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STUDY OF THE PI3K/AKT/MTOR SIGNALING NETWORK AND ITS RELEVANCE TO THE DEVELOPMENT OF NUTRIGENOMICS IN TRANSLATIONAL ONCOLOGY

ESTUDO DA REDE DE SINALIZAÇÃO CELULAR PI3K/AKT/MTOR E SUA IMPORTÂNCIA PARA O DESENVOLVIMENTO DA NUTRIGENÔMICA EM ONCOLOGIA TRANSLACIONAL

ESTUDIO DE LA RED DE SEÑALIZACIÓN CELULAR PI3K/AKT/MTOR Y SU IMPORTANCIA PARA EL DESARROLLO DE LA NUTRIGENÓMICA EN ONCOLOGÍA TRASLACIONAL

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ABSTRACT

Cancer is a complex multifactorial disease with a high incidence and is currently one of the leading causes of death worldwide. In this context, diet plays a decisive role in prevention and acts as an adjuvant in oncological treatment. Modulated by nutrients, the PI3K/Akt/mTOR pathway is a key regulatory axis that is hyperactivated in several types of cancer and is considered a promising therapeutic target in oncology. A bibliographic search was conducted in the PubMed database between 2010 and 2021 using descriptors related to nutrigenomics, phytochemicals, and the PI3K/AKT/mTOR pathway, followed by manual curation of the selected studies according to eligibility criteria. Based on this data, we constructed a protein–protein interaction network (PPIN) comprising 153 nodes and 1,535 edges using Cytoscape, through which we identified the role of quercetin in the negative regulation of biological processes particularly the PI3K/Akt/mTOR pathway, the central focus of our investigation. Furthermore, we observed that quercetin modulates essential signaling molecules, such as EGF, EGFR, STAT, MAPK, caspases, and TP53, involved in cell proliferation, differentiation, and death—processes directly associated with carcinogenesis. Therefore, quercetin may modulate the PI3K/Akt/mTOR signaling pathway, as well as other critical pathways involved in the control of cell proliferation and death, which suggests potential relevance for investigation in the context of cancer treatment. Our study provides in silico evidence for the importance of nutrigenomics in translational oncology.

KEYWORDS: *Oncology. Nutrigenomics. Bioinformatics. Phytochemicals. Quercetin.*

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RESUMO
O câncer é uma doença complexa e multifatorial, com alta incidência, sendo atualmente uma das principais causas de morte em todo o mundo. Nesse contexto, a dieta desempenha um papel decisivo na prevenção e atua como adjuvante no tratamento oncológico. Modulada por nutrientes, a via PI3K/Akt/mTOR é um eixo regulatório chave que se encontra hiperativado em diversos tipos de câncer e é considerado um alvo terapêutico promissor em oncologia. Foi realizada uma busca bibliográfica na base PubMed entre 2010 e 2021, utilizando descritores relacionados à nutrigenômica, fitoquímicos e à via PI3K/AKT/mTOR, seguida de curadoria manual dos artigos selecionados conforme critérios de elegibilidade. Com base nesses dados, construímos uma rede de interação proteína-proteína (PPIN) composta por 153 nós e 1.535 arestas utilizando o Cytoscape, por meio da qual identificamos o papel da quercetina na regulação negativa de processos biológicos — particularmente a via PI3K/Akt/mTOR, foco central de nossa investigação. Além disso, observou-se que a quercetina modula moléculas de sinalização essenciais, como EGF, EGFR, STAT, MAPK, caspases e TP53, envolvidas na proliferação, diferenciação e morte celular, processos diretamente associados à carcinogênese. Portanto, a quercetina pode modular a via de sinalização PI3K/Akt/mTOR, bem como outras vias críticas envolvidas no controle da proliferação e morte celular, o que sugere potencial relevância para investigação no contexto do tratamento do câncer. Nosso estudo fornece evidências in silico da importância da nutrigenômica na oncologia translacional.

PALAVRAS-CHAVE: Oncologia. Nutrigenômica. Bioinformática. Fitoquímicos. Quercetina.

RESUMEN
El cáncer es una enfermedad compleja y multifactorial con una alta incidencia, siendo actualmente una de las principales causas de muerte a nivel mundial. En este contexto, la dieta desempeña un papel decisivo en la prevención y actúa como coadyuvante en el tratamiento del cáncer. Modulada por nutrientes, la vía PI3K/Akt/mTOR es un eje regulador clave que se encuentra hiperactivado en diversos tipos de cáncer y se considera una diana terapéutica prometedora en oncología Se realizó una búsqueda bibliográfica en la base de datos PubMed entre 2010 y 2021 utilizando descriptores relacionados con la nutrigenómica, los fitoquímicos y la vía PI3K/AKT/mTOR, seguida de una selección manual de los estudios elegidos según los criterios de elegibilidad. Con base en estos datos, construimos una red de interacción proteica (PPIN) compuesta por 153 nodos y 1535 aristas utilizando Cytoscape, a través de la cual identificamos el papel de la quercetina en la regulación negativa de procesos biológicos, en particular la vía PI3K/Akt/mTOR, el foco central de nuestra investigación. Además, observamos que la quercetina modula moléculas de señalización esenciales, como EGF, EGFR, STAT, MAPK, caspasas y TP53, implicadas en la discriminación, diferenciación y muerte celular, procesos directamente asociados con la carcinogénesis. Por lo tanto, la quercetina podría modular la vía de señalización PI3K/Akt/mTOR, así como otras vías críticas implicadas en el control de la diferenciación y la muerte celular, lo que sugiere una posible relevancia para la investigación en el contexto del tratamiento del cáncer. Nuestro estudio aporta evidencia in silico de la importancia de la nutrigenómica en la oncología traslacional.

