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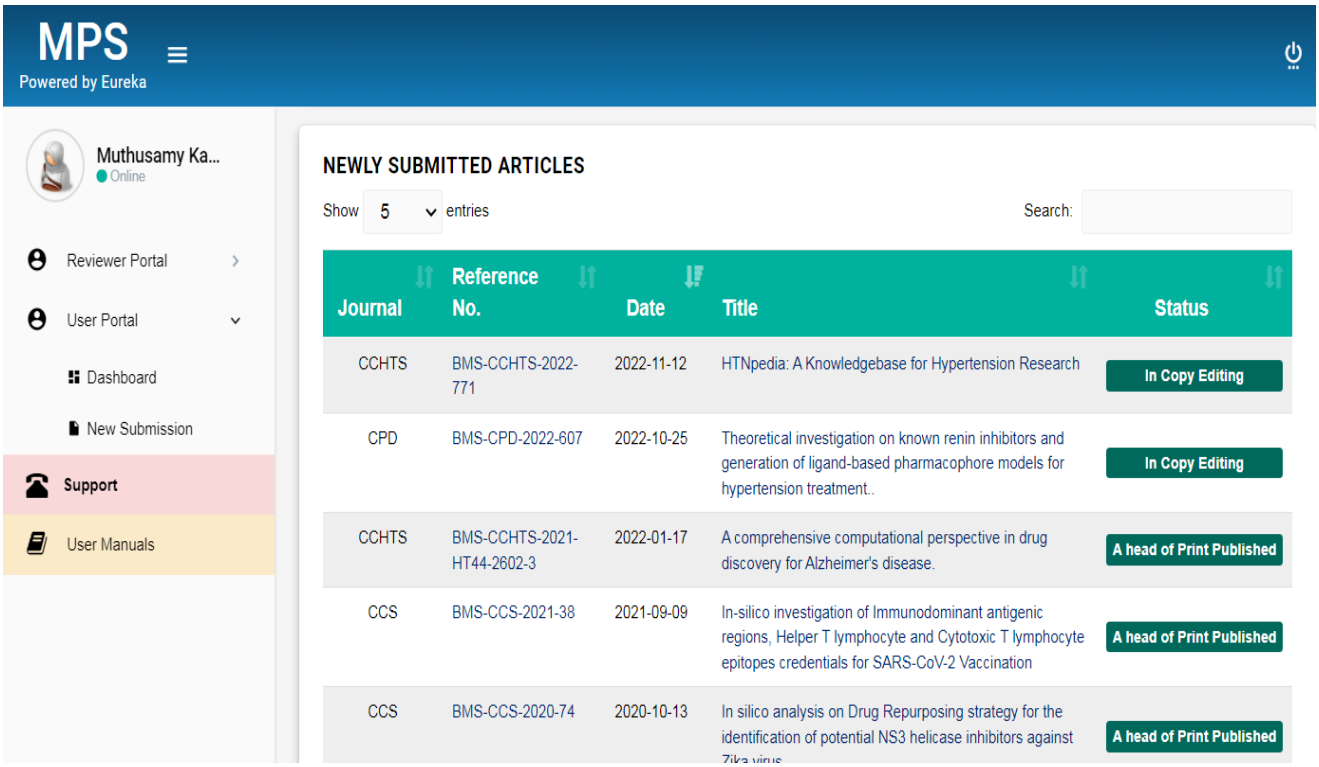

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Submission Title: HTNpedia: A Knowledgebase for Hypertension Research

Dear Dr. Karthikeyan Muthusamy,

I am pleased to inform you that your article Reference No. BMS-CCHTS-2022-771, entitled **"HTNpedia: A Knowledgebase for Hypertension Research"** has been provisionally approved for publication in "**Combinatorial Chemistry & High Throughput Screening**".

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HTNpedia: A Knowledgebase for Hypertension Research

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Abstract

Hypertension is notably a serious public health concern due to its high prevalence and strong association with cardiovascular disease and renal failure. It is reported to be the fourth leading disease that leads to death worldwide. Currently, there was no active operational knowledgebase or database for hypertension or cardiovascular illness. Therefore, we attempted to consolidate disease-related pathways, genes, and proteins by constructing a hypertension protein knowledgebase from primary sources. The primary data source was retrieved from the research outputs obtained from our laboratory team working on hypertension research. We have presented a preliminary dataset and external links to public repository for detailed analysis to readers. As a result, HTNpedia was created to provide information regarding hypertension-related proteins and genes. The complete webpage is accessible via www.mkarthikeyan.bioinfoau.org/HTNpedia.

Keywords: Hypertension; Knowledgebase; SNP; Proteins; Genes; Drug molecules

Introduction

It is widely known that the interaction of biological proteins is highly intricate. Furthermore, they are closely tied to biological, chemical and metabolic signalling pathway(s). Proteins are presumed to be best molecular targets in drug discovery for many disorders. However, no definitive link between the proteins and the disease has been established[1,2]. On the contrary, genomic data analysis reveals that proteins and genes involved in a specific pathway. Alternative splicing and post-translational alterations contribute to this complexity[3,4]. As a result, a comprehensive understanding of hypertension aetiology is expected to overcome barriers in hypertension management strategies[5].

A lot of evidence is available in public domains and open-source databases, which has a significant impact on the development of pathway-based drugs using *in silico* techniques. Evidence on signalling and metabolic pathway(s) provides a basic understanding of the role of cellular proteins in the development of hypertension, allowing for the identification of potential treatment targets[6]. In the event that the target protein does not respond to treatment, an alternate target from a disease-related biochemical pathway(s) may be used to address the issue[7]. The dispersed nature of information important to biochemical pathways and linked proteins in literatures and online biological databases makes mining the necessary data extremely difficult[8,9]. Even when a researcher obtains relevant data for a specific target protein from multiple sources, it is done separately, which takes time to establish a perfect link.

