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Authors

Grijaldo, Sheryl Joyce B
Alvarez, Michael Russelle S
Heralde, Francisco M
et al.

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Article

Integrating Computational Methods in Network Pharmacology and *In Silico* Screening to Uncover Multi-targeting Phytochemicals against Aberrant Protein Glycosylation in Lung Cancer

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Sheryl Joyce B. Grijaldo, Michael Russelle S. Alvarez, Francisco M. Heralde III, Ruel C. Nacario, Carlito B. Lebrilla, Jomar F. Rabajante,* and Gladys C. Completo*

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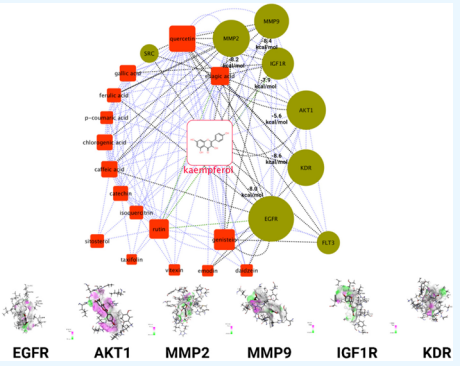
ABSTRACT: Glycoproteins are an underexploited drug target for cancer therapeutics. In this work, we integrated computational methods in network pharmacology and *in silico* docking approaches to identify phytochemical compounds that could potentially interact with several cancer-associated glycoproteins. We first created a database of phytochemicals from selected plant species, *Manilkara zapota* (sapodilla/chico), *Mangifera indica* (mango), *Annona muricata* (soursop/guyabano), *Artocarpus heterophyllus* (jackfruit/langka), *Lansium domesticum* (langsat/lanzones), and *Antidesma bunius* (bignay), and performed pharmacokinetic analysis to determine their drug-likeness properties. We then constructed a phytochemical−glycoprotein interaction network and characterized the degree of interactions between the phytochemical compounds and with cancer-associated glycoproteins and other glycosylation-related proteins. We found a high degree of interactions from α-pinene (*Mangifera indica*), cyanomaclurin (*Artocarpus heterophyllus*), genistein (*Annona muricata*), kaempferol (*Annona muricata* and *Antidesma bunius*), norartocarpetin (*Artocarpus heterophyllus*), quercetin (*Annona muricata, Antidesma bunius, Manilkara zapota, Mangifera indica*), rutin (*Annona muricata, Antidesma bunius, Lansium domesticum*), and ellagic acid (*Antidesma bunius* and *Mangifera indica*). Subsequent docking analysis confirmed that these compounds could potentially bind to EGFR, AKT1, KDR, MMP2, MMP9, ERBB2, IGF1R, MTOR, and HRAS proteins, which are known cancer biomarkers. *In vitro* cytotoxicity assays of the plant extracts showed that the *n*-hexane, ethyl acetate, and methanol leaf extracts from *A. muricata*, *L. domesticum* and *M. indica* gave the highest growth inhibitory activity against A549 lung cancer cells. These may help further explain the reported cytotoxic activities of select compounds from these plant species.



INTRODUCTION

Lung cancer remains a major public health concern, even with female breast cancer surpassing lung cancer as the most diagnosed type of cancer.[1,2] According to the GLOBOCAN (Global Cancer Observatory) database of 185 countries and 36 cancer types, 11.4% of 19.3 million new cases and 18.0% of 9.9 million cancer deaths worldwide are due to lung cancer.[3] Lung cancer continues to be one of the leading causes of cancer deaths among men in 93 countries and among women in 28 countries.[1−3]

Glycosylation is an important post-translational modification wherein sugar moieties are covalently attached to the proteins. Targeting glycoproteins is an underexploited strategy for the development of cancer therapeutics. Carbohydrate-active enzymes such as glycosidases and glycosyltransferases are attractive drug targets due to their involvement in the biosynthesis of glycan structures.[4,5] Relatively few studies have investigated potential small molecule inhibitors with drug-like properties against these enzymes.[5−10] These include plant alkaloids that inhibit glycosidases by inducing inhibition of trimming reactions after the attachment of $Glc_3Man_9GlcNAc_2$ oligosaccharide. An example of a plant alkaloid is swainsonine from an *Astralagus* species known as locoweeds. It inhibits class II α-mannosidases such as Golgi α-mannosidases II, lysosomal α-mannosidases, and cytosolic α-mannosidases (Man2C1) and was previously observed to have an anti-tumor effect on the central nervous system, liver, and lung cancer.[11−13] Further evaluation of N-glycomic alterations caused by swainsonine in HepG2 liver cells revealed accumulation of both fucosylated hybrid-type and fucosylated high mannose 5 (M5) glycans.[13]

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On the other hand, there are plant derivatives that, instead of blocking N-glycosylation, enhance O-glycosylation of proteins and upregulate glycosyltransferases. For example, oridonin, a diterpenoid isolated from *Rabdosia rubescens* and other *Isodon* species, is found to initiate tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL)-mediated apoptosis through formation of death-inducing signaling complexes (DISC) and glycosylation of death receptor 5 (DR5).[14,15] Treatment of A549 lung cancer cells with oridonin revealed enhancement of O-glycosylation of DR5 through upregulation of polypeptide *N*-acetylgalactosaminyltransferase 14 (GALNT14) expression.[15]

Computer-aided drug discovery, such as the use of virtual screening, molecular docking, and *in silico* drug property calculations can greatly expedite the drug discovery and development.*In silico* screening, coupled with high-throughput *in vitro* validation assays, can streamline the drug discovery process. This method was used by Billones *et al.*[16] to discover, among the ENAMINE compounds database, 7,8-diaminopelargonic acid aminotransferase inhibitors that could inhibit the growth of *Mycobacterium tuberculosis* strain Mtb H37Ra.[16] During the recent pandemic, the use of *in silico* methods is one of the drug discovery approaches utilized to address an urgent need to find new drugs against COVID-19 and other diseases like HIV-AIDS and cancer.[17−22] Our previous study also employed an *in silico* method as a preliminary tool to screen 14,000 small molecule inhibitors against glycosylation proteins dysregulated in cancer.[17]