PALABRAS-CLAVE*: Oncología. Nutrigenómica. Bioinformática. Fitoquímicos. Quercetina.*

INTRODUCTION

Cancer is a complex pathology characterized by uncontrolled and abnormal cell growth that invades tissues and organs, potentially triggering the metastatic process (Pan American Health Organization / World Health Organization, 2003). Approximately 18 million people are diagnosed with cancer annually, with an estimated 9.6 million deaths worldwide, making it one of the leading causes of mortality globally (Bray *et al.*, 2018). Around 70% of cancer-related deaths occur in low-

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and middle-income countries (Pan American Health Organization / World Health Organization, 2018). In Brazil, it is estimated that for each year of the 2020–2022 triennium, there will be approximately 625,000 new cases of cancer, according to data released by the National Cancer Institute José Alencar Gomes da Silva (INCA). Given its multifactorial nature, several aspects must be analyzed regarding cancer predisposition, development, and prognosis. In this regard, diet plays a determining role and is gaining increasing relevance in the field of oncology (Irimie *et al.*, 2019). Accordingly, the study of nutrigenomics represents a significant advancement in the current scientific landscape of nutrition applied to cancer treatment. Understanding its vast potential has deepened our awareness of the role of diet in the health disease continuum in a comprehensive and integrative manner. It is now understood that the antitumor properties of certain nutrients can promote DNA maintenance and integrity, as well as reduce the expression of genes associated with carcinogenesis through various mechanisms. These findings have drawn the attention of researchers seeking to explore the relationship between nutrients and gene expression regulation (Sakai & Ribeiro, 2015).

Among the many nutrients associated with cancer, omega-3 fatty acids stand out as a notable example of nutrient gene interactions. Additionally, several other bioactive food compounds have demonstrated a protective role against cancer by modulating gene expression. Polyphenols, for instance, play a significant role in the prevention of various types of cancer, including breast, oral, skin, esophageal, prostate, pancreatic, colorectal, and lung cancers. Moreover, vitamins and minerals such as zinc, selenium, and folate are involved in regulatory processes particularly DNA repair thus contributing to their anticancer properties. Likewise, plant-based phytochemicals and polyunsaturated compounds have demonstrated important functions in the diet–cancer relationship (Nasir *et al.*, 2022). Beyond their preventive role, nutrients present a critical point of vulnerability for cancer cells, which face several metabolic challenges, such as nutrient-deprived microenvironments and exposure to anticancer therapies that may directly or indirectly impact key metabolic pathways (Campbell & Wellen, 2018).

Employing new, integrated, and refined approaches to observe, investigate, and evaluate the association between nutrients and molecular pathways becomes essential for uncovering novel insights and advancing nutrigenomics research. For this purpose, biological networks provide a valuable framework and tools to study such complex systems, particularly in the context of diseases like cancer. These network-based approaches can aid in predicting clinical outcomes, identifying key genes involved in biochemical and metabolic processes, and most importantly pinpointing accurate drug targets (Saint-Antoine & Singh, 2020).

Despite advances in the molecular understanding of cancer, gaps remain regarding how phytochemicals can modulate signaling networks associated with proliferation, apoptosis, and tumor progression, especially those involving the PI3K/AKT/mTOR pathway. Within this integrative

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perspective, considering the scope of nutrigenomics, it becomes possible to analyze how nutrients may influence the PI3K/Akt/mTOR pathway. By identifying the mechanisms and specific points of nutrient interference, we can better understand which genes are associated with neoplastic progression and, consequently, uncover novel therapeutic targets and their potential for modulation.

2. METHODOLOGY

The objective of this study was to understand the association between the disruption/modulation of the PI3K/Akt/mTOR biological network and its relevance to the development of Nutrigenomics, through the use of the Cytoscape platform.

Data collection

The literature search was conducted in the PubMed database between 2010-2021. Using the descriptors “phytochemical compounds”, “nutrients”, “bioactive compounds”, “nutrigenomics”, “anti-inflammatory”, “anti-cancer”, and “PI3K/Akt/mTOR pathway”, combined by boolean operators. Original articles with full text available, published in English and related to the modulation of the PI3K/AKT/mTOR pathway by phytochemicals in an oncological context were included. Duplicate articles, narrative reviews, conference abstracts, and studies not directly related to the proposed theme were excluded. Initially, 100 studies were identified, with 33 included in the final analysis after application of the eligibility criteria.

The manual curation process consisted of reading and extracting the proteins, genes, and signaling molecules associated with the investigated phytochemicals, followed by a review to remove duplicates and standardize the molecular nomenclature. Quercetin was selected as the main compound of interest due to its broad association with central proteins of the PI3K/AKT/mTOR pathway and its potential as a modulator in processes related to cell proliferation, apoptosis, and tumor signaling.