Materials and methods

Data Acquisition

The hypertension related-data such as research articles, gene, protein and drug information were manually collected from several resources available from primary

databases such as SwissProt[10], UniProtKB[11] and Ensembl genome browser[12]. For research articles, we a utilized search engine as Google scholar to find the most relevant articles matching to our keywords. Further reviews, articles were filtered using the combination keyword which includes Hypertension, RAAS pathway, Protein, drug discovery, drug molecules and anti-hypertensive treatment[13]. Finally, curate articles and information were obtained by excluding articles contains lacking relevant information and articles available other than the English language.

Open-source biological databases are critical for assisting life science researchers in gaining access to the most recent information derived from numerous distributed literatures and databases in a concise and easily accessible manner. Changes in gene expression and its products (proteins) are universally acknowledged to cause dysfunction in biochemical pathways related to blood pressure regulation, drug metabolism, and homeostasis, among other things, resulting in hypertension[14].

A significant effort is now being undertaken to define the patho-physiological mechanisms involved, employing precise mapping and functional techniques[15]. As a result, understanding the pathogenesis mechanism in relation to protein is critical for treatment and management planning by identifying key regulatory genes and proteins[7,16]. The search for a new hypertensive medication target and the investigation of associated proteins is an ongoing endeavour[17–19]. Updates on proteins associated with hypertension are accessible in the literature and databases; however, they may not be comprehensive. The hypertension -related processes, genes, and proteins may be linked to offer a solid foundation for hypertension management.

Architecture and web interface

The HTNpedia is built on Apache HTTP server (version 2.2.17), which was installed on machine with Ubuntu and Microsoft windows 10 as the operating system. The responsive front-end, which represents a smart user-friendly interface, was developed using HTML5[20].

Integration of gene and protein information with pathway

In terms of gene and protein information, data available to hypertension and its associated pathway(s) was obtained from Reactome[21] and KEGG[22]. The Reactome server provides a list of proteins and pharmacological information involved in signalling and metabolic processes, and users can retrieve proteins with their corresponding UniProt ID. KEGG Gene IDs were assigned to genes involved in hypertension pathways, which were then matched to UniProt IDs using an identifier mapping tool[23]. The terms KEGG pathway and KEGG disease refer to the pathways associated with human diseases such as cancer, cardiovascular, immunological, neurological, endocrine, metabolic, and infectious disorders. The pathways are highlighted with any query protein from user and display the participation of particular gene in the list of pathways. This could be much helpful to identify the participation of the target protein in associated pathways. In addition, this knowledge base provides the schematic view of all the known major pathways linked with hypertension pathogenesis will improve the data search and easy to obtain information. Further, external links provided close to the target protein search would display the context earlier for their scientific view.

Results and Discussion

Data integration

Open-source biological databases are critical for assisting life science researchers in gaining access to the most up-to-date information generated from various scattered literatures and databases in an easily understandable summarised form[24].

It is well established that altered gene expression and its products (proteins) cause impairment in the biochemical pathways that are linked to the RAAS proteins and CYP450 metabolism and function, resulting in hypertension. A significant effort is now being made to categorise the pathophysiological mechanisms involved, using fine mapping and functional approaches. As a result, understanding the mechanism of pathogenesis in relation to protein is critical for planning treatment and management by highlighting relevant regulatory genes and proteins[25]. The search for a new hypertension drug target, drugs, and SNPs in the study of related proteins is an ongoing process. Updates on proteins associated with hypertension are available in the literature and databases; however, they may not be comprehensive. Linking hypertension-related pathways, genes, and proteins could provide a solid foundation for hypertension management.

HTNpedia contains hypertension-related proteins, SNPs, and drugs from the RAAS pathways. All of the information was gathered from different sources (Reactome, KEGG and PID). Each entry contains information culled from the UniProtKb and Entrez Gene databases. Furthermore, the knowledgebase includes the proteins' physicochemical properties, which can be used to group similar proteins elsewhere in order to gain more information. HTNpedia has links to external databases or knowledgebases where users can obtain additional information, such as SNP details from NCBI dbSNP. Understanding of pharmacogenomics combined with clinical data

from PharmGKB; KEGG orthology, pathway, disease, drug target, motif, and so on; Graphical representation of a gene sequence from NCBI Nucleotide's Graphical View; Details about the transcripts come from Ensembl, and all genetic characteristics brought from OMIM. PDB knowledgebase protein structure; DrugBank knowledgebase drug information Google Scholar and PubMed biomedical literatures. Figure 1 depicts the overall architecture of HTNpedia, including all of its components. Thus, HTNpedia is presumed to be a beneficial tool for gaining an in-depth insight into human hypertension associated proteins in search of a promising target for hypertension management.

