ISSN: 1607-8322, e-ISSN: 2220-5799 Anaesthesia, Pain & Intensive Care
Vol 27(5); October 2023 DOI: 10.35975/apic.v27i5.2293

ORIGINAL RESEARCH PAIN MANAGEMENT

Discovering a combination of natural compounds for treatment of chronic cancer pain based on bioinformatics

Weichen Si [1]

Authors affiliation:

1. Health Management Center, Fengtai District Education Committee of Beijing Municipality, Beijing 100070, China; E-mail: weichensi14@outlook.com; ORCID: {000-0002-8036-9427}

Correspondence: Weichen Si, E-mail: weichensi14@outlook.com; Phone: +86 15311000917

ABSTRACT

Background & Objective: The incidence of malignant disease has been increasing the world over, and with it the number of patients suffering from severe cancer pain is also increasing with every passing day. We aimed to find a potentially effective combination of natural compounds for the treatment of chronic cancer pain (CCP) using bioinformatics methods, and provide a theoretical basis for subsequent laboratory experiments and clinical trials.

Methodology: Six natural compounds, including bakuchiol, cinnamaldehyde, curcumin, eugenol, salicin and xanthoxylin, were selected as candidates for new drugs by consulting a large number of relevant literatures. Their targets were obtained from the Swiss Target Prediction database. The related targets of CCP were obtained from GeneCards, OMIM and DisGent databases. Cytoscape software was used to construct the "compound-target-disease" network. Protein-protein interaction network (PPI) was constructed by STRING platform; GO function and KEGG pathway enrichment analysis were performed by R language software.

Results: A total of 197 targets were obtained from the Swiss Target Prediction database; 10767 CCP of disease targets were obtained after searching and removing duplications in the disease database. Twelve core targets, AKT1, SRC, STAT3, ESR1, RELA, EP300, MAPK1, MAPK14, CCNA2, EGFR, GSK3B and PRKCZ, were identified by PPI analysis. GO functional enrichment analysis yielded 1950 entries. KEGG enrichment analysis revealed 134 pathways with statistical significance, among which pathways related to CCP were more than those related to nerve.

Conclusion: The mechanism of action of these six compounds in the treatment of chronic cancer pain is multi-target and multi-pathway related. Through protein-protein interaction analysis, GO function and KEGG pathway enrichment analysis, it is found that these six compounds can be used as candidate drugs for the treatment of chronic cancer pain, which will be further studied in the future.

Key words: Bioinformatics; Natural Compounds; Chronic Cancer Pain; New Drug Discovery

Citation: Si W. Discovering a combination of natural compounds for treatment of chronic cancer pain based on bioinformatics. Anaesth. pain intensive care 2023;27(5):431–439; **DOI:** 10.35975/apic.v27i5.2293

Received: February 21, 2023; **Reviewed:** March 06, 2023; **Accepted:** April 28, 2023

1. INTRODUCTION

Chronic cancer pain (CCP) is a type of pain caused by cancer or its treatment. It can occur at any stage of the cancer, but is most commonly found in the patients with advanced cancer stage. This manifestation of pain may be caused by the cancer itself, the treatment used to treat the cancer, or a combination of both. The pain may be caused by the tumor pressing on nearby nerves or organs, or it may be caused by the side effects of chemotherapy, radiotherapy or other treatments. It has been reported that up to 80% of cancer patients and up to 90% of people with advanced cancer experience some form of chronic pain.[1] The incidence of CCP increases with the severity of the cancer. CCP can have a significant impact on a patient's quality of life. It can lead to physical and mental

symptoms such as fatigue, depression, anxiety and sleep difficulties for patients. It can also interfere with daily activities such as work, leisure and socializing.

The treatment of CCP is complex and this involves many aspects. Treatment of CCP usually includes medication, physiotherapy, psychotherapy and complementary therapies.[2] Medications are the mainstay of treatment for CCP. These include opioids, non-opioid analgesics, anticonvulsants, antidepressants, and topical agents. Physical therapy can help to reduce pain and improve function.[3] It can include stretching, strengthening, and range of motion exercises, as well as heat and cold therapy.[4] Psychotherapy can help to reduce pain and improve quality of life. It can include cognitive behavioral therapy, relaxation techniques, and stress management. Complementary therapies can help to reduce pain and improve quality of life.[5] These can include acupuncture, massage, yoga, and meditation. Despite the availability of treatment options, there are still some deficiencies in the treatment of CCP.[6,7] One of the main shortcomings is the lack of pain management specialists. Pain management specialists are trained to assess and treat chronic pain and they can provide an integrated approach to pain management. There is also a lack of complementary therapists, which might use therapies such as acupuncture, massage and natural medicines. These therapies may be beneficial for some patients, but they are not widely used.

With the modernization of natural medicines, there is a growing body of research showing the efficacy of natural medicines in the treatment of diseases and providing a new direction in pharmacological research. For example, the Chinese scientist Tu Youyou discovered the natural compound artemisinin from Artemisia annua, which is an effective treatment for malaria and was awarded the Nobel Prize. Traditionally, new drugs have been designed with the disease in mind. In contrast, there are a large number of compounds in natural medicines, and using these compounds as the object of research to find diseases, which can be treated by these, is a new concept in drug discovery. Through a review of the relevant literature, six natural compounds, bakuchiol, cinnamaldehyde, curcumin, eugenol, salici and xanthoxylin, were initially identified as having the potential to treat CCP. In this paper, a bioinformatics approach was used to find their therapeutic mechanisms, laying the foundation for further experiments and the discovery of new drugs.

