Computational ligand–receptor docking simulation of piperine with apoptosis-associated factors

Adrianne Dien-Yu Vong[1], Siaw-San Hwang[2], Xavier Wezen Chee[2], Edmund Ui-Hang Sim[1]*

[1]Faculty of Resource Science and Technology, Universiti Malaysia Sarawak, Sarawak, Malaysia.
[2]School of Chemical Engineering and Science, Faculty of Engineering, Computing and Science, Swinburne University of Technology, Sarawak, Malaysia.

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ABSTRACT

Although widely known for its antioxidant properties, piperine's (a compound from the pepper plant) physiologic involvement in apoptosis (programmed cell death) is unclear. As a prerequisite to unravel its role in this process, computational approaches simulating ligand–receptor docking are sought. Herein, we report the simulated binding of piperine with major apoptotic proteins via combined deployment of AutoDock suite (AutoDock Vina), PyMOL, and LigPlot + software. Our results demonstrated varied binding affinity toward the different apoptosis-associated proteins with a higher to lower affinity pattern in the order of TNFR-1 > Caspase-3 > TNF-α > Caspase-8 > Bcl-2 > Caspase-9 > Bax. Docking scores for all receptor–ligand interactions indicate a strong likelihood of impromptu receptor–ligand binding. Molecularly, the simulated analysis revealed hydrophobic interactions in all receptor–ligand models studied. Receptor–piperine complexes involving TNFR-1 and Caspase-8 showed single hydrogen bonding whereas amino acid residues of TNF-α exhibited double hydrogen bonding to piperine. In the TNFR-1-piperine complex (receptor–ligand docked model with strongest binding affinity) the hydrophobic interaction involves amino acid residues of SER74, LYS75, ASN110 (2), THR94, CYS96, VAL95, and PHE112. Our findings provide novel *in silico* evidence of piperine's binding affinity toward apoptosis-associated proteins and the high likelihood of its influence on apoptosis reaction via the extrinsic pathway.

1. INTRODUCTION

Piperine, a major bioactive compound from the fruits of pepper (*Piper nigrum*), has anti-oxidant, anticarcinogenic, anti-inflammatory, and antimicrobial properties [1]. Black pepper is used in traditional medicine to treat health problems, such as intermittent fever, muscular pain, and migraine [2]. Research conducted to investigate the cytotoxicity effect of piperine on cell lines of epithelial origin such as cervical, oral, colon, and prostate cancer concluded that the piperine compound shows toxicity to these cell lines by increasing the level of reactive oxygen species (ROS), induces DNA fragmentation, and triggers apoptosis reaction [3–6].

Evasion of programmed cell death (apoptosis) by cancer cells via inhibition of caspase activity, upregulation of the antiapoptotic proteins, mutation of the proapoptotic proteins, and loss of the apoptotic activity is amongst the hallmarks of cancer [7]. In fact, the anti-inflammatory nature of apoptosis is crucial for the eradication of virally infected potential cancer cells [8]. Therefore, targeting apoptosis is an effective nonsurgical treatment for cancer. Apoptosis is regulated by two main pathways, the intrinsic and extrinsic pathways. Basically, the intrinsic pathway is controlled by the Bcl-2 family member of proteins which comprises antiapoptotic and proapoptotic proteins that cointeract [9,10]. Proapoptotic proteins, such as Bad and Nova, are apoptosis effectors that work in concert with antiapoptotic proteins (Bcl-2, Bcl-xL, and Mcl-1) and other proapoptotic proteins (Bax, Bak, and Bok) to mediate caspase-associated apoptotic mechanisms [9,10]. The extrinsic pathway, on the other hand, is stimulated by extracellular signals from death ligands from the tumor necrosis factor receptor superfamily (TNFRSF) where TNF-α, TNFR1/CD95, and Fas are amongst the common players in the

Corresponding Author
Edmund Ui-Hang Sim, Faculty of Resource Science and Technology,
Universiti Malaysia Sarawak, Sarawak, Malaysia.
E-mail: uhsim @ unimas.my