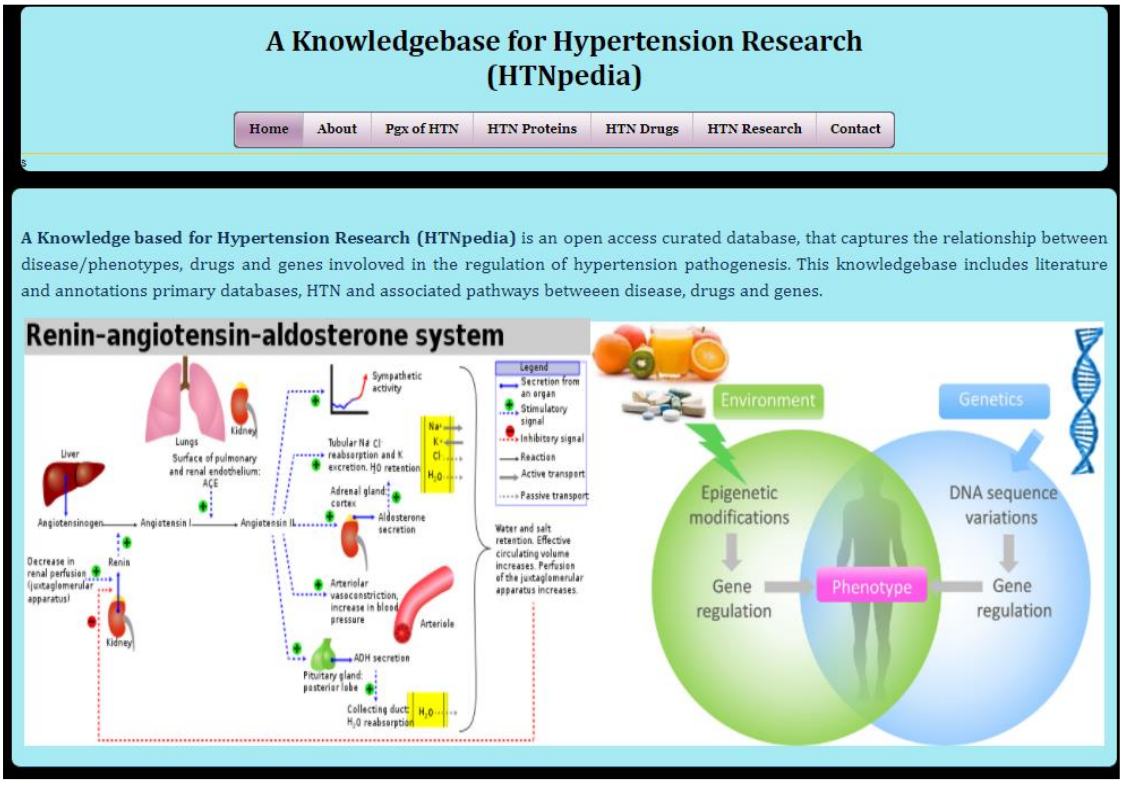
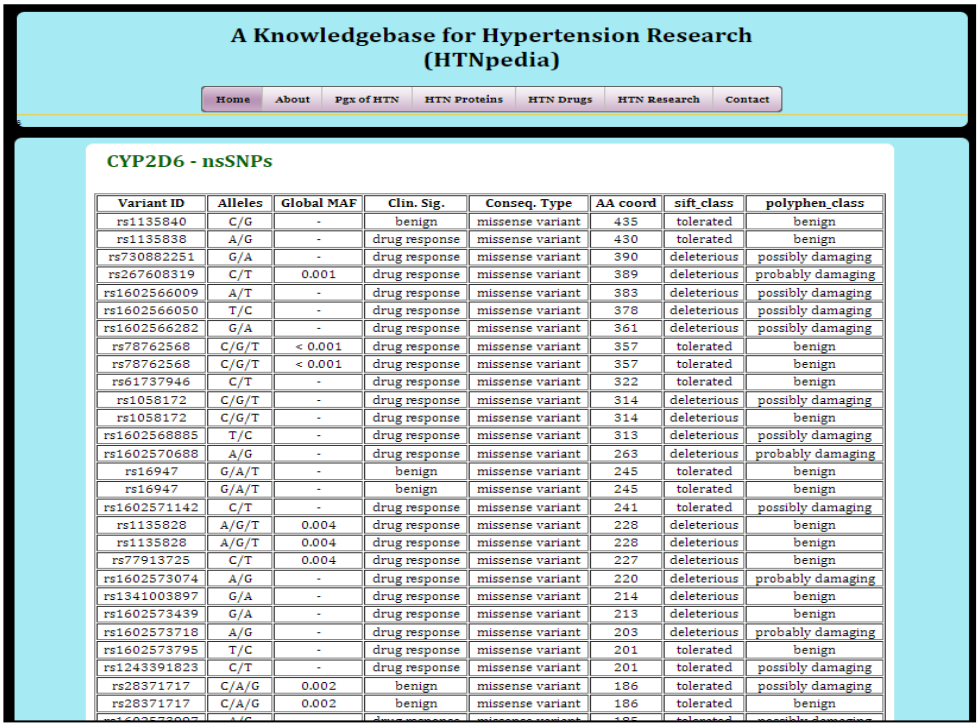


Figure 1. Index page of the HTNpedia knowledgebase

User interface

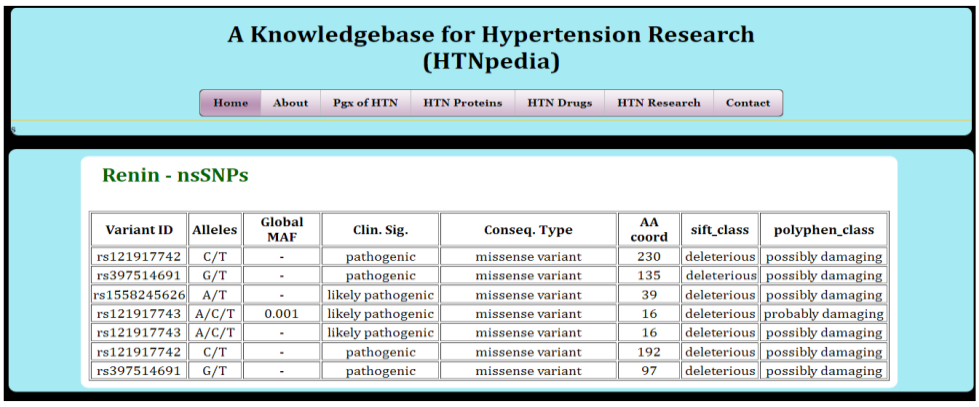
The biochemical pathway approach has been used to choose an appropriate therapeutic target for HTNpedia. A user can directly access protein details by HTN proteins in this section. By selecting the pharmacogenomics (Pgx) of HTN menu, the

polymorphism of hypertension associated proteins and their calculated SNP prediction data show up in the drop-down menu (Figure 2 and 3). The drug information and a link to the drug were provided in the HTN Drugs menu. Moreover, all proteins, drugs, and SNPs are linked to an HTML-enabled PHP file that runs MySQL queries to provide detailed information about each entry. Each SNP's negative effect was predicted and categorised in a table[26].



