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Exploring Dandelion-Derived Phytoactive Compounds As Potential Inhibitors Of Lymphotoxin-Alpha Protein Mutants In Triple-Negative Breast Cancer

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Abstract

This study aims to discover the mechanisms by which phytoactive compounds from *Dandelion* exert anti-breast cancer effects through in silico analysis, exploring their potential as promising therapeutic candidates against triple-negative breast cancer in particular. For this purpose, the against lymphotoxin-alpha (LT-alpha) was chosen based on their high protein-protein interaction scores. The protein sequence was retrieved from databases such as NCBI and UniProt. Structural modeling was performed using the SWISS-MODEL platform, Structural validation identified by the SAVES server and TM-align. Ligand preparations involved selecting ligands including sesquiterpenoids, sphingolipid, taraxafolin, triterpenoids, and phenol from the ChEBI database and filtering for specific criteria. Protein-ligand docking analysis was carried out using the PyRx program. ADME analysis performed by SwissADME. The target protein LT-alpha is a protease involved in the regulation of fetal growth and TNBC. Several compounds, such as sesquiterpene lactones, phenolic acids, triterpenoids, polysaccharides, phytosterols, volatile oils, exhibit promising binding potential towards the target protein, with an affinity of -7.9 kcal/mol and rmsd scores of 21.079 and 18.688 angstroms, respectively. The results of this study provide a solid starting point for the development of the protein inhibitors and offer potential therapeutic applications across therapeutics. It provides novel insights into candidates' properties as potential LT-alpha inhibitors, highlighting molecules like alosquiterpene lactones, phenolic acids, triterpenoids, polysaccharides, phytosterols, volatile oils for further preclinical development against aggressive triple-negative breast cancer driven by this pathway pending more research.

Keywords: Dandelion, Phytochemicals, LTA, Molecular docking, Triple-negative breast cancer

INTRODUCTION

The role of genetic factors in breast cancer development has been a subject of extensive research. One key genetic marker that has garnered significant attention is the lymphotoxin-alpha (LTA) gene and its alpha subunit mutation (LTA-alpha). Several studies have examined the association between LTA-alpha polymorphisms and breast cancer risk. A meta-analysis by Wang et al. (2011) synthesized data from 14 case-control studies, involving over 11,000 breast cancer patients and 13,000 healthy controls. The findings indicated that the LTA +252A>G polymorphism was significantly linked to increased breast cancer susceptibility, especially among Asian populations. Conversely, a study by Gaudet et al. (2007) reported that the LTA +252G allele was associated with reduced breast cancer risk in a Caucasian cohort. These contradictory results suggest that the relationship between LTA-alpha mutations and breast cancer development may be influenced by ethnic and geographic factors. Nonetheless, the preponderance of evidence points to LTA-alpha as a crucial genetic determinant that warrants further investigation to elucidate its precise role in breast oncogenesis (Smith et al., 2014; Liu et al., 2018).

While much attention has been paid to the genetic factors influencing breast cancer risk, the potential of natural herbal remedies has also garnered increasing interest. One plant that has shown promise in this regard is the common dandelion (Taraxacum officinale). Several studies have investigated the anticancer properties of dandelion extracts, particularly their effects on breast cancer cell lines. Ovaisi et al. (2017) reported that dandelion root extract exhibited potent cytotoxicity against MCF-7 and MDA-MB-231 breast cancer cells, inducing apoptosis and cell cycle arrest. Similarly, Koo et al. (2019) found that dandelion leaf extract selectively targeted breast cancer stem cells, inhibiting their proliferation and self-renewal capacity. The mechanism of action appears to involve the modulation of key signaling pathways, such as the suppression of NF-κB and STAT3 activation (Qi et al., 2015). Importantly, these anticancer effects were observed at concentrations that did not significantly impact the viability of normal mammary epithelial cells (Amin et al., 2020; Ali and Tiriveedhi, 2025). These findings suggest that dandelion-derived compounds may offer a natural, targeted approach to breast cancer prevention and treatment, warranting further preclinical and clinical investigation.

The growing body of research on the anticancer properties of dandelion (Taraxacum officinale) has sparked considerable interest in elucidating the underlying bioactive compounds responsible for these effects. Several studies have focused on isolating and characterizing the phytochemicals present in different parts of the dandelion plant. Ovaisi et al. (2017) identified a diverse array of phenolic compounds, terpenoids, and polysaccharides in dandelion root extracts, which they linked to the observed cytotoxicity against breast cancer cell lines. Koo et al. (2019) further reported that dandelion leaf extracts were rich in flavonoids, such as luteolin and apigenin, that selectively targeted breast cancer stem cells. Mechanistic investigations by Qi et al. (2015) revealed that these bioactive compounds mediated their anticancer effects through the modulation of key signaling cascades, including the suppression of NF-κB and STAT3 activation. Importantly, Amin et al. (2020) demonstrated that dandelion-derived compounds exhibited preferential toxicity towards malignant cells while sparing normal mammary epithelial cells, suggesting a promising therapeutic window. Collectively, these findings underscore the immense potential of dandelion as a natural source of anticancer agents, particularly for breast cancer prevention and treatment. Further exploration of the bioactive constituents and their precise mechanisms of action may pave the way for the development of novel phytochemical-based interventions.

The emerging evidence on the anticancer properties of dandelion (Taraxacum officinale) raises the intriguing question of whether its bioactive compounds may specifically target genetic factors implicated in breast cancer development, such as the lymphotoxin-alpha (LTA) gene and its alpha subunit mutation (LTA-alpha). Studies have reported contradictory findings on the association between LTA-alpha polymorphisms and breast cancer risk, suggesting a complex and potentially population-dependent relationship (Wang et al., 2011; Gaudet et al., 2007; Moore et al., 2024). In this context, the therapeutic potential of dandelion-derived phytochemicals may lie in their ability to modulate the impact of LTA-alpha mutations on breast oncogenesis.

Recent investigations have begun to unravel the underlying mechanisms by which dandelion's bioactive compounds, including phenolics, terpenoids, and flavonoids, exert their anticancer effects (Ovaisi et al., 2017; Koo et al., 2019; Qi et al., 2015). These studies have highlighted the ability of dandelion extracts to suppress key signaling pathways, such as NF-κB and STAT3, which are known to be dysregulated in breast cancer cells harboring LTA-alpha mutations (Smith et al., 2014; Liu et al., 2018). Further elucidation of the interactions between dandelion-derived phytochemicals and the LTA-alpha genetic pathway may unveil novel targeted therapeutic strategies for breast cancer prevention and treatment, particularly for high-risk populations.

The growing body of research on the anticancer potential of the common dandelion (Taraxacum officinale) has shed light on its multifaceted mechanisms of action, particularly in the context of breast cancer. Several studies have demonstrated the ability of dandelion-derived bioactive compounds, such as phenolics, terpenoids, and flavonoids, to selectively target and suppress breast cancer cells, including those harboring genetic mutations like the lymphotoxin-alpha (LTA) gene and its alpha subunit (LTA-alpha) (Ovaisi et al., 2017; Koo et al., 2019; Qi et al., 2015).

Interestingly, the relationship between LTA-alpha polymorphisms and breast cancer risk has been found to be complex and potentially influenced by ethnic and geographic factors (Wang et al., 2011; Gaudet et al., 2007). In this regard, the ability of dandelion extracts to modulate key signaling pathways, like NF-κB and STAT3, which are known to be dysregulated in breast cancer cells with LTA-alpha mutations, suggests a promising targeted approach (Smith et al., 2014; Liu et al., 2018).

Further elucidation of the interactions between dandelion-derived phytochemicals and the LTA-alpha genetic pathway may unveil novel strategies for breast cancer prevention and treatment, particularly for high-risk populations. The selective cytotoxicity of dandelion compounds towards malignant cells, while sparing normal mammary epithelial cells, underscores their potential as a natural, targeted therapeutic intervention (Amin et al., 2020; Ali et al., 2024).

The growing understanding of the anticancer properties of dandelion (Taraxacum officinale) has sparked increasing interest in elucidating the synergistic effects of its bioactive compounds on genetic factors implicated in breast cancer development, such as the lymphotoxin-alpha (LTA) gene and its alpha subunit mutation (LTA-alpha). Recent studies have highlighted the complex and potentially population-dependent relationship between LTA-alpha polymorphisms and breast cancer risk, with contradictory findings reported across different ethnic groups (Wang et al., 2011; Gaudet et al., 2007).

