THE QUERCETIN AND QUERCETIN DERIVATIVES INTERACTION WITH CYCLOOXYGENASE-1 AND CYCLOOXYGENASE-2

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ABSTRACT

The cyclooxygenase (COX) enzymes are tumor markers, the inhibition of which can be used in the prevention and therapy of carcinogenesis. It was found that COX-1 and COX-2 are considered as targets for tumor inhibition. In anticancer therapy, plant compounds are considered that can inhibit their activity. Modeling of the COX-1 and COX-2 enzymes was carried out on the basis of molecular models of three-dimensional structures from the PDB database [PDB ID: 3KK6, 5f19] RCSB. For docking analysis, 3D ligand models were created using MarvinSketch based on the PubChem database [CID: 5280343, 5281654]. *In silico* experiments, for the first time, revealed the possible interaction and inhibition of COX-1 and COX-2 by quercetin and quercetin derivatives. Aspirin and Celecoxib [CID: 2244, 2662] were taken to compare the results. Possible biological activities and possible side effects of the ligands have been identified. It is noteworthy that Celecoxib is not active on the studied cell lines, while quercetin and quercetin derivatives are more active than Aspirin.

Key words: COX-1, COX-2, quercetin, quercetin derivatives, Aspirin, Celecoxib, molecular docking

INTRODUCTION

The molecular mechanisms of drugs are the foundation on which can be built the therapy of many diseases accompanied by inflammatory processes. [1]. Molecules of various biochemical origins are involved in the regulation of inflammatory process. Eicosanoids are highly active regulators of cellular functions, have a short T1/ 2, therefore they have effects as "local hormones", occupy one of the central positions in inflammatory processes: they include prostaglandins, thromboxanes and other substances. Excessive secretion of eicosanoids leads to a number of diseases. The main substrate for the synthesis of human eicosanoids is arachidonic acid [8]. The synthesis of arachidonic acid is carried out due to the "work" of varieties of the cytoplasmic enzyme phospholipase A2, which in turn is activated by proinflammatory signaling pathways. After the process of separating arachidonic acid from the phospholipid, it is released into the cytosol and converted into different eicosanoids depending on the cell types. The most famous is the classic type of eicosanoids, which are formed due to the activity of the enzymes cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2). The COX enzyme catalyzes the first step in prostaglandin synthesis. The released arachidonic acid is converted by COX to prostaglandin (PGs) –PGG2, which is reduced to prostaglandin PGH2, and that into other eicosanoids (prostaglandins, thromboxanes, prostacyclins). PGs are cellular mediators of inflammation, the violation of biosynthesis of which can cause the development of severe pathological conditions: participation in the implementation of dysplastic and neoplastic processes (tumor growth), namely, in the suppression of apoptotic cell death, pathological neoangiogenesis and invasion, as well as mediation of immunosuppressive functions [7]. COX-1 is expressed in almost all mammalian tissues, and COX-2 is constitutive in some parts of the central nervous system. At the same time, COX-2 is rapidly activated in response to proinflammatory mediators

and mitogenic stimulants [13]. A decrease in the recurrence rate of many tumors was noted with the use of non-steroidal anti-inflammatory drugs (NSAIDs) that inhibits COX-2, but all these compounds, together with inhibition of COX-2, also inhibit the activity of COX-1, which leads to a negative effect on the implementation physiological processes in the body. Thus, the search for non-toxic and effective COX-2 inhibitors continues to this day [7; 10]. Recently, researchers have been paying special attention to substances of natural origin that have antitumor activity and are capable of selectively inhibiting the activity of COX-2 [10]. Some of these compounds can be quercetin and quercetin derivatives. Numerous studies have revealed the anticarcinogenic effect of quercetin and quercetin derivatives, which can prevent endothelial dysfunction, the production of superoxide caused by angiotensin II, inhibit the proliferation of tumor cells, causing cell apoptosis [2; 6; 9].

The aim of this work is to study the probable interaction of quercetin and quercetin derivatives by molecular docking with COX-1 and COX-2, in comparison with Aspirin and Celecoxib [7; 10; 12].

RESEARCH METHODS

The search for ligands and targets was carried out on the basis of verified articles from the Pubmed data bank. The structural formulas for the ligands were taken from PubChem [CID: 5280343] and constructed by MarvinSketch. All possible targets for each ligand were identified [13]. Repeats were removed from ~ 650 targets and were selected 25 targets belonging to *H. sapiens*. Of the 25 selected targets were examined COX-1 and COX-2. Target modeling was carried out on the basis of molecular models of three-dimensional structures PDB RCSB [ID: 3KK6, 5F19]. Physicochemical parameters were determined using SwissADME (Table 1) [3]. Docking analysis carried out by using AutodockVina, a reliability analysis of which is provided by 40-fold repeatability for each ligand [11].

