Computational Targeting of GSK-3β in Malignant Melanoma Using Compounds Sourced from Clausena Indica

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**Abstract:** New treatment options for malignant melanoma, an aggressive and deadly type of skin cancer, are desperately needed. As a potential target for cancer therapy, glycogen synthase kinase-3 beta (GSK-3β) is involved in a number of essential physiological processes, such as cell proliferation and death. The plant Clausena indica, which is well-known for having a wide range of bioactive chemicals, may open up new options for medicinal research.To assess, by use of computational techniques, the potential of chemicals derived from Clausena indica for targeting GSK-3β in malignant melanoma. To evaluate the pharmacokinetic and drug-like qualities of a library of Clausena indica compounds, computer analysis was performed on the collected material. Molecular weight, hydrogen bond donors and acceptors, rotatable bonds, and hydrophobicity (Log P) were all included in the evaluation. The screening process employed Lipinski's Rule of Five to ascertain the drug-likeness of several compounds. To further guarantee possible effectiveness and safety, ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) profiles were examined.Several substances with advantageous features were found during investigation. Numerous substances fulfilled Lipinski's requirements, suggesting strong oral bioavailability potential. A selection of drugs with promising pharmacokinetic properties were also identified by the ADMET assessment, indicating that they would be safe and effective candidates for further development.  
Compounds derived from Clausena indica show promise as GSK-3β inhibitors, providing a viable avenue for the development of novel treatments for malignant melanoma. To validate these computational results and investigate these drugs' medicinal potential even further, future research will concentrate on in vitro and in vivo validations.

**Keywords:** Malignant Melanoma,GSK-3β Inhibitors,Clausena indica,Drug-likeness, ADMET Analysis

# Introduction

Malignant melanoma, an aggressive skin cancer, frequently shows resistance to conventional treatments, making the search for new therapeutic targets essential. Glycogen synthase kinase-3 beta (GSK-3β) plays a critical role in various cellular processes, such as apoptosis and proliferation, which are dysregulated in melanoma [(Ajay et al., 2023; Chokkattu et al., 2023; Padarthi et al., 2023)](https://paperpile.com/c/2Xxfxg/uwzPa+HwFTt+w9IJN). This kinase has therefore emerged as a promising target for melanoma therapy. Computational methods facilitate the identification and optimization of potential GSK-3β inhibitors, offering a cost-effective and efficient approach to drug discovery [(Dharman et al., 2023; S. Sindhu et al., 2023; Sreenivasagan et al., 2023)](https://paperpile.com/c/2Xxfxg/hcYSt+I2XkH+0o19x). Clausena indica, a medicinal plant known for its diverse bioactive compounds, provides a rich source of potential GSK-3β inhibitors. [(Abeysinghe et al., 2021; Diep et al., 2009)](https://paperpile.com/c/2Xxfxg/oH33+562f)This study aims to leverage computational techniques to identify and optimize Clausena indica compounds that specifically target GSK-3β, presenting a novel therapeutic avenue for malignant melanoma.Despite its rarity in India, malignant melanoma accounts for 0.3% of all cancers with an annual incidence of approximately 3,916 cases, as reported by GLOBOCAN[(Biswas et al., 2021)](https://paperpile.com/c/2Xxfxg/NTX0).Globally, factors such as age, melanin content, latitude, altitude, and ethnicity contribute to its rising incidence. Immune checkpoint inhibitors and targeted therapies are commonly used due to the melanoma cells’ susceptibility to the T-cell-mediated immune response [(Ramakrishnan et al., 2023; N. D. Shenoy & Maiti, 2023; J. S. Sindhu et al., 2023)](https://paperpile.com/c/2Xxfxg/xsGHF+uDhAg+OXxtD). Melanoma is identified by changes in size, color, and shape of skin lesions. The five-year survival rate for localized melanoma is nearly 99%, but drops to 20% if metastases are present [(Bajpai et al., 2021)](https://paperpile.com/c/2Xxfxg/kNM2).The overall survival rate for metastatic melanoma is about 10%, reflecting a poor prognosis [(Kasabwala et al., 2021; Rajeshkumar & Lakshmi, 2021; Varghese et al., 2023)](https://paperpile.com/c/2Xxfxg/PEPUP+C8tQZ+owViD). Additionally, the annual cost of melanoma treatment has increased by 288% in the last decade, posing financial challenges for low- and middle-income populations.Glycogen synthase kinase-3 beta (GSK-3β) is a serine/threonine kinase involved in cell signaling, glycogen metabolism, cell cycle regulation, and neurodevelopment [(Maixner & Weng, n.d.)](https://paperpile.com/c/2Xxfxg/QBh4). It regulates several pathways, including Hedgehog, PI3K/Akt, and Wnt. GSK-3β functions both as a tumour promoter and suppressor in cancer and is implicated in neurodegenerative diseases like Alzheimer's, diabetes, and inflammation[(Hur & Zhou, 2010)](https://paperpile.com/c/2Xxfxg/oYke). Current clinical trials are exploring GSK-3β inhibitors for their potential in treating various conditions, maximising their impact on cell signalling pathways.Computational targeting of GSK-3β involves using techniques such as molecular docking, virtual screening, molecular dynamics simulations, pharmacophore modelling , quantitative structure-activity relationship (QSAR) analysis, and binding free energy calculations[(Hua et al., 2023)](https://paperpile.com/c/2Xxfxg/ybBW).These methods help predict interactions between GSK-3β and potential inhibitors, develop high-specificity inhibitors to reduce off-target effects, and guide the creation of personalised treatment plans.[(Wróblewska-Łuczka et al., 2023)](https://paperpile.com/c/2Xxfxg/WMvQ) These computational techniques offer advantages such as tailored therapy and reduced side effects.Clausena indica, frequently used in traditional remedies and cooking in tropical countries, is known for its antibacterial, anti-inflammatory, antioxidant, analgesic, and hepatoprotective properties [(Lee et al., 2022)](https://paperpile.com/c/2Xxfxg/EZcZ).Its extracts have shown potential in treating infections, reducing inflammation, regulating blood sugar, and providing pain relief. [(Abeysinghe et al., 2021)](https://paperpile.com/c/2Xxfxg/oH33)In this study, a multi-step computational method, including virtual screening, molecular modelling, and bioinformatics, is employed to identify bioactive compounds in Clausena indica that can inhibit GSK-3β. [(La Hoang et al., 2020)](https://paperpile.com/c/2Xxfxg/NHik)The complexity of GSK-3β pathways necessitates careful consideration of toxicity and off-target effects. Thorough experimental validation is essential to ensure the therapeutic promise and biological relevance of computational predictions. [(Arulselvan et al., 2016)](https://paperpile.com/c/2Xxfxg/ggmW)This approach capitalises on the synergy between traditional medical knowledge and modern computational tools, [(Van Quan et al., 2019)](https://paperpile.com/c/2Xxfxg/nuDi)offering a promising method to develop novel treatments for malignant melanoma.7

# Materials and methods

## 1.Preparing Compound Libraries and Analysing Molecular Properties

The first step in the research was to create a compound library using Clausena indica, whose chemical structures were found in academic journals and scientific databases. ChemOffice and MarvinSketch, two cheminformatics programs, were used to analyse molecular properties. These programs gave information on each compound's molecular weight, number of rotatable bonds, and hydrogen bond donors and acceptors. Using Lipinski's Rule of Five, drug-likeness was assessed by determining if the compounds satisfied certain requirements, such as having a molecular weight of less than 500 Daltons, no more than five hydrogen bond donors, no more than ten hydrogen bond acceptors, and a partition coefficient log P of five or less.

