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Review Article

Prediction of the Potential Active Compounds in Cucumber (*Cucumis sativus L*) against Hypertension using Pharmacological Network (Cytoscape)

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Abstract: Hypertension is the leading cause of heart disease, kidney failure and stroke in Indonesia. Antihypertensive drugs have proven effective in managing blood pressure levels. However, long-term use of these medications may lead to side effects, reduce patient compliance and increased healthcare costs. Various studies have reported the cucumber (*Cucumis sativus L)* effect in controlling blood pressure. The purpose of this study is to investigate the molecular basis of these effects and identify the specific pathways involved. This research is a systematic review in silico network pharmacology analysis to forecast the antihypertensive potential of cucumber derived active compounds. By employing computational methods to explore plant-based therapeutic effects, the study identified bioactive components and their targets through the ChEMBL database, followed by protein validation using the Open Targets Platform. The findings contribute to the growing evidence that cucumber plants may play a role in hypertension management through multi-target mechanism.

Keywords: active compounds, cucumber, cytoscape, hypertension

1. INTRODUCTION

In Indonesia, hypertension defined as a persistent systolic reading of at least 140 mmHg or a diastolic reading of 90 mmHg, stands as the primary contributor to stroke, renal failure, and cardiovascular disease. Clinical diagnosis occurs when these elevated pressure levels are maintained consistently over time [1]. Several factors that influence the incidence of hypertension include factors (age, gender), obesity, drugs (steroid, painkillers) [2], [3]. The World Health Organization (WHO) states that relatively young men are at higher risk of developing hypertension which requires treatment and lifestyle changes compared to women [4]. Hypertension remains a significant health burden in Indonesia, with the 2023 Indonesia Health Survey (SKI) reporting a prevalence of 30.8% among adults aged 18 and older [5].

Various studies have reported the benefits of cucumbers (*Cucumis sativus L*) in controlling blood pressure [6], [7], [8]. Cucumber juice has the ability to detoxify the body and regulate blood pressure in essential hypertension [9], [10]. A study of elderly people with a history of hypertension (average 150/90 mmHg) found that after cucumber juice therapy, the average systolic pressure decreased from 149,68 mmHg to 136,65 mmHg and the average diastolic pressure decreased from 95,99 mmHg to 80,99 mmHg [11]. Rich in essential minerals such as potassium, magnesium, calcium, and phosphorus, cucumbers contribute significantly to blood pressure regulation [12], [13]. Furthermore, their high moisture levels and natural diuretic effects allow them to serve as effective dietary agents in the management of hypentension [14].

The interactions of compounds contained in cucumbers that regulate hypertension can be linked to one another through the Cytoscape interaction network. Cytoscape is a bioinformatics software used to visualize molecular interaction networks by integrating them with gene expression

[15]. Characteristics of metabolite compounds, such as molecular formulas and mass spectra in several ionization modes can be obtained through *Knapsack Core Data Base* [16]. In addition, the physicochemical properties of compounds that can be developed into drugs can be known through *ChEMBL* [17]. Then the compouds is linked to a particular disease through an *Open Targets* site [18].

Cucumber (*Cucumis sativus* L.) is widely used for its blood pressure-lowering effects, the specific molecular mechanisms of its active compounds remain unclear. Therefore, the aim of this research is to predict the antihypertensive potential of cucumber through a network pharmacology approach. The correlation between cucumber and hypertension management is investigated by analyzing secondary metabolites, such as flavonoids, and their interaction with cardiovascular targets. To achieve this, metabolite characteristics are retrieved from the Knapsack Core Database, while their drug-like physicochemical properties are verified via ChEMBL. These compounds are then linked to specific disease targets using the Open Targets Platform. Finally, all molecular interactions are visualized using Cytoscape to generate a comprehensive compound-target-disease interaction network.

2. MATERIALS AND METHODS

The Latin names of the cucumber "*Cucumis sativus L*" were input into the online *Knapsack core data-based platform* and further information was sought based on related literature from national journals through the Google Scholar, PubMed, dan Garuda search engines to obtain the composition of active compounds in the cucumbers. A total of 27 relevant articles were initially identified. The active compounds contained in the collected cucumbers were predicted for protein targets through the online *ChEMBL* platform, using the conformal prediction (CP) target prediction method [19]. There are 3 confidence levels for CP method in *ChEMBL*, namely 70%, 80%, and 90%. Each confidence level has its own sensitivity, specificity, and correct classification level [20]. Searching for target code information to find out the target's trust value, then go through the target validation web http://www.platform.opentargets.org/. After that, it is validated to find the interaction between the disease and the disease category with the parameter used being an association value of 0,5 – 1. The target protein is processed through the web www.string-db.org to find the active compound from the target protein that has the most potential in reducing blood pressure with the highest degree value.

