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# Integrated phytochemical profiling, network pharmacology-based in-silico study, and cytotoxicity evaluation of eggplant pulp and by-products

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## Abstract

The global trend towards sustainable development has encouraged the zero-waste approach of certain food by-products, to establish sustainable systems of production and consumption. Eggplant (*Solanum melongena* L.) by-products, particularly peel and calyx, are massively generated and usually discarded without further use despite their richness with beneficial phytochemicals. Therefore, this study aimed to investigate the phytochemical profile and anti-cancer activity of eggplant by-products. UPLC-QTOF-MS/MS phytochemical analysis, network pharmacology, molecular docking, and in-vitro cytotoxicity assay against prostate and cervical cell lines were conducted to investigate the phytochemical profile and anti-cancer potential of eggplant by-products. UPLC-QTOF-MS/MS analysis of eggplant peels and calyx afforded the identification of 50 and 41 secondary metabolites, respectively. The identified compounds mainly belonged to flavonoids and phenolic acid derivatives which showed high targeting towards cancer-related proteins through network pharmacology. Further, multi-target, multi-pathway network analysis showed the interactions of identified compounds with four key proteins including Akt-1, TNF- $\alpha$ , IL-1 $\beta$  and IL-6. Six bioactive compounds were docked to suggested key proteins according to network pharmacology findings, revealing that rutin has the best binding affinity to TNF- $\alpha$ , IL-1 $\beta$  and IL-6, while naringenin showed the best binding affinity to Akt-1. The suggested anti-cancer activity was confirmed by in-vitro cytotoxicity assay against prostate and cervical cancer cell lines which showed potent anti-cancer activity for peel (IC<sub>50</sub> 5.497 and 11.19  $\mu$ g/ml) followed by calyx (IC<sub>50</sub> 17.76 and 28.06  $\mu$ g/ml) and pulp (IC<sub>50</sub> 51.36 and 35.23  $\mu$ g/ml), respectively. These results highlight the potential of eggplant by-products as a sustainable resource for developing functional foods and nutraceuticals.

**Keywords** Sustainability, *Solanum melongena*, UPLC-QTOF-MS/MS analysis, Network pharmacology, Molecular docking, Anti-cancer activity



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## 1 Introduction

Since ancient times, natural product therapy has been employed to cure illnesses. Recently, the world has returned to utilize natural ingredients in modern medication development [1], including drugs fighting cancer, hypertension, migraine, cholera, coronary heart disease, gastrointestinal disorders, anemia, arthritis, atherosclerosis, asthma, bronchitis, and many other health problems [2]. The fruit of eggplant (*Solanum melongena* L.), belonging to the family Solanaceae, is an edible fruit served as a fundamental element of vegetarian food throughout the dawn of time [3]. Numerous bioactive phytochemicals identified in eggplant, such as flavonoids, ascorbic acid, alkaloids, carotenoids, tannins, saponins, steroids and phenolic compounds, are potent antioxidants that provide significant impacts on health [2, 4, 5]. Previous studies have proven the anti-cancer potential of eggplant fruit against different human cancer cells [6, 7]. In addition, it is considered as one of the top 10 vegetables due to its anti-inflammatory properties [8]. It has relatively low caloric value and is regarded as one of the healthiest vegetables due to its high content of dietary fibers, protein, vitamins, minerals, and various biologically active compounds [3, 9]. Eggplant's value extends beyond its edible part; its by-products, mainly peel and calyx, are of great interest and have been employed for nutritional and therapeutic uses in Africa for over two thousand years [2]. These by-products, generated by food processing industries and restaurants, are readily available in large quantities, cost-effective, and rich in valuable bioactive components [10]. Eggplant by-products have been documented to contain several bioactive compounds with various biological activities [4]. Numerous studies have confirmed that the peel is a rich source of polyphenolic compounds, associated with various biological activities [11]. Calyx has been reported to be a valuable by-product with promising antiviral, anticancer, anti-inflammatory, and antioxidant properties [12].

Every year, almost one-third of all food produced worldwide is lost or wasted, which has detrimental impacts on the economy, society, and environment [13]. Meanwhile, the global population is predicted to reach 9 billion by 2050 and more than 10.1 billion by the end of the twenty-first century. Population expansion will lead to rising global demands, putting enormous strain on the world to meet those demands [14]. Due to the magnitude of this crisis, the United Nations has included this challenge among the 17 Sustainable Development Goals in terms of responsible production and consumption, seeking to halve food loss and waste by 2030 [15]. The objective of this study is to investigate the chemical profile, network pharmacology-based in-silico and in-vitro anti-cancer activity of eggplant by-products, compared with eggplant pulp for the first time, to encourage their use as renewable raw materials in pharmaceutical products.

## 2 Materials and methods

### 2.1 Plant materials and preparation of the extracts

Black bell eggplant (*Solanum melongena* L.) fruits were obtained from a local farm in Menoufia, Egypt ([https://maps.app.goo.gl/y898mgs556boXjxY7?g\\_st=afm](https://maps.app.goo.gl/y898mgs556boXjxY7?g_st=afm)) in March 2024. Eggplant fruits were grown using organic farming approaches that depend on natural, health-safe products. The collection of samples was taken place with permission from the farm's owner (Supplementary 1) to be utilized for scientific research purposes. The techniques employed to gather samples complied with all relevant institutional, national, and international regulations. Samples were kindly authenticated by Prof. Dr.

Mona Roshdy Khalil, Department of Horticulture, Faculty of Agriculture, Menoufia University, Egypt. A voucher specimen (19-4-2024 F) was kept in the plant herbarium of pharmacognosy department, faculty of pharmacy, Cairo University, Cairo, Egypt. The plant materials, consisting of peel, calyx, and pulp, were dehydrated at 50 °C for 8 h and ground into fine powder, separately. Two hundred grams of dried powder from each sample were macerated in 500 mL of 80% ethanol at room temperature with continuous stirring for three days. The mixtures were then filtered, and the remaining residues were repeatedly re-extracted until complete exhaustion. The combined filtrates were concentrated using a rotary evaporator in a 40 °C water bath, and the obtained solid extracts were stored at – 20 °C for subsequent analysis.

## 2.2 UPLC-QTOF-MS/MS phytochemical profiling of the extracts

Phytochemical characterization of the ethanol extracts of *S. melongena* L. peel, calyx, and pulp was conducted with the XEVO G3 QTOF instrument (Waters Corporation, Milford, MA01757 U.S.A, Mass Spectrometer) equipped with an electrospray ESI source (voltage, 3.0 kV; sheath gas, nitrogen; capillary temperature, 440 °C). The ion trap MS system was combined with a UPLC apparatus with an ACQUITY UPLC BEH C18 column (1.7 µm particle size, 2.1 × 50 mm column). The analysis was carried out using a binary gradient elution system with a flow rate of 0.4 mL/min, using formic acid, concentrations of 0.1% in water and 0.1% in acetonitrile as mobile phases. The injection's volume was 1 µL from each sample and the running time was 25 min run and a 5 min recovery period. The spectra were acquired in both negative and positive ionization modes, over a mass-to-charge ( $m/z$ ) range from 100 – 1200 [16]. Compounds were identified using Mzmine-2.53, reference literature and Waters Traditional Medicine library.

## 2.3 Network pharmacology

SwissTargetPrediction, Herbal Ingredients' Targets Platform (HIT 2.0), and PharmMapper databases were selected to find the targets of the identified compounds in the calyx, peel, and pulp of eggplant and standardize the naming of gene targets using the UniProt database. The GeneCards, Online Mendelian Inheritance in Man (OMIM), DrugBank Online, and DisGeNET databases were used to identify the human gene targets of prostate cancer and cervical cancer. To find common targets for samples and diseases, the Venny 2.1.0 platform (<https://bioinfogp.cnb.csic.es/tools/venny/>) was utilized. A protein–protein interaction (PPI) network diagram of the essential targets was then created using the Cytoscape 3.10.3 program with the String database (<https://string-db.org/>) and the proteins that are not bound to the main network were removed. ShinyGO v 0.77 (<https://bioinformatics.sdstate.edu/go/>) was used to annotate the Gene Ontology (GO) and Kyoto Encyclopaedia of Genes and Genomes (KEGG) pathways for the designated organism “Homo Sapiens.” GO and KEGG pathway analysis was performed to investigate the protein cluster inside the network and its impact on enriched biological processes, molecular functions, cellular components, and pathway associated with prostate cancer and cervical cancer. The KEGG pathway network and the top 10 GO annotations were obtained by setting the cut-off FDR below 0.05 [17].

## 2.4 Molecular docking

The crystal structure of Serine/threonine protein kinase-1 (Akt-1) inhibitor complexes (PDB ID: 3MV5) <https://www.rcsb.org/structure/3MV5> [18], Tumor necrosis factor alpha (TNF- $\alpha$ ) complexed with a small molecule inhibitor (PDB ID: 2AZ5) <https://www.rcsb.org/structure/2AZ5> [19], Interleukin-1 beta (IL-1 $\beta$ ) Fragment bound to bikinin (PDB ID: 6Y8M) <https://www.rcsb.org/structure/6Y8M> [20], and human interleukin-6 (IL-6) (PDB ID: 1ALU) <https://www.rcsb.org/structure/1ALU> [20], were retrieved from the Protein Data Bank repository (accessed on 25 August, 2025). Protein preparation was carried out in PyRx 0.8 by removing all water molecules, heteroatoms, co-crystallized ligands and energy minimization. The processed protein structure was saved in PDBQT format for docking. Ligands were converted to PDBQT format using OpenBabel-3.1.1. All ligands were energy-minimized using the MMFF94 force field. The active site of each protein was defined based on the co-crystallized ligand binding site. The grid box was centered at X = 4.56; Y = 2.98; Z = 18.539 with dimensions X = 13.27; Y = 11.87; Z = 12.90 Å for 3MV5, while centered at X = -20.31; Y = 74.80; Z = 33.44 with dimensions XYZ: 15 Å for 2AZ5. In addition, IL-1 $\beta$  Fragment 6Y8M were grid box centered at X = 6.98; Y = 25.13; Z = -9.76 with dimensions X = 14.42; Y = 14.32; Z = 11.91 Å while IL-6 1ALU grid box centered at X = -7.72; Y = -13.24; Z = 0.0322 with dimensions X = 11.02; Y = 11.67; Z = 10.70 Å, docking simulations were performed in AutoDock Vina (PyRx interface). Binding affinity score (kcal/mol) were recorded for each ligand, and the scoring pose for each compound was shown in 2D and 3D figures. The resulting protein–ligand complexes were visualized in Discovery Studio Visualizer 2024 [21].