## Molecular Docking and ADMET Profiling

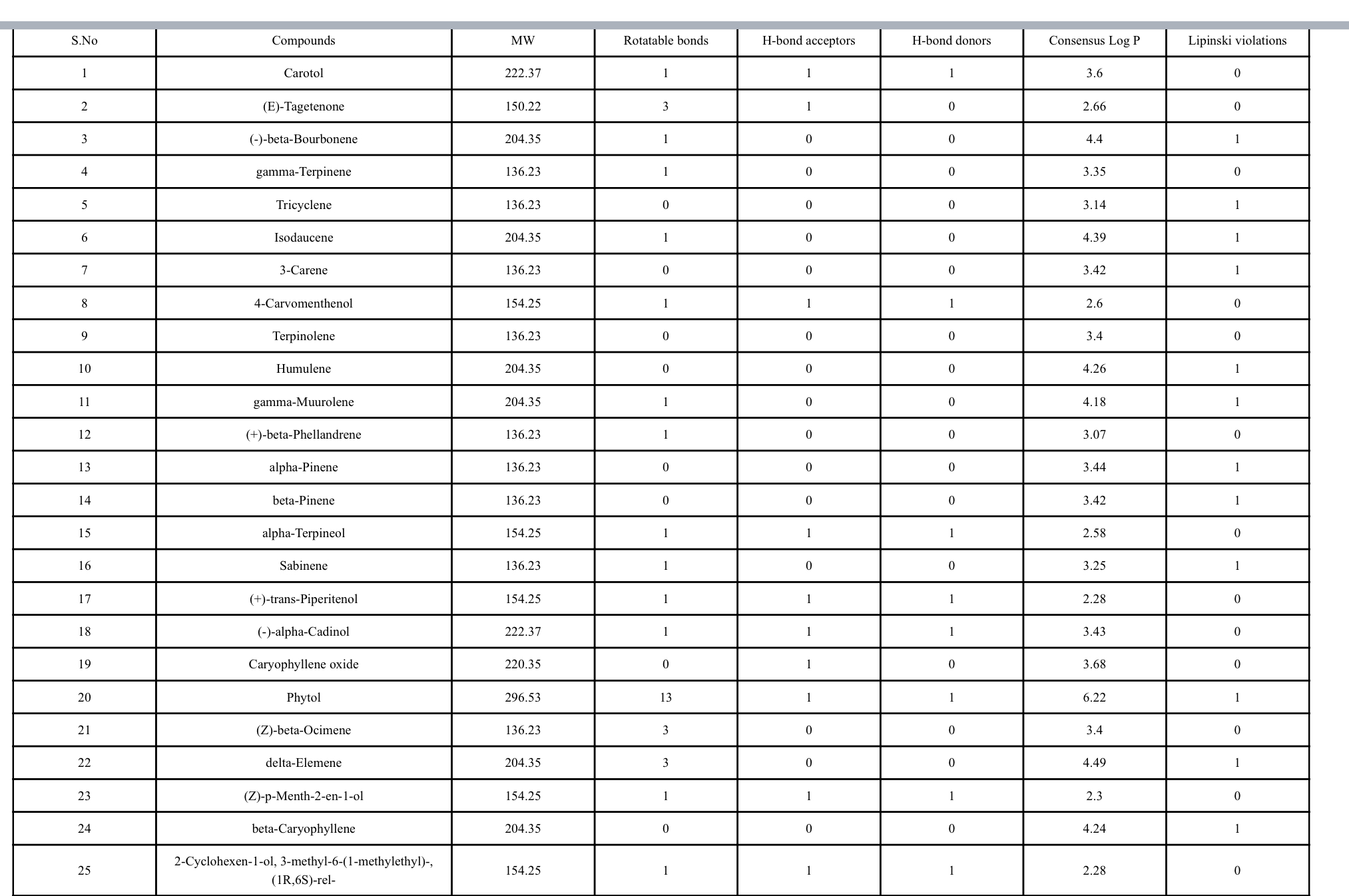
SwissADME and ADMETlab software were used to estimate the Absorption, Distribution, Metabolism, Excretion, and Toxicity (ADMET) properties. These instruments shed light on the substances' possible toxicity and pharmacokinetic characteristics. Molecular docking studies were performed using AutoDock Vina to assess the drugs' binding affinity to GSK-3β after ADMET profiling. The GSK-3β crystal structure was procured from the Protein Data Bank (PDB ID: 1Q3D). The docking simulation process included protein and ligand preparation, grid box configuration around the active site, and simulation execution.

## Analysis, Interpretation of Data, and Upcoming Projects

With an emphasis on important interactions such hydrogen bonds and hydrophobic bonds, the docking data was examined to ascertain the binding affinities and interaction patterns between the Clausena indica molecules and GSK-3β. In order to select compounds that meet the parameters for drug-likeness and have significant binding affinities and good ADMET features, data analysis involves looking at docking scores and ADMET profiles. Additional in vitro and in vivo validation studies will be conducted on the compounds that made the short list in order to evaluate their efficacy and safety as possible melanoma therapies. The following software and tools were utilized in this study: AutoDock Vina, SwissADME, ADMETlab, MarvinSketch, and ChemOffice.