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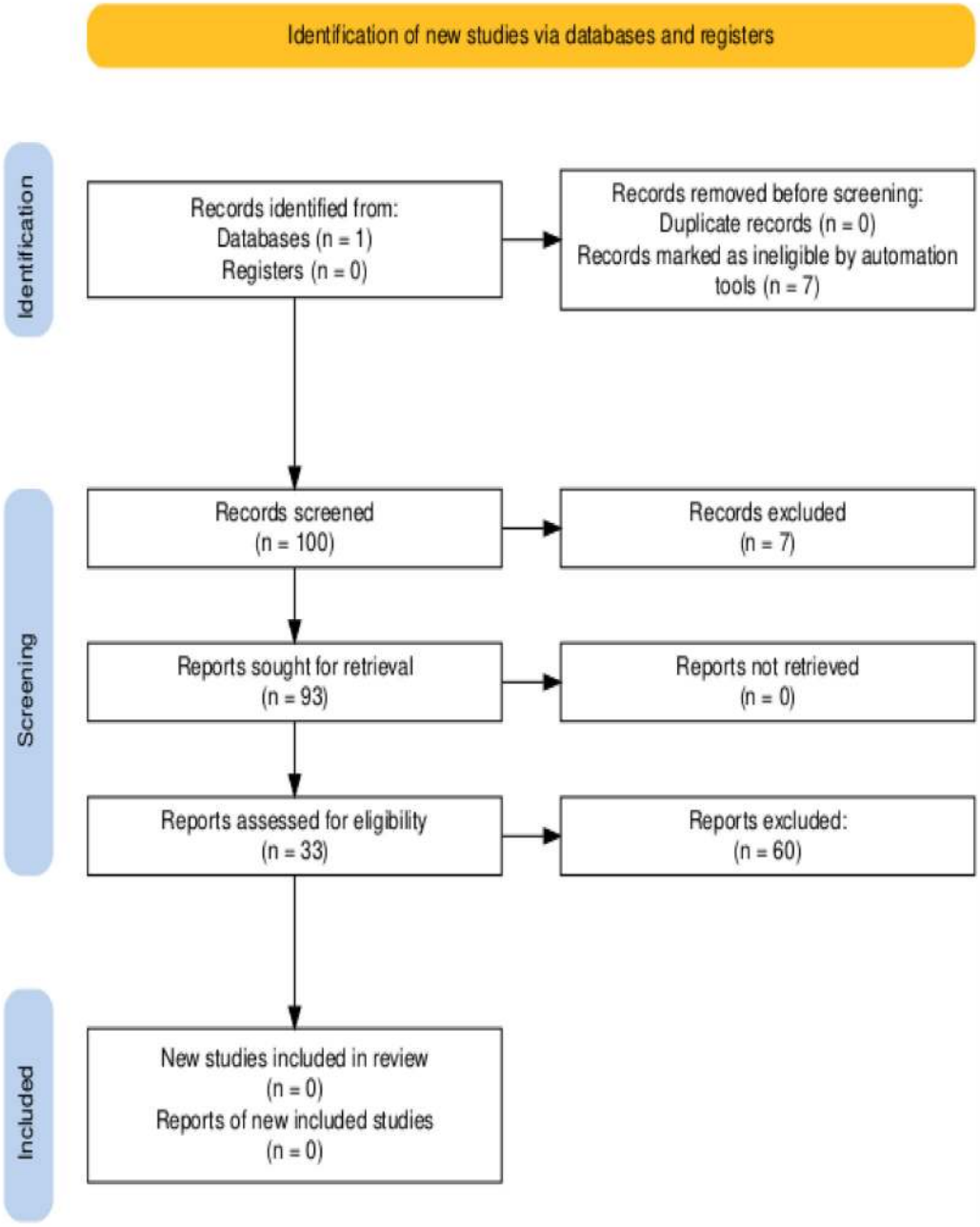
Figure 1. Schematic representation of the inclusion and exclusion criteria used for article selection (Haddaway *et al.*, 2022)



Source: Prepared by the authors based on the PRISMA 2020 checklist.

Construction and Visualization of the Protein–Protein Interaction Network (PPIN)

The next step, using the previously selected targets, involved constructing a PPIN through the STRING online database, version 11.0 (https://string-db.org/) (Szklarczyk *et al.*, 2017). The

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STRING associations were set to a high confidence score of 0.7; interaction sources were based on experimental data and curated databases; and the number of interactors in shells 1 and 2 was set to 50. After completing these procedures in STRING, the network was downloaded in tabular format for interpretation in Cytoscape, version 3.8.1 (https://www.cytoscape.org/).

Protein–Protein Interaction Network (PPIN) Analysis

For the network analysis, Cytoscape (version 3.8.1) was used, following a basic procedure with a plug-in designed to analyze the topological properties of the network, aiming at user-friendly visualization, analysis, and integration.

Modular Analysis of the Protein–Protein Interaction Network and Pathway Enrichment

In network studies, it is understood that clusters or modules are tightly connected nodes within a network that form a dense subnetwork with high biological significance, as they provide detailed information about PPINs. For this reason, the MCODE (Molecular COmplex DEtection) plugin, available in Cytoscape, was used to score each cluster (module) based on algorithmic and statistical approaches. The score is determined by size and density—thus, a high score indicates a large and dense cluster.

In parallel, from these modules, Gene Ontology (GO) analysis can be performed to validate the clusters with respect to specific biological functions. GO analysis provides detailed insights into the biological processes underlying each cluster. For this functional GO enrichment analysis, the BiNGO plugin (version 3.0.4) in Cytoscape was used, employing a p-value threshold of less than 0.05. The statistical method used was a two-tailed hypergeometric test, with Bonferroni correction for multiple testing, comparing the results of this study to reference datasets.

Additionally, functional enrichment analysis of the proteins associated with the most significant biological processes, molecular functions, and cellular components were performed using STRING data. The proteins identified in each GO category were compared, and those present in all three categories were selected for further discussion.

3. RESULTS AND DISCUSSION

Data collection and curation

The nutrients selected as targets were quercetin, curcumin, and resveratrol, based on the data retrieved during the literature review. The list of proteins associated with each phytochemical is presented in Table 1. For the network construction, quercetin was chosen as the primary compound, given the smaller number of studies found in comparison to the other two phytochemicals (curcumin and resveratrol). Quercetin was selected as the lead compound due to

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its potential to modulate core proteins associated with the PI3K/AKT/mTOR pathway and its relevance in processes related to cell proliferation, apoptosis, and tumor signaling.