## 2.5 In-vitro MTT cytotoxicity assay

Viability of human cancer cell lines in the presence of the tested eggplant extracts was examined using MTT (methylthiazolyldiphenyl-tetrazolium bromide) cytotoxicity assay as described by Kainat et al. [11]. The assay in this experiment was performed by seeding prostate cancer cells (strain code: PC3, catalogue: Abcam; ab290466, Homo Sapiens, male) and cervical cancer cells (strain code: Hela, catalogue: Abcam; ab265646, Homo Sapiens, female) at a density of  $1 \times 10^4$  cells/mL in 96-well plates. All cell lines utilized during the current study were obtained from the American type culture collection (ATCC) via Holding company for biological products and vaccines (VACSERA), Cairo, Egypt. After 24-hour incubation, the cells were exposed to different concentrations (0.4 to 100  $\mu$ g/mL) of the samples. Each extract was tested in three replicates using the concentrations (100, 25, 6.3, 1.6 & 0.4  $\mu$ g/mL). Following incubation, the MTT dye (5 mg/mL in sterile phosphate buffered saline (PBS)) was added, and after 4-hour of incubation at 37 °C, formazan precipitates were dissolved in 100  $\mu$ L of concentrated dimethyl sulfoxide (DMSO). The experiment was repeated three times on separate days.

Cell viability was measured at 450 nm using a multi-well plate reader, and the results were expressed as percentages relative to the control. IC<sub>50</sub> values were obtained by plotting cell survival against concentration of the tested extracts using GraphPad Prism software.

The results were expressed as mean  $\pm$  standard deviation and analyzed using t-test with a significant level of  $P < 0.001$  and  $P < 0.05$ . The absorbance values from untreated cells were considered as 100% proliferation. The percentage of viability was calculated as:  $\left[1 - \left(\frac{OD_t}{OD_c}\right)\right] * 100\%$  Where: OD<sub>t</sub> is the mean optical density of wells treated with

the tested sample; ODC is the mean optical density of untreated cells. The 50% inhibitory concentration ( $IC_{50}$ ) defined as the concentration required to cause toxic effect in 50% of intact cells was assessed from graphic plots of the dose response curve for each concentration.

## 2.6 Statistical analysis

For in-vitro study, linear regression was used to calculate 50% inhibitory concentration ( $IC_{50}$ ). Microsoft EXCEL 2010 program and GraphPad Prism Version 6.00 were performed for data analysis and drawing the histograms. Data were presented as mean  $\pm$  SD.

## 3 Results

### 3.1 UPLC-QTOF-MS/MS phytochemical profiling of the extracts

A total of 58 bioactive secondary metabolites were identified through UPLC-QTOF-MS/MS chromatographic analysis in both positive and negative modes of the selected eggplant extracts as shown in Fig. 1. These metabolites, summarized in Table 1, were classified into phenolic acids and their derivatives, organic acids, flavonoids, anthocyanins, coumarins and their glycosides, amino acids, glycoalkaloids, and other miscellaneous compounds.

### 3.2 Network pharmacology

#### 3.2.1 Potential targets of eggplant compounds in prostate cancer and cervical cancer

The potential targets of the corresponding compounds of eggplant peel, calyx, and pulp were analyzed using SwissPrediction, HIT 2.0, and PharmMapper tools. After assessing the database and removing duplicate targets, 157, 119, and 91 proteins targeted by the compounds of peel, calyx, and pulp, respectively were obtained. Meanwhile, after searching GeneCard and OMIM databases and removing repeated proteins, 18,899 and 18,682 prostate and cervical cancer-related proteins were achieved, respectively. Furthermore, groups of proteins (drugs and disease) were intersected using Venn diagrams

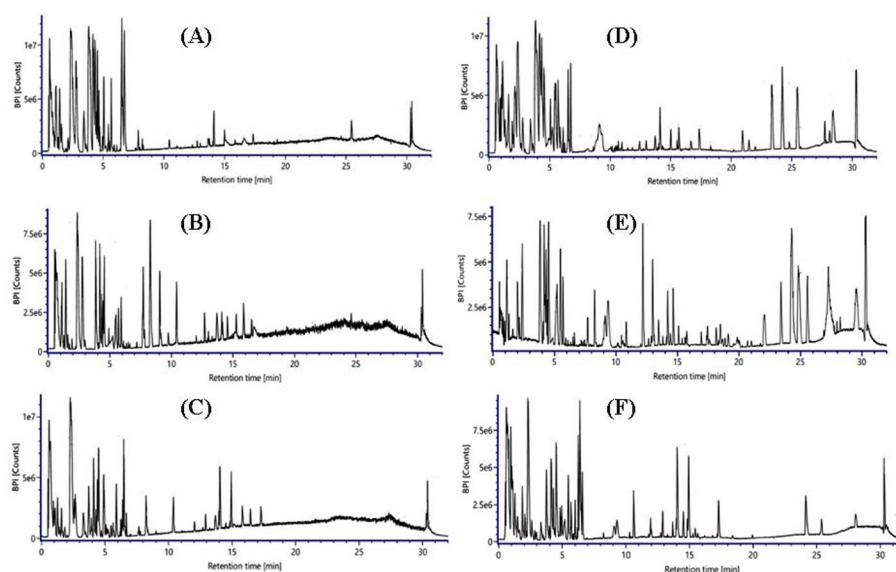


**Fig. 1** UPLC-QTOF-MS/MS chromatograms in negative ion mode of ethanolic extract of eggplant **A** peel, **B** calyx, **C** pulp and in positive ion mode of ethanolic extract of eggplant **D** peel, **E** calyx, **F** pulp

**Table 1** Secondary metabolites tentatively identified from peel, calyx, and pulp of eggplant fruits (*Solanum melongena* L.) using UPLC-QTOF-MS/MS

| No. | Rt   | Identified compound                              | Molecular formula                                             | Exact mass | Negative ion mode<br>[M-H] <sup>-</sup><br>m/z | Positive ion mode<br>[M+H] <sup>+</sup> /[M+Na] <sup>+</sup><br>m/z | Mass error | MS <sup>2</sup><br>m/z  | Peel | Calyx | Pulp | Chemical class      | Refs.    |
|-----|------|--------------------------------------------------|---------------------------------------------------------------|------------|------------------------------------------------|---------------------------------------------------------------------|------------|-------------------------|------|-------|------|---------------------|----------|
| 1   | 0.65 | Malic acid                                       | C <sub>4</sub> H <sub>6</sub> O <sub>5</sub>                  | 134.0215   | 133.0247                                       | -                                                                   |            |                         | ✓    | ✓     | ✓    | organic acid        | [25]     |
| 2   | 1.04 | Syringic acid                                    | C <sub>9</sub> H <sub>10</sub> O <sub>5</sub>                 | 198.0528   | 197.0457                                       | -                                                                   | 1          | 140, 125, 111           | ✓    | ✓     |      | Phenolic acid       | [15]     |
| 3   | 1.06 | Phenylalanine                                    | C <sub>9</sub> H <sub>11</sub> NO <sub>2</sub>                | 165.079    | 164.0717                                       | 166.0859/-                                                          | 0          | 147                     | ✓    | ✓     | ✓    | amino acid          | [31]     |
| 4   | 1.08 | Cinnamic acid                                    | C <sub>9</sub> H <sub>8</sub> O <sub>2</sub>                  | 148.0524   | 147.0448                                       | 149.0598/-                                                          | 0.9        | 103                     |      | ✓     | ✓    | Phenolic acid       | [15]     |
| 5   | 1.15 | Kaempferol-3,7-diglucoside                       | C <sub>27</sub> H <sub>30</sub> O <sub>16</sub>               | 610.1534   | 609.1469                                       | 611.1615/-                                                          | 1.3        | 284, 254, 227, 150      | ✓    |       |      | flavonoid           | [23]     |
| 6   | 1.15 | Cyanidin-3,5-di-O-glucoside                      | C <sub>27</sub> H <sub>30</sub> O <sub>16</sub>               | 610.1534   | 609.1469                                       | 611.1615/-                                                          | 1.3        | 449, 431, 329, 299, 287 | ✓    |       |      | Anthocyanin         | [29]     |
| 7   | 1.41 | 3-Caffeoylquinic acid (Neochlorogenic acid)      | C <sub>16</sub> H <sub>18</sub> O <sub>9</sub>                | 354.0951   | 353.0878                                       | 355.1023/ 377.0841                                                  | -0.4       | 191, 179, 135           | ✓    | ✓     | ✓    | Phenolic acid       | [15, 22] |
| 8   | 1.45 | Protocatechuic acid                              | C <sub>7</sub> H <sub>6</sub> O <sub>4</sub>                  | 154.0266   | 153.0192                                       | -                                                                   | -0.1       | 109, 97, 91, 81         | ✓    | ✓     | ✓    | Phenolic acid       | [10]     |
| 9   | 1.73 | Myricetin-3-neohesperidoside                     | C <sub>27</sub> H <sub>30</sub> O <sub>17</sub>               | 626.1483   | 625.1415                                       | -                                                                   | 0.7        | 479, 316, 270, 179, 151 | ✓    |       |      | flavonoid           | [15]     |
| 10  | 1.9  | Tryptophan                                       | C <sub>11</sub> H <sub>12</sub> N <sub>2</sub> O <sub>2</sub> | 204.0899   | 203.0825                                       | -                                                                   | -0.4       | 188                     | ✓    | ✓     | ✓    | amino acid          | [31]     |
| 11  | 2.31 | Delphinidin-3-rutinoside (Tulipalin)             | C <sub>27</sub> H <sub>31</sub> O <sub>16</sub>               | 610.1534   |                                                | 611.1619/-                                                          | 2          | 465, 303                | ✓    |       |      | Anthocyanin         | [15]     |
| 12  | 2.33 | 5-Caffeoylquinic acid (Chlorogenic acid)         | C <sub>16</sub> H <sub>18</sub> O <sub>9</sub>                | 354.0951   | 353.0877                                       | 355.1023/ 377.0841                                                  | -0.2       | 191                     | ✓    | ✓     | ✓    | Phenolic acid       | [15, 22] |
| 13  | 2.35 | Chlorogenic acid dimer                           | C <sub>32</sub> H <sub>36</sub> O <sub>18</sub>               | 708.1902   | -                                              | -731.1798                                                           | -3.2       | 355, 193                | ✓    | ✓     | ✓    | Phenolic acid       | [4, 5]   |
| 14  | 2.36 | Isoscopoletin                                    | C <sub>10</sub> H <sub>8</sub> O <sub>4</sub>                 | 192.0423   | 191.0346                                       | -                                                                   | -2.3       | 175, 145                |      |       | ✓    | coumarin derivative | [24]     |
| 15  | 2.7  | Caffeic acid                                     | C <sub>9</sub> H <sub>8</sub> O <sub>4</sub>                  | 180.0423   | -                                              | 181.0492/-                                                          | -1.7       | 135                     | ✓    | ✓     | ✓    | Phenolic acid       | [5]      |
| 16  | 2.75 | 4-O-Caffeoylquinic acid (Cryptochlorogenic acid) | C <sub>16</sub> H <sub>18</sub> O <sub>9</sub>                | 354.0951   | 353.0875                                       | 355.1023/ 377.0839                                                  | -0.7       | 191, 179, 173, 135      | ✓    | ✓     | ✓    | Phenolic acid       | [15, 22] |
| 17  | 2.76 | Arginine                                         | C <sub>6</sub> H <sub>14</sub> N <sub>4</sub> O <sub>2</sub>  | 174.1117   | 173.1456                                       | -                                                                   | 0.7        |                         | ✓    | ✓     | ✓    | amino acid          | [31]     |
| 18  | 2.78 | Shikimic acid                                    | C <sub>7</sub> H <sub>10</sub> O <sub>5</sub>                 | 174.0528   | 173.0456                                       | -                                                                   | -0.7       | 155, 137, 111           | ✓    | ✓     | ✓    | organic acid        | [25]     |
| 19  | 2.79 | Delphinidin-3-glucoside                          | C <sub>21</sub> H <sub>21</sub> O <sub>12</sub>               | 465.1033   | -                                              | 466.1112/-                                                          | 1.3        | 303, 229                | ✓    |       |      | Anthocyanin         | [15]     |
| 20  | 3.1  | Vanillic acid                                    | C <sub>8</sub> H <sub>8</sub> O <sub>4</sub>                  | 168.0423   | 167.0345                                       | -                                                                   | -2.9       | 152, 108                |      | ✓     |      | Phenolic acid       | [10]     |
| 21  | 3.82 | p-Coumaric acid                                  | C <sub>9</sub> H <sub>8</sub> O <sub>3</sub>                  | 164.0473   | -                                              | 165.0543/-                                                          | 2.1        | 119, 93                 | ✓    | ✓     |      | Phenolic acid       | [15]     |
| 22  | 3.86 | Quercetin-3-O-rutinoside (Rutin)                 | C <sub>27</sub> H <sub>30</sub> O <sub>16</sub>               | 610.1534   | 609.1467                                       | 611.1615/ 633.1431                                                  | 0.9        | 300, 271, 179, 135      | ✓    |       |      | flavonoid           | [15]     |
| 23  | 3.94 | Scopolin (scopoletin-7-O-glucoside)              | C <sub>16</sub> H <sub>18</sub> O <sub>9</sub>                | 354.0951   | 353.0879                                       | -737.0837                                                           | 0.3        | 191, 175, 145           | ✓    |       |      | coumarin derivative | [24]     |

