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Dietary Curcuma, a Powerful Epigenome Modulator in Breast Cancer: an *In Silico* Study

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Abstract

The inhibition of DNA methyltransferase-1 enzyme can strongly decrease the capacity of cells to enhance the tumour-genesis process. Members of the Estrogen-Related Receptors family regulate several elements of cellular metabolism. These are orphan nuclear receptors that regulate a wide range of functional gene networks involved in breast carcinogenesis and the regulation of associated methionine and folate cycles, providing a proven direct relationship to DNA methylation as a result. Moreover, dietary phytochemicals, such as Curcumin, can involve epigenetic modification, which may decrease the development of many types of cancer, especially breast cancer in women. We conducted this study to investigate the effect of Curcuma (PubChem ID: 969516) on the epigenetic modification and inhibition of the DNA methyltransferase-1 (PDB ID: 3PTA) activity and Estrogen-Related Receptors (PDB ID: 1XB7) using Molecular docking approach and computational tools that may inform whether the Curcuma could provide this protective anticancer effect or not. Interestingly, the DNA methyltrasferase1-Curcumin and Estrogen-Related Receptors-Curcumin complexes display a docking score of -6.9 and -7.1 kcal/mol, respectively. Furthermore, Curcumin displays hydrogen, Pi-Cation, Pi-Anion and Van der Waals bonds with active site residues of the targeted molecules. By targeting DNA methylation via the combined inhibition of estrogen-related receptors and DNMT1, our research opens up a new therapeutic path for breast cancer treatment.

Keywords: *curcumin, breast cancer, epigenetic, molecular docking, treatment.*

INTRODUCTION

Because most breast cancer occurrences are sporadic (Momenimovahed and Salehiniya, 2019), elucidating the epigenetic mechanisms governing tumour growth may provide new avenues for prevention and treatment (Jones, 2016). Sporadic breast tumours account for the great majority of breast cancer cases; they are not associated with germline tumour suppressor gene alterations (Anstine and Keri, 2019). Epigenetic changes occur

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in gene expression profiles, not in gene sequences (Baylin and Jones, 2016). Many epigenome-based alterations could happen, such as DNA methylation by DNA methyltransferase (DNMT), histone post-translational changes, and chromatin remodelling (Baylin & Jones, 2016; Jones, 2016). Notably, epigenetic changes such as CpG methylation can be preserved and passed on to progenies during cell division cycles. DNA methylation is maintained in the presence of S-adenosyl-methionine by a group of enzymes termed DNA methyltransferases (DNMT1, DNMT3a, and DNMT3b). S-adenosyl-methionine acts as a methyl donor, allowing cytosine residues at the C-5 position to be methylated to form 5-methylcytosine (Lyko, 2018). Numerous investigations have established that the transcriptional silence of various tumour suppressor genes is caused by aberrant hypermethylation of promoter CpG islands with a CG concentration greater than 55%, which results in a range of solid malignancies (Baylin and Jones, 2016). The accumulation of these changes in tumour suppressor genes leads to the construction of cancer epigenome. Because epigenetic modifications are theoretically reversible, they present enormous options for cancer therapy (Pouliot, *et al*., 2015; Baylin & Jones, 2016; Cheng, *et al*., 2019). Numerous abnormally methylated genes have critical roles in cell cycle regulation and apoptosis, angiogenesis and tissue invasion and metastasis, and molecular pathway signalling of hormones. Therefore, DNA methylation is a crucial target in tumorigenesis, progression and development.

