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Exploration of the anti-gastric cancer potential of phytocompounds from *Cinnamomum tamala* using Network Pharmacology Approach

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Abstract

Cinnamomum tamala, a traditional Nepali spice and herbal remedy, has shown promising pharmacological potential, including anticancer properties. This study aimed to explore the anti-gastric cancer potential of phytoconstituents from Cinnamomum tamala using a network pharmacology-based in silico approach. This study provides molecular insights supporting the potential therapeutic application of Cinnamomum tamala in gastric cancer treatment. Cinnamomum tamala, a traditional Nepali spice and herbal remedy, has shown promising pharmacological potential, including anticancer properties. GC–MS analysis was performed on methanolic extracts from three samples collected across different locations, identifying thirty compounds, sixteen of which were common volatile constituents. Four major compounds: cinnamaldehyde, cinnamyl acetate, linalool, and caryophyllene oxide–were selected for computational analysis. A total of 105 target proteins of the compounds and 1,012 gastric cancer-associated genes were identified, revealing 48 overlapping targets. Protein–protein interaction (PPI) networks and KEGG pathway enrichment analysis were used for further investigation. Protein–protein interaction (PPI) network analysis highlighted PTGS2, TLR4, NR3C1, RELA, and JAK2 as key hub proteins. KEGG pathway enrichment indicated significant involvement of the PD-L1 expression and PD-1 checkpoint pathway in cancer, Th1 and Th2 cell differentiation, and the NF-κB signaling pathway. These findings suggest that compounds of Cinnamomum tamala may exert anti-gastric cancer effects by modulating immune checkpoints and inhibiting oncogenic signaling pathways, thereby promoting apoptosis of gastric cancer cells.

Keywords
Gastric cancer, *Cinnamomum tamala*, GC-MS, network pharmacology, signaling pathways.

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1 Introduction

Approximately 17 million people have a cancer diagnosis each year, and this number is expected to rise sharply in the near future. Cancer is currently the leading cause of premature death in the majority of countries worldwide [1]. Cancer is a serious disease that causes aberrant cells in the body to grow and spread out of control, posing a threat to life. Human cancer is triggered by several signaling cues, including ageing, lifestyle changes, hormonal changes, and exposure to environmental contaminants [2]. One of the most common cancers in both genders, gastric cancer (GC), is still ranked third in terms of the top causes of cancer-related death worldwide, despite improvements in detection and treatment. A poor prognosis for patients is frequently caused by its complexity, which is typified by tumor heterogeneity, fast metastasis, and high recurrence rates [3, 4]. An aggressive disease with a bad prognosis and a high death rate, gastric cancer is brought on by metastatic lesions [5]. Currently available treatment options, such as targeted therapy, chemotherapy, and surgery, are usually constrained by serious side effects and the emergence of drug resistance [6]. To create next-generation GC treatments, new, safe, and effective molecules must be found, especially those that can affect numerous pathways at once. One promising strategy for preventing cancer is natural chemoprevention. Chemotherapy uses important anticancer treatments that were found to be derived from natural plants [7].

From the Indus to Bhutan, the tropical and subtropical Himalayas are habitats to approximately 270 species of the genus *Cinnamomum* (family Lauraceae). The most well-known of these are *Cinnamomum tamala* (Tej pat), *Cinnamomum verum* (true cinnamon), and *Cinnamomum cassia* (Cassia) [8]. The leaves of *C. tamala* are widely used as spices to enhance the flavor of cuisine in South Asian countries. The essential oils of *Cinnamomum* species are widely used in the food, cosmetic, surfactant, and pharmaceutical industries [9, 10]. *Cinnamomum* has long been valued as a common spice and has been used for thousands of years in Asian traditional medical systems, such as Ayurveda and Traditional Chinese Medicine (TCM), because of its alleged ability to treat a wide range of illnesses, from inflammatory to digestive problems [11]. Tejpat is a special kind of functional food because of its therapeutic benefits, and it fits into people's daily lives. The rich and complex phytochemical profile of Tejpat (*Cinnamomum tamala*) underlies its diverse pharmacological activities, including antidiarrheal, antitumor, anti-inflammatory, anti-arthritic, antiparasitic, gastroprotective, antioxidant, chemopreventive, and genitourinary protective effects, which collectively contribute to its wide range of medicinal benefits [12, 13]. Bioactive substances, including flavonoids and phenolic acids, were isolated and identified by phytochemical analyses of *Cinnamomum* species [14]. The biological activities of the phenolic compounds include cytotoxicity, antiviral, antiulcer, antidiabetic, and anti-inflammatory properties [15]. According to related research, extracts from *Cinnamomum tamala* have anti-cancer properties against a variety of human malignancies, including breast, cervical, and colon cancer [16–18].

The volatile part of *Cinnamomum tamala* is primarily responsible for its strong bioactivity [19]. This study focuses on four key compounds abundant in *Cinnamomum* species: cinnamaldehyde, cinnamyl acetate, linalool, and caryophyllene oxide (Figure 1). The main bioactive ingredient in *Cinnamomum* that gives it its distinctive flavor and smell, cinnamaldehyde (CA), is a thoroughly researched substance that has been shown to have anti-inflammatory and anti-diabetic effects [20]. Cinnamaldehyde inhibits the growth, migration, and invasion of tumors [21]. Cinnamaldehyde exhibits promising antitumor properties in relation to gastric cancer. It causes apoptosis in gastric cancer cells by blocking various signaling pathways, which lowers the anti-apoptotic ratio and causes concentration-dependent cell death. Additionally, endoplasmic reticulum (ER) stress and epigenetic changes in gastric cancer cells cause cinnamaldehyde to trigger autophagy-mediated cell death [22, 23]. Cinnamyl acetate, found in cinnamon leaf and bark oils, has high biological potential, including anti-inflammatory, antibacterial, and antioxidant activities [24, 25].

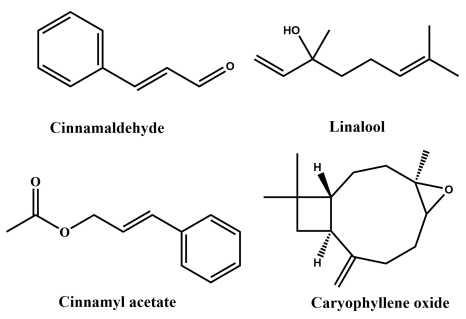

Figure 1: Major compounds of *Cinnamomum tamala* leaves

It is well established that linalool and linalool-rich essential oils exhibit diverse biological activities,

including antibacterial, anti-inflammatory, anticancer, and antioxidant properties [26]. Linalool has been assessed as a possible chemopreventive and chemotherapeutic agent that can be capable of exerting anticancer effects either alone or in combination with other medications. This monoterpene has been shown in numerous *in vitro* and *in vivo* investigations to have anticancer properties in gastric cancer cells [27]. According to multiple studies, caryophyllene oxide (CPO), a sesquiterpene found in medicinal plants like clove (*Eugenia caryophyllata*) and cinnamon (*Cinnamomum* spp.), is a potent anticancer agent that can also inhibit the growth of a wide range of tumor cells, including breast, lung, liver, and prostate adenocarcinomas [28, 29]. Furthermore, caryophyllene oxide extracted from *Cinnamomum tamala* leaf extracts had modest cytotoxic action against the human ovarian cancer cell line A-2780, according to Shahwar et al. [16]. All of these molecules work together to form a potent natural chemical arsenal with numerous health benefits, requiring further research into their specific medicinal properties.