In this study, we incorporated computational methods in network pharmacology and *in silico* docking approaches to predict phytochemical compounds that could potentially interact with several cancer-associated glycoproteins and glycosylation-related proteins. We inferred that the cytotoxicity of select phytochemicals against cancer cells could reveal the effects of these compounds against aberrant glycosylation, and their potential as drug leads in anti-lung cancer drug discovery. We initially created a literature-based database containing phytochemicals from select plant species that have ethnopharmacological evidence against cancer. We then utilized a computational approach to evaluate physicochemical properties such as ADMETox (absorption, distribution, metabolism, excretion and toxicity) information to predict that the phytochemicals are orally bioavailable and effective on human cells/tissues. From the identified phytochemicals, a subset of compounds with drug-like property was further investigated for possible interaction with lung cancer-associated glycoproteins via gene-phytochemical interaction networks. The top interacting phytochemicals were ranked using the greatest number of gene interactions and selected for their "multi-targeting" activity for further molecular docking and screening for inhibition against glycoenzymes, specifically the glycosidase Man1B1 and glycosyltransferases MGAT5, ST6Gal1, and FUT8.

MATERIALS AND METHODS

Database and Ligand Preparation. Six Philippine fruit trees, namely *Lansium domesticum* (langsat/lanzones), *Mangifera indica* (mango), *Artocarpus heterophyllus* (jackfruit/langka), *Antidesma bunius* (bignay), *Manilkara zapota* (sapodilla/chico), and *Annona muricata* (soursop/guyabano), were selected as possible sources of phytochemicals against lung cancer. We previously reported that leaf extract fractions from these plants have high cytotoxic activity against lung cancer cells.[23−26] An in-house database composed of 226 natural product compounds previously isolated from *L. domesticum*,[27−32] *M. indica*,[33−36] *A. muricata*,[37] *A. bunius*,[25,38] *M. zapota*,[39] and *A. heterophyllus* was prepared based on extensive literature search using the PubMed NCBI database (https://pubmed.ncbi.nlm.nih.gov). This was also supplemented with chemical information retrieved from PubChem NCBI database (https://pubchem.ncbi.nlm.nih.gov). Natural product compound classifications were annotated using the ClassyFire methodology (http://classyfire.wishartlab.com/).[40]

ADMETox Analysis. The ADMETox analysis and druggability predictions of the compounds were made using the pkCSM server (https://biosig.lab.uq.edu.au/pkcsm/prediction).[41] The pkCSM method predicts values for the following ADMETox properties: Absorption (water solubility, skin permeability, intestinal absorption, Caco2 permeability, P-glycoprotein I/II inhibitor, P-glycoprotein substrate), distribution (fraction unbound, VDss, BBB permeability, CNS permeability), metabolism (CYP1A2/CYP2C19/CYP2D6/CYP3A4/CYP2C9 inhibitor, CYP2D6/CYP3A4 substrate), excretion (total clearance, renal OCT2 substrate), and toxicity (max. tolerated dose, oral rat acute/chronic toxicity, minnow toxicity, *T. pyriformis* toxicity, skin sensitization, Ames toxicity, hepatotoxicity, hERG I/II inhibitor). The software also provides threshold values for subsequent filtering of the compounds based on predicted ADMETox values.

Network Pharmacology. Network pharmacology was performed to identify potential interactions of phytochemicals with glycosylation-related proteins.[6] Protein−drug interactions of the 161 phytochemicals with 260 glycosylation-related proteins were predicted using BindingDB (https://www.bindingdb.org/bind/index.jsp), Chemical Toxicogenomics Database (http://ctdbase.org/),[42] DGIdb (https://www.dgidb.org/),[43] STITCH (http://stitch.embl.de/),[44] and SWISS Target Prediction (http://www.swisstargetprediction.ch/). The interactions were mapped out using Cytoscape 3.8.2. Pathway involvement of the 260 glycosylation-related proteins were calculated using gene ontology analysis in g:Profiler (https://biit.cs.ut.ee/gprofiler/).[45] Top interacting phytochemicals were ranked using node degree (number of interacting neighbors). Graphs and Venn diagrams were visualized using GraphPad Prism 7 and Interactivenn (http://www.interactivenn.net/).

***In Silico* Screening.** *In silico* screening methods were performed[17] in PyRx[46] using the AutoDock VINA docking protocol[47] at exhaustiveness level 8. The experimentally determined 3D structures of four glycoenzymes, ST6Gal1 (4js2), MGAT5 (5zic), Man1B1 (1x9d), and FUT8 (homology modeled from 3zy6), were selected based on its availability in the data bank and retrieved from RCSB Protein Data Bank (PDB) (https://www.rcsb.org/). Before docking the compounds, the ligands, complexed with the respective enzymes in the PDB crystal structure, were initially docked to validate the docking protocol. The docking protocol was validated when the docked ligand and crystal ligand had an all-atom RMSD less than 1.5. All database compounds were then loaded onto PyRx and minimized using the Universal Force Field[48] as implemented in Open Babel.[49] After docking validation, all database compounds were screened against each of the four enzymes: glycosidase Man1B1 and glycosyltransferases MGAT5, ST6Gal1, and FUT8. The binding energies and all conformations generated were exported as *pdbqt* files for further analysis. The compounds were ranked according to the VINA-predicted binding energy (kcal/mol). The top 10 binding molecules against each enzyme

