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Abstract: The historical and cultural use of food as a remedy for diseases is evident in societies, such as using Hibiscus sabdariffa to address conditions like hypertension and high blood glucose. The natural biocompounds in this plant, including Delphinidin-3-Sambubioside (DS3), Quercetin (QRC), and Hibiscus Acid (HA), have been linked to various health benefits. Despite individual attention, molecular targets for these compounds remain unclear. In this study, in-silico analysis employed bioinformatic tools; including Swiss Target Prediction, ShinnyGo 0.77, KEGG, and Stringdb, to identify molecular targets, pathways, and hub genes. A PubMed literature search complemented the results. DS3 demonstrated potential modifications in genes related to nitrogen and glucose metabolism, inflammation, angiogenesis, and cell proliferation, particularly affecting the PI3K-AKT pathway. QRC displayed interconnected targets across multiple pathways, with overlap with DS3 and a focus on cancer-related pathways. HA showed distinct targets, particularly associated with nervous system-related pathways. These findings highlight the need for targeted research on the molecular effects of DS3, QRC, and HA, providing valuable insights into potential therapeutic pathways.

Keywords: Delphinidin-3-sambubiosid; quercetin; hibiscus acid; bioinformatics; hibiscus sabdariffa

1. Introduction

Hibiscus sabdariffa is a highly popular plant in Asia and America. Therefore, it has been used in a wide array of products ranging from flavored water to facial creams. Its popularity can also be attached to its potential beneficial effects on health, going from hypotensive to anti-cancerogenic, especially since this plant is rich in plenty of biocompounds. The matrix of this plant is rich in quantity of biocompounds, it has anthocyanins, organic acids, and other phenolic compounds, and many of them are quite common in many fruits, vegetables, plants, and especially in Hibiscus *sabdariffa*. They are generally responsible for such foods' characteristics, going from their colors like blue, red, or purple colors (1), to their flavor and odor. As for their potential therapeutic effect, there is substantial

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evidence that most if not all can have an effect in different cells of mammals (2) with some of them directly linked to alterations in biological pathways, multiple biological models have shown that anthocyanins are capable of change the way prognosis of several pathologies. One anthocyanin of particular interest is Delphinidn-3-Sambubiosid, found particularly in high quantities in *Hibiscus sabdariffa.* This anthocyanin (DS3) has shown potential therapeutic effects (3), another compound is quercetin (QRC) one of the most researched phenolic compounds that are not anthocyanins, and finally, hibiscus acid (HA) is the most characteristic of this plant and plays an important role in the flavor and therapeutic effects of *Hibiscus sabdariffa* (4,5). However, there is little evidence of how exactly all these biocompounds affect the cells of humans and what targets it has in them. As such, the objective of this study is to use bioinformatic tools to determine what probable targets D3S, QRC, and HA have on human cells as well as to determine the effects could have in such signaling pathways.

2. Materials and Methods

Bioinformatic analysis

The SwissTargetPrediction site was used to determine possible molecular targets of the interaction of D3S, QRC, and HS. Once the list of possible targets for each of them was obtained, the ShinnyGo 0.77 site was used to obtain the Fold Enrichment (FE) of each one by FDR (cut-off of 0.05). Out of those, the ones with an FE higher than 4 were used in KEGG to identify the pathways where there could be a key interaction caused by those biocompounds. Also, the website Stringdb site was used to obtain a hub of genes gathered from the FE data. From these last ones, evidence was searched using the Pubmed database.

Literature search and data selection

A search was conducted using PubMed to identify relevant articles that have information about the genes obtained from the bioinformatic analysis against D3S, QRC, and HA, these were made with a simple search string “Gene/Protein Name” AND “Biocompound name”. The search used terms in titles, abstracts, or a combination of both. Finally, inclusion and exclusion criteria were used to determine which articles could be considered for the final discussion.

Inclusion and Exclusion criteria

The inclusion criteria were: Any study that checks for any of the genes (or protein derived from them) obtained from the bioinformatic analysis with either DS3, QRC and/or HC. As for the exclusion criteria: studies with duplicated or overlapping data, papers that only presented abstracts, conferences, editorials, or author responses, articles without full text available, and systematic reviews.

3. Results

3.1. Data from the Swiss Target Prediction

Figure 1 shows the top 15 target classes of molecules that each biocompound could interact with, for DS3 most of them being enzymes and lyases followed closely by a family of G protein-coupled receptors. QRC most of them belong to oxidoreductase and kinases, and as for HA, most of the targets are enzymes. Also, the full information on all the possible targets is shown in supplementary material 1.

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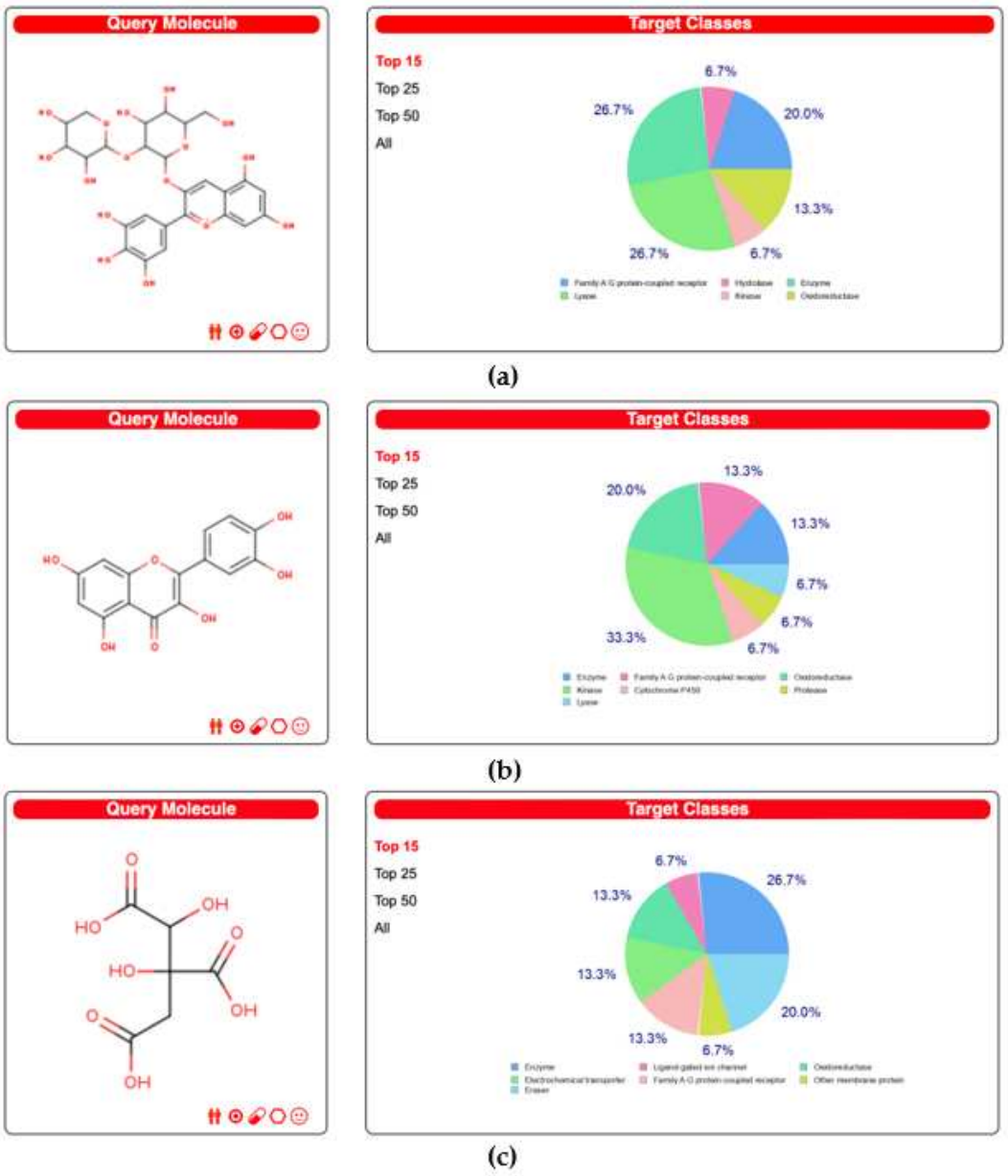

Figure 1. Top 15 molecular targets of the biocompounds according to the Swiss Target Prediction site. a) DS3 Results b) QRC Results c) HA Results.