The main goal of medications used to treat cancer is to cause cancer cells to undergo apoptosis or cell cycle arrest. Therefore, essential oils capable of inducing apoptosis in cancer cells may serve as promising therapeutic agents for cancer management [30]. Furthermore, chromosomal changes, modifications in drug-activating signal transduction pathways, increased efflux leading to decreased drug accumulation, reversal of drug-induced damage due to effective DNA repair, inhibition of apoptosis due to prolonged drug usage, mutations or changes in the expression levels of enzymes like kinases or topoisomerases, drug inactivation leading to increased drug resistance in cancer cells, and changes in DNA, including methylation, acetylation, and alkylation, reduce the effectiveness of synthetic drugs [31]. Because herbal medicines contain several active ingredients that work in concert on a variety of biological targets, traditional "one-drug, one-target" drug discovery models frequently fall short of capturing their holistic effects [32]. Network pharmacology (NP) has become a preferred, state-of-the-art systems biology method in this regard. The intricate, multi-target processes of traditional herbal substances may be systematically predicted due to NP's integration of data from chemical analysis, therapeutic targets, and disease pathways to create extensive interaction networks [33]. The demand for more efficient cancer therapies prompted researchers to look into "drug repurposing," or finding new uses for inexpensive medications that have been approved for other illnesses [34]. There are several facets to the therapeutic properties of natural plants. Because of the toxicities, side effects, and rise in drug resistance of current treatments, effective suppressive drugs must still be developed, even though there are already some medications available to treat gastric cancers [35, 36]. As a result, using natural plants that have multiple features of medical action could open up new possibilities. Determining the therapeutic potential of *Cinnamomum* extracts against the multifactorial pathophysiology of gastric cancer is ideally suited to this methodology. Although the therapeutic benefits of *Cinnamomum tamala* are well known in Himalayan traditional medicine, little is known about its precise molecular mechanisms against gastric cancer. Without establishing the combined effect between specific volatile markers and their corresponding human protein targets, the majority of the research already published focuses on crude extracts. In order to fill this gap, this study utilizes network pharmacology with GC-MS profiling to explain the multi-target regulation mechanisms of *C. tamala* components.

Therefore, by the network pharmacology approach, this study aims to systematically investigate the anti-gastric cancer mechanism of action for the four primary compounds found in cinnamon species. This study aims to lay the groundwork for future experimental validation and provide solid scientific evidence in favor of using *Cinnamomum* compounds as potential multi-target medicines for the treatment of gastric cancer by identifying the primary therapeutic targets and key signaling pathways. We anticipate offering a fresh concept and theoretical underpinnings for identifying and addressing medication targets in gastric cancer. Researchers could use available information to develop efficient, less toxic, and environmentally responsible anticancer medications that treat cancer while also benefiting human health. Thus, this study used *Cinnamomum tamala* chemicals as an entry point, which was then paired with network pharmacology and bioinformatics analysis. Keeping in view the traditional and medicinal importance of this plant, we carried out network pharmacology.

2 Materials and Methods

2.1 Sample collection

The leaves of *Cinnamomum tamala* were collected from different locations at elevations (420 m, 816 m, and 1540 m) of Gandaki Province, Nepal, during the winter season between December 2022 and January 2023. National Herbarium and Plant Laboratories (NHPL) Godawari, Lalitpur, Nepal, verified the authenticity of the plants. The leaves were carefully separated, cleaned, and then air-dried at room temperature. Air-dried samples were pulver-

ized with an electric blender (Philips HL7759/00 Mixer Grinder, 750W, India) and stored in airtight containers with proper labelling.

Table 1: Sample details

S.N	Sample Name (code)	Altitude (m)	Latitude (E)/Longitude (N)
1	001A	1540	84.237951/28.078279
2	001C	816	83.844632/28.185034
3	001H	420	84.080343/28.037212

2.2 Preparation of *Cinnamomum* extract

The powdered leaves (10 g) were carefully weighed and underwent an extraction process involving 100 mL of methanol (99%) (Thermo Fisher Scientific, India) within a 200 mL conical flask. The entire plant extracts were placed in an Ultrasonicator (UC-30A, Biobase Industry (Shandong) Co. Ltd, China) with power 50 Hz, 220V for a duration of at 20°C for 30 minutes [37,38]. Each sample underwent a re-extraction procedure using methanol until a colorless solvent was achieved in order to ensure full extraction. After the extraction process was finished, the resultant fraction was filtered using a Whatman no. 1 size filter (Whatman India) and concentrated using a rotary evaporator (Heidolph 12 Instruments GmbH & Co. KG, Germany) to remove residual methanol via evaporation. In total, 3 dried extracted samples were collected, weighed, and subsequently utilized for GC-MS analysis. GC-MS grade (99.9%) methanol (Thermo Fisher Scientific, India) is used as a solvent for analysis.

2.3 Gas chromatography-mass spectrometry (GC-MS)

GC-MS was used to examine the chemical composition of *C. tamala* extracts, similar to the Wang et al. method [39]. A GC-MS QP 2010 Ultra system (Shimadzu Analytical India Pvt. Ltd, Mumbai, India) was used to conduct the GC-MS analysis. The separation was performed using an HP-5MS column (30 m × 0.25 mm i.d., film thickness 0.25 μm; Shimadzu, Japan). A split ratio of 1:20 was used for injecting the sample (0.2 μL) into the injector. The oven was maintained at 40°C for two minutes, then increased to 120°C at a rate of 10°C per minute and held there for one minute, then increased to 180°C at a rate of 20°C per minute and held there for one minute, and lastly increased to 270°C at a rate of 30°C per minute. Twenty-five minutes was the final run time. The temperature of the detector was 270°C, and the injector was 250°C. The temperature of the ion source was 250°C. With an ionization potential of 70 eV, a scan rate of one scan per second, and a scan range (as m/z 50–600) for every sample analysis, helium was employed as the carrier gas.

