

**BIOACTIVE MARKERS OF IBA HONEY AND THEIR PREDICTED INTERACTIONS
WITH MOLECULAR TARGETS OF PARKINSON'S DISEASE USING NETWORK
PHARMACOLOGY**

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Article Received: 05 Sept. 2026

Article Revised: 25 Sept. 2026

Article Published: 01 October 2026



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Department of Physiology, School of Basic Medical Sciences, Babcock University, Ilisan-Remo, Ogun State, Nigeria. DOI: <https://doi.org/10.5281/zenodo.23339052>

How to cite this Article: Ayodeji David Adeoye*¹, Bayo Olufunso Adeoye², Moromoke Ajisope Fadunsin¹, Okikiola Olamide Olanrewaju¹, Lola Adeola Adelakin³ (2026). Bioactive Markers Of Iba Honey And Their Predicted Interactions With Molecular Targets Of Parkinson's Disease Using Network Pharmacology. World Journal of Advance Healthcare Research, 10(10), 478–495.



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ABSTRACT

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by motor and non-motor symptoms due to the loss of dopaminergic neurons. While current treatments can help manage symptoms, they are limited in their effectiveness and have side effects. This study investigates the potential of honey as an adjuvant therapy for PD by examining its bioactive compounds and their roles in modulating molecular pathways associated with PD. The phytochemical, vitamin, amino acid, and fatty acid composition of a sweet honey sample were analyzed using standard analytical techniques. Network pharmacology-based analyses were then conducted to identify potential target genes and signaling pathways that could be influenced by the honey phytoconstituents. The results revealed that the honey sample contained a diverse array of bioactive compounds, including phenolic compounds, unsaturated fatty acids, vitamins, and amino acids. Network analysis identified 336 consensus genes that were common between the honey components and PD-associated genes. These genes were significantly enriched in pathways related to synaptic signaling, oxidative stress response, and neuronal structure and function - all of which are implicated in PD pathogenesis. The study provides evidence that the bioactive compounds in honey have the potential to exert neuroprotective and disease-modifying effects in PD by targeting key molecular pathways. These findings support the further investigation of honey as a complementary and integrative approach to PD management. However, rigorous experimental validation is needed to fully elucidate the mechanisms of action and determine the optimal dosing and formulations for clinical use.

KEYWORDS: Network pharmacology, neuroprotection, Parkinson's disease, sweet honey.

INTRODUCTION

Parkinson's disease (PD) is a progressive neurodegenerative disease that affects more than 10 million people worldwide (Jagaran & Singh, 2021). It is characterized by motor symptoms such as tremor, stiffness, bradykinesia, and postural instability, as well as non-motor symptoms including sleep disturbances, depression, cognitive impairment, and confusion (Jankovic & Lang, 2021). The motor symptoms of PD are due to the progressive loss of dopamine neurons in

the substantia nigra of the brain, leading to early dopamine depletion (Blesa *et al.*, 2022). The exact cause of PD remains unclear, but genetic and environmental factors are believed to contribute to neurodegeneration in PD. Although there is no cure for PD, medications such as levodopa and dopamine agonists help relieve symptoms by increasing dopamine levels in the brain (Armstrong & Okun, 2020). Additionally, treatments such as deep brain stimulation can help control advanced motor symptoms. However, long-term use of these

therapies is associated with side effects and does not slow disease progression.

This highlights the need for adjuvant therapies that can complement standard PD treatment. In recent years, there has been increasing interest in the potential anti-inflammatory and neuroprotective properties of natural compounds (Rahman *et al.*, 2021). Honey is one of the compounds that has demonstrated antioxidant, anti-inflammatory, and neuroprotective effects in preclinical studies (El-Seedi *et al.*, 2022). Honey is rich in phenolic compounds such as flavonoids, phenolic acids, enzymes, vitamins and minerals (Ranneh *et al.*, 2021). Compounds such as chrysin, galangin, quercetin and kaempferol found in honey have been shown to have antioxidant and anti-inflammatory activity. Through these mechanisms, honey may provide protective benefits to dopamine neurons in PD. Several small clinical studies have suggested the therapeutic potential of honey in PD. In a randomized controlled trial, patients who took 1 g/kg of honey daily for 8 weeks showed significant improvements in motor symptoms, balance, and antioxidant status compared to the control group. Control. An open study found that consuming 70 g of honey daily for 30 days reduced oxidative stress and improved overall antioxidant status in PD patients. Although promising, these studies have limitations, including small sample sizes, lack of placebo control, and short follow-up periods (Iftikhar *et al.*, 2022). Well-designed randomized controlled trials with larger samples and longer interventions are needed to support these preliminary results.

Future research also aims to identify the compounds and mechanisms of action that help honey improve Parkinson's disease treatment outcomes. Efforts are underway to standardize honey composition and determine optimal dosing regimens for clinical use. Parkinson's patients often seek complementary and alternative medicine to improve their quality of life. Honey is an attractive option due to its nutrient content, low cost, and favorable safety profile. Side effects are rare with moderate honey consumption, the main risk being high blood sugar in diabetics. Understanding the impact of honey on the progression and symptoms of PD may guide integrative therapeutic approaches to this chronic and debilitating disease.

MATERIALS AND METHODS

MATERIALS

Honey Clection

The honey was harvested from the branch of community lifestyle improvement project (CLIP) farm (R N: 2930642) located at IBA (7.969051 North and 4.703880 East). The honey sample used (Sample Code: IBA) was procured from Osun State, Southwestern Nigeria in July 2023. The honey was stored in an air-tight sample bottle, and kept in a dark, cool, dry place until when required for analysis.

Chemical Reagents

All reagents used are of analytical grade and were purchased from Sigma-Aldrich, USA, or British Drug House (BDH): Poole, England.

Phytochemical Screening

Based on standard procedures, quantitative and qualitative analyses were carried out on the sweet honey sample.

METHODS

Chemical Profiling of the Honey Variety Using GC-MS

Qualitative and quantitative phytochemical analysis were carried out based on standard methods (Balamurugan, 2019).

Phytochemical analysis was carried out via GC-MS analysis of the honey sample. This was performed using an Agilent 5977B GC/MSD system coupled with Agilent 8860 auto-sampler, a Gas Chromatograph interfaced to a Mass Spectrometer (GC-MS) equipped with an Elite-5MS (5% diphenyl/95% dimethyl polysiloxane) fused a capillary column (30 × 0.25µm ID × 0.25 µm df). For GC-MS detection, an electron ionization system was operated in electron impact mode with an ionization energy of 70 eV. Helium gas (99.999%) was used as a carrier gas at a constant flow rate of 1 ml/min, and an injection volume of 1µl was employed (a split ratio of 10:1).

The injector temperature was maintained at 300 °C, the ion-source temperature was 250 °C, and the oven temperature was programmed from 100 °C (isothermal for 0.5 min); with an increase of 20 °C/min to 280°C (2.5 min); Mass spectra were taken at 70 eV; a scanning interval of 0.5 s and fragments from 45 to 450 Da. The solvent delay was 0 to 3 min.

Vitamins Composition Using HPLC

The analysis of water-soluble vitamins was carried out at the NIMR in Yaba, Lagos using High Performance Liquid Chromatography (HPLC). The HPLC experiments used an advanced Agilent 1260 Infinity II LC System. A binary pump, vacuum degasser, temperature-controlled column container, autosampler, and a diode array detector (DAD) with a 1-litre flow cell were all part of the HPLC. The wavelength of the detector was calibrated to 280 nm for the evaluation of vitamins. A 1260 Infinity II Multicolumn Thermostat Poroshell 120 EC C18 (150 mm 4.6 mm i.d., 4.0 µm) was used in the separation process. At a flow rate of 0.700 mL/min, the mobile phase of 10mM KH₂PO₄ and methanol in a 70:30% ratio facilitated successful separations. Samples were introduced in 20.00 µl and analysed at a column temperature of 30°C.

Amino Acids composition Using HPLC

The amino acid analysis was also carried out by the Nigeria Institute of Medical Research (NIMR): Yaba,

using HPLC. The HPLC studies were carried out using an Agilent 1260 Infinity II LC System, a sophisticated system that included a binary pump, vacuum degasser, temperature-regulated column container, auto-sampler, and a diode array detector (DAD) with a 1-litre flow cell. For the amino acid analysis, the detector's wavelength was set to 200 nm. A 1260 Infinity II Multicolumn Thermostat Poroshell 120 EC C18 (150 mm 4.6 mm i.d., 4.0 µm) was used for the separation process. With a flow rate of 0.600 mL/min, the mobile phase of 0.1% Formic Acid in a mixture of Acetonitrile and Methanol (10:45:45) aided the separations. The samples were introduced in 20.00 µL volumes and analysed at a column temperature of 40°C.