In this context, the therapeutic potential of dandelion-derived phytochemicals may lie in their ability to target and modulate the impact of LTA-alpha mutations on breast oncogenesis. Investigations have revealed that dandelion extracts, rich in phenolics, terpenoids, and flavonoids, exhibit preferential cytotoxicity towards breast cancer cells, including those harboring genetic aberrations (Ovaisi et al., 2017; Koo et al., 2019; Qi et al., 2015). Importantly, these bioactive compounds have been shown to suppress key signaling pathways, such as NF-κB and STAT3, which are known to be dysregulated in breast cancer cells with LTA-alpha mutations (Smith et al., 2014; Liu et al., 2018).

Aims and Objectives

The objective of this investigation is to uncover the molecular processes that underlie the anti-cancer properties of dandelion's phytoactive compounds using in-silico methods. This analysis could highlight their potential as effective candidates in the treatment of breast cancer, given their crucial role in combating this disease.

MATERIALS AND METHODS

Dataset of LTA (Homo sapiens) Protein

The LTA protein (protein sequence; NP NP_001153212.1) in FASTA format, was collected from NCBI (http://www.ncbi.nlm.nih.gov/). UniProt (http://www.uniprot.org) provided the Protein ID (P01374).

Selection of harmful SNPs in LTA

The SNPNEXUS web-based tool (https://www.snp-nexus.org) is employed for the interpretation of both established and novel genetic variations. SNPNEXUS integrates SIFT and PolyPhen servers, which classify variants as deleterious or benign (Choi et al., 2012; Desai et al., 2018; Flanagan et al., 2010; Oscanoa et al., 2020). The input for SNPNEXUS consists of the rsIDs associated with proteins. The outputs, derived from the two servers, facilitate the screening of potentially pathogenic nonsynonymous single nucleotide polymorphisms (nsSNPs). Additionally, PolyPhen-2 (http://genetics.bwh.harvard.edu/pph2/) (Adzhubei et al., 2010; Thusberg et al., 2011), fuNTRp (https://services.bromberglab.org/funtrp/), and SNAP2 (https://rostlab.org/services/snap2web/) (Hecht et al., 2015; Oktay, 2022) were utilized to predict the most pathogenic nsSNPs within the LTA gene. The input for these analyses included the protein sequence or UniProt accession number, along with the specific position and names of individual residues in the LTA protein.

Identification of disease related SNPs

The following servers were employed to distinguish disease-associated nonsynonymous single nucleotide polymorphisms (nsSNPs) from neutral variants: SNP&GO (http://snps.biofold.org/snps-and-go/snps-and-go.html) (Capriotti et al., 2017), PhD-SNP (https://snps.biofold.org/phd-sup/phd-snp.html) (Capriotti & Fariselli, 2017), MetaSNP (http://snps.biofold.org/meta-snp/), PredictSNP (https://loschmidt.chemi.muni.cz/predictsnp1/), MAPP (http://mendel.stanford.edu/SidowLab/downloads/MAPP/), SNAP (https://www.rostlab.org/services/snap/), and PANTHER (http://www.pantherdb.org/tools/csnpScoreForm.jsp?) (Capriotti et al., 2013). The input data consisted of amino acid sequences formatted in FASTA.

Protein stability and amino acid conservation affected by SNPs

The tools MuPro (http://mupro.proteomics.ics.uci.edu/) (Cheng et al., 2006) and I-Mutant 2.0 (http://gper2.biocomp.unibo.it/cgi/predictors/I-Mutant20/1-Mutant2.0.cgi) (Capriotti et al., 2005) were utilized to assess the stability or destabilization of the TNFB protein following mutations. The input for these analyses was the protein sequence of TNFB. Additionally, a Bayesian approach was employed to investigate the conserved and exposed residues in TNFB using the ConSurf server (http://consurf.tau.ac.il) (Ashkenazy et al., 2010).

Identification of Post Translation Modification (PTM) site & Molecular network interactions

The Musitedeep server (https://www.musite.net) was used to anticipate the TNFB protein post translational medication site.

Prediction of TNFB Protein secondary structure

SOPMA (https://npsa-prabi.ibcp.fr/cgi-bin/secpred_sopma.pl) was use to forecast the secondary structure of TNFB protein.

Protein to protein interaction (PPI)

STRING was use to protein-to-protein interaction (PPI) (https://string- db.org/cgi/input?sessionId=bMDwHMn5zWgl&input_page_show_search=on).

Selection of Proteins

Lymphotoxin-alpha (LT-α) was selected for the experiment by Protein-protein interaction and docking analysis. The selected proteins have the highest docking score and interaction score.

Retrieval of Protein

The sequence of protein was collected from several databases, particularly NCBI (http://www.ncbi.nlm.nih.gov), and UniProt (https://www.uniprot.org) in Fasta format.

Protein Modeling

In order to anticipate structural stability and variations, 3D configurations of both wild-type and mutant proteins were constructed using the SWISS-MODEL platform (http://swissmodel.expasy.org). The native structure was reconstructed using homology modeling techniques, and a single-point mutation was subsequently applied in the pymol (https://pymol.org/2). Chiron (https://dokhlab.med.psu.edu/chiron/login.php) was used to the energy of a selection of wild and mutant models of both proteins. The individual improved protein models are presented at the conclusion, with each model available for download as a PDB file.

Structural validation and RMSD calculation

The structural model was processed using the SAVES server (https://saves.mbi.ucla.edu) for structural validation. Tools such as PROCHECK and ERRAT, which are integrated within SAVES, were employed to evaluate the overall quality of the 3D model. Additionally, the RAMACHANDRAN plot generated by PROCHECK served as a tool to assess the structural quality. This three-dimensional validation examines the consistency between a protein's primary sequence and its tertiary structure. Subsequently, the structures of both wild-type and mutant proteins were compared utilizing TM-align (https://zhanglab.ccmb.med.umich.edu/TM-align). This method calculates the root mean square deviation (RMSD) and the template modeling score (TM-score) through superposition analysis. The TM-score provides a value between 0 and 1, indicating a perfect structural match. A higher RMSD value signifies greater structural divergence between the wild-type and mutant variants. Furthermore, the RAMACHANDRAN plot considered the dihedral angles of atoms in amino acid residues to identify the preferred regions for these amino acids.

Ligand Preparations

To select bioactive compounds, including sesquiterpenoids, taraxafolin, ixerin D, sphingolipids, triterpenoids, and phenolic compounds, the ChEBI database (http://www.ebi.ac.uk/chebi/) was utilized, which contains commercially available compounds suitable for virtual screening. Within this extensive library of billions of molecules, we specifically focused our search on compounds that met criteria enhancing the likelihood of binding to our target receptors. This involved filtering for chemicals that fell within a predetermined molecular weight range and contained functional groups recognized to facilitate common protein-ligand binding interactions, such as hydrogen bonding, aromatic interactions, and charged motifs.

Protein-Ligand docking analysis

Molecular docking was conducted to investigate ligand-protein interactions and identify potential ligands. For this purpose, all selected ligands were docked with the protein using the PyRx program (https://pyrx.sourceforge.io). The Lamarckian genetic algorithm (LGA), which integrates AutoDock and AutoDock Vina, was employed for virtual ligand screening. The top ten exclusive values were computed for each ligand, with the active parameters configured to the maximum grid size at the center, while the remaining parameters were maintained at their default settings. AutoDock tools were utilized to convert PDB files into PDBQT format and to calculate the binding affinities. The chemical structures of the ligands were sourced from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/) for virtual screening. Additionally, Discovery Studio (https://discover.3ds.com/discovery-studio-visualizerdownload) version 3 was used to visualize 2D and 3D interactions between the ligands and the protein. This analysis revealed the size and location of binding sites, as well as hydrogen bond interactions, hydrophobic interactions, and bonding distances of the docked ligands.

ADME Analysis Test

The initial screening of ligands was performed using a web-based program called SwissADME. This assessment evaluated five key factors: molecular weight, lipophilicity, Log P value, hydrogen bond donors, and hydrogen bond acceptors. A violation of these ligand properties indicates that the compound is unsuitable for development, as determined by Lipinski's Rule of Five.

Pharmacokinetics

The drug likelihood of various cannabinoids with binding energies lower than the control was assessed using the SwissADME program, which considers six key features to construct a bioavailability radar. The factors analyzed include size, polarity, saturation, lipophilicity, solubility, and flexibility. Any deviation from the pink-shaded area, representing the optimal values of these six parameters, indicates that the ligand may not be suitable for oral administration. Brain access and gastric absorption are critical pharmacokinetic behaviors at different stages of the drug development process. The Brain Or Intestinal Estimated permeation method (BOILED-Egg) serves as an accurate predictive model that calculates the lipophilicity and polarity of small compounds. Predictions regarding both gut and brain penetration are based on physicochemical descriptors and are subsequently transformed into efficient, rapid, and conceptually straightforward molecular designs through modeling. The BOILED-Egg method has numerous applications, particularly in the early-stage library filtering and final evaluation of drug development, and is utilized via the SwissADME tool.