The average peak area of each component was compared to the total chromatographic peak area to determine its relative percentage amount. The NIST mass spectrum library (Search Library Database/W9N08.L), which is integrated into the instrument software, was used to identify the principal volatile compounds. The relative fraction of each compound was then determined. The match score for the library match barrier was set at 95% or higher.

2.4 Identification and ADME Screening of Candidate Compounds of *Cinnamomum tamala*

The four compounds (cinnamaldehyde, cinnamyl acetate, linalool, and caryophyllene oxide), which are pharmacologically active against cancer, were used in the *in silico* analysis [27, 40–43]. Despite being present as a major compound on the GC chromatogram, glycerin was not included in further studies because it is a common solvent/compound, which makes it a likely artifact, and because it is known to promote the growth of cancer tumors [44]. Using these online resources, we assessed plant phytochemical lists and their properties from IMMPAT (https://cb.imsc.res.in/imppat/), and further confirmed from Dr. Duke's Phytochemical and Ethnobotanical Databases (https://phytochem.nal.usda.gov/). Cinnamaldehyde, cinnamyl acetate, linalool, and caryophyllene oxide cheminformatics data, such as PubChem Name, PubChem CID, Molecular Formula, CAS, and Canonical SMILES, were obtained from the PubChem database (https://pubchem.ncbi.nlm.nih.gov). The drug likeness analysis, pharmacokinetic properties, and toxicity for selected compounds were evaluated by using ProTox 3.0 [45], IMMPAT [46], ADMETlab 3.0 (https://admetlab3.scbdd.com), and Molsoft (https://molsoft.com/mprop/) (accessed on 15 September 2025). We used Lipinski's Rule of Five (RO5) to assess phytochemicals' potential as lead candidates. These rules offer a collection of recommendations that support the early detection and screening of compounds with promise [47, 48].

2.5 Prediction of Related Targets of Active Compounds in *Cinnamomum tamala*

Swiss Target Prediction (http://www.swisstargetprediction.ch/) was used to acquire the data of possible active chemical targets by entering the canonical SMILES and designating the species as *Homo sapiens* [49]. Moreover, cinnamaldehyde, cinnamyl acetate, linalool, and caryophyllene oxide target genes were downloaded from Super PRED (http://bioinformatics.charite.de/superpred) and PharmMapper (https://www.lilab-ecust.cn/pharmmapper/) [50,51]. Repetition was eliminated, and the targets of these databases were combined.

2.6 Gastric Cancer Targets Gene Collection

The genes were selected with a GIFtS score $\geq$ 60 in the GeneCards database (https://www.genecards.org/) [52]. To provide more accurate and comprehensible data for bioinformatics and systems biology research, GeneCards data was filtered or excluded of irrelevant genes and pseudogenes [53, 54]. Some gastric cancer target genes were obtained by searching OMIM (https://www.omim.org/), DisGeNET (https://www.disgenet.org/), and genes with clear EntrezGeneID in OMIM (accessed on 3 October 2025) and literature. To identify targets linked to gastric cancer, all of the genes that were extracted from these three datasets were eventually combined and arranged.

2.7 Construction of the PPI network by a common target and core targets screening

Using Venny 2.0.2 (https://bioinfogp.cnb.csic.es/tools/venny/index2.0.2.html), the intersection of cinnamaldehyde, linalool, and caryophyllene oxide targets and gastric cancer targets was carried out. The intersecting genes represented the possible targets of the compound *Cinnamomum tamala* and gastric cancer.

A common gene acquired in the preceding phase was imported into STRING (https://string-db.org/) (accessed on 5 October 2025) [55] to construct the protein-protein interaction (PPI) network, with specific parameters: organism set to "*Homo sapiens*," with a confidence score > 0.9, and other basic settings were the default value. The network was visualized using Cytoscape 3.9.0 software [56]. The top ten hub genes were selected for further pathway analysis.

Core targets were screened in Cytoscape 3.9.0's "cytohubba." The top 10 targets were filtered using Degree, Maximum Neighbourhood Component (MNC), Maximal Clique Centrality (MCC), and Closeness, respectively [57]. The core targets are the intersection of the targets determined by these four algorithms.

2.8 KEGG and GO Pathway Enrichment Analysis

ShinyGO 0.85 bioinformatics (https://bioinformatics.sdstate.edu/go/), a bioinformatics software, was used to conduct the GO and KEGG enrichment analysis of possible targets of cinnamaldehyde, linalool, and caryophyllene oxide for the treatment of gastric cancer [58]. Terms that analyze expressions for functional annotation clustering were gathered; systematic explorer scores of less than 0.05 were selected. Bar plots and tree diagrams were used to illustrate improved biological processes, molecular functions, and pathways, thereby interpreting the functional roles of the identified genes [59, 60]. Less than 0.05 was considered a statistically significant false discovery rate (FDR) [56].

2.9 Network Construction of "Compound-Signaling Pathway-Target gene (DPT)"

The major chemical compounds, core genes, and signaling pathways served as the foundation for building the compound–pathway network [61]. Cinnamaldehyde, cinnamyl acetate, linalool, and caryophyllene oxide—potential target compounds of *Cinnamomum tamala* for the treatment of gastric cancer—as well as the KEGG pathway, were incorporated into Cytoscape to create the drug-target-pathway network. Within the network framework, nodes denote candidate compounds, genes, or signaling pathways, whereas edges represent the interactions among compounds and targets or between targets and biological pathways. The network was built using Cytoscape 3.9.0 software.

3 Results

3.1 The GC-MS analysis

3.1.1 Chemical composition of *Cinnamomum tamala* methanolic extract

A total of 26 volatile chemicals, including aldehydes, alcohols, alkanes, alkenes, ketones, ethers, and sulfides, were found in sample 001A from 1540 m, 30 in sample 001C from 816 m, and 29 in sample 001H from 420 m. Details of molecule names and the relative percentage of the compounds obtained are shown in the supplementary (Table S1), and the chromatogram of the methanolic extracts is shown in Figure 2.

