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DOCKING STUDIES ON ANTICANCER EFFECT OF *MENTHA PIPERITA* AND *OCIMUM*BASILICUM AGAINST BREAST CANCER

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ABSTRACT

Cancer research is the intense scientific effort to understand disease processes and discover possible therapies. Breast cancer is the second most common type of cancer after lung cancer. Normal breast cells and most breast cancer cells have receptors that attach to circulating estrogen and progesterone. In the present study, cha-rasprotein and cytochrome P450 was docked with the two drugs and the energy value obtained for limonene (-6.07762 kcal/mol) with elapsing time of 5 seconds, Eugenol (-6.53482 kcal/mol) with elapsing time of 7 seconds, using Argus lab docking software.

KEY WORDS: ***Limonene ,Eugenol,cha-ras,cytochrome P450.***

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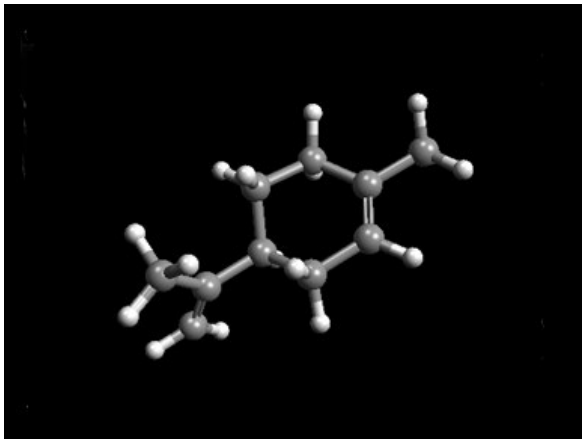
INTRODUCTION

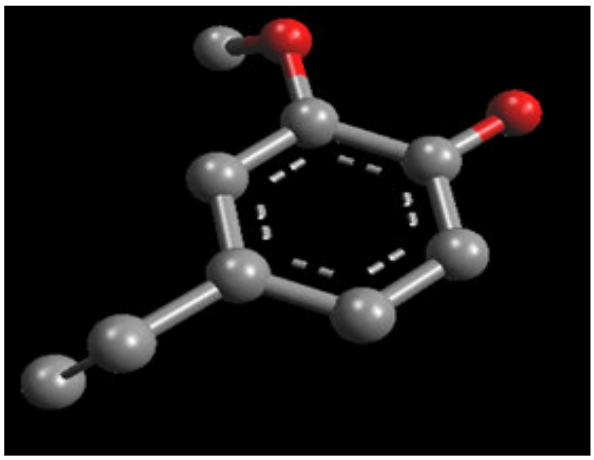
Cancer is ultimately a disease of genes. A series of several mutations is required before a cell becomes a cancerous cell. The process involves both oncogenes and tumor suppressor genes. Oncogenes promote cancer when “switched on” by a mutation whereas tumor suppressor genes prevents cancer unless “switched off” by a mutation. Worldwide breast cancer is the most common cause for cancer death. Cancer drug development is entering a remarkable new phase. Recent studies have shown that monoterpenes exhibit antitumor activity and suggest that these compounds are a new class of cancer chemo-preventive agents. *Menthapiperita* (peppermint) is globally and widely used in the form of oil, extract, leaves and water. *Menthapiperita* has antibacterial effects, strong antioxidant ,antitumor and antiallergenic potential. It was reported that the oil of *Menthapiperita* has a genotoxic effect on human lymphocytes.[5] The major constituent reported is volatile oil, of which the principal component is usually menthol, menthone, carvone and limonene.[6] Limonene has well-established chemo-preventive activity against many cancer types. Dietary limonene also inhibits the development of ras oncogene-induced mammary carcinoma in rats.[4] Limonene distributed extensively to human breast tissue and reduced breast tumor,cyclin D1 expression that may lead to cell-cycle arrest and reduced cell proliferation.[13]