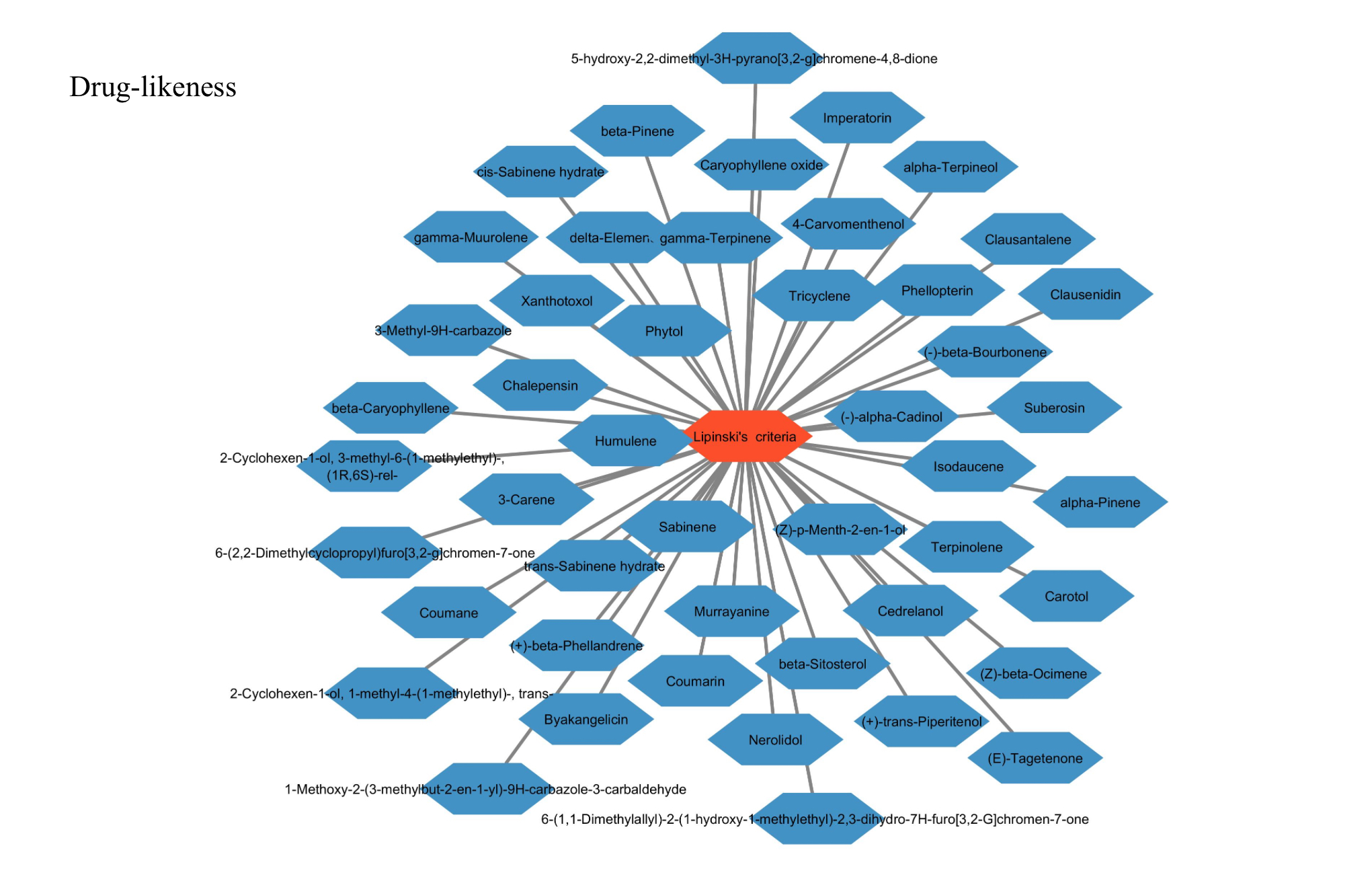
# Results and Discussion

Molecular weights (MW), rotatable bonds, hydrogen bond acceptors and donors, consensus Log P values, and Lipinski rule violations are all included in this table that gives a thorough description of the many compounds found in Clausena indica. Molecularly weighing 222.37 grammes, carbotol exhibits one rotatable bond and balanced hydrogen bonding characteristics (one donor and one acceptor). Its favorable Log P of 3.6 suggests that it has strong potential for therapeutic development and does not violate Lipinski. Log P of 2.66 indicates that (E)-Tagetenone satisfies the requirements even with three rotatable bonds. The higher Log P values (4.4, 3.35, and 6.22, respectively) of (-)-beta-Bourbonene, gamma-Terpinene, and Phytol, on the other hand, indicate enhanced lipophilicity, which may have an effect on their bioavailability. Notwithstanding their potential, compounds like alpha- and beta-pinene exhibit Lipinski violations because to their considerable high lipophilicity.Phytol is notable for having a high molecular weight (296.53) and a large number of rotatable bonds (13), which, although providing flexibility, also raises questions about the drug-likeness of the compound because of its Lipinski violation. Lipinski's principles are not broken by the examination of compounds like gamma-Muurolene and (+)-beta-Phellandrene, which emphasizes the significance of a balanced profile for therapeutic development. The table highlights the diverse physicochemical properties of Clausena indica compounds, which indicate their potential as GSK-3β inhibitors in malignant melanoma. It also emphasizes the need to carefully balance molecular size, flexibility, hydrophilicity, and drug-likeness in order to maximize therapeutic efficacy and minimize bioavailability issues.



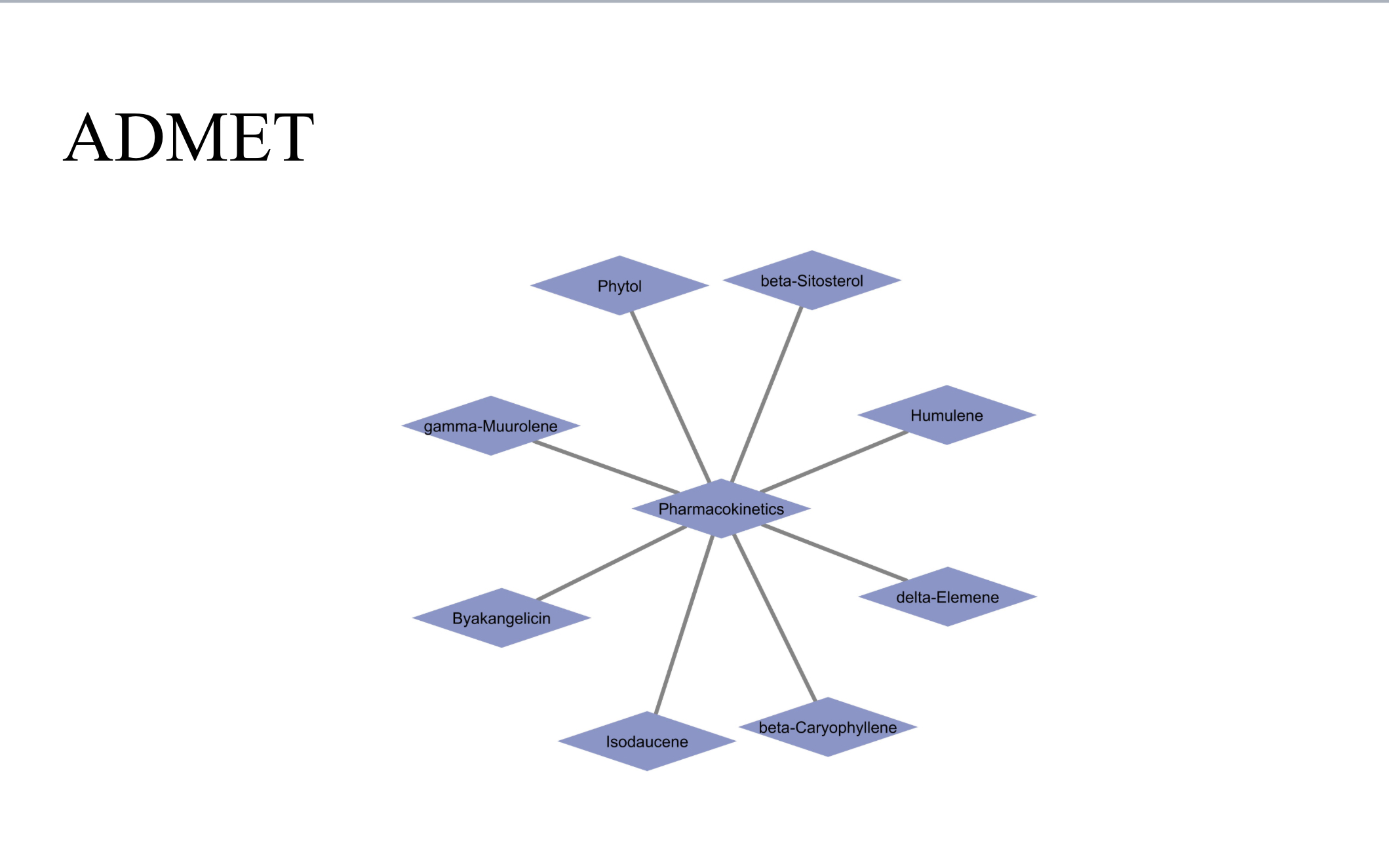
**Figure 1:**presents various compounds sourced from Clausena indica for computational targeting of GSK-3β in malignant melanoma. It includes information on each compound's molecular weight (MW), number of rotatable bonds, hydrogen bond acceptors, hydrogen bond donors, consensus Log P (indicating hydrophobicity), and the number of Lipinski violations (predicting drug-likeness). The serial number (S.No) and compound name are also listed for identification. This data helps evaluate the potential suitability and drug-likeness of these compounds for further research in targeting GSK-3β.