Table 1. Proteins identified through the literature review and manual curation, along with their corresponding phytochemical targets

Targets	Proteins
Quercetin	4EBP1; AKT; p-AKT; Annexin V-FITC; BAD; BAX; BCL2; Snail; Caspase-3/9; c-MET; Cyclin D1/B; E-cadherin; EGFR; EpCAM; ER-α; ERK1/2; Fibronectin (FN); GSK3α/β; HER2; HGF; hnRNPA1; HSP27; HSP70; IGF1; JNK1/2/3; MALAT1; MAPK; MAPKα; MMP-2; MMP-9; mTOR; N-cadherin; NGB; NKX3.1; Notch1; p-EGFR; p38; p38α; p53; p70S6K; PARP; P-gp; PI3K; p-PI3K; PRAS40; PSA; PTEN; ribosomal protein S6 kinase; SAPK/JNK; Slug; STAT1; STAT3; TWIST; TWIST2; VEGF; VEGFR-2; Vimentin; WNK1.
Curcumin	4EBP1; AKT; AKT3; AMPK; AP-1; ATF4; ATG2B; ATG5/7; AXL; BAD; BAK; BAX; BCL-2; BCL-xL; β-actin; β-catenin; BIK; BIM; BRCA1; Caspase-3/7/8/9; CBP; CDK2; CDKs; c-FLIP; CHOP; cIAP1/2; Cyclin A/B1/D1/E; c-JUN; cleaved Caspase-9; cleaved PARP; COX-1 and COX-2; c-RAF; CXCL1 and CXCL2; CXCR4; DNMT1; E-cadherin; EGFR; ER; EPAC; EPAS1; ERBB2; ERK1/2; ERK-NOX; hepatocyte growth factor (HGF)/c-MET; ERK/Snail; HAT; HIF-1α; FAS; FABP5; FEN1; GFP; GRP78; GSK-3β; Hedgehog; HER2; HER2/ERBB2; hTERT; H2AUbK119; IFN; IGF1; IκBα; IKK-β; IKK-α; IL-6; Integrin α/β; JAK/STAT; JAK1/2; JAK2/STAT3; JNK; JNK1/2; Ki-67; LC3B-II;

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	MAPK; MCL-1; McTNs; MEK; MEP50 (WDR77); MMP; MMP13; MMP2; MMP3; MMP9; MAOA; MRP1; mTOR; mTORC1/2; N-cadherin; NF-YA; NF-κB; Notch; Notch1; NOX4; NOXA; NRF2; p16; p21; p27; p300; p38; p44/42; p53; p62; OPN; p65; p70S6K; p-AKT; PAPP; PDK1; p-EGFR; PERK1/2; PGC1; PGE2; P-gp; PI3K; PIK3CA; PKA; PKB; PKC-θ; PKC-α; PPAR; PPARγ; PPARβ/δ; PR; PRMT5; PSMA5; p-SMAD2 and p-SMAD3; PTEN; PUMA; RAC; RAF; RAS; ROCK; thioredoxin reductases; RHO; RHOA; RRM2; SERCA2; androgen receptor signaling; SKP2; Slug; SP1; SRSF1; STAT3; TCF; TCF-4; TfR1; TGFB1; TGF-α; TGF-β; TIMP1 and TIMP4; tyrosine kinase; TLKs; TNF; TNF-α; TRAIL; TSC1/2; TWIST1; VEGF; MAOA/mTOR/HIF-1α signaling pathway; Vimentin; vasoactive intestinal peptide (VIP); Wnt/β-catenin; XIAP; β-catenin; ZRF1.
Resveratrol	AKT; AKT1/PKBα; α-SMA; AP-1; AR; BAK; BAX; BCL2; BCL-xL; BID; BLIMP-1; BMI-1; Caspase-3 and Caspase-8; Cathepsin B; CCL2; CD44; CDC2; CDK1; CDK2; CDK4; CHOP; Cyclin A; Cyclin E; c-MYC; COX-2; CXCR4; Cyclin D1; Cyclin E1; Cyclins; E-cadherin; EGFR; ER; ERK1/2; FAP-α; FGF; Fibronectin; HDAC1; HDAC2; HER2; HGF; hnRNPA1; HO-1; IGF1; IGFBP5; IL-6; JAK; LC3A; MAPK; MCL-1; MMP2; MMP-9; MPP-2; MTA1/NuRD complex; MTA1; MTA2; MTA3; mTOR; mTORC1; N-cadherin; NF-κB; NGB; NKX3.1; ORAI1; p21; p27; p53; p-AKT; PARP-1; PCNA;

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	PDGF-β; PI3K; PKC; PLC; p-PI3K; PR; PSA; p-SMAD2; p-SMAD3; PTEN; RAS and H-RAS; SAHA; SDF-1; Ser727; SIRT1; SKF-96365; SMAD2; SMAD3; Snail1 and Slug; SOCE; SOX2; SPHK; STAT3; STIM1; Survivin; TGF-β; TRPC1; TRPC6; TRPM8; TRPV6; TSA; Tubulin; TWIST1; VEGF; Vimentin; α-SMA; β-TrCP.

Source: Prepared by the authors (2021).

Over the past decades, science has witnessed significant progress in molecular biology and pharmaceutical technology, leading to the development of various novel antineoplastic agents and advancing the overall understanding of cancer (Meira, de Almeida, *et al.*, 2009). Despite the initial expectations in Oncology not being fully met due to the complexity of cancer and its associated signaling networks that promote cell proliferation (Meira, de Almeida, *et al.*, 2009) important advances have been made, especially in the area of natural products for cancer treatment, either as adjuvant or neoadjuvant therapies (Dhasmana *et al.*, 2020). In this context, a crucial question emerges: How do natural products (and their constituents) modulate the main signaling pathways that control cell proliferation and death in cancer? To partially address this question, the present study aimed to extract and select all published proteins demonstrating an association between quercetin and the PI3K/AKT/mTOR signaling pathway, one of the key cancer-related pathways (Meira *et al.*, 2011).

