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Research Article

Evaluation *of* Ophiocephalus striatus, Citrus sinensis (Fructus), *and* Curcuma domestica (Rhizoma) *for Hypoalbuminemia Used Network Pharmacology*

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Abstract: Hypoalbuminemia is a clinical condition defined by serum albumin levels below 3.5 g/dL and is associated with poor health outcomes. Natural products such as snakehead fish (*Ophiocephalus striatus*), *Citrus sinensis* (fructus), and *Curcuma domestica* (rhizoma) have traditionally been used to improve albumin levels; however, their molecular mechanisms remain unclear. This study aimed to elucidate the pharmacological mechanisms of active compounds from these sources in the context of hypoalbuminemia using a network pharmacology approach. Active compounds were identified through the Knapsack database and literature, with molecular structures obtained from PubChem. ADMET and drug-likeness properties were evaluated using SwissADME. Target prediction was performed using SwissTargetPrediction and GeneCards, and overlapping targets were identified with Venny 2.1.0. Protein–protein interaction networks were constructed using STRING-DB and visualized with Cytoscape, followed by GO and KEGG pathway enrichment analyses. A total of 17 compounds from *O. striatus*, 7 from *C. sinensis*, and 7 from *C. domestica* were identified, of which 17, 4, and 7 compounds, respectively, met Lipinski's criteria. Intersection analysis revealed 41, 74, and 45 hypoalbuminemia-related targets. Enrichment analysis indicated involvement in pathways such as the renin–angiotensin system, colorectal cancer signaling, and EGFR tyrosine kinase inhibitor resistance, which are implicated in hepatic albumin regulation.

Keywords: *Ophiocephalus striatus*; *Citrus sinensis*; *Curcuma domestica;* Network pharmacology

1. Introduction

Hypoalbuminemia is a condition where the level of albumin in the blood is below 3.5 g/dL. This condition can disrupt the body's physiological functions, especially in individuals with severe illnesses, which in turn hinders the healing and recovery process [1]. Epidemiological data show that the prevalence of hypoalbuminemia is influenced by age, sex, and comorbidities. Hypoalbuminemia can occur at any age, but its prevalence increases in individuals over 65 years old. Based on research, a total of 9,428 patients showed a decline in albumin levels with increasing age, with a progressively worsening progression. This indicates that hypoalbuminemia is a dangerous condition and a serious public health issue [2].

Albumin is a type of protein found in human plasma, has water-soluble properties, tends to precipitate when heated, and is the most concentrated protein present in blood plasma [3]. Albumin is very beneficial for patients with hypoalbuminemia and post-operative recovery [4].

Research demonstrates that snakehead fish (*Ophiocephalus striatus*/Channa striata) extract represents a promising alternative to expensive human albumin therapy for treating hypoalbuminemia. A randomized controlled trial comparing snakehead fish extract, egg white, and 20% human albumin found that snakehead fish extract increased albumin levels by 0.1625 g/dL, demonstrating its potential as cost-effective alternative therapy [5]. Another double-blind randomized controlled trial with 90 elderly hypoalbuminemic patients showed significant improvements in both albumin levels (0.5 vs 0.10 g/dL, p=0.003) and IGF-1 levels (14.7 vs 1.0 ng/mL, p=0.002) compared to placebo after 14 days of treatment [6]. Systematic literature reviews confirm that snakehead fish extract effectively increases albumin levels while reducing inflammatory markers (neutrophils and lymphocytes) in hypoalbuminemic patients, attributed to its rich content of amino acids, albumin, zinc, iron, copper, and unsaturated fatty acids [7].

Extracts of snakehead fish (*Ophiocephalus striatus*), *Citrus sinensis (Fructus),* and *Curcuma domestica (Rhizoma)* from several studies show that snakehead fish (*Ophiocephalus striatus*) contains nutrients such as amino acids, consisting of glutamic acid, aspartic acid, lysine, and fatty acids including palmitic acid, stearic acid, arachidonic acid (omega-6), and docosahexaenoic acid (omega-3) [8]. The amino acid content in snakehead fish (*Ophiocephalus striatus*) contributes to increasing albumin levels in individuals with hypoalbuminemia [9].

Network pharmacology is a science that systematically describes the complex interactions between biological systems, drugs, and diseases thru networks [10,11]. The emergence of network pharmacology in drug discovery and development is to shift the paradigm that one drug is only for one target (one-drug-one target) [12]. Network pharmacology can conduct integrated research on pharmacodynamics, biological effects, and drug mechanisms, making it an effective approach to understanding the potential of active compounds in *Ophiocephalus striatus*), *Citrus sinensis (Fructus),* and *Curcuma domestica (Rhizoma)* against hypoalbuminemia. Based on the above description, further research is needed on the evaluation of the pharmacological mechanism of *Ophiocephalus striatus*), *Citrus sinensis (Fructus),* and *Curcuma domestica (Rhizoma)* against hypoalbuminemia patients thru Network pharmacology.

2. Materials and Methods

2.1 Type of Research

The type of research conducted is in silico experimental research. This research utilizes the network pharmacology process of compounds found in *Ophiocephalus striatus, Citrus sinensis (Fructus), and Curcuma domestica (Rhizoma)* against the pharmacological mechanisms of hypoalbuminemia. The data obtained from each database (SwissTargetPrediction and GeneCard) is then input into Cystoscape v3.9.1 to create a network.

2.2 Data collection of chemical compounds

Data on chemical compounds in *Ophiocephalus striatus, Citrus sinensis (Fructus), and Curcuma domestica (Rhizoma)* were obtained from various literature sources, and their Canonical SMILES (Simplified Molecular Input Line Entry System) were then further searched thru PubChem (https://pubchem.ncbi.nlm.nih.gov) [12].

2.3 Chemical Compound Screening

Screening is used to find compounds that do not cause toxicity by predicting ADMET characteristics, pharmacokinetics, and even drug similarity quality. The compound's properties can be assessed based on Lipinski's rule of five, which is predicted thru the SwissADME database (http://www.swissadme.ch/) [13].