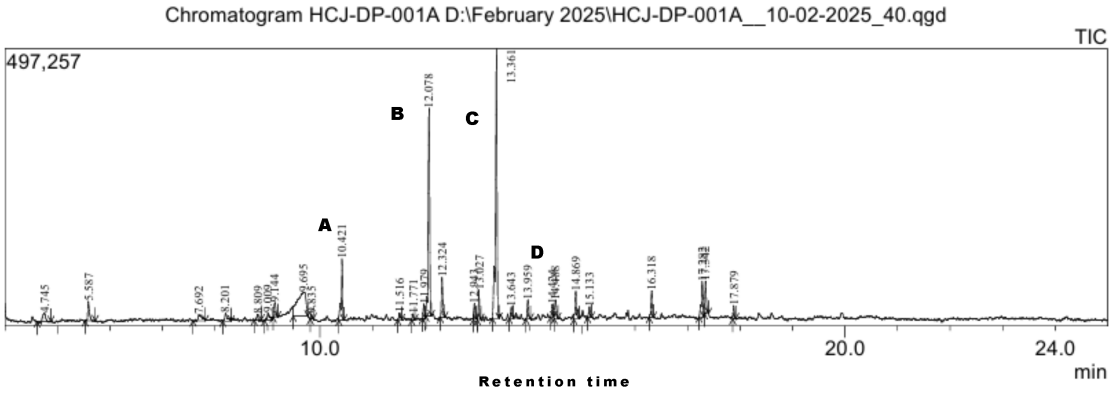

Figure 2: GC-MS chromatogram of the methanolic extract of *Cinnamomum tamala* leaves

Table 2: Major compounds identified from the methanolic extract of three *Cinnamomum tamala* samples

S.N.	Compound	Retention time (min.)	Area (%) 001A	Area (%) 001C	Area (%) 001H
A	Linalool	10.4	5.24	2.93	1.5
B	E-Cinnamaldehyde	12.09	18.42	29.59	14.65
C	Cinnamyl acetate	13.3	27.5	4.23	19.13
D	Caryophyllene oxide	14.4	1.82	0.53	1.89

3.2 Physicochemical and pharmacokinetic properties

The pharmacokinetic analysis of cinnamyl acetate, caryophyllene oxide, linalool, and cinnamaldehyde includes important components that determine how well they work in the human body. Gastrointestinal (GI) absorption serves as a measure of oral bioavailability, and high GI absorption increases the effectiveness of oral delivery. The blood-brain barrier (BBB) permeability of a substance indicates its capacity to penetrate the central nervous system, which is important for medications meant to treat neurological disorders. The pharmacokinetic properties are in Table 3, and the drug likeness graph of cinnamaldehyde, cinnamyl acetate, linalool, and caryophyllene oxide is in Supp. Figure F1.

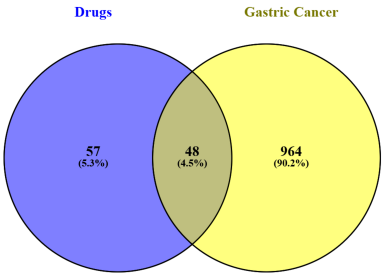

Figure 3: Common target between target proteins and the gastric cancer gene.

3.3 Common-match target acquisition

Under Venny 2.1.0 visualization, target prediction of active components in gastric cancer and the lead compound of *Cinnamomum tamala* were identified. Out of 105 target proteins for lead compounds and 1012 target proteins of gastric cancer, 48 common genes were obtained.

3.4 Protein–protein interaction network construction

In the present study, it was discovered that the cinnamaldehyde, cinnamyl acetate, linalool, and caryophyllene oxide target PPI network graph contained 48 nodes and a total of 163 edges, indicating a complex network between the target proteins of cinnamaldehyde, cinnamyl acetate, linalool, and caryophyllene oxide and the gastric cancer-related protein. According to the determined average node degree of 6.79, each protein interacted with almost seven additional proteins on average. A considerable degree of clustering inside the network was indicated by the average local clustering coefficient, which was 0.5635, as shown in Supp. Figure F2.

Table 3: Pharmacokinetic properties of major compounds

Characteristic	Cinnamaldehyde	Linalool	Caryophyllene oxide	Cinnamyl acetate
Molecular weight (g/mol)	132.16	154.25	220.36	176.21
Log P	1.9	2.67	3.94	2.26
Topological polar surface area (Å^2)	17.07	20.23	12.53	26.3
Number of HBA (hydrogen bond acceptors)	1	1	1	2
Number of HBD (hydrogen bond donors)	0	1	0	0
Number of rotatable bonds	2	4	0	4
Blood-Brain Barrier (BBB) Score (6-High, 0-Low)	4.73	4.62	3.94	4.84
Number of Lipinski's rule of 5 violations	0	0	0	0
Lipinski's rule of 5	Passed	Passed	Passed	Passed
Ghose rule	Failed	Failed	Passed	Passed
Veber rule	Good	Good	Good	Good
Egan rule	Good	Good	Good	Good
GSK 4/400 rule	Good	Good	Good	Good
Pfizer 3/75 rule	Bad	Bad	Bad	Bad
Weighted quantitative estimate of drug-likeness (QEDw) score	0.44	0.62	0.44	0.66
Estimated Solubility [ESOL]	Soluble	Soluble	Soluble	Soluble
Gastrointestinal absorption	High	High	High	High
Drug-likeness model score	-1.54	-0.99	-1.50	-1.14
Bioavailability Score	0.55	0.55	0.55	0.55
Lethal dose (LD50) - mg/kg	3400	2790	>1000	1200

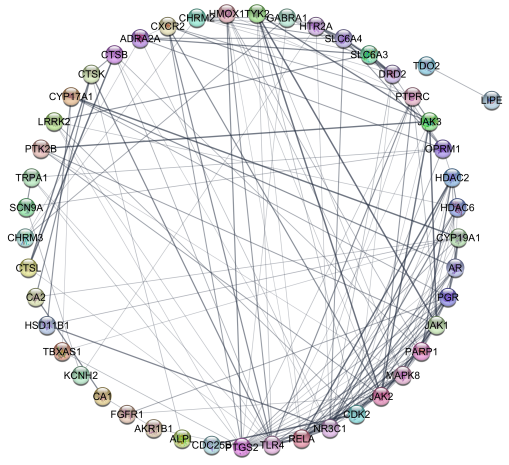

Figure 4: PPI network of the gastric cancer targeted proteins

The obtained PPI data were imported into Cytoscape 3.7 for visualization, and the results showed that the degree of PTGS2 was the highest. A PPI analysis was carried out to screen out the core target protein genes with a degree $\geq$ 10, including PTGS2, TLR4, NR3C1, RELA, JAK2, CDK2, PARP1, MAPK8, JAK1, and AR. Figure 5 shows the details. Identification of the top 10 targets from the common gene using the Cytoscape Cytohubba plugin.