Fatty acid profiling Using GC-MS

Fatty acid was analysed using GCMS. Samples were analysed using an Agilent 8860 Gas chromatograph equipped with a 5977B Mass Spectrometry Detector (MSD): fitted with an HP5 capillary column coated with 5% Phenyl Methyl Siloxane (30m length x 0.32mm diameter x 0.25µm film thickness) (J&W).

1µL of the samples were injected using an Agilent 8860 Automatic Liquid Sampler (ALS) and in splitless mode, injection temperature of 250 °C. The inlet pressure was set at 10.296psi and a total flow of 45.2mL/min. Purge flow to the split vent was set at 40 mL/min at 0.5 min. Helium was used as a carrier gas of 99.9% with a constant column flow of 1mL/minute.

The GC oven temperature was initially programmed at 80 °C (2.0 min) and then ramped at 30°C/min to 320 °C (5min). The MSD temperature was set at 300 °C with Hydrogen: Air flow at 20mL/min: 30mL/min.

Network Pharmacology-based Analysis

Target Identification

The bioactive compounds in IBA Unbranded honey were screened on Pubchem (<https://pubchem.ncbi.nlm.nih.gov/>) and Super-PRED (https://prediction.charite.de/subpages/target_prediction.php) for their canonical SMILES and then the canonical SMILES were entered into the Swisstarget database (<http://www.swisstargetprediction.ch/>) to identify the potential protein and receptor targets and also the Uniprot IDs (<https://www.uniprot.org/>). The gene symbols and protein targets of Parkinson's Disease were screened on Genecards (<https://www.genecards.org/>). The genes, protein molecules and receptors relationship between Parkinson's Disease and IBA honey was illustrated using a Venn diagram on Bioinformatics and Evolutionary Genomics database (<https://bioinformatics.psb.ugent.be/webtools/Venn/>).

Determination of Consensus Targets

A database of human genome was used to plot a venn diagram showing the relationship between between Parkinson's disease and Nigerian SWEET HONEY (<https://bioinformatics.psb.ugent.be/webtools/Venn/>).

Protein-Protein Interactions (PPI) Analysis

The PPI between the target molecules of SH and Parkinson's Disease was done using SwissTarget and STRING database 247 items (human) - STRING interaction network (string-db.org). The consensus genes (247 items) between SH and Parkinson's Disease was used to conduct PPI analysis on STRING database. The confidence level for networking was set to 0.700.

Network Construction

The consensus genes from the intersection between Parkinson's Disease and IBA honey were entered into String database (<https://string-db.org/>) to construct the Protein-protein interaction network. The ShinyGO 0.80 database was used to conduct gene ontology and pathway enrichment analyses on the consensus genes between Parkinson's Disease and IBA.

Gene Ontology and KEGG pathway analyses

The ShinyGO 0.741 database (<http://bioinformatics.sdstate.edu/go74/>) was used to conduct gene ontology and pathway enrichment analyses on the consensus genes between honey and Parkinson's Disease. A KEGG pathway.

CHEMICAL PROFILING OF SWEET HONEY VARIETY USING GC-MS

The chemical profiling of sweet honey variety revealed a diverse array of phytochemical compounds present in the honey sample. Notably, tridecanoic acid, octadecanoic acid, methyl stearate, and heptadecanoic acid were among the identified compounds, along with others such as thymol, 4-tert-butylphenol, and tetrasiloxane. These findings provide valuable insights into the chemical composition of the honey variety, which is further detailed in Table 4.1.

Table 1: Chemical profiling on sweet honey Variety.

Peak Number	Library ID	Retention Time	Area
4	Tridecanoic acid, methyl ester	7.836	2.89
5	Octadecanoic acid, 5,9,13,17-methyl ester	7.859	4.24
7	Methyl Stearate	8.368	10.39
9	Heptadecanoic acid, 14-methyl-, methyl ester	8.471	2.24
11	2,4-Cyclohexadien-1-one, 3,5-bis(1,1-dimethylethyl) -4-hydroxy	9.433	1.64
12	N-Methyl-1-adamantaneacetamide	9.490	1.82
13	Thymol, TMS derivative	9.587	1.91
14	1,4-Bis(trimethylsilyl)benzene	9.730	2.62
15	4-tert-butylphenol, TMS derivative	9.816	6.41
19	Tris(tert-butyl)dimethylsilyloxy)arsane	10.377	2,23
20	1,2-Bis(trimethylsilyl)benzene	10.485	1.47
26	2,4,6-Cycloheptatrien-1-one, 3,5-bis-trimethylsilyl-	13.633	1.34
27	Tetrasiloxane, decamethyl-	14.211	2.84
28	4-tert-Amylphenol, TMS derivative	14.331	1.33

VITAMINS COMPOSITION USING HPLC

The vitamin composition of the SH sample was determined quantitatively. Vitamin A, B12 and C was

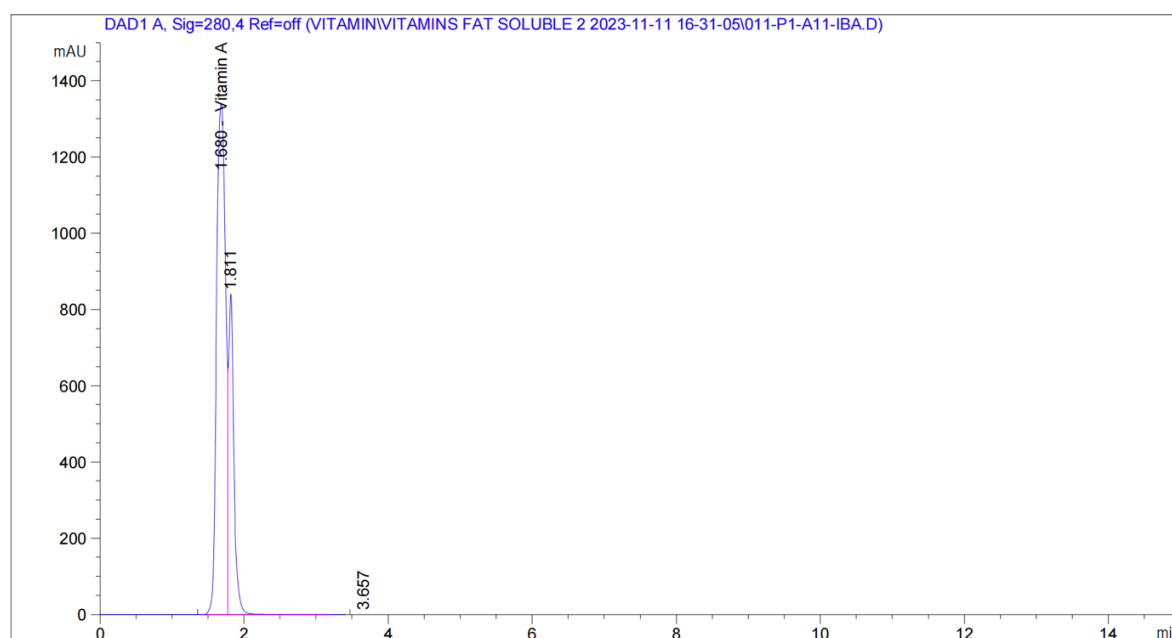
determined and the values are shown in table 4.3. Vitamin D, E, B2 and B9 was not detected and no peaks were observed for the fat soluble vitamin.

Table 4.2: Vitamins Composition of Honey Sample.