3. RESULTS AND DISCUSSION

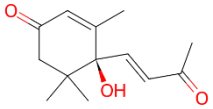
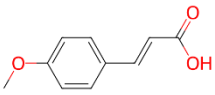
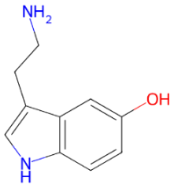
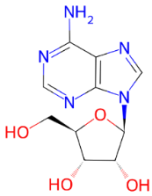
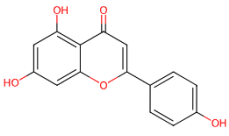
Based on the research results, 71 compounds were obtained in cucumbers. The compounds obtained from the *Knapsack database* search were 49 compounds, including (+)-Dehydrovomifoliol, 2-Benzothiazolinone, (2E,6Z)-Nona-2,6-dien-1-ol, 5-Hydroxytryptamine, 5-Methoxytryptamine, β-Sitosterol, Adenosine, Apigenin 7-(6''-p-coumarylglucoside), CSTI IIb, CSTI IV, Cucumegastigmane I, Cucumegastigmane II, Cucumerin A, Cucumerin B, Cucurbitacin C, D-Sucrose, (E,Z)-2,6-Nonadienal, Galactinol, Gibberellin A3, Gibberellin A20, Gibberellin A5, Gibberellin A4, Gibberellin A8, Gibberellin A34, Hirsutrin, Indole-3-acetaldehyde, Indole-3-carboxaldehyde, Indole-3-carboxylic acid, Indole-3-ethanol, Isoscoparin 2''-(6-(E)-p-coumaroylglucoside), Isoscoparin 4'-O-glucoside, Isovitexin, Isovitexin 2''-O-(6'''-(E)-p-coumaroyl)glucoside, Isovitexin 2''-O-(6'''-feruloyl)glucoside, Isovitexin 2''-O-(6'''-(E)-feruloyl)glucoside 4'-O-glucoside, Isovitexin 2''-O-(6'''-(E)-p-coumaroyl)glucoside 4'-O-glucoside, Lutein, Melatonin, Meloside A, Orientin, p-Coumaric acid, Saponarin, Saponarin 4'-O-glucoside, Schottenol, Spinasterol, Sucrose 6-phosphate, Tryptamine, Vicenin 2, and Vitexin.

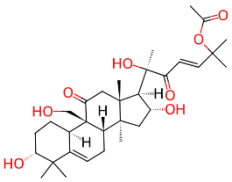
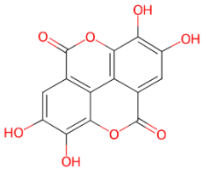
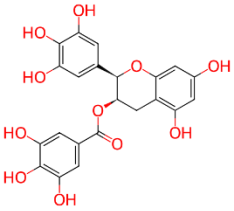
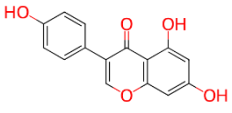
Data obtained from a literature search of 31 compounds contained in cucumbers, including 1,4-Dicaffeoylquinic acid [21], 4-Methoxycinnamic acid [22], α-Tocopherol [23], β-Sitosterol [24], Apigenin [25], Arachidic acid, Ellagic acid [26], Epicatechi, Epigallocatechin gallate, Genistein, Gibberellin A3 [27], Gluconic acid, Hesperidin, Isoferulic acid, Isorhamnetin-3-Oglucoside, Kaempferol, Kaempferol-3-Oglucuronoside/Kaempferol 3-glucuronide, Kaempferol-3-O-glucoside, Kaempferol-3-Orhamnoside [28], Luteolin, Luteolin 7-O glucuronide, Luteolin 7-O-rutinoside [29],

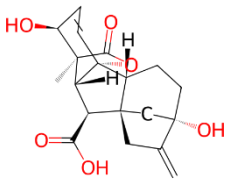
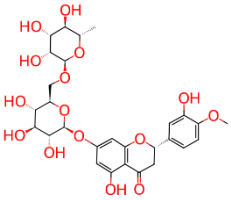
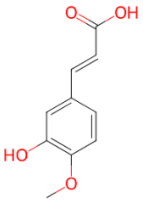
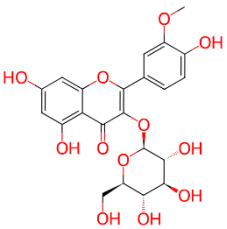
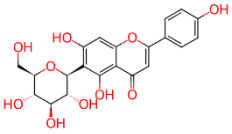
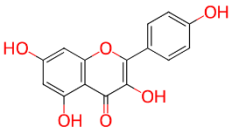
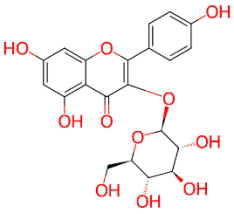
Myristic acid [30], Narcissin/Isorhmnetin 3-O-rutinoside, Orientin, p-Coumaric acid [31], Palmitic acid [32], Quercetin [33], Scopoletin, Isoferulic acid [34], and Umbelliferone [35], [36].