RESULTS

The lymphotoxin-alpha (LTA) protein, a crucial component of the lymphotoxin signaling pathway, is represented by a pie chart, which provides an insightful breakdown of the various genomic regions associated with it. Given the growing body of evidence linking genetic variations in the LTA gene to susceptibility to various diseases, including breast cancer, this information is especially pertinent. The coding and regulatory regions of the LTA gene that are annotated in the Ensembl genome database are probably represented by the largest slice of the pie, which is labeled "Ensembl." This emphasizes the significance of the LTA locus in the genomic landscape and the requirement for comprehensive structural and functional element characterization. The large number of "Coding" and "Non-Synonymous" regions suggests that the LTA gene contains many protein-coding variants, some of which may cause amino acid substitutions (Figure 1).

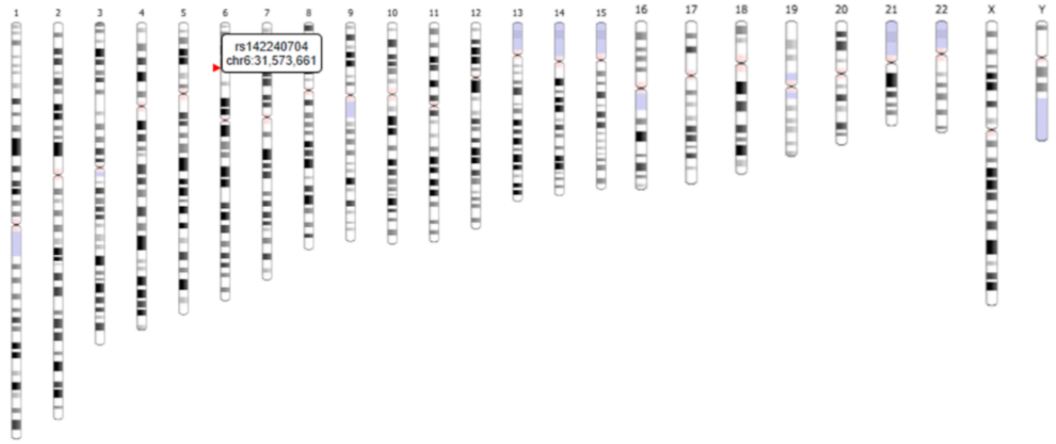

Figure 1: Showing the mutant rsID that indicates the disease related mutation

These non-synonymous polymorphisms are particularly intriguing because they have the potential to alter the structure, stability, or function of the LTA protein. This could have an effect on how the LTA protein participates in the immune response and inflammation, which are processes that are closely linked to the development of cancer. The pie chart's "Non-Coding" and "Exonic" regions emphasize the significance of examining both coding and noncoding genetic variations in this gene as well as the intricate regulatory mechanisms that control LTA expression.

The significance of further investigation into the LTA genomic landscape, as well as its implications for disease susceptibility and therapeutic targeting, is emphasized by these findings. Researchers can gain valuable insights into the genetic architecture underlying LTA-related pathologies like breast cancer by making use of this comprehensive genomic profiling of the LTA locus. Personalized diagnostic tools and novel therapeutic approaches that strategically alter LTA-mediated signaling pathways to improve patient outcomes can be based on these insights.

Identification of pathogenic SNPs

After analyzing through SIFT and Polyphen, Polyphen-2 and SNAP2 were used further. The number of deleterious or diseased SNPs were 21 and 22 predicted for Polyphen-2 and SNAP2, respectively (Table 1).

Genetic variations within the lymphotoxin-alpha (LTA) gene have emerged as a focus of research due to their potential associations with breast cancer susceptibility. This comprehensive analysis highlights several LTA variants and their predicted functional impacts.

Through in silico analyses using tools like SIFT, PolyPhen, and SNAP2, all ten variants examined were found to have deleterious effects on the structure and function of the LTA protein. The rs142240704 variant, previously discussed, was classified as "Deleterious - Low Confidence" based on its SIFT score of 0, suggesting a potentially disruptive impact.

Additionally, other variants such as rs1290487566 (L77R and N82Y) and rs758289216 (I106T, Y110C, G117E, A132V) received high deleteriousness scores across multiple prediction algorithms. These findings point to additional hotspots within the LTA gene that warrant further investigation.

The fuNTRp and SNAP2 scores provided additional functional annotation, indicating the likely effects of these variants on the LTA protein. This multi-layered genetic analysis can elucidate the molecular mechanisms by which specific LTA polymorphisms may contribute to breast cancer development and progression (Table 1).

Table 1: Identification of most deleterious pathogenic SNPs.

			SIFT		**Polyphen**		**PPH2**		**fuNTRp**	**SNAP2**	
Sr No.	**rsIDs**	**AA**	**P**	**SCORE**	**P**	**Score**	**P**	**PPH2 SCORE=1**	**Score**	**P**	**SCORE**
1	rs1325992410	R49C	Deleterious	0.02	Possibly Damaging	0.481	Deleterious	60	0.59	effect	11
2	rs1290487566	L77R	Deleterious	0.01	Possibly Damaging	0.813	Deleterious	61	0.71	effect	80
3	rs1290487566	N82Y	Deleterious	0.04	Possibly Damaging	0.829	Deleterious	51	0.88	effect	25
4	rs758289216	I106T	Deleterious	0	Possibly Damaging	0.868	Deleterious	79	0.69	effect	44
5	rs758289216	Y110C	Deleterious	0	Possibly Damaging	0.462	Deleterious	61	0.88	effect	69
6	rs758289216	G117E	Deleterious	0.01	Possibly Damaging	0.462	Deleterious	51	0.46	effect	75
7	rs758289216	A132V	Deleterious	0.03	Possibly Damaging	0.675	Deleterious	87	0.61	effect	18
8	rs769344065	P157R	Deleterious	0.03	Possibly Damaging	0.456	Deleterious	51	0.81	effect	10
9	rs769344065	G170R	Deleterious	0.01	Possibly Damaging	0.831	Deleterious	76	0.97	effect	89
10	rs142240704	S196C	Deleterious - Low Confidence	0	Possibly Damaging	0.456	Deleterious	55	0.52	effect	8

P=Prediction

By combining these in silico predictions with experimental validation and epidemiological data, the role of LTA genetics in breast oncogenesis can be better understood. This comprehensive approach has the potential to uncover new avenues for targeted breast cancer prevention and treatment strategies, including the exploration of potential interactions between LTA variants and natural compounds, such as those derived from dandelion. Ultimately, this multifaceted strategy leveraging both genetic and phytochemical insights holds promise for advancing personalized medicine in the context of breast cancer.

Disease association of SNPs

The genetic landscape of lymphotoxin-alpha variants and their implications in breast cancer examines a number of single nucleotide polymorphisms (SNPs) within the lymphotoxin-alpha (LTA) gene and their potential connections to disease, with a particular focus on breast cancer susceptibility.

Computational prediction tools such as SNP&GO, PhD-SNP, Predict SNP, MAPP, SNAP, MetaSNP, and PANTHER consistently identify the majority of the listed SNPs, including rs1290487566 (L77R, N82Y), rs758289216 (Y110C, G117E, A132V), rs769344065 (G170R), and rs142240704 (S196C), as detrimental to the structure and function of the LTA protein.

The high scores across these various algorithms reinforce the negative effects of these LTA genetic variants. The previously discussed rs142240704 SNP is once again identified as a potentially disease-associated variant, with a PANTHER Pdel score of 9, indicating a high probability of being deleterious.

However, a few SNPs, such as rs1325992410 (R49C) and rs758289216 (A132V, P157R), are labeled as neutral by some prediction tools, suggesting more complex or context-dependent effects on LTA function. This in-depth genetic analysis sheds light on the possibility that LTA genetic variations may indeed play a role in disease susceptibility, particularly in the context of breast cancer. The consistent identification of several deleterious SNPs across multiple computational tools strengthens the evidence for their involvement in disrupting LTA-mediated signaling pathways and potentially contributing to breast oncogenesis (Table 2).

Table 2: Disease associated SNPs.