3.5 Results of KEGG and GO pathway enrichment analysis

To verify the biological characteristics of the 10 highlighted targets of cinnamaldehyde, cinnamyl acetate, linalool, and caryophyllene oxide out of 48 targets (false discovery rate $<$ 0.05), KEGG and GO pathway enrichment analysis were performed. The KEGG pathway enrichment analysis

indicated that the signal pathways involved in the cinnamaldehyde, cinnamyl acetate, linalool, and caryophyllene oxide targets mainly included PD-L1 and PD-1 checkpoint pathways, pathways related to Th1, Th2, and Th17 cell differentiation, NF-κB signaling pathway, Toll-like receptor signaling pathway, and other pathways like the PI3K-Akt signaling pathway. The bioactive compounds are also involved in non-cancer multi-disease potential pathways related to leishmaniasis, pathways related to toxoplasmosis, necroptosis, hepatitis B, tuberculosis, and measles. Based on these pathways, the *Cinnamomum* compounds' anti-cancer effect on gastric cancer may result from a complex multi-pathway synergetic effect. KEGG tree and network visualized in Supp. Figure F3.

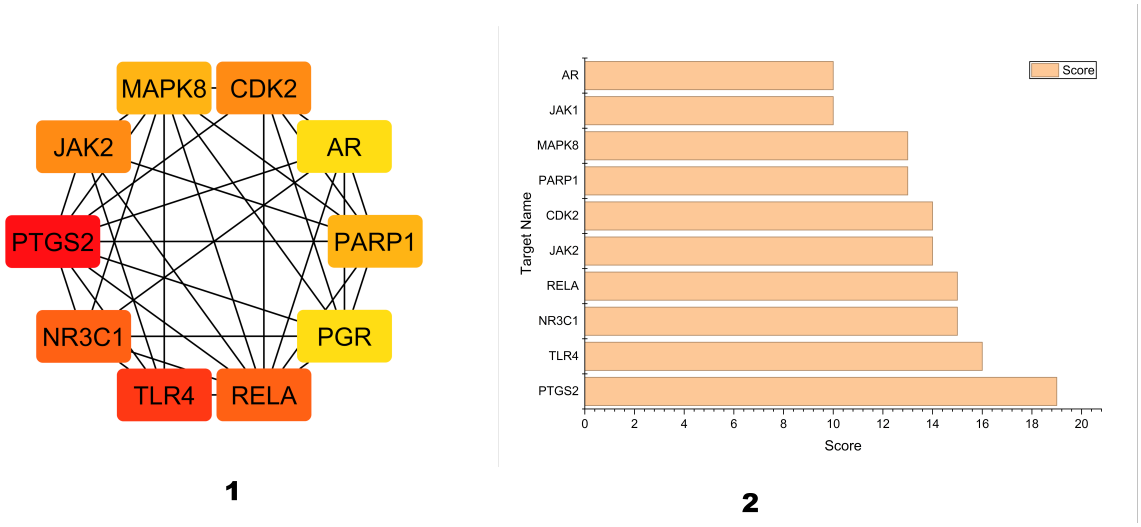

Figure 5: 10 main protein genes identified by the Cytohubba plugin

Note: The decreasing importance indicated by the gradient from red to yellow. Score value of top 10 targets.

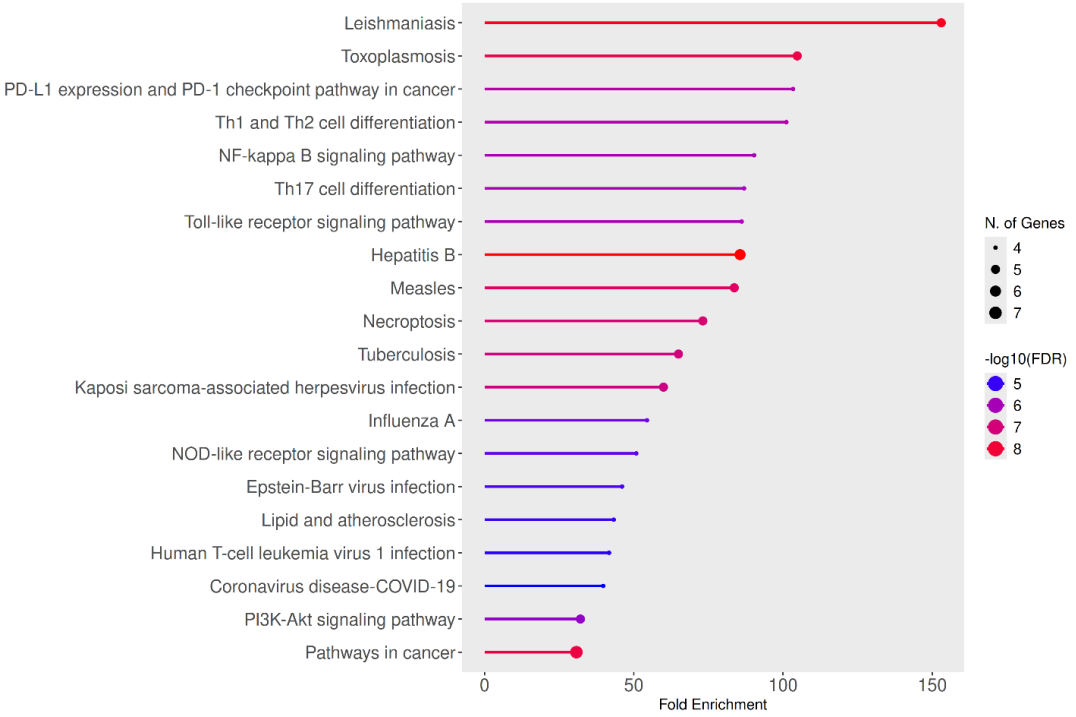

Figure 6: Lollipop plot of KEGG pathway enrichment analysis of *Cinnamomum tamala* compounds

The KEGG analysis revealed that protein targets are primarily associated with pathways involving the PD-L1 and PD-1 checkpoints, as well as the Th1 and Th2 cell differentiation pathway, which are the most significantly enriched functions. Pathways were chosen based on enrichment scores and are depicted in Figure 7 and Supp. Figure F4.