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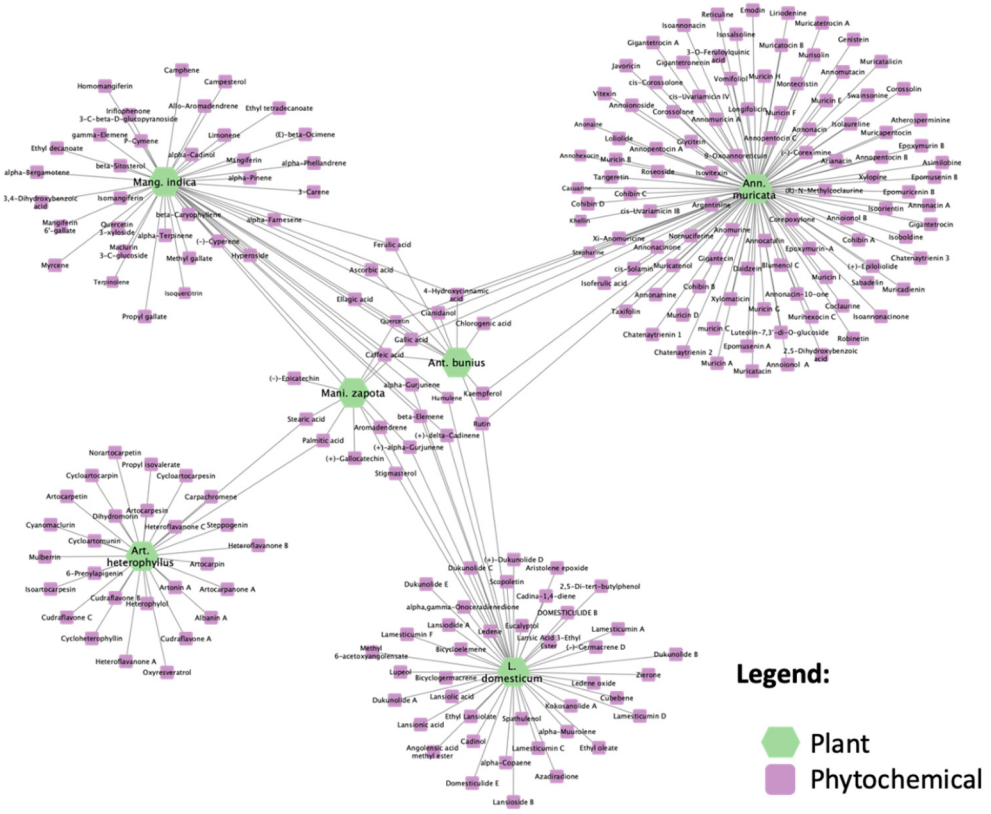

Figure 1. Plant-phytochemical network of 226 unique phytochemicals (in purple) and 6 plant species (in green) with reported cytotoxic activity. *A. muricata* has the greatest number of identified phytochemicals (with 104 unique compounds and 7 common phytochemicals found in other fruit trees). *A. bunius* has 15 identified phytochemicals with no unique compounds.

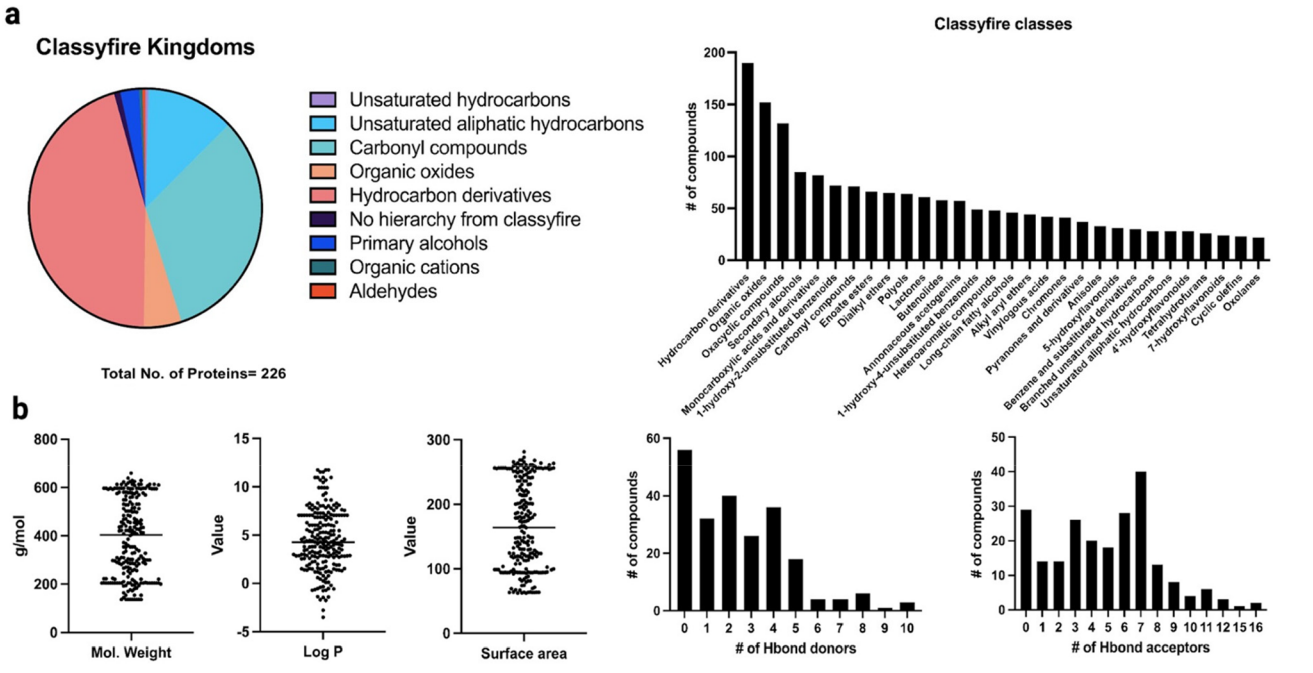

Figure 2. Characterization of 226 phytochemicals, including (a) annotation by compound class (based on Classyfire kingdom and class taxonomies of the phytochemicals); and, (b) physicochemical properties based on a key evaluation parameter for drug-likeness called Lipinski's rule of 5 on molecular weight, lipophilicity (expressed as log *P*), surface area, and number of H-bond donors and acceptors. Physicochemical properties were calculated using pkCSM software.[41]

were visualized for residue interactions with the target enzyme using Discovery studio. Compound cross-reactivity (i.e., binding