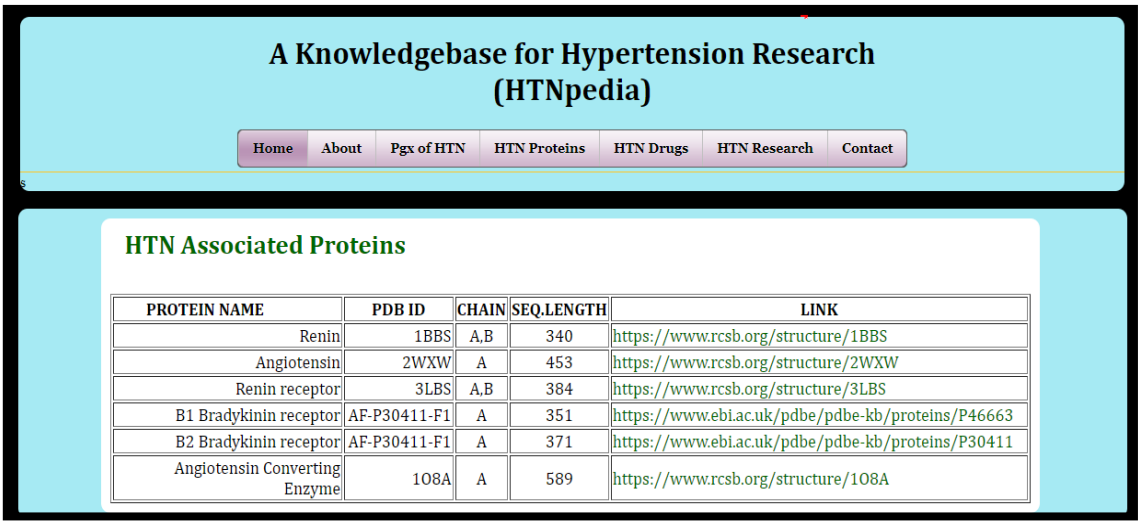
Variant ID	Alleles	Global MAF	Clin. Sig.	Conseq. Type	AA coord	sift_class	polyphen_class
rs1135840	C/G	-	benign	missense variant	435	tolerated	benign
rs1135838	A/G	-	drug response	missense variant	430	tolerated	benign
rs730882251	G/A	-	drug response	missense variant	390	deleterious	possibly damaging
rs267608319	C/T	0.001	drug response	missense variant	389	deleterious	probably damaging
rs1602566009	A/T	-	drug response	missense variant	383	deleterious	possibly damaging
rs1602566050	T/C	-	drug response	missense variant	378	deleterious	possibly damaging
rs1602566282	G/A	-	drug response	missense variant	361	deleterious	possibly damaging
rs78762568	C/G/T	< 0.001	drug response	missense variant	357	tolerated	benign
rs78762568	C/G/T	< 0.001	drug response	missense variant	357	tolerated	benign
rs61737946	C/T	-	drug response	missense variant	322	tolerated	benign
rs1058172	C/G/T	-	drug response	missense variant	314	deleterious	possibly damaging
rs1058172	C/G/T	-	drug response	missense variant	314	deleterious	benign
rs1602568885	T/C	-	drug response	missense variant	313	deleterious	possibly damaging
rs1602570688	A/G	-	drug response	missense variant	263	deleterious	probably damaging
rs16947	G/A/T	-	benign	missense variant	245	tolerated	benign
rs16947	G/A/T	-	benign	missense variant	245	tolerated	benign
rs1602571142	C/T	-	drug response	missense variant	241	tolerated	possibly damaging
rs1135828	A/G/T	0.004	drug response	missense variant	228	deleterious	benign
rs1135828	A/G/T	0.004	drug response	missense variant	228	deleterious	benign
rs77913725	C/T	0.004	drug response	missense variant	227	deleterious	benign
rs1602573074	A/G	-	drug response	missense variant	220	deleterious	probably damaging
rs1341003897	G/A	-	drug response	missense variant	214	deleterious	benign
rs1602573439	G/A	-	drug response	missense variant	213	deleterious	benign
rs1602573718	A/G	-	drug response	missense variant	203	deleterious	probably damaging
rs1602573795	T/C	-	drug response	missense variant	201	tolerated	benign
rs1243391823	C/T	-	drug response	missense variant	201	tolerated	possibly damaging
rs28371717	C/A/G	0.002	benign	missense variant	186	tolerated	possibly damaging
rs28371717	C/A/G	0.002	benign	missense variant	186	tolerated	benign

Figure 2. Results page displaying the list of SNPs with complete information



Variant ID	Alleles	Global MAF	Clin. Sig.	Conseq. Type	AA coord	sift_class	polyphen_class
rs121917742	C/T	-	pathogenic	missense variant	230	deleterious	possibly damaging
rs397514691	G/T	-	pathogenic	missense variant	135	deleterious	possibly damaging
rs1558245626	A/T	-	likely pathogenic	missense variant	39	deleterious	possibly damaging
rs121917743	A/C/T	0.001	likely pathogenic	missense variant	16	deleterious	probably damaging
rs121917743	A/C/T	-	likely pathogenic	missense variant	16	deleterious	possibly damaging
rs121917742	C/T	-	pathogenic	missense variant	192	deleterious	possibly damaging
rs397514691	G/T	-	pathogenic	missense variant	97	deleterious	possibly damaging