S/N	VITAMINS	AMOUNT UG/ML	Retention time(min)
1	Vitamin A	275.09983	1.680
2	Vitamin D	0.00000	2.764
3	Vitamin E	0.00000	7.305
4	Vitamin B2	0.00000	7.506
5	Vitamin B9	0.00000	4.050
6	Vitamin B12	20.42457	1.968
7	Vitamin C	3.71467	1.960

The vitamin composition of the SH sample was determined quantitatively using the Agilent 8860 GC-MSD (5977B). . Vitamin A, B12 and C was determined,

and the values are shown in table 4.2. Vitamin D, E, B2 and B9 was not detected and no peaks were observed for the fat soluble vitamin

**Figure 1: Chromatogram of Fat-Soluble Vitamins Composition of Honey Sample.**

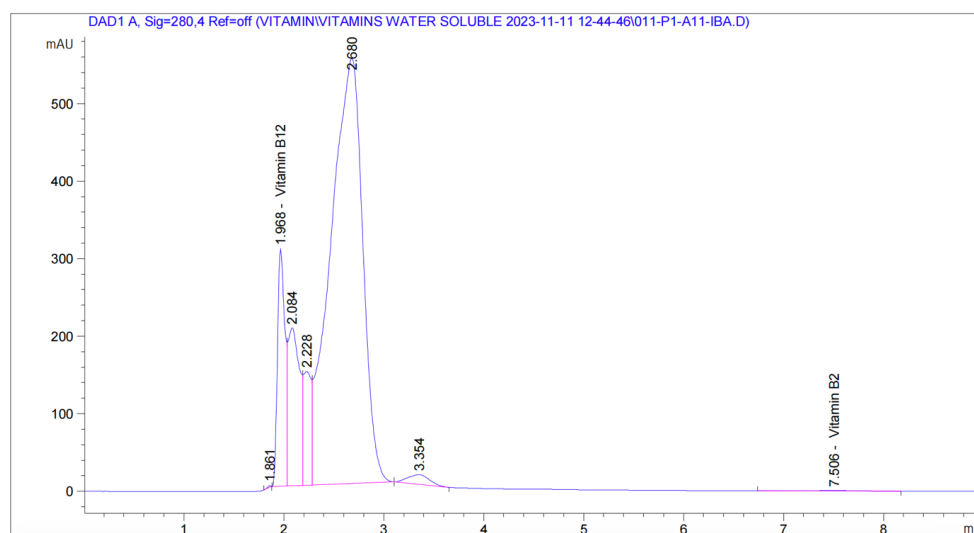


Figure 2: Chromatogram of Water-Soluble Vitamins Composition of Honey Sample.

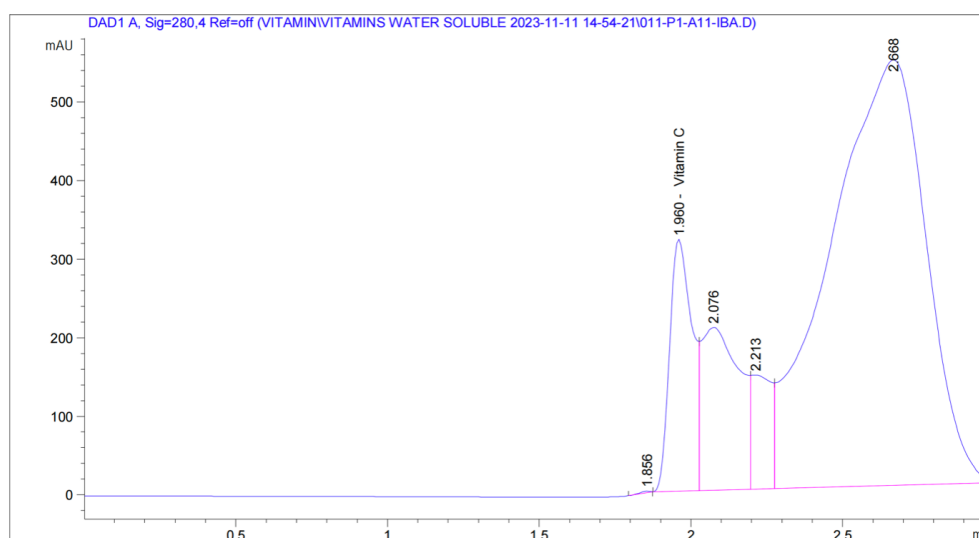


Figure 3: Chromatogram of Vitamin C Composition of Honey Sample.

AMINO ACID COMPOSITION OF HONEY SAMPLE USING HPLC

The result of the amino acid composition of IBA SWEET HONEY is as depicted in table 4.3 and figure 6 distinctively. According to table 4.4 and figure 6, the most abundant amino acid in IBA SH is Cystine (287.92234); followed by leucine and Glycine. The values for some amino acids including Arginine,

Aspartic Acid, lysine, Leucine, serine, threonine, Tyrosine, Histidine, Isoleucine, methionine, Phenylalanine and Proline was not detected but their peaks were observed (Adeoye, 2022).

The table below shows the amino acid content of IBA unbranded honey along with their retention time. The amino acid content was analysed using HPLC.

Table 3: Amino acid composition of Honey Sample.

S/N	Amino Acids	Value(ug/L)	Retention Time(Min)
1	Arginine	0.00000	1.329
2	Arginine	0.00000	1.799
3	Aspartic Acid	0.00000	2.122
4	Cystine	287.92234	2.558
5	Glutamine Acid	7.52994e-2	2.863
6	Leucine	10.93032	5.607
7	Lysine	0.00000	7.343
8	Serine	0.00000	8.889
9	Threonine	0.00000	10.280
10	Tyrosine	0.00000	12.109

11	Valine	2.44517e-1	12.465
12	Histidine	0.00000	13.874
13	Isoleucine	0.00000	15.395
14	Methionine	0.00000	15.501
15	Phenylalanine	0.00000	21.048
16	Proline	0.00000	21.237
17	Glycine	4.47299	23.336

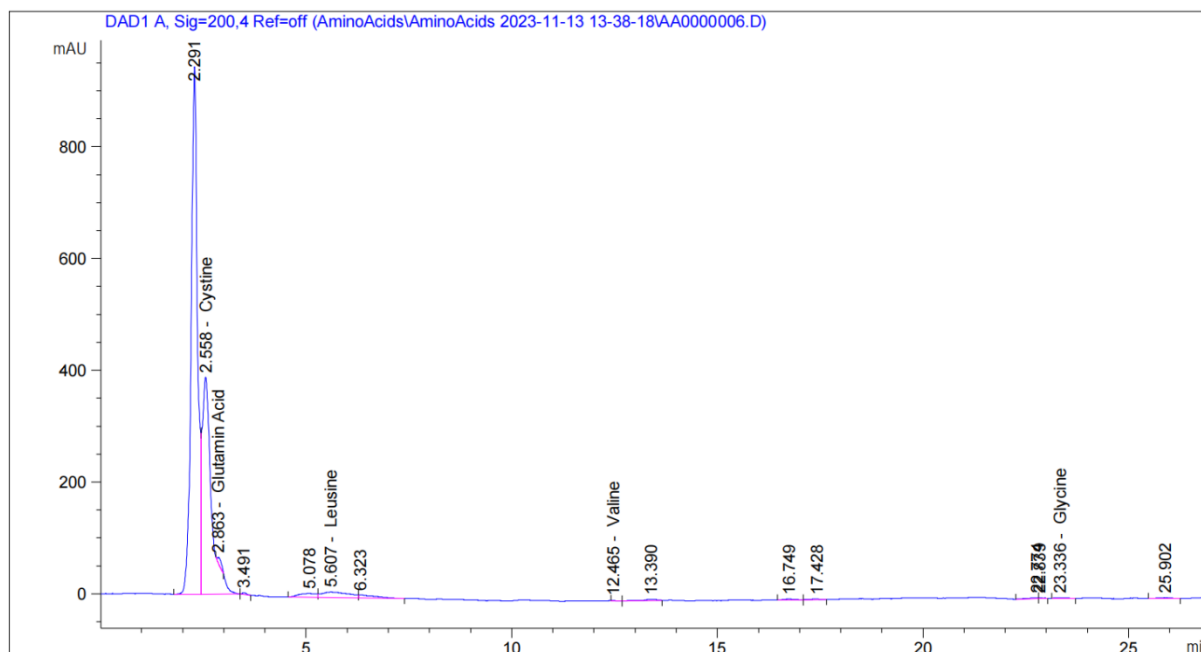


Figure 4: Chromatograph Of Amino Acid Composition of Honey Sample.

FATTY ACID METHYL ESTER (FAMES) COMPOSITION USING GC-MS

As shown in table 4., the most abundant fatty acid in the SWEET HONEY is Methyl myristoleate. This is followed by Methyl tetradecanoate, 4,7,10,13,16,19-docosa, 9-Hexadecanoic acid, methyl ester etc. Also, Undecanoic acid, methyl ester, gamma-linolenic acid,

methyl ester,15-tetracosanoic acid, methyl ester and Pentadecanoic acid, methyl ester was not detected.).