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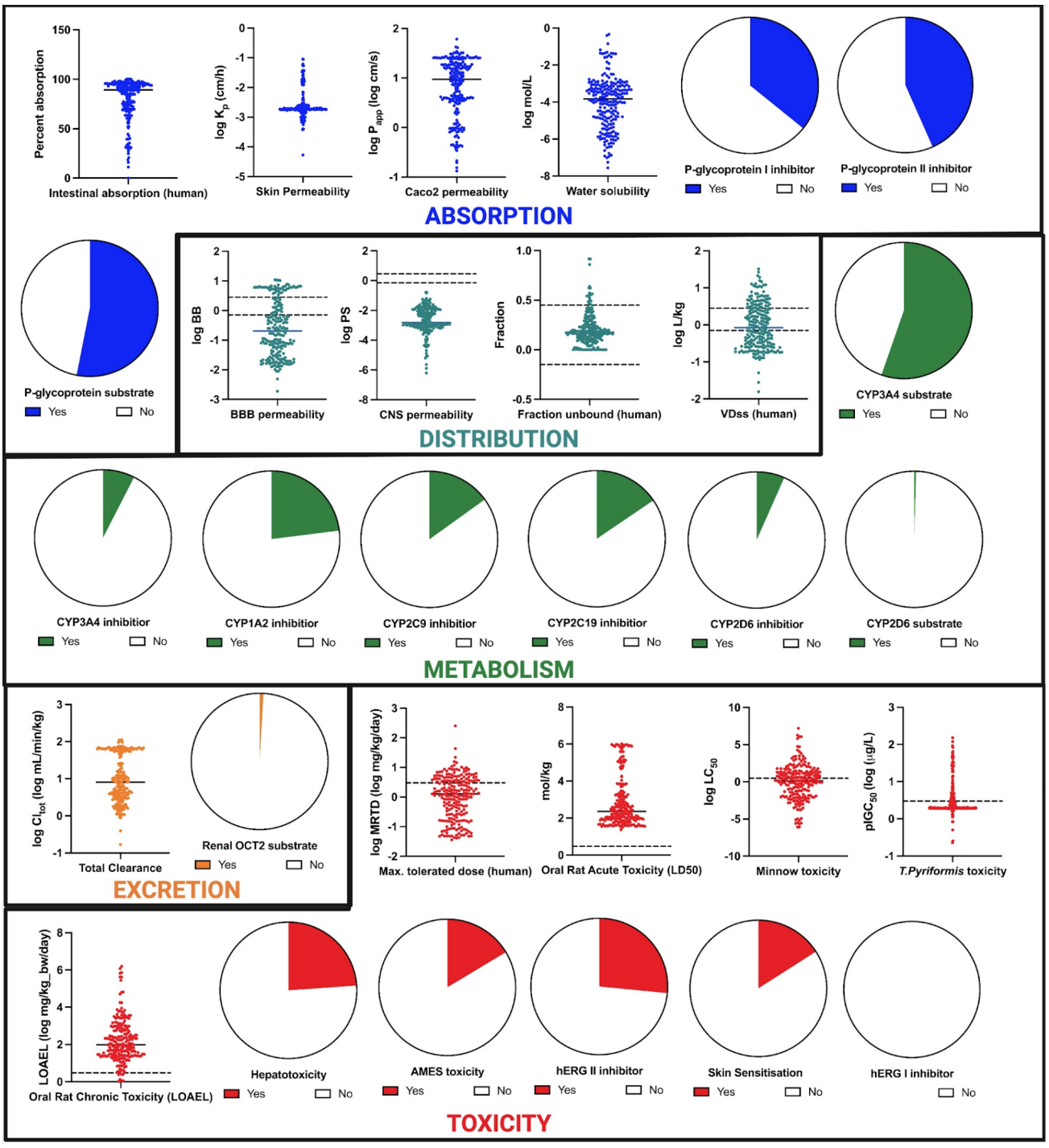

Figure 3. Calculation of the ADMETox properties of the 226 phytochemical compounds: Absorption (intestinal absorption, skin permeability, Caco2 permeability, water solubility, P-glycoprotein I and II inhibitor, P-glycoprotein substrate), distribution (BBB and CNS permeability, fraction unbound, VDss), metabolism (CYP3A4 and CYP2D6 substrate, CYP3A4, CYP1A2, CYP2C9, CYP2C19, and CYP2D6 inhibitor), excretion (total clearance, renal OCT2 substrate), and toxicity (max. tolerated dose, oral rat acute and chronic toxicity, Minnow, *T. pyriformis*, and Ames toxicity, hepatoxicity, hERG I and II inhibitor, skin sensitization). pkCSM cutoff values are represented as dashed lines.

to multiple enzyme targets) was analyzed by evaluating each compound's binding energy against each enzyme, and visualized by generating a heatmap.

RESULTS

A total of 226 phytochemicals, previously isolated from *L. domesticum*, *M. indica*, *A. heterophyllus*, *A. bunius*, *M. zapota*, and *A. muricata*, were used in the generation of a plant-pytochemical network.[27−34,36,37,50−52] We mapped the phytochemicals into a plant-phytochemical network based on their source plant species (Figure 1). *A. muricata* was found to contain the highest number of unique phytochemicals (104 out of 111 isolated compounds) but it also contained common natural product compounds such as chlorogenic acid, rutin, quercetin, 4-hydroxycinnamic acid, cianidanol, gallic acid, and kaempferol. Majority of which were also found in *A. bunius* (chlorogenic acid,

