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Docking investigations between *Beta-elemene* and MC1R (Melanocyte Stimulating Hormone Receptor), a skin cancer gene, employing *Insilico* protocols

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Abstract
The Melanocortin 1 Receptor (MC1R) gene is a protein found in skin cells that regulates melanin production and skin tone. MC1R gene mutations can increase the risk of developing melanoma, a kind of skin cancer. *Beta-elemene* is a phytochemical constituent of *Ocimum tenuiflorum* (Tulsi) as proved by current medical investigations. Hence the test chemical constituent, *beta elemene* against MC1R is used for the development of novel chemical compound against skin cancer. Next, we use *insilico* methods to observe the interaction between *beta-elemene* and MC1R. To conduct drug docking investigations, the normal sequence of MC1R was modified with the aid of *insilico* tools, and the mutant 3D structure was examined using an automated homology modelling server. CB Dock, an automated drug docking server, was used to determine the binding affinities between the test chemical, *beta-elemene* and MC1R, and the control medication, 5-Fluorouracil. The docking data made it abundantly evident that *beta-elemene* had a greater binding affinity for MC1R than the currently used anti-cancer medication, 5-flourouracil. To increase the effectiveness of current medications, beta-elemene can be taken as a supplement. Since *beta-elemene* is a natural substance, less adverse effects are to be expected. The results of our investigation unequivocally showed that *beta-elemene* is a possible treatment for skin sarcoma.

Keywords: MC1R (Melanocortin 1 Receptor) *beta-elemene*, Drug Docking

Introduction
In this research work, we focused on an important chemical constituent of the Indian medicinal plant, Tulsi, namely, Beta-elemene. Numerous scientific studies have been conducted on tulsi, and in the past ten years alone, more than a hundred papers have addressed its pharmacological properties and broad spectrum of medicinal uses. The strong pharmacological actions of tulsi leaf, which have been thoroughly reviewed previously, are confirmed by numerous *in vitro* and animal studies. These actions include adaptogenic [1-3], metabolic [4-6], immunomodulatory [7-9], anticancer [10-12], anti-inflammatory [13, 14], antioxidant [15, 16], hepatoprotective [17, 18], radioprotective [19, 20], antimicrobial [21-24], and antidiabetic effects.
Studies on the use of tulsi as a component of a polyherbal formulation in humans have been thoroughly evaluated, in addition to the substantial body of literature on *in vitro* and animal research [25].
In 1804, 1827, and 1912, respectively, Laennec (melanoma), Jacob (basal cell carcinoma), and Bowen (squamous cell carcinoma in situ) described skin sarcoma as one of the most deadly forms of cancer [26-29]. According to World Health Organization [30], skin sarcoma is the fifth most frequent cancer worldwide as of 2020. According to data released by the American Academy of Dermatology (AAD) in 2022, almost 9,500 Americans receive a skin cancer diagnosis per day. Additionally, according to AAD, at least one in five Americans will have skin cancer at some point in their lives [31, 32].
With an average of 33 cases per 1,000,000 inhabitants, Australia and New Zealand have the highest incidence rate of skin cancer outside of the US. Norway and Denmark, which are in northern Europe, come in second and third, respectively. Exposure to UV radiation, chemical carcinogens, genetic modification, fair skin, immunosuppression, and other variables are among of the established risk factors for skin cancer.

Skin cancer is classified into two categories based on its cellular origin: non-melanoma skin cancer (keratinocytes) and melanoma skin cancer (melanocytes). Additionally, non-melanoma skin cancer is separated into two categories according to severity: squamous cell carcinoma (SCC) and basal cell carcinoma (BCC). Despite the fact that non-melanoma skin cancer makes up 95% (BCC: 75%, SCC: 20%) of all skin cancer cases that are documented, melanoma is responsible for 80% of skin cancer mortality, which is a serious medical concern [33]. The G protein-coupled receptor known as the melanocyte-stimulating hormone receptor (MSHR) interacts with the melanocortins, a class of pituitary hormones1. Melanocortin 1 receptor (MC1R) [34] is another name for it (Mun Y, *et al*., 2023).