3.2. Analysis of Gene Ontology and Metabolic Pathways

The site ShinnyGo 0.77 was used to perform the Gene Ontology and KEGG. The full results from the Gene Ontology are shown in Table 1 for DS3, Table 2 for QRC, and Table 3 for HA. The results of KEGG are also shown as images of each pathway with the signaling of the potential changes in the protein are displayed in supplementary material 2.

Table 1. Functional enrichment analysis of the genes that have a prediction of interaction with DS3.

Enrichment FDR	nGenes	Pathway Genes	Fold Enrichment	Pathway	Genes
4.20E-18	10	17	141.151703	Nitrogen metabolism	CA2 CA9 CA14 CA6 CA1 CA3 CA4 CA7 CA5A CA13

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1.49E-09	fifteen	354	10.1677074	PI3K-Akt signaling pathway	GSK3B PIK3CG MET IL2 FLT3 PKN1 KDR IGF1R AKT1 MCL1 PIK3R1 EGFR SYK PTK2 INSR
2.21E-09	9	79	27.3369754	EGFR tyrosine kinase inhibitor resistance	GSK3B MET KDR IGF1R AKT1 PIK3R1 EGFR AXL SRC
2.73E-09	27	1527	4.24287044	Metabolic pathways	CD38 PTGS2 CA12 AKR1B1 HSD17B2 PYGL CA2 SQLE PIK3CG CA9 ALOX12 ALDH2 CA14 GLO1 CA6 CA1 CYP19A1 PDE5A XDH ALOX15 CA3 CA4 CA7 PLA2G1B CA5A CA13 MAOA
1.98E-07	8	95	20.2069806	Endocrine resistance	MMP2 MMP9 IGF1R AKT1 PIK3R1 EGFR PTK2 SRC
3.94E-06	7	108	15.5528265	Insulin resistance	NR1H3 GSK3B PYGL AKT1 PIK3R1 INSR RPS6KA3
4.89E-06	6	70	20.5678196	Central carbon metabolism in cancer	HIF1 A MET FLT3 AKT1 PIK3R1 EGFR
2.28E-05	8	214	8.97038859	Lipid and atherosclerosis	CAMK2B GSK3B MMP9 AKT1 PIK3R1 MMP3 PTK2 SRC
2.52E-05	5	56	21.424812	Regulation of lipolysis in adipocytes	PTGS2 AKT1 PIK3R1 ADORA1 INSR
0.0001554	8	294	6.52946652	MAPK signaling pathway	MET FLT 3 KDR IGF1R AKT1 EGFR INSR RPS6KA3
0.00042661	5	112	10.712406	TNF signaling pathway	PTGS 2 MMP 9 AKT1 PIK3R1 MMP3
0.0008788	5	137	8.7575874	Insulin signaling pathway	GSK3 B PYGL AKT1 PIK3R1 INSR
0.00134156	5	155	7.74057725	Non-alcoholic fatty liver disease	NR1H 3 GSK 3B AKT1 PIK3R1 INSR
0.0024404	3	47	15.3164614	Carbohydrate digestion and absorption	SLC5A1 AKT1 PIK3R1

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0.00373995	4	120	7.99859649	AMPK signaling pathway	IGF1R AKT1 PIK3R1 INSR
0.01950816	3	107	6.72779144	Glucagon signaling pathway	CAMK2B PYGL AKT1
0.02834824	2	46	10.432952	Type II diabetes mellitus	PIK3R1 INSR
0.02929805	2	47	10.2109742	Pyruvate metabolism	ALDH2 GLO1

Table 2. Functional enrichment analysis of the genes that have a prediction of interaction with QRC.

Enrichment FDR	nGenes	Pathway Genes	Fold Enrichment	Pathway	Genes
4.83E-18	10	17	138.241358	Nitrogen metabolism	CA2 CA9 CA14 CA6 CA1 CA3 CA4 CA7 CA5A CA13
3.54E-08	7	51	32.256317	Ovarian steroidogenesis	HSD17B2 HSD17B1 CYP19A1 CYP1B1 IGF1R INSR AKR1C3
5.91E-09	8	61	30.8210242	Steroid hormone biosynthesis	HSD17B2 HSD17B1 CYP19A1 CYP1B1 AKR1C2 AKR1C1 AKR1C3 AKR1C4
1.77E-09	9	79	26.7733264	EGFR tyrosine kinase inhibitor resistance	GSK3B MET KDR IGF1R AKT1 PIK3R1 EGFR AXL SRC
6.38E-09	9	95	22.2641346	Endocrine resistance	MMP2 MMP9 ESR2 IGF1R AKT1 PIK3R1 EGFR PTK2 SRC
9.14E-09	9	100	21.1509278	Progesterone-mediated oocyte maturation	CDK2 CCNB1 IGF1R AKT1 PIK3R1 CCNB3 CCNB2 PLK1 CDK1
9.27E-07	7	84	19.5841924	ErbB signaling pathway	CAMK2B GSK3B AKT1 PIK3R1 EGFR PTK2 SRC
1.38E-07	8	97	19.3822935	prostate cancer	GSK3B MMP9 CDK2 IGF1R AKT1 PIK3R1 EGFR MMP3
6.03E-09	10	131	17.9397183	FoxO signaling pathway	CDK2 CCNB1 IGF1R AKT1 PIK3R1 EGFR CCNB3 CCNB2 PLK1 INSR
4.57E-11	14	223	14.7540104	Chemical carcinogenesis	NOX4 MET AHR AKR1A1 CYP1B1 AKT1 PIK3R1 EGFR AKR1C2 PTK2 AKR1C1 AKR1C3 SRC AKR1C4

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1.98E-07	9	148	14.2911675	Phospholipase D signaling pathway	PIK3CG AVPR2 AKT1 PIK3R1 EGFR CXCR1 SYK INSR F2
1.98E-08	eleven	202	12.7975911	Proteoglycans in cancer	CAMK2B MMP2 MMP9 MET KDR IGF1R AKT1 PIK3R1 EGFR PTK2 SRC
2.87E-06	8	148	12.70326	Gastric cancer	GSK3B ABCB1 MET CDK2 AKT1 PIK3R1 EGFR TERT
3.85E-06	8	156	12.0518107	Cellular senescence	CDK6 CDK2 CCNB1 AKT1 PIK3R1 CCNB3 CCNB2 CDK1
1.98E-07	10	200	11.7505155	Focal adhesion	MYLK GSK3B MET KDR IGF1R AKT1 PIK3R1 EGFR PTK2 SRC
4.65E-06	8	161	11.6775309	MicroRNAs in cancer	ABCB1 MMP9 CDK6 MET PIM1 CYP1B1 PIK3R1 EGFR
3.35E-06	9	210	10.0718704	Rap1 signaling pathway	MET KDR ADORA2A IGF1R AKT1 PIK3R1 EGFR INSR SRC
1.13E-09	fifteen	354	9.95806395	PI3K-Akt signaling pathway	GSK3B CDK6 PIK3CG MET FLT3 PKN1 CDK2 KDR IGF1R AKT1 PIK3R1 EGFR SYK PTK2 INSR
4.57E-11	19	530	8.42489788	Pathways in cancer	CAMK2B GSK3B MMP2 MMP9 CDK6 MET FLT3 CDK2 PIM1 ESR2 IGF1R AKT1 PIK3R1 EGFR TERT PTK2 ALK F2 DAPK1
8.98E-12	31	1527	4.77100169	Metabolic pathways	CD38 CA12 TYR AKR1B1 HSD17B2 PYGL CA2 PIK3CG CA9 HSD17B1 ALOX12 AKR1A1 CA14 ARG1 GLO1 CA6 CA1 CYP19A1

Table 3. Functional enrichment analysis of the genes that have a prediction of interaction with HA.