2. METHODOLOGY

2.1. Screening of natural analgesic compounds for their targets of action

TCMSP (Traditional Chinese Medicine Systems Pharmacology)[8] database is a unique systems pharmacology platform of Chinese herbal medicines that captures the relationships between drugs, targets and diseases. The database includes chemicals, targets and drug-target networks, and associated drug-target-disease networks, as well as pharmacokinetic properties for natural compounds involving oral bioavailability, drug-likeness, intestinal epithelial permeability, blood-brain barrier, and aqueous solubility etc. This breakthrough has sparked a new interest in the search of candidate drugs in various types of traditional Chinese herbs. PubChem[9] is a free public chemical substance database developed and maintained by the National Library of Medicine (NLM) at the National Institutes of Health (NIH) in the United States. It contains detailed information on millions of organic compounds, biological molecules, and other chemical compounds, including molecular structures, physical and chemical properties, pharmacology, and toxicity data. Swiss Target Prediction Database[10] is an online tool developed and maintained by the Swiss Institute of Bioinformatics, which aims to predict the interactions between small molecule compounds and protein targets.

Searching the TCMSP database for natural compounds that may treat CCP, “Bakuchiol", "Cinnamaldehyde", "Curcumin", "Eugenol", "Salicin" and "Xanthoxylin" were eventually found to be potential compounds for the treatment of CCP. These six compounds were entered into the PubChem database (https://pubchem.ncbi.nlm.nih.gov/). The structural information of these compounds was retrieved after searching the obtained structures in the Swiss Target Prediction Database (http://www.swisstargetprediction.ch/) for relevant targets. Targets were screened using a ‘P > 0’ as a screening criterion.

2.2. Disease target acquisition

Using ‘chronic cancer pain’ as the search term and ‘human’ as the search target, the human genome annotation database (GeneCards, https://www.genecards.org/),[11] the online human Mendelian genetic database (OMIM, https://www.omim.org/),[12] and the database of gene-disease associations (DisGeNET, https://www.disgenet.org/)[13] were used to obtain disease targets.

2.3. Acquisition of intersectional targets

Venny (https://bioinfogp.cnb.csic.es/tools/venny/) software was used to create VEEN plots of compounds and diseases and to obtain intersecting targets. Using intersecting targets as potential targets for compounds to treat CCP

2.4. "Compound-target-disease" network construction

Prepare compound gene "network" files and Type files, import the relevant files using Cytoscape (3.9.1) software, and draw a "compound-target-disease" network map.

2.5. PPI network construction and network topology analysis

STRING (Search Tool for the Retrieval of Interacting Genes/Proteins)[14] is an online protein interaction network database that integrates protein interaction information from around the world. It provides experimentally determined and computationally predicted protein-protein interaction network diagrams, as well as information on protein families, functions, and expression profiles. The goal of STRING is to help researchers better understand protein interactions and their roles in cell function, signal transduction, and diseases.

Using STRING (https://string-db.org/) platform, imported the intersecting targets, set the object as "homo sapiens" with the highest confidence level of 0.900, hide the free gene nodes, and obtained the protein interaction relationship. The results were imported into Cytoscape software, and the network topology parameters were obtained by selecting 'network analyzer' software and analyzing the Degree, betweenness centrality (BC) and closeness centrality (BC) of PPI network nodes. The Degree, betweenness centrality (BC) and closeness centrality (CC) of the PPI network nodes were calculated. The targets with Degree values ≥ 10 were used as core targets.

2.6. GO and KEGG enrichment analysis

GO Function (Gene Ontology) is a standardized classification system for bioinformatics that aims to describe the molecular functions, cellular components and biological processes of genes and their products. The KEGG pathway (Kyoto Encyclopedia of Genes and Genomes) is a comprehensive bioinformatics database designed to study the functions and interactions of genes and gene products.

The GO and KEGG enrichment analyses were performed using the bioinformatics open-source software packages clusterProfiler,[15] DOSE,[16] and Pathview[17] et al. installed and running in R, and visualized via the microbiology platform (https://www.bioinformatics.com.cn/). The enrichment analysis was performed to annotate the functions of the six compounds in terms of Biological Process (BP), Cellular Component (CC) and Molecular Function (MF) for the treatment of CCP. The top ten GO entries of BP, CC and MF were screened according to P-value and plotted in a bar chart. The top ten KEGG pathways were selected according to enrichment scores and plotted in bubble diagrams.

3. RESULTS

3.1. Screening results for compounds, diseases and intersecting targets

The Swiss Target Prediction database was searched and 197 compound-related targets were obtained using 'P > 0' as the screening criteria. The results were obtained by searching the Swiss Target Prediction database. The GeneCards, OMIM and DisGeNET databases were searched and 10,767 targets were obtained by removing duplicates. Using Venny software to intersect the compound targets with the disease targets, 190 intersecting targets were obtained, which are the potential targets for the combination of six compounds for the treatment of CCP (Figure 1).

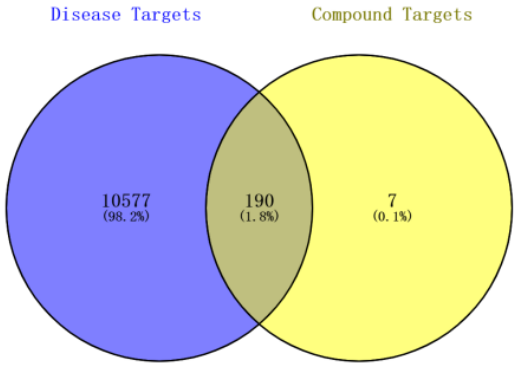

Figure 1: Venn diagram of compound targets and disease targets

3.2. "Compound-target-disease" network construction

The potential targets of the six compounds for the treatment of CCP were aggregated and the information was mapped into a "compound-target-disease" network using Cytoscape software. The network diagram has 192 nodes and 380 edges (Figure 2).