**Table 1** (continued)

| No. | Rt   | Identified compound                               | Molecular formula                                             | Exact mass | Negative ion mode [M-H] <sup>-</sup> m/z | Positive ion mode [M+H] <sup>+</sup> /[M+Na] <sup>+</sup> m/z | Mass error | MS <sup>2</sup> m/z                    | Peel | Calyx | Pulp | Chemical class      | Refs.       |
|-----|------|---------------------------------------------------|---------------------------------------------------------------|------------|------------------------------------------|---------------------------------------------------------------|------------|----------------------------------------|------|-------|------|---------------------|-------------|
| 24  | 4.61 | Quercetin-3-O-galactoside-7-O-glucoside           | C <sub>27</sub> H <sub>30</sub> O <sub>17</sub>               | 626.1483   | 625.1416                                 | 627.1561/-                                                    | 0.8        | 463, 300, 271, 255, 234, 229, 179, 151 | ✓    |       |      | flavonoid           | [15]        |
| 25  | 4.64 | Delphinidin-3,5-diglucoside                       | C <sub>27</sub> H <sub>30</sub> O <sub>17</sub>               | 626.1483   | 625.1416                                 | 627.1574/ 649.1374                                            | 0.9        | 465, 303                               | ✓    | ✓     |      | Anthocyanin         | [27]        |
| 26  | 4.65 | Myricetin-3-galactoside                           | C <sub>21</sub> H <sub>20</sub> O <sub>13</sub>               | 480.0904   | -                                        | 481.0977/-                                                    | 0.1        | 318, 273                               | ✓    |       |      | flavonoid           | [15]        |
| 27  | 4.72 | Kaempferol                                        | C <sub>15</sub> H <sub>10</sub> O <sub>6</sub>                | 286.0477   | -                                        | 287.0544/-                                                    | -2.2       | 181, 153                               | ✓    |       |      | flavonoid           | [26, 27]    |
| 28  | 4.98 | Scopoletin                                        | C <sub>10</sub> H <sub>8</sub> O <sub>4</sub>                 | 192.0423   | 191.0348                                 | -                                                             | -1.1       | 175, 145                               | ✓    | ✓     | ✓    | coumarin derivative | [24]        |
| 29  | 5.12 | Ferulic acid                                      | C <sub>10</sub> H <sub>10</sub> O <sub>4</sub>                | 194.0579   | 193.0506                                 | -                                                             | -0.3       | 178, 149, 134                          | ✓    | ✓     | ✓    | Phenolic acid       | [10]        |
| 30  | 5.16 | N-Caffeoyl tyramine                               | C <sub>17</sub> H <sub>17</sub> NO <sub>4</sub>               | 299.1158   | 298.1085                                 | -                                                             | 0.2        | 161                                    | ✓    | ✓     | ✓    | phenolic amide      | [24]        |
| 31  | 5.2  | Tyrosine                                          | C <sub>9</sub> H <sub>11</sub> NO <sub>3</sub>                | 181.0739   | 180.0669                                 | -                                                             | -0.8       | 163                                    |      | ✓     |      | amino acid          | [31]        |
| 32  | 5.27 | Kaempferol-3-O-rutinoside (Nicotiflorin)          | C <sub>27</sub> H <sub>30</sub> O <sub>15</sub>               | 594.1585   | -                                        | 595.1489/ 617.1479                                            | 0.3        | 449, 287                               | ✓    | ✓     |      | flavonoid           | [28]        |
| 33  | 5.3  | Apigenin 6,8-C-diglucoside                        | C <sub>27</sub> H <sub>30</sub> O <sub>15</sub>               | 594.1585   | -                                        | -/617.1480                                                    | 0.4        | 271, 153                               | ✓    | ✓     |      | flavonoid           | [27]        |
| 34  | 5.44 | Quercetin-3-O-rhamnoside                          | C <sub>21</sub> H <sub>20</sub> O <sub>11</sub>               | 448.1006   | -                                        | 449.1082/-                                                    | 0.7        | 303, 273, 257, 153                     | ✓    |       |      | flavonoid           | [15]        |
| 35  | 5.56 | 3,5-Dicaffeoylquinic acid (Isochlorogenic acid B) | C <sub>25</sub> H <sub>24</sub> O <sub>12</sub>               | 516.1268   | 515.1196                                 | 517.1169/ 539.1167                                            | 0.1        | 353, 191, 179, 135                     | ✓    | ✓     | ✓    | Phenolic acid       | [15, 22]    |
| 36  | 5.61 | Kaempferol-3-O-glucoside                          | C <sub>21</sub> H <sub>20</sub> O <sub>11</sub>               | 448.1006   | 447.0936                                 | 449.1075/-                                                    | -0.8       | 284, 255, 227                          | ✓    | ✓     |      | flavonoid           | [15]        |
| 37  | 5.66 | 3,4-Dicaffeoylquinic acid                         | C <sub>25</sub> H <sub>24</sub> O <sub>12</sub>               | 516.1268   | 515.1195                                 | -                                                             | 0.1        | 353, 335, 191, 179, 135                | ✓    |       | ✓    | Phenolic acid       | [15, 22]    |
| 38  | 5.74 | Luteolin-7-O-glucoside                            | C <sub>21</sub> H <sub>20</sub> O <sub>11</sub>               | 448.1006   | 447.0934                                 | -                                                             | 0.4        | 287, 147, 129                          | ✓    | ✓     |      | flavonoid           | [29]        |
| 39  | 5.8  | N-p-coumaroyl octopamine                          | C <sub>17</sub> H <sub>17</sub> NO <sub>4</sub>               | 299.1158   | 298.1087                                 | -                                                             | 0.8        | 135                                    | ✓    | ✓     | ✓    | phenolic amide      | [24]        |
| 40  | 5.84 | 4,5-Dicaffeoylquinic acid                         | C <sub>25</sub> H <sub>24</sub> O <sub>12</sub>               | 516.1268   | 515.12                                   | -                                                             | 0.9        | 353, 191, 179, 173                     | ✓    | ✓     | ✓    | Phenolic acid       | [4, 22, 23] |
| 41  | 6.26 | Solasone                                          | C <sub>45</sub> H <sub>73</sub> NO <sub>16</sub>              | 883.4929   | -                                        | 884.5012/-                                                    | 1.1        | 576, 454, 414                          | ✓    |       | ✓    | Glycoalkaloid       | [32]        |
| 42  | 6.39 | Solamargine                                       | C <sub>45</sub> H <sub>73</sub> NO <sub>15</sub>              | 867.498    | -                                        | 868.5058/-                                                    | 0.5        | 722, 576, 445                          | ✓    |       | ✓    | Glycoalkaloid       | [32]        |
| 43  | 6.66 | N-Feruloyl putrescine                             | C <sub>14</sub> H <sub>20</sub> N <sub>2</sub> O <sub>3</sub> | 264.1474   | 263.1297                                 | -                                                             | -2.4       | 175, 143                               | ✓    | ✓     | ✓    | phenolic amide      | [24]        |
| 44  | 6.97 | Naringenin                                        | C <sub>15</sub> H <sub>12</sub> O <sub>5</sub>                | 272.0685   | 271.0608                                 | -                                                             | -1.4       | 203, 161                               | ✓    | ✓     | ✓    | flavonoid           | [26]        |
| 45  | 7.15 | Caffeic acid ethyl ester                          | C <sub>11</sub> H <sub>12</sub> O <sub>4</sub>                | 208.0736   | 207.0657                                 | -                                                             | -2.6       | 179, 133                               |      | ✓     |      | Phenolic ester      | [5]         |