Previous research has shown that natural products (131 extracts from 63 plant species) possess considerable potential for controlling pathogens (Diana *et al.*, 2016), reinforcing their importance in the development of therapeutic agents—particularly antineoplastic drugs. Quercetin is a flavonol subclass flavonoid known for its broad biological and pharmacological activities, including antioxidant, antitumor, antiproliferative, and anti-inflammatory effects (Feitelson *et al.*, 2015; Pan *et al*., 2015; Rivera *et al.*, 2016; Sarkar *et al.*, 2016; Wang P *et al.*, 2016). It is found in a wide range of vegetables and fruits, especially apples, onions, berries, capers, and red wine (Li *et al.*, 2016; Wang P *et al.*, 2016; F. Yang *et al.*, 2015), and is the most abundant flavonoid in the Western diet, with an estimated daily intake of 15-40 mg/kg and 30–50% absorption (Li *et al.*, 2016).

The anticancer potential of quercetin has been demonstrated both in vitro and in vivo studies across multiple cancer types including breast, prostate, bladder, hepatocellular, and glioma (Tao *et al.*, 2017). However, the antineoplastic mechanism of quercetin, particularly its ability to modulate signaling pathways, remains to be fully elucidated.

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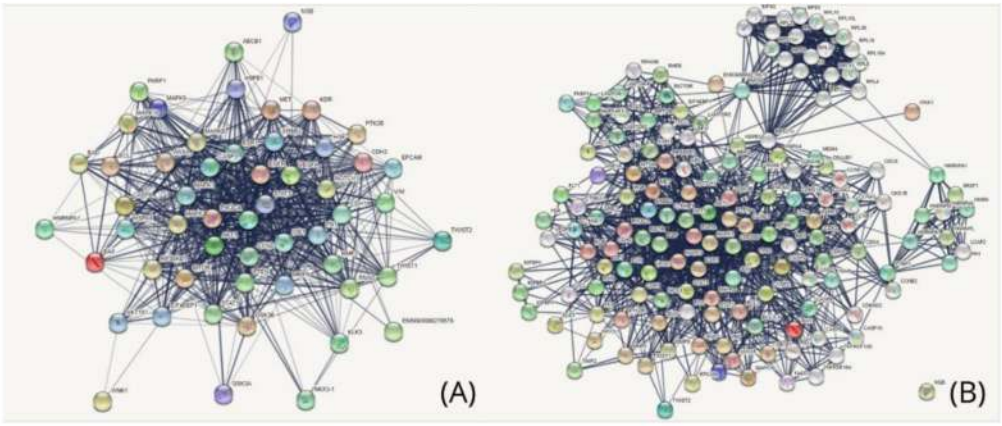
Network construction and analysis

The STRING database, version 11.0 (https://string-db.org), was used to generate the PPIN. A total of 56 seed proteins were input, and the resulting network is shown in Figure 2A. Associations followed the parameters described in the methodology section. After the addition of interactors in shells 1 and 2, the network assumed the structure presented in Figure 2B. The reconfigured network yielded an average node degree of 19.9 and a PPI enrichment p-value of <1.0e-16. The network was then exported in a plain text table format for further analysis in Cytoscape.

Regarding visual styling, white (RGB 255,255,255) was assigned to the lowest degree values, blue (RGB 0,0,255) to represent medium values, and red (RGB 255,0,0) to the highest degree values. Figure 2 illustrates the results of these settings and the resulting visualization, highlighting Akt and TP53 as the proteins with the highest degree centrality. The NetworkAnalyzer plugin efficiently calculates various topological parameters of networks loaded into Cytoscape (Assenov *et al.*, 2008). Table 2 presents the values for the following parameters: number of nodes, number of edges, clustering coefficient, heterogeneity, diameter, network density, and characteristic path length.

Figure 2. Network constructed in STRING. (A) Network generated from the input seed proteins. (B) Network obtained after the addition of interactors and application of association parameters in the settings panel



Source: Adapted from STRING database (Szklarczyk *et al.*, 2017).

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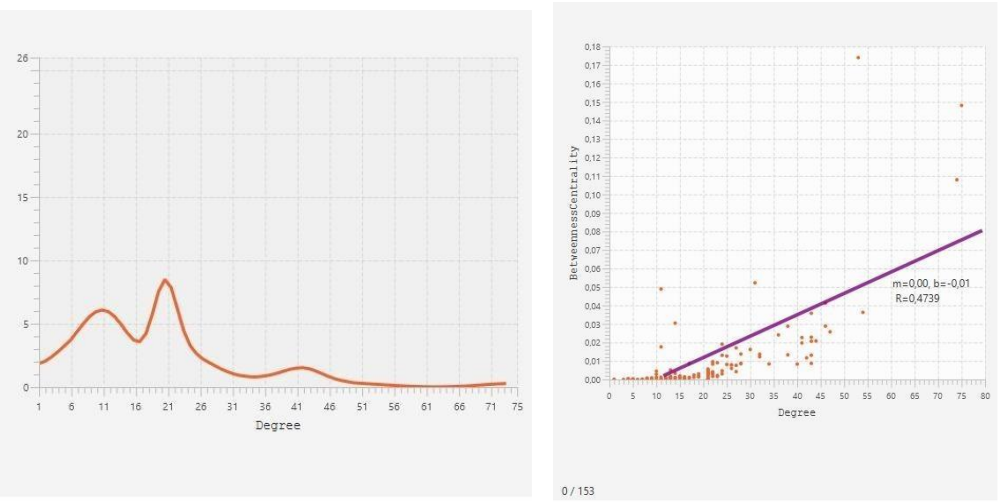
Figure 3. Network obtained in Cytoscape, highlighting the proteins with the highest degree values



Source: Prepared by the authors in Cytoscape 3.8.1 (2021).