2.4 Protein Target Prediction

The SMILES data for each compound obtained from SwissADME (http://www.swissadme.ch/) was then entered into the SwissTargetPrediction database (http://swisstargetprediction.ch/) to obtain its predicted protein targets. Then, target protein analysis for hypoalbuminemia was performed using GeneCard (https://genecards.org/). The results of both analyzes were then combined and analyzed in a Venn diagram to see the relationship between active compound proteins and hypoalbuminemia proteins using Venny 2.1.0 (https://bioinfogp.cnb.csic.es/tools/venny/). The associated proteins were then entered into STRING-DB (http://string-db.org/) to obtain data on biological activity, predicted protein-related diseases, and protein network diagrams. Then the results were entered into Cytoscape 3.10.3 for analysis [14,15]

2.5 Data Analysis

GO & KEGG Pathway Enrichment Analysis was performed using the DAVID database (https://david.ncifcrf.gov/tools.jsp).

3. Results

3.1 Data collection of chemical compounds

Based on the screening results from Knapsack and journals, the compounds contained in *Ophiocephalus striatus, Citrus sinensis (Fructus), and Curcuma domestica (Rhizoma)* include 17 active compounds in *Ophiocephalus striatus*, 7 active compounds in *Citrus sinensis (Fructus*), and 7 active compounds in *Curcuma domestica (Rhizoma)*. The SMILES codes and molecular structures of each compound were predicted using PubChem. Physicochemical properties were predicted based on Lipinski's rule of five as an indicator of compound solubility and its potential to passively penetrate cell membranes [16,17]. The failure of a compound to meet these criteria can hinder the oral absorption process of the drug [18]. Analysis according to Lipinsky's rule of five yielded 28 derivative compounds that fell under the "Yes" indication, meaning they met the criteria of Lipinsky's rule of five, and 3 derivative compounds that fell under the "No" category, meaning they did not meet the criteria of Lipinsky's rule of five (**Table 1.1**). These indications include the criteria of Molecule Weight <500, Lipophicity (MLogP) <5, H-Bond Acceptors <10, H-Bond Donors <5, Rotatable Bonds <10, and Lipinsky's rule of five indicated as Yes with a maximum of one violation [19].

Table 1.1 Results of Compound Physicochemical Property Determination

Content	Active compounds	Molecular weigh (g/mol)	*Log P*	Hidrogen bonds	Hidrogen bond acceptors	*Lipinsky*
		<500	**<5**	**<10**	**<10**	***Yes/No***
Ophiocephalus striatus	Prolin	115,13	-0,92	2	3	Yes
	Serin	105,09	-1,97	3	4	*Yes*
	Arginin	174,2	-2,04	4	4	*Yes*
	Tirosin	181,19	-0,48	3	4	*Yes*
	Glisin	75,07	-1,69	2	3	*Yes*
	Glutamat	147,13	-1,68	3	5	*Yes*
	Alanin	89,09	-1,46	2	3	*Yes*
	Asparagin	132,12	-2,22	3	4	*Yes*
	Leusin	131,17	-0,38	2	3	*Yes*
	Isoleusin	131,17	-0,39	2	3	*Yes*
	Valin	117,15	-0,78	2	3	*Yes*
	Triptofan	204,23	0,18	3	3	*Yes*
	Fenilalanin	165,19	-0,01	2	3	*Yes*
	Metionin	149,21	-0,59	2	3	*Yes*

	Treonin	119,12	-1,73	3	4	*Yes*
	Lisin	146,19	-1,19	3	4	*Yes*
	Histidin	155,15	-1,54	3	4	*Yes*
Citrus sinensis (Fructus)	Limonoid	506,5	1,28	4	10	*No*
	Synephrine	167,2	0,55	3	3	*Yes*
	Hesperidin	610,6	-0,6	8	15	*No*
	Niacin	123,11	0,32	1	3	*Yes*
	Pectin	150,13	-1,9	4	5	*Yes*
	Folacin	441,4	-0,36	6	10	*No*
	Thiamin	265,36	0,53	2	3	*Yes*
Curcuma domestica (Rhizoma)	Curcumin	368,38	3,03	2	6	*Yes*
	Demetoksi curcumin	338,35	3	2	5	*Yes*
	Bisdesmetoksi curcumin	218,33	3,59	0	1	*Yes*
	Tumeron	218,33	3,59	0	1	*Yes*
	Karvakrol	150,22	2,82	1	1	*Yes*
	α -Felandren	136,23	2,97	0	0	*Yes*
	Terpinolen	136,23	3,4	0	0	*Yes*

3.2 Protein Target Prediction

The molecules of that compound also underwent a probability analysis process > 0 thru SwissTargetPrediction to obtain a more absolute similarity target [20]. The SwissTargetPrediction results for each are 368 proteins for Ophiocephalus striatus, 360 proteins for *Citrus sinensis (Fructus), and 372 proteins for Curcuma domestica (Rhizoma)*, combined with 1733 proteins by GeneCard using the keyword "hypoalbuminemia," which provides comprehensive data related to all annotated and predicted genes associated with human diseases. Visualization using Venny 2.1.0 yielded 41 slices of Ophiocephalus striatus, 74 slices of *Citrus sinensis (Fructus),* and 45 slices of Curcuma domestica (Rhizoma) **(Figure 1.1** and **Table 1.2).**

