as baicalin and isovitexin may be candidate molecules that meet these requirements to suggest PPARG agonistics. The survival curves of KIRC, UVM, and GBM tumor patients grouped according to PPARG gene and ATP8B3 expression (Figure 1) validated the previous results at the clinical data level. Furthermore, it has been demonstrated using a random forest model and molecular docking that small molecule flavonoids such as baicalin and isovitexin have a higher pEC50 for PPARG protein and can bind to ATP8B3 with reduced binding energy.

Patients with KIRC or UVM who had high PPARG expression but low ATP8B3 expression had a better prognosis (Figure 3F-H), but this tendency did not exist in GBM patients. Although no study has explicitly confirmed the relationship between PPARG and ATP8B3, the fat metabolism regulated by the PPARG gene may interact with the ATP breakdown process influenced by ATP8B3, enhancing the effect of PPARG single gene expression on tumor cell survival[17][18]. Changes in the PPAR pathway, in addition to the effect of the ATP8B3 gene, may also be a probable explanation for why KIRC and UVM patients benefit from high PPARG expression, but GBM patients with high PPARG expression have a bad prognosis. The patients' differentially expressed genes in the groups and the low-expression group were not enriched in signaling pathways like PPAR (Figure 3C). Although several studies have shown that the PPAR pathway plays a role in the emergence and progression of malignancies, the clinical variations of the PPAR pathway in various cancers have received little attention[19] . Distinct signaling pathways influence the emergence and progression of different malignancies to variable degrees depending on the relative changes in original tissues or unique tumor pathological circumstances. These changes may influence how the PPAR pathway influences energy metabolism and tumor growth, but at the clinical level, the differences in PPAR pathways and their consequences remain unknown.[20].

In comparison to toxic TZD-type PPARG agonists. Natural compound-based PPARG agonists with minimal toxicity are on the horizon. At the moment, an increasing number of researchers are attempting to identify potent PPAR protein agonists from natural chemical compounds with low toxicity and adverse effects [2][26]. Significant progress has been made in demonstrating the ability of quercetin, naringenin, and other flavonoids to stimulate PPARG and other PPAR family proteins in animals and suppress the establishment of phenotypes such as fatty liver or increased blood sugar[13] . We created a machine learning model based on the available QSAR properties of PPARG agonist compounds and showed that isovitexin, baicalin, and other flavonoids had good agonistic effects on PPARG protein. Docking demonstrated that these two flavonoids may replace the original ATP location, completing the docking with the ATP8B3 protein and inhibiting its biological activity. Based on the preceding discussion of PPARG and ATP8B3's synergistic action in KIRC and UVM, these small molecule flavonoids have the potential for clinical translation in the prevention and treatment of KIRC and UVM. At the same time, an earlier study has shown that yellow tea contains high levels of the aforementioned small-molecule flavonoids[27] . It is also worth investigating if a diet strong in flavonoids, such as yellow tea, might help with the prognostic management of KIRC and UVM patients.

Based on a predictive analysis of patients with differential PPARG gene expression in 34 TCGA cancers, this study concludes that high PPARG expression is exclusively advantageous for KIRP and UVM patients and that PPARG protein may collaborate with ATP8B3 protein to achieve the aforementioned results. Patients with both malignancies benefitted, which may be connected to the PPAR pathway and energy metabolism. We preliminary showed that isovitexin and baicalin in flavonoids may inhibit ATP8B3 protein while activating PPARG protein using machine learning and molecular docking. More in vivo and in vitro studies are required to validate these compounds as KIRP Potential with UVM medication candidates.

5. Conclusion

Our study's overall analysis of tumor clinical data highlights differences in the impact of PPARG on the prognosis of different tumors, and further analysis elucidates the biological processes that cause these differences, allowing future researchers to investigate the application of the PPARG gene in tumor clinics. More importantly, the findings of this study show that the flavonoids found in yellow tea, such as baicalin and isovitexin, may be useful in the prognostic treatment of KIRP and UVM patients.

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Author contributions

MS: Methodology, Data curation, Writing-Original draft preparation. XL, LW: Conducted data analysis. SS: Revised the manuscript. MS: Conducted experiments. HL: Conceptualization, supervision, project administration, funding acquisition. All data were generated in-house, and no paper mill was used. All authors agree to be accountable for all aspects of the work, ensuring integrity and accuracy. All authors read and approved the final manuscript.

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Declarations

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