In this study, we used STRING to construct a PPIN from the seed proteins identified through this selection process. After adding connector proteins, the resulting network comprised 153 nodes. Its topological properties were analyzed using the Cytoscape plugin. Network heterogeneity is a parameter that indicates the tendency of a PPIN to contain hub nodes—high-degree proteins with numerous interactions (Assenov *et al.*, 2008). One essential property is degree distribution, which helps determine whether the network is scale-free. A low number of biomolecules with high degrees (hubs) and a large number with low degrees indicates a scale-free network, allowing for global node interaction (Dhasmana *et al.*, 2020). As shown in Figure 3, AKT and TP53 exhibited the highest degrees, indicating their role as central hubs that modulate cell proliferation in cancer findings consistent with previous studies from our research group (Almeida *et al.*, 2018; Meira *et al.*, 2011). Figure 4 shows the degree distribution, clearly depicting a scale-free network. Additional properties such as characteristic path length (2.273) and clustering coefficient (0.676) suggest rapid information flow across the network and potential binding site availability due to lower clustering (Dhasmana *et al.*, 2020).

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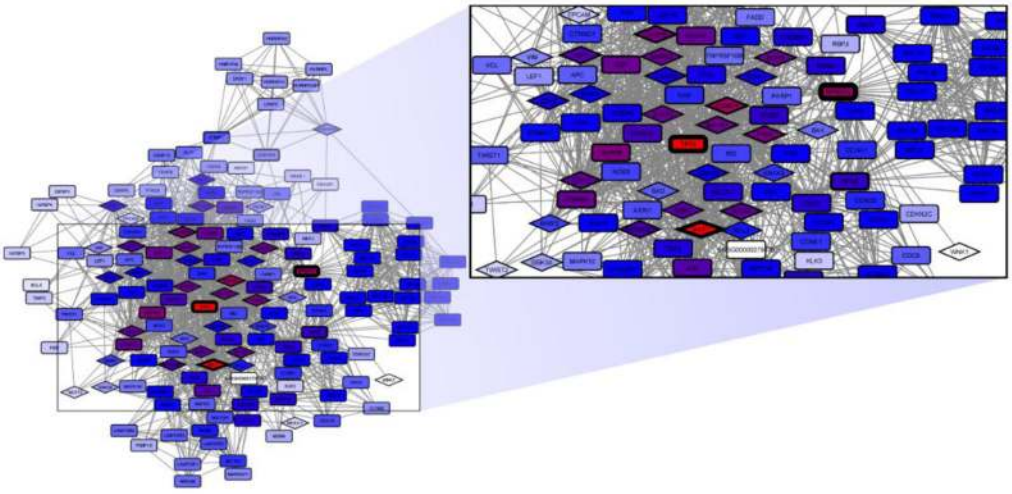
Figure 4. Topological analysis of Degree Distribution (2.A) and the mathematical relationship between Betweenness Centrality and Degree (2.B)



Source: Prepared by the authors from data obtained in STRING and analyzed in Cytoscape 3.8.1 (2021).

Table 2. Topological parameters of the network obtained in Cytoscape

Topological Parameters	Values
Number of hubs	153
Number of edges	1535
Clustering coefficient	0,676
Network heterogeneity	0,645
Network diameter	4
Network density	0,132
Characteristic path length	2,273

Source: Prepared by the authors (2021).

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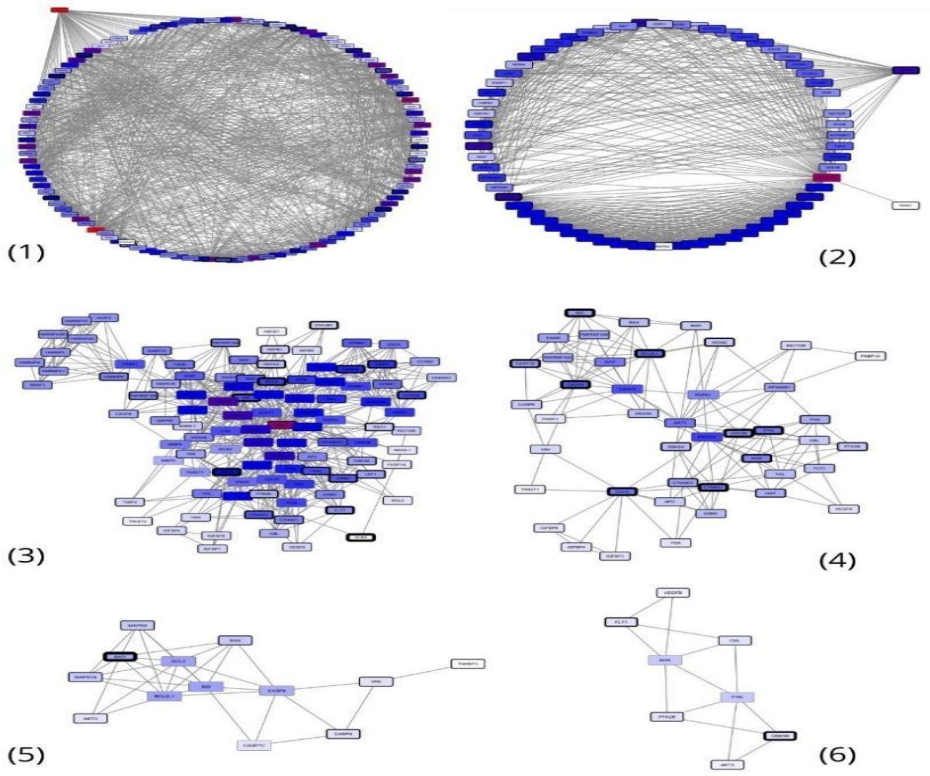
Subcluster Analysis and Gene Ontology Enrichment