FIGURE 1
STRUCTURE OF LIMONENE



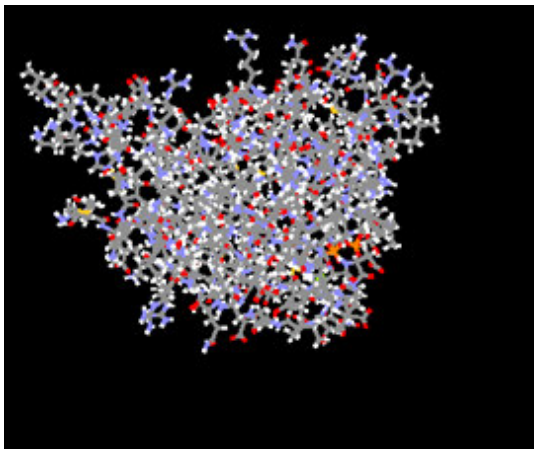
The genus*Ocimum*belonging to family ofLamiaceaeis widely distributed in tropical and warm temperate regions of the world. It is usually named as sweet basil with extraordinary medicinal properties and contains several antioxidant compounds.[8] Eugenol is a major component of the essential oil of *Ocimumbasilicum* and widely used as a flavouring agent in food products, pharmaceutical products and also as an analgesic in dentistry. Molecular mechanism of eugenol-induced apoptosis in melanoma, skin tumours, osteosarcoma, leukemia, gastric and mast cells has been well documented.[7]Eugenol exhibits anti-breast cancer properties both in vitro and in vivo indicating that it could be used to consolidate the adjuvant treatment of breast cancer through targeting the E271/surviving pathway.

FIGURE 2
STRUCTURE OF EUGENOL



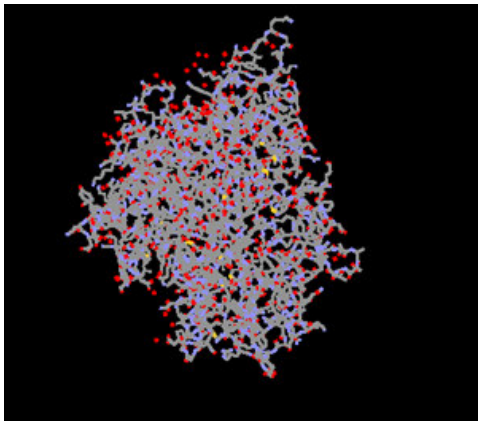
Genetic ras mutations are infrequent in breast cancer but ras may be pathologically activated in breast cancer by overexpression of growth factor receptors which signal through ras. Ras was abnormally activated in breast cancer overexpressing the EG7 and/or ErbB-2 receptors indicating there are sufficient ligands in vivo to activate these receptors and this work provides a basis for new target-based treatments of this disease.[10]

FIGURE 3
STRUCTURE OF CHA-RAS PROTEIN



Cytochrome P_{450}, family I, subfamily A, polypeptide I is a protein present in humans is encoded by the cyp1a gene. The protein is a member of the cytochrome P_{450}superfamily of enzymes.Cyp1aplays an important role in the detoxification of environmental carcinogens, as well as in the metabolic activation of dietary compounds with cancer preventative activity. Ultimately the contribution of cyp1ato cancer progression or prevention may depend on the balance of procarcinogen activation/detoxicationof dietary natural product [9]

FIGURE 4
STRUCTURE OF CYTOCHROME P $_{450}$ PROTEIN



Recently research collaborator for structural bioinformatics (RCSB) is a non-profit consortium dedicated to improving our understanding of the function of biological systems through the study of the 3D structure of biological macromolecules. A promising tool for RCSB is virtual screening (Insilco screening) in which small molecules are virtually docked into a drug target of the binding affinities which are estimated using simplified free energy calculation methods. For virtual screening, docking programs carry out three steps: prediction of target-ligand complex structures (pose construction), selection of the most reasonable pose from the predicted poses (pose selection) and selection of probable drug compounds from a virtual library. Although many programs capable of carrying out virtual screening have been developed most of them are payware. Consequently freeware for computational docking is expected to plays an important role in the study of education of RCSB. One freely available docking software packaging potentially capable and offsetting these costs is Arguslab. Arguslab was originally developed as molecular modeling software. It provides users with molecular building analyses, the ability to perform various molecular calculations and molecular structure visualization capabilities. Molecular docking analysis capability was added to the latest version of Argus lab (ver 4.0.1)[12]

TOOLS AND MATERIALS USED

The activities of obtained plant based constituents were observed through various software. Biological database are used in the study to retrieve the compounds and receptor molecules. PubMed, Drug Bank, PDB (Protein Data Bank), NCBI (National Centre for Biotechnology Information), RCSB (Research Collaboratory for structural bioinformatics) and softwares like Arguslab, Chem sketch were used.