Table 1 (continued)

| No. | Rt    | Identified compound                         | Molecular formula                                             | Exact mass | Negative ion mode [M-H] <sup>-</sup> m/z | Positive ion mode [M+H] <sup>+</sup> /[M+Na] <sup>+</sup> m/z | Mass error | MS <sup>2</sup> m/z | Peel | Calyx | Pulp | Chemical class   | Refs. |
|-----|-------|---------------------------------------------|---------------------------------------------------------------|------------|------------------------------------------|---------------------------------------------------------------|------------|---------------------|------|-------|------|------------------|-------|
| 46  | 13.25 | N-p-coumaroyl putrescine                    | C <sub>13</sub> H <sub>18</sub> N <sub>2</sub> O <sub>2</sub> | 234.1368   | 233.1553                                 | -                                                             | 2.8        | 216, 145            | ✓    | ✓     | ✓    | phenolic amide   | [24]  |
| 47  | 13.33 | 9-Oxo-(10,12)-octadecadienoic acid          | C <sub>18</sub> H <sub>30</sub> O <sub>3</sub>                | 294.2195   | 293.2122                                 | -                                                             | -0.2       | 185                 | ✓    | ✓     | ✓    | fatty acid       | [12]  |
| 48  | 14.14 | N-p-coumaroyl putrescine (isomer)           | C <sub>13</sub> H <sub>18</sub> N <sub>2</sub> O <sub>2</sub> | 234.1368   | 233.1551                                 | -                                                             | 2.6        | 216, 145            | ✓    | ✓     | ✓    | phenolic amide   | [24]  |
| 49  | 15.28 | 9-Oxo-(10,12)-octadecadienoic acid (isomer) | C <sub>18</sub> H <sub>30</sub> O <sub>3</sub>                | 294.2195   | 293.2116                                 | -                                                             | -2.1       | 185                 | ✓    | ✓     | ✓    | fatty acid       | [12]  |
| 50  | 15.58 | 9-Oxo-(10,12)-octadecadienoic acid (isomer) | C <sub>18</sub> H <sub>30</sub> O <sub>3</sub>                | 294.2195   | 293.2131                                 | -                                                             | 3          | 203                 | ✓    | ✓     | ✓    | fatty acid       | [12]  |
| 51  | 15.88 | N-Hexadecanoic acid (Palmitic acid)         | C <sub>16</sub> H <sub>32</sub> O <sub>2</sub>                | 256.2402   | 255.2337                                 | -                                                             | 2.8        | 203                 | ✓    | ✓     | ✓    | fatty acid       | [11]  |
| 52  | 15.89 | Pyroglutamic acid (oxoprolinone)            | C <sub>5</sub> H <sub>7</sub> NO <sub>3</sub>                 | 129.0426   | 128.0354                                 | -                                                             | -1.1       | 84, 82              | ✓    | ✓     | ✓    | amino acid       | [31]  |
| 53  | 16.96 | Delphinidin-3-O-(6'-O-malonyl)-glucoside    | C <sub>24</sub> H <sub>23</sub> O <sub>15</sub> <sup>+</sup>  | 551.1037   | -                                        | 552.1094/-                                                    | -2.9       | 303, 229            | ✓    | ✓     | ✓    | Anthocyanin      | [30]  |
| 54  | 25.51 | Stigmasteryl-glucopyranoside                | C <sub>35</sub> H <sub>58</sub> O <sub>6</sub>                | 574.4233   | -                                        | -/597.4132                                                    | 1          | 395                 | ✓    | ✓     | ✓    | steryl glycoside | [33]  |
| 55  | 26.32 | Sitosteryl-glucopyranoside                  | C <sub>35</sub> H <sub>60</sub> O <sub>6</sub>                | 576.439    | -                                        | -/599.4291                                                    | 1.4        | 397                 | ✓    | ✓     | ✓    | steryl glycoside | [33]  |
| 56  | 29.65 | N-cafeoyl putrescine                        | C <sub>13</sub> H <sub>18</sub> N <sub>2</sub> O <sub>3</sub> | 250.1317   | 249.1495                                 | -                                                             | 1.2        | 232, 161            | ✓    | ✓     | ✓    | phenolic amide   | [23]  |
| 57  | 30.2  | N-cafeoyl putrescine (isomer)               | C <sub>13</sub> H <sub>18</sub> N <sub>2</sub> O <sub>3</sub> | 250.1317   | 249.1494                                 | -                                                             | 1.1        | 232, 161            | ✓    | ✓     | ✓    | phenolic amide   | [23]  |
| 58  | 30.2  | Isoleucine                                  | C <sub>6</sub> H <sub>13</sub> NO <sub>2</sub>                | 131.0946   | -                                        | 132.1017/-                                                    | -1.7       | 115                 | ✓    | ✓     | ✓    | amino acid       | [31]  |

(Venny 2.1.0). It showed that all proteins that were considered potential targets of eggplant compounds are overlapped with prostate and cervical cancer therapy (Fig. 2). It provided 70 common targets in eggplant peel, calyx, pulp, and prostate/cervical cancer, 51 common targets in peel and prostate/cervical cancer, 31 common targets in peel, calyx, and prostate/cervical cancer, 16 common targets in calyx, pulp, and prostate/cervical cancer, 5 common targets in peel, pulp, and prostate/cervical cancer and 2 common targets in calyx and prostate/cervical cancer.

### 3.2.2 Compound-target-disease network

The target proteins obtained from venn diagram were utilized to construct four Compound-Target-Disease Networks by using Cytoscape 3.10.3 and the networks were analyzed according to degree, closeness, and betweenness centralities to compare the anti-cancer activities of eggplant peel, calyx, and pulp. As shown in (Fig. 3A; Table 2), the compounds identified in eggplant peel targeted more prostate/cervical related proteins that those in calyx and pulp. By building and analyzing the second network (Fig. 3B; Table 2) to illustrate the core compounds in eggplant peel that target cancer related proteins, the anticancer activity of eggplant peel may be due to the existence of valuable bioactive compounds such as kaempferol, rutin, naringenin, caffeic acid, ferulic acid, *p*-coumaric acid, 3-caffeoylquinic acid, syringic acid, quercetin-3-*O*-rhamnoside, protocathechuic acid, kaempferol 3-*O*-glucoside, luteolin-7-*O*-glucoside, scopoletin, myricetin-3-galactoside, solamargine, scopolin, myricetin-3-neohesperidoside, kaempferol-3-*O*-rutinoside, 5-caffeoylquinic acid, 3,5-dicaffeoylquinic acid, *N*-caffeoyltyramine, 4-*O*-caffeoylquinic acid, delphinidin-3 glucoside, and phenylalanine. The anti-cancer activity of eggplant calyx, according to its compound-target-disease network (Fig. 3C; Table 2), may be a result of its bioactive compounds, such as naringenin, caffeic acid, ferulic acid, *p*-coumaric acid, *N*-hexadecanoic acid, 3-caffeoylquinic acid, syringic acid, kaempferol 3-*O*-glucoside, protocathechuic acid, luteolin-7-*O*-glucoside, scopoletin, cinnamic acid, vanillic acid, kaempferol-3-*O*-rutinoside, *N*-caffeoyltyramine, 1,3 dicaffeoylquinic acid, 5-caffeoylquinic acid, 4-*O*-caffeoylquinic acid, and phenylalanine. While the compound-target-disease network of the pulp (Fig. 3D; Table 2) showed that its anti-cancer activity is may be due to caffeic acid, ferulic acid, *N*-hexadecanoic acid, 3-caffeoylquinic acid, protocathechuic acid, scopoletin, solamargine, cinnamic acid,

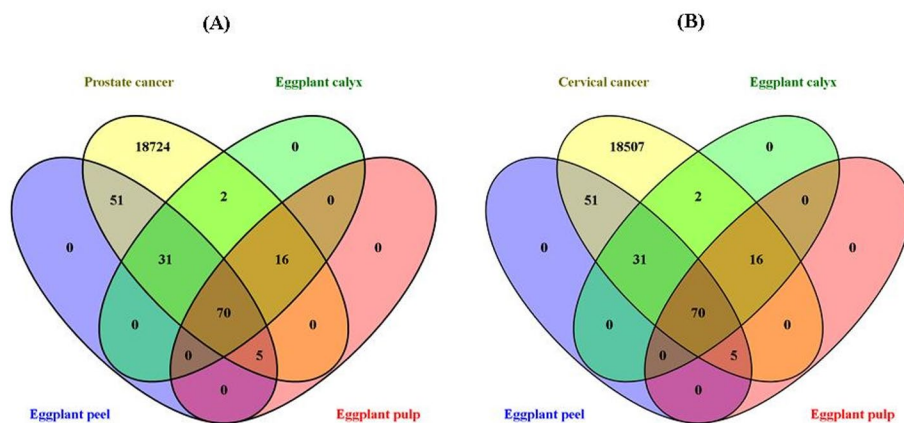


**Fig. 2** Venn Diagram Analysis Intersection of **A** Prostate cancer related protein with eggplant compound target and **B** Cervical cancer related protein with eggplant compound target