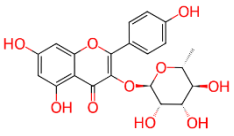
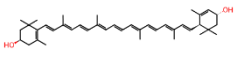
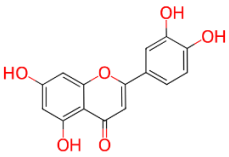
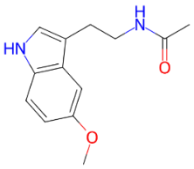
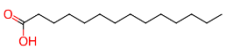
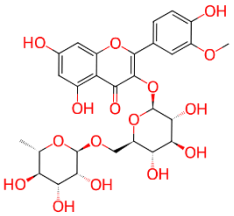
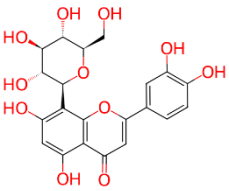
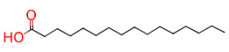
ChEMBL analysed 71 active compounds in cucumbers, found 34 with *canonical SMILES* or chemical structures. These 34 compounds were then analysed using open targeting, which generates various target proteins in the body (Table 1).

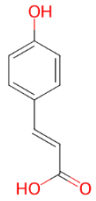
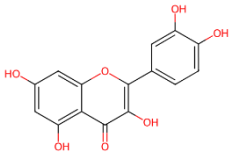
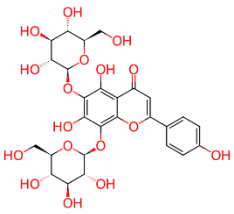
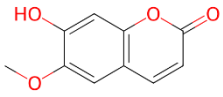
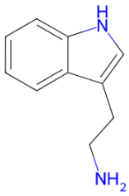
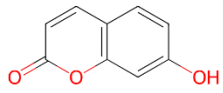
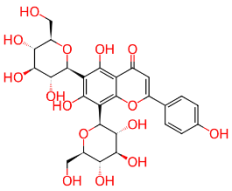
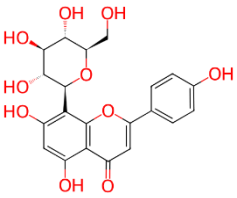
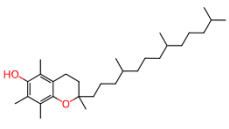
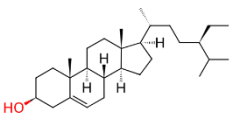
Table 1. Active compounds of cucumber (*Cucumis sativus L.)* and target proteins

No	Compound Name	*ChEMBL* ID	Chemical Structure	Target Protein
1	(+)-Dehydrovomifoliol	CHEMBL461278		Carbonic Anhydrase 1 (CA1), Cystic Fibrosis Transmembrane Conductance Regulator (CFTR), 5-Hydroxytryptamine Receptor 3A (HTR3A), Legumain (LGMN), Peptidyl-Prolyl Cis-Trans Isomerase NIMA-Interacting 1 (PIN1), and ROS Proto-Oncogene 1 (ROS1)
2	4-Methoxycinnamic acid	CHEMBL95770		Calpain 1 (CAPN1), Cholinergic Receptor Nicotinic Alpha 3 & Beta 4 Subunits (CHRNA3/B4), Dipeptidyl Peptidase 9 (DPP9), HTR3A, and ROS1
3	5-Hydroxytryptamine	CHEMBL39		ROS1, CAPN1, DPP9, Kynurenine 3-Monooxygenase (KMO), Methionyl Aminopeptidase 2 (METAP2), CFTR, Cell Division Cycle 7-Related Protein Kinase (CDC7), Integrin Subunit Alpha 4 (ITGA4), 5-Hydroxytryptamine Receptor 2A (HTR2A), CHRNA3/B4, 5-Hydroxytryptamine Receptor 1D (HTR1D), HTR3A, Integrin Subunit Alpha V (ITGAV), Coactivator Associated Arginine Methyltransferase 1 (CARM1), and Microtubule Associated Protein 2 (MAP2)
4	Adenosine	CHEMBL477		Adenosine Kinase (ADK), Dipeptidyl Peptidase 4 (DPP4), HTR3A, ITGA4, LGMN, Farnesyl Diphosphate Synthase (FDPS), NAD(P)H Quinone Dehydrogenase 2 (NQO2), ROS1, CFTR, Sodium Voltage-Gated Channel Alpha Subunit 3 (SCN3A), and Lysine Demethylase 5A (KDM5A)
5	Apigenin	CHEMBL28		CHRNA3/B4, Glutamate Ionotropic Receptor NMDA Type Subunit 1 and 2A (GRIN1/GRIN2A), Adenosine A2b Receptor (ADORA2B), AKT Serine/Threonine Kinase 3 (AKT3), SCN3A, Alkaline Phosphatase (ALPL), Carbonic Anhydrase 7 (CA7), KMO, CFTR,

