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Systematic analysis of *Ocimum sanctum* revealed key genes and pathways related to various molecular processes and pathways

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Abstract

The plant kingdom is a significant source of phytoconstituents with therapeutic potential, many of which may one day lead to the creation of novel chemical entities for a variety of pathological conditions. Alternatives to antibiotics that boost growth performance, gut health, and immunity without having any unfavourable side effects are regarded as phytoconstituents. *Ocimum* species (holy basil) have a high index in a variety of pharmacological activities. The aim of this study was to assess the phytoconstituents of *Ocimum sanctum* from literature and find their interacting genes and pathways involving various molecular processes, diseases etc., in this study binding DB database was used to find interacting components and Cytoscape for visualization. A total of 50 high confidence phytochemicals are considered for this study. Binding DB database has found a total of 116 interacting genes and their involvements in different pathways. Notably, EGFR gene for EGFR tyrosine kinase inhibitor resistance, Endocrine resistance. CA1 gene for metabolic pathways and Nitrogen metabolism etc., this approach will be helpful in designing herbal therapy and to support scientifically for the promotion of traditional herbs.

Keywords: Network analysis, *Ocimum sanctum*, pathways, genes, herbal therapy, phytoconstituents

Introduction

The plant kingdom has long been a prolific source of phytoconstituents with immense therapeutic potential, offering a vast reservoir of natural compounds that can serve as the basis for developing innovative chemical entities to combat various pathological conditions [1]. Recently, there has been a growing interest in exploring alternatives to conventional antibiotics that not only enhance growth performance but also promote gut health and immunity in livestock and other animal species [2]. These alternatives, known as phytoconstituents, are derived from various plant sources and have garnered attention for their potential to improve animal health without causing adverse side effects [3]. The concerns about antibiotic resistance development and the ban on antibiotics have fueled the exploration of alternatives with similar antimicrobial and growth-promoting effects. Such feed additives are expected to avoid inducing bacterial resistance and causing any potential side effects in animals. Some feed additives, such as probiotics [4], prebiotics [5], organic acids, enzymes and phytoconstituents [6] are used as substitutes for antibiotic growth promoters. Phytoconstituents have been reported to enhance animal performance, improve feed conversion ratios, and enhance carcass meat safety and quality [6]. In addition to their performance-enhancing properties, phytoconstituents also exhibit antioxidant characteristics, mainly associated with essential oils (EOs) and their components.

Among the multitude of plant species containing pharmacologically active compounds, members of the *Ocimum* genus, commonly referred to as holy basil, have emerged as particularly promising candidates. These plants are renowned for their rich phytochemical content and have exhibited a wide range of pharmacological activities [6]. *Ocimum sanctum*, also known as *Ocimum tenuiflorum* and commonly referred to as Basil or Tulsi, is often attributed with medicinal properties and is frequently used in the treatment of various diseases. It possesses several properties, including anti-cancer, antidiabetic, analgesic, anti-fertility, antimicrobial, antispasmodic, and adaptogenic effects [7].

However, to fully harness their therapeutic potential, it is essential to comprehensively explore and understand the underlying molecular mechanisms, gene interactions, and pathways associated with the phytoconstituents found in *Ocimum sanctum*.

The current study aims to bridge this critical knowledge gap by utilizing network analysis techniques to unveil the complex network of interactions between the phytochemicals of *Ocimum sanctum* and their associated genes and pathways. By systematically investigating the molecular processes and diseases implicated in these interactions, we aim to shed light on the therapeutic potential of this plant and provide valuable insights for the development of herbal therapies.

In this endeavor, we have utilized the Binding DB database (<https://www.bindingdb.org/rwd/bind/index.jsp>) to identify high-confidence phytochemicals present in *Ocimum sanctum* and their corresponding interacting genes. Through this comprehensive analysis, we have identified key genes and pathways intricately linked to various molecular processes, diseases, and pathways, shedding new light on the potential applications of *Ocimum sanctum* in therapeutic contexts. The insights gained from this study not only contribute to a deeper understanding of the pharmacological properties of *Ocimum sanctum* but also pave the way for the rational design of herbal therapies. Additionally, our findings provide scientific support for the utilization and promotion of traditional herbs in modern healthcare systems, bridging the gap between traditional knowledge and contemporary research.