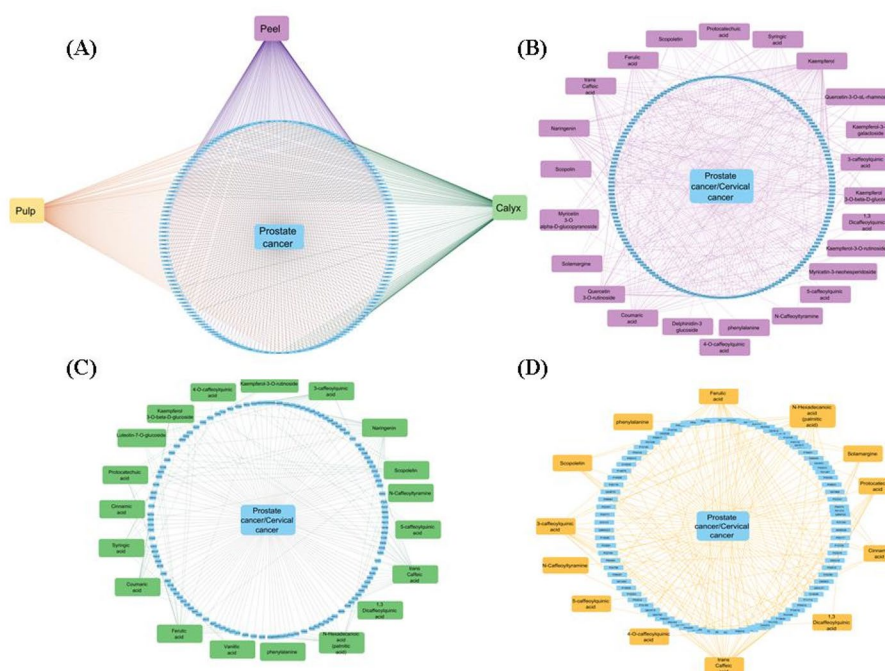


**Fig. 3** Compound-Target-Disease Networks **A:** Compounds of eggplant peel, calyx, and pulp-Target-Prostate/cervical cancer Network. **B:** Peel compounds-Target-Prostate/cervical cancer Network. **C:** Calyx compounds-Target-Prostate/cervical cancer Network. **D:** Pulp compounds-Target-Prostate/cervical cancer Network

*N*-caffeoyltyramine, 1,3-dicaffeoylquinic acid, 5-caffeoylquinic acid, 4-*O*-caffeoylquinic acid, and phenylalanine. The pulp is expected to have the lowest anti-cancer properties compared to peel and calyx, as illustrated in its compound-target-disease-network, due to the absence of many bioactive compounds which encourage the bioactivities of peel and calyx.

### 3.2.3 Protein-protein interaction

The online tools STRING and the Cytoscape software program were used to construct protein-protein interactions. According to the PPI data shown in Fig. 4A, certain proteins in the main cluster network were further away, and others showed no interaction at all. Protein interactions in the final network consist of 141 nodes and 959 edges (Fig. 4B). Additionally, network analysis was performed using Cytoscape, which offered distinct scores for three critical topological parameters: degree, betweenness, and closeness centrality. Top 10 proteins displaying the highest scores (Table 3) were obtained by using Cytohubba and further intersected by venn diagram (Fig. 5A–D). This analysis revealed five potential proteins in the interaction, including IL1 $\beta$ , IL6, TNF, Akt-1, and INS and suggested as key proteins. The Compound-Target network has showed that IL1 $\beta$ , IL6, and INS are targeted by rutin, TNF is targeted by caffeic acid, kaempferol, quercetin 3-*O*-rutinoside, naringenin, and solamargine, and Akt-1 is targeted by protocatechuic acid and naringenin.

### 3.2.4 Gene ontology enrichment and KEGG signal pathway analysis

To investigate and compare the molecular function, cellular components, and biological processes related to prostate/cervical cancer that bioactive compounds of peel, calyx,

**Table 2** Analysis of compound-target-disease network according to degree, closeness, and betweenness centralities

| Name                                                              | Degree | Closeness centrality | Betweenness centrality |
|-------------------------------------------------------------------|--------|----------------------|------------------------|
| (A) Eggplant peel, calyx, and pulp-target-cancer network analysis |        |                      |                        |
| Peel                                                              | 157    | 0.8202               | 0.3223                 |
| Calyx                                                             | 119    | 0.6075               | 0.1446                 |
| Pulp                                                              | 91     | 0.5100               | 0.0750                 |
| (B) Peel compounds-target-cancer network analysis                 |        |                      |                        |
| Kaempferol                                                        | 58     | 0.4279               | 0.0551                 |
| Rutin                                                             | 28     | 0.3720               | 0.0123                 |
| Naringenin                                                        | 28     | 0.3733               | 0.0123                 |
| Caffeic acid                                                      | 26     | 0.3733               | 0.0107                 |
| Ferulic acid                                                      | 23     | 0.3678               | 0.0089                 |
| p-coumaric acid                                                   | 20     | 0.3638               | 0.0069                 |
| 3-caffeoylquinic acid                                             | 16     | 0.3585               | 0.0046                 |
| Syringic acid                                                     | 11     | 0.3473               | 0.001                  |
| Quercetin-3-O-rhamnoside                                          | 11     | 0.3547               | 0.0016                 |
| Protocatechuic acid                                               | 10     | 0.3461               | 0.0012                 |
| Kaempferol-3-O-glucoside                                          | 10     | 0.3535               | 0.0012                 |
| Luteolin-7-O-glucoside                                            | 9      | 0.3522               | 9.81E-04               |
| Scopoletin                                                        | 8      | 0.3449               | 0.0010                 |
| Myricetin-3-galactoside                                           | 7      | 0.3497               | 5.31E-04               |
| Solamargine                                                       | 7      | 0.3344               | 5.31E-04               |
| Scopolin                                                          | 6      | 0.3413               | 5.17E-04               |
| Myricetin-3-neohesperidoside                                      | 4      | 0.3367               | 1.38E-04               |
| Kaempferol-3-O-rutinoside                                         | 4      | 0.3367               | 1.38E-04               |
| 5-caffeoylquinic acid                                             | 2      | 0.3322               | 5.38E-05               |
| 3,5-Dicaffeoylquinic acid                                         | 2      | 0.3236               | 2.54E-05               |
| N-Caffeoyltyramine                                                | 2      | 0.3246               | 2.73E-05               |
| 4-O-caffeoylquinic acid                                           | 1      | 0.3311               | 0                      |
| Delphinidin-3 glucoside                                           | 1      | 0.3225               | 0                      |
| Phenylalanine                                                     | 1      | 0.3225               | 0                      |
| (C) Calyx compounds-target-cancer network                         |        |                      |                        |
| Naringenin                                                        | 28     | 0.3887               | 0.0243                 |
| Caffeic acid                                                      | 26     | 0.3909               | 0.0219                 |
| Ferulic acid                                                      | 23     | 0.3802               | 0.0169                 |
| p-coumaric acid                                                   | 20     | 0.3781               | 0.0147                 |
| N-Hexadecanoic acid                                               | 18     | 0.3547               | 0.0084                 |
| 3-caffeoylquinic acid                                             | 16     | 0.3680               | 0.0096                 |
| Syringic acid                                                     | 11     | 0.3529               | 0.0028                 |
| Kaempferol-3-O-glucoside                                          | 10     | 0.3584               | 0.0032                 |
| Protocatechuic acid                                               | 10     | 0.3494               | 0.0021                 |
| Luteolin-7-O-glucoside                                            | 9      | 0.3566               | 0.002                  |
| Scopoletin                                                        | 8      | 0.3476               | 0.0019                 |
| Cinnamic acid                                                     | 6      | 0.3424               | 0.0012                 |
| Vanillic acid                                                     | 5      | 0.332                | 5.86E-04               |
| Kaempferol-3-O-rutinoside                                         | 4      | 0.3358               | 4.47E-04               |
| N-Caffeoyltyramine                                                | 2      | 0.3247               | 5.68E-05               |
| 3,5-Dicaffeoylquinic acid                                         | 2      | 0.3232               | 5.29E-05               |
| 5-caffeoylquinic acid                                             | 2      | 0.3309               | 9.17E-05               |
| Phenylalanine                                                     | 1      | 0.3217               | 0                      |
| 4-O-caffeoylquinic acid                                           | 1      | 0.3293               | 0                      |
| (D) Pulp compounds-target-cancer network                          |        |                      |                        |
| Caffeic acid                                                      | 26     | 0.4078               | 0.0446                 |
| Ferulic acid                                                      | 23     | 0.3754               | 0.0263                 |

**Table 2** (continued)

| Name                      | Degree | Closeness centrality | Betweenness centrality |
|---------------------------|--------|----------------------|------------------------|
| N-Hexadecanoic acid       | 18     | 0.3701               | 0.0235                 |
| 3-caffeoylquinic acid     | 16     | 0.3782               | 0.0216                 |
| Protocatechuic acid       | 10     | 0.3388               | 0.0040                 |
| Scopoletin                | 8      | 0.336                | 0.0029                 |
| Solamargine               | 7      | 0.3432               | 0.0944                 |
| Cinnamic acid             | 6      | 0.3301               | 0.0015                 |
| N-Caffeoyltyramine        | 2      | 0.3180               | 1.00E-04               |
| 3,5-Dicaffeoylquinic acid | 2      | 0.3161               | 9.34E-05               |
| 5-caffeoylquinic acid     | 2      | 0.3200               | 1.24E-04               |
| Phenylalanine             | 1      | 0.3142               | 0                      |
| 4-O-caffeoylquinic acid   | 1      | 0.3180               | 0                      |

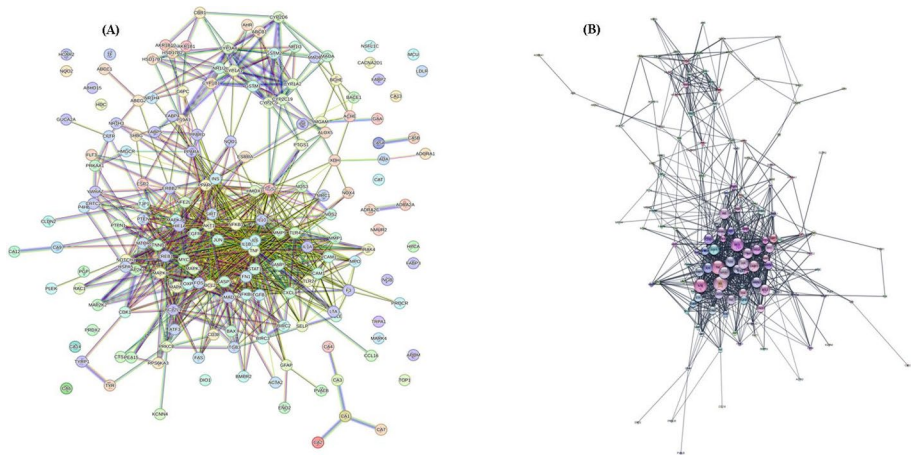


**Fig. 4** Protein–Protein Interaction network of eggplant compound target in prostate/cervical cancer. **A:** The PPI Network of 175 protein targets of eggplant compounds targeting prostate/cervical cancer therapy according to STRING. **B:** The PPI Network of 141 protein targets of eggplant compounds targeting prostate/cervical cancer therapy after clearing non interaction protein with the main network