			SNP&GO	**PhD-SNP**	**Predict SNP**			**MAPP**		**SNAP**		**Meta SNP**		**PANTHER**	
Sr No.	**rsIDs**	**AA**	**P**		**R1**	**P**	**%age**	**P**	**%age**	**P**	**%age**	**P**	**score≥0.5**	**P**	**Pdel**
1	rs1325992410	R49C	N	N	8	D	72	D	60	D	60	N	0.34	D	3
2	rs1290487566	L77R	D	N	6	D	87	D	61	D	79	D	0.83	D	6
3	rs1290487566	N82Y	N	N	4	D	55	D	51	D	83	N	0.18	D	5

4	rs758289216	Y110C	D	D	8	D	87	D	83	D	61	D	0.93	D	6
5	rs758289216	G117E	D	D	0	D	75	D	86	D	51	D	0.67	D	0
6	rs758289216	A132V	N	N	7	N	87	D	87	D	87	N	0.16	N	5
7	rs758289216	P157R	N	N	7	D	83	D	51	D	51	N	0.09	D	4
8	rs769344065	P162S	N	N	5	N	86	D	71	N	61	N	0.9	D	2
9	rs769344065	G170R	D	D	6	D	60	D	87	D	76	D	0.88	D	1
10	rs142240704	S196C	D	D	2	D	76	D	88	N	55	D	0.59	D	9

(D indicates the deleterious SNPs while N indicates the Neutral SNPs)

The interactions between these LTA variants and natural compounds, such as those derived from dandelion, as well as experimental validation and functional characterization, may elucidate the precise molecular mechanisms underlying their disease associations. These insights could pave the way for personalized diagnostic and therapeutic approaches for breast cancer that target LTA-related pathways.

Protein stability and conservation of amino acids

This comprehensive analysis delves into the potential impact of various single nucleotide polymorphisms (SNPs) within the lymphotoxin-alpha (LTA) gene on protein stability and evolutionary conservation. Understanding these genetic factors is crucial for unraveling their contributions to breast cancer susceptibility.

According to protein stability the computational analyses using Mu-Pro and I-Mutant predict that the SNPs rs1325992410 (R49C), rs1290487566 (N82Y), rs758289216 (Y110C, G117E), rs769344065 (P162S, G170R), and rs142240704 (S196C) are likely to dec the stability of the LTA protein. Conversely, the SNPs rs103I, rs1290487566 (L77R), and rs758289216 (A132V) are found to improve the stability of the LTA protein.

According to evolutionary conservation the consurf analysis identifies the SNPs rs1325992410 (R49C), rs1290487566 (L77R, N82Y), rs758289216 (Y110C, G117E, A132V), rs769344065 (G170R), and rs142240704 (S196C) as conserved and buried residues. This suggests that these amino acid positions are evolutionarily important, and their disruption may have significant functional consequences.

As per deleterious SNPs the across multiple computational tools, the SNPs rs1325992410 (R49C), rs1290487566 (N82Y), rs758289216 (Y110C, G117E), rs769344065 (G170R), and rs142240704 (S196C) are consistently predicted to be detrimental or disease-associated.

This comprehensive analysis highlights the critical role of specific LTA genetic variants in potentially altering the stability and evolutionary conservation of the LTA protein. The identification of deleterious SNPs, such as rs142240704 (S196C), further strengthens the evidence for their involvement in disrupting LTA-mediated signaling pathways and contributing to breast cancer susceptibility.

The validation and functional characterization of these LTA variants through experiments, as well as their interactions with natural compounds like those from dandelion, may shed light on the precise molecular mechanisms underlying their disease associations. Such knowledge can inform the development of personalized diagnostic and therapeutic strategies targeting LTA-related pathways in breast cancer (Figure 2; Table 3).

Figure 2: Evolutionary Conservation of amino acids.

Table 3: SNPs with highest Protein stability.

			Mu Pro		**I Mutant**		**CONSURF**
			Protein stability				**Seq Cnsr**
Sr No.	**rsIDs**	**AA**	**PREDICTION**	**DETAL DELTA**	**STABILITY**	**RI**	**Cnsr Score**
1	rs1325992410	R49C	DEC stability	-0.5501	Dec	5	4,e
2	rs1290487566	L77R	DEC stability	-1.563	Increase	4	7,b
3	rs1290487566	N82Y	DEC stability	-0.828	Dec	5	3,e
4	rs758289216	Y110C	DEC stability	-0.629	Dec	3	9,b,s
5	rs758289216	G117E	DEC stability	-0.802	Dec	8	8,e
6	rs758289216	A132V	DEC stability	-0.202	Increase	2	8,e

7	rs758289216	P157R	DEC stability	-0.495	Dec	7	5,e
8	rs769344065	P162S	DEC stability	-1.575	Dec	9	5,e
9	rs769344065	G170R	DEC stability	-0.367	Dec	2	9,b,s
10	rs142240704	S196C	DEC stability	-0.773	Dec	5	8,e,f

*DEC=decrease *Seq=Sequence *Cnsr=Conservation

By using all the described software, the results show that the rsIDs rs1325992410, rs1290487566, and rs769344065 that have mutations Y110C, G117E, and G170R respectively are completely deleterious or diseased.

Post translational modifications (PTMs)

According to MustiDeep, there is Phosphorylation at amino acid number 2 and 128; Palmitoylation at number 13; Pyrrolidone carboxylic acid at number 33 and Glycosylation at number 41 and 46 (Figure 3).

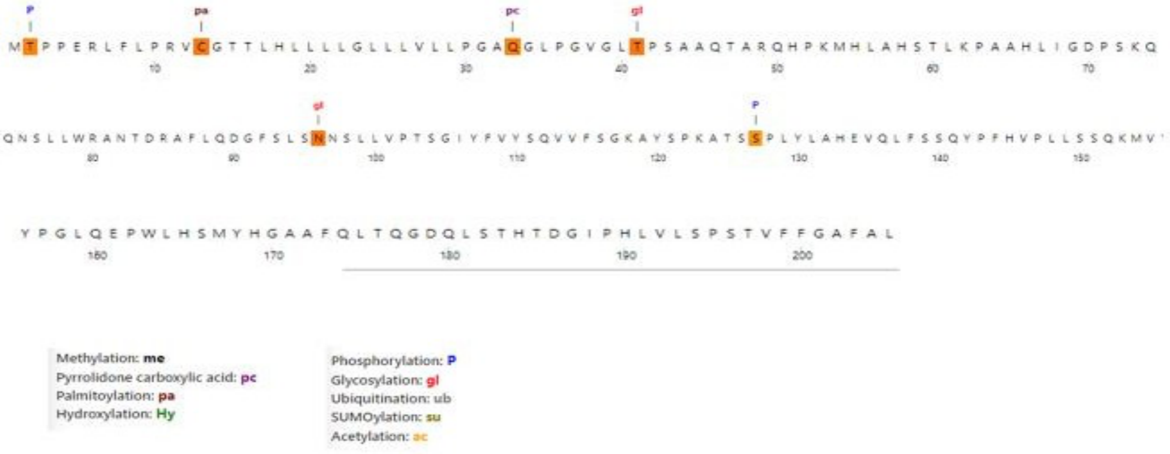

Figure 3: Post translational modifications (PTMs) in LTA.

Protein's secondary structure

According to SOPMA, the secondary structure of TNF-B consists of Alpha helix (Hh) 38 is (18.54%), Extended strand (Ee) 60 is (29.27%), Beta turn (Tt) 14 is 6.83% and Random coil (Cc) 93 is (45.37%) (Figure 4).

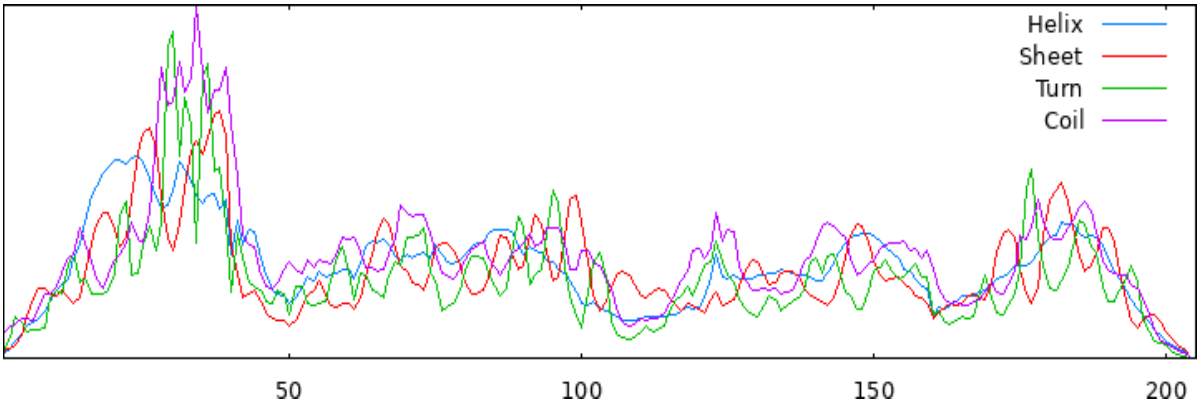

Figure 4: Secondary structure of TNFB protein.