Figure 3. Results page displaying the list of SNPs with complete information



PROTEIN NAME	PDB ID	CHAIN	SEQ.LENGTH	LINK
Renin	1BBS	A,B	340	https://www.rcsb.org/structure/1BBS
Angiotensin	2WXW	A	453	https://www.rcsb.org/structure/2WXW
Renin receptor	3LBS	A,B	384	https://www.rcsb.org/structure/3LBS
B1 Bradykinin receptor	AF-P30411-F1	A	351	https://www.ebi.ac.uk/pdbe/pdbe-kb/proteins/P46663
B2 Bradykinin receptor	AF-P30411-F1	A	371	https://www.ebi.ac.uk/pdbe/pdbe-kb/proteins/P30411
Angiotensin Converting Enzyme	1O8A	A	589	https://www.rcsb.org/structure/1O8A

Figure 4. Result page displaying the list of potential protein targets with structural information

HTNpedia offers trustworthy scientific information because the data is sourced from leading online database and knowledgebase. The current version of HTNpedia is expected to help anyone in the research community who is looking for a potential hypertension target in order to design an effective drug for hypertension management using computational drug design. HTNpedia could be a useful platform because it connects the biochemical pathways involved in different stages of hypertension via its participating proteins. The protein is thought to be a potential target for successful drug discovery. We have provided the complete data of the well-known, recently targeted and novel proteins associated with hypertension. The structural information of the protein is linked with same entry, which helps the user to find the relevant information in external websites (Figure 4). The sequence length and coverage are believed to have the significant factor in selecting the proper tertiary structure for molecular docking studies. Therefore, we have provided the important data close to the protein entry. These proteins are also linked to candidate genes, genetic information, and physio-chemical properties.

Implementation

HTNpedia was created and tested on a WAMP server. HTNpedia is hosted on a Linux server and is accessible via the internet from anywhere in the world. The complete webpage is accessible via www.mkarthikeyan.bioinfoau.org/HTNpedia.

How HTNpedia can help?

Target identification is important in drug discovery because the world desperately needs new therapeutic strategies for hypertension management. Linking structurally and functionally defined targets to disease remains a challenge. As a result, the primary goal of HTNpedia is to aid in the identification of therapeutic targets for hypertension treatment and management. Acquiring information at different levels ultimately aids in the focus and comprehension of therapeutic targets. As a result, it may aid in the identification of novel therapeutic targets that were not previously focused on for hypertension management, as well as making new users aware of existing molecular targets. The current version of HTNpedia contains drug information on direct renin inhibitors, diuretics, ACE-II inhibitors, and calcium channel blockers (Figure 5). The knowledgebase contained drug information as well as their structure and functions. The external web-link provides detailed information about the drug molecule and assists the user in locating similar drug molecules that are currently under investigation or in clinical trials (Figure 6). The choice of drug molecule is always influenced by several factors such as drug dosage, side effects, and potent activity with the target. This website also provides the drug's drug-nature and the agonist/antagonist property of the drug molecule. The Drug bank link was provided in order to gain access to the structural and related information for those specific drugs (Figure 7). Figures 8 to 11 show the other new features available on the webpage.

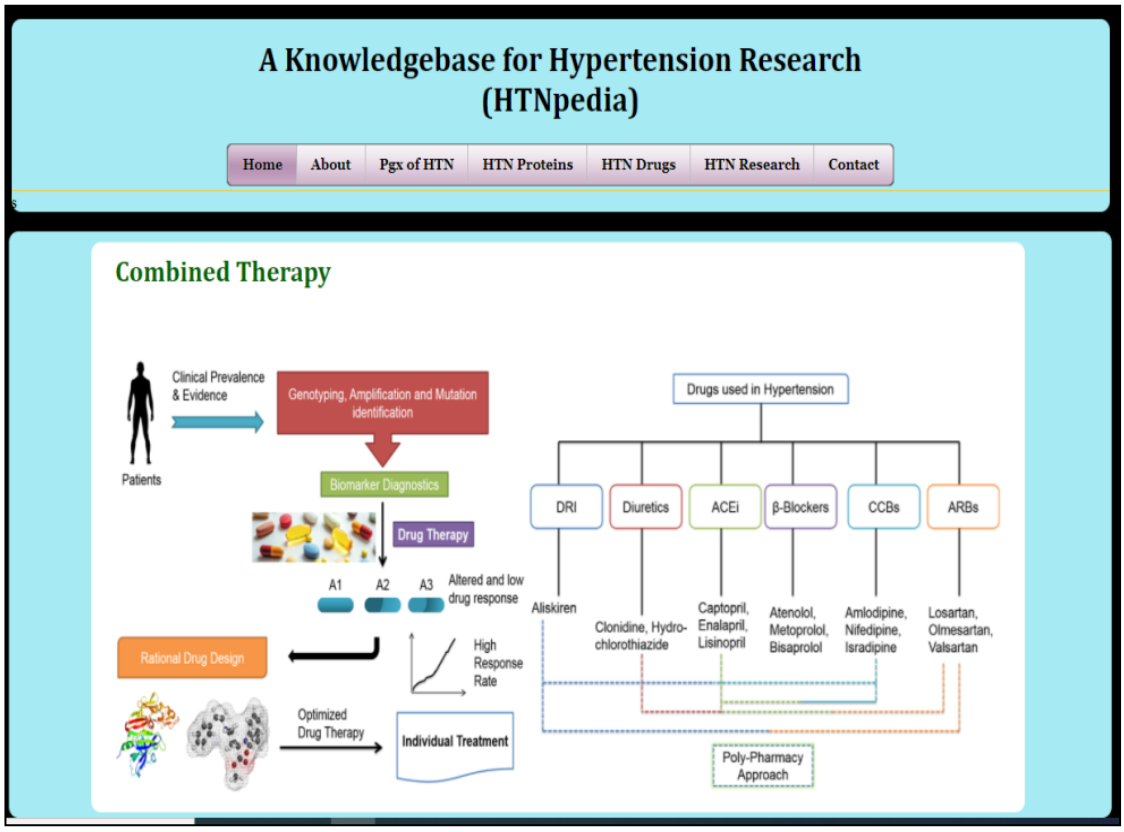


Figure 5. Common page of drug information with illustration of pharmacogenomics workflow in drug discovery, displaying the categorized drugs figure emphasis on the polypharmacy approach.