The MCODE plugin was used for network modularization, resulting in six clusters, as shown in Figure 5. This procedure aims to remove noise (connector proteins with low degree values) and select the most relevant seed proteins for subsequent analysis. The BiNGO plugin was employed for functional enrichment analysis of cluster 1, with the results presented in Figure 5. The data highlight biological processes (emphasized in the image), molecular functions, and cellular components, evaluating the representation of Gene Ontology (GO) categories. Yellow nodes represent GO classes that are overrepresented at the significance level, with node color intensifying to orange for more significant p-values (BiNGO website). According to the STRING database and based on the lowest false discovery rate (FDR) values, the main GO terms identified were: negative regulation of biological process, protein complex, and binding enzyme, as shown in Table 3. The proteins associated with each of these GO terms were listed, and those present in all three categories were selected. Table 4 lists the name, symbol, and Universal Protein Resource (UniProt) code for each of these enriched proteins.

Figure 5. Clustering results using the MCODE plugin. Highlight on the AKT protein in (1) and (2).



Source: Prepared by the authors using Cytoscape 3.8.1 and the MCODE plugin (2021).

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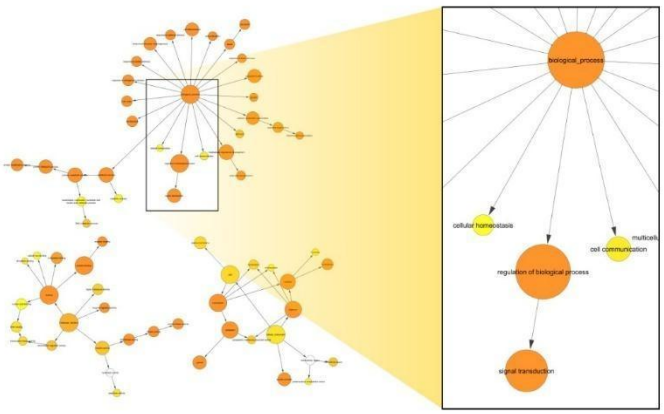
Figure 6. Functional enrichment results obtained using the BiNGO plugin, highlighting the regulation of the biological process



Source: Prepared by the authors using Cytoscape 3.8.1 and the BiNGO plugin (2021).

Table 3. Functional enrichment results obtained through the STRING database

Molecular Function – Description	Observed Gene Count	FDR (False Discovery Rate)
GO:0048519 – Negative regulation of biological process	128	6.18e-47
GO:0032991 – Protein complex	106	4.72e-28
GO:0019899 – Binding enzyme	79	3.04e-31

Source: Prepared by the authors (2021).

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Table 4. Description of the proteins resulting from the enrichment process, including their symbols, UniProt codes, and corresponding names

No.	UniprotID	Symbol	Name
1	P31749	AKT1	RAC-alpha serine/threonine-protein kinase
2	P25054	APC	Adenomatous polyposis coli protein
3	O15169	zAXIN1	Axin-1
4	P10415	BCL2	Apoptosis regulator Bcl-2
5	Q07817	BCL2L1	Bcl-2-like protein 1
6	P42574	CASP3	Caspase-3
7	Q14790	CASP8	Caspase-8
8	P22681	CBL	E3 ubiquitin-protein ligase CBL
9	P14635	CCNB1	G2/mitotic-specific cyclin-B1
10	P24385	CCND1	G1/S-specific cyclin-D1
11	P30279	CCND2	G1/S-specific cyclin-D2
12	P24864	CCNE1	G1/S-specific cyclin-E1

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13	P19022	CDH2	Cadherin-2
14	P38936	CDKN1A	Cyclin-dependent kinase inhibitor 1
15	P46527	CDKN1B	Cyclin-dependent kinase inhibitor 1B
16	P35222	CTNNB1	Catenin beta-1
17	O60716	CTND1	Catenin delta-1
18	P01133	EGF	Pro-epidermal growth factor
19	P00533	EGFR	Epidermal growth factor receptor
20	P04626	ERBB2	Receptor tyrosine-protein kinase erbB-2
21	Q13158	FADD	FAS-associated death domain protein
22	P02751	FN1	Fibronectin type III domain containing
23	P62993	GRB2	Growth factor receptor-bound protein 2
24	P49840	GSK3A	Glycogen synthase kinase-3 alpha
25	P49841	GSK3B	Glycogen synthase kinase-3 beta
26	P04792	HSPB1	Heat shock protein beta-1

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27	P05412	JUN	Transcription factor AP-1
28	Q6IAA8	LAMTOR1	Regulator complex protein LAMTOR1
29	Q9Y2Q5	LAMTOR2	Regulator complex protein LAMTOR2
30	Q9UJU2	LEF1	Lymphoid enhancer-binding factor 1
31	P28482	MAPK1	Mitogen-activated protein kinase 1
32	Q9BPZ7	MAPKAP1	Target of rapamycin complex 2 subunit MAPKAP1
33	Q00987	MDM2	E3 ubiquitin-protein ligase Mdm2
34	P42345	MTOR	Serine/threonine-protein kinase mTOR
35	P46531	NOTCH1	Neurogenic locus notch homolog protein 1
36	P09874	PARP1	Poly [ADP-ribose] polymerase 1
37	Q14289	PTK2B	Protein-tyrosine kinase 2-beta
38	P06400	RB1	Retinoblastoma-associated protein
39	Q15382	RHEB	GTP-binding protein Rheb
40	P23396	RPS3	40S ribosomal protein S3

