Predication the suppressing human oral cancer cell line by curcumin through the research of Fas receptor

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Abstract—Curcumin is commonly applied as food coloring and seasoning but recent research show that curcumin is able to enhance the activation of Fas receptor to the cancer cell apoptosis through extrinsic pathway. Oral cancer results from the particular habit of chewing betel nuts that Taiwanese have. The additive in betel nuts (such as lime) is the main reason that increase the cancer rate of people chewing betel nuts and further increase the death rate gradually. The major treatments for oral cancer are still chemotherapy and surgery. This research expects to perform the computer simulation to calculate the activity of curcumin to oral cancer as medicine. The pharmaceutical activity are evaluate by the score from docking procedure perform by simulation program. We hope this experiment can be the evidence that curcumin can practically be used as medicine for oral cancer therapy in future.

Keywords- curcumin; Fas receptor; cell apoptosis; oral cancer; docking

I. MOTIVATION AND PROBLEMS

The occurrence rate and death rate of oral cancer increased year by year according to the statistic value from Department of Health. The statistical report published by DOH in 2009 indicates that the death rate of oral cancer rank number 6 in Taiwan among all 10 kinds of cancer and the occurrence rate rank number 4 in male among 10 kinds of cancer. These values persist very high in recent years. Tongue cancer and buccal cancer are the cancer with highest frequency in oral cancer. These two cancers take almost 90% of oral cancer and tongue cancer take 60% among all which is the highest. The effect of treating tongue cancer is far less than buccal cancer which makes the five year survival rate of oral cancer decrease gradually. Curcumin is able to activate the apoptosis pathway to make cancer cell apoptosis and achieve the anti-cancer effect. The purpose of this research is to simulate the pharmaceutical activity and evaluate the degree of activity to determine: (1) whether curcumin is able to activate cell apoptosis to oral cancer cells? (2) Is the pharmaceutical activity of curcumin to oral cancer cells higher than those medicines on market?

II. LITERATURE REVIEW AND DISCUSSION

A. Introduction to oral cancer

Oral cancer is a subtype cancer of head and neck with the tumor tissue grow randomly around oral cavity and the nidus can be originates from any oral cavity tissues or metastasis from other nidus (regardless of distance) but about 90% are squamous cell carcinoma. The most common sites for oral cancer to occur is on tongues but others may locate on the bottom of oral cavity, inner part of cheek,
gums, lips, jar, or both sides on neck. Most oral cancer looks very similar and name as squamous cell carcinoma under microscopic view. This is often malignant and spread rapidly. The happen of oral cancer is related to the long term stimulation at oral cavity and result in cell degeneration. The chewing of betel nuts in Asia countries (especially in Taiwan) is the major cause. Others such as: smoking, drinking, syphilis, over sunlight exposing, long term nutrition deficiency, bad oral hygiene, taking foods too hot or too spicy for long term, sharp dental caries, wrecked dental prosthesis, inappropriate denture and teeth braces. These are all possible reasons for oral cancer. The alkaloid contains in betel nuts is carcinogenic and also the major factor for accelerating cell mutation. About 90% of oral cancer patients in Taiwan have the habit of chewing betel nuts. Smoking is also one of the major ringleaders to cause oral cancer. Furthermore, some reports even indicate that people who use tobacco pipe are easier to meet lip cancer. Those people with chronic or considerable drinking habit can also increase the risk of meeting oral cancer.

Clinical symptoms of oral cancer (http://oralcancerfoundation.org/facts/cancer.htm):
- White and Red Patches on the surface of mucous membrane in mouth.
- Blister in mouth with no reason. Discomfort may not take place while touching.
- Unhealed mucous canker over two weeks
- Bleeding in mouth with no reason. Neck mass.
- Tongue activity restricted and the loss of feeling or having numbed on the half side of tongues.

B. Stages of oral cancer

The stages of cancer are often divided in accordance to the size of tumor, lymph nodes metastasis and the metastasis from distant place. Beside lymph nodes on neck are easier to metastasis, the bones, liver, and skin). Tumors intrude into neighboring tissue (such as: pass through the outer layer of bone and even deep into the inner muscle, frontal sinus, and skin).

1. The number of neck lymph node metastasis is over one (regardless of happening on the same side, other side, or both side of the primary nodule) or the maximum length of lymph nodes is larger than 3cm.

