IN SILICO STUDY OF GINGER EXTRACT AND CAPSAICIN EFFECTS ON PROSTATE CANCER

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*Abstract***.** Ginger extract and capsaicin are used as phytochemical drugs. These components can affect the growth of prostate cancer and decrease its rate of development without affecting the normal cells comparing to current chemotherapy drugs. And whereas the more suitable molecular structure, will result in more drugs that are potent. The aim of this study is to predict the binding of capsaicin, 6-gingerol, and 6-shogaol to the over expressed androgen receptor (NR3C4) using an *in silico* model. The docking analysis was performed using SCIGRESS 3.0 software. The results showed that the capsaicin and 6-gingerol have close values of binding energy, while 6-shogaol takes relatively higher value, 6-shogaol having the strongest binding energy (≈ –181 kcal/mol) to the active sites of NR3C4. The 6-shogaol has the capacity to establish 8 hydrogen bonds with NR3C4 receptor. Therefore, 6-shogaol have a potential to be developed as an efficient treatment for prostate cancer.

Key words: Ginger, prostate cancer, androgen receptor, 6-shogaol.

INTRODUCTION

Prostate cancer is the most common non-cutaneous malignancy in American men, affecting one in six men. It is estimated that in the USA, one new case occurs every 2.4 min and a death, every 16.4 min from prostate cancer [22, 33]. The weight of prostate changes with disease, as individuals who died after protracted disease had lower prostatic weight, while periurethral adenomas was associated with a higher weight of the prostate proper [19]. Prostate cancer is a very slow growing cancer and manifests symptoms mainly in its late stage [4, 28]. But, when prostate cancer starts to grow, it quickly spreads into the whole body. The prostate cancer seems to be caused by the change in the cellular DNA. The DNA changes can be either inherited from a parent, or can be provoked during a person's lifetime. Prostate cancer can be treated in its early stages with very good chances for survival. Common treatments of prostate cancer are radiation therapy, surgery, hormone

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therapy, chemotherapy, and vaccine treatment [14, 24]. Here, we are interested in prostate cancer treatment using natural components such as phytochemical compounds. Capsaicin and ginger are phytochemical extracts related to the growth inhibition of prostate cancer cells [16, 26]. Capsaicin is the active ingredient in red-hot chili peppers [10]. It is a member of the vanilloid family of alkaloids. It was shown that capsaicin plays an important role in suppressing prostate cancer cells [6]. Oral uptake of capsaicin can provide pain for oral mucositis in patients undergoing such a chemotherapy [2]. Ginger extract is an excellent source of several bioactive phenolics, including non-volatile compounds such as gingerols, shogaols, paradols and zingerone [30]. Ginger has been known to display anti-inflammatory [29], antioxidant [18], and antiproliferative activities [32], indicating its promising role as a chemopreventive agent. Here, we are interested in prostate cancer treatment using capsaicin and two ginger extract compounds (6-gingerol and 6-shogaol), which have been proved to affect the growth of prostate cancer with minimum side effects as compared to other treatments. It was noticed that 6-gingerol has induced dose- and time-dependent inhibition of cell viability in pancreatic cancer cells [9]. 6-shogaol is a constituent of ginger and is similar in chemical structure to 6-gingerol. It is produced when ginger is dried or cooked [13]. Shogaols are artifacts formed during storage or by excess heat, probably created by a dehydration reaction of the gingerols. The ratio of shogaols to gingerols sometimes is taken as an indication of product quality [27]. 6-shogaol inhibits mouse and human prostate cancer cells in culture, accompanied by induction of apoptosis. 6-shogaol has activity and biochemical properties that makes it a potential natural chemopreventive agent in prostate cancer with a low toxicity [35].

The androgen receptor, also known as NR3C4 (nuclear receptor subfamily 3, group C, member 4), is a type of nuclear receptor that is activated by the binding of the androgenic hormones such as testosterone from the cytoplasm which is translocated into the nucleus [1, 11, 25]. The main function of NR3C4 is as a DNA binding transcription factor that regulates the gene expression. Also, the androgen regulated genes are critical for the development and maintenance of the male sexual phenotype [5]. Over production of androgen can be detected in circulating tumor cells of metastatic prostate cancer patients [31]. The androgen receptor is important for therapeutic target in prostate cancer and therefore, many inhibitors are needed to be developed [36].