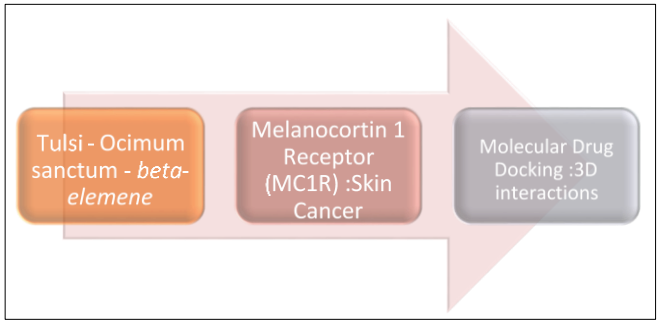
Today, computational biology is an advanced subject for the delivery of novel chemical compounds against various human diseases to Pharmaceutical industries. Here, we focus on the skin cancer gene, MC1R, against one of the phytochemical constituent, beta-elemene, using Drug docking studies.

Materials and Methods

Target Selection

The amino acid sequence of MC1R Melanocortin 1 Receptor Q01726 MSHR_HUMAN was obtained using the proteomics database UniProt (https://www.uniprot.org/), and the sequence [35] was 3D modelled using the SwissModel server (https://swissmodel.expasy.org/). In 2018, Waterhouse A *et al*. conducted a molecular drug docking research using beta-elemene (CID: 6918391) (https://pubchem.ncbi.nlm.nih.gov/compound/6918391) and the control drug 5-fluorouracil (CID: 3385) (https://pubchem.ncbi.nlm.nih.gov/compound/3385). A powerful molecular visualization program called Discovery Studio Software was used to forecast three dimensional structures.

Molecular Drug Docking and 3D Interactions: CB-Dock2, an improved protein-ligand blind docking tool, inherits the AutoDock Vina-based molecular docking mechanism and curvature-based cavity recognition method from the CB-Dock server. The automated molecular drug docking server, CB dock (https://cadd.labshare.cn/cb-dock2/index.php) has been used in molecular drug docking research. (https://cadd.labshare.cn/cb-dock2/index.php) [36, 37]. Using a 3D Ligand-Protein docking approach, the molecular affinities of beta-elemene and MC1R (melanocyte-stimulating hormone receptor) were ascertained. The Discovery Studio software was used to conduct the post-docking research. Based on the docking score, the molecular dynamics concept was used to extensively analyse the 3D image (3D Hbond/Electrostatic interactions).



Results

MAVQGSQRRL LGSLNSTPTA IPQLGLAANQ TGARCLEVSI SDGLFLSLGL VSLVENALV ATIAKNRNLH SPMYCFICCL ALSDLLVSGS NVLETAVILL LEAGALVARA AVLQQLDNVI DVITCSSMLS SLCFLGAIAV DRYISIFYAL RYHSIVTLPR ARRAVAAIWV ASVVFSTLFI AYYDHVAVLL CLVVFFLAML VLMAVLYVHM LARACQHAQG IARLHKRQRP VHQGFGLKGA VTLTILLGIF FLCWGPFFLH LTLIVLCPEH PTCGCIFKNF NLFLALIICN AIIDPLIYAF HSQELRRTLK EVLTCSW

Fig 1: Amino acid sequence of MC1R retrieved from UniProt database. Natural variant is highlighted in yellow which is present in the 60th position

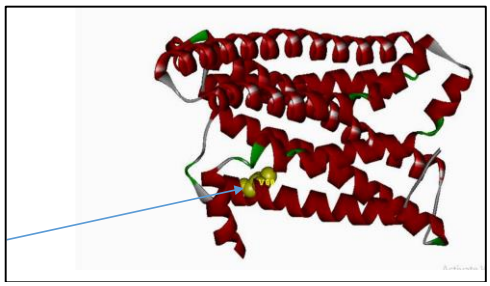


Fig 2: 3D structure of MC1R, The yellow-coloured structure represents the natural variant

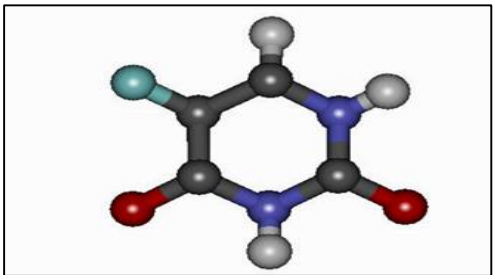


Fig 3: 3D structure of the control drug, 5-fluorouracil retrieved from PubChem Compound database and viewed using Discovery Studio Software

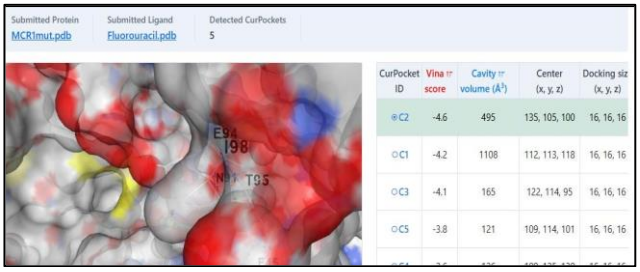


Fig 4: Output page of CB-Dock server showing the binding scores between MC1R and the control drug, 5-fluorouracil.