5-azacytidine (azacytidine) and 5-aza-deoxycytidine (decitabine) are the erected inhibitors of cytosine-5 DNA methyltransferases (Cheng, *et al*., 2003). These chemicals act by substituting for the native base cytosine in DNA during replication, resulting in the covalent trapping of DNMTs (Stresemann and Lyko, 2008). Having few disadvantages, they are poisonous, toxic, and extremely unstable in neutral solutions, complicating therapy regimens for these well-established medicines, encouraging the research for natural alternative agents to block and inhibit DNMT activity in cancerous breast cells (Gnyszka, *et al*., 2013). Several gene networks and molecular pathways are controlled by members of the estrogen-related receptor (ERR) family in the setting of breast cancer (Deblois and Giguère, 2013). As orphan nuclear receptors, ERR control a wide range of metabolic gene networks involved in glycolysis and mitochondrial biogenesis (Giguère, 2008). ERR is also a transcriptional regulator of a metabolic pathway closely connected to the methionine cycle (Audet-Walsh, *et al*., 2016). Interestingly, members of the estrogen-related receptor family (ERR alpha) regulate several elements of cellular metabolism in breast cancer. Additionally, ERR is critical for regulating adaptive metabolic pathways (Deblois and Giguère, 2013). Vernier, *et al*. (2020) established a direct relationship between ERR and DNA methylation. Inhibiting ERR activity decreases methionine cycle enzyme expression and significantly decreases DNMT1 transcription, and suppression of ERR increases the susceptibility of breast cancer cells to the anti-neoplastic DNMT inhibitors (Vernier, *et al*., 2020).

On the other hand, Polyphenols have been found to have many biological functions beneficial to human health. Polyphenols reverse DNA methylation and enhance chromatin remodelling or directly interact with enzymes, resulting in de Novo activation tumour suppressor genes or suppression of oncogenes (Russo, *et al*., 2017). Consequently, epigenetics mediated by dietary polyphenols becomes an appealing strategy for disease prevention and treatment. Interestingly, Curcumin, a polyphenolic metabolite found in turmeric, is well known for its substantial anti-inflammatory, antioxidant, and anti-cancer activities and has significant potential as an epigenetic regulator (Hassan, *et al*., 2019). In this study, we discuss the potential effect of Cur-

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cumin to reverse unfavourable DNA methylation through the inhibition of DNA methyltransférase-1 and ERR-DNMT1 as an alternative reliable and safe potential modulator of the breast cancer epigenome.

METHODS

Drug Ability and Pharmacophore Features of Curcumin

Absorption, distribution, metabolism, excretion, and sides toxicity (ADMET) are very important data in discovering and developing new drugs. It helps researchers find drug-like molecules that possess physicochemical properties that might become therapeutic drugs. Moreover, hydrophobicity, molecular size, and the existence of numerous Pharmacophore traits all affect the pharmacokinetics and pharmacodynamics behaviour of molecules in the living organism, including bioavailability. In our study, We obtained the SDF file of curcumin from the PubChem database (ID: 969516), and the geometry and coordinates were optimized in mol2 format using the general Amber force field (GAFF). We used the ADMETlab2.0 webserver was used to obtain physic-chemical features and Pharmacophore criteria of curcumin.

Molecular Docking Analysis

We explored Protein Data Bank (PDB) database to download the targeted proteins 3D structures in PDB format. In this study, we retrieved the 3D structure of DNMT1 and ERRalpha according to their IDs: 3PTA and 1XB7, respectively. The selected macromolecules were purified using BIOVIA Discovery Studio Visualizer. Heteroatoms (water, ions, *etc*.) were deleted, and polar hydrogen was added. DNMT1 and ERRalpha 3D structure was loaded to PyRx software then made into Autodock macromolecules using Vina Wizard. The ligand (Curcumin) was loaded, minimized with 200 steps, and converted to Autodock ligands in Pdbqt format using the built-in OpenBabel program. We visualize the interaction using BIOVIA Discovery Studio Visualizer. We chose the best pose according to the lowest binding score and null deviation.

