ORIGINAL RESEARCH PAPER
Volume - 10 | Issue - 05 | May - 2021 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

MOLECULAR DOCKING WORKS IN BREAST CANCER USING NATURAL COMPOUNDS – A REVIEW

Oncology

Lakshmi. S* Post Graduate Student, Department Of Botany, Queen Mary`s College, Mylapore, Chennai. *Corresponding Author

Dr.T.V.Poonguzhali Associate Professor, Department Of Botany, Queen Mary`s College, Mylapore, Chennai.

ABSTRACT

Cancer being a dreadful disease is becoming a big challenge to mankind. Though there are a lot of research works providing a complete database over the causative agents of cancer, a complete cure is not available till now. The existing drugs are still posing a lot of side effects and at the same time there are also certain evidence for the existence of drug resistance cancer. Now the research fellows believes that there is a need for natural way to cure the disease. Hence, they have taken the natural compounds in hands to exploit their ability to cure cancer. This review article focuses on such natural components (catechins, curcumin, resveratrol, genistein and piperine) based works and explain their ability to cure cancer via molecular docking studies. This study is based on the Warburg effect and the role of oxidative stress on cancer. Overall conclusion of this study shows effectiveness of curcumin in cancer treatment.

KEYWORDS

Breast cancer, Molecular Docking, Warburg Effect, Curcumin.

INTRODUCTION

Cancer is a disease where occurs uncontrollable growth of cells in an abnormal way leading to tumour growth caused as a result of environmental impacts, gene mutation or due to undesirable habits.

Reports on Cancer Prevalence

According to **World Caner Report** released on World Cancer Day by IARC (International Agency for Research on Caner) a specialised unit of WHO, the estimated cancer burden in India **in 2020**

In India, six **most common cancer** types are
1) Breast cancer (162,500 cases),
2) Oral cancer (120,000 cases),
3) cervical cancer (97,000 cases),
4) lung cancer (68,000 cases),
5) stomach cancer (57,000 cases), and
6) colorectal cancer (57,000).

As per the report of Mathur *et al.,* (2020) which provides the statistical data of the cancer within India showed that **Aizawl,** Mizoram and **Papum Pare**, Arunachal Pradesh marked the highest prevalence of cancer with AAR of 269.4 and 219.8 respectively. Chennai marked the seventh position with AAR of 119.9.

Breast Cancer

Tumors may develop within different areas of the breast. Based on that, there are different types of breast cancer. Most breast cancers begin in the ducts lining cells (ductal cancers) and some in the cells lining the lobules (lobular cancers), while a small number start in the other tissues

Breast cancer is one among the common types of malignancies in women worldwide. The risk of breast cancer is high due to lack of awareness among the public about its symptoms, availability of screening resources, diagnostic centres, etc., as the result of it, majority of patients were **diagnosed with cancer only at advanced stage (Stage 3- 4).** Most of the patients approach hospital only in the final stage.

Breast cancer shows symptoms such as a *lump in the breast, a change in breast shape, dimpling of the skin and fluid coming from the nipple, a newly-inverted nipple, or a red or scaly patch of skin* depending on cancer type, stage and patient's age.

Many different pathways mainly mediate the Breast Cancer aetiology. There are many factors like lifestyle, family history, hormonal, genetic variation affecting Breast Cancer, having said that, the one specific factor causing Breast Cancer was out of reach.

But most of them believe that cancer is caused due to genetic damage in cells which show faulty division due to mutation. The glandular tissues of breasts are highly sensitive to hormonal changes in the body hence breast cancer is considered to be a type of hormonal cancer.

During puberty, the concentration of estrogen gets increased which in turn augments the synthesis of estrogen and progesterone receptor in mammary glands. They are said to create potential risk factors for the initiation and development of breast cancer. On the other hand, pregnancy and lactation controls the production and help in reducing the risk. Other than this, some studies shows that higher breast mass is associated with breast cancer since estradiol is made from cholesterol.
The treatment of breast cancer involves medication using drugs such as *tamoxifen, methotrexate*, etc., radiation therapy, chemotherapy, nanoparticle delivery system, bio- conjugates delivery system and other methods of targeted drug and gene therapies

Despite improvements in early diagnosis and development of several targeted therapeutic methods, mortalities related to breast cancer still remain high. The existing therapeutic approaches are found to be associated with high toxicity, low efficacy, therapeutic resistance and therapy-related morbidity.

For breast cancer patients taking medications the side effects observed are nausea, vomiting, numbness or weakness in peripheral extremities, mood swing, abdominal pain or diarrhoea, hair fall, joint pains, gum pain, gum bleeding, deafness, vision problems, shortness of breath and non- productive cough.

Recent studies have reported that the natural products will pave the way for more effective and nontoxic therapeutic approaches for anticancer therapies. Historically, phyto-molecules have played a key role in the discovery and development of novel anticancer agents.

DISCUSSION

The molecular docking studies by virtual screening method is a widely used computational analysis in the field of drug discovery. This virtual screening studies facilitate the process of drug discovery by reducing the time, cost, analysis and helps to easily analyse the effectiveness of compound.