Table 4.4 below shows 28 fatty acid compounds found in IBA unbranded honey using the Gas Chromatography-Mass Spectrometry (GCMS) detector. It also shows their corresponding concentration and their retention time.

Table 4: Fatty acid methyl ester (FAMES) composition of Honey Sample.

peak number	FAMES	Concentration(Mg/L)	Retention Time(Min)
1	Octanoic acid	0.14	4.008
2	Capric acid methyl ester	0.07	5.204
3	Undecanoic acid, methyl ester	0.00	5.685
4	Dodecanoic acid, methyl ester	0.08	6.125
5	Tridecanoic acid, methyl ester	0.21	6.520
6	Methyl myristoleate	0.50	6.863
7	Methyl tetradecanoate	0.36	6.921
8	Cis-10-pentadecenoic a	0.18	7.241
9	Pentadecanoic acid, methyl ester	0.00	7.264
10	9-Hexadecanoic acid, methyl ester	0.27	7.573
11	Hexadecenoic acid, methyl ester	0.21	7.836
12	Cis-10-heptadecenoic acid	0.04	7.882
13	Heptadecanoic acid, methyl ester	0.07	7.945
14	.gamma-linolenic acid, methyl ester	0.00	8.174
15	Oleic acid, methyl ester	0.19	8.134
16	Methyl stearate	0.20	8.351
17	Arachidonic acid	0.18	8.712
18	5,8,11,14,17-Eicosapentaenoic acid	0.11	8.740

19	Cis-11,14-Eicosadienoic	0.27	8.763
20	Cis-11-Eicosenoic acid	0.26	8.803
21	Eicosanoic acid, methyl	0.09	8.855
22	Heneicosanoic acid, methyl	0.12	9.147
23	4,7,10,13,16,19-docosa	0.28	9.261
24	13-Docosenoic acid, methyl ester	0.17	9.370
25	Docosanoic acid, methyl ester	0.08	9.427
26	Tricosanoic acid, methyl ester	0.16	9.696
27	15-Tetracosenoic acid, methyl ester	0.00	9.879
28	Tetracosanoic acid, methyl ester	0.04	9.953

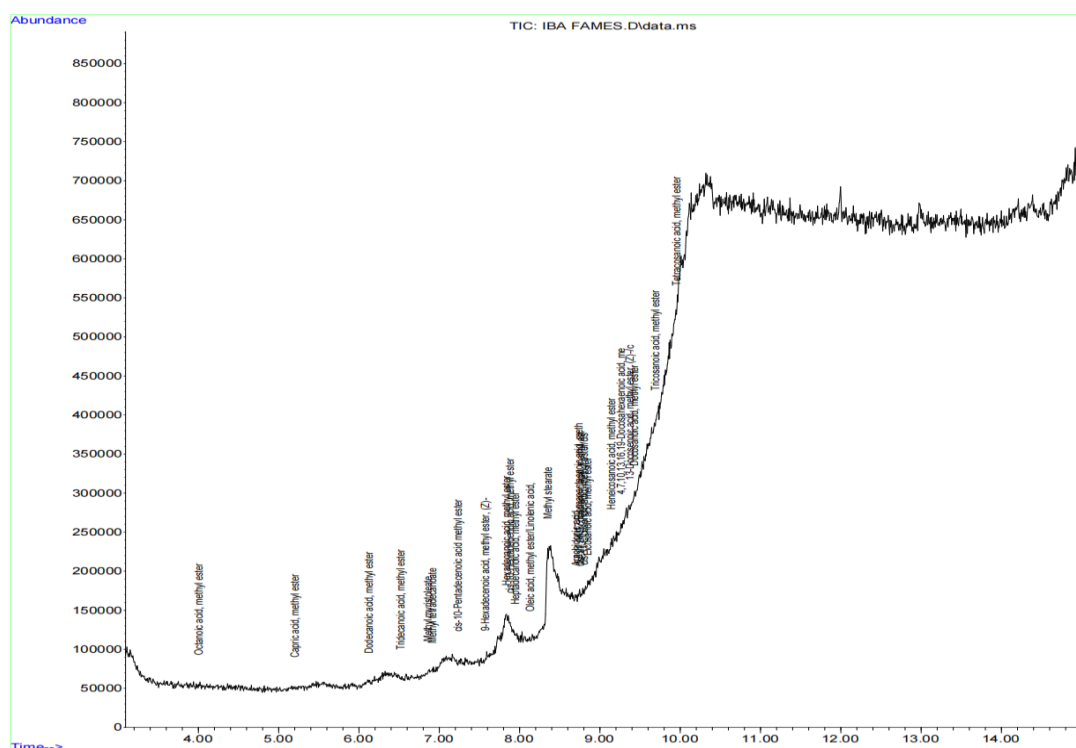


Figure 5: Chromatogram of Fatty Acid Profile of Honey Sample.

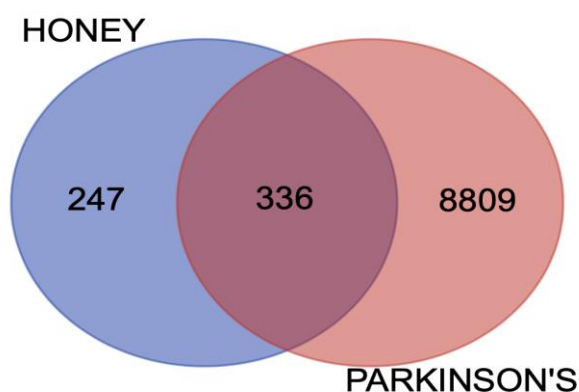


Figure 6: Venn diagram representing common target genes for Parkinson's and honey.

NETWORK PHARMACOLOGY RESULT

A total of Forty (40) compounds (phytochemicals, vitamins, amino acids, and fats) were identified using GC-MSD analysis then further subjected to network pharmacology-based analysis. Some target genes linked to the selected constituents were identified by using STRING DB 336 items (human) - STRING interaction

network (string-db.org). The results obtained included a total of 336 potential target genes of which 8809 disease target genes were retrieved using Gene Cards. A Venn diagram was plotted using the Bioinformatics Venn Diagram Tool (<https://bioinformatics.psb.ugent.be/webtools/Venn/>) and out of the 8809 disease target genes of Parkinson's Disease, 336 consensus

genes were discovered to interact with the disease via specific pathways. The results showed that the components selected from the SH sample had high binding activity with target proteins and could be used as potential target genes of GC-MSD in the treatment of Parkinson's Disease by interacting with 336 consensus genes (Mir et al., 2023).

Figure 6 shows a Venn diagram representing common target genes for compound prescription and disease. The size denotes the number of target genes, the red circle symbolizes the target genes of Parkinson's Disease, the blue circle represents the target genes of the quantitative compounds in GC-MSD analysis, and its coincident part depicts the common target genes, signaling pathway via which the BH sample regulates Parkinson's Disease.

Disease target screening

In the current study, 8809 targets related to Parkinson's Disease were retrieved from Gene Cards database. Among these, some were also potential targets of pharmacodynamic components of SH. 247 target genes were predicted from SH using Swiss Target Prediction and Super Pred databases. The interactions between the genes was further analysed.

Determination of Consensus Targets

The Venn diagram that shows the relations between genes, protein molecules and receptors and also the intersection (consensus genes) between Parkinson's Disease and sweet honey was constructed on Bioinformatics and Evolutionary Genomics database. A total of 336 consensus genes as shown in the red circle in Figure 6 were identified to interact with Parkinson's Disease and regulate its various signaling pathways.

PROTEIN-PROTEIN INTERACTION OF CONSENSUS GENES

Figure 7 represents the common target genes PPI diagram, indicating that 238 nodes and 2527 edges were in the PPI. The frequency of occurrence of the top 30 most common genes including CCR1, MMP3, CRHR1, MMP2, CES1, PLA2, and other target genes exhibited a high frequency protein interaction, serving as the node protein of the whole network. The diagram indicates that the selected compounds of the SH sample had a high binding activity with these target proteins and could be used as potential target genes of GC-MSD in the treatment of Parkinson's Disease (Mir et al., 2023). AT 0.700 confidence interval.