Enrichment FDR	nGenes	Pathway Genes	Fold Enrichment	Pathway	Genes
2.73E-08	6	40	55.1516129	Nicotine addiction	GABRG2 GRIA2 GABRB2 GABRA2 GRIA4 GRIA1
1.31E-23	17	114	54.82908885	Glutamatergic synapse	GRIK5 SLC1A1 SLC1A2 GRM6 GRIA2 GRM4 GRIA4 GRM1 GRIA1 GRIK3 GRM2 GRIK2 GRM5 GRIK1 GRM8 GRM7 GRM3
0.000306466	3	22	50.13782991	Terpenoid backbone biosynthesis	HMGCR FNTA FNTB
0.005845035	2	17	43.25616698	Nitrogen metabolism	CA9 CA1

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9.26E-06	5	61	30.13749339	Steroid hormone biosynthesis	HSD11B1 HSD17B3 CYP19A1 UGT2B7 HSD11B2
8.88E-07	6	75	29.41419355	PPAR signaling pathway	CPT1A PPARD FABP3 FABP5 FABP4 PPARA
0.002418552	3	49	22.51086241	Cocaine addiction	GRIA2 GRM2 GRM3
7.85E-09	9	148	22.35876199	Phospholipase D signaling pathway	GRM6 PTGFR GRM4 GRM1 GRM2 GRM5 GRM8 GRM7 GRM3
2.25E-21	twenty-one	350	22.06064516	Neuroactive ligand-receptor interaction	GRIK5 GRM6 GABRG2 GRIA2 PTGFR GRM4 PTGER2 GABRB2 GABRA2 GRIA4 GRM1 GRIA1 GRIK3 GRM2 GRIK2 GRM5 GRIK1 GRM8 GRM7 GRM3 ADORA3
0.000324344	4	67	21.95089071	Long-term potentiation	GRIA2 GRM1 GRIA1 GRM5
1.27E-07	8	148	19.8744551	Retrograde endocannabinoid signaling	GABRG2 GRIA2 GABRB2 GABRA2 GRIA4 GRM1 GRIA1 GRM5
0.004067259	3	60	18.38387097	Long-term depression	GRIA2 GRM1 GRIA1
0.005712018	3	69	15.98597475	Amphetamine addiction	GRIA2 GRIA4 GRIA1
0.008700522	3	85	12.97685009	Taste transduction	GRM4 GABRA2 GRM1
0.009404411	3	89	12.39362088	GABAergic synapse	GABRG2 GABRB2 GABRA2
0.009520584	3	91	12.12123361	Morphine addiction	GABRG2 GABRB2 GABRA2
0.001753072	5	197	9.331914197	Chemical carcinogenesis	VDR CDC25A AR UGT2B7 PPARA
0.002418552	5	219	8.394461629	CAMP signaling pathway	GRIA2 PTGER2 GRIA4 GRIA1 PPARA
0.008334	5	306	6.00780097	Huntington's disease	SLC1A2 GRIA2 GRIA4 GRIA1 GRM5
0.000129008	fifteen	1527	3.611762469*	Metabolic pathways	FOLH1 HAO1 CA9 HMGCR HSD11B1 HSD17B3 ACLY CA1 CYP19A1 PGD PTGES G6PD UGT2B7 HSD11B2 AKR1B10

*Only value with a FE lower than 4.

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3.3. Protein-Protein Interaction Network

The STRING database was used to predict the associations of protein targets of the three biocompounds. The network was constructed with a medium confidence of 0.400. Figure 2 shows the interactome for DS3 which has 257 edges, 57 nodes, an average node degree of 9.02, and a PPI enrichment p-value of <1.0e-16. Figure 3 shows the interactome for QRC, which has 328 edges, 71 nodes, an average node degree of 9.24, and a PPI enrichment p.value <1.0e-16. Figure 4 shows the interactome for HA. Table 4 shows the hub genes with at least 10 interactions of DS3, Table 5 shows the hub genes with at least 10 interactions of QRC, and Table 6 shows the hub genes with at least 10 interactions of HA.

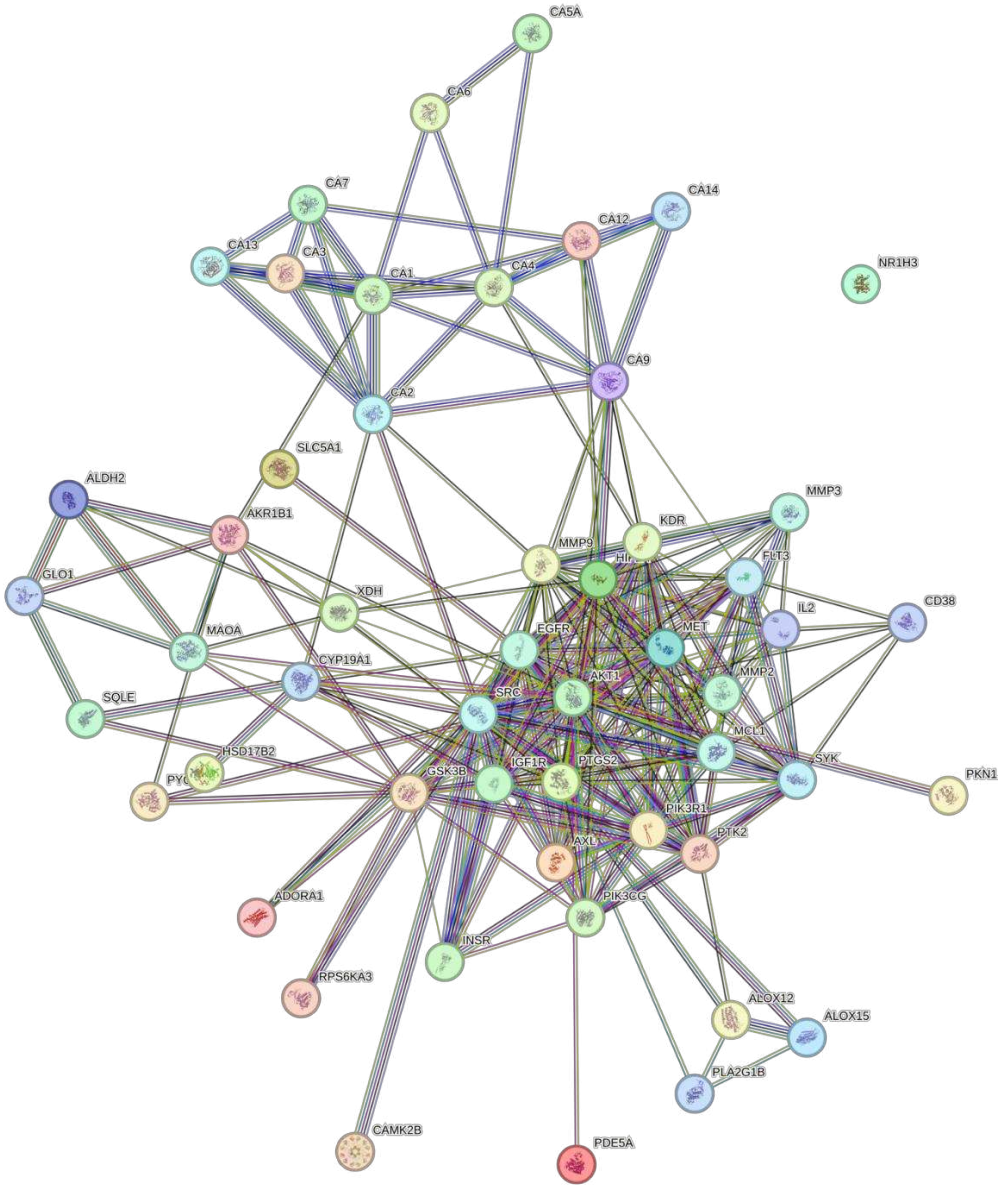

Figure 2. PPI network of DS3. Each of the edges is a specific protein with a significant protein-protein association. The blue and purple borders are known interactions from plentiful databases (previously curated and experimentally curated). As for the predicted interactions of each neighborhood gene, gene fusion, and gene concurrence are identified as green, red, and navy blue. Other borders such as grass green, black, and gray are text-mining, coexpression, and protein homology respectively.