This paper focuses on the molecular docking work done by various researchers using the biological components obtained from various plant source. The plants components were selected based on their efficacy in anti-oxidant activity. Bukhari *et al.,* (2013) proved that analogues too where effective in their pharmacological activity and hence they too possess anti- cancerous activity.

Oxidative Stress And Cancer

Oxidative stress is found to be linked with cancer. For a normal functioning of the body, there required a balance between the level of ROS\RNS and the anti-oxidants. The higher level of ROS generated by Warburg effect increases receptor and oncogene activity, which stimulates the growth factor dependent pathway or oxidation of enzymes. This in turn induce genetic instability there by leading to

Cancer.

Catechins

The docking studies on breast cancer gene (BRCA1) by Khare and Thomas, 2014 analysed all the polyphenols in green tea and narrowed down their work over the three important polyphenols Epicatechin 3 gallate with the highest docking score of (-50878989) followed by Catechin (-456872) and Epicatechin (-2853385).

Jankowska *et al.,* 2020 in their work have found that epigallocatechin, epigallocatechin gallate, epicatechin, and epicatechin gallate are able to decrease enzymatic activity of PTP1B phosphatase as well as the viability of MCF-7 cells. Overall, they concluded that Epigallocatechin among the three was the strongest inhibitor of PTP1B activity.

Bharadwaj *et al.,*2019 predicted the significant interaction of secondary metabolites of green tea with p23 protein, and concluded epicatechin and cis.theaspirone as lead bioactive. The docking score for Epigallocatechin gallate, Epicatechin 3 gallate and Epigallocatechin are −10.221, −9.945 and −8.517.

Curcumin

According to Sohilait *et al.,* study (2017), three analogues of Curcumin could successfully dock into COX-2 active site. Their binding energies were -8.2, -7.6, and -7.5 kcal/mol, respectively.

Based on Pushpalatha *et al.,* study (2017), the binding score results of Curcumin with breast cancer proteins HER2, estrogen receptor, ERBB2, tyrosine kinase, and HSP90 were -12.1, -9.92, -8.30, -8.22, and -8.05 kcal mol, respectively. The study revealed that Curcumin showed the highest docking score with HER2 (-12.1 kcal/mol).

Elengoe and Sundaramoorthy 2019 made a study on Molecular Docking of Curcumin with Breast Cancer Cell Line Proteins. Docking analysis showed a strong bond between NFkappa- B-p105 subunit and Curcumin because it had the lowest energy value (3.165) compared with the other orientations.

Resveratrol

Pushpalatha *et al.,* 2017 provided a good data on the glide score of Resveratrol with breast cancer proteins HER2, estrogen receptor, ERBB2, tyrosine kinase and protein HSP90 as -7.56, -8.81, -6.37, -5.99 and -6.47 kcal/mol respectively, and the glide energy being -36.39, -36.23, -33.18, -31.74 and -39.77 kcal/mol respectively.

The work done by Megana and Suneetha in 2019 against breast cancer utilized eleven components including Resveratrol and their related analogues. The best binding compound was found to be CID: 25113755 (an analog of resveratrol) with docking score -7.7.

As per their study of Mathi *et al.,* 2019, Resveratrol had a glide score of -8.787 with VEGFR1 and with a glide score of -8.226 VEGFR2

Geinstein

Mukund *et al.,* 2019 performed molecular docking analysis and in vitro studies to determine whether genistein binds to HIF-1α. Their results proposed that genistein can exert its inhibitory function on HIF-1α by a similar mechanism to FIH-1.

Megana and Suneetha , 2018 work against estrogen receptor alpha came across four analogs of Geinstein. These compounds showed good binding energies and in ADMET (Absorption, Distribution, Metabolism, Excretion and Toxicity) analysis these analogues had excellent pharmacokinetic and drug-likeness properties.

The work done by Mukund *et al.,*2019 predicted binding free energy of NF-κB1-genistein complex to be -6.29 kcal/mol.

Piperine

According to the docking results of Paarakh *et al.,*2015, Piperine had binding energy of −7.6 kJ mol−1 with two hydrogen bonds formed.

Tawani *et al.,*2016 showed that the Piperine had a binding energy of −7.18 kcal/mol to form a stable model of Piperine- Pu24T complex.

Valdelúcia *et al.,*2019 in their study predicted that pose L1 of Piperine at ATP binding site (RMSD= 0.000) had lowest affinity binding energy (-8.2 kcal/mol) and also had hydrophobic interactions (47.96261) with CDK2 while Piperine at pose L2 had the highest hydrophobic predicted interactions (53.99747) with CDK2.

CONCLUSION

The docking result against various proteins is compared as their effect over the cancer cells and the result is drawn based on their glide score as follows. On comparison of the glide score values provided in various paper Curcumin is defined to be highly effective against cancer receptors with the maximum glide score of -12.1, followed by Epigallocatechin gallate with – 10.2 followed by Resveratrol with -8.7, Piperine with -7.6 and Geinstein with -6.29. The effect of the compound, as explained in some of the articles, increased on using their analogue. Hence drug designing is recommended. The physiological study explains that these compounds get easily exercised from the body and hence their effectiveness get reducing on in vivo analysis. So, most of them prefer to use these compounds on targeted drug therapy using nanoparticles. But till now effective scaffold is not discovered. Until a desired drug delivery scaffold is discovered these compounds can be used in combination with existing chemotherapeutic drugs and radiation therapy to reduce their damage to normal cells and at the same time to increase their effect over the cancer cells. The main motto of this article is to impede over the idea of "Food as Medicine". Have healthy food, make better anti-oxidants in body, have a healthy life.