The diagram provides an in-depth analysis of the pharmacological potential of compounds derived from Clausena indica that have been evaluated for their capacity to selectively target GSK-3β in malignant melanoma. Hydrogen bond donors and acceptors, rotatable bonds, molecular weight, and lipophilicity (Log P), which are important variables in predicting a drug's longevity, are all taken into consideration by Lipinski's criteria. Compounds with high lipophilicity, such as beta-pinene, gamma-Muurolene, and phytol, may present issues due to potential Lipinski violations, even if they are pharmacokinetically favorable. Both imperatorin and alpha-terpineol show promise as therapeutic agents due to their exceptional drug-like properties and lack of Lipinski criterion violations.However, despite their potential, compounds such as trans-Sabinene hydrate, beta-Caryophyllene, and humulene have drawbacks that impact their bioavailability and effectiveness, such as huge molecular weight or excessive lipophilicity.In the picture, compounds that are partially compliant—such as 4-Carvomenthenol, Tricyclene, and Clausenidin—are highlighted, suggesting that more optimization is required. By combining drug-like properties with practical limits, this comprehensive mapping makes it easier to identify and optimize Clausena indica molecules for effective GSK-3β targeting in the treatment of melanoma.It also emphasizes how important it is to consider pharmacokinetic and pharmacodynamic characteristics while creating new medications to ensure that the selected compounds have the necessary properties and therapeutic potential for successful application in clinical settings. This study highlights the need for a holistic approach to drug development, integrating computational forecasts with experimental validations to enhance the safety and efficacy profiles of potential therapeutic agents. Furthermore, a deeper understanding of the connection between molecular properties and biological activity may aid in the creation of more targeted and effective therapies.



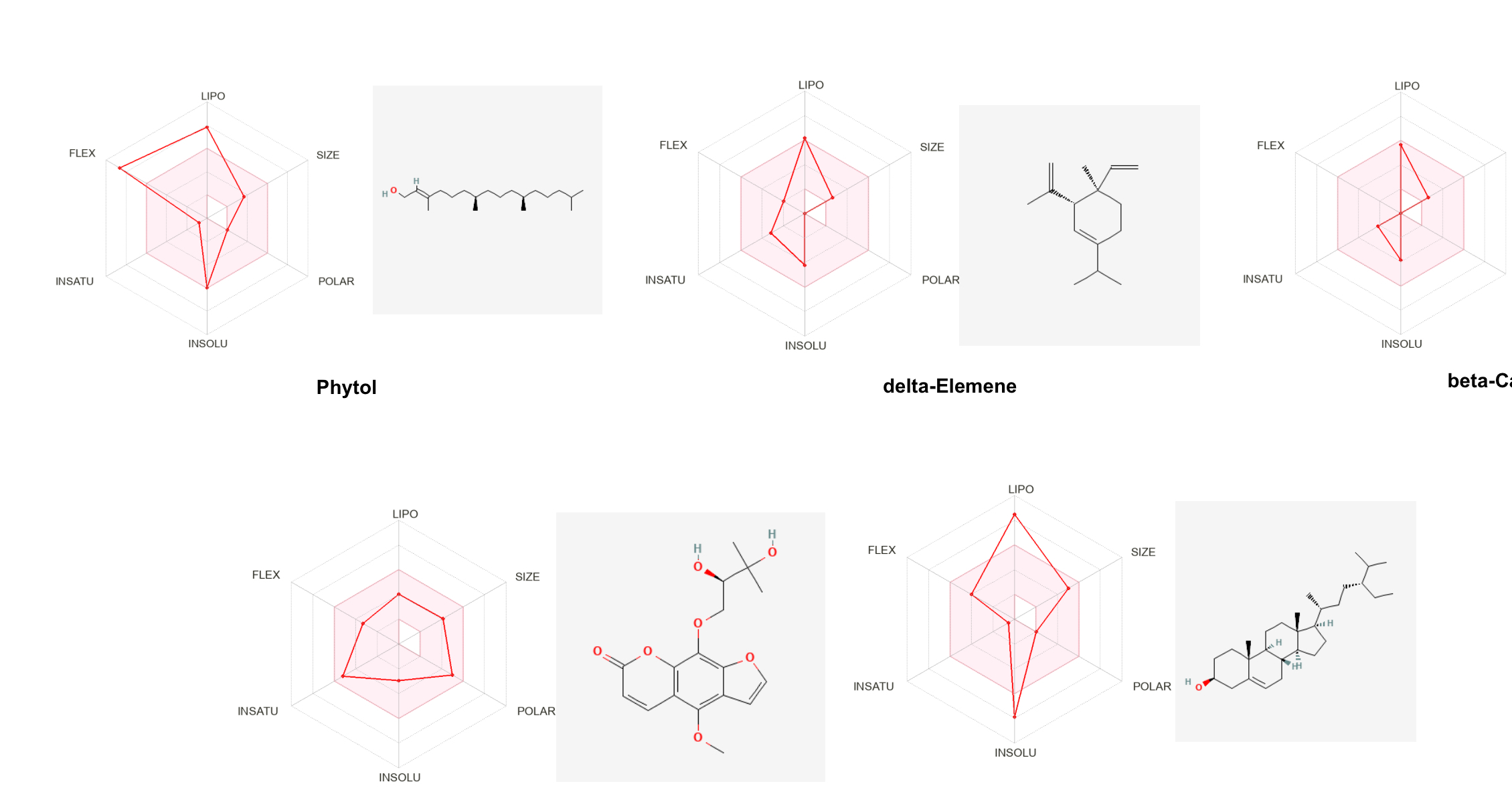
**Figure2:** shows various compounds from Clausena indica connected to "Lipinski's criteria" in the center. Each blue node represents a compound, indicating its assessment against Lipinski's Rule of Five for evaluating drug-likeness based on properties like molecular weight, hydrogen bond donors and acceptors, and hydrophobicity.