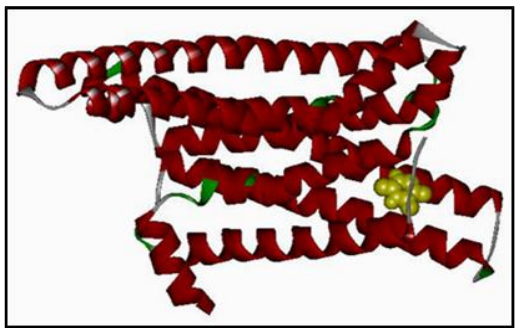


Fig 5: 3D structure of the complex form of MC1R and the control drug, 5-fluorouracil viewed using Discovery Studio Software. Yellow-coloured structure represents 5-fluorouracil

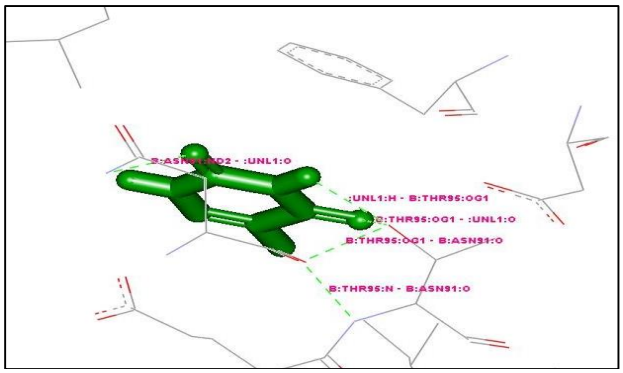


Fig 6: H-bond interaction between MC1R and the control drug, 5-fluorouracil viewed using Discovery Studio Software. Green coloured structure represents 5-fluorouracil with amino acid labels

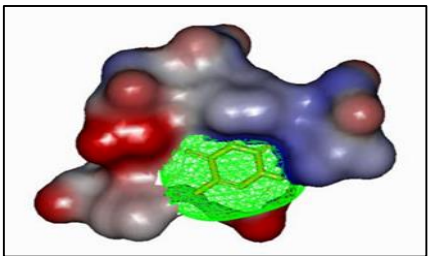


Fig 7: Van der Waals interaction between MC1R and the control drug, 5-fluorouracil viewed using Discovery Studio Software. Green-coloured structure represents 5-fluorouracil

MAVQGSQRRL LGSLNSTPTA IPQLGLAANQ TGARCLEVSI SDGLFLSLGL VSLVENALVL
ATIAKNRNLH SPMYCFICCL ALSDLLVSGS NVLETAVILL LEAGALVARA AVLQQLDNVI
DVITCSSMLS SLCFLGAIAV DRYISIFYAL RYHSIVTLPR ARRAVAAIWV ASVVFSTLFI
AYYDHVAVLL CLVVFFLAML VLMAVLYVHM LARACQHAQG IARLHKRQRP VHQGFGLKGA
VTLTILLGIF FLCWGPFFLH LTLIVLCPEH PTCGCIFKNF NLFLALIICN AIIDPLIYAF
HSQELRRTLK EVLTCSW

Fig 8: Amino acid sequence of MC1R retrieved from UniProt database. The mutated variant (L) is highlighted in yellow which is present in the 60th position

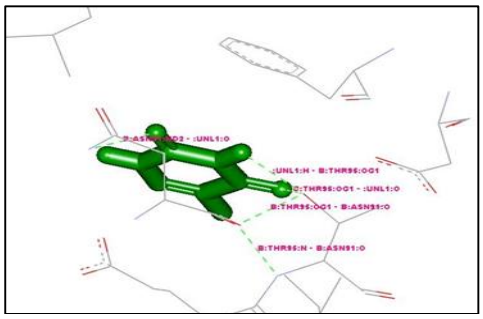


Fig 6: H-bond interaction between MC1R and the control drug, 5-fluorouracil viewed using Discovery Studio Software. Green coloured structure represents 5-fluorouracil with amino acid labels

