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INTRODUCTION Cancer is one of the significant health problems in developed and developing countries. It is the second leading cause of death globally1. Unfortunately, despite their structural diversity, most currently approved anticancer drugs have drawbacks, mainly due to their harmful effects extended to normal cells, with further consequences on health2. Up to date, secondary metabolites continued to be a potential source of anticancer leads and utilized as a source of many therapeutic and preventive anticancer agents.

Interestingly, more than 60 % of currently used anticancer drugs are derived from natural sources3. Haplophyllum tuberculatum (Forsk.) of the Rutaceae family is used in folk medicine for malaria and parasitic infections4. Moreover, H. tuberculatum is used for many digestive, gynecological, respiratory, cardiovascular, and CNS disorders5,6. A literature survey showed that H. tuberculatum contains more than 50 phytoconstituents, including polyphenols, alkaloids, lignans, flavonoids, and essential oils6-10.

Therefore, it is necessary to conduct research to investigate the biological activity, safety, and determination of the appropriate biological target of the phytochemical constituents of H. tuberculatum. Although identifying drug targets is an essential step in understanding the mechanism of action, it is a challenging task mainly because of its complexity. Therefore, there is a need to use advanced technologies such as computer-aided drug design tools, including virtual screening molecular docking, to identify drug targets.11,12.

With this background information, this study aims to investigate the anticancer effect of H. tuberculatum aerial parts ethanol extract and fractions on HeLa (cervical) and HepG2 (liver) cell lines, as well as to reveal the potential anticancer targets, binding modes, pharmacokinetics, and toxicity properties of reported phytoconstituents using virtual computational methods. MATERIALS AND METHODS Materials Aerial parts (stem, leaves, flowers, fruits) of H. tuberculatum were collected from the Southern region of Saudi Arabia. The plant material was authenticated by Dr.

Mohammed Yusuf, a taxonomist at the Department of Pharmacognosy, College of Pharmacy, King Saud University, with a voucher specimen (No. 16324) was deposited. Human cancer cell lines HeLa and HepG2 were grown ingrown in T 75 culture flasks (Corning, US) at 37°C in a humi?ed incubator with 5% CO2 supply. The basic culture medium, DMEM (Invitrogen, US), was supplemented with 10% heat-inactivated bovine serum (Gibco, US) and 1x penicillin-streptomycin (HyClone, US).

Methods Preparation of ethanol extract and fractions Dried powdered plant materials (60 g) were soaked in 80% ethanol (Merck, Germany) for three days at 25-30°C and then

filtered. Extraction was repeated twice, as described previously. The extract was collected through Whatman filter paper No.1, and then evaporated using a rotary evaporator (Buchi, Switzerland) under reduced pressure at 40°C. The obtained semi-solid extract (5.79 g) was suspended in distilled water and then fractionated three times successively with the same volume of hexane (Merck, Germany), dichloromethane (Merck, Germany), ethyl acetate (Merck, Germany), and aqueous saturated n-butanol (Loba Chemie, India) to provide the corresponding fractions. Then, organic solvents were evaporated at reduced pressure using a rotatory evaporator. After drying, ethanol extract and fractions were stored at -20°C until subsequent use for screening.

In vitro cytotoxicity assay Ethanolic extract, as well as fractions of H. tuberculatum, were tested for cytotoxic activity using a 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) cell proliferation assay using TACS MTT Cell Proliferation Assay kit (Tervigen, US). The MTT assay was based on the metabolic reduction of soluble MTT by mitochondrial enzyme activity of viable cells into an insoluble colored formazan product which can be solubilized and measured optically13.

Cells were seeded in flat-bottom 96 well plates (0.5×105 cells/well) and grown for 20 hours. Haplophyllum tuberculatum extract and organic fractions were dissolved in dimethyl sulphoxide (DMSO; 100 mg/mL), then diluted in culture media to prepare five doses (0, 12.5, 25, 50, and 100 μg/mL) of each. The final concentration of DMSO used was less than 0.1%, thus had no toxicity, and cells were treated in triplicate/dose and incubated. Untreated cells (0.1% DMSO in media) and blank (only media) controls were also included.

After 48 hours post-treatment, cells were treated with MTT reagent (10 μL/well) and incubated at 37°C for 4 hours. Upon the appearance of a purple color, the detergent solution (100 μL) was added to each well and further incubated at 37°C for an hour. Optical density (OD) was recorded at 570 nm using a microplate reader ELx800 and cell survival fraction was determined using the equation in Formula 1: ???????????????? ??????????????? % = (??????-??????) (??????-??????) ×100 ... [1] In which ODs, ODb, and ODc were the optical density of the sample, blank and negative control, respectively14. Data were subjected to analysis using Microsoft Excel software, and the survival fraction was plotted against the concentration.