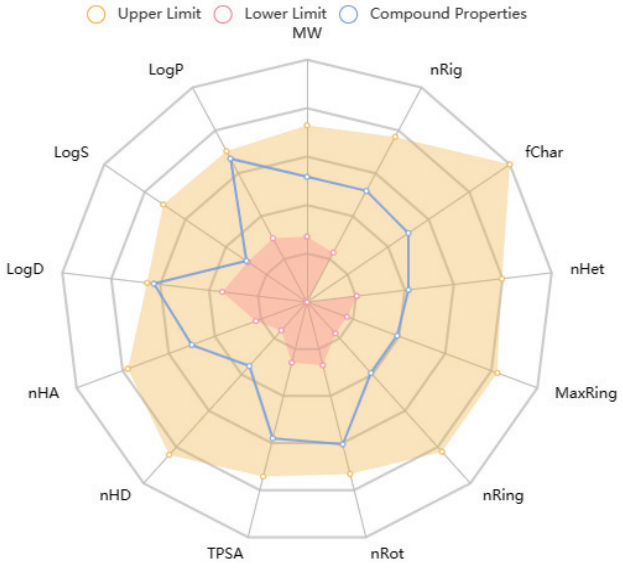

Figure 1. Curcumin properties ranged between upper and lower limits. (Generated by ADMETlab2.0)

Table 1. Physicochemical properties of curcumin.

Physicochemical properties	Curcumin
Molecular weight (MW)	368.130
Volume	381.036
Density	0.966
Number of hydrogen bond donors (nHD)	2
Number of hydrogen bond acceptors (nHA)	6
Number of rotatable bonds (nRot)	8
Number of rings (nRing)	2
Number of atoms in the biggest ring (MaxRing)	6
Number of heteroatoms (nHet)	2
Formal charge (fChar)	0
Number of rigid bonds (nRig)	16
Flexibility	0.5
Number of stereocenters	0
Topological polar surface area (TPSA)	93.060
The logarithm of the solubility in water (logS)	-3.921 log mol/L
The logarithm of the distribution coefficient of n-octanol in water (logP)	2.742 log mol/L
The logarithm of the n-octanol/water distribution coefficients at pH=7.4 (logD7.4)	2.820 log mol/L

RESULTS

Physicochemical Properties and Medicinal Chemistry of Curcumin

Quantitative estimate of drug-likeness (QED) is a drug-likeness indicator based on the desirability concept (Bickerton, *et al*., 2012). QED is calculated by integrating desirability functions related to drug-likeness properties, including molecular weight, log*P*, number of hydrogen bond acceptor and donor, aromatic rings and rotatable bonds, Polar surface area, and numbers of alerts of unfavourable functional areas, as shown in Figure 1. The mean QED is 0.67 for the attractive compounds, 0.49 for the unattractive molecule and 0.34 for the unattractive compounds considered too complex (Dong, *et al*., 2018). Curcumin displays a QED of 0.548 (Empirical decision: Poor).

Considering Synthetic accessibility score, which is intended to evaluate the ease with which drug-like compounds can be synthesized using a mix of fragment contributions and a complexity penalty (Ertl and Schuffenhauer, 2009). The score is between 1 (easy to make) and 10 (very difficult to make). Curcumin displays a Sa-Score of 2.426 (Empirical decision: Excellent).

Based on physicochemical properties and medicinal chemistry results (Table 1), curcumin is an excellent candidate according to the Lipinski rule, so it displays good absorption and

Table 2. Absorption, distribution and excretion profile of curcumin.

Absorption	
The human colon adenocarcinoma cell lines Caco-2 permeability	**-4.834 Log cm/S**
Human intestinal absorption HIA	**>30%**
Distribution	
Plasma protein binding PPB	**99.799%**
Volume Distribution VD (L/Kg)	**0.369**
Excretion	
Clearance (ml/min/Kg)	**13.839**
$T_{1/2}$	**0.948**