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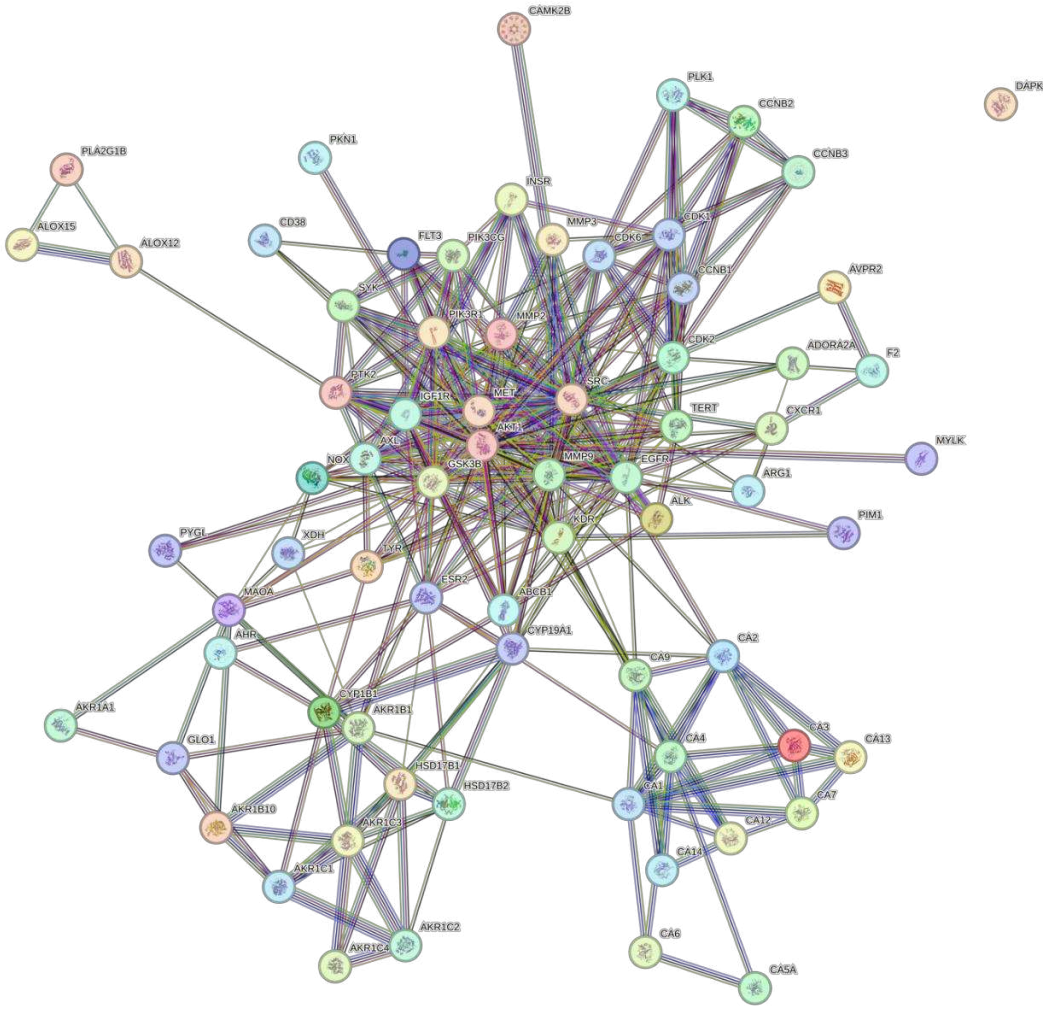

Figure 3. PPI network of QRC. The colored notes indicate query proteins and the first shell of interactors, as for white nodes those are the second shell of interactors. The edges represent protein-protein associations, the colors indicate the origin of those interactions, sky blue color indicates the information comes from curated databases, purple shows that those have been experimentally determined, green, red, and navy blue indicate predicted interactions, lime green, black and light blue represent associations as text mining, co-expression, and protein homology respectively.

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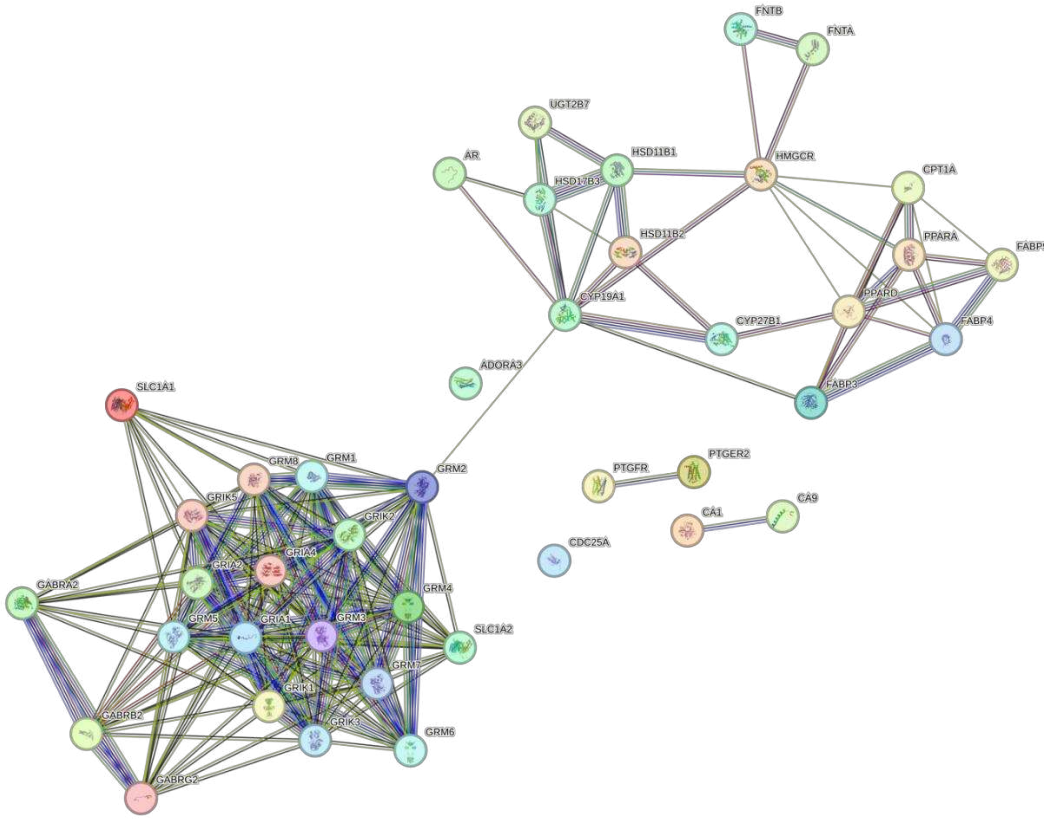

Figure 4. PPI network of HA. The colored notes indicate query proteins and the first shell of interactors, as for white nodes those are the second shell of interactors. The edges represent protein-protein associations, the colors indicate the origin of those interactions, sky blue color indicates the information comes from curated databases, purple shows that those have been experimentally determined, green, red, and navy blue indicate predicted interactions, lime green, black and light blue represent associations as text mining, co-expression, and protein homology respectively.

Table 4. Hub genes with at least 10 interactions in humans were obtained from the predictions of interactions with DS3.

Gene symbol	Protein name	Protein-Function
AKT1	RAC-alpha serine/threonine-protein kinase	Regulates many processes including metabolism, proliferation, cell survival, growth, and angiogenesis.
PTK2	Focal adhesion Kinase 1	Related to the increase in glucose uptake and glycogen synthesis in insulin-sensitive tissues.
IL2	Interleukin-2	Required for T-cell proliferation and other cells of the immune system
PIK3R1	Phosphoinositide -3-kinase regulatory subunit alpha/beta/delta	Necessary for the insulin-stimulated increase in glucose uptake and glycogen synthesis

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SYK	Spleen-associated tyrosine kinase	Regulates biological processes including immunity, cell adhesion, vascular development, and others.
PTGS2	Prostaglandin G/H synthase 2	Plays a role in the production of inflammatory prostaglandins
MMP9	Matrix metalloproteinase-9	Key in local proteolysis of the extracellular matrix and leukocyte migration
HIF1A	Hypoxia-inducible factor 1-alpha	Master transcriptional regulation in response to hypoxia
MMP2	Matrix metalloproteinase-2 (gelatinase a)	Involved in angiogenesis, tissue repair, tumor invasion, inflammation, and atherosclerotic plaque rupture
KDR	Vascular endothelial growth factor receptor 2	Essential in the regulation of angiogenesis, promotes the proliferation, survival, and migration of endothelial cells
MET	Hepatocyte growth factor receptor	Regulates processes like proliferation, scattering, morphogenesis, and survival
HGF	Hepatocyte growth factor	Growth factor for a broad spectrum of tissues and cell types
EGFR	Epidermal growth factor receptor	Converts extracellular cues into appropriate cellular responses
IGF1R	Insulin-like growth factor 1 receptor	Involved in cell growth and survival control
CA9	Carbonic anhydrase 9	Involved in pH regulation
BLNK	B-cell linker protein	Important for the activation of NF-kappa-B and NFAT

Table 5. Hub genes with at least 10 interactions in humans were obtained from the predictions of interactions with QRC.