The pharmacokinetic characteristics of several compounds obtained from Clausena indica are shown in the ADMET diagram. These compounds are studied for their ability to target GSK-3β in malignant melanoma. Drug development heavily relies on ADMET, which stands for Absorption, Distribution, Metabolism, Excretion, and Toxicity. Because of their advantageous pharmacokinetic characteristics, important substances including Phytol, beta-Sitosterol, Humulene, and delta-Elemene are emphasized as possible candidates for therapeutic uses. In particular, phytol's wide distribution and metabolism, along with beta-sitosterol's low toxicity and effective absorption, make them both very promising. Although gamma-Muurolene and Byakangelicin have favorable pharmacokinetic characteristics, more refinement is necessary to augment their therapeutic effectiveness and mitigate any possible adverse reactions.While compounds such as beta-Caryophyllene and isodaucene have balanced pharmacokinetic characteristics, suggesting that they might be promising candidates for drugs, more changes may be necessary to bring them up to ideal therapeutic standards. This research emphasizes how crucial thorough pharmacokinetic evaluation is to finding promising natural source medication candidates and guaranteeing their safety, effectiveness, and low toxicity. Furthermore, by anticipating the in vivo behavior of these compounds, knowledge of the ADMET characteristics aids in the development of safer and more effective medicinal treatments. This strategy may expedite the drug development process and find new therapies for malignant melanoma by combining computational predictions with experimental validations.



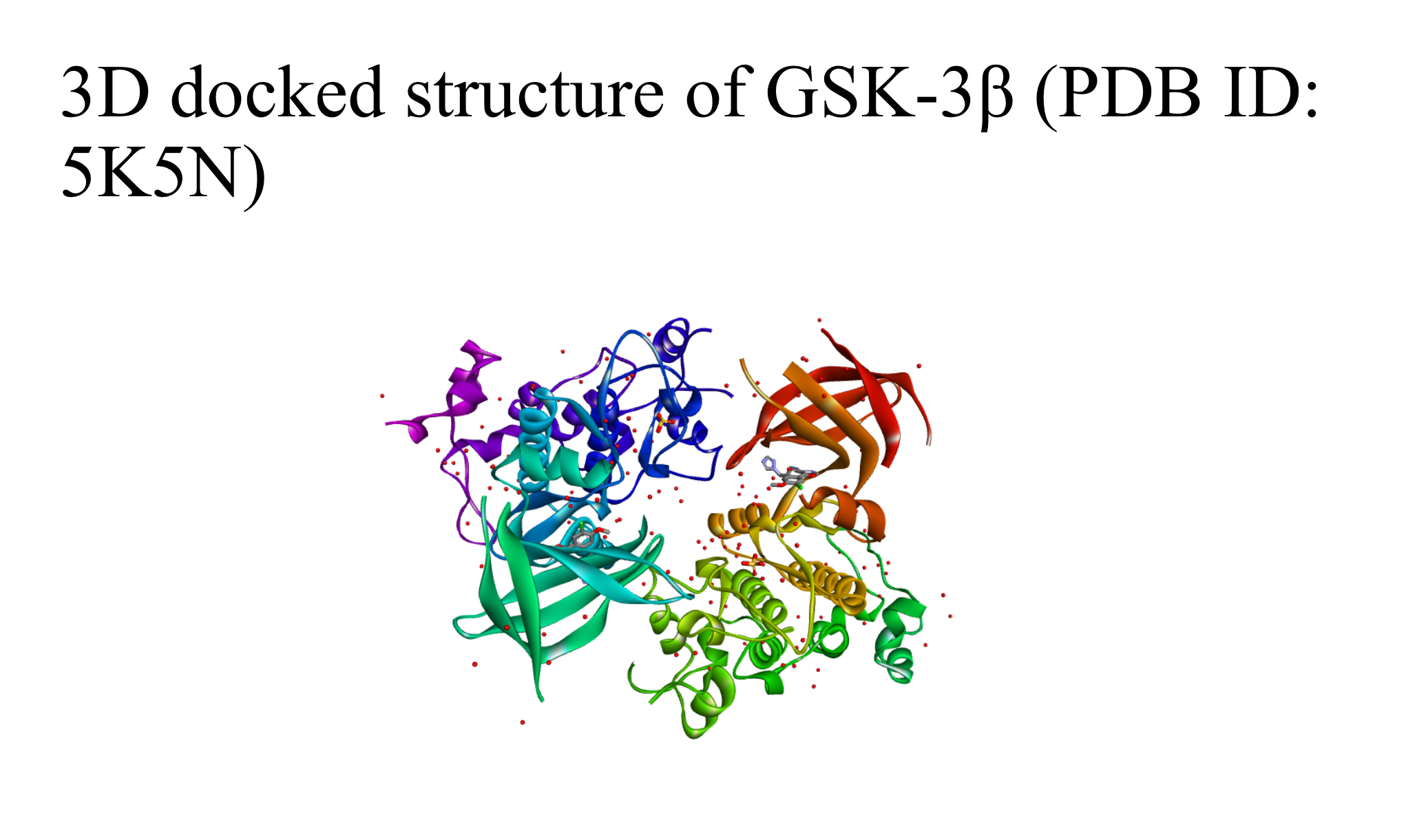
**Figure 3:** shows compounds from Clausena indica evaluated for ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) properties. The central node "Pharmacokinetics" connects to various compounds, indicating their pharmacokinetic profiles. Each connected blue node represents a compound assessed for its ADMET characteristics.

The physicochemical characteristics of three important compounds—Phytol, delta-Elemene, and beta-Caryophyllene—derived from Clausena indica for computational targeting of GSK-3β in malignant melanoma are illustrated by the radar plots and molecular structures that are supplied. A number of characteristics that are essential for determining a drug's similarity are shown in each radar plot, including lipophilicity (LIPO), flexibility (FLEX), size (SIZE), polarity (POLAR), and solubility (INSOLU). By balancing lipophilicity and flexibility, phytol has high membrane permeability and bioavailability, as evidenced by its molecular structure. Due to its intermediate size and favorable lipophilicity, delta-elemene may be useful in engaging with intracellular targets and breaking through cell membranes. Because of its complex structure, beta-caryophyllene exhibits strong lipophilicity and flexibility, which may improve its capacity to influence protein targets such as GSK-3β.In order to maximize these compounds' pharmacokinetic and pharmacodynamic properties and guarantee their efficacy as therapeutic agents, certain physicochemical characteristics are crucial. By incorporating these many characteristics, the development of new therapies for malignant melanoma is advanced by gaining a better grasp of the drug's overall resemblance and likelihood of success in clinical settings. Furthermore, the structural visualization allows targeted alterations to increase efficacy and decrease toxicity, which helps with rational medication design.