				CTSS, Acetylcholinesterase (ACHE), Cytochrome P450 Family 1 Subfamily A Member 2 (CYP1A2), CAPN1, Estrogen Receptor 2 (ESR2), Coagulation Factor VII and Coagulation Factor III (F7/F3), Histone Deacetylase 10 (HDAC10), Cyclin Dependent Kinase 2 and Cyclin E1 Complex (CDK2/CCNE1), Lysine Demethylase 1A (KDM1A), LGMN, Monoamine Oxidase A (MAOA), Arachidonate 5-Lipoxygenase Activating Protein (ALOX5AP), MAP Kinase Interacting Serine/Threonine Kinase 1 (MNK1), ROS1, and HTR3A
6	Cucurbitacin C	CHEMBL449220		KDM1A, AKT3, METAP2, ALOX5AP, CAPN1, CFTR, Sphingosine Kinase 2 (SPHK2), CHRNA3/B4, Cathepsin S (CTSS), GRIN1/GRIN2A, Xanthine Dehydrogenase (XDH), HDAC10, KMO, LGMN, MAP2, Mitogen-Activated Protein Kinase 14 (MAP3K14), Progesterone Receptor (PGR), PIN1, F7/F3, PTK2, Protein Tyrosine Phosphate Non-Receptor Type 2 (PTPN2), ROS1, Sphingosine-1-Phosphate Receptor 1 (S1PR1), CDK2/CCNE1, and Sphingosine-1-Phosphate Receptor 3 (S1PR3)
7	Ellagic acid	CHEMBL6246		SCN3A, CFTR, CYP1A2, FDPS, Tryptase Alpha/Beta 1 (TPSAB1), Indoleamine 2,3-Dioxygenase 1 (IDO1), CAPN1, KDM5C, NQO1, and ROS1
8	Epigallocatechin gallate	CHEMBL297453		XDH, Ataxia Telangiectasia Mutated (ATM), CAPN1, Cyclin-Dependent Kinase 9/Cyclin T1 (CDK9/CCNTI), Dipeptidyl Peptidase 8 (DPP8), GRIN1B/GRIN2B, HDAC10, F10, KDM1A, CDK2/CCNE1, KMO, MAP2, Metabotropic Glutamate Receptor 2 (GRM2), MNK1, ROS1, 5-Hydroxytryptamine Receptor 1B (HTR1B), SPHK2, Steroid 5-Alpha Reductase 2 (SRD5A2), and Aldo-Keto Reductase Family 1 Member B10 (AKR1B10)
9	Genistein	CHEMBL44		ESR2, KMO, CA7, CFTR, SCN3A CYP1A2, ROS1, HTR3A, KDM5C, MNK1, ALPL, and Carbonic Anhydrase 12 (CA12)