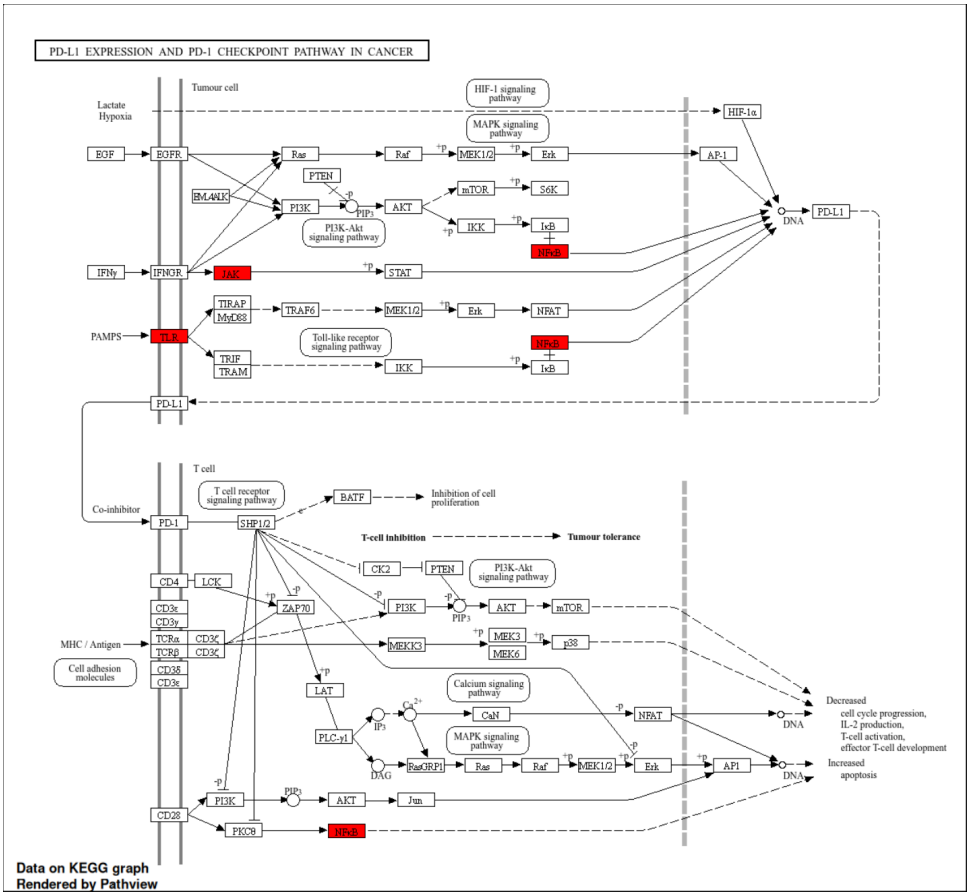

Figure 7: PD-L1 and PD-1 checkpoint pathway (Potential targets for *Cinnamomum tamala* compound intervention are indicated by red marks)

The results of Gene Ontology (GO) analysis, as shown in Supp. Figure F5, suggest that the proposed targets are predominantly involved in biological processes, including the interleukin-12 receptor complex, the cyclin A2-cdk2 complex, and the cyclin E1-cdk2 complex. The targets are related to cellular component analysis response to ketone, hormone-mediated signaling pathway, and cellular response to lipopolysaccharides. Molecular function analysis showed enrichment in the growth hormone receptor binding, estrogen response element binding, and histone kinase activity.

3.6 Construction of "*Cinnamomum tamala* compound target disease" network

The major 10 cancer-related KEGG pathways were imported into Cytoscape to construct a compound-target-pathway network (Figure 8). The results showed that cinnamaldehyde, cinnamyl acetate, linalool, and caryophyllene oxide may interact with more than one target, and that each target might respond significantly to different active components and pathways in treating gastric cancer through multiple targets and signaling pathways.

4 Discussion

GC-MS analysis of the methanolic extract showed that all three *C. tamala* samples contain cinnamaldehyde, cinnamyl acetate, linalool, and caryophyllene oxide, indicating that cinnamaldehyde, cinnamyl acetate, and linalool are dominant compounds. This result is similar to the previous study by Tandukar et al. (2022), which used GC-MS profiling of the hydro distilled extract of *C. tamala* (Buch.-Ham.) Nees & Eberm. leaves collected from Kathmandu Valley, at an altitude of 1320 m [62], contained these lead compounds.

The significant variation seen in three samples, especially the 6.5-fold variation in cinnamyl acetate, suggests that the extracts probably correspond to distinct chemotypes [63, 64]. The findings of a GC-MS analysis of *Cinnamomum tamala* extracts previously made public led to the conclusion that four chemicals in particular are important for a wide range of illnesses [19,39]. Several studies have reached the same conclusion: these chemicals are a therapeutic component of the extracts they studied and have been shown to exhibit antioxidant activities [17,37,62]. In three samples, different essential oils (EOs) and volatile compounds are recorded during GC-MS analysis. Study shows EOs induce cancer cells to undergo programmed cell death by necrosis, apoptosis, cell cycle halt, and malfunctioning of the primary cell organelles. A decrease in adenosine triphosphate (ATP) production, a change in the pH gradient, a loss of mitochondrial potential, and an increase in the fluidity of the affected cell's membrane all work together to cause this [65].

Figure 8: Drug-target-pathway network diagram (The blue diamond represents target genes, the outer green rectangles are pathways, and the inner yellow ovals are *Cinnamomum tamala* lead compounds)

We utilize the network pharmacology approach to clarify the chemical process involved in the therapy of gastric cancer. The network pharmacology produced by the combination of bioinformatics and pharmacology can clarify the mechanism of action of herbs, multi-target, multipathway, and multi-action mechanisms [66, 67]. As mentioned earlier, the "single drug-protein-disease theory," which forms the basis of the traditional drug research approach, has been repeatedly shown to be factually incorrect because a single chemical moiety can interact with many proteins and alter multiple pathways [68]. Therefore, a more comprehensive strategy to treating these problems can be achieved through alternative traditional medical systems using a multi-target network pharmacology approach. It involves targeting disease-causing proteins and their pathways through the use of medicinal plants that contain various bioactive ingredients [69].

In this study, a significant pharmacological risk is indicated by the chosen compounds' simultaneous failure of several supplemental rules (Ghose, Pfizer) and their poor overall drug-likeness scores. This is a crucial sign of difficulties in maximizing oral bioavailability and other growth parameters, rather than a minor divergence. Despite the intrinsic characteristics of the compounds, the risk can be decreased by structural change to address rule failures and negative scores or formulation strategies, including creating nanoparticles or encapsulation techniques, to improve absorption and

target specificity [70, 71]. ADMET (absorption, distribution, metabolism, excretion, and toxicity) profiles, biological activity data, and additional experimental validation should all be used in conjunction with drug likeness scores [72]. Important bioactive natural leads may be overlooked if substances are strictly filtered out based only on drug likeness ratings. Thus, compounds from plants with negative drug likeness scores can still be developed as drugs if supported by further pharmacological and biological studies [73, 74]. Among 1012 genes of gastric cancer having a GIFtS score of 60 or more, only 48 common genes are found with selected phytochemicals. From common target genes with high gene count, low p-value, and high fold enrichment, 10 hub genes, PTGS2, TLR4, NR3C1, RELA, JAK2, CDK2, PARP1, MAPK8, JAK1, and AR were recognized. Many studies reveal that the genes identified as core are druggable pathways relevant to multiple diseases [75, 76].