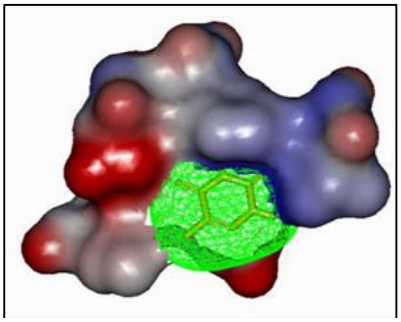


Fig 7: Van der Waals interaction between MC1R and the control drug, 5-fluorouracil viewed using Discovery Studio Software. Green-coloured structure represents 5-fluorouracil

MAVQGSQRRL LGSLNSTPTA IPQLGLAANQ TGARCLEVSI SDGLFLSLGL VSLVENALVL
ATIAKNRNLH SPMYCFICCL ALSDLLVSGS NVLETAVILL LEAGALVARA AVLQQLDNVI
DVITCSSMLS SLCFLGAIAV DRYISIFYAL RYHSIVTLPR ARRAVAAIWV ASVVFSTLFI
AYYDHVAVLL CLVVFFLAML VLMAVLYVHM LARACQHAQG IARLHKRQRP VHQGFGLKGA
VTLTILLGIF FLCWGPFFLH LTLIVLCPEH PTCGCIFKNF NLFLALIICN AIIDPLIYAF
HSQELRRTLK EVLTCSW

Fig 8: Amino acid sequence of MC1R retrieved from UniProt database. The mutated variant (L) is highlighted in yellow which is present in the 60th position

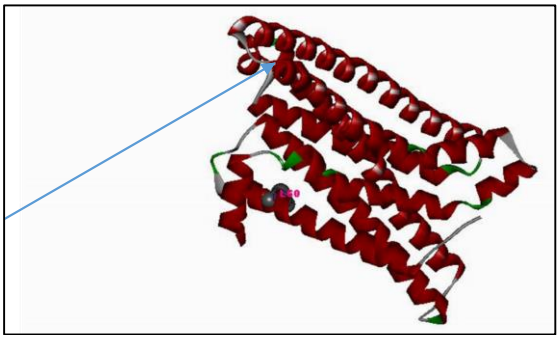


Fig 9: 3D structure of MC1R, Mutated variant is highlighted in pink

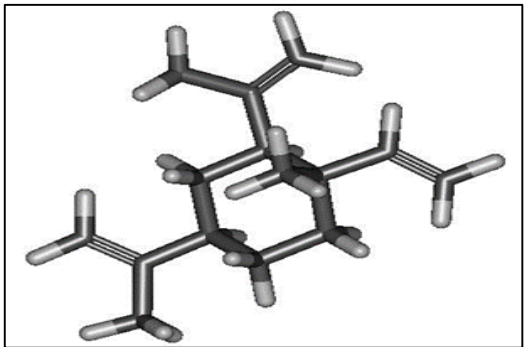


Fig 10: 3D structure of the control drug, *beta-elemene* retrieved from PubChem Compound database and viewed using Discovery Studio Software

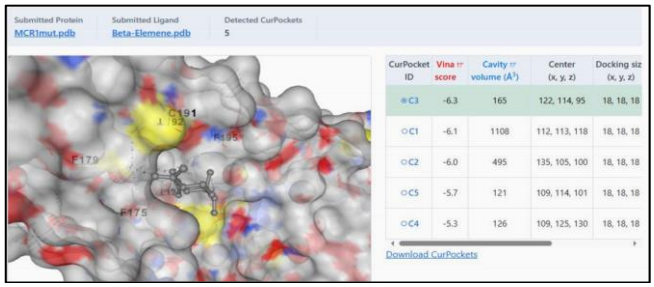


Fig 11: Output page of CB-Dock server showing the binding scores between MC1R and the control drug, *beta-elemene*

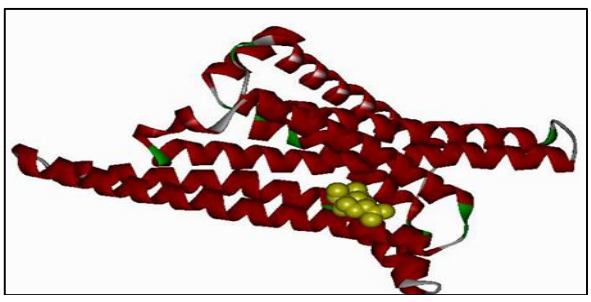


Fig 12: 3D structure of the complex form of MC1R and the control drug, *beta-elemene* viewed using Discovery Studio Software. Yellow-coloured structure represents *beta-elemene*