Materials and Methods

In our research, we embarked on a comprehensive journey to identify and compile the phytochemical constituents of *Ocimum sanctum*, also known as Basil or Tulsi, a plant renowned for its medicinal properties. To achieve this, we harnessed valuable resources and databases to gather and organize essential data for subsequent molecular analysis. Our primary source for acquiring information on the phytochemicals present in *Ocimum sanctum* was Dr. Duke's Phytochemical and Ethnobotanical Databases, which are maintained by the U.S. Department of Agriculture (USDA). These databases are reliable repositories of botanical and chemical information, making them invaluable in our quest to explore the plant's chemical composition and therapeutic potential.

To facilitate further molecular analysis and ensure consistent representation of chemical structures, we utilized the Simplified Molecular Input Line Entry System (SMILES) notation. SMILES notation is a standardized format used to encode chemical structures, enabling efficient processing and analysis of chemical information. This step was crucial in ensuring that our data could be readily employed in subsequent computational and molecular modeling endeavors. In our pursuit of understanding the potential interactions between the identified phytochemicals from *Ocimum sanctum* and biological molecules, we turned to the Binding DB database. This resource provided us with insights into the binding targets of these phytochemicals. To maintain a high level of confidence in our findings, we applied a stringent threshold of 0.8, ensuring that only strong binding interactions

were considered. This step allowed us to unravel the intricate molecular relationships between the compounds from *Ocimum sanctum* and their respective binding partners, shedding light on potential therapeutic mechanisms. To gain deeper insights into the biological implications of the identified binding targets, we harnessed the power of panther, a web tool designed to elucidate molecular and biological processes. By inputting the target genes obtained from the Binding DB database into panther, we aimed to uncover the specific molecular and biological processes associated with these interactions. This step was instrumental in broadening our understanding of how the phytochemicals from *Ocimum sanctum* might impact various biological pathways and processes.

Results

In our quest to unravel the intricate molecular interactions and pathways associated with phytochemicals from various herbs, we embarked on an integrated analysis that has yielded valuable insights. Our focus was on 50 specific phytochemicals found in *Ocimum Sanctum*, sourced from Dr. Duke's Phytochemical and Ethnobotanical Databases, a reliable resource maintained by the U.S. Department of Agriculture (USDA) (Table 1). One noteworthy discovery from our analysis was the interaction of the phytochemical 4-hydroxybenzoic acid with several genes, namely CA1, CA12, CA2, CA7, DRD1, and EGFR, highlighting the multifaceted nature of these compounds. These interactions shed light on potential therapeutic pathways and molecular mechanisms. Notably, some phytochemicals stood out due to their extensive network of interactions with genes. Circisilineol, Linoleic Acid, and Ursolic Acid emerged as key players, each interacting with a substantial number of genes, specifically 17, 17, and 20 genes, respectively (Table 2). This suggests their potential significance in modulating various biological processes.

Furthermore, our analysis extended to identifying enriched KEGG pathways associated with specific genes. For instance, Carbonic Anhydrase 1 (CA1) was found to be linked to pathways related to nitrogen metabolism and metabolic processes, providing insights into its potential role in these vital biological functions. On the other hand, the epidermal growth factor receptor (EGFR) genes were associated with an extensive array of pathways, ranging from those involved in tyrosine kinase inhibitor resistance to pathways linked to PD-L1 expression and the PD-1 checkpoint pathway in cancer. This extensive network of pathways suggests the importance of EGFR in diverse cellular processes and potential implications in cancer biology.

Interestingly, the target of L-Ascorbic Acid i.e., CASP1 (cysteine-aspartic acid protease (caspase)1) gene was found to be involved immune related functions like in Neutrophil extracellular trap formation, Pathogenic *Escherichia coli* infection, Shigellosis, *Salmonella* infection, Pertussis, Legionellosis, *Yersinia* infection, Influenza A, Coronavirus disease - COVID-19. CYP1A1 gene was involved in various metabolic pathways as it plays a role in steroid hormone biosynthesis, tryptophan metabolism, retinol metabolism and metabolism of xenobiotics etc.