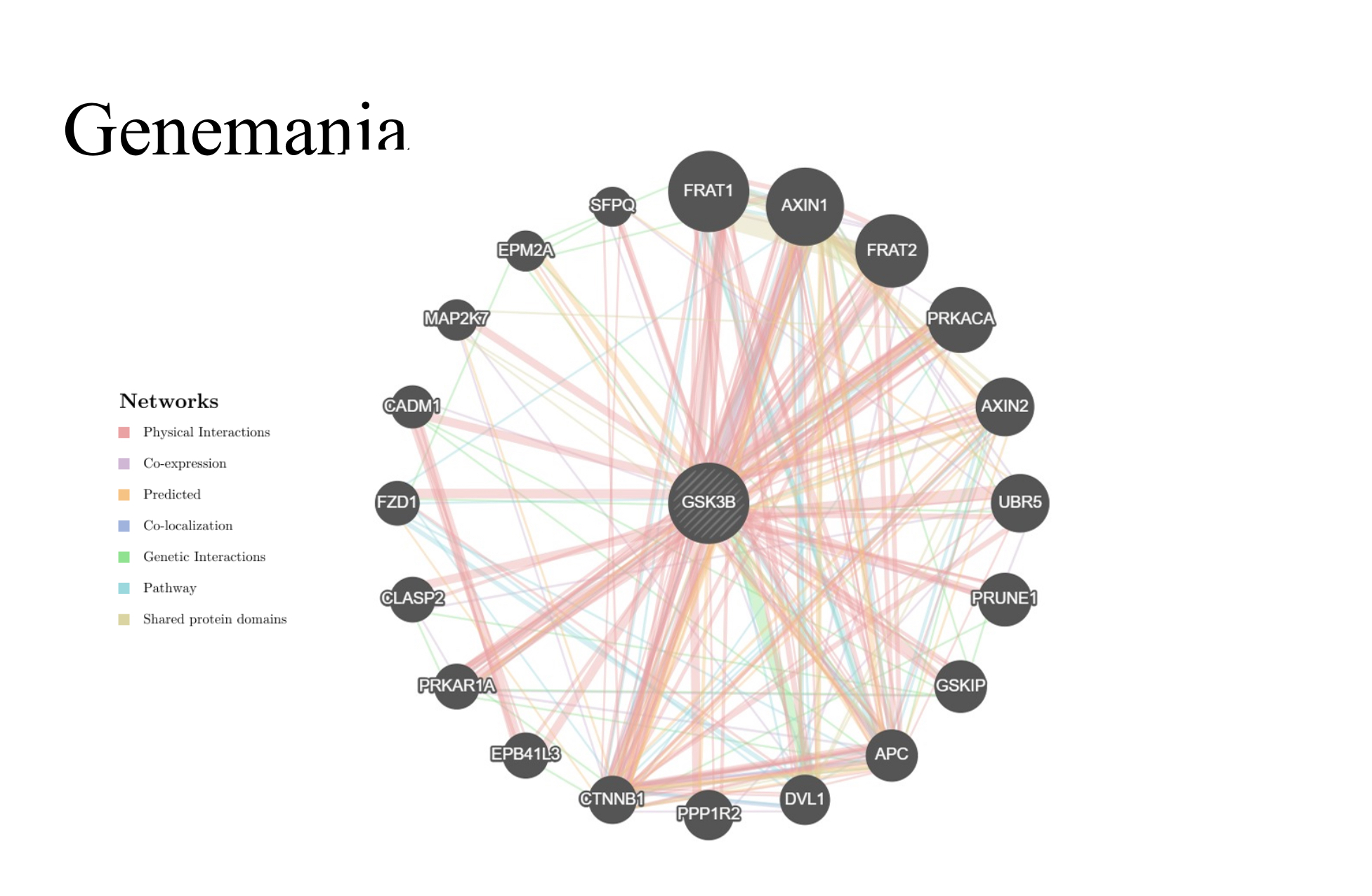
**Figure 4:**shows chemical structures and radar plots of four compounds: Phytol, delta-Elemene, beta-Carotene, and an unidentified compound. Each radar plot evaluates six properties: Lipophilicity (LIPO), Size (SIZE), Polarity (POLAR), Solubility (INSOLU), Saturation (INSATU), and Flexibility (FLEX). Phytol is shown with a chemical structure and a corresponding radar plot, indicating a high degree of flexibility and lipophilicity, moderate size, and low polarity, solubility, and saturation. Delta-elemene's radar plot indicates moderate values for lipophilicity and flexibility but low values for the other properties. Beta-carotene shows high lipophilicity, moderate size, and low values for polarity, solubility, saturation, and flexibility. The unidentified compound has moderate values for lipophilicity and size, with low values for the other properties.

Clausena indica is the source of possible inhibitory chemicals. The binding conformation of these compounds is illustrated in the GSK-3β 3D docked structure (PDB ID: 5K5N). The image illustrates the delicate folding required for GSK-3β's function by showcasing its complex tertiary structure, which consists of alpha-helices, beta-sheets, and loops. Finding out how these substances interact with GSK-3β's active site in hopes of blocking its kinase activity—a process that is essential to the development of malignant melanoma—is the goal of the docking investigation. The compounds' molecular interactions and binding affinities are better understood thanks to this structural research, which also sheds light on how effective the compounds are as GSK-3β inhibitors. Through the examination of these compounds' binding positions and stability inside the GSK-3β active site, scientists can forecast their potential as therapeutic agents, directing future development.



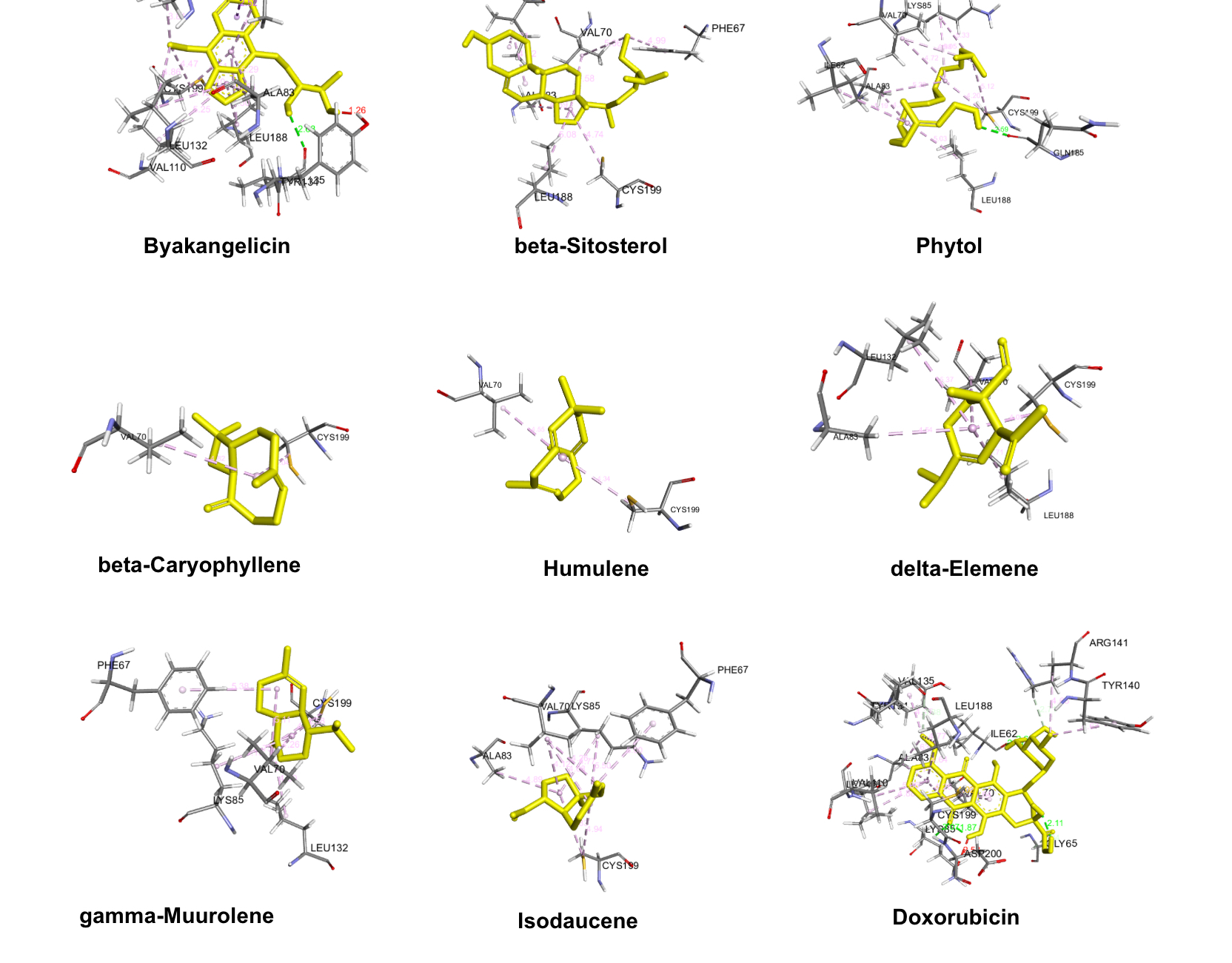
**Figure 5:** depicts the 3D docked structure of Glycogen Synthase Kinase-3 beta (GSK-3β) with the Protein Data Bank (PDB) ID: 5K5N. The structure is represented in a ribbon format with different colors indicating various regions or domains of the protein. This visualization helps in understanding the spatial arrangement and interactions within the protein, essential for studying its function and potential inhibitor binding sites.