**Table 3** Top 10 proteins related to prostate/cervical cancer targeted by eggplant compounds

| Name         | Degree | Closeness centrality | Betweenness centrality |
|--------------|--------|----------------------|------------------------|
| IL-6         | 57     | 0.5472               | 0.0637                 |
| TNF          | 54     | 0.5451               | 0.0616                 |
| IL-1 $\beta$ | 53     | 0.5387               | 0.0523                 |
| AKT1         | 52     | 0.5451               | 0.0938                 |
| NFKB1        | 44     | 0.5110               | 0.0199                 |
| CASP3        | 41     | 0.5110               | 0.0338                 |
| JUN          | 41     | 0.5110               | 0.0156                 |
| BCL2         | 40     | 0.4964               | 0.0276                 |
| INS          | 40     | 0.5091               | 0.1421                 |
| CTNNB1       | 38     | 0.5054               | 0.0376                 |

and pulp target, Gene Ontology analysis was conducted as shown in (Fig. 6) that illustrate the top 10 molecular functions, cellular components, biological processes, and KEGG pathways related to each part of eggplant. Gene Ontology analysis intended to forecast a comprehensive understanding of the changes in biological processes, cellular components, and molecular functions that take place in prostate/cervical cancer when the selected eggplant parts were challenged into the disease. There were 531, 448,

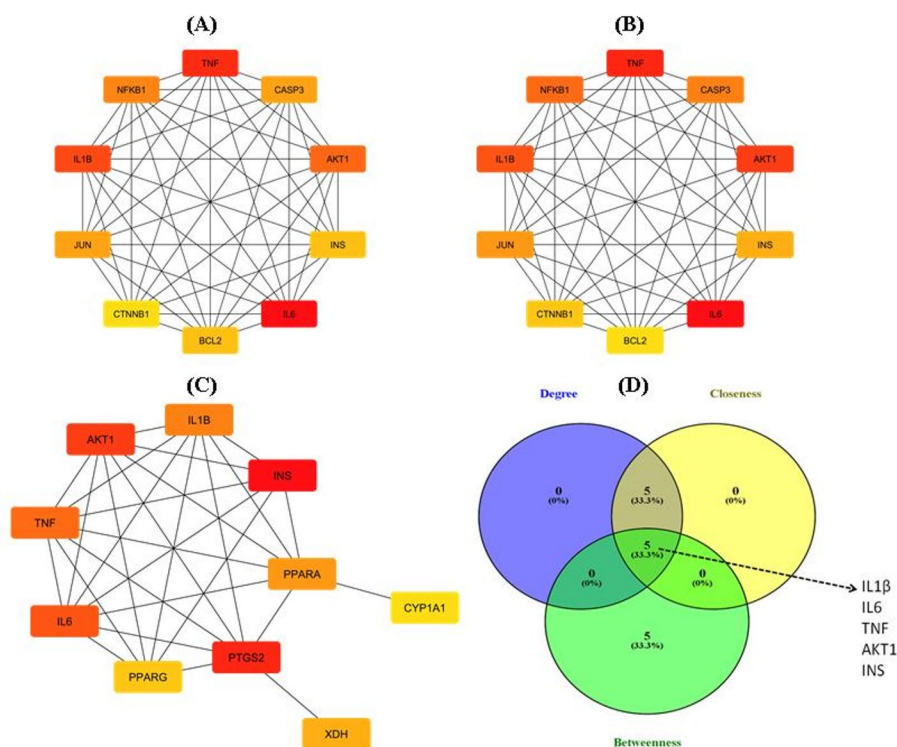


**Fig. 5** Top 10 potential target protein in different centrality based on highest score. **A:** Degree **B:** Closeness **C:** Betweenness **D:** Venn diagram of top 10 proteins that figurize five obtained key proteins including IL1 $\beta$ , IL6, TNF, Akt-1, and INS

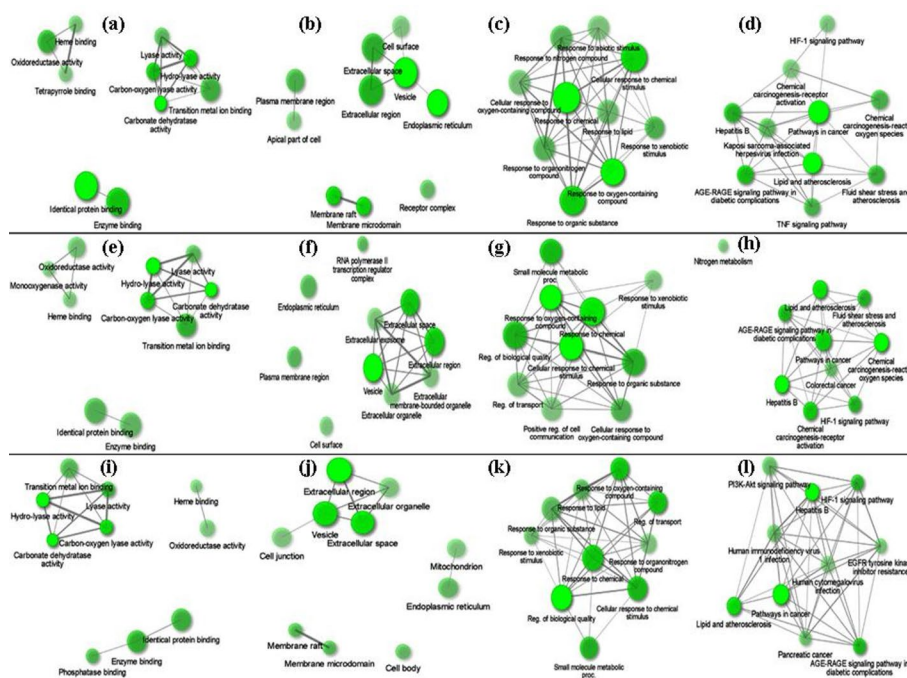


**Fig. 6** Network of the top 10 molecular functions, cellular components, biological processes, and KEGG pathways, respectively of: **(a, b, c, d)** eggplant peel, **(e, f, g, h)** eggplant calyx, and **(i, j, k, l)** eggplant pulp

and 349 molecular functions detected for peel, calyx, and pulp, respectively, including essential molecular functions, which have a significant relationship with cancer development and progression, such as transition metal ion binding, oxidoreductase activity, and lyase activity. Meanwhile, 257, 213, and 167 cellular components of the input proteins of peel, calyx, and pulp, respectively were also detected including extracellular region and vesicle. Another finding was that the proteins of the selected eggplant parts involved 1000 biological processes for each, including cellular response to chemical stimulus and response to oxygen containing compounds. KEGG analysis revealed 237, 217, and 220 pathways implicated in 157, 119, and 91 proteins targeted by peel, calyx, and pulp, respectively. Several critical protein-related pathways have been identified, comprising pathways in cancer, chemical carcinogenesis-reactive oxygen species, and chemical carcinogenesis receptor activation.

### 3.3 Molecular docking

Based on the findings from network pharmacology and protein-protein interactions, docking simulations were performed to evaluate the binding affinities and interactions of various identified compounds showing promising pharmacology networking interactions with target proteins with top four key inflammatory and signaling proteins: Akt-1, TNF- $\alpha$ , IL-1 $\beta$  and IL-6. The binding affinity scores are summarized in Table 4. These computational studies aim to elucidate the proposed key molecular interactions for the binding of these compounds to their respective targets.

#### 3.3.1 Molecular interactions with TNF- $\alpha$

Rutin, naringenin, kaempferol, solamargine, and caffeic acid exhibited a binding affinity of -7.8, -7.7, -7.1, -6.7, and -6.2 kcal/mol, respectively, with TNF- $\alpha$ . The interaction details for these complexes are shown in Fig. 7. Rutin showed multiple conventional hydrogen bonds interactions with GLY A:121, GLN A:61 ILE B:58, SER B:60, LEU B:120 and GLY B:122 amino acid residues. These interactions indicate the strong binding affinity of rutin to the active binding site. Naringenin showed conventional hydrogen bond interactions with TYR A:151 and SER A:60 as well as  $\pi$ - $\pi$  interaction with TYR 59. In addition, it showed van der waals hydrophobic interaction with GLY 121. Kaempferol displayed multiple conventional hydrogen bonds interactions with GLN 61, LEU 120, GLY 121 and TYR 151. In addition, the compound showed interaction with TYR 119. The interaction complex of solamargine revealed the binding with the active site with a

**Table 4** Binding affinity scores (kcal/mol) of eggplant compounds with target proteins

| Ligand                | Binding affinity scores (kcal/mol) |       |              |      |
|-----------------------|------------------------------------|-------|--------------|------|
|                       | TNF- $\alpha$                      | Akt-1 | IL-1 $\beta$ | IL-6 |
| Naringenin            | -7.7                               | -7.3  | –            | –    |
| Rutin                 | -7.8                               | –     | -5.7         | -4.2 |
| Kaempferol            | -7.1                               | –     | –            | –    |
| Solamargine           | -6.7                               | –     | –            | –    |
| Caffeic_acid          | -6.2                               | –     | –            | –    |
| Protocatechuic_acid   | –                                  | -6    | –            | –    |
| 2AZ5 complexed ligand | -9.9                               | –     | –            | –    |
| 3MV5 complexed ligand | –                                  | -6.8  | –            | –    |
| 6Y8M complexed ligand | –                                  | –     | -4.7         | –    |
| 1ALU complexed ligand | –                                  | –     | –            | -4   |