Table 1: Phytochemicals and their PubChem ID (PCID) of *Ocimum sanctum* downloaded for analysis

PCID	Compound name	PCID	Compound name
26049	3-Carene	162350	Isovitexin
126	4-hydroxybenzaldehyde	5280450	Linoleic Acid
135	4-hydroxybenzoic acid	5280934	Linolenic Acid;
5281417	Esculin	5280445	Luteolin
10398656	Alpha-Cadinol	13607752	Luteolin-7-O-Glucuronide
54670067	L-Ascorbic Acid;	637520	Methyl Cinnamate
521569	Bergamotene	7127	METHYLEUGENOL
441005	Delta-Cadinene	8815	Estragole
10364	Carvacrol	44258315	Molludistin
5281515	Beta-caryophyllene	5281553	(E)-Beta-Ocimene
1794427	Chlorogenic Acid	445639	Oleic Acid
162464	Cirsilineol	5281792	Rosmarinic Acid
188323	Cirsimaritin	222284	Beta-Sitosterol
638011	Citral	5281	Stearic Acid
8815	Estragole	11230	4-Carvomenthenol
2758	Eucalyptol	64945	Ursolic Acid
3314	Eugenol	8468	Vanillic Acid
370	Gallic Acid	3084407	Vicenin 2
13250	Ethyl Gallate	442664	Vicenin 2
7428	Methyl Gallate	5280441	Apigenin 6,8-Di-Glucopyranoside
5280637	Cynaroside	6654	ALPHA-PINENE
44257986	Isorientin 4'-O-Glucoside 2''-O-P-Hydroxybenzoagte	14896	BETA-PINENE
11726019	Isothymonin	173183	CAMPESTEROL
630253	Isothymusin	87098	DE 2
222284	BETA-SITOSTEROL	5280489	Beta-Carotene

Table 2: Phytochemical of *Ocimum sanctum* and their interacting target gene

Phytochemical	Target gene	Phytochemical	Target gene	Phytochemical	Target gene	Phytochemical	Target gene
4-hydroxybenzoic acid	CA1	Cirsilineol	gyrA	Linoleic Acid	FABP5	Ursolic Acid	CTSD
4-hydroxybenzoic acid	CA12	Cirsilineol	IP6K2	Linoleic Acid	FABP4	Ursolic Acid	CD81
4-hydroxybenzoic acid	CA2	Cirsilineol	MKNK2	Linoleic Acid	FABP1	Ursolic Acid	CES1
4-hydroxybenzoic acid	CA7	Cirsilineol	KIT	Linoleic Acid	FFAR1	Ursolic Acid	CDC25B
4-hydroxybenzoic acid	DRD1	Cirsilineol	Oprm1	Linoleic Acid	Slc22a6	Ursolic Acid	ELANE
4-hydroxybenzoic acid	EGFR	Cirsilineol	NOX4	Linoleic Acid	FABP3	Ursolic Acid	PNLIP
Esculin	CA9	Cirsilineol	NROB1	Linoleic Acid	NR1I2	Ursolic Acid	PTGS1
Alpha-Cadinol	ACHE	Cirsilineol	Alox5	Linoleic Acid	PPARA	Ursolic Acid	PTPRC
Alpha-Cadinol	LSS	Cirsilineol	FLT3	Linoleic Acid	PTPN7	Ursolic Acid	F3
Alpha-Cadinol	Mgl1	Cirsilineol	LCK	Linoleic Acid	SLCO1B3	Ursolic Acid	RELA
L-Ascorbic Acid;	CASP1	Eugenol	fabI	Linoleic Acid	Q9Y6L6	Ursolic Acid	PTPN2
BETA-CARYOPHYLLENE	CNR2	Gallic Acid	FUT7	Linoleic Acid	PPARD	Ursolic Acid	fabG
CHLOROGENIC ACID	AKR1B10	Gallic Acid	CA14	Linoleic Acid	LTB4R2	Ursolic Acid	CSNK2A3
CHLOROGENIC ACID	APP	Gallic Acid	GALNT2	Linoleic Acid	FFAR4	Ursolic Acid	Top1
CHLOROGENIC ACID	HDAC1	ETHYL GALLATE	SERPINE1	Linoleic Acid	FABP2	Ursolic Acid	Gsk3b
CHLOROGENIC ACID	pol	ETHYL GALLATE	Sqle	Linoleic Acid	AKR1C3	Ursolic Acid	MMP12
CHLOROGENIC ACID	PTPN1	ETHYL GALLATE	PLAU	Linoleic Acid	LOX1.1	Ursolic Acid	MKNK1
Cirsilineol	Akr1b1	Cynaroside	IL2	Luteolin-7-O-Glucuronide	ALPI	Ursolic Acid	XDH
Cirsilineol	MAOA	Cynaroside	TNF	Methyl Cinnamate	TNKS2	Ursolic Acid	TTR
Cirsilineol	MAOB	Isothymonin	ABCG2	Rosmarinic Acid	SNCA	Ursolic Acid	PIM1
Cirsilineol	ABCB1	Isothymonin	CA4	Rosmarinic Acid	MMP1	Ursolic Acid	PTGS2
Cirsilineol	CYP1A2	Isothymonin	CCNT1	Rosmarinic Acid	MMP9	Ursolic Acid	PSMB1
Cirsilineol	CYP1B1	Isothymonin	PSIP1	Stearic Acid	GPR84	Beta-Carotene	SLCO1B1
Cirsilineol	DPP4	Isovitexin	GAA	Ursolic Acid	HSD11B1		