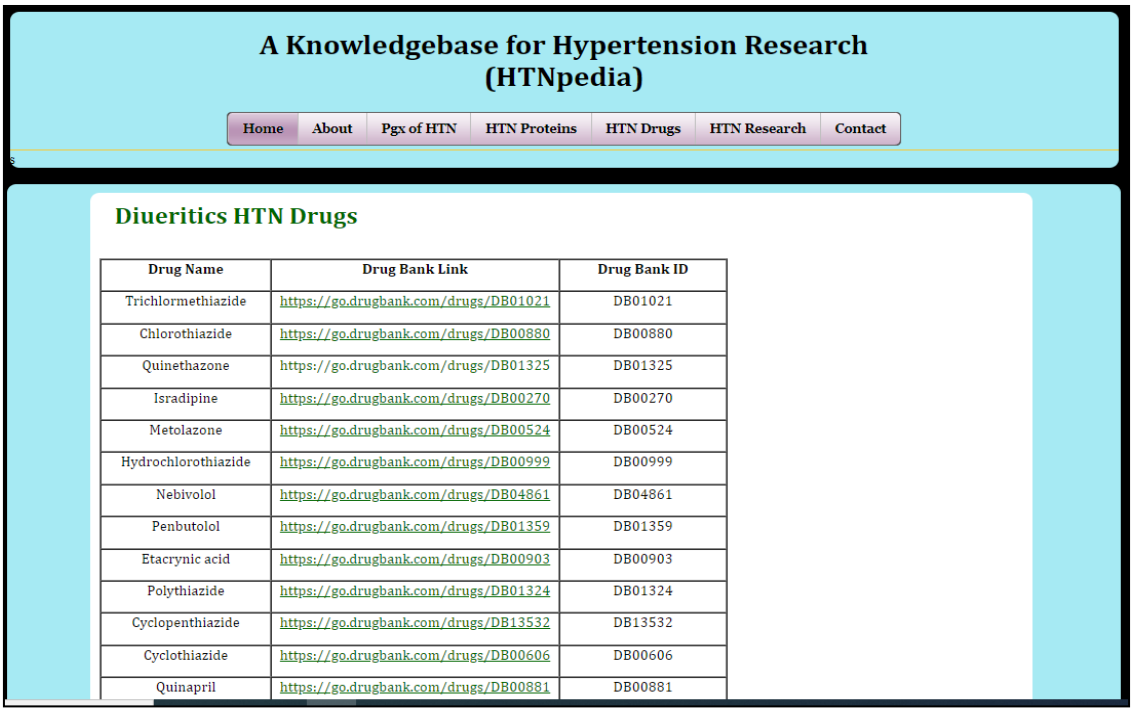


Figure 6. Webpage displays the Diuretics category drugs with external Drug bank link.

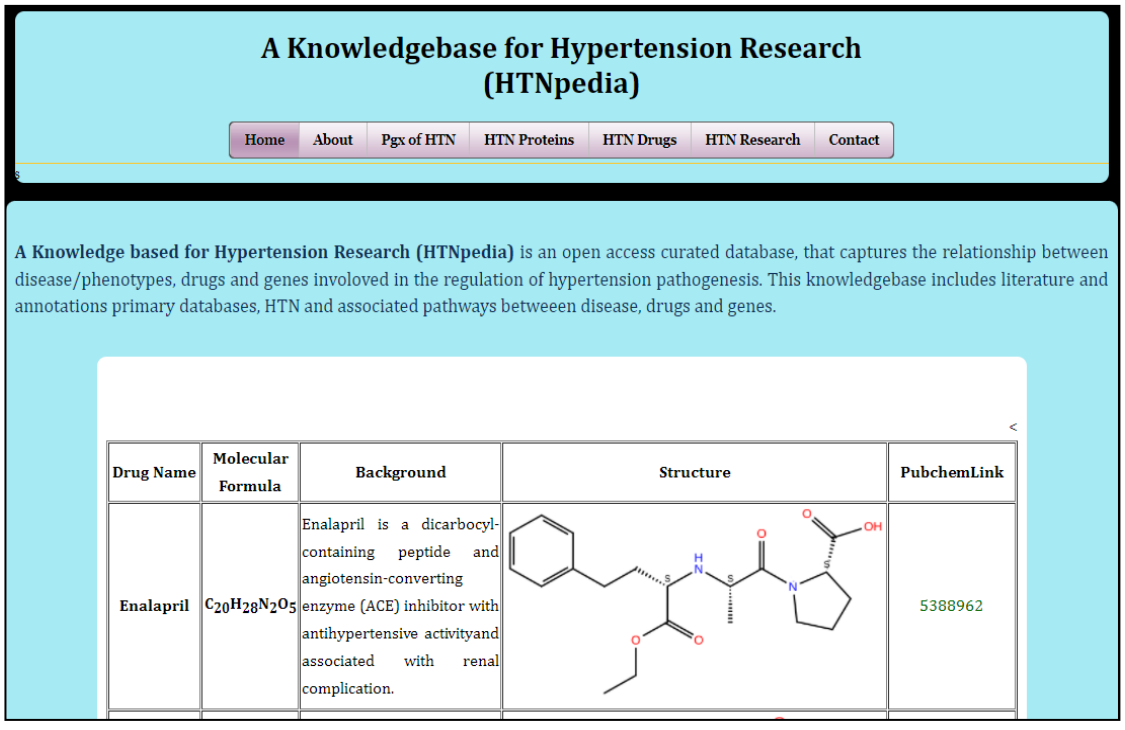


Figure 7. Webpage displays the list of known ACE inhibitors with structural details