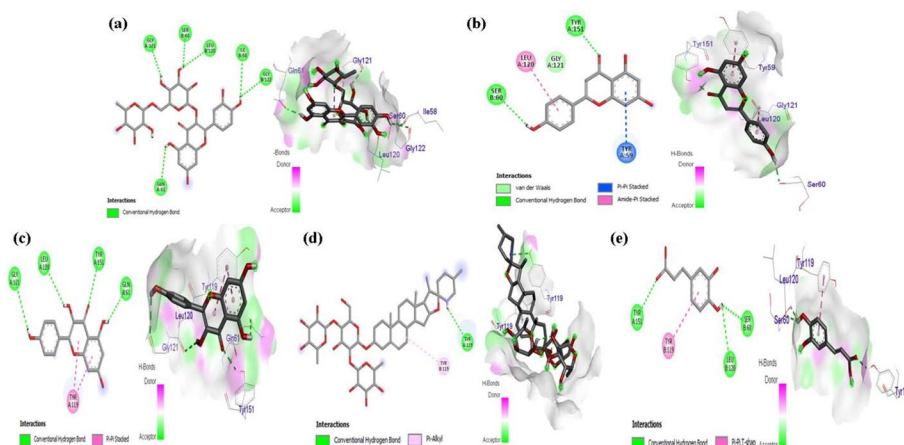


**Fig. 7** Visualization of 2D and 3D of molecular docking results of best protein–ligand (TNF- $\alpha$  and eggplant compounds) complexes **a** rutin, **b** naringenin, **c** kaempferol, **d** solamargine, and **e** caffeic acid

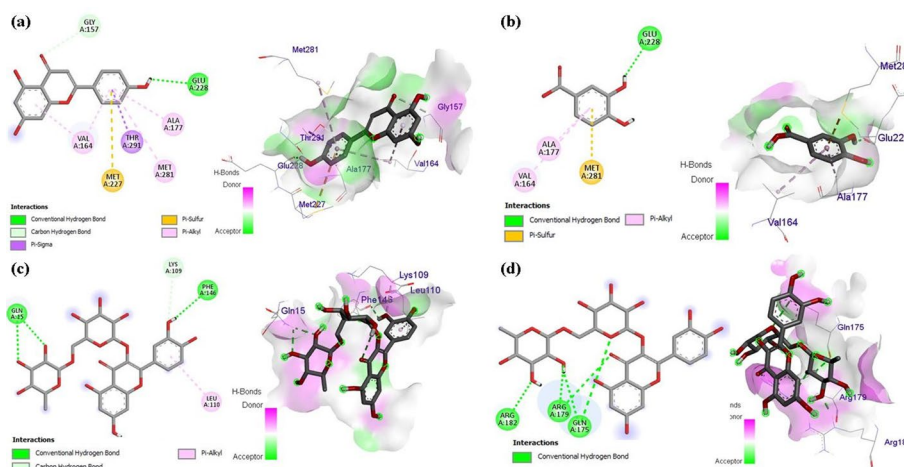


**Fig. 8** Visualization of 2D and 3D of molecular docking results of protein–ligand complexes **a** Naringenin with AKT1 **b** Protocatechuic acid with AKT1 **c** Rutin with IL-1 $\beta$  **d** Rutin with IL-6

conventional hydrogen bond with TYR A:119, while interacting with TYR b:119 through  $\pi$ -alkyl bond. The interaction of caffeic acid with the active site includes three conventional hydrogen bonds with TYR A:151, SER B:60 and LEU B:120, in addition to  $\pi$ - $\pi$  interaction with TYR B:119.

### 3.3.2 Molecular interactions with Akt-1

Naringenin exhibited a binding affinity of -7.3 kcal/mol with Akt-1. The 2D and 3D interaction diagrams (Fig. 8a) reveal several key interactions contributing to its stable binding. A conventional hydrogen bond is observed between the hydroxyl group of naringenin and GLU 228. Additionally,  $\pi$ -sigma interactions are formed with THR 291.  $\pi$ -alkyl interactions are noted with VAL 164, ALA 177 and MET 281 and MET 281. Its aromatic ring also engages in  $\pi$ -sulfur bond with MET 227. These diverse interactions collectively stabilize the Naringenin-AKT1 complex within the binding pocket. Protocatechuic acid showed a binding affinity of -6.0 kcal/mol with AKT1. As depicted in the interaction diagrams (Fig. 8b), a significant conventional hydrogen bond is formed

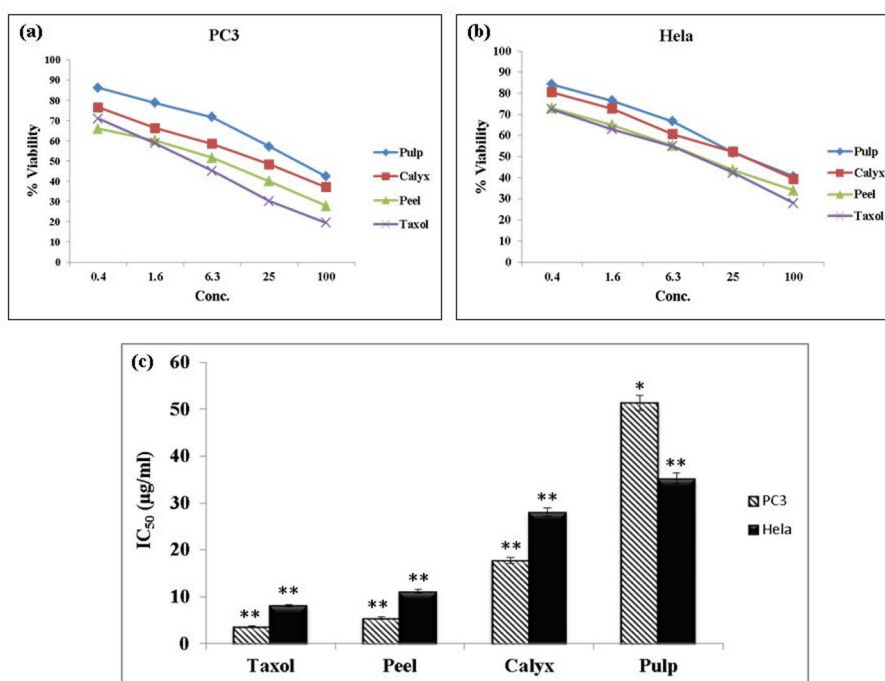


**Fig. 9** In-vitro cytotoxicity evaluation of the ethanolic extracts of eggplant peel, calyx and pulp **a** % cell viability against prostate cancer cell line **b** % cell viability against cervical cancer cell line **c** IC<sub>50</sub> values (µg/ml) against prostate (PC3) and cervical (Hela) cell lines. Taxol was used as reference positive control. Error bars represent standard deviation of one experiment carried out in triplicate. \**p* < 0.05 versus control considered statistically significant, \*\**p* < 0.001 versus control considered statistically highly significant

between protocatechuic acid and GLU 228. Furthermore,  $\pi$ -sulfur interactions are observed with MET 281, and  $\pi$ -alkyl interactions contribute to the binding stability through interactions with ALA 177 and VAL 164. These interactions highlight the importance of both hydrogen bonding and hydrophobic contacts in the binding of protocatechuic acid to AKT1.

### 3.3.3 Molecular interactions with interleukins

Rutin exhibited a binding affinity of -5.7 and -4.2 kcal/mol with IL-1 $\beta$  and IL-6, respectively. Figure 8c illustrates that rutin forms conventional hydrogen bonds with GLN 45 and PHE 146. Additionally,  $\pi$ -alkyl interactions are observed with LEU 110. These interactions suggest that rutin's binding to IL-1 $\beta$  is primarily driven by a combination of hydrogen bonding and hydrophobic forces involving alkyl groups. While the analysis of its interaction with IL-6 (Fig. 8d) showed that rutin forms multiple conventional hydrogen bonds with ARG 179, GLN 175, and ARG 182. These hydrogen bonds indicate a polar interaction network contributing to the binding of rutin within the IL-6 binding site.

### 3.4 In-vitro MTT cytotoxicity assay

The findings of the in-vitro cytotoxicity activity of eggplant peel, calyx, and pulp against prostate cancer cell line (PC3) and cervical cancer cell line (Hela) revealed that the peel has more potent anti-cancer activity followed by calyx, and pulp, respectively according to their viability percentage and IC<sub>50</sub> values as illustrated in Fig. 9. Taxol, which utilized as a positive control, had IC<sub>50</sub> value equals to 3.632 ± 0.12 µg/ml against PC3

cell line. While the three ethanolic extracts of eggplant peel, calyx, and pulp gave  $IC_{50}$  values equal to  $5.497 \pm 0.18$ ,  $17.76 \pm 0.57$ , and  $51.36 \pm 1.66$   $\mu\text{g/ml}$  against PC3 cell line, respectively. In case of Hela cell line, the  $IC_{50}$  values for taxol, peel, calyx, and pulp were  $8.16 \pm 0.26$ ,  $11.19 \pm 0.36$ ,  $28.06 \pm 0.91$ , and  $35.23 \pm 1.14$   $\mu\text{g/ml}$ .

#### 4 Discussion

More than ten million tons of by-products, mainly peel and calyx, are generated from the annual consumption of eggplant which documented to have various bioactive compounds [34]. In line with the global sustainable development goals, this work highlights the promising utilization of eggplant by-products as a complementary therapy in cancer patients due to their beneficial anti-cancer activity, safety, availability, and inexpensive cost. Based on the UPLC-QTOF-MS/MS phytochemical screening of the extracts of eggplant peel and calyx compared to its pulp, the peel is considered as a richer source of bioactive compounds than calyx and pulp, respectively. The tentatively identified phenolic acids and their derivatives appeared in almost all samples (19, 20, 18 compounds in peel, calyx, and pulp, respectively), mainly represented as caffeic acid conjugates which support the antioxidant, anti-inflammatory and anticancer activity [35]. Also, organic acids, amino acids, and fatty acid derivatives are shared among all samples. Glycoalkaloids, which display a variety of pharmacological activities, including anti-cancer and acetylcholinesterase inhibitory properties [36], are identified in peel and pulp only. Meanwhile, flavonoids and anthocyanins are shown to be more accumulated in peel (16 compounds) than calyx (7 compounds) while absent in pulp. Flavonoids are one of the most beneficial classes of secondary metabolites that have a variety of therapeutic effects, as they have antimicrobial, antiviral, antioxidant, anti-inflammatory, anti-mutagenic, and anti-carcinogenic effects [37]. The anti-cancer potential of eggplant peel was verified against many types of cancer, including breast cancer [38], gastric cancer [39], and liver cancer as a result of the abundance of phenolic compounds, especially phenolic acids, flavonoids and anthocyanins [40]. Calyx also showed cytotoxic activities on ovarian, breast, and colorectal carcinoma cell lines due to the presence of conjugates of *p*-coumaric acid, caffeic acid, and ferulic acid [12], and 9-oxo-(10,12)-octadecadienoic acid [41].