SCIGRESS 3.0 is a molecular modeling software suite that can dock the ligands into active sites [37] to all types of molecular systems using linear scaling semi empirical quantum methods for protein optimization and ligand docking. It enables researchers to study and design wide range of molecular systems. Its potential work is a knowledge-based approach from structure information of known protein ligand complexes contained in the Protein Data Bank. It has been demonstrated a significant correlation between experimental binding affinities and its computed score for diverse protein-ligand complexes.

MOLECULAR MODELING AND DOCKING STUDY

LIGAND PREPARATION

The chemical structures of capsaicin, 6-shogaol and 6-gingerol as tested ligands, were collected from literature [7, 12, 20, 21]. The chemical structures for capsaicin, 6-shogaol, and 6-gingerol are shown in Figure 1.

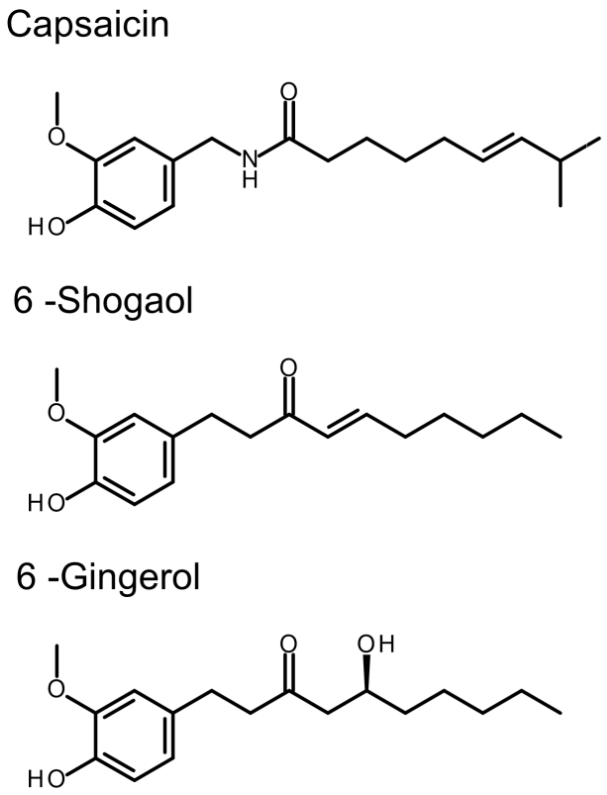

Fig. 1. Chemical structures of capsaicin, 6-shogaol, and 6-gingerol [23]. One can notice that all the three compounds are very similar. However, there are some minor differences in their aliphatic tails which explain their different interaction with the androgen receptor.

TARGET PREPARATION AND VALIDATION OF DOCKING METHOD

The structure of NR3C4 (3D, 1T73) was taken from Protein Data Bank (rscb.org). PyMOL programs from www.pymol.org [34], used to virtual screening of ligands against NR3C4. In the present study, NR3C4 site residues were the target of the ligands. The interaction between these molecules was analyzed using

SCIGRESS 3.0 software. The binding energies of the structures are minimized by geometry-optimization using MM3 force field followed by semi-empirical parameterization method 6 (PM6) and, finally, by quantum mechanics using density function theory (DFT) with B3LYP basis set. The vibrational IR spectra are calculated for each structure at the same level of computation to ensure that the structures are not in a transition states (i.e., not imaginary structures) [15].

RESULT AND DISCUSSION

The interaction between the over expression of NR3C4 in prostate cancer and the ligands is a competitive process. The chemical structures of capsaicin, 6-shogaol, and 6-gingerol, as already was illustrated in Fig. 1, although very similar, however, are differences. Therefore, the SCIGRESS 3.0 software was used to predict the most fitting drug of them (Fig. 2). The ability of ligands to interact with NR3C4 can be predicted from the docking score. The scoring function of the interaction between androgen receptor and each drug is an indication for the free binding energy. Our data show that 6-shogaol has the lowest binding energy, in fact, the greatest in absolute value (≈ –181 kcal/mol), which proves its high affinity towards NR3C4, while the binding energy for 6-gingerol and capsaicin are ≈ –147 kcal/mol and ≈ –144 kcal/mol, respectively, that is, about 80% from that of 6-shogaol.