3.3. PPI network construction and network topology analysis

The topology of the PPI network was analyzed using Cytoscape software. The network diagram contained 120 nodes and 286 edges (Figure 3). The Degree values of the compounds were analyzed using the 'network analyzer' plug-in. The compounds were sorted by Degree value. The targets with Degree values >10 were

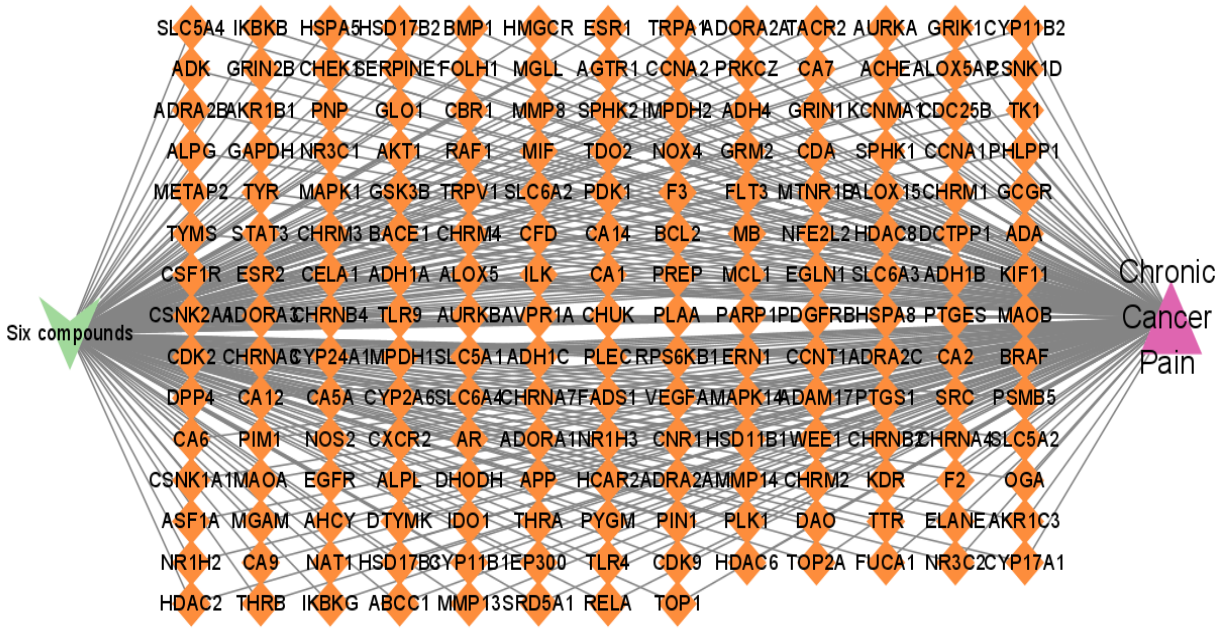

Figure 2: "Compound-target-disease" network diagram (green represents compounds; orange represents targets; purple represents diseases)

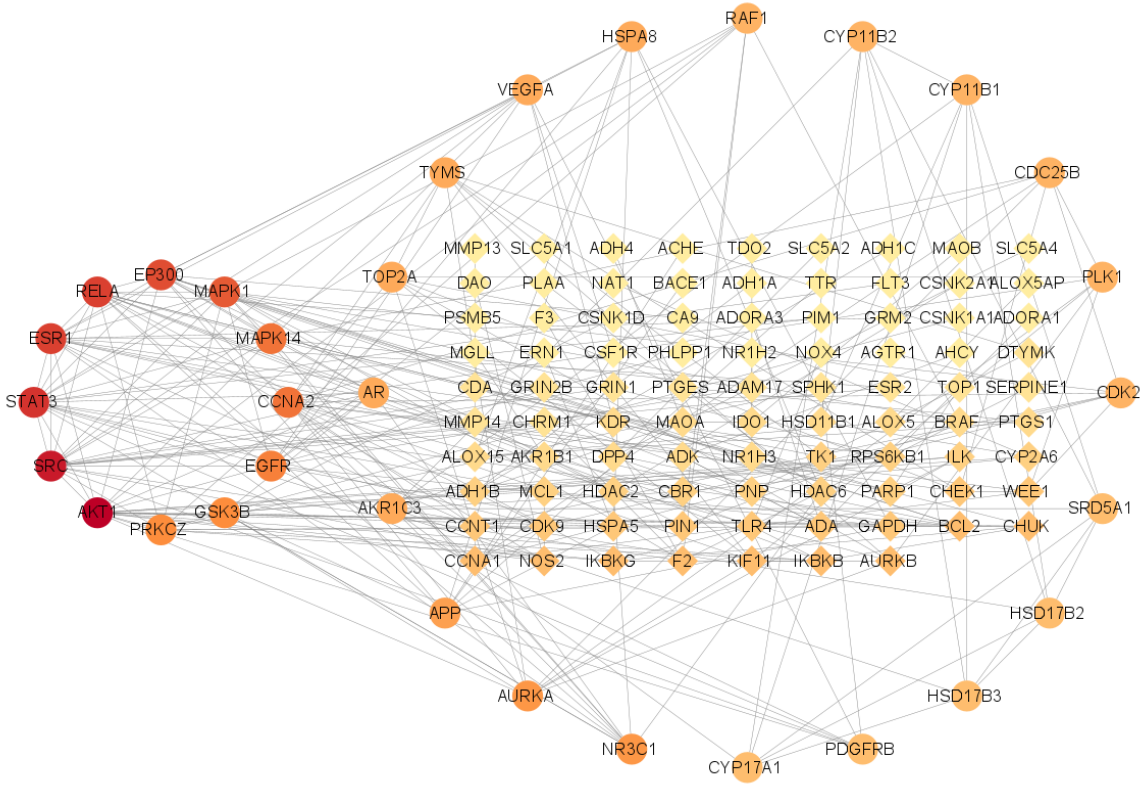

Figure 3: Topology analysis of the PPI network. (The left side of the diagram shows the core targets; darker dots represent larger Degree values)