10	Gibberellin A3	CHEMBL1232952		CA12, ROS1, Carbonic Anhydrase 9 (CA9), Lysine Demethylase 5C (KDM5C), ITGA4, CAPN1, ALPL, CFTR, HTR3A, ROS1, ALOX5AP, HDAC1, IDO1, METAP2, LGMN, KMO, and CFTR
11	Hesperidin	CHEMBL449317		IDO1, AKT3, MNK1, CA12, F7/F3, CFTR, Transmembrane Serine Protease 6 (TMPRSS6), CTSK, Embryonic Ectoderm Development (EED), CDK2/CCNE1, FDPS, Heat Shock Protein 90 Alpha Family Class A Member 1 (HSP90AA1), HTR1B, KMO, AKR1B10, MAP3K14, ROS1, MAP2, Muscarinic Acetylcholine Receptor M5 (CHRM5), and HDAC10
12	Isoferulic acid	CHEMBL233295		MAP Kinase-Activated Protein Kinase 2 (MAPKAPK2), ROS1, ITGA4, HTR3A, MAP2, and DPP9
13	Isorhamnetin-3-Oglucoside	CHEMBL234316		S1PR3, Prostaglandin E Receptor 2 (PTGRE2), ADAM10, ALOX5AP, SCN3A, CTSK, GRIN1A/GRIN1B, IDO1, KMO, AKR1B10, CAPN1, KDM5C, MNK1, ROS1, SCN3A, MAP2, ACHE, MAP3K14, HDAC10, METAP2, PIK3CA, PTPN2, CREB-Binding Protein (CREBBP), ROS1, and CDK2/CCNE1
14	Isovitexin	CHEMBL465360		CA7, MNK1, GRIN1A/GRIN1B, SPHK2 HDAC10, Nicotinamide Phosphoribosyl Transferase (NAMPT), IDO1, KDM1A, KDM5C, ATM, MAP3K14, HSP90AA1, CTSS, MAPKAPK2, ROS1, and B-Cell Lymphoma 2 (BCL2)
15	Kaempferol	CHEMBL150		NQO2, CA7, ROS1, CFTR, HTR3A, SCN3A KMO, MAOA, ALPL, KDM5C, and CYP1A2
16	Kaempferol-3-O-glucoside	CHEMBL233930		GRIN1/GRIN2B, ATM, MAP2, CA7, CTSK, FDPS, IDO1, DNA Topoisomerase I (TOP1), KMO, ACHE, MAP3K14, MNK1, Prostaglandin E Receptor 2 (PTGER2), HDAC10, ROS1, SCN3A, SPHK2, CAPN1, and CA12,

17	Kaempferol-3-Orhamnoside	CHEMBL515798		MAP3K14, ATM, KDM5C, CA12, CA7, CDK2/CCNE1, CTSK, MAP2, CTSS, FDPS, SCN3A GRIN1/GRIN2B, CFTR, IDO1, KMO, MNK1, PIK3CA, ACHE, ROS1, and HTR1B
18	Lutein	CHEMBL173929		CA12, IMPDH1, CAPN1, Transmembrane and Immunoglobulin Domain Containing (TMIGD3), CHRNA3/B4, ITGA4, LGMN, CDC7, MAP2, Myeloid Cell Leukaemia 1 (MCL1), NAMPT, CFTR, Phosphodiesterase 4A (PDE4A), ATM, PIN1, Prostaglandin E Synthase (PTGES), AKT3, ROS1, S1PR3, Thyroid Hormone Receptor Alpha (THRA), and Neurotensin Receptor 1 (NTSR1)
19	Luteolin	CHEMBL151		CA7, ROS1, ALPL, CFTR, HTR3A, KDM1A, ADORA2B, KDM5C, SCN3A, MAOA, and NQ02
20	Melatonin	CHEMBL45		DPP9, CAPN1, METAP2, HTR3A, CFTR, ITGA4, MAP2, ROS1, KDM5C, and TPSAB1
21	Myristic acid	CHEMBL111077		TPSAB1, CDC7, MAP2, CHRNA3/B4, ALPL, DPP9, CYP1A2, HTR3A, ROS1, and LGMN
22	Narcissin/Isorhmnetin 3-O-rutinoside	CHEMBL258394		ACHE, HDAC10, ATM, CA12, MAP2, CDK2/CCNE1, GRIN1/GRIN2B, CHRM5, CTSK, KMO, CTSS, FDPS, GRM2, IDO1, CREBBP, and ALOX5AP
23	Orientin	CHEMBL520866		HSP90AA1, ATM, CA7, IDO1, GRIN1/GRIN2B, KDM5C, HDAC10, MAP3K14, GRM2, ITGA4, NAMPT, ADORA2B, ROS1, KDM1A, and SPHK2
24	Palmitic acid	CHEMBL82293		CDC7, LGMN, CHRNA3, ROS1, CYP1A2, ALPL, HTR3A, MAP2, and Sodium Voltage-Gated Channel Alpha Subunit 3 (SCNA3)