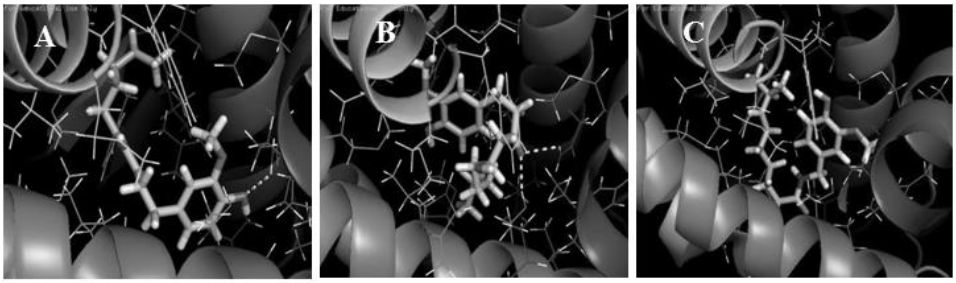

Fig. 2. The prediction binding site of the lowest docking energy conformations of A) capsaicin, B) 6-gingerol, and C) 6-shogaol in NR3C4. These images were obtained by applying the SCIGRESS 3.0 software. Domains of the NR3C4 protein are represented in gray. The hydrogen bonds (dashed lines) formed between capsaicin, 6-gingerol, and 6-shogaol with amino acids chains of NR3C4.

Comparing the structure of each drug, before and after the interaction with androgen receptor, we found that each drug changes its conformation to enhance binding with the receptor, in order to reach the minimum energy and achieve stability.

Figure 2 shows that all three drugs can fit into the active sites of the receptor, as obtained from the scoring function value. 6-gingerol and capsaicin have close binding energy values, while 6-shogaol has a relatively higher (in absolute value) energy.

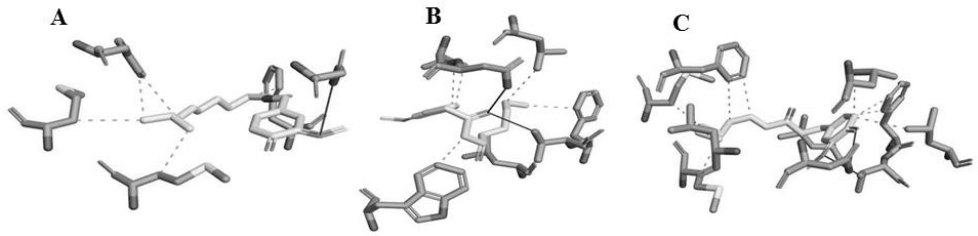

Fig. 3. The hydrogen bonds are represented by dashed lines in each receptor-drug complex. A) Capsaicin form 4 hydrogen bonds with the receptor, B) 6-gingerol form 5 hydrogen bonds, while C) 6-shogaol form 8 hydrogen bonds.

Dashed lines in Figure 3 represent hydrogen bonds in each receptor-drug complex. Capsaicin form 4 hydrogen bonds with the receptor, as it was known that capsaicin can potently suppress the growth of human prostate carcinoma cells both in vitro and in vivo. The anti-proliferative activity of capsaicin correlates with oxidative stress induction and apoptosis [8]. 6-gingerol form 5 hydrogen bonds, while 6-shogaol form 8 hydrogen bonds. Therefore, it is clear why capsaicin and 6-gingerol have close binding energy values, while that of 6-shogaol is higher, in absolute value. Hydrogen bonds are not the only binding forces, but they are more significant than the electrostatic forces. Whole ginger extract exerts significant growth-inhibitory effects in prostate cancer cells by inducing caspase pathways in mitochondria producing apoptosis in human prostate cancer cells [17]. It is important to note that 6-gingerol is found in fresh ginger roots, while 6-shogaol is found only in dried ones. This may be taken into consideration for a prostate cancer patient or in case of herbal treatment, that dried ginger is relatively more useful than fresh ginger, because the active component in dried ginger get into prostate cancer cells in larger quantities.

This theoretical study shows that the androgen receptor can interact with capsaicin, 6-gingerol, and 6-shogaol. The change in the growth of human prostate carcinoma cells when exposed to capsaicin, 6-gingerol, and 6-shogaol can be approached by this study. They may cause signal transduction proteins, changes in cell function, such as changes in ion transport or changes in gene transcription [3]. Their effects can lead to suppress the growth of human prostate carcinoma cells.

CONCLUSION

All studied drugs show a good interaction with androgen receptor and form stable drug-receptor complexes. Our results suggest that capsaicin, 6-gingerol, and 6-shogaol can be used in drug delivery to treat prostate cancer, 6-shogaol being the most efficient, judging after their interaction with androgen receptor.

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