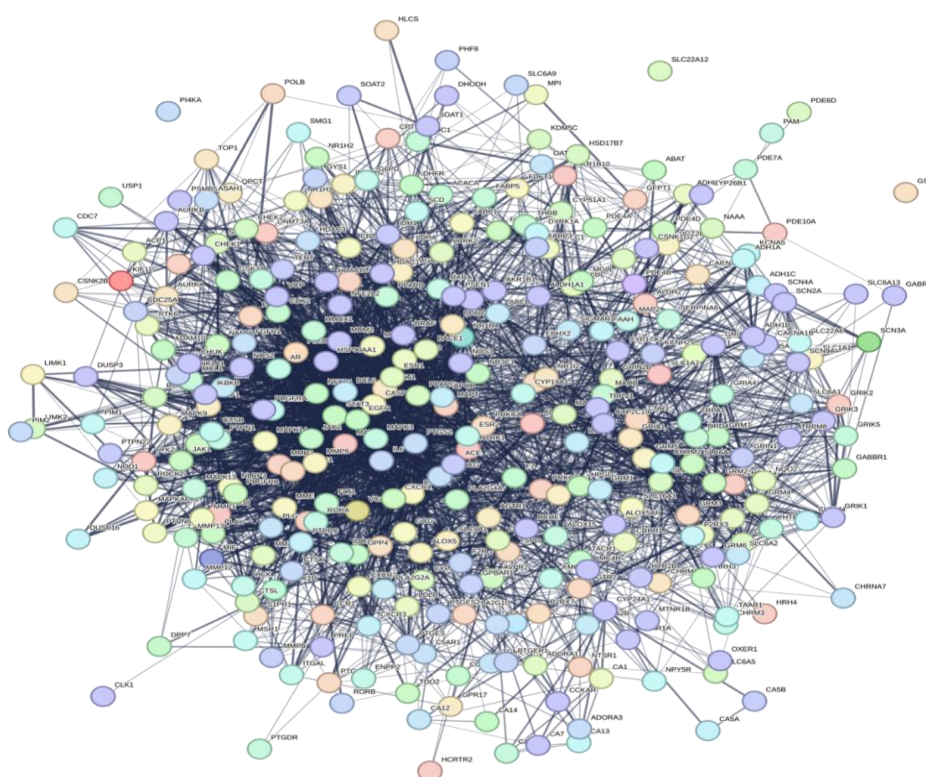


Figure 7: represents the common target genes PPI diagram, indicating that 238 nodes and 2527 edges were in the PPI.

GENE ONTOLOGY ANALYSIS FOR IBA HONEY AND PARKINSON'S DISEASE

Gene Ontology Biological processes

Table 5 presents the results of pathway enrichment analysis for Biological Processes related to Parkinson's

Disease, showcasing the percentage of genes within the consensus genes list associated with each pathway. Notably, several pathways exhibited significant enrichment, as indicated by low false discovery rates (FDR) and high fold enrichment values.

For instance, pathways such as cellular response to organonitrogen compound, cellular response to nitrogen compound, and trans-synaptic signaling demonstrated considerable enrichment, with FDR values ranging from $6.6\text{E-}35$ to $4.7\text{E-}37$ and fold enrichment values between 6 and 6.4.

Similarly, pathways related to synaptic signaling, response to organic cyclic compound, and cellular response to oxygen-containing compound exhibited

substantial enrichment, with FDR values in the order of 10^{-43} to 10^{-36} and fold enrichment values ranging from 5.6 to 5.8.

Additionally, pathways associated with response to lipid, chemical homeostasis, and cellular response to endogenous stimulus also showed notable enrichment, with FDR values ranging from 10^{-30} to 10^{-39} and fold enrichment values around 4.

Table 5: Pathway enrichment analysis for Biological Processes in relation to Parkinson's Disease, showing the percentage of genes in consensus genes list that belongs to a pathway.

Enrichment FDR	nGenes	Pathway Genes	Fold Enrichment	Pathways
6.6E-35	72	654	6.4	cellular response to organonitrogen compound
5.1E-36	77	734	6.1	cellular response to nitrogen compound
4.7E-37	80	773	6	trans-synaptic signaling
9.3E-36	78	764	5.9	chemical synaptic transmission
9.3E-36	78	764	5.9	anterograde trans-synaptic signaling
1.7E-36	81	810	5.8	synaptic signaling
4.2E-43	95	958	5.7	response to organic cyclic compound
9.8E-56	122	1272	5.6	cellular response to oxygen-containing compound
2.1E-44	101	1061	5.5	response to organonitrogen compound
2.4E-74	160	1752	5.3	response to oxygen-containing compound
4.6E-44	105	1172	5.2	response to nitrogen compound
2.4E-30	80	967	4.8	cellular homeostasis
1.0E-30	81	980	4.8	response to lipid
2.5E-36	98	1241	4.6	chemical homeostasis
1.4E-39	117	1660	4.1	response to endogenous stimulus
7.8E-32	98	1409	4	cellular response to endogenous stimulus
2.1E-40	122	1777	4	cell-cell signaling
5.4E-41	126	1874	3.9	reg. of transport
4.2E-37	122	1916	3.7	homeostatic proc.
2.7E-33	117	1936	3.5	small molecule metabolic proc.

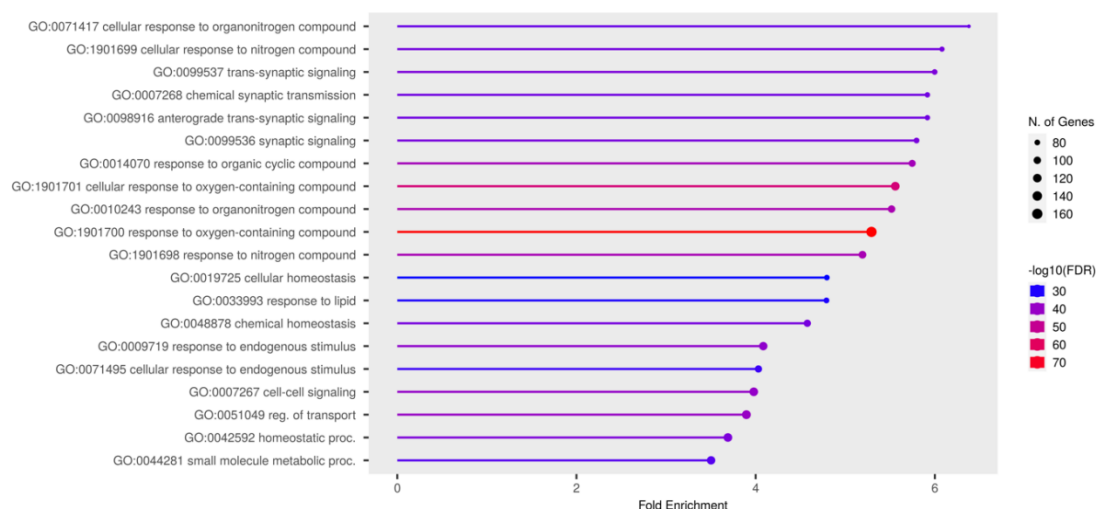


Figure 8: Fold enrichment analysis (top 20). The node size represents the number of target genes enriched, and the node colour from blue to red represents the p-value from large to small.

NETWORK CHART OF BIOLOGICAL PROCESS

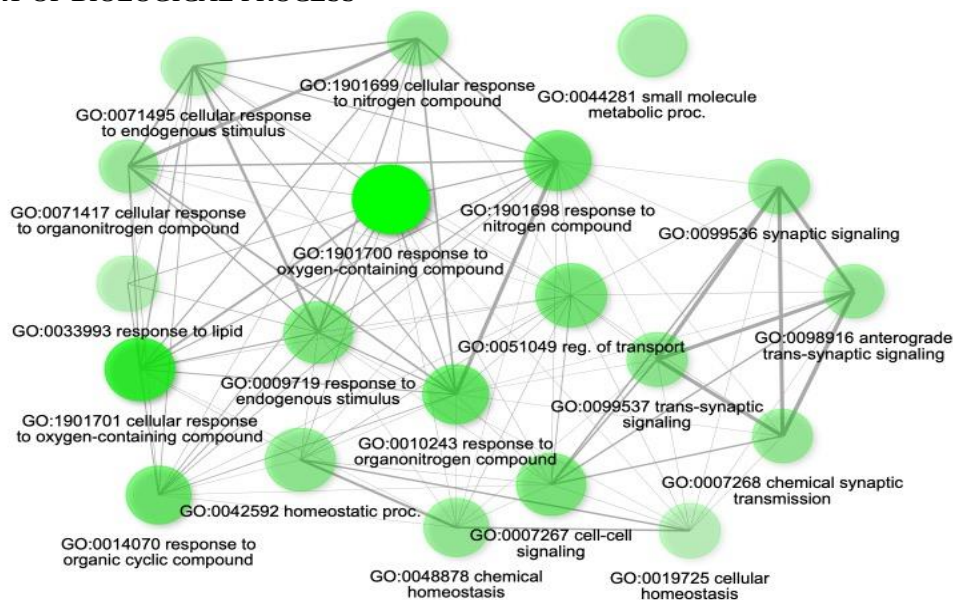


Figure 9: Network showing the relationship between enriched pathways of Biological processes. Nodes are connected if they share 20% or more genes. Darker nodes are more significantly enriched gene sets. Bigger nodes represent larger gene sets. Thicker edges represent more overlapped genes.