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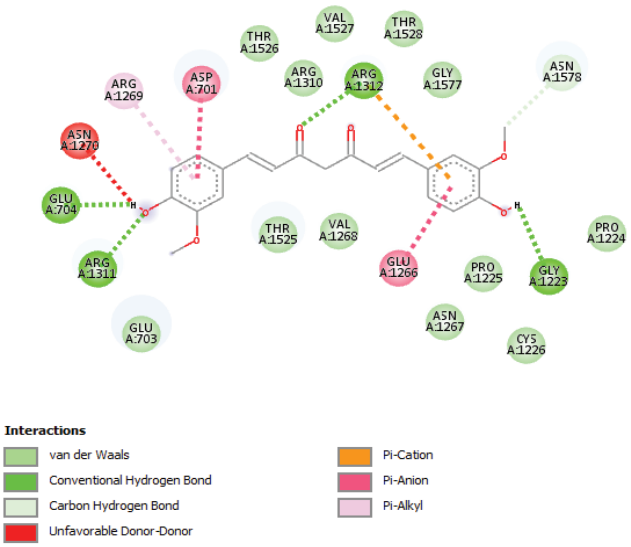

Figure 2: Visualization of intermolecular interactions in DNMT1-curcumin complex.

permeability. According to Pfizer Rule, Curcumin is considered a safe candidate because it displays a low Log *P* (<3) and a high TPSA (>75).

Our candidate also satisfied GSK Rule and the Golden Triangle with a molecular weight lower than 400, Log *P* <4 and Log *D* <5, therefore, it may have a more favourable pharmacological profile (Table 2).

Molecular Docking

DNA methyltrasferase1-Curcumin and ERRalpha-Curcumin complex displayed a docking score of -6.9 and -7.1 kcal/mol and binding free energy of 544.1 Kcal/mol. Curcumin interacts with three residues within the CXXC domain in DNMT1 N-terminal domain: via Pi-Anion and Carbon Hydrogen bound with Asp A: 701, Van Der Waal and Carbon Hydrogen bound with Glu A: 703, and a conventional hydrogen bond with Glu A: 703 (Figure 2).

Regarding the interaction within the C-terminal domain of DNMT1, Curcumin display three Hydrogen bonds (with Arg A: 1312, Gly A: 1223 and Arg A: 1311), one Pi-Cation, Pi-Anion and Pi-Alkyl bound (with Arg A: 1312, Glu A: 1266 and Arg A: 1269 respectively). Twelve Van Der Waals bounds support and enforce the interaction within the DNMT1-Curcumin complex. Furthermore, Curcuma displays four significant interactions with three residues of the enzyme' active site: a hydrogen bond and a Pi-Cation bound with ARG A: 1312, a Van der Waals bond with ARG A: 1310 and a Pi-Anion bound with GLU A: 1266 (Figure 2). In the context of ERRalpha, the intermolecular interaction was forced by a variety of bounds type with several amino acids residues of its active site, as shown in Figure 3.

DISCUSSION

Curcumin is a constituent of the rhizomes of turmeric (Curcuma longa) (Zhang, *et al*., 2015). (Zhang, *et al*., 2015). This Phytochemical has been shown to have anti-inflammatory and antioxidant properties. Hydrophobic molecules like Curcumin are essentially insoluble in digestive fluids. Curcumin has low oral bioavailability due to poor absorption from the gut and quick breakdown in the liver, as observed in human and animal research, and is swiftly removed from the digestive tract

(Madhavi and Kagan, 2014). Under physiological pH conditions (pH 7.2) at 37°C, approximately 90% of Curcumin is degraded within 30 minutes (Kurita and Makino, 2013). Researchers have discovered a rapid conversion to mono-glucuronidated conjugates once Curcumin is reduced to its dihydro and tetrahydro forms. Thus, curcumin-, dihydrocurcumin-, and tetrahydrocurcumin-glucuronides, as well as tetrahydrocurcumin, are the principal in vivo curcumin metabolites documented (Schiborr, *et al*., 2014).

