

RESEARCH ARTICLE

Molecular docking studies of glycyrrhetic acid derivatives as anti-colorectal cancer agents

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Abstract: In this study, the anti-CRC activities of 40 glycyrrhetic acid derivatives were proposed and evaluated by the molecular docking method, which allowed the flexibility of both ligand-receptor, with twelve CRC-related targets. The proposed derivatives, which clearly distinguish isomers at position 18 as well as the different tautomers, were divided into five groups including (1) glycyrrhetic acid and its oxidation derivatives, (2) glycoside derivatives, (3) 3 β -amine derivatives, (4) five-membered heterocyclic ring-combined derivatives, and (5) six-membered heterocyclic ring-combined derivatives. Finally, we selected four out of twelve proposed targets related to CRC with good binding affinities to the proposed glycyrrhetic acid derivatives including Epidermal Growth Factor Receptor (EGFR), Focal Adhesion Kinase (FAK), Lactate Dehydrogenase A (LDHA), and Thymidylate Synthase (TS). From there, we also gained 9/40 derivatives for EGFR ($pK_d \geq 9$); 10/40 derivatives for FAK ($pK_d \geq 10$); 9/40 derivatives for LDHA ($pK_d \geq 10$), and 6/40 derivatives for TS ($pK_d \geq 9$). The glycoside derivatives showed the best binding affinity (especially the glucuronide derivative **5b**), followed by the 3 β -amino derivatives (especially the 3 β -(phenylamino) derivative **8b**) and the five-membered heterocyclic ring-combined derivatives (especially the pyrrole derivative **10a** or pyrazole derivative **11.2a**), while the six-membered heterocyclic ring-combined derivatives had less potential to inhibit selected targets.

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1. INTRODUCTION

Colorectal Cancer (CRC), also known as bowel cancer and colon cancer, is the development of cancer from the colon or rectum (parts of the large intestine), was the most common cause of death in the United States in the late 1940s and early 1950s¹. Globally, CRC is the third most common cancer worldwide, with 1.8 million new cases and nearly 861,000 deaths in 2018 according to the World Health Organization GLOBOCAN database. This rate was significantly higher in men than in women². The incidence of CRC in the region varies more than 10 times with the highest is found in Australia, New Zealand, Europe, and North America; the lowest is found in Africa and South Central Asia³. In the United States, morbidity and mortality rates due to CRC decline slowly but steadily⁴. Each year, about 145,600 new colon cancer cases were diagnosed, of which 101,420 were colon, the rest were rectal cancer⁵ and about 50,630 Americans died from CRC, accounting for about 8% of all cancer deaths². In Japan, when the Western-style diet

was introduced, the incidence of cancer increased significantly⁶. Studies showed that the majority of CRC tumors are located in the rectum, accounting for 23 - 32%; in which 20 - 23% in the sigma colon; only 7 - 10% in the ascending colon; 6 - 8% in the transverse colon and 6 - 7% in the descending colon⁷. The following are some proven factors related to CRC:

Epidermal Growth Factor Receptor (EGFR) is a transmembrane glycoprotein that defines a family of tyrosine kinase receptors (TKRs) including ErbB2/HER2, ErbB3/HER3 and ErbB4/HER4⁸. As a cell surface protein that binds to epidermal growth factor, binding of EGFR to a ligand induces receptor dimerization and tyrosine auto-phosphorylation and leads to cell proliferation, of which altered activity has been implicated in the development and growth of many tumors⁹. EGFR is recognized as an important player in CRC initiation and progression¹⁰. Currently, chemotherapy have focused on developing anti-cancer agents that can interfere with EGFR activity such as monoclonal antibodies (Cetuximab, Panitumumab) or small-molecule inhibitors (Erlotinib, Gefitinib)¹¹.

Focal Adhesion Kinase (FAK) has overexpression in both primary CRC or CRC metastases with high levels of FAK

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