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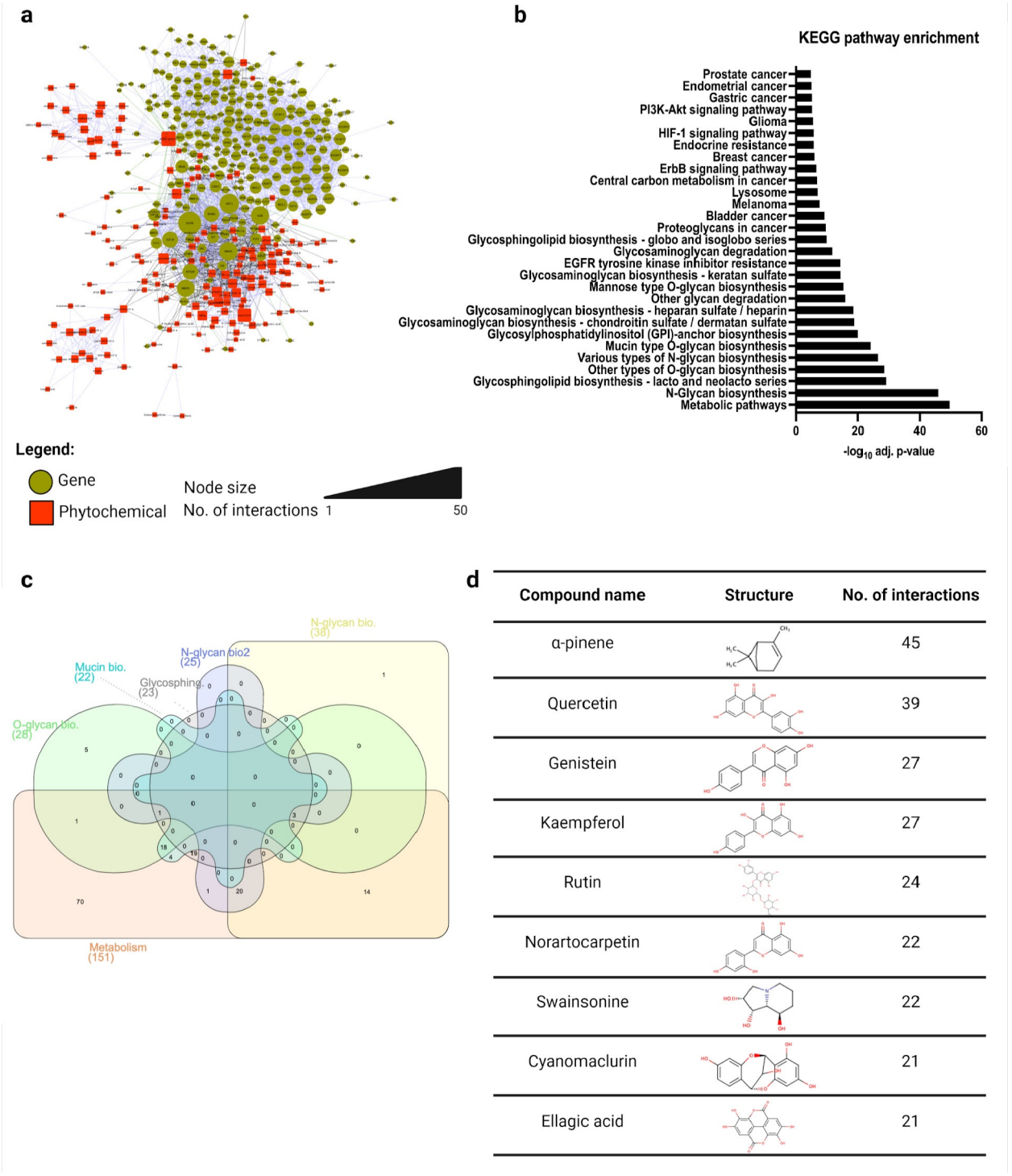

Compound name	Structure	No. of interactions
α-pinene		45
Quercetin		39
Genistein		27
Kaempferol		27
Rutin		24
Norartocarpetin		22
Swainsonine		22
Cyanomaclurin		21
Ellagic acid		21

Figure 4. Construction of the protein-phytochemical interaction network between the 260 glycosylation-related proteins and 161 phytochemicals (a). KEGG pathway enrichment of 260 glycosylation-related genes show these genes are enriched in metabolism and glycosylation pathways (b). The glycosylation genes overlap in the KEGG pathways for metabolism and glycosylation (c). The top phytochemicals with the greatest number of protein interactions: α-pinene, quercetin, genistein, kaempferol, rutin, norartocarpetin, swainsonine, cyanomaclurin, and ellagic acid (d).

rutin, quercetin, 4-hydroxycinnamic acid, and cianidanol), *M. indica* (4-hydroxycinnamic acid, cianidanol, and gallic acid), *L. domesticum* (rutin), and *M. zapota* (quercetin and gallic acid). *M. indica*, *L. domesticum*, and *A. heterophyllus* contained unique phytochemicals, accounting to 33, 40, and 27 compounds, respectively. While *A. bunius* and *M. zapota* contained the fewest unique compounds, with 0 and 2 compounds, respectively.

The plant phytochemicals were annotated with their corresponding compound classes using ClassyFire hierarchy (Figure 2a). Most of these phytochemicals were classified as belonging to the hydrocarbon derivatives, followed by carbonyl compounds, and unsaturated aliphatic hydrocarbons kingdoms. In terms of ClassyFire hierarchical classes, majority of the phytochemicals were primarily classified as hydrocarbon derivatives, organic oxides, oxacyclic compounds, and secondary