According to the network pharmacology analysis in this study, the anti-cancer activity against prostate/cervical cancer of peel is predicted to be more potent than calyx and pulp based on degree, closeness, and betweenness centralities. The peel is shown to target more cancer-related proteins than calyx and pulp, as it targets 157 proteins while calyx and pulp target 119 and 91 proteins, respectively. Kaempferol, rutin, naringenin, caffeic acid, ferulic acid, *p*-coumaric acid, 3-caffeoylquinic acid, syringic acid, quercetin-3-*O*-rhamnoside, protocatechuic acid, kaempferol-3-*O*-glucoside, luteolin-7-*O*-glucoside, scopoletin, myricetin-3-galactoside, solamargine, scopolin, myricetin-3-neohesperidoside, kaempferol-3-*O*-rutinoside, 5-caffeoylquinic acid, 1,3-dicaffeoylquinic acid, *N*-caffeoyltyramine, 4-*O*-caffeoylquinic acid, delphinidin-3 glucoside, and phenylalanine, which are identified in the peel, are targeting prostate/cervical cancer. While the anti-cancer activity of the calyx is expected to be as a result of the existence of naringenin, caffeic acid, ferulic acid, *p*-coumaric acid, *N*-hexadecanoic acid, 3-caffeoylquinic acid, syringic acid, kaempferol 3-*O*-glucoside, protocatechuic acid, luteolin-7-*O*-glucoside, scopoletin, cinnamic acid, vanillic acid, kaempferol-3-*O*-rutinoside, *N*-caffeoyltyramine,

3,5-dicaffeoylquinic acid, 5-caffeoylquinic acid, phenylalanine, and 4-*O*-caffeoylquinic acid. The pulp is shown to have lower anti-cancer properties due to lack of flavonoids and anthocyanins. Meanwhile, the presence of caffeic acid, ferulic acid, *N*-hexadecanoic acid, 3-caffeoylquinic acid, protocatechuic acid, scopoletin, solamargine, cinnamic acid, *N*-caffeoyltyramine, 3,5-dicaffeoylquinic acid, 5-caffeoylquinic acid, phenylalanine, and 4-*O*-caffeoylquinic acid in pulp made it target cancer but with less extent than peel and calyx.

Moreover, the analysis of PPI and the compound-target network revealed five potential key proteins in the interaction, including IL1 $\beta$ , IL6, INS, targeted by rutin which is present only in peel, TNF, targeted by caffeic acid, kaempferol, rutin, naringenin, and solamargine, and Akt-1, targeted by protocatechuic acid and naringenin.

The Gene Ontology analysis aimed to predict an exhaustive comprehension of the alterations in biological processes, cellular components, and molecular functions that occur in prostate/cervical cancer when the selected eggplant parts were challenged into the disease. Peel, calyx, and pulp exhibited 531, 448, and 349 molecular functions, respectively, including crucial molecular functions that have a strong link with cancer development and progression, such as transition metal ion binding, oxidoreductase activity, and lyase activity. Meanwhile, 257, 213, and 167 cellular components of the peel, calyx, and pulp input proteins were identified, including an extracellular region and a vesicle. These vesicles have received a lot of interest in recent years due to their function in tumor immunomodulation. They enhance intercellular communication for transporting proteins, nucleic acids, and other physiologically active molecules [42]. The proteins of each selected eggplant part performed 1000 biological processes, including cellular response to chemical stimulus and response to oxygen-containing compounds. KEGG was conducted to analyze the pathway mainly enriched in cancer-related proteins targeted by eggplant compounds. In this analysis, 237, 217, 220 pathways involved in 157, 119, 91 proteins, targeted by peel, calyx, and pulp, respectively, inputted were detected, including various critical protein-related pathways, such as pathways in cancer, chemical carcinogenesis-reactive oxygen species, and chemical carcinogenesis receptor activation.

In addition, the molecular docking study evaluated the binding affinities and interactions of six compounds in eggplant, rutin, naringenin, kaempferol, solamargine, caffeic acid, and protocatechuic acid, which exhibit significant pharmacology networking interactions with target proteins, with the key proteins identified from PPI analysis: Akt-1, TNF- $\alpha$ , IL-1 $\beta$  and IL-6. Akt-1 has a crucial role in regulating the metabolism of cancer cells as well as in cell proliferation [43]. Moreover, the pro-inflammatory cytokines TNF- $\alpha$ , IL-1 $\beta$ , and IL-6 are implicated in angiogenesis, cancer cell proliferation, and metastasis; they appear to reinforce one another's mechanisms of action [44]. Based on the binding affinity scores, rutin showed the lowest binding affinity score of -7.8, -5.7, -4.2 kcal/mol against TNF- $\alpha$ , IL-1 $\beta$  and IL-6, respectively in their site of action. Meanwhile naringenin displayed the lowest binding affinity score of -7.3 kcal/mol against Akt-1. The docking results are supported by recent studies confirming that rutin is a potent ligand of TNF- $\alpha$ , IL-1 $\beta$  and IL-6 [45, 46] and naringenin is a high-affinity ligand for Akt-1 [47, 48]. All the findings from the displayed computerized studies, including network pharmacology, PPI, GO, KEGG, and molecular docking analysis, indicate that the peel is predicted to be the most effective part of eggplant fruit against cancer, followed by the calyx and then the pulp.

These findings were validated through in-vitro cytotoxicity assays against cervical and prostate cancer cell lines, which demonstrated that the peel extract exhibited the strongest anticancer activity, followed by the calyx, as reflected by their  $IC_{50}$  values. The superior activity of the peel may be attributed to its high flavonoid content, particularly rutin, naringenin, and kaempferol, which have been scientifically proven to be effective against several cancer cell lines, especially prostate and cervical cell lines [49, 50]. In contrast, the anticancer potential of the calyx could be linked to the presence of several active constituents, including naringenin, caffeic acid, ferulic acid, and *p*-coumaric acid, which possess therapeutic potential in the treatment of different types of cancer, including prostate and cervical cancers [51].

## 5 Conclusion

This study conducted a phytochemical screening, network pharmacology analysis, molecular docking, and in-vitro anti-cancer activity of eggplant by-products, peel and calyx, in comparison with its pulp to highlight their benefits and recycle them as sustainable raw materials for the pharmaceutical industries rather than throwing them away as garbage that harms the environment, human health, and the state of the economy. In summary, a total of 50, 41, and 33 secondary metabolites have been identified in eggplant peel, calyx, and pulp, respectively. By building and analysis the network pharmacology of the selected eggplant parts toward prostate/cervical cancer, the peel is predicted to target more cancer-related proteins than calyx and pulp. The in-vitro cytotoxicity assay accompanied with network pharmacology and molecular docking studies indicated that peel showed the most potent anti-cancer effect among calyx and pulp due to the existence of various biologically active compounds, mainly flavonoids. Calyx also displayed moderate anti-cancer properties due to the presence of naringenin, caffeic acid, ferulic acid, and *p*-coumaric acid. It is encouraged that future research focuses on improving the calyx's biological activity. Additionally, it is recommended to conduct additional in-vivo and clinical anti-cancer studies to invest those by-products as a profitable complementary therapy in cancer treatment strategies. Moreover, the evaluation of the anti-inflammatory potential of eggplant by-products is highly recommended as they particularly target cytokines that induce inflammation, including  $TNF-\alpha$ ,  $IL-1\beta$  and  $IL-6$ . Therefore, our results confirm that eggplant by-products reutilization can not only be a sustainable management approach, but it can also be a renewable source of raw materials in the pharmaceutical industry.

### Abbreviations

|              |                                                               |
|--------------|---------------------------------------------------------------|
| HIT 2.0      | Herbal ingredients' targets platform                          |
| OMIM         | Online Mendelian Inheritance in Man                           |
| PPI          | protein–protein interaction                                   |
| GO           | Gene ontology                                                 |
| KEGG         | Kyoto encyclopaedia of genes and genomes                      |
| Akt          | Serine/threonine protein kinase                               |
| $TNF-\alpha$ | Tumour necrosis factor alpha                                  |
| $IL-1\beta$  | Interleukin-1 beta                                            |
| $IL-6$       | Interleukin-6                                                 |
| MTT          | 3-(4,5-Dimethylthiazol-2-yl)-2,5 diphenyl tetrazolium bromide |
| PC3          | Prostate cancer cell line                                     |
| Hela         | Cervical cancer cell line                                     |
| PBS          | Phosphate buffered saline                                     |
| DMSO         | Dimethyl sulfoxide                                            |

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### Author contributions

NEM, SSE, DIH, MMH, and ISAK designed research; NEM wrote the first draft of the paper, analyzed UPLC-QTOF-MS/MS data, built and analyzed network pharmacology, protein-protein interaction, gene ontology, and KEGG analysis; MEA conducted and analyzed molecular docking study; All authors contributed significant review and edits to the final manuscript, contributed to the interpretation of results, and have read and approved the final manuscript.

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### Data availability

The datasets generated and/or analyzed during the current study are available in the article and the datasets of target protein structures analyzed in the current study were retrieved from the Protein Data Bank repository (accessed on 25 August, 2025), through the following links; (PDB ID: 3MV5) [<https://www.rcsb.org/structure/3MV5>](<https://www.rcsb.org/structure/3MV5>) , (PDB ID: 2AZ5) [<https://www.rcsb.org/structure/2AZ5>](<https://www.rcsb.org/structure/2AZ5>) , (PDB ID: 6Y8M) [<https://www.rcsb.org/structure/6Y8M>](<https://www.rcsb.org/structure/6Y8M>) and (PDB ID: 1ALU) [<https://www.rcsb.org/structure/1ALU>](<https://www.rcsb.org/structure/1ALU>).

### Declarations

#### Ethics approval and consent to participate

Not applicable.

#### Consent for publication

Not applicable.

#### Competing interests

The authors declare no competing interests.

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