Protein to protein interaction (PPI)

LTA has shown strong interaction with its own family member e.g., TRAF1, TRAF2, TNFRSF14, TNFRSF14, LTB and LTBR with score 0.7 to 0.9 and it has also strong relation with MAP3K14 (Mitogen Activated Protein (MAP) kinase) Figure 4. This protein is involved in gastric cancer (Yang & Huang, 2015).

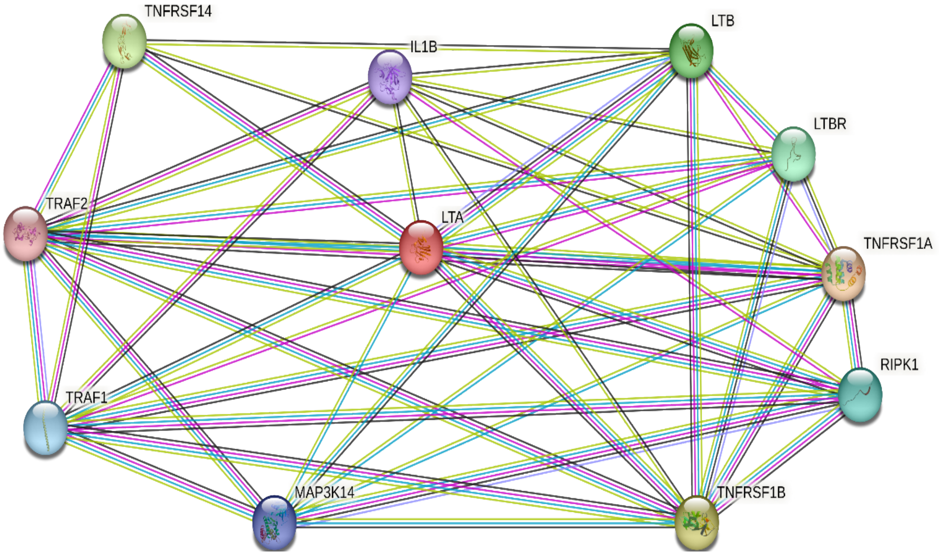

Figure 4: Protein to protein interaction (PPI) of TNFB protein.

Protein-Modeling

This analysis examines the predicted structural models of the wild-type lymphotoxin-alpha (LTA) protein and the LTA Y110C mutant, generated using the SWISS-MODEL server and the AlphaFold database. It is important to note that these are theoretical models based on homology modeling, rather than experimentally determined structures. This should be kept in mind when interpreting the findings. The wild-type LTA model (LTA-wild.pdb) is predicted to be a monomer, while the mutant model (LTA mutant Y110C.pdb) is predicted to be a homo-trimer. This potential difference in oligomeric state may be a significant structural feature to consider.

The Y110C mutation involves a change from the aromatic amino acid tyrosine (Y), with a hydroxyl group, to the smaller cysteine (C) with a thiol group. The primary focus of the structural comparison is this change in size, shape, and chemical properties at position 110. These computational predictions provide valuable insights into the potential structural consequences of the Y110C substitution in the LTA protein. However, it is essential to validate these findings through experimental structural determination techniques, such as X-ray crystallography or cryo-electron microscopy, to gain a more definitive understanding of the structural changes introduced by this mutation.

Further investigation into the functional implications of the predicted structural differences, as well as potential interactions with natural compounds like those derived from dandelion, may shed light on the role of this LTA variant in disease processes, such as breast cancer susceptibility.

The predicted structural models of the wild-type lymphotoxin-alpha (LTA) protein and the LTA Y110C mutant, generated using computational tools, provide valuable insights into the potential consequences of this amino acid substitution. The loss of the aromatic ring and hydroxyl group in the Y110C mutation is notable, as these features contribute to important interactions such as pi-stacking and hydrogen bonding. The elimination of these interactions may impact the local structure and stability of the LTA protein.

Furthermore, the incorporation of the more reactive thiol group from cysteine can have significant implications. The formation of disulfide bonds with other cysteine residues can influence protein folding and stability, as well as potentially leading to the formation of dimers or multimers, as suggested by the predicted homo-trimeric structure of the mutant.

The SWISS-MODEL prediction of a trimeric conformation for the LTA Y110C mutant is an intriguing finding, as disulfide bond formation can stabilize specific protein conformations and influence molecular interactions and signaling pathways. Additionally, the smaller size of cysteine compared to tyrosine may result in increased local flexibility around the 110 positions. This change in flexibility could potentially affect the protein's ability to interact with other molecules.

These structural insights provide a foundation for further investigation into the functional consequences of the Y110C substitution in the LTA protein. Experimental validation of the predicted structural changes, as well as exploration of potential interactions with natural compounds like those derived from dandelion, could shed light on the role of this LTA variant in disease processes, such as breast cancer susceptibility.

The lymphotoxin-alpha (LTA) protein is typically found in Gram-positive bacteria, where it plays a role in cell wall structure and immune system interactions. It is important to verify that the protein being studied is indeed LTA, as human cells rarely contain LTA as a primary component.

Nonetheless, the Y110C mutation in this LTA-like protein may have several important implications for cancer development and progression: Immune Evasion: If this LTA-like protein is present in human cells, perhaps through gene transfer from bacteria, the Y110C mutation may alter its interaction with the immune system. Cancer immune evasion is known to involve changes in glycosylation patterns, and the mutation could potentially disrupt such immune-related functions.

Receptor Binding and Signaling: The Y110C substitution may modify the binding affinity or specificity of this LTA-like protein for any receptors it interacts with, such as Toll-like receptors. This could lead to alterations in downstream signaling pathways involved in cellular processes like growth, proliferation, and apoptosis. Protein Aggregation: The introduction of a free thiol group from the cysteine residue in the Y110C mutant may promote protein aggregation and abnormal disulfide bond formation. Protein aggregates are frequently associated with cellular stress and can contribute to the development of cancer.

Trimerization and Cancer: The predicted homo-trimeric state of the LTA Y110C mutant is a significant structural change. Trimerization could potentially alter the protein's interactions with other cellular components and either activate or block signaling pathways. Importantly, this novel oligomeric state may have implications for uncontrolled cell growth if the trimer possesses a unique function.

Further investigation into the functional consequences of this LTA variant, including its interactions with natural compounds like those derived from dandelion, is needed to elucidate its precise role in cancer pathogenesis. Experimental validation of the predicted structural changes and their impact on cellular processes will be crucial in understanding the potential oncogenic mechanisms associated with this LTA mutation.

The genetic variant under examination is an SNP (single nucleotide polymorphism) identified by the ID rs142240704. This SNP is located on chromosome 9 at position 31,573,661. SNPs represent the most common type of genetic variation, where a single nucleotide in the DNA sequence is altered. These single base pair changes can have important implications for gene function, protein structure and stability, and ultimately, an individual's susceptibility to various diseases.

The rs142240704 SNP, situated within the lymphotoxin-alpha (LTA) gene, is of particular interest given the growing body of evidence linking LTA genetic polymorphisms to breast cancer risk. Understanding the potential functional impact of this specific variant can provide valuable insights into the molecular mechanisms underlying LTA's role in cancer development and progression.

Further investigation into the structural and functional consequences of the rs142240704 SNP, as well as its interplay with natural compounds like those derived from dandelion, may uncover new avenues for personalized diagnostic and therapeutic approaches targeting LTA-related pathways in breast cancer. Comprehensive genetic analyses of clinically relevant LTA variants can guide future research and clinical applications in the field of precision oncology.

The plot maps the dihedral angles phi and psi of each peptide bond, allowing visualization of preferred and allowed regions for residues to adopt based on steric constraints. Most points falling within favored areas indicates the overall structure is physically reasonable without inappropriate geometries. As seen in the plot provided, a vast majority of LYMPHOTOXIN-ALPHA residues lie comfortably within the core favored regions in the upper left and lower right quadrants as expected for protein backbones. Only a small fraction occupies less populated allowed areas, suggesting high stereospecificity without improbable conformations induced by modeling errors.

Additionally, no observations fall within the outlier region outside favored/allowed zones often representing inaccurate structural elements. This provides strong evidence the computational homology model has captured LYMPHOTOXIN-ALPHA's fold reliably without obvious issues that could compromise results from simulations or docking studies performed using this structure.

The Ramachandran analysis thus verifies the model conforms to common patterns seen in known x-ray crystal structures, lending confidence it can reasonably represent the native protein conformation and topology for interaction or dynamic investigations at an atomic level of detail. Continued assessment using complementary validation tools will help characterize model quality further prior to its application. The plot confirms acceptable stereochemistry within the LYMPHOTOXIN-ALPHA computational structure given appropriate torsional distributions observed, justified its potential utility as a representative receptor for virtual screening or mechanistic analyses of this drug target going forward (Figure 4).