Ligand preparation

The compounds Limonene andEugenol were generated using chemsketch. Chemsketch is all-purpose chemical drawing and graphics package to help chemists quickly and easily draw molecules. Reactions and schematic diagrams calculate chemical properties.[1] Using chemsketch the structures of the drugs were generated by their SMILES notation obtained from drug bank, the structural analogous of these drugs were sketched, molecular corrections were done and hydrogen added. Drug Bank is a unique bioinformatics resource that combines detailed drug (i.e, chemical) data with comprehensive drug target (i.e, protein). Each drug card entry contains greater than 80 data fields with half of the information being devoted to dry/chemical data of the other half devoted to dry target or protein data.

Protein preparation

The 3D structure of the receptor molecule was retrieved from the PDB (Protein Data Bank). The structure of Cha-ras and Cytochrome $_{P450}$ was obtained from PDB data bank(PDB Code: 1aa9,cyp1a)It contains structural information of the macromolecules determined

by X-ray crystallographic, NMR methods etc. Arguslab provides users with molecular building analysis, ability to perform various molecular calculations and molecular structure visualization capabilities.

METHODOLOGY

Bioinformatics is a field with the potential to significantly improve how drugs are found, brought to the clinical trials and eventually released to the market place. Computer-aided drug design (CADD) is a specialized discipline that uses computational methods to simulate drug-receptor interactions,CADD methods are heavily dependent on bio informatics tools, applications and databases. The docking analysis of limonene and eugenol with breast cancer receptor was carried by Argus Lab software. Docking allows the scientist to virtually screen a database of compounds and predict the strongest binders based on various scoring functions. It explores ways in which two molecules such as drugs and breast cancer receptor fit together and docks to each other well. The molecules binding to a receptor inhibit its function and thus act as drug.[2]The collection of limonene, eugenol and receptor complexes were identified via docking and their relative stabilities were evaluated using molecular dynamics and their binding affinities using free energy simulations. All the parameters used for Argus lab docking are selected by default.

RESULTS

The proteins (cha-ras, and cytochrome P450) were docked with Limonene and Eugenol using server Argus lab which is depicted in figure 5 and 6.

FIGURE 5
LIMONENE DOCKED RESULT

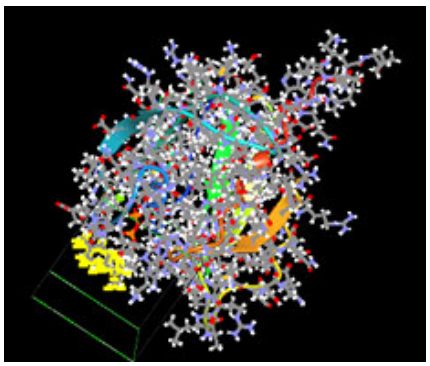
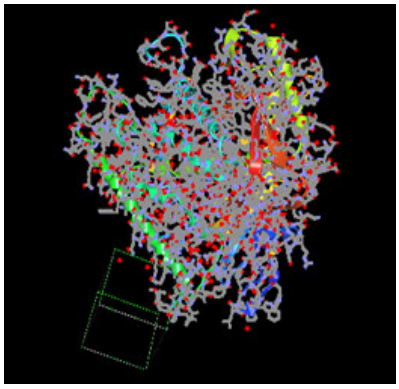


FIGURE 6
EUGENOL DOCKED RESULT



After molecular docking, calculated binding free energies (kcal/mol) and elapsed time for calculation were extracted for each ligand were listed in TABLE 1.

TABLE 1
DOCKING SCORES OF LIMONENE AND EUGENOL

S No	Compound	Dock scores kcal/mol	Elapsed time for calculation
1	Limonene	-6.07762	5 seconds
2	Eugenol	-6.53482	7 seconds

CONCLUSION

The protein-ligand interaction plays a significant role in structural based drug designing.[11] The cha-ras and cytochrome P450were selectedasbreast cancer receptors. When the receptors were docked with the drugs, the energy value obtained for limonene was (-6.07762),andEugenol (-6.53482). It was revealed that limonene and Cha-ras receptor were docked at different poses. Because of this, Cha-ras proteins get dislocated and inhibit the growth of cancerous cell by inducing apoptosis. Eugenol docking may induce the total cytochrome P_{450}concentration by enhancing the activity of carcinogen metabolizing enzymes, resulting in detoxification of the carcinogen. This leads to the growthinhibition and apoptosis.

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