Molecular function, Biological processes and Cellular components associated with phytochemicals

The phytochemicals associated with genes were enriched for different molecular functions, biological processes, cellular components, and protein classes. Molecular functions include ATP-dependent activity, binding, catalytic activity, and more, detailing the roles of proteins in processes like energy

utilization, molecular interactions, and enzymatic reactions (Figure 1A). Biological processes encompass a wide array of activities occurring within living organisms, ranging from cellular processes and growth to immune system responses, development, and reproduction. These categories provide insights into the fundamental functions and behaviors of biological systems (Figure 1B).

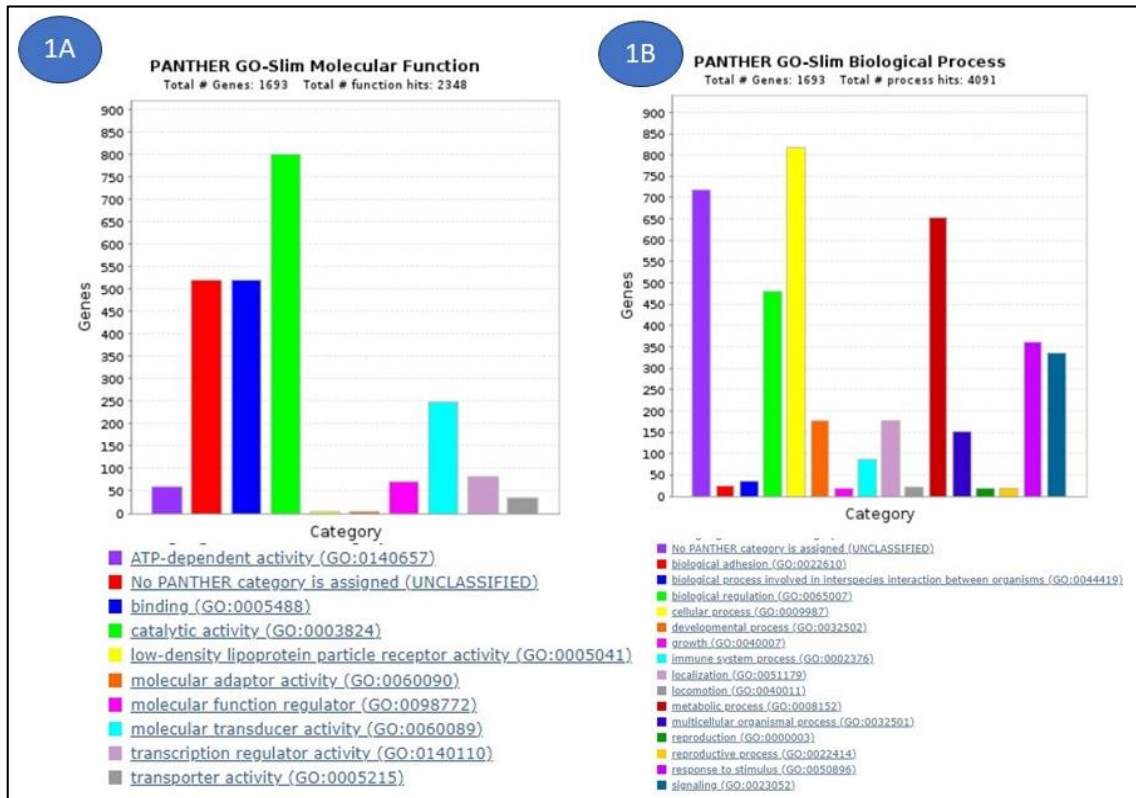


Fig 1: Panther molecular functions and biological process of *Ocimum sanctum* phytochemicals.

Cellular components highlight the structural entities within a cell, such as organelles and protein-containing complexes. These components are crucial for understanding cellular organization and function (Figure 2A). Protein classes offer a classification system based on specific roles and functions of proteins, including DNA and RNA metabolism, cell adhesion, chromatin regulation, immunity, and more. These categories

help elucidate the diversity of proteins and their contributions to various cellular processes (Figure 2B). Together, these classification systems provide a comprehensive framework for studying and understanding the roles and functions of proteins in biology, enabling researchers to delve deeper into the molecular intricacies of living organisms.