Table 1: Core target information

Name	Degree	BC	CC
AKT1	22	0.225240726	0.284009547
SRC	20	0.130463108	0.272311213
STAT3	18	0.065868592	0.271689498
ESR1	17	0.161407052	0.286746988
RELA	17	0.092433891	0.260964912
EP300	16	0.130099483	0.28
MAPK1	15	0.072322464	0.268623025
MAPK14	13	0.046213676	0.268018018
CCNA2	13	0.047789723	0.23151751
EGFR	12	0.080902387	0.262693157
GSK3B	11	0.082529001	0.262693157
PRKCZ	11	0.017341531	0.243852459

elected as core targets and a table of core targets was created (Table 1). There were 12 core targets, namely AKT1, SRC, STAT3, ESR1, RELA, EP300, MAPK1, MAPK14, CCNA2, EGFR, GSK3B and PRKCZ. The highest Degree value among the core targets was AKT1.

3.4. GO and KEGG enrichment analysis

The results of GO enrichment analysis involved a total of 1950 statistically significant pathways ($P < 0.05$) (Figure 4), of which 1690 were statistically significant BP entries, mainly related to sensory perception of pain, glucose transmembrane transport, response to heat, sodium ion transport, etc.; there were 83 statistically significant CC entries, mainly related to

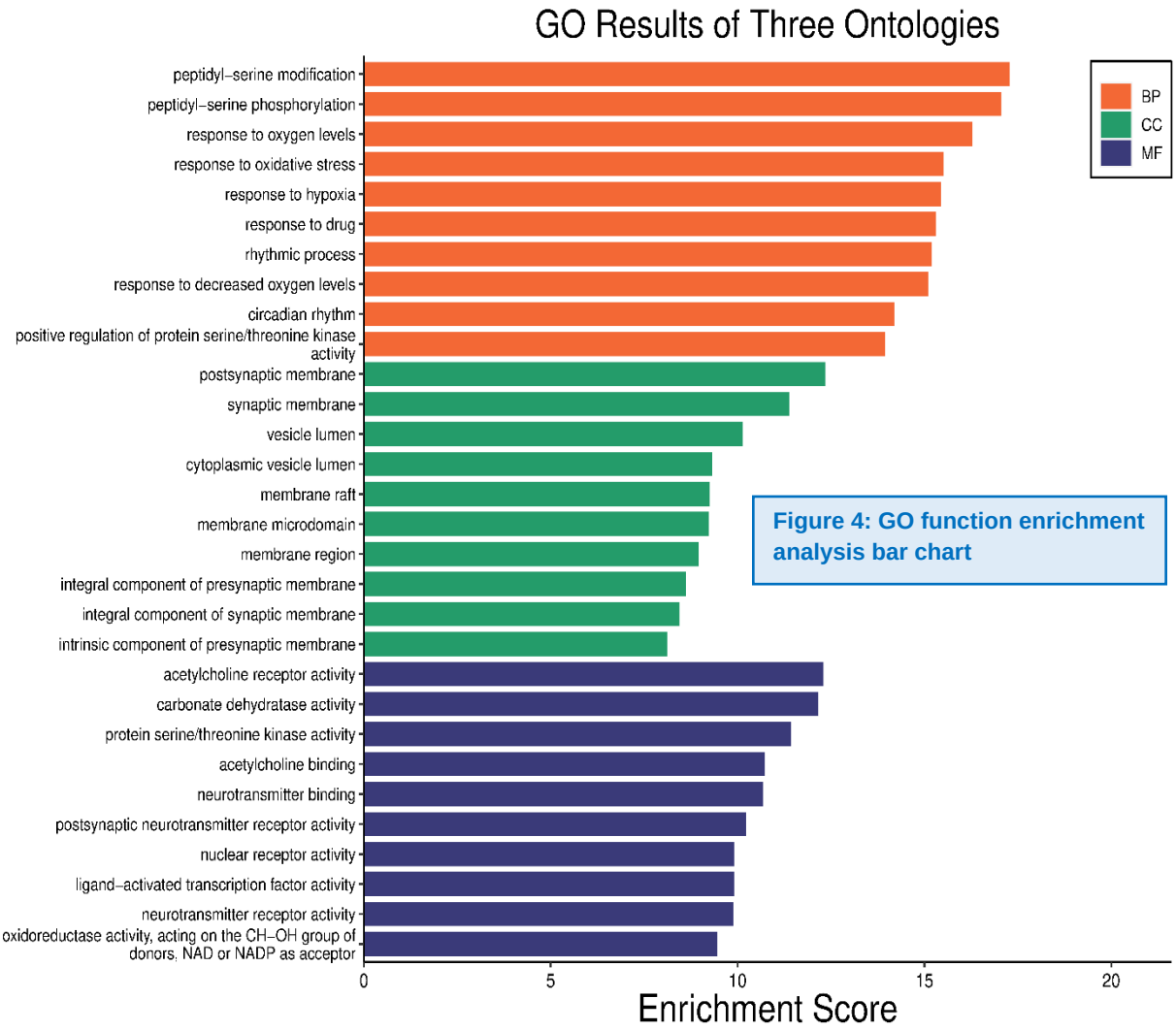

Figure 4: GO function enrichment analysis bar chart

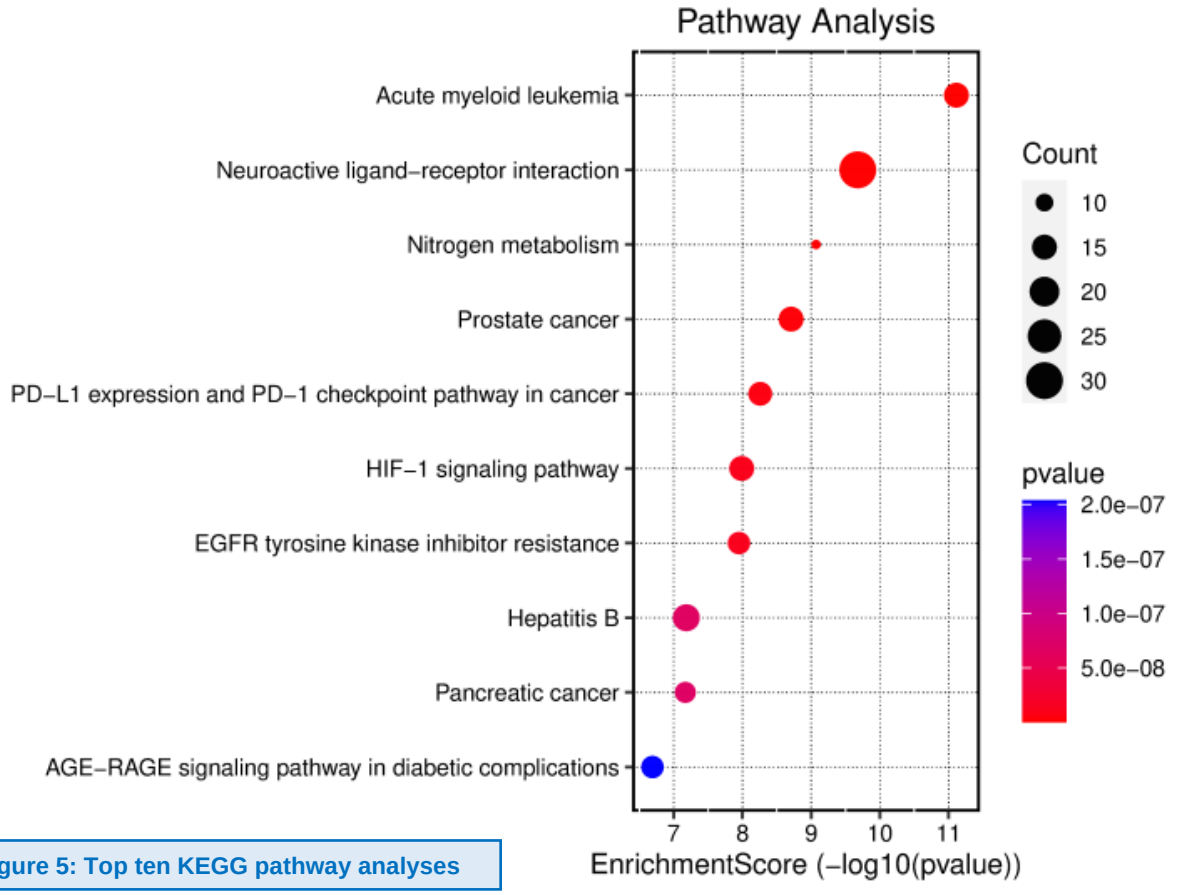

Figure 5: Top ten KEGG pathway analyses

CCP. The CC entries were mainly related to glucose transmembrane transport, response to heat, sodium ion transport, etc.; there were 83 statistically significant CC entries, mainly related to CCP. The CC entries were mainly related to plasma membrane raft, neuronal cell body membrane, stereocilium bundle, voltage-gated potassium channel complex, synaptic membrane, etc. There were 177 statistically significant MF entries, mainly related to calcium-release channel activity, acetylcholine receptor activity, carbonate dehydratase activity. The KEGG enrichment analysis yielded 134 statistically significant pathways, and the top ten KEGG enrichment analyses are shown in Figure 5. The top ten KEGG enrichment scores are shown in Table 2. In the KEGG pathway analysis, it was found that most of the pathways used by the six compounds to treat CCP were related to the nervous system and had direct therapeutic effects on a variety of cancers.

4. DISCUSSION

In this study, a network pharmacology approach was used to analyze 190 potential targets of six compounds for the treatment of CCP. The PPI analysis of the intersecting targets identified 12 core targets, namely AKT1, SRC, STAT3, ESR1, RELA, EP300, MAPK1, MAPK14, CCNA2, EGFR, GSK3B and PRKCZ.