The concentration required for 50% inhibition of cell viability (IC50) was calculated. The extracts that fail to inhibit 50% of cell viability up to 100 μg/mL were considered inactive. In silico cytotoxicity and drug-likeness prediction The cytotoxic effect of about 70 compounds reported H. tuberculatum phytochemical constituents6-10 were predicted using Cell Line Cytotoxicity Predictor (CLC-Pred)15. The probability of

phytochemical constituents to be a drug candidate was predicted using the SwissADME webserver16. Virtual screening and molecular docking Virtual screening for anticancer targets depended on a protocol described by Al-Nour et al.12 with a modification. The chemical structures of reported H. tuberculatum phytochemical constituents were sketched by Marven Sketch software version 18.5 and saved as a mol. file format.

The 3D structures were generated and optimized accurately using Cresset Flare software17. The virtual screening for anticancer targets was conducted by submitting the structures to TargetNet18, ChemProt version 2.019, and CLC-Pred20 web servers in SMILES format. The predicted targets were for further validation via molecular docking. The 3D structures of the predicted targets were downloaded from the RCSB protein data bank21, prepared for docking, and minimized via Cresset Flare software17. For the validation, two 3D structures with different PDB IDs were downloaded.

The molecular docking calculations were conducted using Cresset Flare software17 at the normal mode and default setting. The co-crystallized ligands were used to determine the grid box; however, in the absence of a co-crystallized ligand, the grid box was determined by selecting the active site amino acids. The co-crystallized ligands and the known target's ligands were used as positive controls.

Pharmacokinetics and toxicity prediction The pkCSM22 and SwissADME16 web servers were used to predict intestinal absorption, the apparent volume of distribution, clearance, and CYP-450 enzyme inhibition. Furthermore, the pkCSM22 and eMolTox20 web servers were used to predict the toxicity of phytochemical constituents on major organs (cardiotoxicity, hepatotoxicity, and renal toxicity). RESULTS AND DISCUSSION In vitro cytotoxicity assay The in vitro cytotoxic activity of H. tuberculatum ethanol extract and fractions was evaluated against HeLa and HepG2 cancer cell lines.

The IC50 was calculated by plotting the survival fraction against concentration, as shown in Figure 1. Haplophyllum tuberculatum ethanol extract showed cytotoxic activity against HeLa and HepG2 with IC50 values of 54.12 and 48.1 µg/mL, respectively. In comparison, the IC50 values for hexane, chloroform, and ethyl acetate fractions against HeLa cells were 61.12, 79.4, and 52.31 µg/mL, respectively. Only hexane and ethyl acetate fractions showed activity against HepG2 cells with IC50 values of 75.6 and 41.7 µg/mL, respectively. / Figure 1. In vitro cytotoxic activity of the H.

tuberculatum ethanol extract and fractions against HeLa and HepG2 cell lines by MTT assay; IC50, half-maximal inhibitory concentration; EtOH: ethanol extract, Hex: hexane fraction, Chl: chloroform fraction, EtAc: ethyl acetate fraction These findings revealed that the crude ethanol extract exhibited marked inhibition in both HeLa and HepG2 lines

in a dose-dependent manner with IC50 values of 54.12 and 48.1 µg/mL, respectively. Therefore, it was subjected to sequential fractionation and subsequent screening. The highest anticancer activity was associated with the ethyl acetate fraction, followed by the hexane fraction (Figure 1).

Notably, the variable activities shown by the different fractions might be attributed to the diversity of structure and/or uneven distribution of phytochemical constituents present in these fractions. Nevertheless, this further suggests that the bioactive compounds were of low to intermediate polarity. Virtual screening and molecular docking Once the biological activity was confirmed, identifying the drug target was a valuable subsequent step that leads to further success in the drug development pipeline11.

It was challenging work; hence, it requires sophisticated tools to reduce the difficulty12. Recently, the use of computer-aided drug design tools leads to the successful prediction of many drug targets. Several studies reported the involvement of computational tools in discovering natural drugs23-26. Consequently, in this study, virtual screening and molecular docking were used to predict the targets that phytochemical constituents exert their cytotoxicity through.