25	p-Coumaric acid	CHEMBL66879		CAPN1, LGMN, ROS1, CHRNA3/B4, HTR3A, and DPP9
26	Quercetin	CHEMBL50		MAOA, ALOX5AP, CAPN1, IDO1, CFTR, Cathepsin K (CTSK), HTR3A, ROS1, KDM1A, NQO2, SCN3A, ADORA2B, XDH, and KDM5C
27	Saponarin	CHEMBL538921		IDO1, ACHE, MAP2, ATM, FDPS, BCL2, CDK2/CCNE1, SPHK2, CTSK, CYP1A2, S1PR3, GRIN1/GRIN2B, GRM2, HDAC10, TMPRSS6, HSP90AA1, SCN3A, KDM5C, NAMPT, PTPN2, MNK1, and ROS1
28	Scopoletin	CHEMBL71851		ITGA4, CAPN1, SCN3A, KMO, and ROS1
29	Tryptamine	CHEMBL6640		METAP2, CAPN1, ROS1, CYP1A2, FDPS, HTR2A, LGMN, MAP2, DPP9, SCN3A, and ITGAV
30	Umbelliferone	CHEMBL51628		ROS1, AKR1B10, MNK1, CAPN1, KDM5C, and SCN3A
31	Vicenin 2	CHEMBL1442950		GRIN1/GRIN2B, HSP90AA1, HDAC10, IDO1, Inosine Monophosphate Dehydrogenase 2 (IMPDH2), KDM5C, MNK1, GRM2, NAMPT, BCL2, CTSK, CDK2/CCNE1, and CYP1A2
32	Vitexin	CHEMBL487417		SPHK2, ADORA2B, MAP3K14, ATM, HSP90AA1, CA7, MAPKAPK2, CYP1A2, FDPS, HDAC10, MNK1, GRIN1/GRIN2B, IDO1, KDM5C, NAMPT, and ROS1
33	α-Tocopherol	CHEMBL3989859		ROS1, ATM, TMIGD3, BCL2, PGR, CHRNA3/B4, SRD5A2, Free Fatty Acid Receptor 1 (FFAR1), KDM1A, MAP2, HSP90AA1, and PIN1
34	β-Sitosterol	CHEMBL221542		CDC7, MPA2, and Cholinergic Receptor Nicotinic Alpha 3/Beta 4 Subunits (CHRNA3/B4)

Out of the 34 bioactive constituents in cucumber identified with *canonical SMILES* via ChEMBL, 17 were found to possess antihypertensive potential. These include compounds such as 5-Hydroxytryptamine, α-Tocopherol, Apigenin, CA9, Ellagic acid, Epigallocatechin gallate, Genistein, Gibberellin A3, Hesperidin, Isorhamnetin-3-O glucoside, Isovitexin, Kaempferol, Kaempferol-3-O-glucoside, Lutein, Quercetin, Saponarin and TOP1. These 17 molecules interact with a network of 18 specific proteins, including ACHE, ADAM10, ADK, ALOX5AP, ALPL, BCL2, CAPN1, CFTR, CTSK, CTSS, CYP1A2, ESR2, F10, FDPS, FFAR1, HTR2A, IDO1, and MCL1, which play critical roles in the physiological regulation of blood pressure (Figure 1).

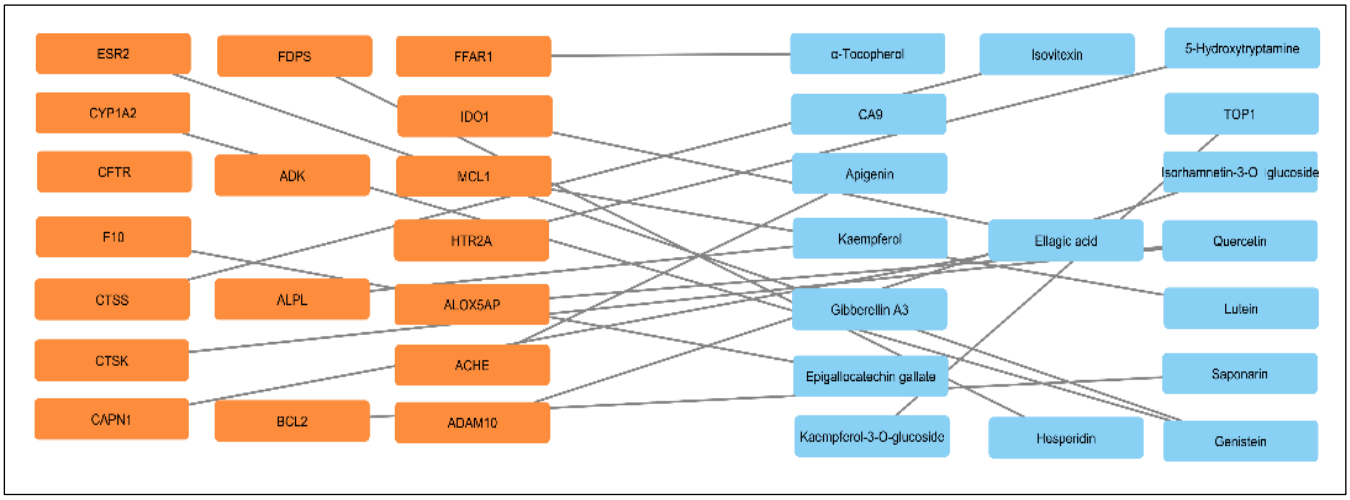


Figure 1. Active compounds in cucumbers linked to lowering blood pressure and their target proteins, analysis via *Cytoscape*