AKT1 encodes one of the three members of the human AKT serine-threonine protein kinase family, which are often referred to as protein kinase B alpha, beta, and gamma. These highly similar AKT proteins all have an N-terminal pleckstrin homology domain, a serine/threonine-specific kinase domain and a C-terminal regulatory domain.[18] These proteins are phosphorylated by phosphoinositide 3-kinase (PI3K). AKT/PI3K forms a key component of many signaling pathways that involve the binding of membrane-bound ligands such as receptor tyrosine kinases, G-protein coupled receptors, and integrin-linked kinase.[19] These AKT proteins therefore regulate a wide variety of cellular functions including cell proliferation, survival, metabolism, and angiogenesis in both normal and malignant cells.[18] AKT proteins are recruited to the cell membrane by phosphatidyl inositol 3,4,5-trisphosphate (PIP3) after phosphorylation of phosphatidyl inositol 4,5-bisphosphate (PIP2) by PI3K.[20] Subsequent phosphorylation of both threonine residue 308 and serine residue 473 is required for full activation of the AKT1 protein encoded by this gene. Phosphorylation of

Table 2: Data table of the top ten KEGG enrichment analysis by enrichment score

ID	Description	GeneRatio	BgRatio	P-value	Count
hsa04080	Neuroactive ligand-receptor interaction	30/178	367/8223	2.09993E-10	30
hsa05010	Alzheimer disease	24/178	384/8223	2.42075E-06	24
hsa04151	PI3K-Akt signaling pathway	22/178	354/8223	7.24988E-06	22
hsa05022	Pathways of neurodegeneration - multiple diseases	21/178	476/8223	0.001411889	21
hsa05165	Human papillomavirus infection	19/178	331/8223	9.35399E-05	19
hsa05207	Chemical carcinogenesis - receptor activation	18/178	212/8223	6.67696E-07	18
hsa05161	Hepatitis B	17/178	162/8223	6.56341E-08	17
hsa05417	Lipid and atherosclerosis	17/178	215/8223	3.70347E-06	17
hsa04010	MAPK signaling pathway	17/178	294/8223	0.000203568	17
hsa04015	Rap1 signaling pathway	16/178	210/8223	1.16239E-05	16

additional residues also occurs, for example, in response to insulin growth factor-1 and epidermal growth factor. Protein phosphatases act as negative regulators of AKT proteins by dephosphorylating AKT or PIP3. The PI3K/AKT signaling pathway is crucial for tumor cell survival. Survival factors can suppress apoptosis in a transcription-independent manner by activating AKT1 which then phosphorylates and inactivates components of the apoptotic machinery.[21] AKT proteins also participate in the mammalian target of rapamycin (mTOR) signaling pathway which controls the assembly of the eukaryotic translation initiation factor 4F (eIF4E) complex and this pathway, in addition to responding to extracellular signals from growth factors and cytokines, is dysregulated in many cancers.[22] Mutations in this gene are associated with multiple types of cancer and excessive tissue growth including Proteus syndrome and Cowden syndrome 6, and breast, colorectal, and ovarian cancers.[20] Multiple alternatively spliced transcript variants have been found for this gene. SRC is highly similar to the v-Src gene of Rous sarcoma virus. This proto-oncogene may play a role in the regulation of embryonic development and cell growth. The protein encoded by this gene is a tyrosine-protein kinase, whose activity can be inhibited by phosphorylation by c-Src kinase.[23] Mutations in this gene could be involved in the malignant progression of colon cancer.[24] Two transcript variants encoding the same protein have been found for this gene. The protein encoded by STAT3 is a member of the STAT protein family. In response to cytokines and growth factors, STAT family members are phosphorylated by the receptor associated kinases, and then form homo- or heterodimers, that translocate to the cell nucleus, where they act as transcription activators.[25] This protein is activated through phosphorylation in response to various cytokines and growth factors including IFNs, EGF, IL5, IL6, HGF, LIF and BMP2.[26] This protein mediates the expression of a variety of genes in response to cell stimuli, and thus plays a key role in many cellular processes such as cell growth and apoptosis. The small GTPase Rac1 has been shown to bind and regulate the activity of this protein. PIAS3 protein is a specific inhibitor of this protein.[27] This gene also plays a role in regulating host response to viral and bacterial infections. Mutations in this gene are associated with infantile-onset multisystem autoimmune disease and hyper-immunoglobulin E syndrome. ESR1 encodes an estrogen receptor and ligand-activated transcription factor. The canonical protein contains an N-terminal ligand-independent transactivation domain, a central DNA binding domain, a hinge domain, and a C-terminal ligand-dependent transactivation domain.[28] The protein localizes to the nucleus where it may form either a homodimer or a heterodimer with estrogen receptor 2. The protein encoded by this gene regulates the transcription of many estrogen-inducible genes that play a role in growth, metabolism, sexual development, gestation, and other reproductive functions and is expressed in many non-reproductive tissues. The receptor encoded by this gene plays a key role in breast cancer, endometrial cancer, and osteoporosis. This gene is reported to have dozens of transcript variants due to the use of alternate promoters and alternative splicing; however, the full-length nature of many of these variants remain uncertain.[29] RELA is a protein coding gene. Diseases associated with RELA include mucocutaneous ulceration, chronic and Rela fusion-positive ependymoma. Among its related pathways are MyD88 dependent cascade initiated on endosome and bacterial infections in cystic fibrosis (CF) airways.[30] Gene Ontology (GO) annotations related to this gene include DNA-binding transcription factor activity and identical

protein binding.[31] EP300 is a protein coding gene. Diseases associated with EP300 include Rubinstein-Taybi syndrome 2 and Menke-Hennekam syndrome 2 (MKHK2). Among its related pathways are RNA polymerase I promoter opening and regulation of activated PAK-2p34 by proteasome mediated degradation.[32] Gene Ontology (GO) annotations related to this gene include chromatin binding and transcription coactivator activity.[33] MAPK1 is a protein coding gene. Diseases associated with MAPK1 include Noonan syndrome 13 and heart disease. Among its related pathways are prolactin signaling and MyD88 dependent cascade initiated on endosome.[34] Gene Ontology (GO) annotations related to this gene include transferase activity, transferring phosphorus-containing groups and protein tyrosine kinase activity.[35]