The GeneMANIA network visualization highlights the critical function that GSK-3β (Glycogen Synthase Kinase 3 Beta) plays in cellular processes related to malignant melanoma by illuminating the protein's broad interaction network with a variety of other proteins. The network includes many different kinds of connections, such as common protein domains, genetic relationships, co-expression, co-localization, physical interactions, and anticipated interactions. Among the notable interaction partners of GSK-3β are AXIN1, AXIN2, CTNNB1, and PRKACA. This suggests that GSK-3β is involved in a number of signaling pathways, including the Wnt/β-catenin pathway, which is essential for cell division and proliferation. Connections with elements such as PPP1R2 and PRUNE1 imply modulation of protein phosphatase activity and cellular motility, whereas interactions with proteins such as FRAT1 and FRAT2 suggest functions in carcinogenic signaling.This intricate network highlights the importance of GSK-3β as a therapeutic target and the possible role that chemicals from Clausena indica may have in modifying these interactions to prevent the advancement of melanoma. Through the mapping of these connections, scientists may get a deeper comprehension of the molecular underpinnings of GSK-3β's function in cancer and pinpoint crucial nodes for therapeutic intervention, offering fresh perspectives on drug discovery and development methodologies.



**Figure 6**: shows a GeneMANIA network interaction map for GSK-3β, with GSK-3β at the center connected to various proteins. The legend explains the color-coded interactions: red for physical interactions, purple for co-expression, yellow for predicted interactions, blue for co-localization, green for genetic interactions, light blue for pathway associations, and orange for shared protein domains. This visual representation highlights the complex network of GSK-3β, illustrating its various interactions and functional associations with other proteins.

Docking studies are used in the computational targeting of GSK-3β in malignant melanoma to assess the binding interactions of different drugs with the GSK-3β protein. These chemicals are obtained from Clausena indica. In the picture, nine distinct molecules are shown in their binding positions: byakangelicin, phytol, beta-caryophyllene, humulene, delta-elemene, gamma-muurolene, isodaucene, and the common anticancer medication doxorubicin. Based on their individual docking poses, these drugs have strong binding affinities with important residues of GSK-3β, including CYS199, LEU188, and others. These substances have persistent contacts with the GSK-3β active site, which suggests that they may have inhibitory effects, according to the structural study. For instance, the interaction patterns of phytol, delta-elemene, and beta-caryophyllene resemble those of doxorubicin, suggesting their potential as therapeutic agents.The research emphasizes the potential of these organic compounds derived from Clausena indica as viable contenders for the creation of innovative GSK-3β inhibitors intended for the management of malignant melanoma.



**Figure 7:**shows molecular docking interactions of various compounds with a target protein, as indicated by the labels on each sub-image. The labels indicate the names of the compounds being studied: Byakangelicin, beta-Sitosterol, Phytol, beta-Caryophyllene, Humulene, delta-Elemene, gamma-Muurolene, Isodaucene, and Doxorubicin.

By examining binding interactions with important residues of GSK-3β, chemicals from Clausena indica are used in the computational targeting of GSK-3β in malignant melanoma. Significant binding affinities range from -6.1 to -7.8 kcal/mol for compounds such byakangelicin, beta-sitosterol, phytol, beta-caryophyllene, humulene, delta-elemene, gamma-muurolene, isodaucene, and doxorubicin. Byakangelicin has the greatest affinity at -7.8 kcal/mol. The network graphic demonstrates how GSK-3β interacts with many proteins through genetic pathways, co-expression, and physical interactions. These interactions contain key residues such as Cys199, Val70, Asp200, Leu188, and Ala83, indicating that these drugs may be able to effectively block the activity of GSK-3β and perhaps impede the advancement of melanoma. A sustained and robust binding of the drugs to GSK-3β is shown by the extensive interaction table, which displays many hydrogen bonds and hydrophobic interactions.