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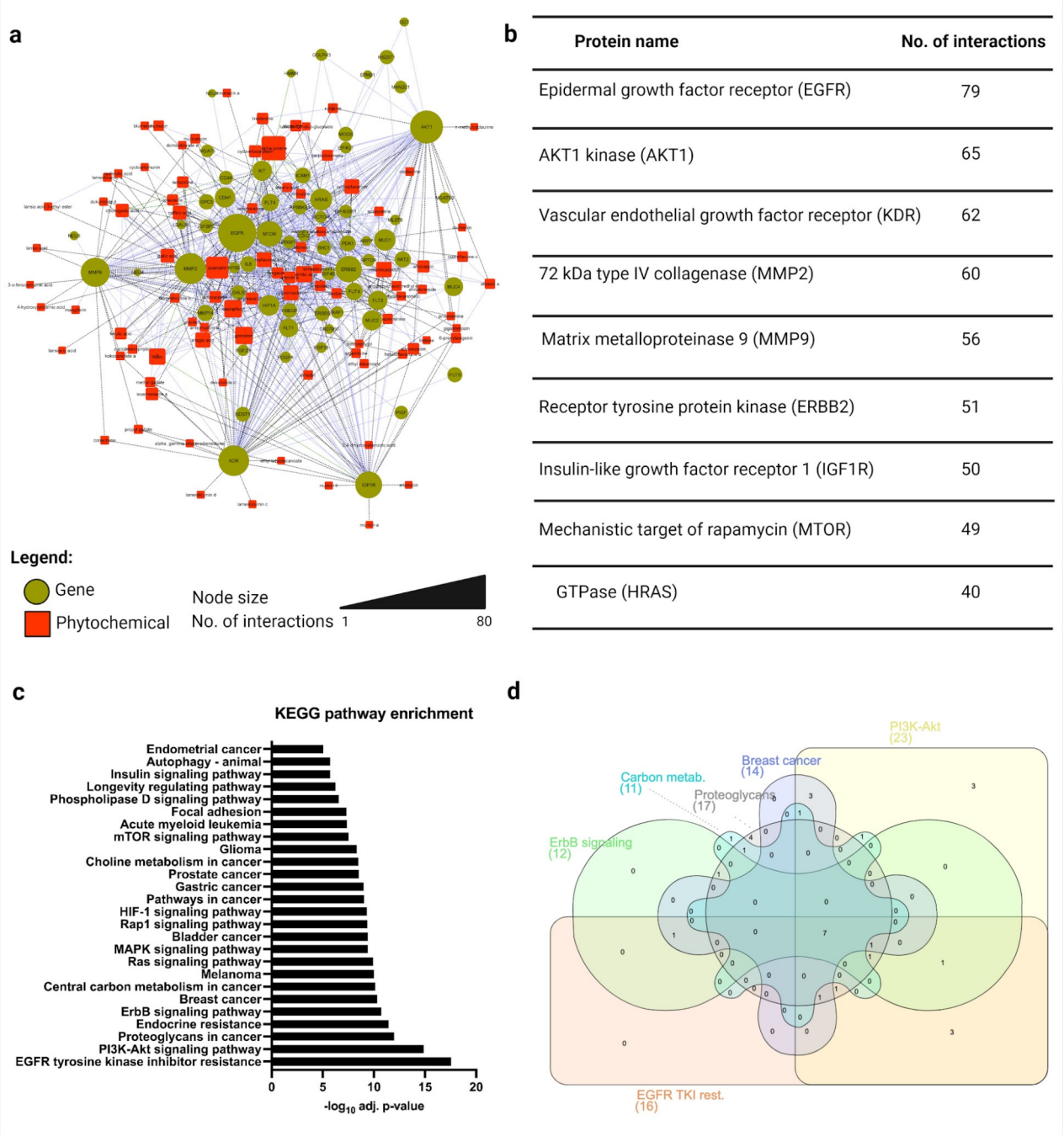

Figure 5. Construction of the protein−phytochemical interaction network between the top nine (9) hub proteins and related phytochemicals (a). The top nine (9) hub proteins are EGFR, AKT1, KDR, MMP2, MMP9, ERBB2, IGF1R, MTOR, and HRAS. KEGG pathway enrichment of the top nine (9) hub proteins, including number of interactions (b), and the cancer pathways involved (c). Gene overlap of top KEGG-enriched pathways (d).

alcohols. The physicochemical properties of these plant phytochemicals were quantified based on a key evaluation parameter for drug-likeness called Lipinski's rule of 5 on molecular weight, lipophilicity (expressed as log *P*), surface area, and number of H-bond donors and acceptors (Figure 2b). On the basis of these molecular descriptors (i.e., molecular weight, log P, surface area, no. of H-bond donors, no. of H-bond acceptors), 152 phytochemicals were found to have molecular weight <500, 132 compounds have log $P < 5$, 208 compounds have <5 H-bond donors, and 214 compounds have <10 H-bond acceptors. Applying all the parameters of the Lipinski filter, 111 total compounds were predicted to have 0 violations.

Furthermore, the ADMETox properties were calculated using the pkCSM software (Figure 3).[41] The algorithm provides quantitative and qualitative predictions of some known ADMETox properties, as well as threshold values. For the absorption parameters, water solubility, Caco-2 permeability, skin permeability, intestinal absorption, P-glycoprotein I/II inhibitor, and P-glycoprotein substrate were predicted. High Caco-2 permeability translates to log $P_{app} > 0.90$, which was predicted for 121 compounds; while high intestinal absorption translates to %absorption > 30% as predicted for 219 compounds which means they are good drug candidates in terms of absorption. P-glycoproteins are ATP-binding cassette

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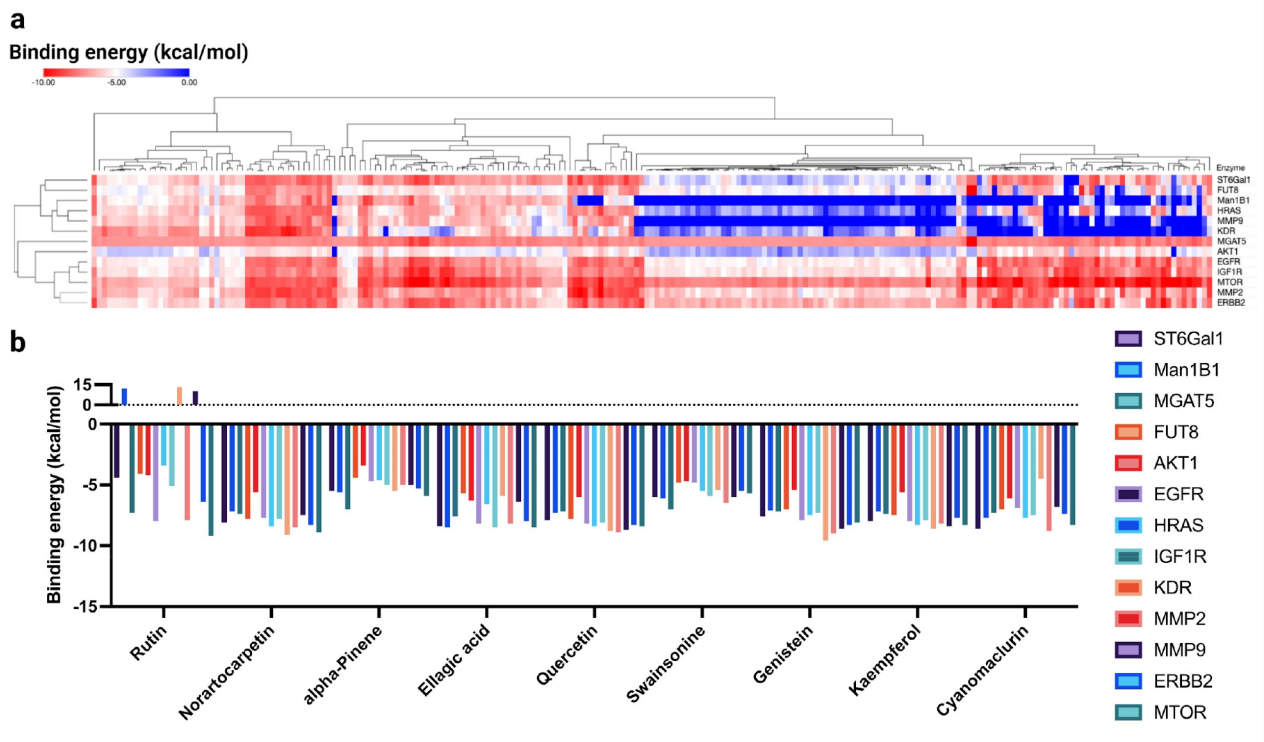