As a result of pure bioactive Curcumin's weak bioavailability and absorption, numerous researchers have concentrated on studies to improve those characteristics' bioavailability, pharmacological activity, and therapeutic chemopreventive utility (Kurita and Makino, 2013). Curcumin and its derivatives are still being studied for their anti-cancer, antioxidant, anti-bacterial and anti-inflammatory wound healing acceleration, and digestion process improvement potential, as well as their analgesic properties. According to current research, numerous natural or synthetic adjuvants can increase the bioavailability of pure Curcumin. In addition, considering Curcumin's hydrophobic qualities, other kinds of conjugates, such as liposomes, polymeric micelles, phospholipid complexes, and microemulsions, can boost its bioavailability and retention time (Kurita & Makino, 2013; Madhavi & Kagan, 2014; Schiborr, *et al*., 2014; Yallapu, *et al*., 2015; Rahimi, *et al*., 2016; Yavarpour-Bali, *et al*., 2019; Gupta, *et al*., 2020; Stohs, *et al*., 2020). However, Curcumin's entire therapeutic potential remains untapped, owing to its poor absorption, fast metabolism, and systemic clearance, all of which contribute to its low bioavailability. Additionally, Curcumin is insoluble, unstable at a range of pH values, and susceptible to photodegradation. Nanotechnology can significantly enhance the therapeutic potential of medicinal compounds with impaired biopharmaceutical characteristics (Gupta, *et al*., 2020).

Interestingly, DNA methylation has emerged as a promising potential therapeutic target for cancer. Moreover, Curcumin, one of nature's beneficial substances, is being studied for its ability to influence cancer cells' epigenetic machinery. Curcumin has been found in multiple studies to exert potent anti-cancer effects on epigenetic mechanisms in breast cancer. Mirza, *et*

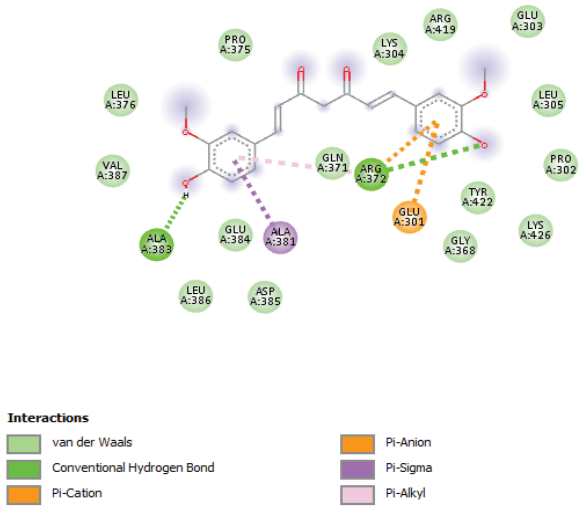

Figure 3: Visualization of intermolecular interactions in ERRalpha-Curcumin complex.

al. (2013) and Chatterjee, *et al*. (2019) reported a significant reduction in mRNA and protein level of DNMT after application in the MDF-7 cell line.

Experts and we have proven that Curcumin may play a critical role in regulating epigenetic modifier genes, hence aiding in the prevention of numerous malignancies such as breast cancer. In 2009, based on molecular docking results, Liu, *et al*. proved that Curcumin covalently blocks DNMT1' catalytic thiolate to exert its inhibitory effect, as shown in our study. Moreover, they observed in *in vitro* tests that Curcumin can inhibit the activity of CpG Methyltransferase M.SssI, which is a DNMT1 analogous with a structurally similar catalytic domain (Liu, *et al*., 2009).

Methylation of CpG promoter regions alter gene transcription and, therefore, enhance genome stability and genetic imprinting leading to the development of Many cancers such as intestinal and breast maligned tumours (Sheaffer, *et al*., 2016; Duijf, *et al*., 2019). Hypomethylating drugs are efficient to restore normal gene expression and differentiation and apoptosis patterns in cancer cells (Stresemann & Lyko, 2008; Jones, 2016). Bioactive components derived from dietary supplements, such as the powerful hypomethylating agent curcumin, may be interesting candidates for cancer prevention or treatment (Liu, *et al*., 2009). Similarly, Curcumin has been demonstrated in studies on the Prostate LNCaP Cells to suppress or increase the expression of several genes involved in the regulation of the cell cycle, apoptosis, cell adhesion, phosphatases, and kinases such as Neurog 1 (Shu, *et al*., 2011) and nuclear factor erythroid-2 (Nrf2) (Khor, *et al*., 2011).