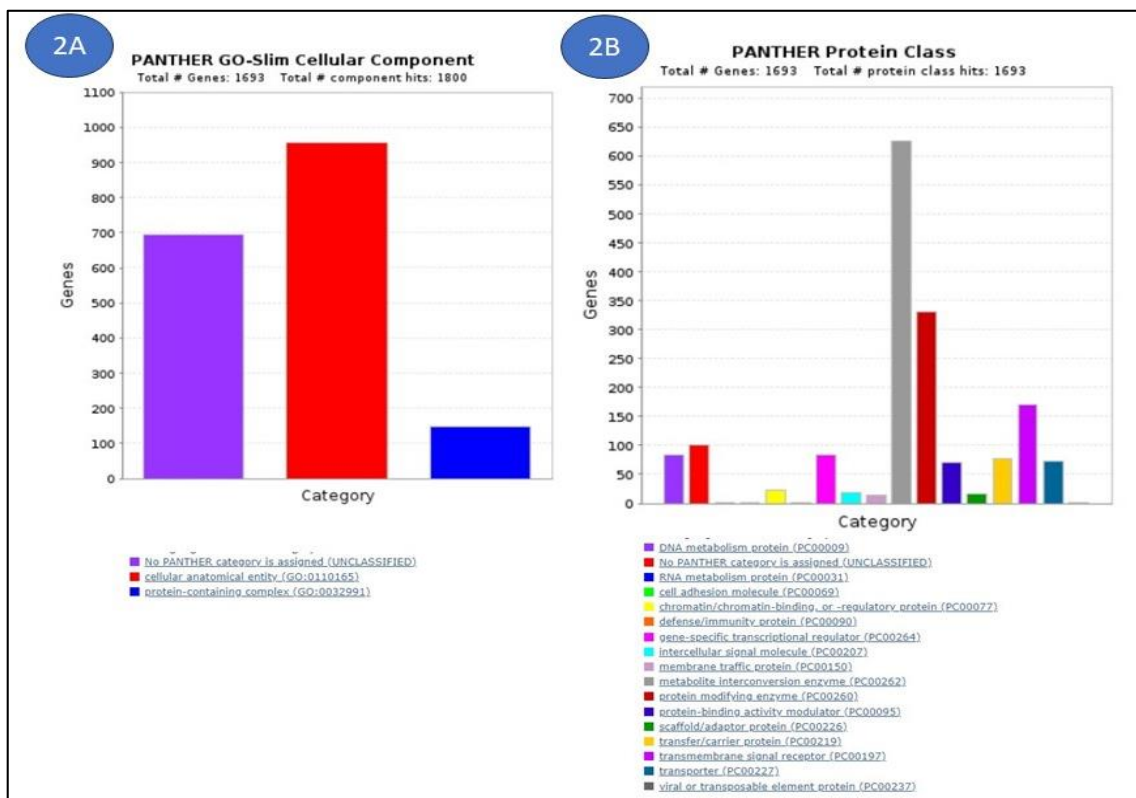


Fig 2: Panther cellular components and protein class of *Ocimum sanctum* phytochemicals

Discussion

The present study delves into the intricate network of molecular interactions and pathways associated with phytochemicals obtained from various herbs. Through a systematic analysis that includes data compilation, molecular target identification, and pathway mapping, we have gained valuable insights into the potential therapeutic actions of these compounds. This discussion section highlights the significance of our findings and their implications for herbal therapy and modern healthcare. The initial step of our investigation involved the compilation of phytochemical data from the literature, resulting in a diverse set of compounds. Subsequently, we employed a rigorous computational approach to identify the binding targets (genes) of these compounds, leveraging the Binding DB database. This step revealed a multitude of genes associated with the compounds, providing a foundation for understanding the molecular interactions underlying the therapeutic potential of these phytoconstituents. Our analysis uncovered a range of genes linked to specific KEGG pathways, shedding light on the molecular functions and biological processes through which these compounds may exert their effects.