The KEGG pathways enrichment results showed that many disease pathways that were relevant to the gastric cancer study were enriched. To link protein targets to relevant biological pathways, KEGG enrichment analysis is utilized. The purpose of the investigation was to find possible biochemical pathways associated with the disease and the projected protein targets of the chosen phytochemicals [75]. The therapeutic impact of selected phytochemicals on gastric cancer may be produced by PD-L1 and PD-1 checkpoint pathways, NF-κB signaling pathway, pathways in cancer, and pathways related to Th1, Th2, and Th17 cell differentiation, and other pathways like Toll-like receptor signaling pathway, PI3K-Akt signaling pathway. Studies show that one of the most important cellular signaling routes, the NF-κB signaling pathway, is essential for both cell survival and apoptosis. Unchecked NF-κB signals cause many malignancies, and one of the primary anti-apoptotic factors in GC cells may be the aberrant activation of NF-κB in tumors. When activated, it can speed up the growth of tumors and produce potent anti-apoptotic signals [77]. Inhibitory immunological checkpoints are essential for the immune system's suppression, which is directly linked to the development and spread of cancer. In gastric cancer, PD-1, PD-L1, and PD-L2 are associated with lymph node metastases and staging [78, 79]. Furthermore, a previous study shows that cinnamaldehyde may enhance the sensitivity of gastric cancer cells to chemotherapy by regulating the PI3K-Akt pathway [80]. The GO study's functional annotation of 10 selected hub genes produced insightful and reliable findings for the current investigation. The technique of interpreting gene or protein sets by linking them to recognized biological functions, such as molecular functions (MFs), cellular components (CCs), and biological processes, is known as GO enrichment analysis [81].

A few disease pathways that were irrelevant to gastric cancer were also found, and have a shared set of hub proteins (RELA, TLR4, JAK2) that were common regulatory nodes for noncancerous diseases. A single gene can be found in dozens of KEGG pathways, which are maps of molecular interactions, due to its various roles [82]. Therefore, for the study, we chose signaling pathways that are closely associated with gastric cancer. Irrelevant KEGG enrichment results included necroptosis, pathways related to leishmaniasis, pathways related to toxoplasmosis, and Kaposi sarcoma-associated virus infection. Necroptosis is involved in pathological diseases like cancer, inflammation, and different organ damage, as well as physiological activities like host defense and development. Infection is strongly associated with gastric cancer, especially *Helicobacter pylori*, which produces chronic gastritis, a condition that precedes cancer [83]. Leishmaniasis is an infection with parasitic protozoa that can lead to internal organ infections or severe skin ulcers (cutaneous leishmaniasis). A parasite infection combined with a compromised immune system of cancer shares the molecular pathways that drive this inflammation, such as NF-κB activation [84]. Growing tumors and invasive pathogens frequently need unchecked cell proliferation and an expanded blood supply (angiogenesis), which causes the genes governing both processes to overlap [85].

5 Limitations

Except for the GC-MS analysis, the work was completely completed *in silico*. To validate these findings, *in vitro* and *in vivo* studies are required. This study is a depiction of pharmacological target data with predictive significance to the physiological system. The data on the target protein of cinnamaldehyde, cinnamyl acetate, linalool, and caryophyllene oxide is sparse, and the probability score for these three drugs is quite low. The selected compounds have a poor drug likeness score in ADMET. Despite these limitations, the study establishes a solid computational platform for future experimental and rational drug discovery efforts employing *Cinnamomum tamala*.

6 Conclusions

In conclusion, our study used network pharmacology with GC-MS profiling to clarify *Cinnamomum tamala*'s potential to prevent gastric cancer. The key bioactive components have been identified by chemical analysis to be cinnamaldehyde, cinnamyl acetate, linalool, and caryophyllene oxide. These

molecules regulate a network of 48 overlapping targets, according to a computational *in silico* study. The major hub proteins responsible for therapeutic activity were found to include PTGS2, TLR4, NR3C1, RELA, and JAK2.

The enrichment of the PD-L1 expression and PD-1 checkpoint pathway, together with the NF-κB signaling pathway, is a remarkable result of this study, indicating that *C. tamala* may prevent the progression of gastric cancer by modifying immune checkpoints and promoting apoptosis. Additionally, the finding of common protein targets between gastric cancer and a number of infectious diseases, including hepatitis B, toxoplasmosis, and leishmaniasis, indicates a shared regulatory mechanism in host defense and inflammatory responses.

These findings provide a molecular basis for the development of multi-target approaches to therapy and the repurposing of existing drugs. This study provides a cost-effective and time-efficient resource to guide future *in vitro* validation and clinical studies for the treatment of gastric cancer by identifying specific interactions between Himalayan phytochemicals and cancer-generating pathways.

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Author's contribution statement

Dipak Paudel: methodology, sample collection, laboratory work, software, and manuscript writing; **Dhaka Ram Bhandari, Santosh Koirala**: study design, data analysis, software, and manuscript review; **Dhaka Ram Bhandari, Megh Raj Pokhrel, Achyut Adhikari**: designed the study, supervised, analyzed the data, reviewed, and finalized the manuscript.

Conflict of interest

The authors do not have any conflicts of interest pertinent to this work.

Ethical statement

The research conducted is not related to either human or animal use.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Appendix

A Additional Tables

Table T1: Common major volatile compounds identified from the methanolic extract of three *C. tamala* experimental samples

S.N.	Compound	RT (min)	001A (%)	001C (%)	001H (%)
1	E-Cinnamaldehyde	12.09	18.42	29.59	14.65
2	Linalool	10.4	5.24	2.93	1.5
3	Glycerin	9.7	12.52	27.75	12.42
4	Propanoic acid, 2-oxo-, methyl ester	5.5	1.94	0.36	1.42
5	Acetic acid, cinnamyl ester	13.3	27.5	4.23	19.13
6	Hexadecanoic acid, methyl ester	16.3	1.98	1.19	1.82
7	2-Propenoic acid, 3-phenyl-, methyl ester (cinnamic acid)	12.9	1.02	0.55	0.86
8	Cinnamyl alcohol/2-Propen-1-ol, 3-phenyl-	12.3	3.27	2.51	3.31
9	Phenol	9.0	1.21	0.47	0.2
10	Phytol	17.3	2.59	2.62	2.72
11	9-Methoxybicyclo[6.1.0]nona-2,4,6-triene	13.0	2.09	6.9	3.31
12	2-Hydroxy-gamma-butyrolactone	9.1	1.6	–	1.26
13	Caryophyllene oxide	14.4	1.82	0.53	1.89
14	Cyclohexene,3-(1,5-dimethyl-4-hexenyl)-6-methy	13.95	1.55	–	1.19
15	1H-Cycloprop[e]azulen-7-ol, decahydro-1,1,7-trimethyl-4/(-)-Spathulenol	14.4	1.04	0.45	2.14
16	Benzofuran, 2,3-dihydro	11.5	0.7	1.09	0.41