Gene Ontology Cellular Component

Table 6: Pathway enrichment analysis for Cellular Component in relation to Parkinson's Disease, showing the percentage of genes in consensus genes list that belongs to a pathway.

Enrichment FDR	nGenes	Pathway Genes	Fold Enrichment	Pathways
1.5E-11	16	76	11.3	integral component of presynaptic membrane
2.3E-13	23	151	8.2	presynaptic membrane
6.4E-19	43	395	5.8	synaptic membrane
1.1E-16	38	351	5.8	membrane raft
1.1E-16	38	352	5.8	membrane microdomain
1.0E-13	31	288	5.8	postsynaptic membrane
7.5E-15	39	429	4.9	receptor complex
4.3E-15	43	513	4.5	neuronal cell body
1.0E-15	47	588	4.3	cell body
1.2E-16	51	653	4.2	dendrite
1.2E-16	51	655	4.2	dendritic tree
4.7E-21	67	888	4	somatodendritic compartment
1.5E-12	40	533	4	presynapse
4.3E-15	49	664	4	postsynapse
6.5E-13	46	676	3.7	axon
6.4E-19	79	1332	3.2	plasma membrane region
6.0E-17	79	1440	2.9	neuron projection
1.2E-16	78	1435	2.9	synapse
2.9E-21	101	1894	2.9	integral component of plasma membrane
2.8E-21	104	1978	2.8	intrinsic component of plasma membrane

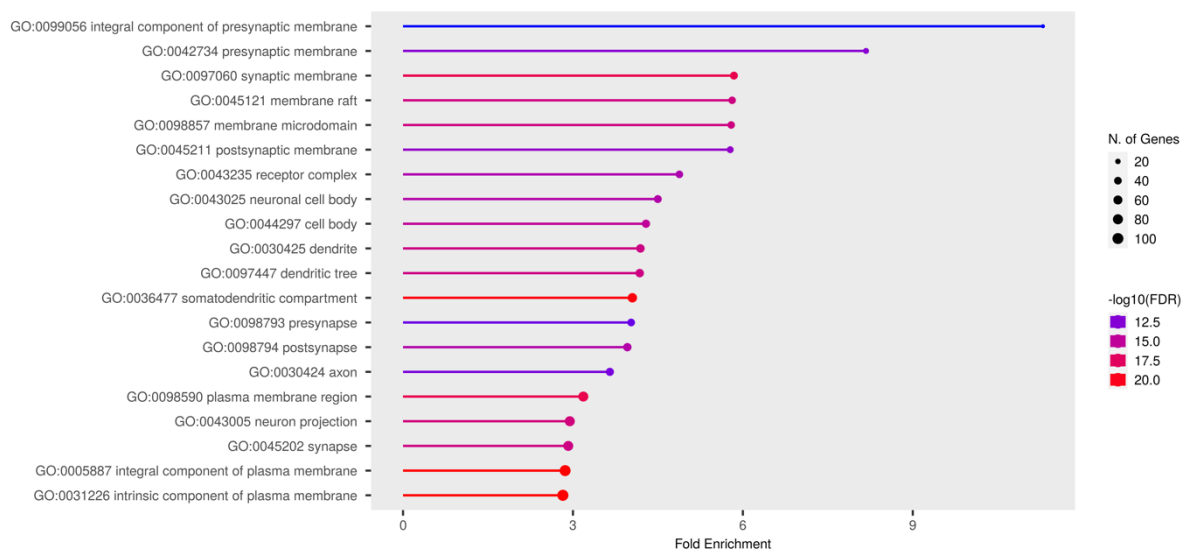


Figure 10: Fold enrichment analysis (top 20). The node size represents the number of target genes enriched, and the node colour from violet to blue represents the p-value from large to small.

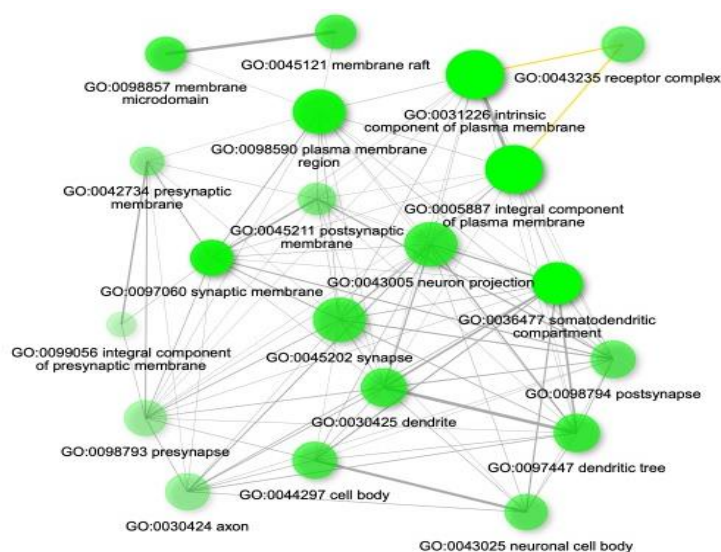


Figure 11: Network showing the relationship between enriched pathways of Cellular component. Nodes are connected if they share 20% or more genes. Darker nodes are more significantly enriched gene sets. Bigger nodes represent larger gene sets. Thicker edges represent more overlapped genes.

Gene Ontology Molecular Function

Table 7: Pathway enrichment analysis for Molecular Function in relation to Parkinson's Disease showing the percentage of genes in consensus genes list that belongs to a pathway.

Enrichment FDR	nGenes	Pathway Genes	Fold Enrichment	Pathways
1.8E-14	9	9	53.6	adenylate cyclase inhibiting G protein-coupled glutamate receptor act
1.8E-14	9	9	53.6	G protein-coupled glutamate receptor activity
1.0E-20	17	27	33.8	glutamate receptor activity
8.3E-16	18	57	16.9	nuclear receptor activity
8.3E-16	18	57	16.9	ligand-activated transcription factor activity
2.3E-14	18	69	14	postsynaptic neurotransmitter receptor activity
4.6E-19	26	113	12.3	neurotransmitter receptor activity
4.3E-12	22	151	7.8	organic acid binding
1.3E-21	51	470	5.8	protein serine/threonine/tyrosine kinase activity
1.6E-15	38	376	5.4	protein serine kinase activity

7.2E-16	43	471	4.9	protein serine/threonine kinase activity
2.5E-19	55	632	4.7	protein kinase activity
5.2E-17	56	748	4	phosphotransferase activity alcohol group as acceptor
8.7E-15	56	849	3.5	kinase activity
1.7E-12	51	820	3.3	oxidoreductase activity
2.0E-13	59	1008	3.1	transferase activity transferring phosphorus-containing groups
1.2E-15	71	1247	3.1	transition metal ion binding
3.9E-19	98	1908	2.8	signaling receptor activity
3.9E-19	98	1908	2.8	molecular transducer activity
1.3E-13	79	1646	2.6	transmembrane signaling receptor activity

