Chapter 4
Application of Molecular Docking in Studies on the Binding Mechanism of Three Enzymes with Natural Products

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ABSTRACT

Enzymes play an important role in many biologically relevant processes and are some attractive targets in the therapy and pharmaceutical research. The interaction between drugs and enzymes in vitro might account for a variety of biological processes and has attracted scientists' great interest for several decades. Investigation of the interaction can explore their mechanism of biological activities and provide useful knowledge for optimizing molecular structure of drug, prescriptions and route of administration and it can also provide the information for their bioavailability and bioactivity. In this chapter, the bindings of natural products (including flavionoids and coumarins) with three enzymes, including pepsin, hyaluronidase and acetylcholinesterase, were investigated by fluorescence spectroscopy and molecular docking. The present studies provide direct evidence at a molecular level to understand the mechanism of inhibitory effect of natural products against enzymes.

1. INTRODUCTION

Enzymes play an important role in many biologically relevant processes and are some attractive targets in the therapy and pharmaceutical research (Li, Zhang, Xu, & Ji, 2011). The nature and magnitude of drug-enzyme interaction significantly influences the biological behaviors of the drug, such as the metabolism, distribution, toxicity and the effectiveness of drug. The study on the drug-enzyme interaction is very

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useful to explore the action mechanism and metabolic process of drug, which can benefit for providing useful knowledge for optimizing molecular structure of drug, prescriptions and route of administration, and the information for their bioavailability and bioactivity (Ma, Yin, Liu, & Xie, 2011). In recent years, several public and scientific interests have been focused on the interactions of drugs with some enzymes (Yadava, Singh, & Roychoudhury, 2013; Cui, Yang, & Li, 2015; Masood et al., 2015; Yadava, Gupta, & Roychoudhury, 2015; Shanmugaraj, Anandakumar, & Ilanchelian, 2015; Yadava, Shukla, Roychoudhury, & Kumar, 2015), including pepsin (Shen et al., 2015; Ying et al., 2015), hyaluronidase (Liu et al., 2013) and acetylcholinesterase (Sinko, Brglez, & Kovarik, 2010; Dounin, Constantinof, Schulze, Bachmann, & Kerman, 2011; Puiatti et al., 2013).

Flavonoids belong to a major group of polyphenols that possess a common diphenylpropane ($C_6C_3C_6$) skeleton. According to the variations in their heterocyclic C_3-ring, flavonoids can be categorized mainly into flavones, flavonols, flavanones, flavanol, isoflavones, chalcones, aurones and anthocyanidins (Teillet, Boumendjel, Boutonnat, & Ronot, 2008). Until now, more than 8000 varieties of flavonoids have been identified in fruits, vegetables and other plant sources, many of which are responsible for the attractive colors of flowers, fruits and leaves (de Groot, & Rauen, 1998). Flavonoids exhibit extensive biological effects and broad-spectrum pharmacological activities, and intake of plants and their products which are rich in flavonoids has been associated with a reduced risk of various diseases (Hertog, Feskens, Hollman, Katan, & Kromhout, 1993; Blot, McLaughlin, & Chow, 1997; Duthie, Duthie, & Kyle, 2000). Recently, several scientists have found that some flavonids can inhibit the activity of enzymes in some biological processes and can be used as inhibitors of these enzymes, such as xanthine oxidase (Lin, Zhang, Liao, Pan, & Gong, 2015), beta-ketoacyl acyl carrier protein synthase I(Ghalia, & Noura, 2015), human lactate dehydrogenase (Bader et al., 2015), deoxyxylulose phosphate reductoisomerase (Tritsch, Zingle, Rohmer, & Grosdemange-Billiard, 2015), carbonyl reductase 1 (Arai et al., 2015) and aldose reductase (Utpal, Tanusree, Debanjan, & Sudhan, 2015). Flavonoids can bind to enzymes according to different mechanisms owing to their multiple binding possibilities: hydrogen bonding, hydrophobic interactions, metal chelation and π-π stacking, with a tendency to occupy hydrophobic pocket (Dangles, & Dufore, 2005). However, to the best of our knowledge, little concerns were placed on the binding of flavonoids to pepsin and hyaluronidase and their effect on the activity of these enzymes.

The general methods for the investigation of interaction between drug and biomacromolecules *in vitro* mainly include fluorescence (Hui, Quan, Jian, Jian, & Ming, 2008; Yang, Hu, Fan, & Shen, 2008; Stan et al., 2009), fourier transform infrared (FT-IR) (Qin, Xie, & Liu, 2007; Li, Yao, Jin, Chen, & Hu, 2007), UV absorption (Gentili, Ortica, & Favaro, 2008) and circular dichroism (CD) spectra (Mahesha, Singh, Srinivasan, & Rao, 2006), nuclear magnetic resonance (NMR) (Richard, Lefeuvre, Descendit, Quideau, & Monti, 2006), mass spectrometry (MS) (Liu, Wang, Cai, & Lee, 2008), capillary electrophoresis (CE) (Lu, Ba, & Chen, 2008), electrochemistry (EC) (Lin et al., 2008), etc. Each method can characterize the mechanism of drug-protein interactions on one or several aspects. FT-IR and CD spectra are usually used to analyze protein conformation. NMR is the primary analytical tool to obtain structural information relating to protein-ligand binding sites, dissociation and binding constants at atomic level and protein conformation changes induced by complex formation. However, the NMR instrument is expensive and complicated and is not suitable for most scientists. MS is emerging as powerful tools for studying non-covalent interactions including protein interactions with drugs, metal ions, or other peptides in recent years. But MS does not provide direct structural data. Although high sensitivity and small amounts of samples have been obtained in CE and EC methods, a drawback of these methods ap-