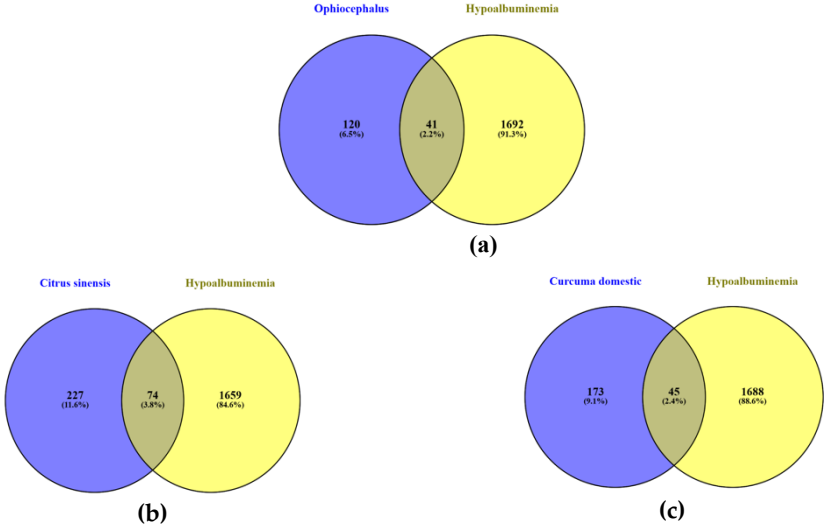


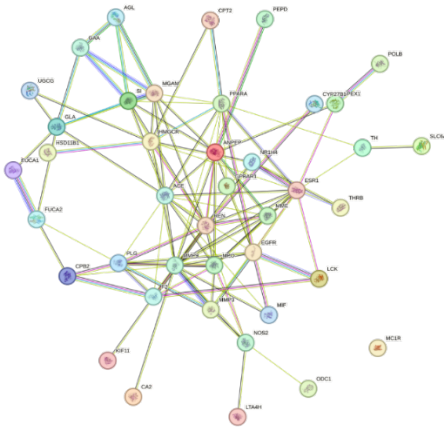
Figure 1.1 Results of Slicing Using Venny 2.1.0 **(a)** *Ophiocephalus striatus* against Hypoalbuminemia, **(b)** *Citrus sinensis (Fructus)* against Hypoalbuminemia, **(c)** *Curcuma domestica (Rhizoma*) against Hypoalbuminemia)

Table 1.2 List of Protein Codes Resulting from Venny 2.1.0 Interaction

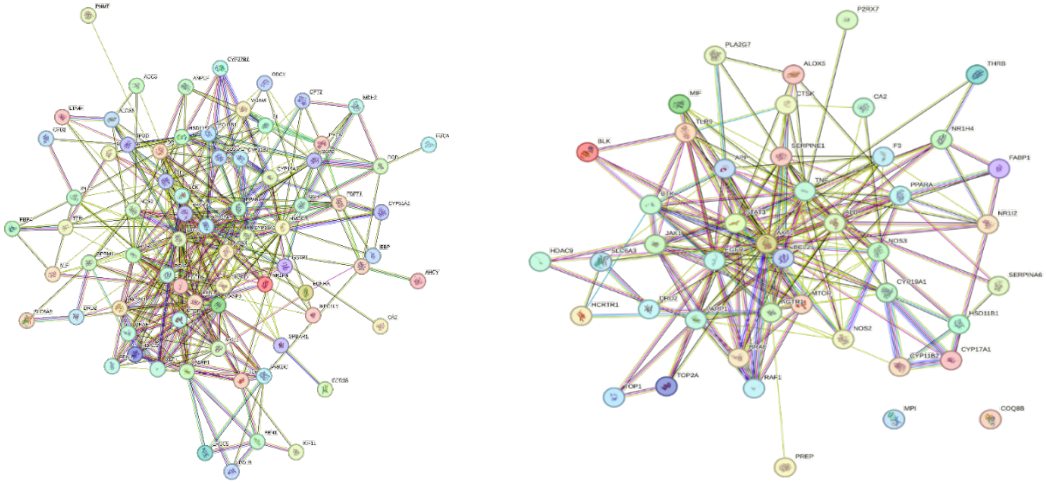
Content	Protein Code

Ophiocephalus striatus	*APEX1, GLA, ACE, F2, GPBAR1, NOS2, MPO, REN, GAA, PPARA, HMGCR, CPT2, NR1H4, SI, MMP3, ANPEP, UGCG, KIF11, PEPD, ESR1, MMP9, CA2, ODC1, VDR, AGL, EGFR, HSD11B1, PLG, MIF, MC1R, CPB2, LTA4H, LCK, MME, TH, SLC6A3, FUCA1, THRB, MGAM, FUCA2, POLB*
Citrus sinensis (Fructus)	*FDFT1, HMGCR, CA2, PYGM, NPC1L1, G6PD, CYP19A1, CASP3, PPARA, MGAM, SI, SERPINA6, HSD11B1, FUCA1, VDR, NR1H4, PGD, HSD11B2, GPBAR1, POLB, ACE, TLR4, DPP4, HPGD, PPARG, GPR35, RBP4, MCL1, BCL2, CPT2, PTGS2, MAP2K1, EDNRA, BRAF, PRKDC, PIK3CD, ALOX5, MTOR, LCK, CYP11B2, PARP1, ERN1, NOS2, NOS3, CYP3A4, FEN1, CYP17A1, TOP2A, RAF1, CPB2, ERCC5, KIF11, HDAC2, TTR, MDH2, CYP51A1, MIF, DRD2, OPRM1, ANPEP, PNP, SLC6A3, GSR, EBP, AOC3, AHCY, PLG, LTA4H, EGFR, PNMT, ODC1, ESR1, GSTP1, SLC5A1*
Curcuma domestica (Rhizoma)	*APP, BCL2, CYP17A1, TLR9, THRB, HCRTR1, TOP2A, F3, NR1I2, ALOX5, MTOR, SERPINA6, EGFR, BLK, FABP1, STAT3, BTK, PLA2G7, HSD11B1, COQ8B, MPI, AKT1, NOS2, NR1H4, TOP1, MIF, PARP1, RAF1, HDAC9, CYP11B2, BRAF, TNF, ALB, CA2, CYP19A1, JAK1, SERPINE1, DRD2, SLC6A3, AGTR1, CTSK, NOS3, PREP, P2RX7, PPARA*

The results of the intersection were then analyzed using STRING-DB to construct a protein-protein interaction (PPI) network. Based on these analysis results, 41 nodes and 111 edges were obtained for *Ophiocephalus striatus*, 74 nodes and 388 edges for *Citrus sinensis (Fructus)*, and 45 nodes and 207 edges for *Curcuma domestica (Rhizoma)* **(Figure 1.2).**



(a)



(b) (c)

Figure 1.2 Results of Protein-Protein Interaction (PPI) Analysis (a) *Ophiocephalus striatus, (b) Citrus sinensis (Fructus), (c) Curcuma domestica (Rhizoma)*

The formed network was analyzed using Cytoscape software. This network formation process involved importing interaction data from STRING-DB into the Cytoscape network visualization software, resulting in a graphical representation of interacting protein networks **(Figure 1.3).**