5. CONCLUSION

In this study, six compounds, bakuchiol, cinnamaldehyde, curcumin, eugenol, salicin and xanthoxylin, were selected as alternative drugs. A bio-informatics approach was used to predict the key targets and pathways of action of these six compounds for the treatment of chronic cancer pain. The study revealed that the therapeutic mechanism is a multi-target and multi-pathway interaction. The key targets of the six compounds for the treatment of chronic cancer pain were found to be AKT1, SRC, STAT3, ESR1, RELA, EP300, MAPK1, MAPK14, CCNA2, EGFR, GSK3B and PRKCZ. In this study, six compounds, namely bakuchiol, cinnamaldehyde, curcumin, eugenol, salicin and xanthoxylin, were proposed as potential new drugs, and laid the foundation for the next step of laboratory and clinical trials on the biological mechanism of these six compounds for the treatment of chronic cancer pain.

6. Data availability

The numerical data generated during the conduct of this study is available with the authors.

7. Conflict of interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

9. Authors' contribution

All authors took part in the concept and conduct of the study, data collection and statistical analysis and manuscript preparation. All authors have read the manuscript and approve it for publishing.

10. REFERENCES

1. Culp C, Kim HK, Abdi S. Ketamine Use for Cancer and Chronic Pain Management. Front Pharmacol. 2021 Feb 2;11:599721. [PubMed] DOI: 10.3389/fphar.2020.599721
2. Tran K, McCormack S. Ketamine for Chronic Non-Cancer Pain: A Review of Clinical Effectiveness, Cost-Effectiveness, and Guidelines. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2020 May 28. [PubMed]
3. Habibi BA, Kim C, Elsharkawy H. Persistent and Chronic Perioperative Pain After Cancer Surgery. Curr Oncol Rep. 2022 Feb;24(2):215-222. [PubMed] DOI: 10.1007/s11912-021-01152-5
4. Fink RM, Gallagher E. Cancer Pain Assessment and Measurement. Semin Oncol Nurs. 2019 Jun;35(3):229-234. [PubMed] DOI: 10.1016/j.soncn.2019.04.003
5. Yang J, Wahner-Roedler DL, Zhou X, Johnson LA, Do A, Pachman DR, et al. Acupuncture for palliative cancer pain management: systematic review. BMJ Support Palliat Care. 2021 Sep;11(3):264-270. [PubMed] DOI: 10.1136/bmjspcare-2020-002638
6. Magee D, Bachtold S, Brown M, Farquhar-Smith P. Cancer pain: where are we now? Pain Manag. 2019 Jan 1;9(1):63-79. [PubMed] DOI: 10.2217/pmt-2018-0031
7. Swarm RA, Paice JA, Anghelescu DL, Are M, Bruce JY, Buga S, et al. Adult Cancer Pain, Version 3.2019, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2019 Aug 1;17(8):977-1007. [PubMed] DOI: 10.6004/jnccn.2019.0038
8. Ru J, Li P, Wang J, Zhou W, Li B, Huang C, et al. TCMSP: a database of systems pharmacology for drug discovery from herbal medicines. J Cheminform. 2014 Apr 16;6:13. [PubMed] DOI: 10.1186/1758-2946-6-13
9. Kim S, Chen J, Cheng T, Gindulyte A, He J, He S, et al. PubChem in 2021: new data content and improved web interfaces. Nucleic Acids Res. 2021 Jan 8;49(D1):D1388-D1395. [PubMed] DOI: 10.1093/nar/gkaa971
10. Daina A, Michielin O, Zoete V. SwissTargetPrediction: updated data and new features for efficient prediction of protein targets of small molecules. Nucleic Acids Res. 2019 Jul 2;47(W1):W357-W364. [PubMed] DOI: 10.1093/nar/gkz382
11. Stelzer G, Rosen N, Plaschkes I, Zimmerman S, Twik M, Fishilevich S, et al. The GeneCards Suite: From Gene Data Mining to Disease Genome Sequence Analyses. Curr Protoc Bioinformatics. 2016 Jun 20;54:1.30.1-1.30.33. [PubMed] DOI: 10.1002/cpbi.5
12. Amberger JS, Bocchini CA, Schiettecatte F, Scott AF, Hamosh A. OMIM.org: Online Mendelian Inheritance in Man (OMIM®), an online catalog of human genes and genetic disorders. Nucleic Acids Res. 2015 Jan;43(Database issue):D789-98. [PubMed] DOI: 10.1093/nar/gku1205
13. Piñero J, Ramírez-Anguita JM, Saüch-Pitarch J, Ronzano F, Centeno E, Sanz F, et al. The DisGeNET knowledge platform for disease genomics: 2019 update. Nucleic Acids Res. 2020 Jan 8;48(D1):D845-D855. [PubMed] DOI: 10.1093/nar/gkz1021
14. Szklarczyk D, Gable AL, Lyon D, Junge A, Wyder S, Huerta-Cepas J, et al. STRING v11: protein-protein association networks with increased coverage, supporting functional discovery in genome-wide experimental datasets. Nucleic Acids Res. 2019 Jan 8;47(D1):D607-D613. [PubMed] DOI: 10.1093/nar/gky1131
15. Yu G, Wang LG, Han Y, He QY. clusterProfiler: an R package for comparing biological themes among gene clusters. OMICS.