On the other hand, certain studies using pyrosequencing demonstrated that Curcumin has no demethylation activity of tumour suppressor genes in leukemia. Still, its epigenetic action for cancer treatment was increased when 5-azacytidine and decitabine were used sequentially (Hassan, *et al*., 2016). Therefore, Curcumin has demonstrated that it can be used as a chemosensitizer in cancer treatment.

In a recent study conducted by Yu, *et al*. in 2015, the expression of DNMT1 and 3 (A and B) on breast cancer and breast fibroadenoma cases were studied. DNMT1 expression was considerably higher than in fibroadenoma samples, and it was linked to BRCA1 promoter hypermethylation and transcriptional downregulation (Yu, *et al*., 2015). Most cancer-associated fibroblasts showed an increase in DNMT1 expression when compared to their normal fibroblast counterparts. When DNMT1 was overexpressed, it triggered the proliferation of normal breast fibroblasts, accelerating the cancer-promoting effects (Al-Kharashi, *et al*., 2018).

Breast cancer is the greatest cause of cancer death among women globally (Feng, *et al*., 2018). Predominantly a hormone-dependent condition that can be modulated by the status of steroid hormones such as estrogen and progesterone (Elbasyouni, *et al*., 2021). Unfortunately, the appearance of hormone-resistant cancerous cells over years of treatment is a significant issue confronting patients with breast cancer (Lei, *et al*., 2019).

Moreover, ERR may contribute to establishing a glycolytic profile necessary for the proliferation of abnormal growth cells in normal tissues with a high energy requirement and malignancies, encouraging cellular proliferation (Deblois and Giguère, 2013). The findings suggest that ERR may contribute to a metabolic shift away from normal mitochondrial oxidative phosphorylation and toward aerobic glycolysis characteristic of cancer cells, a phenomenon known as the Warburg effect (Cai, *et al*., 2013). This metabolic shift results in increased glucose consumption and ATP production (Deblois and Giguère, 2013). The role of ERR in breast cancer has received much attention, as they are orphan nuclear receptors connected to estrogen receptors. ERR expression is frequently high in breast cancers, prevalent in tumours with a poor prognosis (Cai, *et al*., 2013). Vernier, *et al*. (2020)

has proved that *in vitro* proliferation of breast cancer cells is suppressed by dual inhibition of ERR and DNMT1. Accordingly, ERR inhibition using Curcumin may increas the efficacy of DNMT1 inhibitors in preventing the growth of breast tumours and vice versa.

CONCLUSION

Dietary curcumin-targeted epigenetics becomes an appealing strategy for breast cancer prevention and treatment through chromatin remodelling and modulation of the transcription factors' accessibility via its capacity to induce DNMT1 repression, ERR alpha blockage, DNMT1-ERRallpha crosstalk suppression, and tumour repressor genes expression enhancing. While there are compelling reasons to believe that targeting ERR for breast cancer treatment is realistic, the biological repercussions of altering ERR activity to affect cancer cell metabolism should be carefully explored in a systemic context. In this study, we used an *in silico* pharmacology paradigm. This field is ongoing and provides a vast array of prospects that will emerge of new targets, and eventually lead to compounds with anticipated and predicted biological activity for these novel targets. Nevertheless, the main challenges in future nutria-epigenomic expertise of curcumin as an epigenetic anti-cancer agent is increasing its bioavailability to enhance the efficacy of the metabolites and determine its role alone or in combination with other turmeric-derived compounds or other polyphenols. Whilst there is much more to be done, our study and the available data so far indicate that curcumin can be a potential target/candidate of drug development against breast cancer, and further studies of this research can be conducted through lab work and more experiments.

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