Molecular functions

ATP-dependent activity (GO: 0140657) encompasses various cellular processes that require ATP as an energy source, such as ATP-dependent DNA helicase or ATP-dependent RNA polymerase. It involves activities that utilize ATP for various biochemical reactions [8]. Binding function (GO: 0005488) encompasses a wide range of molecular interactions, including protein-protein, protein-DNA, and protein-ligand interactions. This molecular function category includes proteins that bind to other molecules, facilitating essential biological processes [9]. Proteins with catalytic activity (GO: 0003824) are enzymes that accelerate chemical reactions. They play a critical role in catalyzing a wide array of biochemical reactions within cells, driving metabolic pathways and cellular functions [10]. Low-density lipoprotein particle receptor activity (GO: 0005041) function relates to proteins that function as receptors for low-density lipoprotein (LDL) particles. These receptors are involved in the uptake of LDL cholesterol from the bloodstream and are crucial for regulating cholesterol levels in cells [10]. Molecular adaptor activity (GO: 0060090) serves as intermediaries in signaling pathways by facilitating the interaction between different molecules. They play a role in transmitting signals and coordinating cellular responses [11].

Biological processes

These molecular functions represent diverse roles that proteins play in cells, encompassing essential activities such as catalysis, signaling, and regulation of cellular processes. Biological Adhesion (GO:0022610) process refers to the ability of cells or organisms to bind to each other or to surfaces. It plays a fundamental role in various biological functions, including cell-to-cell interactions, wound healing, and the attachment of microorganisms to host tissues [12]. Biological Process Involved in Interspecies Interaction Between Organisms (GO:0044419) process encompasses interactions between different species of organisms. It includes various ecological and symbiotic relationships, such as mutualism, predation, and parasitism, where organisms interact and influence each other's survival and reproduction [13]. Biological Regulation (GO:0065007) refers to the control

and coordination of various cellular and physiological activities to maintain homeostasis. It involves processes that adjust or modulate cellular functions in response to internal and external cues, ensuring that biological systems operate efficiently [14]. Cellular Processes (GO: 0009987) are the fundamental activities that occur within a cell to maintain its structure and function. These processes include cell division, metabolism, signal transduction, and protein synthesis, among others [15]. Developmental Process (GO: 0032502) encompass the series of events that lead to the growth, differentiation, and maturation of an organism from a single cell (e.g., fertilized egg) to a complex multicellular organism. This process includes embryonic development and tissue formation [16]. Response to Stimulus (GO: 0050896) involves an organism's ability to detect and react to external or internal stimuli. Responses can be physiological, behavioral, or molecular, and they help organisms adapt to changing environments [17].

Cellular components

Cellular Anatomical Entity (GO: 0110165) refers to any distinct part or structure within a cell that can be identified based on its anatomical features. Cellular anatomical entities include organelles (such as the nucleus, mitochondria, and endoplasmic reticulum), cellular compartments, and subcellular structures. These entities play vital roles in the organization and function of cells [18]. Protein-Containing Complex (GO: 0032991) is a molecular structure composed of multiple proteins that interact with each other to perform a specific biological function. These complexes can have various roles within cells, such as enzymatic activity, DNA replication, or signal transduction. Examples include the ribosome (involved in protein synthesis), the proteasome (involved in protein degradation), and the spliceosome (involved in RNA processing). Protein-containing complexes are essential for many cellular processes and functions [19].

Protein class

These terms describe various classes of proteins based on their functions and roles in biological processes. DNA Metabolism Protein (PC00009) category are involved in processes related to DNA metabolism, including DNA replication, repair, and recombination. They play essential roles in maintaining the integrity and stability of the genome [20]. RNA Metabolism Protein (PC00031) participate in RNA-related processes, such as RNA transcription, splicing, processing, and degradation. They are critical for gene expression and RNA regulation [21]. Cell Adhesion Molecules (PC00069) are proteins that mediate cell-cell and cell-extracellular matrix interactions. They play crucial roles in tissue development, immune responses, and maintaining cell cohesion [22]. Defense/Immunity Proteins (PC00090) are part of the immune system and are responsible for defending the organism against pathogens and foreign invaders. They include antibodies, immune receptors, and immune response modulators [22]. Gene-Specific Transcriptional Regulators (PC00264) are transcription factors that specifically regulate the expression of target genes. They control the initiation of transcription and play a central role in gene regulation [23].

Conclusion

These results provide a comprehensive view of the interactions between specific phytochemicals and their associated genes, shedding light on potential molecular

processes and pathways involved in the therapeutic actions of these compounds. One of the key strengths of this study is its ability to bridge the gap between traditional herbal knowledge and contemporary scientific research. The identified genes and their linked pathways offer valuable insights into the mechanisms through which these phytoconstituents may exert their beneficial effects. Further studies and molecular docking analyses will help validate and expand upon these findings, paving the way for the development of herbal therapies and the promotion of traditional herbs in modern healthcare systems.

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