2. Despite the size of tumor or metastasis of lymph nodes, distal metastasis takes place counts.

C. Recognized therapy and medicine on market for oral cancer

Surgery, Radiotherapy, Chemotherapy, Immunotherapy, gene therapy, or other biological agent therapy are still immature and still under development.

D. Cell apoptosis

Cell apoptosis is one of the steps in programmed cell death and also called as type I cell death which is initiative and programmed death method. Cell apoptosis mostly result from the physiological or pathological reason. The cell volume will decrease and the DNA will be degenerated into small segments by endonuclease during cell apoptosis. Tissues can clean those unnecessary or damaged cells to sustain the function integrity by cell apoptosis. 

E. Fas receptor

Fas receptor (FasR) is a kind of death receptor on cell surface which can initiate the programmed cell death (cell apoptosis) through extrinsic pathway. Another one is the intrinsic pathway (mitochondria). These are two types of cell apoptosis. FasR can also be called as CD95 which is the member of superfamily of Apo-1 and TNF receptor [5,9]. FasR is located on the 10th chromosome in human and 19th chromosome in rate. There are similar sequences in most mammal chromosomes [10]. The death-inducing signaling complex (DISC) formed by Fas can combine with receptor (FasL). FasL trimer makes the adjacent FasR to shape into trimer on the membrane and active the DISC below to attract and combine with Fas associated death domain (FADD). FADD will further attract pro-caspase 8 for combination and cut the pro-caspase 8 into caspase 8. The caspase 8 will further cut and activate pro-caspase, therefore the caspase cascave magnifying effect is aroused to reinforce the activation of caspase 3. The caspase 3 will destruct the structural proteins such as cytoplasmatic protein and finish the apoptosis (reference: Eksp Klin Farmakol. 2010 Dec;73(12):44-9).

F. Introduction of Curcumin

Curcumin, which is a kind of yellowish pigment extract from roots of turmeric. 70% of Curcumin is composed of curcuminoid which takes 3%~6% of turmeric (http://curcumin-turmeric.net/). The application of curcumin is far from now which curcumin were used as nature pigment in food industry. Beside, curcumin is stable to reductant and with good coloring ability but sensitive to light, heat and iron ions. The major application the coloring for canned food, sausages, and stewed soy sauce produce. Curcumin is also applied as acid-base indicator [pH 7.8 (yellow)-9.2 (reddish brown)] (http://www.lookchem.cn/4150/productproperty.html). Curcumin have critical value and pharmaceutical action such as decreasing the blood fat, anti-oxidation, anti-inflammatory, and anti-atherosclerosis. Research in 2004 even found that curcumin can be use to suppress the activity of HIV-1 integrase and applied in AIDS clinical trial [11]. Beside the above functions, curcumin is also proved to have the pharmaceutical activity to anticancer and the effect of suppressing carcinoma have been verified repeatedly during many animal experiments [12-15].

III. METHODOLOGY[14-18]

The program suite used during experiment is Discovery Studio 2.5 from Accelrys Software and the “Docking and Score” inside. The condition to evaluate the score are PLP1, PLP2 and PMF which are used to evaluate the advantages over receptor ligand poses (poses after receptor combine with ligand) by Dock Score. Two types of scoring method from Dock Score are list as below, the first is referring from the force-field and the second one is from Piecewise Linear Potential function (PLP) (http://en.wikipedia.org/wiki/Macromolecular_docking).

- Equation (1):DockScore (forcefield) = - (ligand/receptor interaction energy + ligand internal energy)
Equation (2): 

\[ \text{DockScore(PLP)} = - (\text{PLP potential}) \]

IV. RESULTS AND DISCUSSIONS

This research hopes to calculate and simulate the pharmaceutical activity of anticancer effects of curcumin to oral cancer and get quality evaluation results. The preliminary results are listed as figures and tables below. The receptor applied is curcumin-derivatives: bisdemethoxy curcumin; target protein: FAS/FADD death domain assembly (Protein PDB ID: 3OQ9) to perform Docking and Score.

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Figure 1. Experimental flow-charts overview.

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Capitalize only the first word in a paper title, except for proper nouns and element symbols.

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Figure 2. (a) Bind Site-A & Ligand poses (I) (b) Bind Site-A & Ligand poses (III) (c) Bind Site-B & Ligand poses (I) (d) Bind Site-B & Ligand poses (II) (e) Bind Site-B & Ligand poses (III).