Gene symbol	Protein name	Protein-function
ABCB1	ATP-dependent translocase	Translocates drugs and phospholipids across the membrane.
AHR	Aryl hydrocarbon receptor	Ligand-activated transcriptional activator

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AKR1A1	Aldo-keto reductase family 1 member A	Displays enzymatic activity towards endogenous metabolites such as aromatic and aliphatic aldehydes, ketones, monosaccharides and bile acids, with a preference for negatively charged substrates, such as glucuronate and succinic semialdehyde.
AKR1B1	Aldo-keto reductase family 1 member B1	Displays enzymatic activity towards endogenous metabolites such as aromatic and aliphatic aldehydes, ketones, monosaccharides and bile acids, with a preference for negatively charged substrates, such as glucuronate and succinic semialdehyde.
AKR1B10	Aldo-keto reductase family 1 member B10	Catalyzes the NADPH-dependent reduction of a wide variety of carbonyl-containing compounds to their corresponding alcohols.
AKR1C1	Aldo-keto reductase family 1 member C1	Converts progesterone to its inactive form, 20-alpha-dihydroxyprogesterone (20-alpha-OHP). In the liver and intestine, may have a role in the transport of bile
AKR1C2	Aldo-keto reductase family 1 member C2	Works in concert with the 5-alpha/5-beta-steroid reductases to convert steroid hormones into the 3-alpha/5-alpha and 3-alpha/5-beta-tetrahydrosteroids.
AKR1C3	Aldo-keto reductase family 1 member C3	; Catalyzes the conversion of aldehydes and ketones to alcohols. Catalyzes the reduction of prostaglandin (PG) D2, PGH2 and phenanthrenequinone (PQ) and the oxidation of 9-alpha,11-beta-PGF2 to PGD2.
AKR1C4	Aldo-keto reductase family 1 member C4	;Catalyzes the transformation of the potent androgen dihydrotestosterone (DHT) into the less active form, 5-alpha-androstan- 3-alpha,17-beta-diol (3-alpha-diol).
AKT1	RAC-alpha serine/threonine-protein kinase	Regulate many processes including metabolism, proliferation, cell survival, growth and angiogenesis. This is mediated through serine and/or threonine

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		phosphorylation of a range of downstream substrates.
ALK	ALK tyrosine kinase receptor	Important role in the genesis and differentiation of the nervous system. Transduces signals from ligands at the cell surface, through specific activation of the mitogen-activated protein kinase (MAPK) pathway.
ALOX12	Arachidonate 12-lipoxygenase 12S-type	Mainly converts arachidonic acid to (12S)-hydroperoxyeicosatetraenoic acid/(12S)-HPETE but can also metabolize linoleic acid. In contrast does not react towards methyl esters of linoleic and arachidonic acids (By similarity).
ALOX15	Arachidonate 15-lipoxygenase	; Non-heme iron-containing dioxygenase that catalyzes the stereo-specific peroxidation of free and esterified polyunsaturated fatty acids generating a spectrum of bioactive lipid mediators.
AXL	Tyrosine-protein kinase UFO receptor	Receptor tyrosine kinase that transduces signals from the extracellular matrix into the cytoplasm by binding growth factor GAS6 and which is thus regulating many physiological processes including cell survival, cell proliferation, migration and differentiation.
CA1	Carbonic anhydrase 1	Reversible hydration of carbon dioxide
CA12	Carbonic anhydrase 12	Reversible hydration of carbon dioxide
CA13	Carbonic anhydrase 13	Reversible hydration of carbon dioxide
CA14	Carbonic anhydrase 14	Reversible hydration of carbon dioxide
CA2	Carbonic anhydrase 2	Essential for bone resorption and osteoclast differentiation. Reversible hydration of carbon dioxide.
CA3	Carbonic anhydrase 3	Reversible hydration of carbon dioxide
CA4	Carbonic anhydrase 4	Reversible hydration of carbon dioxide
CA7	Carbonic anhydrase 7	Reversible hydration of carbon dioxide
CA9	Carbonic anhydrase 9	Reversible hydration of carbon dioxide
CAMK2B	Calcium/calmodulin-dependent protein kinase type II subunit beta	Calcium/calmodulin-dependent protein kinase that functions autonomously after Ca(2+)/calmodulin-binding and

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		autophosphorylation, ansport in skeletal muscle.
CCNB1	G2/mitotic-specific cyclin-B1	Essential for the control of the cell cycle at the G2/M (mitosis) transition
CCNB2	G2/mitotic-specific cyclin-B2	Essential for the control of the cell cycle at the G2/M (mitosis) transition
CCNB3	G2/mitotic-specific cyclin-B3	Plays an essential role in the control of the cell cycle, notably via their destruction during cell division. Its tissue specificity suggest that it may be required during early meiotic prophase I.
CDK1	Cyclin dependent kinase 1	Cyclin-dependent kinase 1; Plays a key role in the control of the eukaryotic cell cycle by modulating the centrosome cycle as well as mitotic onset; promotes G2-M transition, and regulates G1 progress and G1-S transition via association with multiple interphase cyclins. Required in higher cells for entry into S-phase and mitosis. Q
CDK2	Cyclin dependent kinase 2	Cyclin-dependent kinase 2; Serine/threonine-protein kinase involved in the control of the cell cycle; essential for meiosis, but dispensable for mitosis.
CDK6	Cyclin dependent kinase 6	Cyclin-dependent kinase 6; Serine/threonine-protein kinase involved in the control of the cell cycle and differentiation; promotes G1/S transition.
CXCR1	CXC chemokine receptor type 1;	Receptor to interleukin-8, which is a powerful neutrophils chemotactic factor.
CYP19A1	Aromatase	A cytochrome P450 monooxygenase that catalyzes the conversion of C19 androgens, androst-4-ene-3,17-dione (androstenedione) and testosterone to the C18 estrogens, estrone and estradiol, respectively.
CYP1B1	Cytochrome P450 1B1	A cytochrome P450 monooxygenase involved in the metabolism of various endogenous substrates, including fatty acids, steroid hormones and vitamins.

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DAPK1	Death-associated protein kinase 1	Calcium/calmodulin-dependent serine/threonine kinase involved in multiple cellular signaling pathways that trigger cell survival, apoptosis, and autophagy.
EGFR	Epidermal growth factor receptor	Receptor tyrosine kinase binding ligands of the EGF family and activating several signaling cascades to convert extracellular cues into appropriate cellular responses.
ESR2	Estrogen receptor beta	Nuclear hormone receptor. Binds estrogens with an affinity similar to that of ESR1, and activates expression of reporter genes containing estrogen response elements (ERE) in an estrogen-dependent manner.
FLT3	Receptor-type tyrosine-protein kinase FLT3	Tyrosine-protein kinase that acts as cell-surface receptor for the cytokine FLT3LG and regulates differentiation, proliferation and survival of hematopoietic progenitor cells and of dendritic cells.
GLO1	Lactoylglutathione lyase	Involved in the regulation of TNF-induced transcriptional activity of NF-kappa-B.
GSK3B	Glycogen synthase kinase-3 beta	Constitutively active protein kinase that acts as a negative regulator in the hormonal control of glucose homeostasis,
HSD17B1	Estradiol 17-beta-dehydrogenase 1	Estradiol 17-beta-dehydrogenase 1; Favors the reduction of estrogens and androgens.
HSD17B2	Estradiol 17-beta-dehydrogenase 2	Estradiol 17-beta-dehydrogenase 2; Capable of catalyzing the interconversion of testosterone and androstenedione, as well as estradiol and estrone.
IGF1R	Insulin-like growth factor 1 receptor alpha chain	Receptor tyrosine kinase which mediates actions of insulin-like growth factor 1 (IGF1). Binds IGF1 with high affinity and IGF2 and insulin (INS) with a lower affinity.
INSR	Insulin receptor subunit alpha	Receptor tyrosine kinase which mediates the pleiotropic actions of insulin. Binding of insulin leads to phosphorylation of