Initially, the cytotoxicity and the drug-likeness probability of known phytoconstituents of H. tuberculatum were predicted. Out of the 70 screened compounds, 47 were predicted as cytotoxic drug candidates. Their probable targets were predicted, and their interactions were studied using the molecular docking technique. The promised compounds with their target were listed in Table I. According to the virtual screening and molecular docking, the cytotoxic effect of H.

tuberculatum was due to the interaction with vital targets that were involved in cell growth, proliferation, and survival, migration, tumor suppression, induction of apoptosis, resistance to apoptosis, metastasis, as well as drug resistance. Table I shows polygamain, justicidin A, justicidin B, ?-fagarine, skimmianine, haplotubine, kusunokinin, and flindersine were the phytochemical constituents that contribute to the cytotoxicity of H. tuberculatum. Virtual screening was based on strictly evaluated and validated QSAR models18. Besides, the molecular docking study was performed using Cresset Flare software characterized by well-respected accuracy and efficiency17,26.

The predicted cytotoxicity was due to the inhibition of tumor cells growth, proliferation, and survival via the interaction with Dual specificity protein kinase CLK1, Dual specificity tyrosine-phosphorylation-regulated kinase 1A, topoisomerase II enzyme, transcription factor p65, peroxisome proliferator-activated receptor-?, mitogen-activated protein

kinase 14, thyrotropin receptor, and phosphatidylinositol-4 5-bisphosphate 3-kinase catalytic subunit a. Besides, the predicted cytotoxicity was due to tumor suppression via the interaction with Cellular Tumor antigen p53, Menin, Runt-related transcription factor 1, and Serine-protein kinase ATM, as well as the inhibition of tumor cells migration via the interaction with Tubulin ß-2B chain, Receptor-interacting serine/threonine-protein kinase 2, and Protein kinase C atype.

Furthermore, the predicted cytotoxicity was due to the induction of apoptosis via the interaction with Caspase 3 and 8 enzymes tumor necrosis factor receptor superfamily member 6, the inhibition of anti-apoptotic protein Bcl-2 and BAX, as well as the inhibition of drug resistance via the interaction with multidrug resistance protein 1 and 2. Table I. Molecular docking results of the H. tuberculatum phytochemical constituents with their predicted targets Target _Compounds _Docking score _ _Tubulin ß-2B chain _ Polygamain Justicidin A Justicidin B Haplotubine Kusunokinin A GTP 502 A GTP 501 _6E7C _5ITZ _ _ _ _-9.925 -8.593 -9.194 -8.127 -8.063 -9.052 ---- _-9.175 -7.572 -8.604 -8.555 -8.037 ---- -8.672 _ _Dual specificity protein kinase CLK1 _ Polygamain Justicidin A Justicidin B A DBQ 1 A FG9 502 _1Z57 _6Q8K _ _ _ _-9.313 -9.098 -9.266 -8.971 ---- _-9.483 -10.163 -9.549 ---- -9.332 _ _Dual specificity tyrosine-phosphorylation-regulated kinase 1A _ Polygamain Dyphylline Skimmianine A B5Z 501 A 2K2 501 _6EIJ _4NCT _ _ _ _-8.966 -8.004 -6.384 -10.072 ---- _-9.877 -7.942 -5.71 ---- -17.596 _ _Receptor-interacting serine/threonine-protein kinase 2 _ Polygamain Justicidin A Justicidin B A EJY 301 A Q1A 402 _6C3E _4NEU _ _ _ _-6.408 -6.332 -7.304 -7.913 ---- _-7.675 -7.944 -7.161 ---- -13.12 _ _Cellular Tumor Antigen p53 _ Polygamain Kusunokinin Flindersine A EY2 401 A 9H5 402 _6GGA _5O1A _ _ _ _-8.885 -7.831 -7.194 -8.323 ---- _-8.125 -9.274 -7.935 ---- -8.89 _ _Menin protein _ Polygamain Justicidin A Justicidin B Dyphylline A 0RO 601 A 0BR 612 _4GQ3 _3U88 _ _ _ _-8.505 -8.141 -7.901 -8.598 -9.778 ---- _-8.883 -8.075 -7.878 -8.383 ---- -8.505 _ _Runt-related transcription factor 1 _ Polygamain _4L0Y _1IO4 _ _ _ _-7.563 _-7.313 _ _Caspase 3 enzyme _ Polygamain Justicidin A Justicidin B Dyphylline Kusunokinin A 161 1278 F ACE 1 _1NMS _3EDQ _ _ _ _-8.628 -8.28 -9.025 -8.738 -8.374 -9.822 ---- _-7.764 -7.623 -8.274 -8.376 -7.655 ---- -12.374 _ _Topoisomerase II enzyme _ Polygamain A EVP 1 _3QX3 _5ZAD _ _ _ _-8.575 -8.68 _-8.572 ---- _ _Multidrug resistance protein 1 and 2 _ Polygamain A CLR 1306 A D6T _6QEX _6FEQ _ _ _ _-10.035 -7.008 ---- _-9.3 ---- -10.498 _ _Topoisomerase I enzyme _ Polygamain Justicidin A Justicidin B Dyphylline Kusunokinin D AI3 901 D SA3 990 _1TL8 _1SEU _ _ _ _-10.996 -10.893 -9.959 -11.278 -10.363 -12.126 ---- _-10.555 -12.381 -11.945 -11.976 -10.631 ---- -15.519 _ _Caspase 8 enzyme _ Polygamain Justicidin A Justicidin B Dyphylline A B94 480 _3KJQ _1F9E _ _ _ _-9.995 -9.545 -8.736 -9.07 -10.132 _-9.777 -7.023 -7.959 -7.448 ---- _ _Transcription factor p65 _ P-cymene-8-ol Justicidin A Justicidin B Bortezomib _2RAM _5U01 _ _ _ _-5.597 -6.821 -7.221 -6.232 _-5.766 -7.159 -8.214 -6.29 _ _Protein kinase C a type _ Justicidin A