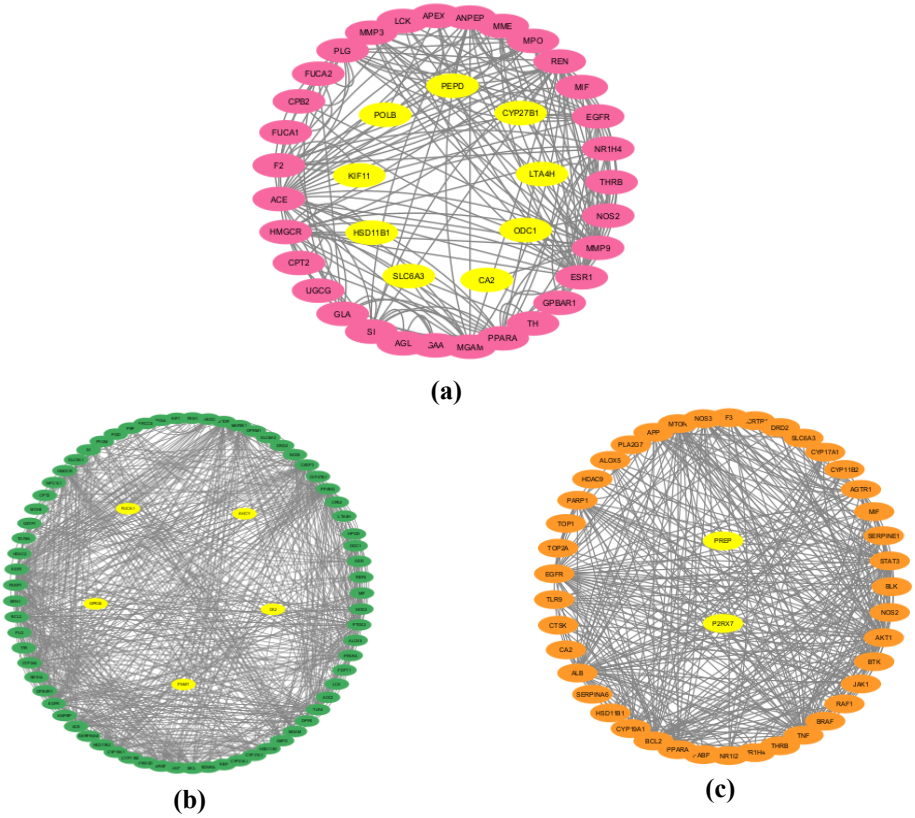


Figure 1.3 Visualization of Protein-Protein Interaction (PPI) Using Cytoscape (a) Ophiocephalus striatus against Hypoalbuminemia, (b) Citrus sinensis (Fructus) against Hypoalbuminemia, (c) Curcuma domestica (Rhizoma)

There was four main centrality parameters that will be evaluated to identify important nodes in the network, namely Maximal Clique Centrality (MCC), Degree, Closeness, and Betweeness, which are calculated using the externally downloaded cytoHubba application [21,22]. The MCC algorithm identifies the frequency of a node being part of a maximal clique, while Degree measures the number of direct interactions a

node has. Furthermore, Closeness Centrality is used to measure the average shortest distance from a node to all other nodes in the network, and Betweenness Centrality is used to measure the frequency of a node being on the shortest path between other node pairs, depending on the type of network being analyzed. The resulting centrality values were then used to identify key nodes that could potentially play a significant role in the biological system. Analysis using Cytoscape software identified the top 5 genes clustered in each of the *Ophiocephalus striatus, Citrus sinensis (Fructus),* and *Curcuma domestica (Rhizoma)* clusters, as visualized in the Cytoscape clustering data table **(Table 1.3).**

Table 1.3 Data Klasterisasi *Cytoscape*

Content	Gene Name	*Degree*
Ophiocephalus striatus	ACE	30
	MME	29
	REN	28
	ESR1	28
	PPARA	22
Citrus sinensis (*Fructus*)	EGFR	64
	CASP3	54
	BCL2	52
	MTOR	46
	PPARA	48
Curcuma domestica (*Rhizoma*)	AKT	58
	MTOR	56
	EGFR	46
	STAT3	43
	JAK	38

The data shows that the highest and most dominant value of Ophiocephalus striatus is ACE (Angiotensin-Converting Enzyme). ACE is a key component of the Renin-Angiotensin System (RAS), a hormonal system that regulates blood pressure and fluid/electrolyte balance in the body [23]. The primary function of ACE is to convert angiotensin I (an inactive form) into angiotensin II (an active form). Angiotensin II is a potent vasoconstrictor and stimulates the release of aldosterone, which causes the kidneys to retain sodium and water. The main relationship between the ACE gene and hypoalbuminemia is thru its role in the pathogenesis of kidney disease, particularly diabetic nephropathy and nephrotic syndrome, which often leads to albumin loss thru urine and ultimately causes hypoalbuminemia [24].

The highest and most dominant value of *Citrus sinensis* (Fructus) is EGFR (Epidermal Growth Factor Receptor). Excessive activation of the EGFR signaling pathway, particularly in the context of cancer, triggers a cascade of events leading to chronic systemic inflammation and cachexia. These conditions suppress albumin synthesis in the liver, which can increase albumin catabolism, leading to hypoalbuminemia [25]. The highest and most dominant value in Curcuma domestica (Rhizome) is AKT (Threonine Kinase/Protein Kinase B alpha (PKBα)), which is an important cellular protein involved in various cellular proce1sses including cell growth, proliferation, survival, and metabolism [26]. One of its important roles is in the regulation of protein synthesis. AKT can activate the MTOR (Mammalian Target of Rapamycin) pathway, which is a major regulator of protein synthesis, including albumin produced in the liver [27]. Additionally, AKT is also involved in the regulation of glucose and lipid metabolism in the liver [28]. Disorders of liver function can also affect this metabolism, which will impact albumin production, leading to hypoalbuminemia. The results of the analysis using Cytoscape were

followed by GO & KEGG Pathway Enrichment analysis using the DAVID database (https://davidbioinformatics.nih.gov/). The results of the enrichment analysis can be seen in (**Figure 1.4.** and **Figure 1.5**).