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		several intracellular substrates, including, insulin receptor substrates (IRS1, 2, 3, 4), SHC, GAB1, CBL and other signaling intermediates.
KDR	Vascular endothelial growth factor receptor 2	Tyrosine-protein kinase that acts as a cell-surface receptor for VEGFA, VEGFC and VEGFD. Plays an essential role in the regulation of angiogenesis, vascular development, vascular permeability, and embryonic hematopoiesis.
MAOA	Amine oxidase [flavin-containing] A	Catalyzes the oxidative deamination of biogenic and xenobiotic amines and has important functions in the metabolism of neuroactive and vasoactive amines in the central nervous system and peripheral tissues.
MET	Hepatocyte growth factor receptor	Receptor tyrosine kinase that transduces signals from the extracellular matrix into the cytoplasm by binding to hepatocyte growth factor/HGF ligand.
MMP2	72 kDa type IV collagenase	Ubiquitinous metalloproteinase that is involved in diverse functions such as remodeling of the vasculature, angiogenesis, tissue repair, tumor invasion, inflammation, and atherosclerotic plaque rupture.
MMP3	Stromelysin-1	Can degrade fibronectin, laminin, gelatins of type I, III, IV, and V; collagens III, IV, X, and IX, and cartilage proteoglycans. Activates procollagenase
MMP9	67 kDa matrix metalloproteinase-9	May play an essential role in local proteolysis of the extracellular matrix and in leukocyte migration. Could play a role in bone osteoclastic resorption.
NOX4	NADPH oxidase 4	Constitutive NADPH oxidase which generates superoxide intracellularly upon formation of a complex with CYBA/p22phox. Regulates signaling cascades probably through phosphatases inhibition.

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PIK3CG	Phosphatidylinositol 4,5-bisphosphate 3-kinase catalytic subunit gamma isoform;	Phosphoinositide-3-kinase (PI3K) that phosphorylates PtdIns(4,5)P2 (Phosphatidylinositol 4,5-bisphosphate) to generate phosphatidylinositol 3,4,5-trisphosphate (PIP3).
PIK3R1	Phosphatidylinositol 3-kinase regulatory subunit alpha	Necessary for the insulin-stimulated increase in glucose uptake and glycogen synthesis in insulin-sensitive tissues.
PLA2G1B	Phospholipase A2	PA2 catalyzes the calcium-dependent hydrolysis of the 2-acyl groups in 3-sn-phosphoglycerides, this releases glycerophospholipids and arachidonic acid that serve as the precursors of signal molecules.
PLK1	Serine/threonine-protein kinase PLK1	Serine/threonine-protein kinase that performs several important functions throughout M phase of the cell cycle, including the regulation of centrosome maturation and spindle assembly, the removal of cohesins from chromosome arms, the inactivation of anaphase-promoting complex/cyclosome (APC/C) inhibitors, and the regulation of mitotic exit and cytokinesis.
PTK2	Focal adhesion kinase 1	Non-receptor protein-tyrosine kinase that plays an essential role in regulating cell migration, adhesion, spreading, reorganization of the actin cytoskeleton, formation and disassembly of focal adhesions and cell protrusions, cell cycle progression, cell proliferation and apoptosis.
PYGL	Glycogen phosphorylase, liver form	Phosphorylase is an important allosteric enzyme in carbohydrate metabolism.
CRS	Proto-oncogene tyrosine-protein kinase Src	Non-receptor protein tyrosine kinase which is activated following engagement of many different classes of cellular receptors including immune response receptors, integrins and other adhesion receptors, receptor protein tyrosine

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		kinases, G protein-coupled receptors as well as cytokine receptors.
SYK	Tyrosine-protein kinase SYK	Non-receptor tyrosine kinase which mediates signal transduction downstream of a variety of transmembrane receptors including classical immunoreceptors like the B-cell receptor (BCR). Regulates several biological processes including innate and adaptive immunity, cell adhesion, osteoclast maturation, platelet activation and vascular development.
TERT	Telomerase reverse transcriptase	Telomerase is a ribonucleoprotein enzyme essential for the replication of chromosome termini in most eukaryotes. Active in progenitor and cancer cells. Inactive, or very low activity, in normal somatic cells.
TYR	Tyrosinase	This is a copper-containing oxidase that functions in the formation of pigments such as melanins and other polyphenolic compounds. Catalyzes the initial and rate limiting step in the cascade of reactions leading to melanin production from tyrosine. Yo

Table 6. Hub genes with at least 10 interactions in humans were obtained from the predictions of interactions with HA.

Gene symbol	Protein	Protein-Function
CPT1A	Carnitine O-palmitoyltransferase 1, liver isoform	Catalyzes the transfer of the acyl group of long-chain fatty acid-CoA conjugates onto carnitine, an essential step for the mitochondrial uptake of long-chain fatty acids and their subsequent beta-oxidation in the mitochondrion.
CYP19A1	Aromatase	A cytochrome P450 monooxygenase that catalyzes the conversion of C19 androgens, androst-4-ene-3,17-dione (androstenedione) and testosterone to the C18 estrogens, estrone and estradiol, respectively.

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CYP27B1	25-hydroxyvitamin D-1 alpha hydroxylase, mitochondrial	A cytochrome P450 monooxygenase involved in vitamin D metabolism and in calcium and phosphorus homeostasis.
FABP3	Fatty acid-binding protein, heart	FABP are thought to play a role in the intracellular transport of long-chain fatty acids and their acyl-CoA esters
FABP4	Fatty acid-binding protein, adipocyte	Lipid transport protein in adipocytes. Binds both long chain fatty acids and retinoic acid. Delivers long-chain fatty acids and retinoic acid to their cognate receptors in the nucleus. Belongs to the calycin superfamily. Fatty-acid binding protein (FABP) family. (132 years)
FABP5	Fatty acid-binding protein 5	Intracellular carrier for long-chain fatty acids and related active lipids, such as the endocannabinoid, that regulates the metabolism and actions of the ligands they bind. In addition to the cytosolic transport, it selectively delivers specific fatty acids from the cytosol to the nucleus, wherein they activate nuclear receptors.
GABRA2	Gamma-aminobutyric acid receptor subunit alpha-2	Ligand-gated chloride channel which is a component of the heteropentameric receptor for GABA, the major inhibitory neurotransmitter in the brain (By similarity). Plays an important role in the formation of functional inhibitory GABAergic synapses in addition to mediating synaptic inhibition as a GABA-gated ion channel (By similarity).
GABRB2	Gamma-aminobutyric acid receptor subunit beta-2	Ligand-gated chloride channel which is a component of the heteropentameric receptor for GABA, the major inhibitory neurotransmitter in the brain. Plays an important role in the formation of functional inhibitory GABAergic synapses in addition to mediating synaptic inhibition as a GABA-gated ion channel.
GABRG2	Gamma-aminobutyric acid receptor subunit gamma-2	Ligand-gated chloride channel which is a component of the heteropentameric receptor for GABA, the major inhibitory neurotransmitter in the brain. Plays an important role in the formation of functional inhibitory GABAergic synapses in addition to mediating synaptic inhibition as a GABA-gated ion channel.
GRIA1	Glutamate receptor 1	Ionotropic glutamate receptor. L-glutamate acts as an excitatory neurotransmitter at many synapses in the central nervous system.