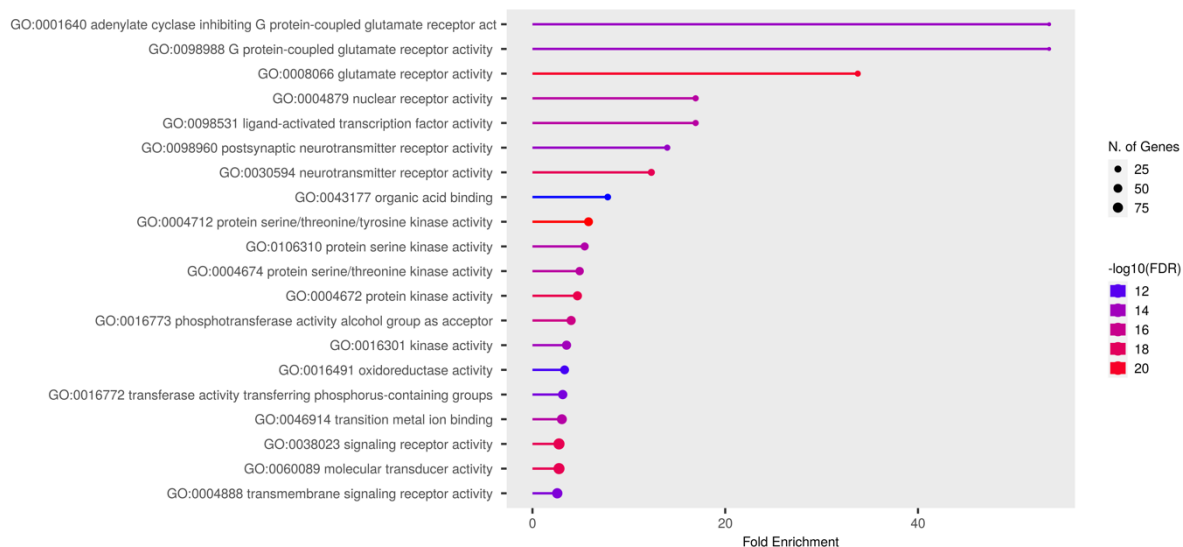


Figure 12: Fold enrichment analysis (top 20). The node size represents the number of target genes enriched, and the node colour from violet to blue represents the p-value from large to small.

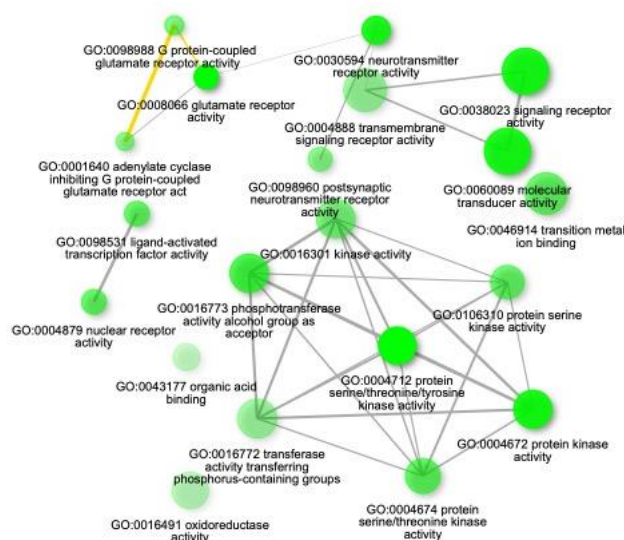


Figure 13: Network showing the relationship between enriched pathways of Cellular component. Nodes are connected if they share 20% or more genes. Darker nodes are more significantly enriched gene sets. Bigger nodes represent larger gene sets. Thicker edges represent more overlapped genes.

KEGG PATHWAY ANALYSIS

Multiple signaling pathways were found. The Parkinson's Disease signaling pathway indicates that SH

can potentially reduce tissue damage in nonimmune cells (alveolar and epithelial cells, endothelial cells) through the inhibition of the TNF signaling pathway by

suppressing $TNF\alpha$ and Jak1 genes. At the same time, the IL-6 gene, a crucial target of SH, may suppress ROS-induced tissue injury, therefore averting acute lung injury, severe acute respiratory disease syndrome (ARDS): macrophage activation syndrome (MAS): acute kidney injury (AKI): and stroke. Importantly the toll-like

signaling pathway for Parkinson's Disease indicates that specific key targets of SH have the potential to influence various pathways related to damage-associated molecular pattern (DAMP) and pathogen-associated molecular pattern (PAMP) by inhibition of the TLR214 gene.

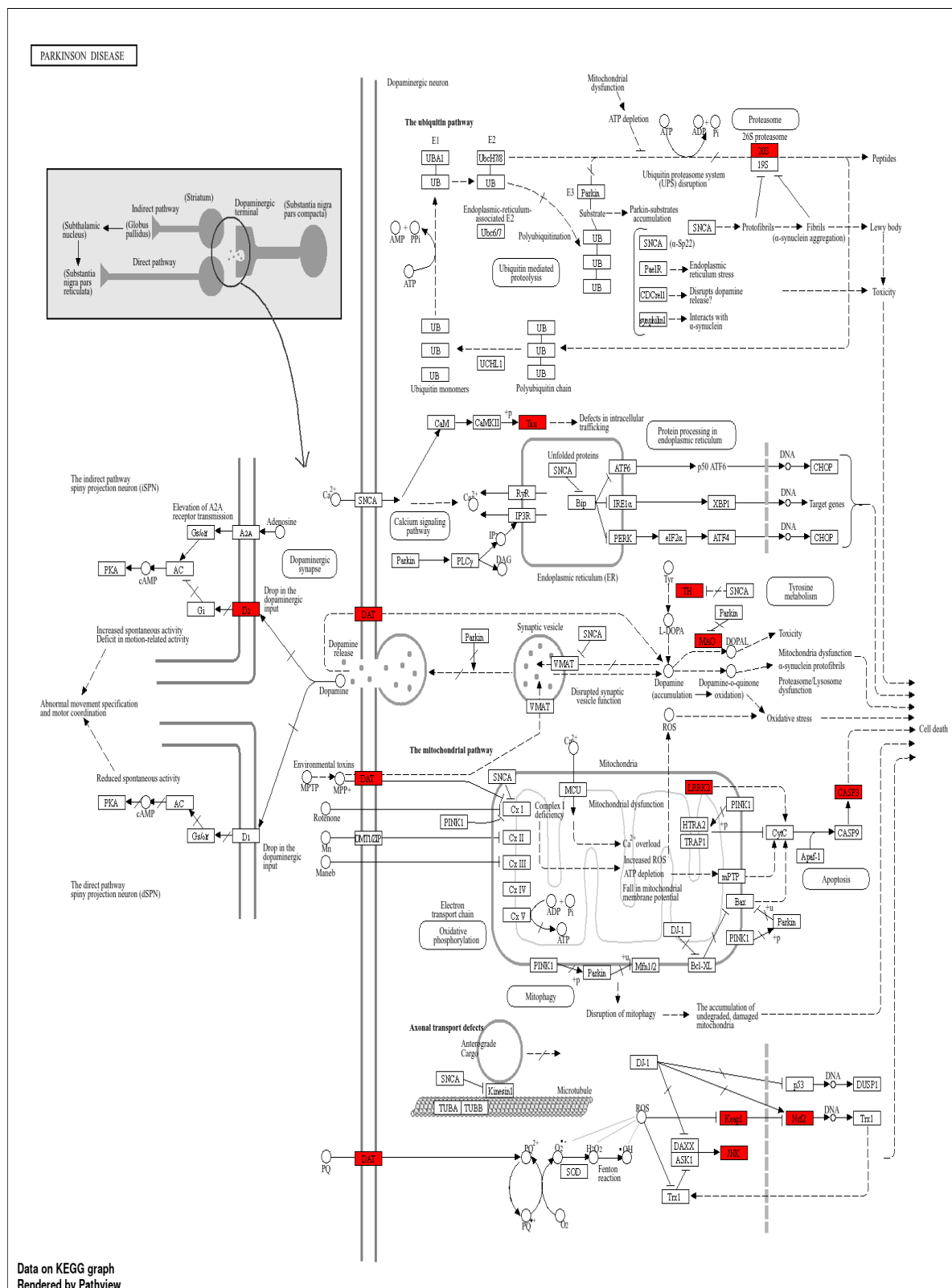


Figure 14: Kegg Pathway On Parkinson's Disease.

DISCUSSION

This study seeks to elucidate the bioactive markers of sweet honey and their roles in modulating molecular pathways associated with Parkinson's disease using network pharmacology-based approach.