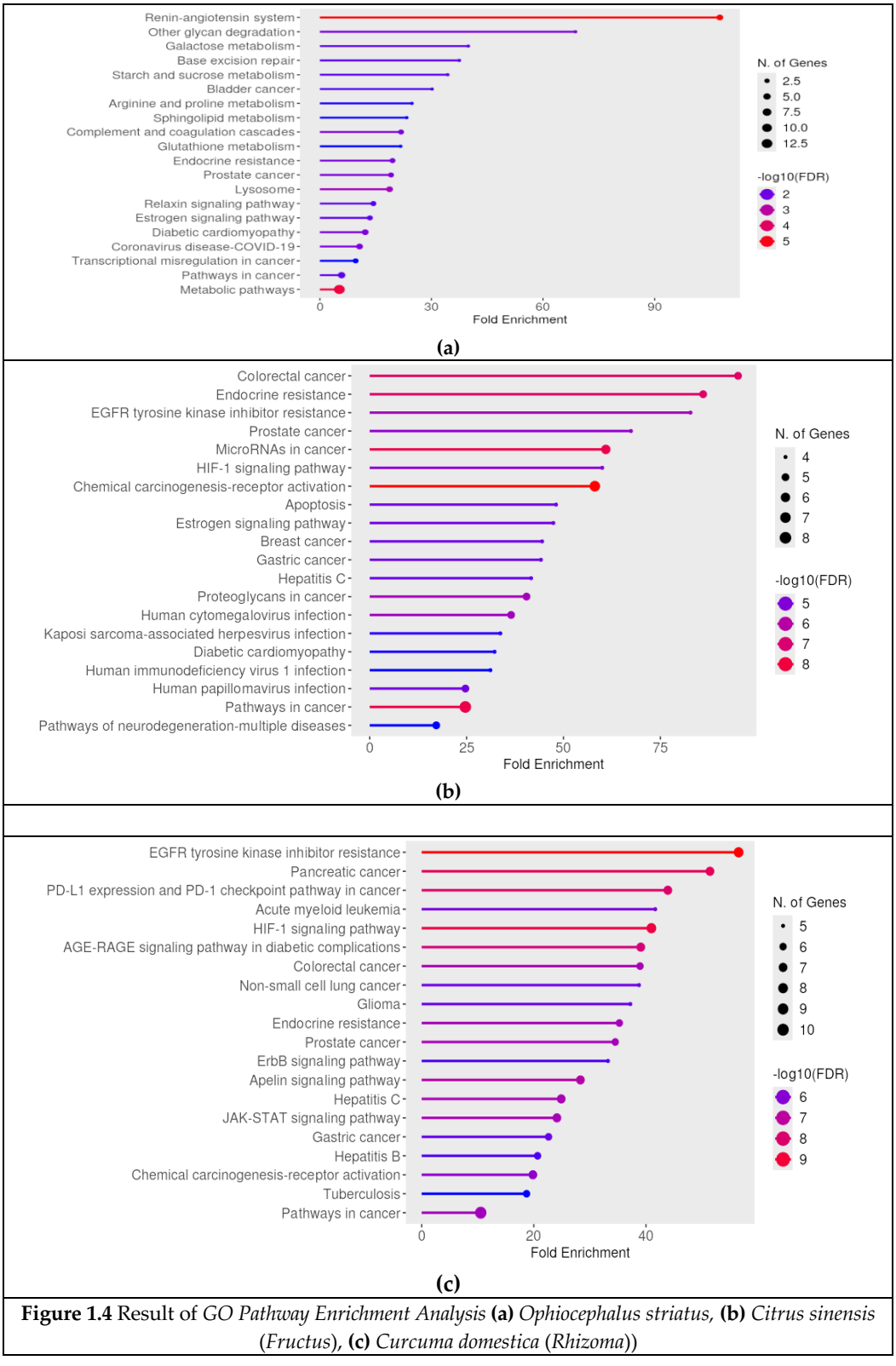
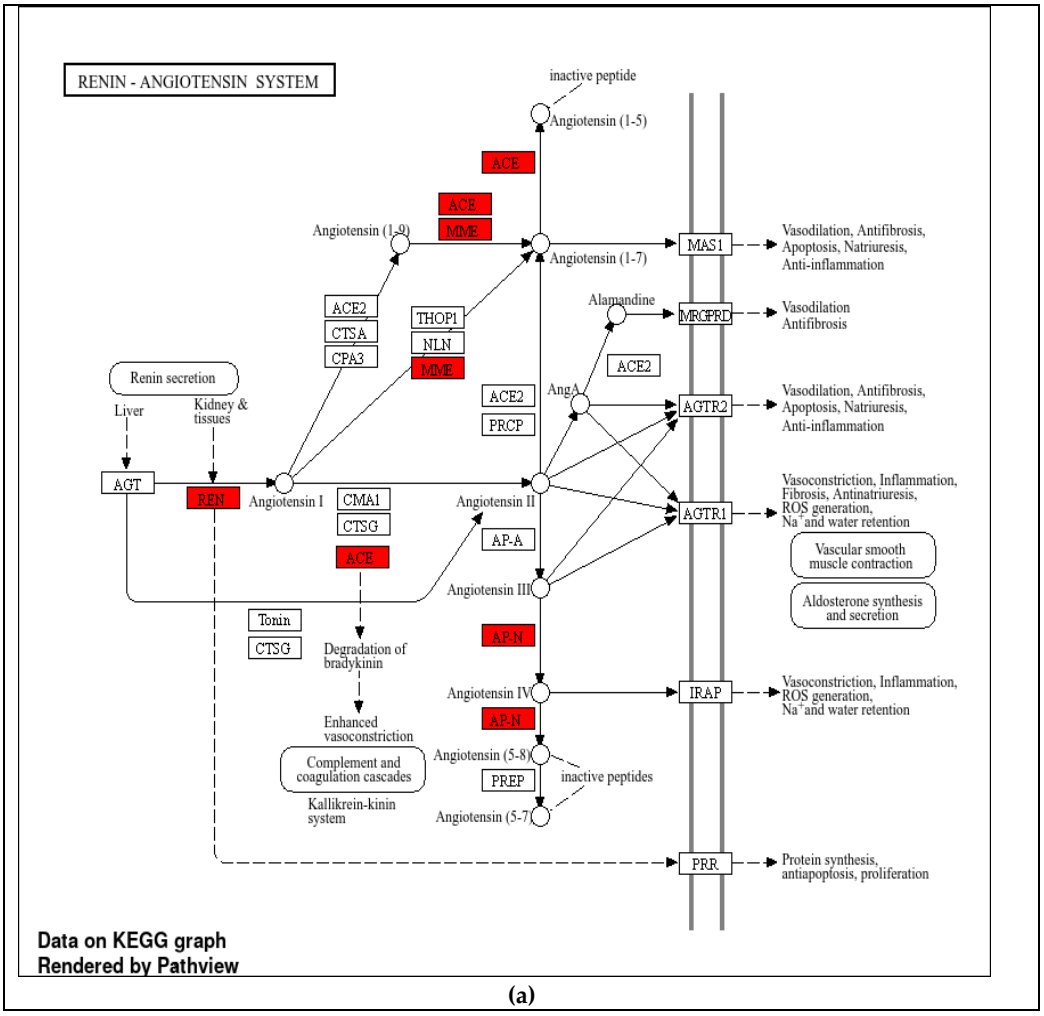
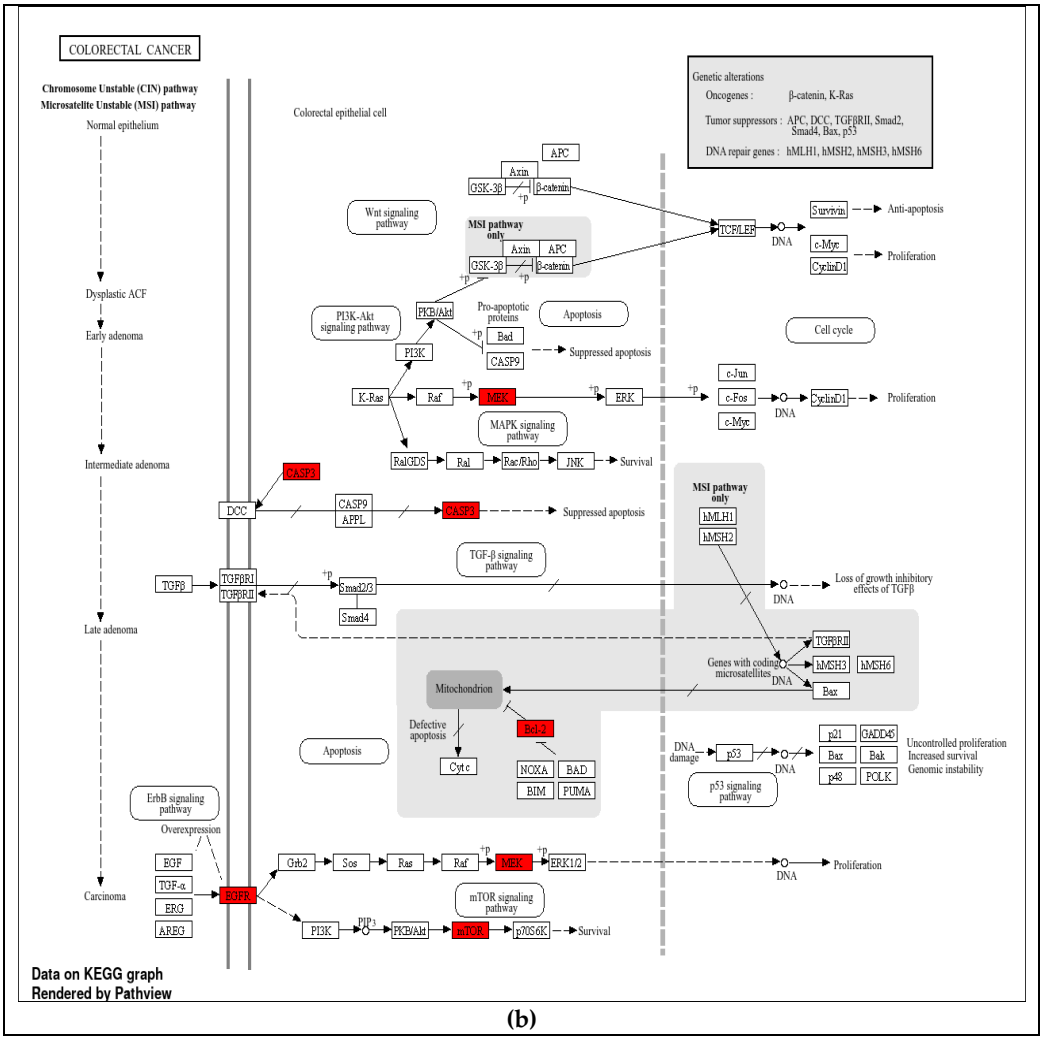