Figure 6. A total of 161 phytochemicals were predicted to bind against glycosidase Man1B1, glycosyltransferases MGAT5, ST6Gal1, and FUT8, metalloproteinases MMP9 and MMP2, glycosylation-related proteins HRAS, KDR, AKT1, EGFR, IGF1R, MTOR, and ERBB2 (a). The top interactors identified from the network protein−phytochemical interaction network were predicted to bind strongly against the selected glycosylation-related proteins (b).

(ABC) transporters, functioning as biological carriers of xenobiotics for extrusion out of cells.[53] Majority of the compounds are predicted as P-glycoprotein substrates and non-inhibitors of P-glycoproteins, thereby reducing their bioavailability and accumulation within the cell to produce cytotoxicity.

In terms of the distribution parameter, the BBB (blood−brain barrier) and CNS (central nervous system) permeabilities, fraction unbound, and VDss were predicted. The volume of distribution at steady-state (VDss) measures the total dose of a drug that would need to be uniformly distributed to give the same concentration in blood plasma. A high VD (log VDss >0.45) suggests that a drug is distributed more in tissue rather than in plasma, as predicted for 58 compounds in our database. The BBB (log BB) and CNS (log PS) permeabilities signify the drugs' ability to penetrate the blood−brain barrier and central nervous system, respectively. For anticancer drugs targeting the lungs, it is desirable for these parameters (log BB and log PS) to be lower. The results showed that 131 compounds have log BB less than −1 while 72 compounds have log PS less than −3.

The metabolism parameter in ADMETox pertains to compounds that are suitable for biotransformation and detoxification. These enzymatic reactions are catalyzed by cytochrome P450s: CYP2D6, CYP3A4, CYP1A2, CYP2C9, and CYP2C19. It is desirable for drugs to be substrates of either of these enzymes and not as inhibitors. On the basis of the results, the majority of the compounds from the 6 plant leaf fractions are CYP3A4 substrates.

The toxicity parameters were predicted using maximum tolerated/recommended dose (MTRD), acute toxicity (LD50, median lethal dose) and chronic (LOAEL, lowest observed adverse effect level) oral toxicity, *T. pyriformis* and minnow toxicity, Ames toxicity (potential to cause DNA mutations), and hERG I/II inhibition. MTRD estimates the toxic dose threshold of chemicals in humans; for a given compound, an MTRD > 0.477 log (mg/kg/day) is considered high. hERG I and II are genes encoding for potassium channels that are the principal causes of acquired long QT syndrome. Our results showed that 72 compounds were predicted to have high MTRD while 60 compounds are predicted to be hERG I/II inhibitors which disqualify them as potential drugs as usage may lead to fatal heartbeat irregularities and eventual death.

The protein−drug interactions of 161 phytochemicals and 260 glycosylation proteins were predicted by analysis of several databases and algorithms [BindingDB (https://www.bindingdb.org/bind/index.jsp), Chemical Toxicogenomics Database (http://ctdbase.org/), DGIdb (https://www.dgidb.org/), STITCH (http://stitch.embl.de/), and SWISS Target Prediction (http://www.swisstargetprediction.ch/)] and used to generate a protein−drug interaction network (Figure 4a). Gene ontology analysis of the 260 glycosylation genes show enrichment in KEGG pathways (http://www.kegg.jp) pertaining to metabolism, N-glycan biosynthesis, glycosphingolipid biosynthesis, and O-glycan biosynthesis (Figure 4b,c). In this network, the proteins and phytochemicals with high degree of interactions (interactions with neighboring nodes) were enlarged. This allowed us to identify proteins that are "hub proteins" and phytochemicals that are "multi-targeting". As such, the compounds α-pinene, quercetin, genistein, kaempferol, rutin, norartocarpetin, swainsonine, cyanomaclurin, and ellagic acid were identified to have the the highest number of interactions (Figure 4d).

Analysis of the protein−drug interaction network (Figure 5a) identified several glycosylation-related proteins and glycopro-

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teins (also called here as hub proteins): EGFR, AKT1, KDR, MMP2, MMP9, ERBB2, IGF1R, MTOR, and HRAS (Figure 5b). Gene ontology analysis of the identified hub proteins shows enriched pathways such as cancer pathways, proteoglycans in cancer, and central carbon metabolism in cancer (Figure 5c,d).

In addition to the network pharmacology approach, an *in silico* docking approach was also employed to assess whether the phytochemicals can bind to specific glycosyltransferases ST6Gal1 (4js2), MGAT5 (5zic), FUT8 (homology modeled from 3zy6), and the glycosidase, Man1B1 (1 × 9d), as well as the top "hub proteins" EGFR, AKT1, KDR, MMP2, MMP9, ERBB2, IGF1R, MTOR, and HRAS (Figure 6a). Majority of the identified 161 phytochemicals was found to bind to these proteins with significant binding affinity. Furthermore, the top "multi-targeting" compounds were able to bind efficiently to the proteins, with some compounds having bindng affinity up to −10 kcal/mol (Figure 6b).