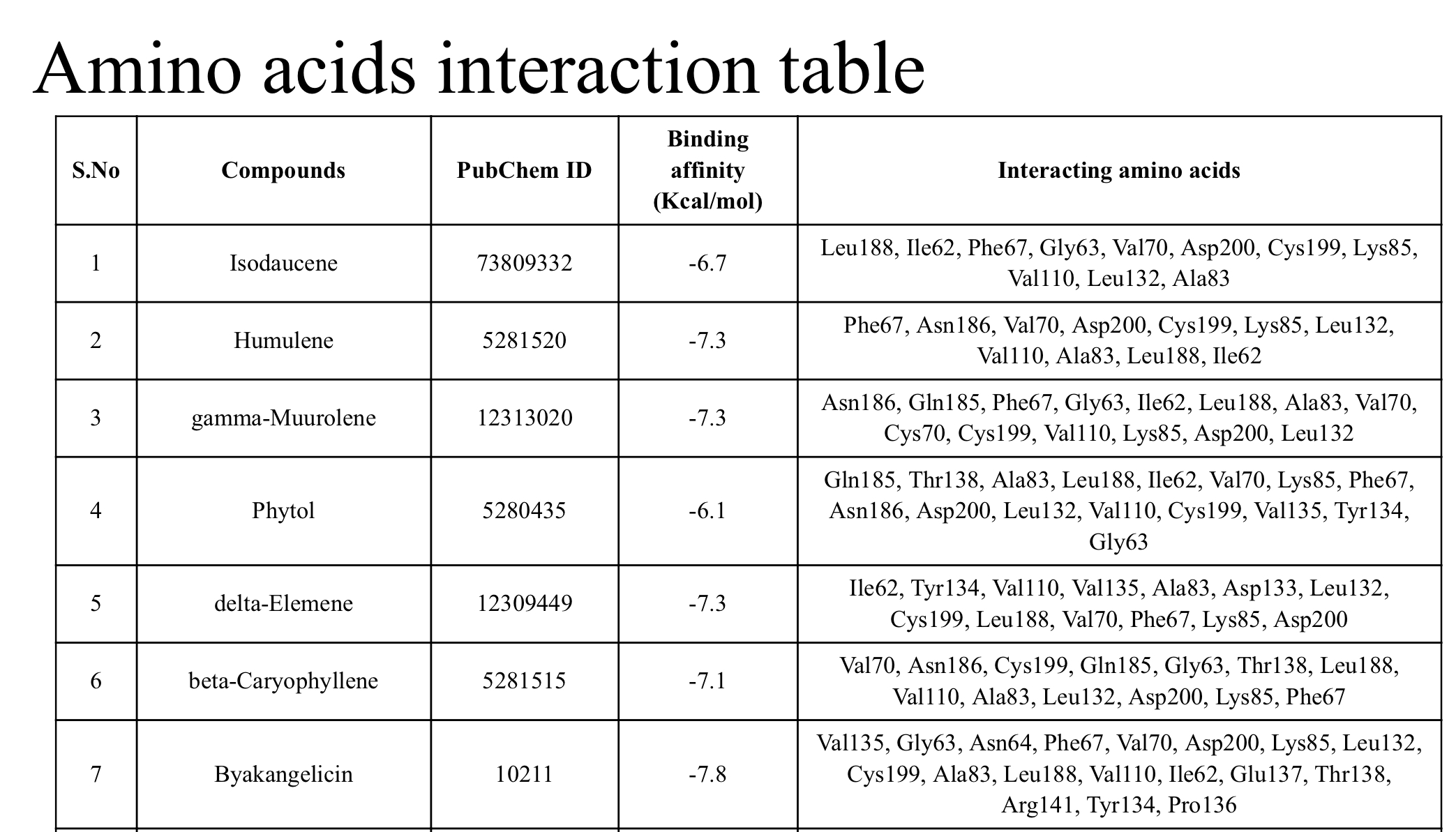


Figure 8: displays the interaction details of seven compounds (Isodaucene, Humulene, gamma-Muurolene, Phytol, delta-Elemene, beta-Caryophyllene, and Byakangelicin) with specific amino acids in a target protein, alongside their PubChem IDs and binding affinities (ranging from -6.1 to -7.8 kcal/mol). Each compound interacts with a unique set of amino acids, with Byakangelicin showing the strongest binding affinity (-7.8 kcal/mol), indicating potentially significant interactions with amino acids such as Val135, Gly63, and Asn64.

The table highlights key residues involved in these interactions, which could be critical for understanding the molecular docking behavior of these compounds.In a study on GSK-3β targeting in malignant melanoma using Clausena indica phytochemicals, 47 compounds from the IMPPAT database, all compliant with Lipinski's rule of five, were initially evaluated [(Keerthana & Ramesh, 2021; Murugesan, 2021; Tiwari & Jain, 2021)](https://paperpile.com/c/2Xxfxg/lyoJ3+x6l7C+VZ86U). After ADMET analysis, 39 compounds permeable to the blood-brain barrier were excluded, leaving 8 for docking studies. These 8 compounds, assessed for drug-likeness and ADMET properties via SwissADME, showed significant binding affinity to GSK-3β (ranging from -6.1 to -9.8 Kcal/mol) similar to doxorubicin. GeneMANIA analysis of the GSK3B gene revealed complex interaction networks, underscoring their potential as therapeutic agents [(Keerthana & Ramesh, 2021; Murugesan, 2021; Subramanian et al., 2021; Tiwari & Jain, 2021)](https://paperpile.com/c/2Xxfxg/lyoJ3+x6l7C+VZ86U+M5J7c).The study on Clausena indica chemicals used in computational targeting GSK-3β in melanoma shows the integration of molecular biology, computer methodologies, and phytochemical studies in drug development. Eight promising candidates with binding affinities similar to doxorubicin were identified, indicating potential cancer treatment roles [(Pranati et al., 2021; Sakthi 2021)](https://paperpile.com/c/2Xxfxg/ZetjV+8CRlB). GSK-3 is a serine/threonine kinase that regulates glycogen synthesis and is involved in various signaling pathways [(A. Shenoy et al., 2023; Singh, Maiti, et al., 2024; Singh, Shenoy, et al., 2024)](https://paperpile.com/c/2Xxfxg/Dm5hQ+OgoXD+q9phP). Recent studies have shown its role in various cancers, autophagy modulation, oxidative stress, and aging [(Mancinelli et al., 2017)](https://paperpile.com/c/2Xxfxg/L9xN). GSK-3 has shown to induce apoptosis or inhibit apoptosis, and its modulation of mammalian aging is related to metabolic alterations in senescent cells and age-related diseases. It is also a potential therapeutic target for natural substances and synthetic inhibitors.GSK-3β, a key kinase in metabolic and cell growth signaling pathways, is a promising cancer therapeutic target [(Sahin et al., 2019)](https://paperpile.com/c/2Xxfxg/1Owc). Despite its involvement in malignancy pathogenesis, no inhibitor has been approved for cancer treatment. Its regulatory role in apoptosis, cell cycle, DNA repair, tumor growth, invasion, and metastasis suggests drug combinations.GSK-3β, a serine/threonine kinase, regulates tumor progression, survival, and chemoresistance, making it a promising target for treatment.GSK-3, a serine/threonine kinase, regulates glycogen synthesis and functions in various cellular processes. [(McCubrey et al., 2014)](https://paperpile.com/c/2Xxfxg/VVED)Its abnormal activity has been linked to various human pathologies, including cancer, bipolar depression, Alzheimer's, Parkinson's, and diabetes.GSK3β, a multifunctional protein kinase, is involved in various diseases like diabetes, neurodegenerative disorders, and cancer. [(Domoto et al., 2020)](https://paperpile.com/c/2Xxfxg/zAO7)Its abnormal expression contributes to disease progression and therapy resistance (Almatrafi et al., 2024). Inhibition of GSK3β has shown therapeutic benefits in 25 cancer types.Fisetin, found in fruits and plants, has anti-inflammatory, anti-proliferative, and anticancer properties(Saadh et al., 2024). [(Molagoda et al., 2020)](https://paperpile.com/c/2Xxfxg/zBns)However, its regulation of melanogenesis has not been extensively studied. This study found that fisetin increases melanin production in melanoma cells and zebrafish larvae, regulating GSK-3β and activating β-catenin.[(Aditya et al., 2021)](https://paperpile.com/c/2Xxfxg/GTXI)

# Conclusion

According to the study's findings, chemicals produced from Clausena indica show promise as novel therapeutic agents by successfully targeting GSK-3β in malignant melanoma. The discovered compounds show excellent binding affinities and interaction patterns with GSK-3β by computational methods, indicating that they may be able to limit the activity of this kinase, which is essential for the advancement of melanoma. These results emphasize the significance of chemicals derived from natural products in the creation of tailored treatments for malignant melanoma and the necessity of additional experimental verification to verify their safety and effectiveness in clinical settings.

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