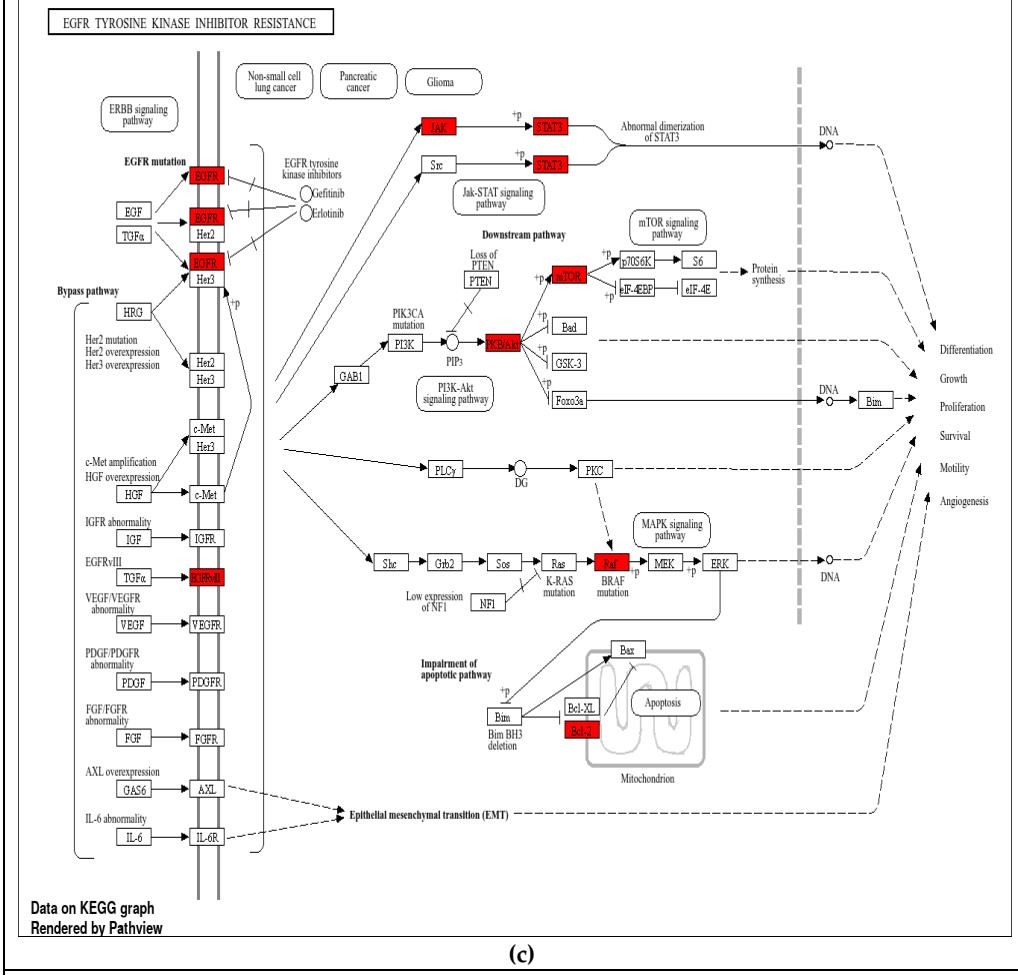
Figure 1.4 Result of *GO Pathway Enrichment Analysis* **(a)** *Ophiocephalus striatus,* **(b)** *Citrus sinensis* (*Fructus*), **(c)** *Curcuma domestica* (*Rhizoma*))