DISCUSSION

Glycoproteins are an underexploited drug target for cancer therapeutics. In this work, we integrated computational methods in network pharmacology and *in silico* docking to predict phytochemical compounds that could potentially interact with several cancer-associated glycoproteins. First, we created a database of all known and reported compounds found in select plant species that were reported to have cytotoxic activities: *Mangifera indica*,[23] *Artocarpus heterophyllus*, *Annona muricata*,[24] *Lansium domesticum*,[15] *Manilkarazapota*,[26] *Antidesma bunius*. Using a LC-MS/MS metabolomics[54] workflow, it was previously reported that leaf extract fractions from these plant species contained characteristic phytochemicals (phenolics and flavonoids) that exhibited cytotoxic activities.[23−26]

Specifically, we examined the interactions of the top interacting compounds determined from our preliminary analyses and their plant sources: α-pinene (*Mangifera indica*), cyanomaclurin (*Artocarpus heterophyllus*), genistein (*Annona muricata*), kaempferol (*Annona muricata* and *Antidesma bunius*), norartocarpetin (*Artocarpus heterophyllus*), quercetin (*Annona muricata*, *Antidesma bunius*, *Manilkara zapota*, *Manigfera indica*), rutin (*Annona muricata*, *Antidesma bunius*, *Lansium domesticum*), and ellagic acid (*Antidesma bunius*, *Mangifera indica*) (Figures S1−S8). These compounds were predicted to bind against several target proteins associated with cancer. Several compounds such as α-pinene (binding affinity = −5.3 kcal/mol), genistein (−7.9 kcal/mol), kaempferol (−8.0 kcal/mol), norartocarpetin (−7.7 kcal/mol), quercetin (−8.2 kcal/mol), rutin (−8.0 kcal/mol), and ellagic acid (−8.2 kcal/mol) were predicted to bind to a known cancer receptor, EGFR. Similarly, for another growth factor receptor, ERBB2 was found to bind α-pinene (−4.7 kcal/mol), ellagic acid (−8.0 kcal/mol), and genistein (−8.3 kcal/mol), while IGF1R was predicted to bind kaempferol (−7.9 kcal/mol), norartocarpetin (−7.8 kcal/mol), quercetin (−8.9 kcal/mol), rutin (−5.1 kcal/mol), and ellagic acid (−8.5 kcal/mol). While the compounds cyanomaclurin (−4.5 kcal/mol), kaempferol (−8.6 kcal/mol), norartocarpetin (−9.1 kcal/mol), quercetin (−8.8 kcal/mol), and ellagic acid (−5.9 kcal/mol) were predicted to bind to KDR. On the other hand, against AKT1, genistein (−6.4 kcal/mol), kaempferol (−5.6 kcal/mol), norartocarpetin (−5.6 kcal/mol), quercetin (−6.0 kcal/mol), and ellagic acid (−6.3 kcal/mol) were found to weakly interact. Interestingly, these compounds were also predicted to bind against matrix metalloproteinases MMP2 and MMP9. The binding affinities of these compounds against MMP2 are as follows: cyanomaclurin (−8.8 kcal/mol), genistein (−9.0 kcal/mol), kaempferol (−8.2 kcal/mol), norartocarpetin (−8.5 kcal/mol), quercetin (−8.9 kcal/mol), rutin (−7.9 kcal/mol), and ellagic acid (−8.2 kcal/mol). While binding affinities with MMP9 are the following: cyanomaclurin (−6.8 kcal/mol), genistein (−8.6 kcal/mol), kaempferol (−8.4 kcal/mol), norartocarpetin (−7.5 kcal/mol), quercetin (−8.7 kcal/mol) − proteins. Against both enzymes, the compounds were able to bind more strongly against MMP2 compared to MMP9.

Taken together, these results may further help explain the reported cytotoxic activities of the phytochemicals found in the selected plant species. Thus, to validate our results, we also conducted *in vitro* cytotoxicity assays of these plant extracts against lung cancer cells (Figure S9). The *n*-hexane, ethyl acetate and methanol leaf extracts of these plants showed <50% growth inhibition against A549 lung cancer cells, with *A. muricata*, *L. domesticum* and *M. indica* having the highest activity. Additional proteomic experiments will be done toward efforts to further understand the mechanism of action of the top compound hits against cancer-associated glycosylation proteins.

ASSOCIATED CONTENT

Data Availability Statement

Structures, networking files, and raw data are available on Open Science Framework repository (https://osf.io/e7fdg/).

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.2c07542.

Additional details on the interactions of the top interacting compounds and their corresponding plant sources shown in Figures S1−S8, and results of the cytotoxicity assays of plant extracts against A549 lung cancer cells in Figure S9 (PDF)

AUTHOR INFORMATION

Corresponding Authors

Jomar F. Rabajante − *Institute of Mathematical Sciences and Physics, University of the Philippines, Los Baños, Philippines 4031*; Email: jfrabajante@up.edu.ph

Gladys C. Completo − *Institute of Chemistry, University of the Philippines, Los Baños, Philippines 4031*; orcid.org/0000-0002-7815-8954; Email: gjcompleto@up.edu.ph

Authors

Sheryl Joyce B. Grijaldo − *Institute of Chemistry, University of the Philippines, Los Baños, Philippines 4031; Department of Chemistry, University of California, Davis, California 95616, United States*; orcid.org/0000-0001-7822-6462

Michael Russelle S. Alvarez − *Department of Chemistry, University of California, Davis, California 95616, United States*; orcid.org/0000-0001-6411-9906

Francisco M. Heralde III − *Lung Center of the Philippines, Quezon City, Philippines 1100; Department of Biochemistry and Molecular Biology, College of Medicine, University of the Philippines, Manila, Philippines 1000*

Ruel C. Nacario − *Institute of Chemistry, University of the Philippines, Los Baños, Philippines 4031*

Carlito B. Lebrilla − *Department of Chemistry, University of California, Davis, California 95616, United States*; orcid.org/0000-0001-7190-5323

Complete contact information is available at: https://pubs.acs.org/10.1021/acsomega.2c07542

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