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GRIA2	Glutamate receptor 2	Receptor for glutamate that functions as ligand-gated ion channel in the central nervous system and plays an important role in excitatory synaptic transmission. L-glutamate acts as an excitatory neurotransmitter at many synapses in the central nervous system.
GRIA4	Glutamate receptor 4	Receptor for glutamate that functions as ligand-gated ion channel in the central nervous system and plays an important role in excitatory synaptic transmission. L-glutamate acts as an excitatory neurotransmitter at many synapses in the central nervous system.
GRIK1	Glutamate ionotropic receptor, kainate 1	Ionotropic glutamate receptor. L-glutamate acts as an excitatory neurotransmitter at many synapses in the central nervous system. b
GRIK2	Glutamate ionotropic receptor, kainate 2	Ionotropic glutamate receptor. L-glutamate acts as an excitatory neurotransmitter at many synapses in the central nervous system.
GRIK3	Glutamate ionotropic receptor, kainate 3	Receptor for glutamate that functions as ligand-gated ion channel in the central nervous system and plays an important role in excitatory synaptic transmission.
GRIK5	Ionotropic receptor glutamate, kainate 5	Receptor for glutamate. L-glutamate acts as an excitatory neurotransmitter at many synapses in the central nervous system.
GRM1	Metabotropic glutamate receptor 1	G-protein coupled receptor for glutamate.
GRM2	Metabotropic glutamate receptor 2	G-protein coupled receptor for glutamate.
GRM3	Metabotropic glutamate receptor 3	G-protein coupled receptor for glutamate.
GRM4	Metabotropic glutamate receptor 4	G-protein coupled receptor for glutamate.
GRM5	Metabotropic glutamate receptor 5	G-protein coupled receptor for glutamate.
GRM6	Metabotropic glutamate receptor 6	G-protein coupled receptor for glutamate.
GRM7	Metabotropic glutamate receptor 7	G-protein coupled receptor for glutamate.
GRM8	Metabotropic glutamate receptor 8	G-protein coupled receptor for glutamate.

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HMGCR	3-hydroxy-3-methylglutaryl-coenzyme A reductase	Transmembrane glycoprotein that is the rate-limiting enzyme in cholesterol biosynthesis as well as in the biosynthesis of nonsterol isoprenoids that are essential for normal cell function including ubiquinone and geranylgeranyl proteins.
HSD11B1	Corticosteroid 11-beta-dehydrogenase isozyme 1	Catalyzes reversibly the conversion of cortisol to the inactive metabolite cortisone. Catalyzes reversibly the conversion of 7-ketocholesterol to 7-beta-hydroxycholesterol.
HSD11B2	Corticosteroid 11-beta-dehydrogenase isozyme 2	Catalyzes the conversion of cortisol to the inactive metabolite cortisone.
HSD17B3	Testosterone 17-beta-dehydrogenase 3	Favors the reduction of androstenedione to testosterone.
PPARA	Peroxisome proliferator-activated receptor alpha	Ligand-activated transcription factor. Key regulator of lipid metabolism. Activated by the endogenous ligand 1-palmitoyl-2-oleoyl-sn-glycerol-3-phosphocholine (16:0/18:1-GPC). Activated by oleylethanolamide, a naturally occurring lipid that regulates satiety.
PPARD	Peroxisome proliferator-activated receptor delta	Ligand-activated transcription factor. Receptor that binds peroxisome proliferators such as hypolipidemic drugs and fatty acids.
SLC1A1	Excitatory amino acid transporter 3	Sodium-dependent, high-affinity amino acid transporter that mediates the uptake of L-glutamate and also L-aspartate and D-aspartate.
SLC1A2	Excitatory amino acid transporter 2	Sodium-dependent, high-affinity amino acid transporter that mediates the uptake of L-glutamate and also L-aspartate and D-aspartate.
HSD17B3	Testosterone 17-beta-dehydrogenase 3	Favors the reduction of androstenedione to testosterone.
PPARA	Peroxisome proliferator-activated receptor alpha	Ligand-activated transcription factor. Key regulator of lipid metabolism.
PPARD	Peroxisome proliferator-activated receptor delta	Ligand-activated transcription factor. Receptor that binds peroxisome proliferators such as hypolipidemic drugs and fatty acids. Has a preference for poly-unsaturated fatty acids, such as gamma-linoleic acid and eicosapentaenoic acid.
SLC1A1	Excitatory amino acid transporter 3	Sodium-dependent, high-affinity amino acid transporter that mediates the uptake of L-glutamate and also L-aspartate and D-aspartate.

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SLC1A2	Excitatory amino acid transporter 2	Sodium-dependent, high-affinity amino acid transporter that mediates the uptake of L-glutamate and also L-aspartate and D-aspartate.

3.4. Data recollection from the evidence of the hub genes with the biocompounds

The results from the search in the PubMed database results from the articles of the hub genes when tested in a study with DS3 and QRC are shown in Table 7 and Table 8, respectively. As for HA, no information about its relationship with any of the hub genes was found at the date of data collection. These results are presented separately if the evidence is found at RNA, protein, or pathways level directly.

Table 7. Evidence found of the Hub genes when tested against DS3.

Genes	Results at the gene expression level	Results at the protein level	Results of pathway impact
MET		Deeba N. 2008 (6): Suppress the phosphorylation of the protein	
IGF1R		Teller et al, 2009 (7): Inhibition of its kinase activity	
EGFR	Harish Chandra Pal(8), et al, 2013: Reduction in the expression of the gene	Fridrich D, Et all, 2008 (4): Suppress phosphorylation of the protein.	Harish Chandra Pal, et al, 2013 (8): Inhibition of the PI3K-Akt pathway

*The hub genes that are not shown had no relevant information (if any) for this study in the PubMed database at the date of collection of the data.

Table 8. Evidence found of the Hub genes when tested against QRC.

Genes	Results at the gene expression level	Results at the protein level	Results of pathway impact
AHR		Mohammadi-Bardbori (9), 2012: reduces protein activation	Ciolino H, 1999(10): Generates changes in the pathway for Chemical carcinogenesis. Hamidullah , 2015: Changes in the Akt- mTor pathway
AK1RC3		Skarydová et al, 2014(11): Inhibition of the activity of the enzyme	
CDK2		Chou, et al, 2010 (12): Decreased levels of the protein	

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CDK6	Mohd et al, 2020 (13): Decreases the expression of the gene.	Teler et al, 2009 (4): Inhibition of its kinase activity
CYP1B1	Mense S, 2008 (14): Increase in RNA transcription	Mense S, 2008 (14): Increase in levels of the protein in epithelial cells
EGFR		Yiqi et al, 2022 (15): Decreases the phosphorylation of the protein/receptor Huang Y, 1999: Decreses the phosphorylation of the protein/receptor
GSK3B		Chen K, et al, 2018(16): Decrease in the phosphorylation, promotes the activity of the protein
IGF1R		Wei-Jen, 2021(17): Reduces the phosphorylation of the protein
MAOA		Yauhen, 2014(18): The activity of the protein is decreased, it is probable that quercetin inhibits the protein, there is no decrease in the levels of protein
MET	Hui et al, 2015 (19): Reduction on the transcription of the gene	Hui et al, 2015 (19) Reduced phosphorylation of the protein.
PIK3R1		Haitao et al, 2021(20): Inhibits the function of the protein (is this protein level

*The hub genes that are not shown had no relevant information (if any) for this study in the PubMed database at the date of collection of the data.

4. Discussion

The results of the SwissTargetPrediction software (Figure 1) have their bases in the mathematical foundation of SwissTargetPrediction which assesses targets of molecular binding by comparing the molecules to others like them in a 2-way analysis (21), it (SwissTargetPrediction) makes a physical

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5D analysis of the molecules (3 dimensions being the spatial dimensions and the other 2 being the atomic charge and the lipophilicity respectively) and also makes a chemical comparison by Tanimoto Index . It is important to remark on how SwissTargetPrediction has been used in the determination of molecular targets of small molecules that come from plants or foods (not dissimilar to the one in this study). For example, in a study of 2022, a team of researchers from China led by Lili Yan (22) looked at Erianin (a biphenyl compound) information regarding its predicted molecular targets on this site, then, they compared the matches of those targets (along with the results of other bio-informatic tools) with then-current information published by other authors getting plenty of overlap in their results. This shows how this tool (SwissTargetPrediction) has been used to successfully find information regarding molecular target information.