REFERENCES

1. Bharadwaj, S., Lee, K.E, Dwivedi, V.D., Yadava, U., and Kang, S.G. (2019). Computational aided mechanistic understanding of Camellia sinensis bioactive compounds against co.chaperone p23 as potential anticancer agent. *J Cell Biochem.* 1-12.
2. Bukhari, S.N.A., Janatan, B., Jasamai, M., Ahmad, W., Amjad, M.W.B. (2013) Synthetic and Biological Evaluation of Curcumin Analogues. *J. Med. Sci.,* 13(7): 501- 513
3. Elengoe, A. and Sundaramoorthy, N.D. (2019). Molecular Docking of Curcumin with Breast Cancer Cell Line Proteins. *Pharmaceutical and Biomedical Research* · Volume 6. Number 1 DOI: 10.18502/pbr.v6i1.3425
4. Jankowska, A.K., Kostrezewa, T., Musial, C., Barone, G., Lo-Bosco, G. (2020) Green Tea Catechins Induce Inhibition of PTP1B Phosphatase in Breast Cancer Cells with Potent Anti-Cancer Properties: In Vitro Assay, Molecular Docking, and Dynamics Studies. *Antioxidants* 9, 1208; doi:10.3390/antiox9121208
5. Khare, N., Thomas, J., (2014) Docking Studies on Breast Cancer Genes (BRCA1) With Tea Components. National Conference on Synergetic Trends in engineering and Technology (STET-2014) *International Journal of Engineering and Technical Research* ISSN: 2321-0869, Special Issue
6. Mathi, P., Musunuru, N., Adurthi, U., Botlagunta, M. (2019) Comparative in vitro and in silico characterization of anticancer compounds piceatannol, biochanin-A and Resveratrol on breast cancer cells. *Phcog Mag* 15:S410-8.12.
7. Mathur, P., Sathishkumar, K., Chaturvedi, M., Das, P., Sudarshan, K.L., Santhappan, S., Nallasamy, V., John, A., Narasimhan, S., Roselind, F.S. (2020). ICMR-NCDIR-NCRP Investigator Group. Cancer Statistics, 2020: *Report From National Cancer Registry Programme,* India
8. Megana, K.S.N.M, Suneetha, Y., (2018) Molecular screening and analysis of Genistein analogues for the identification of novel therapeutic inhibitors against estrogen receptor alpha. *JIPBS*, Vol 5 (2), 108-112, 2018
9. Megana, K.S.N.M., Suneetha, Y. (2019) In-silico molecular screening of natural plant products for the identification of novel potential chemotherapeutic agents against breast cancer. DOI: 10.13040/IJPSR.0975-8232.10(10).4546-51. ISSN (Online): 0975-8232,ISSN (Print): 2320-5148
10. Mukund, V., Behera, S.K., Alam, A., Nagaraju, G.P., (2019) Molecular docking analysis of nuclear factor-κB and genistein interaction in the context of breast cancer. *Bioinformation* 15(1): 11-17
11. Mukund, V., Saddala, M.S., Farran, B., Mannavarapu, M., Alam, A., Nagaraju, G.P., (2019) Molecular docking studies of angiogenesis target protein HIF-1α and genistein in breast cancer. *Gene* S0378-1119(19)30329-4.
12. Paarakh, P.M., Sreeram, D.C., Shruthi, S.D., Ganapathy, P.S., (2015) In vitro cytotoxic and in silico activity of Piperine isolated from Piper nigrum fruits Linn. *In Silico Pharmacology* 3:9
13. Pushpalatha, R., Selvamuthukumar, S., Kilimozhi, D. (2017). Comparative in silico docking analysis of Curcumin and Resveratrol on breast cancer proteins and their Synergistic Effect on MCF-7 cell line. *Young Pharm*. 2017; 9(4):480-5.
14. Sohilait, M.R., Pranowo, H.D., Haryadi, W. (2014). Molecular docking analysis of Curcumin analogues with COX-2. *Bioinformation.* 13(11):356-9.
15. Tawani, A., Amanullah, Mishra, A., Kumar, A., (2016). Evidences for Piperine inhibiting cancer by targeting human G-quadruplex DNA sequences. *Scientific Reports* 6:39239 DOI: 10.1038/srep39239
16. Valdelúcia, M.A.S.G., Andrade, K.S., Mota N.S.R.S, Bretanha L.C, Felipe K.B., Ferreira, S.R.S., Pedrosa, R.C. (2019). CDK2 and Bcl-xL inhibitory mechanisms by docking simulations and anti-tumor activity from Piperine enriched supercritical extract. *Food and Chemical Toxicology.* S0278-6915(19)30433-8