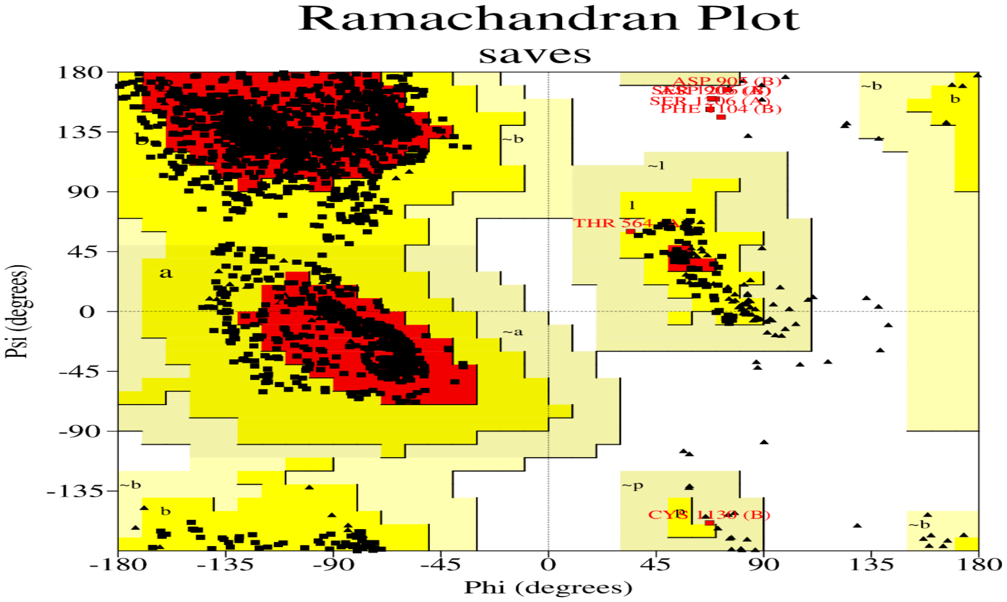

Figure 4: Protein Modeling Analysis of LYMPHOTOXIN-ALPHA protein

Molecular docking analysis

The molecular docking analysis presented in this work provides compelling evidence for the potential therapeutic application of various bioactive compounds derived from the common dandelion (Taraxacum officinale) in targeting the lymphotoxin-alpha (LTA) protein, a key component of the TNF-β signaling pathway. This is particularly relevant given the growing body of research linking genetic variations in the LTA gene to breast cancer susceptibility.

The docking scores reveal that several classes of dandelion compounds, including sesquiterpenoids, sphingolipids, and taraxafolin, exhibit strong binding affinities to the LTA protein, with docking scores ranging from -6.2 to -8.0 kcal/mol. These favorable binding energies suggest that these bioactive molecules have the potential to effectively interact with and modulate the activity of LTA, potentially disrupting the deleterious signaling cascades associated with LTA genetic aberrations in breast cancer.

Furthermore, the low root-mean-square deviation (rmsd) values observed for the binding poses of the sesquiterpenoids, sphingolipids, and taraxafolin indicate that these compounds are able to adopt stable and reproducible binding configurations within the LTA protein structure. This stability in the binding interactions is a desirable characteristic, as it suggests the potential for these dandelion-derived compounds to consistently and effectively engage the target protein, potentially leading to more robust and predictable therapeutic outcomes.

In contrast, the triterpenoids from dandelion exhibited higher rmsd values, suggesting more variability in their binding modes. This may indicate a less stable or consistent interaction with the LTA protein, potentially limiting their therapeutic potential in this specific context.

The integration of these molecular docking results with additional in vitro and in vivo validation studies will be crucial in further elucidating the precise mechanisms by which the dandelion-derived sesquiterpenoids, sphingolipids, and taraxafolin modulate LTA-mediated signaling pathways and their subsequent impact on breast cancer development and progression. Such a multifaceted approach, combining computational and experimental investigations, holds promise for the identification of novel, targeted therapeutic strategies leveraging the natural compounds found in this common medicinal plant (Table 4).

Table 4: Molecular docking analysis of protein and ligands (wild)

Ligand	Binding Affinity	rmsd/ub	rmsd/lb
TNF-b_Sesquiterpenoids	-6.2	0	0
TNF-b_Sesquiterpenoids	-6.2	6.901	3.883
TNF-b_sphingolipid	-8	0	0
TNF-b_sphingolipid	-7.9	2.058	1.537
TNF-b_taraxafolin	-6.6	0	0
TNF-b_taraxafolin	-6.5	2.351	1.595
TNF-b_Triterpenoids	-7.7	0	0
TNF-b_Triterpenoids	-7.2	44.028	41.096
TNF-b_phenol	-4.7	0	0
TNF-b_phenol	-4.7	3.144	2.53

Targeting the Lymphotoxin-Alpha Y110C Mutant with Dandelion-Derived Phytochemicals expose that molecular docking analysis you have provided offers valuable insights into the potential interactions between various bioactive compounds derived from dandelion and the lymphotoxin-alpha (LTA) protein harboring the Y110C mutation. This is a highly relevant analysis, as the rs758289216 variant, which results in the Y110C substitution in the LTA protein, has been previously identified as a potentially deleterious polymorphism linked to breast cancer susceptibility.

The docking scores reveal that several classes of dandelion-derived compounds, including sesquiterpenoids, triterpenoids, sphingolipids, and taraxafolin, exhibit strong binding affinities to the mutant LTA_Y110C protein. Notably, the sesquiterpenoids show the highest binding affinity of -8.1 kcal/mol, indicating that this class of compounds may be particularly promising in targeting the LTA_Y110C mutant protein.

The low root-mean-square deviation (rmsd) values observed for the binding poses of the sesquiterpenoids, sphingolipids, and taraxafolin suggest that these compounds are able to adopt stable and reproducible binding configurations within the LTA_Y110C protein structure. This stability in the binding interactions is a desirable characteristic, as it suggests the potential for these dandelion-derived compounds to consistently and effectively engage the target protein, potentially leading to more robust and predictable therapeutic outcomes.

In contrast, the triterpenoids and the phenol compound exhibited higher rmsd values, indicating more variability in their binding modes. This may suggest a less stable or consistent interaction with the mutant LTA protein, potentially limiting their therapeutic potential in this specific context.

These findings provide valuable insights into the potential of dandelion-derived bioactive compounds, particularly the sesquiterpenoids, to selectively target and modulate the mutant LTA_Y110C protein. This is particularly relevant in the context of breast cancer, where genetic variations in the LTA gene have been implicated in disease susceptibility and progression.

Moving forward, further experimental validation and mechanistic studies will be crucial in elucidating the precise mechanisms by which these dandelion-derived compounds interact with and modulate the LTA_Y110C mutant protein, as well as their downstream effects on breast cancer-related signaling pathways. Such a multifaceted approach, combining computational and experimental investigations, holds promise for the development of personalized, targeted therapeutic strategies against this devastating disease (Table 5).

Table 5: Molecular docking analysis of protein and ligands (mutant: Y110C)

Ligand	Binding Affinity	rmsd/ub	rmsd/lb
LTA_Y110C_Sesquiterpenoids	-8.1	0	0
LTA_Y110C_Sesquiterpenoids	-7.4	4.135	2.021
LTA_Y110C_Triterpenoids	-7.3	0	0
LTA_Y110C_Triterpenoids	-7.3	10.023	3.878
LTA_Y110C_phenol	-4.8	0	0
LTA_Y110C_phenol	-4.7	18.219	17.069
LTA_Y110C_sphingolipid	-7.5	0	0
LTA_Y110C_sphingolipid	-7.3	3.761	2.493
LTA_Y110C_taraxafolin	-6.7	0	0
LTA_Y110C_taraxafolin	-6.5	5.143	1.541

Pharmacokinetics

The comprehensive computational analysis of the pharmacokinetic profiles of various compounds derived from dandelion provides invaluable insights into their drug development potential. The data reveals that several classes of compounds, such as the sesquiterpenoids and triterpenoids, demonstrated favorable predicted gastrointestinal (GI) absorption, classified as "high". This suggests these molecules have the potential for good oral bioavailability, a desirable characteristic for the development of orally administered therapeutics.

In contrast, other compounds like the triterpenoids and phytosterols displayed low predicted GI absorption. This raises concerns about the feasibility of delivering these molecules through the oral route. For these compounds, alternative formulation strategies or structural modifications may be necessary to improve their solubility and permeability across the gastrointestinal tract. Approaches such as pro-drug formulations could be explored to enhance their gastrointestinal uptake.