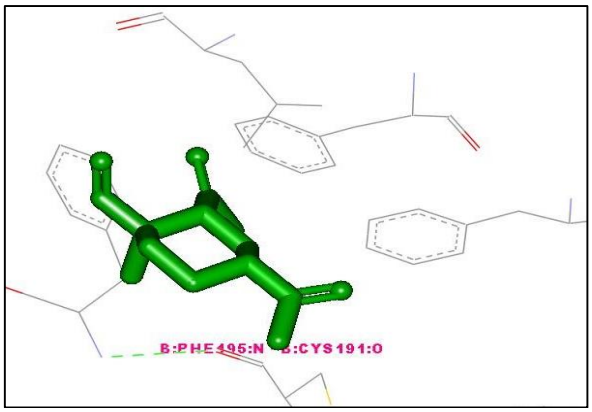


Fig 13: H-bond interaction between MC1R and the control drug, *beta-elemene* viewed using discovery studio software, Green-coloured structure represents *beta-elemene* with respective amino acid labels

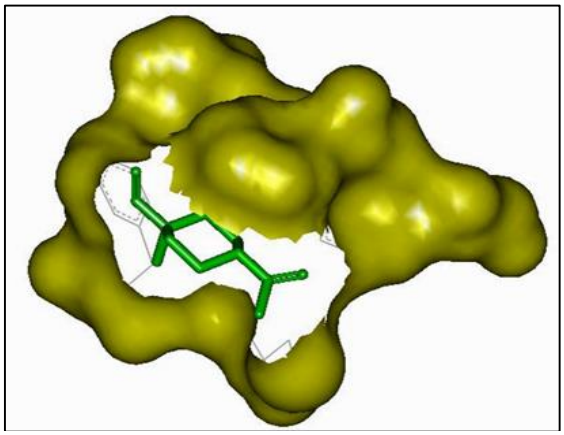


Fig 14: Van der Waals interaction between MC1R and the control drug, *beta-elemene* viewed using Discovery Studio Software. Green-coloured structure represents *beta-elemene*

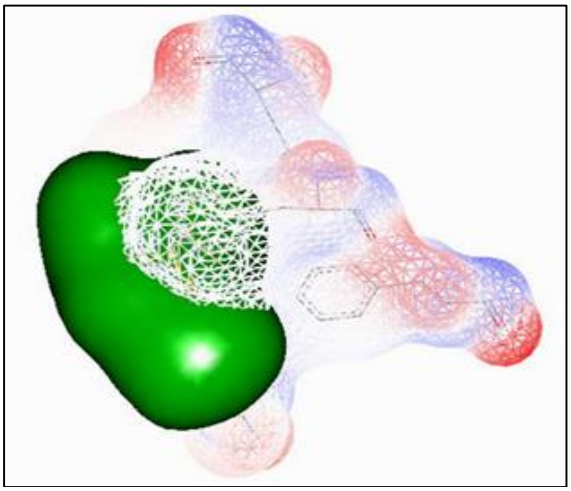


Fig 15: Van der Waals interaction between MC1R and the control drug, *beta-elemene* viewed using Discovery Studio Software. Green-coloured structure represents *beta-elemene*

Table 1: Beta-elemene, the test chemical, and 5-fluorouracil, the control medication, had different drug docking scores. A greater negative value denotes a better binding affinity between the chosen chemicals and the skin cancer protein, MC1R (CB dock server)

	Test Compound	**Control Drug**
Target Protein	***beta-elemene***	**5-fluorouracil**
MC1R(Melanocortin 1 Receptor-Q01726 MSHR_HUMAN)	-6.3 *kcal/mol*	-4.6 *kcal/mol*

According to the table above, beta-elemene has a higher binding score with MC1R.

Discussion

Leucine (L) is located in the 60th position of the mutant protein, whereas valine (V) is located in the 60th position of the normal MC1R protein product (Figure 1-2 and 8-9). The validity of the mutated viewpoint was confirmed by clinical literature investigations. The modified protein was created using the *Insilico* techniques, shown using Discovery Studio software, and modelled using Swiss Modelled Server. The CB Dock service was used in this docking study to dock the MC1R sequence with *beta-elemene* and with 5-fluorourac.