Justicidin B Dyphylline A LW4 901 _4DNL _3IW4 _ _ _ _-7.37 -7.48 -7.442 ---- _-8.928 -8.928 -10.394 -12.252 _ _Peroxisome proliferator-activated receptor ? _ Justicidin A Justicidin B Dyphylline A Y1N 1468 A V77 601 _4CI4 _6MS7 _ _ _ _-8.329 -9.245 -9.801 -10.537 ---- _-8.421 -8.781 -6.78 ---- -7.283 _ _Receptor tyrosine-protein kinase erbB-2 _ Justicidin A Justicidin B Dyphylline _2A91 _3BE1 _ _ _ _-7.344 -8.243 -7.711 _-9.024 -8.799 -9.223 _ _Mitogen-activated protein kinase 14 _ ?-fagarine A 09J 500 A P37 361 _3U8W _3GFE _ _ _ _-11.738 -11.738 ---- _-6.368 ---- -12.126 _ _Thyrotropin receptor _ ?-fagarine Skimmianine Kusunokinin Flindersine _2XWT _3G04 _ _ _ _-6.029 -6.319 -7.016 -6.657 _-6.126 -6.172 -6.961 -7.058 _ _Phosphatidylinositol-4 5-bisphosphate 3-kinase catalytic subunit a _ ?-fagarine Skimmianine _5XGH _6GVF _ _ _ _-6.74 -6.605 _-6.117 -7.031 _ _Serine-protein kinase ATM _ Skimmianine A ADP 2601 _6FH5 _3JBZ _ _ _ _-7.356 -9.672 ---- _-6.257 ---- -10.074 _ _Tumor necrosis factor receptor superfamily member 6 _ ?-fagarine Skimmianine Kusunokinin Flindersine _3OQ9 _3THM _ _ _ _-7.234 -7.305 -7.172 -7.936 _-5.852 -5.748 -7.294 -7.429 _ _Apoptosis regulator Bcl-2 _ Haplotubine Kusunokinin Flindersine Venetoclax _2VM6 _5WHH _ _ _ _-8.216 -7.08 -7.055 -9.339 _-6.934 -6.257 -7.116 -8.807 _ _Apoptosis regulator BAX _ Flindersine _5W5X _6EB6 _ _ _ _-6.726 _-6.87 _ _Note: The bolded code was the target 3D structure were the PDB IDs. The italic compounds were the co-crystallized ligands.

The bolded compounds were positive controls According to molecular docking, the lowest energy score indicates the highest binding affinity27. Hence, polygamain, justicidin A, justicidin B, haplotubine, kusunokinin, and flindersine were the compounds with the highest binding affinity. The 3D interaction of the best-predicted compounds shows a ligand superimposing between the best-predicted compounds and the controls.

However, polygamain binds at a different position on the active site of the multidrug resistance protein 1 from the co-crystallized ligand A CLR 1306, as shown in Figure 2. Polygamain has the highest binding affinity to the vast majority of the predicted targets among the best-predicted compounds. Due to the vast number of predicted targets, a representative example was given to illustrate the 3D and 2D interactions. The results showed that polygamain interacts with the Dual specificity tyrosine-phosphorylation-regulated kinase 1A and Cellular Tumor antigen p53 in the same binding sites of their co-crystallized ligands.