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41	P62753	RPS6	40S ribosomal protein S6
42	Q8N122	RPTOR	Regulatory-associated protein of mTOR
43	Q5VZM2	RRAGB	Ras-related GTP-binding protein B
44	P42224	STAT1	Signal transducer and activator of transcription 1-alpha/beta
45	P40763	STAT3	Signal transducer and activator of transcription 3
46	P04637	TP53	Cellular tumor antigen p53
47	P49815	TSC2	Tuberin
48	P26368	U2AF2	Splicing factor U2AF 65 kDa subunit
49	P18206	VCL	Vinculin

Source: Prepared by the authors (2021).

In addition to the PI3K/AKT/mTOR pathway, the mitogen-activated protein kinase (MAPK) pathway is also partially mediated by quercetin. Previous studies have shown that quercetin negatively regulates the Ras/MAPK/ERK signaling cascade (Pan *et al.*, 2015) and limits tumor growth by inhibiting angiogenesis, a critical step in cancer progression, as demonstrated by our group (Bizzo *et al.*, 2011; Maria *et al.*, 2010). STAT3, a transcription factor activated by cytokines and growth factors, enters the nucleus upon phosphorylation to regulate genes involved in cell growth, survival, and motility. Combined treatment with quercetin and green tea inhibited STAT3 signaling, reducing cellular invasion and colony formation in cancer cell lines (Wang *et al.*, 2016).

These findings highlight the role of quercetin in modulating key pathways that regulate cancer proliferation, thereby supporting its antineoplastic potential. Understanding these signaling mechanisms is essential, as our previous research has shown that monoclonal antibodies (matuzumab and cetuximab) induce cell death in cervical and vulvar cancer cells through differential

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modulation of these pathways (Meira; de Almeida, *et al.*, 2009). Hence, understanding how quercetin impacts signaling pathways such as AKT and MAPK provides insights into its potential to control cell proliferation in cancer.

Moreover, quercetin interacts with several cell surface receptors to modulate downstream signaling molecules such as p53, p21, survivin, and Ras (Pan *et al.*, 2015), which are also involved in cell death pathways. Bcl-2 family proteins are crucial mediators of mitochondrial apoptosis. Studies have shown that quercetin suppresses anti-apoptotic Bcl-2 and increases pro-apoptotic Bax expression, elevating the Bax/Bcl-2 ratio (Pan *et al.*, 2015; F. Yang *et al.*, 2015). Quercetin also increases levels of cleaved PARP and caspase-3 (CASP3), both involved in apoptosis. CASP3, a cysteine protease, plays a central role in programmed cell death and its high expression is considered an independent predictor of breast cancer recurrence (L. Yang *et al.*, 2021). These findings confirm that quercetin inhibits cancer cell growth via apoptosis induction (Kumar *et al.*, 2015). In our PPINs, TP53 was consistently observed as a quercetin-modulated target. This is noteworthy since TP53 and its protein product, p53, are key regulators of cell death either by arresting the cell cycle for repair or inducing apoptosis earning the title of "guardians of the genome" (Hanahan *et al.*, 2000; Hanahan & Weinberg, 2011). Supporting this, quercetin treatment has been shown to increase the expression of p21, p27, and p53, resulting in cell cycle arrest and apoptosis in retinoblastoma cells (Erdogan *et al.*, 2018).

Despite the relevance of the findings obtained, this study presents limitations inherent to in silico analyses and protein-protein interaction networks based on predictive databases, such as STRING. The identified interactions may include indirect associations or potential false positives, since part of the data derives from computational predictions, literature mining, and integration of different experimental sources. Furthermore, the functional interpretation of the identified proteins should be carried out with caution, considering the biological complexity and heterogeneity of tumor microenvironments. Although the results suggest a potential modulating effect of quercetin on the PI3K/AKT/mTOR pathway and associated proteins, these findings do not allow for direct clinical extrapolations; further experimental validation and clinical studies are necessary to confirm the observed mechanisms.

This study is of great importance as we employed bioinformatics and systems biology tools to compile data from the literature and construct protein–protein interaction networks that elucidate the mechanism of action of quercetin. Our findings indicate that quercetin effectively modulates major cancer-related signaling pathways (EGFR, AKT, STAT, MAPK, CASPASES, and TP53), reinforcing its antineoplastic potential. To validate our findings, further in vitro and in vivo experimental studies, as well as clinical trials in humans, are essential to determine the effective doses of quercetin for cancer prevention and/or treatment.

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4. FINAL CONSIDERATIONS

It is concluded that quercetin modulates the main signaling pathways that control cell proliferation and death and, therefore, it is suggested that it may play an important role in both the prevention and treatment of cancer. Since current therapeutic modalities for this disease are aggressive (and with many side effects), it is essential that new therapeutic targets and anticancer molecules be proposed and that the mechanisms associated with them be clarified. In the case of quercetin, the focus of this study, we identified the role of negative regulation of the biological process (including the PI3K/AKT/mTOR pathway, the central point of our search), as well as the modulation of other important agents responsible for cell signaling in cancer (EGF, EGFR, STAT, MAPK, CASPASES and TP53) and, in this context, we provide relevant evidence of how nutrigenomics can contribute to the development of translational oncology.

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