RENIN - ANGIOTENSIN SYSTEM
inactive peptide
Angiotensin (1-5)
ACE
ACE
MME
Angiotensin (1-9)
Angiotensin (1-7)
MAS1
Vasodilation, Antifibrosis, Apoptosis, Natriuresis, Anti-inflammation
ACE2
CTSA
CPA3
THOP1
NLN
MME
Alamandine
MRGPRD
Vasodilation Antifibrosis
Renin secretion
Liver
Kidney & tissues
ACE2
PRCP
AngA
ACE2
AGTR2
Vasodilation, Antifibrosis, Apoptosis, Natriuresis, Anti-inflammation
AGT
REN
Angiotensin I
CMA1
CTSG
ACE
Angiotensin II
AP-A
AGTR1
Vasoconstriction, Inflammation, Fibrosis, Antinatriuresis, ROS generation, Na+ and water retention
Vascular smooth muscle contraction
Aldosterone synthesis and secretion
Angiotensin III
Tonin
CTSG
Degradation of bradykinin
AP-N
Angiotensin IV
IRAP
Vasoconstriction, Inflammation, ROS generation, Na+ and water retention
Enhanced vasoconstriction
AP-N
Angiotensin (5-8)
Complement and coagulation cascades
PREP
inactive peptides
Kallikrein-kinin system
Angiotensin (5-7)
PRR
Protein synthesis, antiapopfosis, proliferation
Data on KEGG graph
Rendered by Pathview

(a)


COLORECTAL CANCER
Chromosome Unstable (CIN) pathway
Microsatelite Unstable (MSI) pathway
Normal epithelium
Dysplastic ACF
Early adenoma
Intermediate adenoma
Late adenoma
Carcinoma
Colorectal epithelial cell
Genetic alterations
Oncogenes : β-catenin, K-Ras
Tumor suppressors : APC, DCC, TGFβRII, Smad2, Smad4, Bax, p53
DNA repair genes : hMLH1, hMSH2, hMSH3, hMSH6
Wnt signaling pathway
MSI pathway only
TCF/LEF
Survivin
Anti-apoptosis
c-Myc
Proliferation
CyclinD1
PI3K-Akt signaling pathway
Pro-apoptotic proteins
Apoptosis
Cell cycle
Suppressed apoptosis
MAPK signaling pathway
c-Jun
c-Fos
Survival
TGF-β signaling pathway
Loss of growth inhibitory effects of TGFβ
Genes with coding microsatellites
Mitochondrion
Defective apoptosis
Cyt c
NOXA
BAD
BIM
PUMA
DNA damage
p53
p53 signaling pathway
p21
GADD45
Bak
p48
POLK
Uncontrolled proliferation
Increased survival
Genomic instability
ErbB signaling pathway
Overexpression
EGF
TGF-α
ERG
AREG
EGFR
Grb2
Sos
Ras
ERK1/2
mTOR signaling pathway
PIP3
PKB/Akt
Data on KEGG graph
Rendered by Pathview

(b)



(c)

Figure 1.5 Result of KEGG *Pathway Enrichment Analysis* **(a)** *Ophiocephalus striatus,* **(b)** *Citrus sinensis* (*Fructus*), **(c)** *Curcuma domestica* (*Rhizoma*))

Gene Ontology (GO) analysis of Ophiocephalus striatus represents the Renin-Angiotensin System (RAS) as the pathway with the highest enrichment level **(Figure 1.4).** This indicates its central involvement in the biological context being studied. Nevertheless, the correlation between the renin-angiotensin system (RAS) and hypoalbuminemia is indirect, as RAS activation can worsen the pathophysiological conditions that often accompany or cause hypoalbuminemia, such as chronic kidney dysfunction and systemic inflammation [29].

Gene Ontology (GO) analysis of Citrus sinensis (Fructus) identified Colorectal cancer as the pathway with the highest fold enrichment, followed by Endocrine resistance and EGFR tyrosine kinase inhibitor resistance, as well as several other cancers that also showed substantial levels of enrichment and significance **(Figure 1.4).**

4. Discussion

Hypoalbuminemia is a common and significant finding in cancer patients, including those with colorectal cancer, reflecting a complex n between malnutrition, tumor-induced systemic inflammatory response, and protein loss [30]. This condition is not only a marker but also a significant contributor to poor prognosis and increased complications [31]. The relationship between endocrine resistance and EGFR tyrosine kinase inhibitor resistance with hypoalbuminemia is highly relevant in the context of cancer treatment, particularly in breast cancer (for endocrine resistance) and non-small cell lung cancer (NSCLC) (for EGFR tyrosine kinase inhibitor resistance). These two conditions often indicate disease

progression and can correlate with hypoalbuminemia thru systemic inflammation, malnutrition, and cachexia [32].