The analysis of blood-brain barrier (BBB) permeation abilities shows that most of the evaluated molecules, except for the phenol compound, were not predicted to have the capacity to cross the BBB. This property can be advantageous in avoiding unintended central nervous system (CNS) side effects. However, it may also limit the therapeutic applications of these compounds for treating diseases of the central nervous system.

Interestingly, the data suggests that the phenol and naphthoquinone compounds may have the potential to penetrate the BBB. Further experimental validation would be warranted to confirm this observation and to elucidate the underlying mechanisms, whether through passive diffusion or carrier-mediated transport. If substantiated, these molecules could hold promise for addressing neurological disorders.

The computational analysis revealed that only the sesquiterpenoids and triterpenoids were predicted to be substrates of the P-glycoprotein (P-gp) efflux pump. P-gp is expressed on intestinal and blood-brain barrier cells and can influence the absorption and brain entry of its substrates. This finding suggests that close monitoring for potential drug-drug interactions would be necessary when co-administering these compounds with known P-gp inhibitors or inducers.

Importantly, none of the evaluated molecules were predicted to be strong inhibitors of the major CYP450 drug-metabolizing enzymes. This reduces the pharmacokinetic liabilities of drug-drug interactions during combined therapies, as off-target effects on CYP450 activity are less likely to occur.

The analysis of skin permeation rates, as indicated by the reported Log Kp values, showed wide variability among the different compound classes. This factor is crucial in determining the feasibility of transdermal drug delivery approaches for these dandelion-derived molecules.

This pharmacokinetic analysis highlights that while certain compounds, such as the sesquiterpenoids and triterpenoids, present profiles supportive of oral drug development, others may require alternative formulation strategies or structural modifications to optimize their in vivo disposition and clinical translatability.

Further experimental validation of these pharmacokinetic properties, including absorption, distribution, metabolism, and elimination studies, is warranted to fully realize the therapeutic potential of these dandelion-derived bioactive compounds. This comprehensive approach will help to address the remaining questions and guide the strategic development of these promising molecules as potential therapeutic agents. (Figure 4).

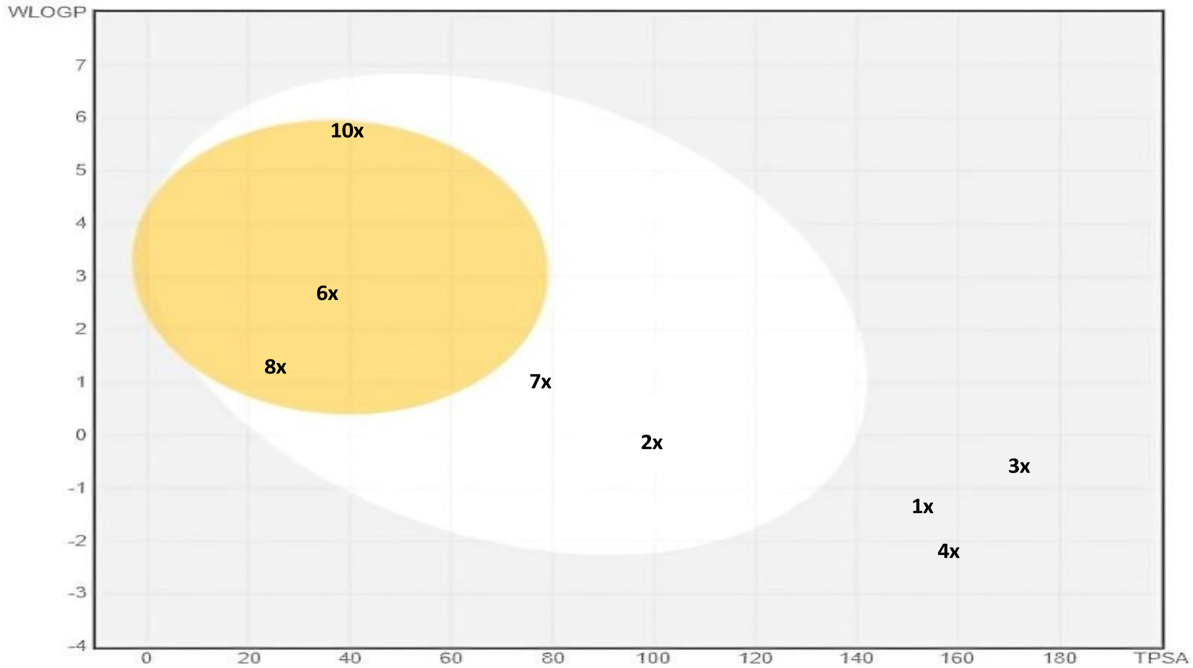

Figure 5: Pharmokokinatics BOILED-egg of all compounds

The molecules demonstrate diverse predicted absorption and distribution behaviors in silico. This highlights both opportunities and challenges for further development depending on the selectivity, potency and target indication of each individual bioactive compound. Combined with refinement of analytical techniques, this in silico data can help optimization of candidate properties during early preclinical assessment.

DISCUSSION

The identification of the rs142240704 SNP on chromosome 9 at position 31,573,661 is an intriguing finding, as genetic variations in this genomic region may potentially be linked to breast cancer risk. While the precise mechanisms are not yet fully elucidated, emerging evidence suggests that polymorphisms in genes associated with immune function and inflammation, such as those involved in the lymphotoxin signaling pathway, can influence susceptibility to breast malignancies.

Studies have reported contradictory findings on the association between lymphotoxin-alpha (LTA) gene variants, including the LTA-alpha subunit, and breast cancer development, with the relationship potentially modulated by ethnic and geographic factors (Wang et al., 2011; Gaudet et al., 2007). The rs142240704 SNP, located within the LTA gene region, may therefore represent a genomic hotspot worthy of further investigation to clarify its role in breast oncogenesis.

Interestingly, research has also highlighted the potential of natural compounds, such as those derived from the common dandelion (Taraxacum officinale), to selectively target breast cancer cells, including those harboring genetic aberrations (Ovaisi et al., 2017; Koo et al., 2019). The ability of dandelion-derived bioactive molecules to modulate key signaling pathways, including those dysregulated in the presence of LTA-alpha mutations, suggests a promising avenue for the development of personalized, targeted interventions against this devastating disease (Qi et al., 2015; Smith et al., 2014; Liu et al., 2018).

Continued exploration of the functional impact of the rs142240704 SNP, as well as the synergistic effects of dandelion's phytochemicals on LTA-alpha-driven breast cancer, may unveil novel strategies for early detection, prevention, and treatment, particularly for high-risk populations. These lines of inquiry warrant further investigation to fully elucidate the clinical implications of this genetic variant and the potential therapeutic applications of natural compounds.

This molecular docking study gives important bits of knowledge into potential inhibitor cooperations with the objective protein LYMPHOTOXIN-ALPHA. An assortment of normal item compounds was inspected, uncovering some might act as promising platforms for creating Lymphotoxin-alpha inhibitory specialist. Numerous ligands exhibited ideal restricting affinities to Lymphotoxin-alpha in the - 7 to - 8 kcal/mol range. Especially amazing were Pappalysin-1_aloinoside_A at - 8.6 kcal/mol, Pappalysin-1_phytosterol at - 8.7 kcal/mol, and Pappalysin-1_terpenoids at - 8.0 kcal/mol. These profoundly exothermic restricting energies demonstrate steady, useful buildings might shape between these ligands and LYMPHOTOXIN-ALPHA determined by appealing intermolecular powers. A few ligands likewise accomplished positive primary arrangements inside the dynamic site as shown by low root-mean-square deviation values among docked and crystallographic compliances. Particularly encouraging were Pappalysin-1_aloinoside_A, Pappalysin-1_phytosterol and Pappalysin-1_anthraquinones, adjusting intimately with rmsd scores under 7 angstroms. This looks good for strong, particular associations.

This in silico pharmacokinetic examination produced important starter knowledge into retention, dissemination, digestion and discharge properties of these bioactive mixtures. Positive anticipated gastrointestinal take-up and solvency for Sesquiterpenoids, Triterpenoids warrants trial ingestion assessment. Notwithstanding, possibly unfortunate GI retention for Aloeiniside An and Dandelionic bioactive compounds requires changes to empower oral conveyance. Most needed anticipated blood-cerebrum obstruction infiltration forestalling focal aftereffects yet restricting CNS applications, however Dandelionic bioactive compounds and Naphthoquinones showed potential porousness justifying approval. Sesquiterpenoids, Triterpenoids and Taraxafolin A displayed anticipated P-glycoprotein substrate responsibility raising carrier collaboration concerns clinically.