The score calculations use degree calculations based on the graph concept. In this network model, biological entities such as proteins, pathways, and orthologs are defined as nodes, whereas the functional relationships between them are represented as edges. Utilizing graph theory principles, nodes possessing a high degree of connectivity are identified as central hubs, signifying their critical influence within the overall system [37]. Based on the analysis of proteins interactions, 3 target proteins were obtained which had a relationship of more than 2, the highest value being BCL2, CTSS and CTSK. This target is the central regulator of hypertension (Figure 3).

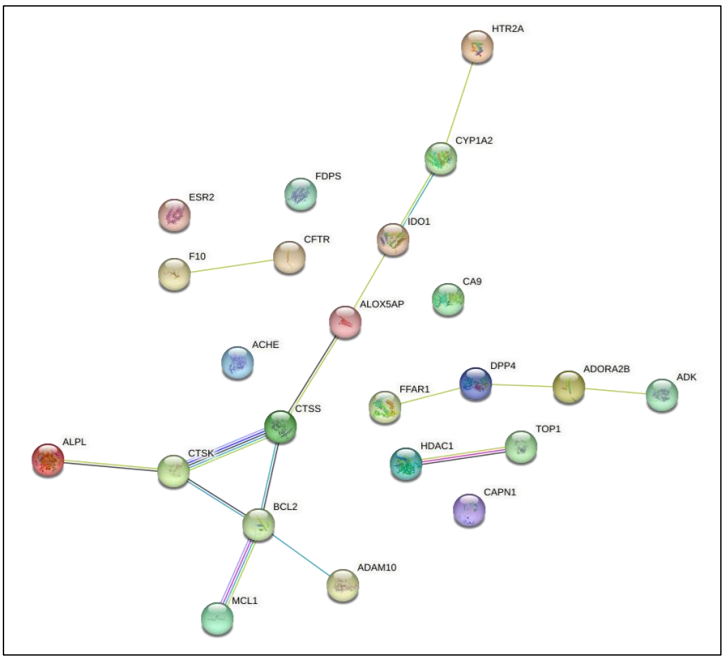


Figure 2. Proteins interaction

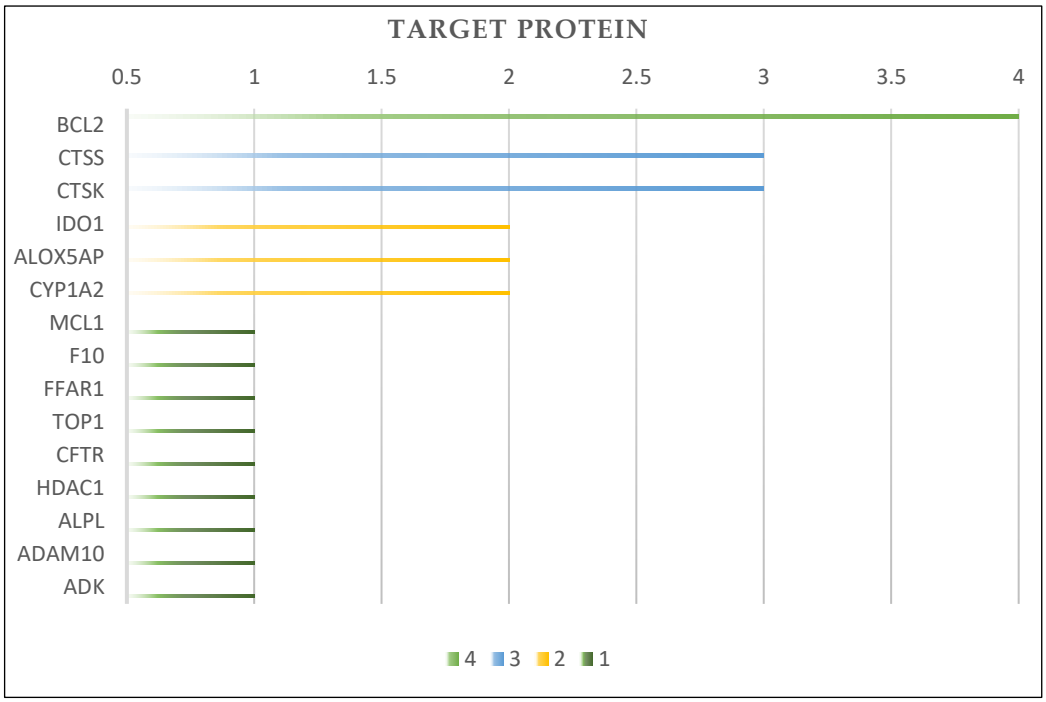


Figure 3. The relationship of active compounds to target proteins that play a role in hypertension