Gene Ontology (GO) analysis of *Curcuma domestica* (Rhizome) showed that the EGFR tyrosine kinase inhibitor resistance pathway, which is associated with resistance to cancer drugs, was the most significant pathway (**Figure 1.4**). Additionally, the AGE-RAGE signaling pathway in diabetic complications, endocrine resistance, hypoxia (HIF-1 signaling), growth factor signaling (ErbB, Apelin), cytokine signaling (JAK-STAT), chemical carcinogenesis, response to infection (hepatitis C, hepatitis B, tuberculosis), and actin cytoskeleton regulation pathways were also identified as significant [33,34,35]. This analysis does not identify the major biological pathways that directly control albumin levels. However, there is an indirect relationship that can be traced thru the influence of the identified significant pathways on disease conditions that often cause low albumin levels, such as cancer, diabetes complications, and chronic infections[32]. These conditions can disrupt liver function or trigger systemic inflammation that inhibits albumin production [36,37].

The presence of the AGE-RAGE signaling pathway in diabetic complications indicates a potential indirect relationship with insulin metabolism and its complications. Advanced Glycation End-products (AGEs) are formed due to chronic hyperglycemia and interact with RAGE receptors, which trigger various pathological processes in diabetes complications. Chronic inflammation can increase the formation of AGEs and activate the AGE-RAGE pathway. Additionally, hypoalbuminemia can reflect the presence of underlying comorbidities that exacerbate diabetes complications [38]. Although the insulin pathway itself is not prominent in the top list, the involvement of the AGE-RAGE pathway in diabetes complications exacerbated by conditions like hypoalbuminemia suggests a complex interaction between glucose metabolism, inflammation, and kidney function that needs to be considered in the context of this research. Analysis of KEGG Pathway Enrichment for Ophiocephalus striatus indicates that the genes ACE (Angiotensin-Converting Enzyme) and REN (Renin) are highly significant in relation to hypoalbuminemia, particulary the Renin-Angiotensin System (RAS) is crucial for blood pressure regulation and fluid homeostasis. Dysregulation can lead to hypertension and organ damage. Pharmacological agents inhibiting angiotensin II synthesis or activity, and angiotensin receptor blockers (ARBs), are effective in treating cardiovascular diseases and slowing kidney disease progression [39].

Angiotensin II causes vasoconstriction in renal efferent arterioles, increasing glomerular pressure and contributing to glomerular damage. Intervention studies support this by showing reduced proteinuria and delayed renal insufficiency progression with Angiotensin II blockade [40]. This chronic increase in pressure can damage the kidney filters, causing protein, especially albumin, to leak from the blood into the urine. This condition is known as albuminuria or proteinuria. Proteinuria is an early sign of kidney damage and is an important predictor of the progression of chronic kidney disease. If the body continuously and in large quantities excretes albumin thru urine, the body cannot synthesize albumin quickly enough to replace it. As a result, albumin levels in the blood decrease, leading to hypoalbuminemia. The use of medications targeting the RAS, such as ACE inhibitors, can help reduce proteinuria in kidney disease, thereby indirectly helping to maintain albumin levels and address symptoms associated with hypoalbuminemia, such as edema [41].

Analysis of KEGG Pathway Enrichment for *Citrus sinensis* (Fructus) with hypoalbuminemia reveals a complex and multifactorial relationship, particularly in the context of colorectal cancer. This relationship is complex and involves various mechanisms, such as systemic inflammatory responses and dysregulation of cellular signaling pathways controlled by genes like EGFR, CASP3, BCL2, and MTOR. EGFR (Epidermal Growth Factor Receptor), which is overactivated in colorectal cancer cells, can trigger intracellular signaling pathways like MAPK/ERK and PI3K/Akt/MTOR, contributing to cancer cell proliferation, invasion, and metastasis. These pathways can

also induce the production of pro-inflammatory cytokines, such as IL-6 and TNF-α, by tumor cells or cells in the tumor microenvironment. These pro-inflammatory cytokines are released into the systemic circulation, causing a chronic systemic inflammatory response in cancer patients. Systemic inflammation is a major cause of hypoalbuminemia in cancer. These cytokines directly suppress albumin synthesis in the liver [42]. The liver shifts from producing positive acute-phase proteins (such as albumin) to producing acute-phase proteins as part of the inflammatory response [43].

CASP3 (Caspase-3) is a major effector of apoptosis. If there is a significant increase in hepatocyte (liver cell) apoptosis due to liver damage (related to cancer or treatment), the liver's capacity to synthesize albumin will decrease, leading to hypoalbuminemia. BCL2 (B-cell lymphoma 2) is an anti-apoptotic protein that is often overactivated in cancer cells, including colorectal cancer, allowing cancer cells to survive. Although BCL2 is anti-apoptotic, an imbalance leading to increased pro-apoptosis or liver cell damage from other factors (e.g., chemotherapy, inflammatory cytokines) can cause hepatocyte apoptosis and decreased albumin production [44,45].

Analysis of KEGG Pathway Enrichment for Curcuma domestica (Rhizome) with hypoalbuminemia reveals a highly complex relationship involving various mechanisms, particularly thru its role in EGFR tyrosine kinase inhibitor resistance, inflammatory response, and regulation of protein synthesis (including albumin) in the liver. EGFR (Epidermal Growth Factor Receptor) is involved in various cellular processes, acting as a transmembrane tyrosine kinase receptor crucial for cell growth, proliferation, and survival, including in the liver. EGFR signaling plays a significant role in hepatocyte regeneration following acute or chronic damage, and in this context, EGFR signaling can influence albumin synthesis [46].

Many conditions cause hypoalbuminemia, such as sepsis, chronic liver disease, chronic kidney disease, or cancer involving systemic inflammation. The pro-inflammatory cytokines (especially IL-6) released during this inflammation will activate the JAK/STAT3 pathway, which directly suppresses albumin synthesis in the liver and increases vascular permeability, leading to albumin leakage into the interstitial space. Signaling pathways like mTOR and AKT are crucial for efficient protein synthesis in the liver. Dysfunction in these pathways can reduce the liver's ability to produce albumin. Additionally, severe disease conditions such as increased protein catabolism in the body, including albumin, can be exacerbated by dysregulation of these signaling pathways [47].

5. Conclusions

Based on the overall research results, the genes or proteins that play an important role in hypoalbuminemia. ACE, REN, CASP3, BCL2, AKT, MTOR, EGFR, STAT3, and JAK were most potential genes to be specific receptors in the treatment of hypoalbuminemia.

Conflict of Interest

The authors declare no conflict of interest

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