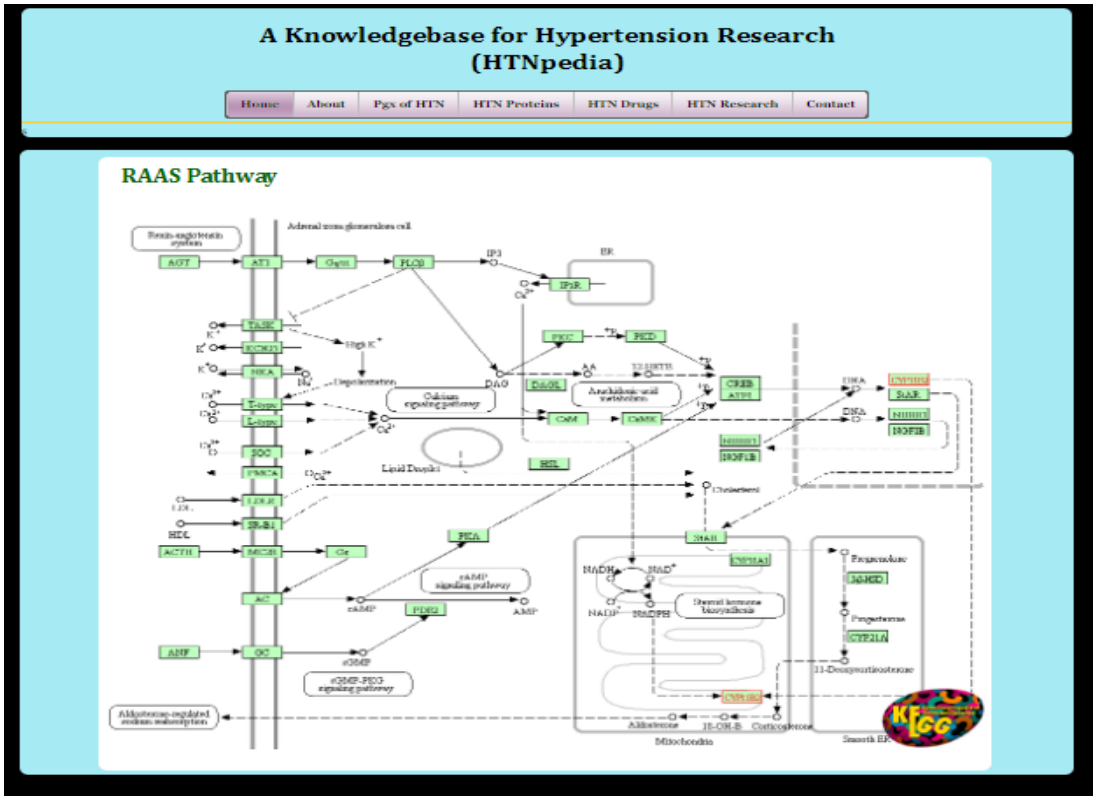


Figure 8. Webpage displays the RAAS pathway from KEGG database

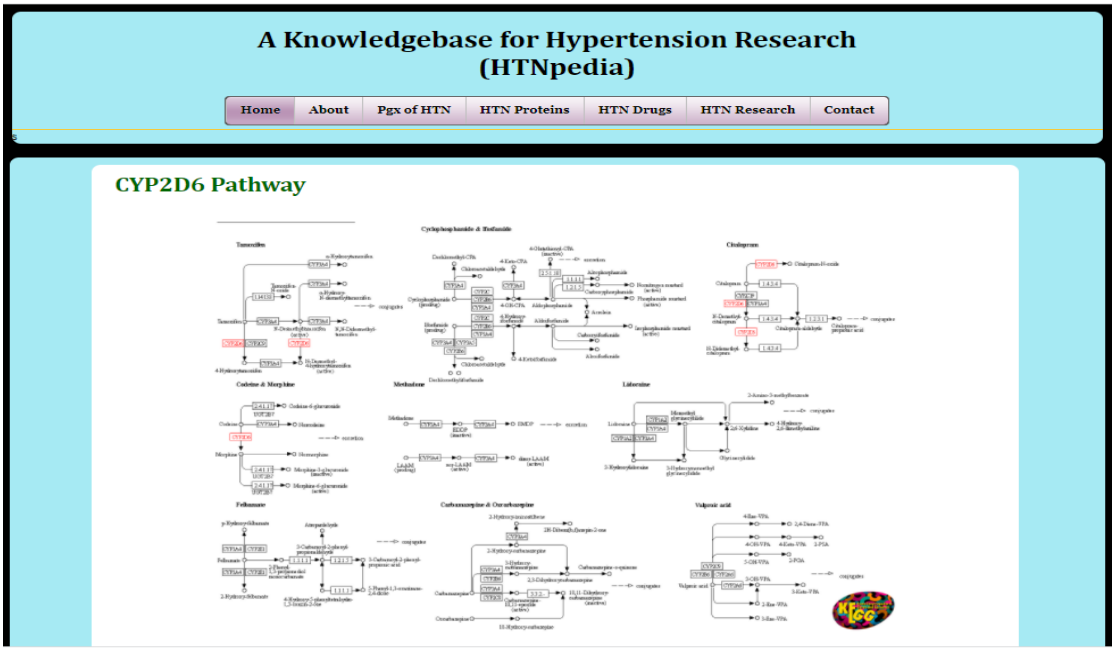


Figure 9. Webpage displays the CYP2D6 pathway from KEGG database

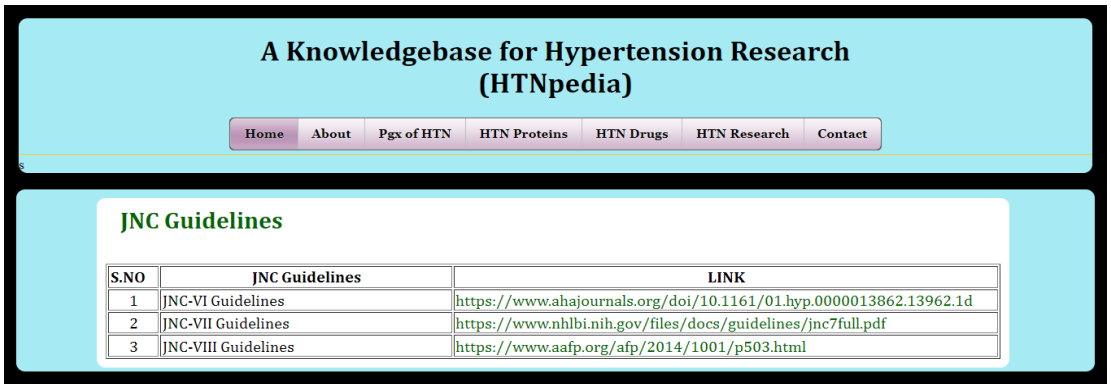


Figure 10. Webpage display of JNC guidelines.

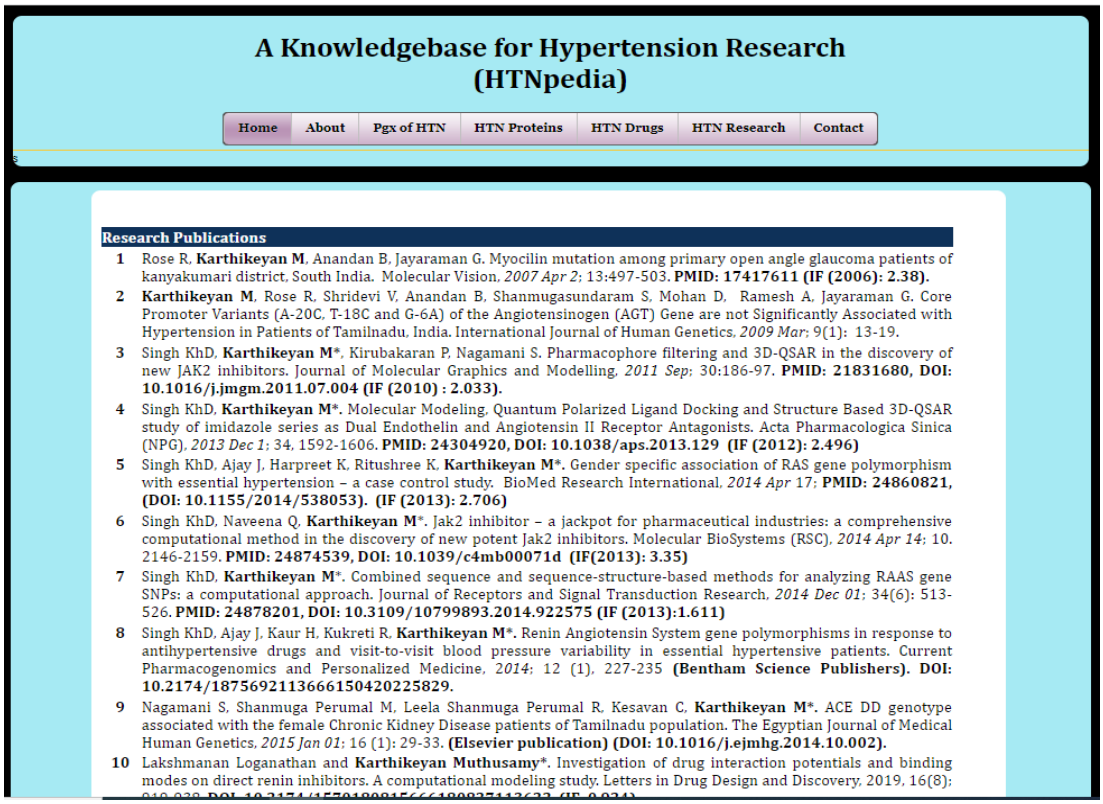


Figure 11. Research Publications of HTN Research.

Conclusion

Knowledge on gene, protein signalling and metabolic pathway(s) provides a basic understanding of the role of cellular proteins in the pathogenesis of hypertension, allowing potential therapeutic targets to be identified and validated. Hypertension-related protein information is widely disseminated in a variety of prominent sources, making it difficult to select a therapeutic target for hypertension management. Thus, an effort has been made to link the hypertension-associated genes, pathways, and proteins in order to provide a solid foundation for hypertension treatment and planning management strategies. MySQL and PHP have been used to develop the web source "Hypertension Knowledgebase (HTNpedia)" to provide information pertinent to the biochemical pathways and its associated proteins on a single open access webpage. HTNpedia was created using proteins associated with various types of hypertension and biochemical pathways. HTNpedia contains several proteins from various hypertension-related pathways, several drug molecules, and numerous SNPs associated with hypertension. Furthermore, HTNpedia has been linked to external databases to access the information about SNP; Pharmacogenomics knowledgebase with clinical data from pathway, disease, drug target, motif; PharmGKB; Orthology, transcript details and all genetic features; Gene related transcriptomic, genetic, proteomic, functional, and disease information; Biomedical literatures. Thus, HTNpedia is presumed to be a useful tool for understanding and research on human hypertension associated proteins related information's to better drug discovery for hypertension management.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

HUMAN AND ANIMAL RIGHTS

No animals/humans were used for studies that are the basis of this research.

CONSENT FOR PUBLICATION

Not applicable.

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AVAILABILITY OF DATA AND MATERIALS

Not applicable.

CONFLICT OF INTEREST

Dr. Karthikeyan Muthusamy is an Associate Editorial Board Member of the journal CCS of Bentham Science Publishers.

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None declared.

Author Contribution

The authors confirm contribution to the paper as follows: Data Collection: LL, KM; Study Design: LL, KM, JJ; Interpretation and Data Analysis: LL, KM; Read and Approval of final draft: LL, JJ, KM.

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