The phytochemicals, fatty acids, vitamins, and amino acids identified in the sweet honey sample have the potential to play important roles in various neurological processes, particularly in the context of Parkinson's disease and neuroprotection. The phenolic compounds found in the honey possess potent antioxidant and anti-inflammatory properties, which can help mitigate oxidative stress and neuroinflammation, both of which are hallmarks of Parkinson's disease pathogenesis (Iftikhar *et al.*, 2022). Siddique (2021) has suggested that flavonoids, such as quercetin which has been identified in the sweet honey sample have shown neuroprotective effects by modulating cell signaling pathways, inhibiting protein aggregation, and promoting neuronal survival.

The fatty acid methyl esters (FAMES) identified in the sweet honey sample provide valuable insights into the potential roles of these compounds in neurological processes, particularly in the context of Parkinson's disease. One of the notable fatty acids present is methyl myristoleate (peak 6). Myristoleic acid, the corresponding free fatty acid, has been investigated for its potential neuroprotective effects. Iranshahy *et al.*, (2022) have shown that myristoleic acid can modulate neuroinflammation, inhibiting the aggregation of alpha-synuclein, and protecting against oxidative stress-induced neurodegeneration, all of which are key pathological mechanisms in Parkinson's disease.

Myristic acid is a medium-chain saturated fatty acid present in the honey sample. Myristic acid has been explored for its potential therapeutic applications in Parkinson's disease due to its ability to cross the blood-brain barrier and modulate neuronal function (Shen *et al.*, 2022). Shen *et al.* (2022) has also shown anti-inflammatory and neuroprotective properties of myristic acid, which could be beneficial in the context of Parkinson's disease as shown in this study.

The presence of unsaturated fatty acids like omega-3 and omega-6 fatty acids have been associated with improved neuronal function, synaptic plasticity, and neuroprotection (Stachowicz, 2023). The unsaturated fatty acids identified in this study can help reduce neuroinflammation and oxidative stress, which are key factors in Parkinson's disease pathogenesis. Polyunsaturated fatty acids have been investigated for their potential to modulate neuroinflammation, promote neuronal survival, and improve cognitive function, all of which are relevant in the context of Parkinson's disease (Giacobbe *et al.*, 2020).

The vitamins identified in the honey sample, such as vitamin A, vitamin B12, and vitamin C, also play

important roles in the proper functioning of the nervous system and have been investigated for their potential neuroprotective effects in Parkinson's disease (Kumar *et al.*, 2022). Calderón-Ospina & Nava-Mesa (2020) linked vitamin A has been linked to the regulation of dopaminergic neuron function, while vitamin B12 is essential for maintaining nervous system health. Vitamin C, as a potent antioxidant, can help mitigate oxidative stress and neuroinflammation, which are key contributors to Parkinson's disease pathogenesis (Jayaram & Krishnamurthy, 2021).

The amino acids present in the honey, such as cystine, leucine, isoleucine, and glycine, also have the potential to contribute to neuroprotection and this is in agreement with a study conducted by Rzetecka *et al.* (2024) which highlighted that cystine is a precursor for the synthesis of the antioxidant glutathione, which is crucial for protecting against oxidative stress in the brain. Branched-chain amino acids, like leucine and isoleucine, have been studied for their potential to modulate dopaminergic neurotransmission and provide neuroprotective effects, while glycine has been investigated for its ability to attenuate neuroinflammation and provide neuroprotection (Yoo *et al.*, 2022).

The diverse array of phytochemicals, fatty acids, vitamins, and amino acids identified in the sweet honey sample indicates its potential as a rich source of natural compounds with therapeutic applications in Parkinson's disease. These bioactive compounds can contribute to neuroprotection by reducing oxidative stress, modulating cell signaling pathways, inhibiting protein aggregation, and promoting neuronal survival and function. Further research is warranted to fully elucidate the mechanisms by which these honey-derived compounds can protect against the development and progression of Parkinson's disease.

The network analysis revealed that 238 nodes and 2,527 edges were present, with the top 30 most common genes, including CCR1, MMP3, CRHR1, MMP2, CES1, and PLAU, exhibiting a high frequency of protein interactions. This suggests that these genes may serve as critical nodes within the broader network, potentially mediating the effects of the sweet honey sample compounds on Parkinson's disease pathogenesis. The described observation is similar to the findings of Zhang *et al.*, (2022) in a similar study on Alzheimer's disease.

The analysis of biological processes highlights several pathways that are significantly enriched among the consensus genes identified earlier. Pathways related to cellular response to organonitrogen compounds, nitrogen compounds, synaptic signaling, response to organic cyclic compounds, and cellular response to oxygen-containing compounds exhibit high fold enrichment and low false discovery rates. Previous studies has implicated these pathways in the progression of Parkinson's disease

(Bach, 2021). These enriched pathways suggest that the compounds in the SH sample may have a modulatory effect on key biological processes implicated in Parkinson's disease pathogenesis, such as neurotransmission, oxidative stress response, and cellular homeostasis.

The analysis of cellular components reveals that the consensus genes are significantly enriched in various synaptic and neuronal structures, including presynaptic and postsynaptic membranes, membrane rafts and microdomains, neuronal cell bodies, dendrites, and axons. This indicates that the sweet honey sample compounds may target and influence the localization and function of proteins within these specific subcellular compartments, which are known to be disrupted in Parkinson's disease (Beegum *et al.*, 2022).

The molecular function analysis further elucidates the potential mechanisms of action of the SH sample compounds. Significant enrichment is observed in pathways related to neurotransmitter receptor activity, nuclear receptor activity, protein kinase activity, and signaling receptor activity. These findings suggest that the sweet honey compounds may exert their effects by modulating the activity of key receptors, enzymes, and signaling molecules involved in Parkinson's disease pathways. This is in tandem with the report of Iftikhar *et al.*, 2022 which highlighted the potential benefit of honey on various neurological disorders.

The selected compounds from the sweet honey sample have a high binding potential with the target proteins highlighted in red in the KEGG analysis and could be used as potential target genes for the treatment of Parkinson's disease.

The central dopaminergic pathway is a crucial component, as the loss of dopaminergic neurons in the substantia nigra is a hallmark of Parkinson's (Guatteo *et al.*, 2022). The KEGG analysis highlights several points where disruptions can occur, such as impaired dopamine synthesis, altered vesicular transport, and dysregulation of the ubiquitin-proteasome system. Honey contains a variety of phytochemicals and antioxidants that could potentially have a stabilizing effect on this pathway.

The elements related to alpha-synuclein aggregation and Lewy body formation are intriguing targets identified in the pathways as possible sites where sweet honey can interact. Certain polyphenols in honey, like quercetin and kaempferol, have been shown to inhibit alpha-synuclein oligomerization and promote its clearance (Fadzil *et al.*, 2022). This could help mitigate the toxic accumulation of these misfolded proteins.

Additionally, the mitochondrial dysfunction pathway is a major contributor to Parkinson's pathology. Honey contains compounds like coenzyme Q10 and flavonoids that could help maintain mitochondrial integrity, improve

bioenergetics, and reduce oxidative stress - all of which are critical in this context (Navarro-Hortal *et al.*, 2023).

This network pharmacology-based approach provides valuable insights into the complex interplay between the identified compounds and Parkinson's disease-associated genes, paving the way for novel, targeted therapeutic strategies.

CONCLUSION AND RECOMMENDATION

The comprehensive analysis presented in this study highlights the power of integrating various bioinformatics tools and databases to unravel the intricate mechanisms underlying complex diseases like Parkinson's. By leveraging network pharmacology, the study was able to identify a set of consensus genes that may serve as promising therapeutic targets, opening up new avenues for further exploration and validation through experimental studies. This holistic approach demonstrates the potential of combining chemical analysis, computational biology, and disease-specific knowledge to inform the development of more effective and personalized treatment options for Parkinson's disease.

It's important to note that the pathways involved in Parkinson's are highly complex and interconnected. While honey's antioxidant, anti-inflammatory, and neuroprotective properties make it an intriguing candidate, the impact on the specific red-marked elements would require rigorous experimental validation. Specifically it is necessary to understand if there is an up regulatory or down regulatory effect on those points and how that impacts the pathway.

Factors like bioavailability, specificity of interactions, and synergistic effects with other therapies would need to be carefully assessed. Moreover, the complex etiology of Parkinson's, involving both genetic and environmental factors, means that a single intervention may not be sufficient to fully address the disease.

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