The receptor known as the melanocortin 1 receptor (MC1R) combines with heterotrimeric G proteins to create a complex. The Gαs protein separates when agonistic ligands attach to MC1R, and MC1R then triggers adenylyl cyclase, which results in the synthesis of cAMP, an essential second messenger that controls a variety of biological functions. Protein kinase A (PKA) is activated in melanocytes by cAMP, which also sets off downstream signaling pathways that activate other effector pathways, such as the MITF and CREB networks. Tyrosinase and dopachrome tautomerase, two enzymes involved in melanin synthesis, are expressed more frequently as a result of these pathways, which causes melanin to be produced. The melanin generated is subsequently transferred to neighboring keratinocytes, forming a barrier that enhances the skin's resistance to more UV deterioration [38-40].

Furthermore, previous research that examines the state-of-the-art *Insilico* docking tests serves as the foundation for our analysis. The test material used in this investigation, betaelemene [41], has antioxidant properties, according research by Bai Z, *et al*., 2021 [42]. (Figure 3) The control drug molecule in this instance is 5-fluorouracil, a medication frequently used to treat a variety of malignancies [43]. 5-fluorouracil is a nucleobase analogue of uracil that has fluorine in place of the hydrogen atom at position 5. This antineoplastic drug is converted into the active deoxynucleotide and then functions as an antimetabolite, preventing the cellular enzyme, thymidylate synthetase from converting deoxyuridylic acid to thymidylic acid, which inhibits DNA synthesis and slows tumor growth. It has antimetabolite, xenobiotic, radiosensitizing, immune-suppressive, and antineoplastic qualities in addition to being an environmental pollutant. It is an analog of both an organofluorine and a nucleobase. (Figure 10).

Its function is similar to that of uracil. Cavity detection-guided blind docking looks for potential binding pockets using cavity detection algorithms such as Fpocket and P2Rank [44]. Furthermore, COACH-D and GalaxySite use blind docking to identify binding sites instead of cavity discovery. After binding site identification, cavity detection-guided blind docking approaches such as CB-Dock and E-Dock were used to perform local docking at the anticipated binding sites [45-49].

Figures 4-7 and 11-15 show the interactions between the MC1R protein with 5-fluorouracil, and with *beta-elemene* at various binding amino acid locations. The drug-receptor complex view and associated drug binding scores for MC1R, 5-fluorouracil, and beta-elemene are displayed in the figures. The binding affinity value of MC1R for 5-fluorouracil is -4.6 *kcal/mol*. However, the binding affinity value of MC1R for *beta-elemene* is -6.3 *kcal/mol*. The

locations where the skin cancer gene, MC1R interacts with *beta-elemene* are indicated by H-bond interactions (PHE: 195, CYS: 191) [PS50262] (G-protein coupled receptors family 1 signature and profile).

The regions of MC1R that interact with the control drug, 5-fluorouracil, are visible through H-bond interactions (ASN: 91, THR: 95) [PS50262] (G-protein coupled receptors family 1 signature and profile) [50]. These interactions suggest that the *beta-elemene* molecule interacts with the functional motif region of the MC1R. 5-fluorouracil, an anti-cancer drug that is currently available on the market, interacts with the functional domains of the MC1R protein. Similarly, the test chemical interacts with the functional regions of the MC1R protein. Consequently, we showed that the test chemical, *beta-elemene*, can block the MC1R protein, which is involved in skin cancer.

Conclusion

A test compound called *beta-elemene* binds directly to the mutated MC1R protein, suppressing the expression of the protein that causes skin sarcoma. The 3D molecular contact between the MC1R and the test compound, *beta-elemene*, has a higher docking score than the one between the MC1R and the control medication, 5-fluorouracil. Therefore, we draw the conclusion that *beta-elemene* molecule can be employed as a drug to treat human skin sarcoma. In this study, we demonstrate unequivocally how the natural substance, *beta-elemene* is inhibited by the derived skin cancer protein, MC1R. Therefore, it can be shown that *beta-elemene* has pharmacological effects against the human vulnerable skin-cancer gene, MC1R, and that it may down regulate MC1R. In the end, we determine that *beta-elemene*, a natural test compound obtained from *Tulsi*, is a unique substance for the treatment of skin cancer.

Conflict of interest

The author declares that there are no conflicts of interest with regard to this article.

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