2012 May;16(5):284-7. [PubMed] DOI: 10.1089/omi.2011.0118

16. Yu G, Wang LG, Yan GR, He QY. DOSE: an R/Bioconductor package for disease ontology semantic and enrichment analysis. Bioinformatics. 2015 Feb 15;31(4):608-9. [PubMed] DOI: 10.1093/bioinformatics/btu684
17. Luo W, Brouwer C. Pathview: an R/Biocondutor package for pathway-based data integration and visualization. Bioinformatics. 2013;29(14):1830-1831. [PubMed] DOI: 10.1093/bioinformatics/btt285
18. Chen C, Marcus A, Li W, Hu Y, Calzada JP, Grossniklaus U, et al. The Arabidopsis ATK1 gene is required for spindle morphogenesis in male meiosis. Development. 2002 May;129(10):2401-9. [PubMed] DOI: 10.1242/dev.129.10.2401
19. Marcus AI, Ambrose JC, Blickley L, Hancock WO, Cyr RJ. Arabidopsis thaliana protein, ATK1, is a minus-end directed kinesin that exhibits non-processive movement. Cell Motil Cytoskeleton. 2002 Jul;52(3):144-50. [PubMed] DOI: 10.1002/cm.10045
20. Dockx J, Quaedvlieg N, Keultjes G, Kock P, Weisbeek P, Smeekens S. The homeobox gene ATK1 of Arabidopsis thaliana is expressed in the shoot apex of the seedling and in flowers and inflorescence stems of mature plants. Plant Mol Biol. 1995 Jul;28(4):723-37. [PubMed] DOI: 10.1007/BF00021196
21. Hotta T, Lee YJ, Higaki T, Hashimoto T, Liu B. Two Kinesin-14A Motors Oligomerize to Drive Poleward Microtubule Convergence for Acentrosomal Spindle Morphogenesis in Arabidopsis thaliana. Front Cell Dev Biol. 2022 Jul 22;10:949345. [PubMed] DOI: 10.3389/fcell.2022.949345
22. Lu S, Chen L, Tang L. Upregulation of AKT1 and downregulation of AKT3 caused by dysregulation of microRNAs contributes to pathogenesis of hemangioma by promoting proliferation of endothelial cells. J Cell Physiol. 2019 Nov;234(11):21342-21351. [PubMed] DOI: 10.1002/jcp.28741
23. Roskoski R Jr. Src protein-tyrosine kinase structure and regulation. Biochem Biophys Res Commun. 2004 Nov 26;324(4):1155-64. [PubMed] DOI: 10.1016/j.bbrc.2004.09.171
24. De Kock L, Freson K. The (Patho)Biology of SRC Kinase in Platelets and Megakaryocytes. Medicina (Kaunas). 2020 Nov 24;56(12):633. [PubMed] DOI: 10.3390/medicina56120633
25. Hillmer EJ, Zhang H, Li HS, Watowich SS. STAT3 signaling in immunity. Cytokine Growth Factor Rev. 2016 Oct;31:1-15. [PubMed] DOI: 10.1016/j.cytogfr.2016.05.001
26. Zou S, Tong Q, Liu B, Huang W, Tian Y, Fu X. Targeting STAT3 in Cancer Immunotherapy. Mol Cancer. 2020 Sep 24;19(1):145. [PubMed] DOI: 10.1186/s12943-020-01258-7
27. Guanizo AC, Fernando CD, Garama DJ, Gough DJ. STAT3: a multifaceted oncoprotein. Growth Factors. 2018 Apr;36(1-2):1-14. [PubMed] DOI: 10.1080/08977194.2018.1473393
28. Dustin D, Gu G, Fuqua SAW. ESR1 mutations in breast cancer. Cancer. 2019 Nov 1;125(21):3714-3728. [PubMed] DOI: 10.1002/cncr.32345
29. Brett JO, Spring LM, Bardia A, Wander SA. ESR1 mutation as an emerging clinical biomarker in metastatic hormone receptor-positive breast cancer. Breast Cancer Res. 2021 Aug 15;23(1):85. [PubMed] DOI: 10.1186/s13058-021-01462-3
30. Nakazato A, Mochizuki M, Shibuya-Takahashi R, Fujimori H, Fujii K, Saijoh S, et al. RELA is required for CD271 expression and stem-like characteristics in hypopharyngeal cancer. Sci Rep. 2022 Oct 22;12(1):17751. [PubMed] DOI: 10.1038/s41598-022-22736-6
31. Korc M. RelA: a tale of a stitch in time. J Clin Invest. 2016 Aug 1;126(8):2799-801. [PubMed] DOI: 10.1172/JCI89156
32. Durbin AD, Wang T, Wimalasena VK, Zimmerman MW, Li D, Dharia NV, et al. EP300 Selectively Controls the Enhancer Landscape of MYCN-Amplified Neuroblastoma. Cancer Discov. 2022 Mar 1;12(3):730-751. [PubMed] DOI: 10.1158/2159-8290.CD-21-0385
33. Attar N, Kurdistani SK. Exploitation of EP300 and CREBBP Lysine Acetyltransferases by Cancer. Cold Spring Harb Perspect Med. 2017 Mar 1;7(3):a026534. [PubMed] DOI: 10.1101/cshperspect.a026534
34. Deng R, Zhang HL, Huang JH, Cai RZ, Wang Y, Chen YH, et al. MAPK1/3 kinase-dependent ULK1 degradation attenuates mitophagy and promotes breast cancer bone metastasis. Autophagy. 2021 Oct;17(10):3011-3029. [PubMed] DOI: 10.1080/15548627.2020.1850609
35. Hirota Y, Yamashita S, Kurihara Y, Jin X, Aihara M, Saigusa T, et al. Mitophagy is primarily due to alternative autophagy and requires the MAPK1 and MAPK14 signaling pathways. Autophagy. 2015;11(2):332-43. [PubMed] DOI: 10.1080/15548627.2015.1023047