In Table 1 the results from the Gene Ontology assay shows (23) that DS3 affected several processes involving metabolism and inflammation, in particular nitrogen metabolism, insulin resistance signaling, PI3k-Akt pathway, metabolic pathways, insulin signaling pathway, regulation of lipolysis, TNF signaling pathway, lipid and atherosclerosis, and endocrine resistance. As for Table 2, the Gene Ontology Assay shows that QRC affected other processes, while it also included metabolism and inflammation, it had plenty of differences, those are: Nitrogen metabolism, Ovarian steroidogenesis, Steroid hormone biosynthesis, EGFR tyrosine kinase inhibitor resistance, Endocrine resistance, Progesterone-mediated oocyte maturation, ErbB signaling pathway, Prostate cancer, FoxO signaling pathway, Chemical carcinogenesis, Phospholipase D signaling pathway, Proteoglycans in cancer, Gastric cancer, Cellular senescence, Focal adhesion, MicroRNAs in cancer, Rap1 signaling pathway, PI3K- Akt signaling pathway, Pathways in cancer, and Metabolic pathways. Finally, the Gene Ontology assay of HA, had interesting results, while some of them are similar to the ones in DS3 and QRC, it has different pathways not present in any of the previous compounds, most intriguing many of them are related to the nervous system somehow, all of the pathways are as follows: Nicotine addiction, Glutamatergic synapse, Terpenoid backbone biosynthesis, Nitrogen metabolism, Steroid hormone biosynthesis, PPAR signaling pathway, Cocaine addiction, Phospholipase D signaling pathway, Neuroactive ligand-receptor interaction, Long-term potentiation, Retrograde endocannabinoid signaling, Long-term depression, Amphetamine addiction, Taste transduction, GABAergic synapse, Morphine addiction, Chemical carcinogenesis, cAMP signaling pathway, Huntington disease, Metabolic pathways. These results are supported by the foundation of the database, the use of the FE of each one by FDR (cut-off of 0.05) has been widely accepted as a tool in bioinformatics to delimit the possibility of false positives (27). These processes are related to a significant number of the effects described for DS3, QRC, or HA (2,3).

Regarding the KEGG analysis on the pathways affected, Table 1 (DS3) indicates, a dysregulation in the metabolism of nitrogen (key in the regulation of energy metabolism and protein metabolism) and glucose metabolism (especially in muscle and adipose tissue). Interestingly, as for the glucose metabolism alterations seem to be attached mostly to alterations in the PI3K-Akt pathway, this result agrees with multiple studies that have studied the effects of DS3 in PI3K-AKT (21–24) For QRC, Table 2 suggests various possible pathways and there's information that indicates such predictions could be the cause of some reported effects, for example, Vaez et al, gave seventy-two women with polycystic ovary syndrome 500 mg of QRC, here they found that the serum levels of LH hormone, FSH hormone, and IL-6 (24), the authors then conclude that QRC can decrease inflammatory and LH parameters. Results such as these also suggest that QRC has some implications for ovarian steroidogenesis just like the bioinformatic test predicts but also it could be explained by the potential effect that QRC has on the PI3K-Akt pathway. Furthermore, QRC has been shown to affect nutrient metabolism, while the information provided by the KEGG analysis suggests changes in the nitrogen metabolism and metabolic pathways, there is some information published that may prove those predictions. For instance, Leyva-Soto et al found in a randomized placebo-controlled study (n=156) of patients with metabolic syndrome supplemented with enriched bread with QRC that in comparison with controls, total cholesterol, LDL-cholesterol, total triglycerides, and fasting plasma glucose significantly decreased (25). As for the results of KEGG for HA, while the results suggest it has an impact on pathways associated with the nervous system and others like PPAR, to date, there

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is little to no information regarding tests in the areas of most of the pathways described for HA. However, there has been some research regarding the impact of HA on rats and their results have shown some potential therapeutic effect (26,27).

The protein-to-protein analysis also supports varies ideas (28–35), for PI3K-AKT pathway is a major target of DS3, by having AKT being the most linked node of the whole analysis. Also, the information on the hub genes (Table 2) shows the trend of the genes to be related to the metabolism of glucose and nitrogen, inflammation, and angiogenesis. This not only has concordance with the previous results shown but also includes angiogenesis, a process related to the production of nitric oxide and therefore to blood pressure. This is of interest since another of the most reported effects of DS3 is its potential as a hypotensive (36) . The protein-to-protein analysis for QRC is vastly different. In general, as Figure 4 shows, there are many more interactions between proteins than in the other two figures, even so, it seems that most of the interactions congregate around proteins related to cancer or inflammation in some way. Such results are interesting since plenty of the research available presents an interest in using QRC for cancer treatment (12,14,17–19,37). Finally, the protein-to-protein for HA is drastically different from the other two, there is a greater separation between interactions where the focus relies upon the interactions of different glutamate-related proteins/receptors but there is little if any information published about this interaction.

As for the evidence research, using the PubMed database was looked for any information regarding the hub genes obtained from the protein-to-protein analysis and each of the biocompounds. In the case of DS3, it is fascinating to see the effects on EGFR, being the one that has more evidence of what happens when exposed to DS3: reducing the expression of the gene, suppressing the function of the protein transcribed from it, and, finally, being associated with inhibiting the whole PI3K-AKT pathway in this condition (4,7,8,38). However, it is important to note how most of the other genes do have some predicted alterations but, there was not much information to be found about their relationship with DS3 (if any), therefore the importance of studying them a posteriori is suggested. In the case of QRC, plenty of the interactions are correlated with pathways associated with cancer, and most of them influence the proteins, changing phosphorylation effects of receptors like EFGR or PI3K (15–20), even so, most of the hub genes gathered from the protein- to-protein analysis didn't have any information present, therefore it's important to remark how much more information could be gathered in the future. Lastly, HA have no information regarding it and its hub genes/proteins.

5. Conclusions

The predictive analysis indicates that DS3 has the potential to trigger changes in genes related to nitrogen and glucose metabolism, inflammation, angiogenesis, and cell proliferation. The available information suggests those changes can also occur directly in the protein and not only in mRNA. Also, quite possibly the most important result according to the bioinformatic tools is the potential modification in the function of plenty of signaling pathways, in particular the effects that DS3 has in the PI3K-AKT, these results are also supported by the findings that were discussed before. However, there are not enough published studies about DS3 and its other potential targets (suggested by the bioinformatic tools), the lack of research in that area opens a wide field to conduct new studies with a high probability of showing significant relevance to understand the mechanisms that DS3 has in human cells. In many instances, the same can be said about QRC, while this biocompound seems to have many more potential targets and it has been more studied than any other, there is still much more to research about it, especially in its relationship with cancer treatment, because most of the effects suggested by the bioinformatic tools have a direct (or indirect) relationship with the cancer disease. Finally, the results of HA may be the most interesting one, this compound is to our knowledge the least researched of all, the results of the bioinformatic assay suggest that the effects of HA could be mostly on the nervous system, something that it seems under-reported. In the end, it is important to remark that the results of this study suggest the need to generate more research to understand better the mechanisms and applications that not only DS3, QRC, or HA have in humans but, also the natural products that contain them, such as *Hibiscus sabdariffa.*

Supplementary Materials: The following supporting information can be downloaded at the website of this paper posted on Preprints.org, See the file named Supplementary Material

Author Contributions: Conceptualization, Sergio Zúñiga-Hernández and Christian Rodríguez-Razón; Data curation, Alejandro Pérez-Larios; Formal analysis, Alejandro Pérez-Larios; Funding acquisition, Christian Rodríguez-Razón; Investigation, Sergio Zúñiga-Hernández and Monserrat Macías-Carballo; Methodology, Yanet Karina Gutiérrez-Mercado and Christian Rodríguez-Razón; Project administration, Yanet Karina Gutiérrez-Mercado; Resources, Monserrat Macías-Carballo; Supervision, Trinidad García-Iglesias and Christian Rodríguez-Razón; Visualization, Gabriela Camargo-Hernández; Writing – original draft, Sergio Zúñiga-Hernández; Writing – review & editing, Trinidad García-Iglesias, Monserrat Macías-Carballo, Alejandro Pérez-Larios, Yanet Karina Gutiérrez-Mercado, Gabriela Camargo-Hernández and Christian Rodríguez-Razón. "All authors have read and agreed to the published version of the manuscript.

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