It binds with the exact position of A B5Z 501 and a different position from A EY2 401. In contrast, justicidin A binds in a position similar to D SA3 990, as shown in Figure 2. In comparison between interactions of polygamain, justicidin A, and the co-crystallized ligands, A B5Z 501 forms additional hydrogen bond with the dual specificity tyrosine-phosphorylation-regulated kinase 1A binding site making its virtual screening

score (-10.072) better than polygamain (-8.966). The A EY2 401 forms six hydrophobic bonds with the binding sites of the Cellular Tumor antigen p53, much than polygamain (three bonds).

However, the amino acids clashes made its virtual screening score (-8.323) lower than polygamain (-8.885). In contrast, the atom clashes and fewer bonds in the interaction of justicidin A with the topoisomerase I enzyme made its virtual screening score (-10.893) lower than D SA3 990 (-15.519), as shown in Figure 3. / / A / / B / / C Figure 2. The 3D interaction between the best predicted H. tuberculatum phytochemical constituents with their predicted targets. A: Polygamain (dark yellow) and A B5Z 501 (turquoise) with dual-specificity tyrosine phosphorylation-regulated kinase 1A.

B: Polygamain (dark yellow) and A EY2 401 (turquoise) with Cellular Tumor antigen p53. C: Justicidin A (violet) and D SA3 990 (turquoise) with Topoisomerase I enzyme.

/ A / B / C Figure 3. The 2D interaction between the best predicted H. tuberculatum phytochemical constituents with their predicted targets. A: Polygamain (left) and A B5Z 501 (right) with dual-specificity tyrosine phosphorylation-regulated kinase 1A. B: Polygamain (left) and A EY2 401 (right) with Cellular Tumor antigen p53. C: Justicidin A (left) and D SA3 990 (right) with Topoisomerase I enzyme.

Pharmacokinetics and toxicity prediction Web servers were used to predict the promised anticancer phytochemical constituents of H. tuberculatum compounds' toxicity, and results are summarized in Table II. Polygamain, skimmianine, kusunokinin, and flindersine had the best pharmacokinetics and safety profile among those compounds. Moreover, the pharmacokinetics and toxicity prediction results of polygamain showed that it had the highest absorption (100%), was permeable to the blood-brain-barrier BBB, and was free from significant organ toxicity (cardiotoxicity hepatotoxicity, nephrotoxicity, and CNS toxicity). Consequently, polygamain would be a promising drug-like compound for the treatment of many types of cancers. Table II. Pharmacokinetics and toxicity prediction of the promising H.

tuberculatum phytochemical constituents Compounds _GIT absorption _BBB * _Vd** _Cl*** _CYP450 enzymes inhibition _Toxicity on major organs _ _Polygamain _High (100%) _Yes _-0.855 _-0.042 _CYP3A4, CYP1A2 _No _ _Ammoidin _High (98.341) _Yes _-0.198 _0.744 _CYP1A2 _No _ _Skimmianine _High (97.967) _Yes _0.046 _0.757 _CYP3A4, CYP1A2 _No _ _Kusunokinin _High (97.192) _Yes _-0.435 _0.115 _CYP3A4, CYP2C19, CYP2C9 _No _ _Flindersine _High (95.319) _Yes _0.543 _0.196 _CYP1A2 _No _ _*Blood brain barrier permeability, **Volume of distribution (-log/Kg), ***Clearance (log mL/min/kg) In agreement, polygamain from Amyris madrensis was found to has a cytotoxic effect against human PC3 cells28.

Justicidin B was found to had a potent cytotoxic and pro-apoptotic effect on human breast cancer-derived cell lines29 and acute myeloid leukemia-derived cell line HL-6030. Though the effectiveness of using virtual screening and molecular docking for drug targets prediction12,17,18, experimental studies were recommended to validate the predicted targets to develop strong evidence regarding the role of the predicted target in the cytotoxicity of H. tuberculatum phytochemical constituents. Moreover, RMSD calculations and molecular dynamics simulation are recommended to validate docking calculations. CONCLUSION Our findings concluded that H. tuberculatum has anticancer potential.

Polygamain, justicidin A, justicidin B, ?-fagarine, skimmianine, haplotubine, kusunokinin, and flindersine were the phytochemical constituents that contribute to the cytotoxicity of H. tuberculatum. They exert their cytotoxic effect via the interaction with vital targets involved in cell growth, proliferation, and survival, migration, tumor suppression, induction of apoptosis, resistance to apoptosis, metastasis, as well as drug resistance. However, further phytochemical and biological studies are required to isolate the active principle(s) responsible for the novel anticancer potential.

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