B-Cell Lymphoma 2 (BCL2) is an apoptosis regulator know to have significantly decreased expression in hypertensive groups. BCL-2 modulates cell survival in an oxidative stress environment, which indirectly influences the progression of hypertension and vascular damage [38], [39]. Cathepsin S (CTSS) is a cysteine proteinase involved in diverse tissue remodelling. In this study, osthole was visualized as having the ability to restore CTSS expression, thus this compound can treat pulmonary arterial hypertension (PAH) by partially ameliorating the inflammatory process, which is characterized by down-regulation [40]. Osthole is a novel pulmonary vasodilator in isolated rat and human pulmonary artery rings and its cardiovascular protective activity has been characterized by selective inhibition of vascular smooth muscle cell proliferation [41], [42]. Cathepsin K (CTSK) is a protease whose function is to prevent the formation of fibrinogen. This can prevent blood clots, thereby reducing the risk of hypertension or indirectly lowering blood pressure [43] (Figure 4).

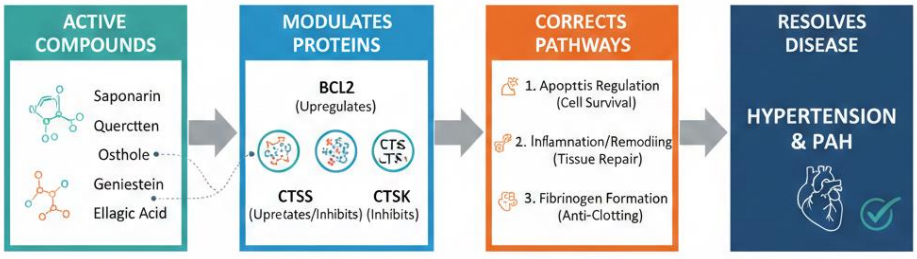


Figure 4. Molecular mechanism of hypertension regulation

There are five compounds linked to the target protein for regulating hypertension, namely saponarin, isovitexin, quercetin, ellagic acid, and genistein [44]. Research has shown that saponarin and isovitexin are polyphenolic compounds with various biological and medicinal properties, such as antioxidant, antiatherosclerosis, antihypertensive, and anti-inflammatory activities. It has been shown that the ACE inhibitory activity of barley seedlings methanol extract originates from the polyphenolic compounds present in barley seedlings [45]. The author views these compounds as precise biological tools. The author emphasizes their ability to inhibit the ACE and regulate cell signalling, treating them as natural alternatives to pharmaceutical ACE inhibitors. Quercetin is a flavanol compound that has antihypertensive effects, reduces oxidative stress, inhibits angiotensin

converting enzyme activity, increases vascular endothelial relaxing, and regulates cell signalling and gene expression [46]. Based on research, treatment with captopril and quercetin was given to male Wistar rats separately, which had been made hypertensive using angiotensin I and bradykinin injections. Both caused significant antihypertensive reactions and quercetin was equivalent to captopril orally or intravenously [47]. A bold stance is taken regarding Quercetin. By comparing it directly to captopril (a standard pharmaceutical drug), the author suggests that natural flavanols can achieve a therapeutic equivalence, positioning plant-based compounds as legitimate clinical contenders. Ellagic acid is known to possess antioxidant and antiproliferative properties. Ellagic acid can repair cardiovascular damage caused by hypertension in rats induced by N'-Nitro-L-arginine methyl ester hydrochloride for 6 weeks [48]. Genistein is isoflavone commonly found in plants that has been extensively studied for its health effects. Genistein has been reported to lower blood pressure in laboratory animals [45], [49]. In study in female spontaneously hypertensive rats (SHR), estrogen or genistein treatment inhibited the hypertensive effects of a high-NaCl diet, but the treatment effects were not additive. This suggest that estrogen and genistein may influence blood pressure through a common pathway, possibly related to the estrogen ERβ receptor. Several in vivo studies have shown that genistein can reduce the production of genes that express ACE through inhibition of cell signalling pathways [50]. The author argues that these compounds do not just treat the symptom but also the damage caused by it.

4. CONCLUSION

The analysis identified ellagic acid, genistein, isovitexin, quercetin, and saponarin as viable alternatives for hypertension treatment. Their ability to reduce blood pressure is attributed to their regulatory influence on the BCL2, CTSK dan CTSS signalling pathways.

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Conflicts of interest: The authors declare no conflict of interest.

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