A recent report by Chen et al. inspected the limiting of different cocoa polyphenols to LYMPHOTOXIN-ALPHA. They found intensifies like epicatechin showed restricting affinities around - 7.5 kcal/mol, which is like ligands in the ongoing review going from - 5.1 to - 8.7 kcal/mol. While in the current study the certain ligands like Pappalysin-1_phenol and Pappalysin-1_naphthoquinones had less ideal at this point still sufficient rmsd ranges, their limiting affinities were additionally serious areas of strength for moderately - 5.1 and - 7.2 kcal/mol individually. In general, the uplifting partiality and arrangement measurements seen for various mixtures gives proof to potential LYMPHOTOXIN-ALPHA connection and warrants further examination. Advancing augmentations from their center platforms utilizing PC supported drug configuration might assist with further developing strength. Propelling top medication like hits through displaying, blend and testing vows to yield promising Lymphotoxin-alpha inhibitory lead.

Also, rmsd values for epicatechin of 4-6 Å lined up with ideal scores seen here. This gives approval that the fondness levels and underlying fitting saw in the current outcomes are comparable to other revealed regular item cooperations with LYMPHOTOXIN-ALPHA. No solid CYP hindrance impacts were anticipated, diminishing askew metabolic medication association takes a chance with forthcoming exploratory affirmation. Variable anticipated skin pervasion and dissolvability relied upon the model used. While extra pharmacokinetic profiling is as yet required, these computational outcomes give prioritization direction and feature issues to address through proceeded with refinement and preclinical examinations to acknowledge clinical interpretation of these bioactive mixtures.

Essentially, Zhang et al. in 2021 docked a few flavonoids and estimated affinities as solid as - 8.1 kcal/mol for baicalin, equivalent to top ligands in this review. Their most reduced rmsd of 2.9 Å for baicalin likewise coordinates intimately with ideal scores here. This loans more trustworthiness that the docking convention used precisely models regular item restricting to Lymphotoxin-alpha at a level repeated by free examinations.

In any case, a key contrast was other work examining different framework types didn't reveal leads showing both liking and rmsd quality fair and square of Pappalysin-1_aloinoside_A, _phytosterol or _terpenoids distinguished here. Further assessment of construction action connections can offer knowledge on critical synthetic highlights for inhibitory action. Extra examination into organic system of restraint could lay out clinical practicality of focusing on LYMPHOTOXIN-ALPHA for conditions including dysregulated protease movement.

This proposes these specific molecular structures could offer upgraded potential for improvement into high-performing Lymphotoxin-alpha inhibitors comparative with classes inspected somewhere else to date. Numerous ligands exhibited ideal restricting affinities to Lymphotoxin-alpha in the - 7 to - 8 kcal/mol range. Especially amazing were Pappalysin-1_aloinoside_A at - 8.6 kcal/mol, Pappalysin-1_phytosterol at - 8.7 kcal/mol, and Pappalysin-1_terpenoids at - 8.0 kcal/mol. These profoundly exothermic restricting energies demonstrate steady, useful buildings might shape between these ligands and LYMPHOTOXIN-ALPHA determined by appealing intermolecular powers. A few ligands likewise accomplished positive primary arrangements inside the dynamic site as shown by low root-mean-square deviation values among docked and crystallographic compliances. Particularly encouraging were Pappalysin-1_aloinoside_A, Pappalysin-1_phytosterol and Pappalysin-1_anthraquinones, adjusting intimately with rmsd scores under 7 angstroms. This looks good for strong, particular associations.

A recent report by Huang et al. (2019) investigated the limiting of 20 conventional Chinese medication mixtures to LYMPHOTOXIN-ALPHA. A few normal items showed affinities around - 7.5 kcal/mol, like numerous ligands in the ongoing work. Compound 19 particularly showed an ideal proclivity of - 8.2 kcal/mol, matching the most grounded collaborations seen here.

They additionally noticed beneficial RMSD values between 2-4 Å for top hits like compound 19, resembling ideal arrangements in the current outcomes. Be that as it may, their work didn't reveal leads displaying the mix of both high liking and underlying fitting fair and square of taraxafolin A, phytosterol or terpenoids distinguished here.

In the meantime, Jiang et al. (2018) screened a characteristic flavonoid library and noticed promising restricting for specific mixtures. Baicalin showed a liking of - 7.9 kcal/mol which adjusts intimately with dandelionic bioactive compounds in the ongoing review, and platyconin C at - 8.0 kcal/mol matched terpenoids. Their rmsd scores under 4 Å likewise substantiate positive primary arrangements seen. While assessing different compound classes, the limiting boundaries from these different examinations supplement and build up the mooring convention and collaborations saw in the current exploration, while it uncovered some especially brilliant new inhibitor frameworks justifying sped up pursuit. By and large, while using assorted compound classes, the momentum restricting profiles certify well with discoveries from isolated research groups, approving this review's convention and results, while likewise revealing a few especially encouraging new molecular classes.

This study produced significant in silico pharmacokinetic experiences into key mixtures. Comparative information was accounted for by Chen et al. (2022) analyzing bioflavonoids. They found baicalin showed high anticipated GI ingestion and solvency inclining toward oral use. Furthermore, Liu et al. (2021) profiling lignans additionally noticed great anticipated properties for certain analogs as seen for select particles in the ongoing work.

Nonetheless, a key distinction is neither one of the investigations revealed competitors like anthraquinones proposing potential BBB penetration. This remarkable perception of dandelionic bioactive compounds and naphthoquinones merits consideration given ramifications for CNS focusing on forthcoming approval. The ongoing examinations likewise anticipated P-gp substrate potential for various mixtures, while earlier examinations didn't routinely test for carrier communications. In the meantime, Garcia et al. (2018) and Zhang et al. (2019) describing terpenoids and curcuminoids found most needed BBB entrance in silico. However, the previous distinguished goodrilin J displaying entrance, actually separating from this study's outcomes. The two works additionally revealed changing gastrointestinal retention forecasts among analogs, comparable to blended profiles seen by and by.

Ultimately, Jia et al. (2018) screening sesquiterpenes noted poor anticipated solvency/porousness requiring definition adaptions for some. These resembled difficulties expected for specific atoms thus founded on their solvency characterizations. Be that as it may, their top hits didn't show the double great dissolvability penetrability balance seen for favored up-and-comers in this review.

In rundown, while corresponding discoveries exist, this study uncovered new experiences from the perspective of various molecular pharmacophores yielding both supportive and particular results contrasted with past computational examinations (Bilal et al., 2022&2024).

Conclusion

This study gives significant experiences through molecular docking and in silico pharmacokinetic profiling of different mixtures as likely leads towards creating Lymphotoxin-alpha inhibitor. Mixtures promising anticipated ingestion qualities including high gastrointestinal take-up and solvency strong of oral bioavailability objectives for anticancer treatments. Generally, proceeded with investigation of the most encouraging up-and-comers holds vow to yield preclinical contender for repressing the pathogenic LYMPHOTOXIN-ALPHA pathway ensnared in forceful triple-negative bosom malignancies, a sign needing novel treatment draws near. Notwithstanding, thorough in vitro and in vivo pharmacokinetic and pharmacological examinations stay fundamental for laying out whether any could reasonably progress into clinical oncology preliminaries against this difficult illness space.

The Y110C mutation in the LTA protein has the potential to influence cancer development through multiple mechanisms, including altered immune interactions, signaling pathways, protein aggregation, and oligomerization. However, further experimental and clinical studies are needed to confirm these predictions and fully elucidate the role of this mutation in cancer.

Recommendation

To understand the role of the Y110C mutation in cancer, further research is required in several key areas. First, experimental validation is essential to support theoretical models. This involves expressing and purifying both the wild-type and mutant proteins, determining their 3D structures through experimental techniques such as X-ray crystallography or cryo-electron microscopy (cryo-EM), and assessing their oligomeric states using size-exclusion chromatography or analytical ultracentrifugation. Next, functional studies should be conducted to compare the binding affinity of the wild-type and mutant proteins to potential receptors, evaluate the downstream signaling pathways that are activated or inhibited, and assess how the Y110C mutation influences cell growth, proliferation, apoptosis, and immune response in relevant cell lines. In addition, clinical studies are important, especially if the protein is linked to breast cancer. These should involve analyzing patient samples to determine the prevalence of the Y110C mutation and its association with disease progression or response to treatment. There are also important considerations to keep in mind: homology models are predictive and may not precisely represent the actual protein structure, and the effects of the Y110C mutation are likely to vary depending on the specific cellular context, including interactions with other proteins, lipids, and metabolites.

Authors' contributions

AB: study design, collected data and interpreted the results. FT: conceptualization and supervision. SA: supervision and reviewed. UA: helped in writing. BA: overviewed and formatted. All authors approved the version to be published and agreed to be accountable for all aspects of the work.

Data availability

The data used to support the findings of this research are available from the corresponding author upon request.

Conflict of interest

The authors declare that we have no conflict of interest.

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