B Additional Figures

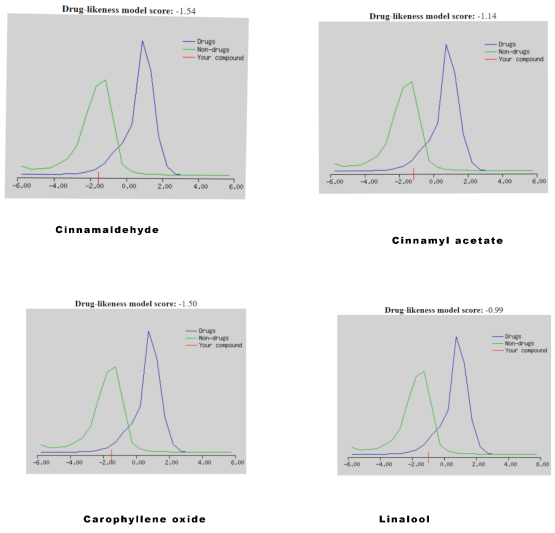

Figure F1: Drug likeness score of major compounds

Figure F2: Network status for common 48 target proteins.

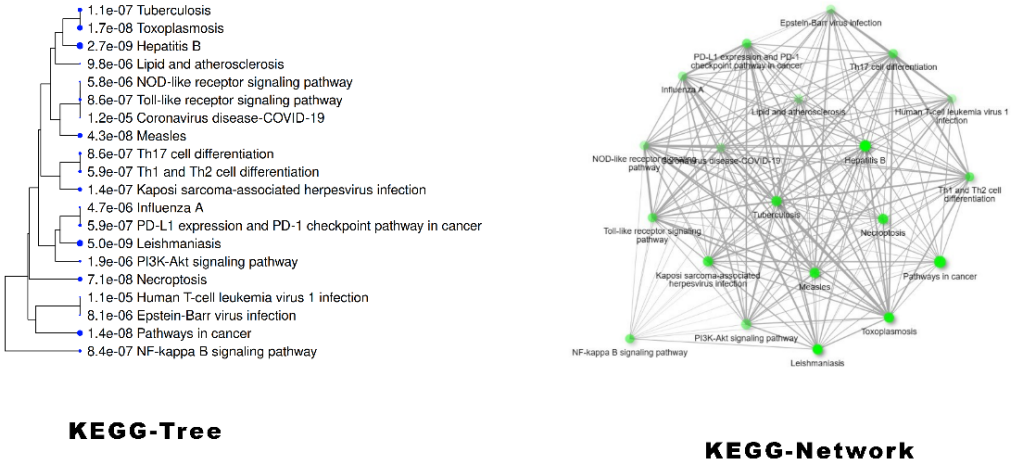

Figure F3: KEGG tree and pathway Network.

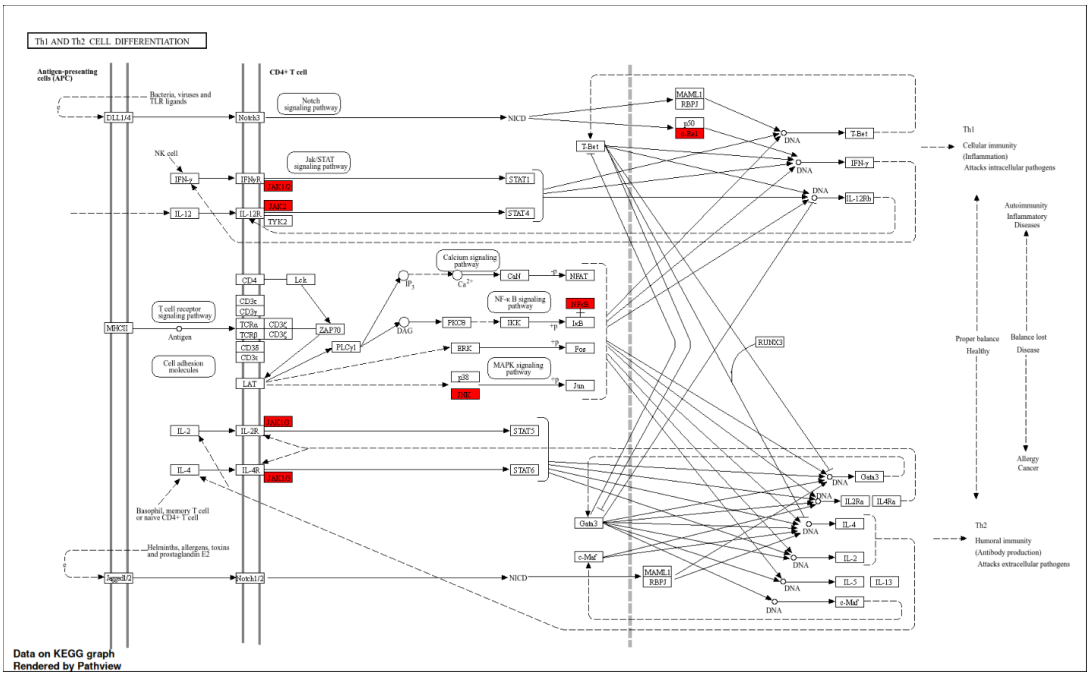

Figure F4: Gastric cancer related pathophysiology through Th1 and Th2 cell differentiation.

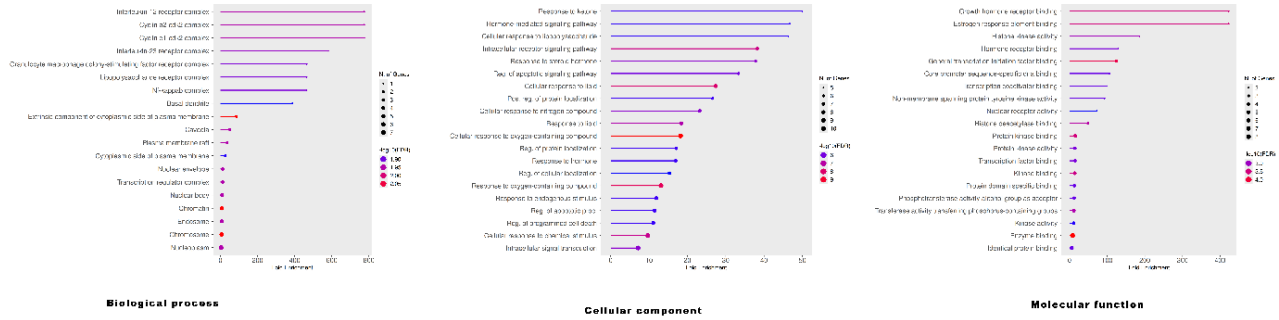

Figure F5: Gene Ontology (GO) analysis.