Table 1

Physico-chemical parametres of the ligands	Aspirin	Celecoxib	Quercetin	3-Methylquercetin	Quercetin 3-O-rhamnoside
Formula	$C_9H_8O_4$	$C_{17}H_{14}F_3N_3O_2S$	$C_{15}H_{10}O_7$	$C_{16}H_{12}O_7$	$C_{21}H_{20}O_{11}$
IUPAC name	2-acetyloxybenzoic acid	4-[5-(4-methylphenyl)-3-(trifluoromethyl)pyrazol-1-yl]benzenesulfonamide	2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxychromen-4-one	2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-3-methoxychromen-4-one	2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-3-[(3S,4S,5S,6R)-3,4,5-trihydroxy-6-methyloxan-2-yl]oxychromen-4-one
Num. rotatable bonds	3	4	1	2	3

H-acceptors; donors	4;1	7;1	7; 5	7; 4	11; 7
Solubility	$2.54\ e^{0.2}$	$1.04\ e^{-0.2}$	$2.11\ e^{0.1}$	$4.07\ e^{-0.3}$	$3{,}69\ e$
GI absorbtion	high	high	high	high	low
BBB permeant	yes	no	no	no	no
log Kp (skin permeation) sm/s	-6.55	-6.21	-7.05	-6.31	- 8.42
Lipinski rule	yes	yes	yes	yes	yes
Ghose	yes	no	yes	yes	yes
Veber	yes	yes	yes	yes	no
Bioavailability Score	0.56	0.55	0.55	0.55	0.17

RESULTS AND DISCUSSION

For a detailed study of the ligands interaction with targets, docking analysis was performed with the detection of binding sites (Table 2) and energy characteristics (Tables 3, 4).

The active sites of COX-1 and COX-2 are similar - R120, Y355, E524, the folding of these amino acids leads to the formation of a pocket. Unlike COX-1, COX-2 replaced I523 with V523 and R513 with H513, which leads to the formation of an additional side pocket, which makes the active site of COX-2 more accessible, in addition, the last D helix curls up and facilitates binding to R120. The catalytic sites of COX-1 and COX-2 are also similar, and amino acid residues are formed by Y385 and S530.

It was found that when ligands interacted with COX-1, all bound to the active site Y385, R120, and also all ligands except quercetin bind to H90, forming hydrophilic bonds. Quercetin and quercetin derivatives bind to V349, and Celecoxib to F381, forming hydrophobic bonds.

In the case of COX-2, the ligands form hydrophilic bonds with V523, which is an additional pocket of the catalytic center. Aspirin and Celecoxib form hydrophilic bonds with R120 and Y385. Quercetin and quercetin derivatives, in contrast to Aspirin and celecoxib, interact with R513 and P156, which are involved in the organization of the catalytic center.

Table 2

Target	Aspirin	Celecoxib	Quercetin	3-methyl-quercetin	quercetin 3-*O*-rhamnoside
COX-1	S530; R120; Y385; H90; P156	S530; R120; Y385; H90; F381	Y355; V349; Y385; R120	Y355; V349; Y385; R120, H90	Y355; V349; Y385; R120, H90
COX-2	S530; R120; Y385; V523; H90; P156	V523; R120; Y355; Y385; S530; H90	P156; H39; P153, V523, R513	G135;P156; H39; V523, P153, R513	P156; H39; V523, P153, R513

The data obtained indicate the possible binding of all ligands to targets.

For each ligand, the prediction of the cytotoxic effect of chemical compounds with non-transformed (HaCaT) and transformed (Hs683) cell lines was carried out, as a result of which the probable biological activities and possible side effects of the ligands were identified (Tables 3, 4).

It is noteworthy that Celecoxib is not active on the studied cell lines, while quercetin and quercetin derivatives are more active than Aspirin.

Table 3

Ligand	COX-1		COX-2	
	Gibbs energy (kcal/m)	Binding constant K_b (10^4)	Gibbs energy (kcal/m)	Binding constant K_b (10^4)
Aspirin	-6.5±0.05	7,8	-6.5±0.05	7,8
Celecoxib	-9.1±0.05	11,2	-8.8±0.05	10,8
Quercetin	-9.4±0.05	11,4	-9.7±0.05	11,7
3-methylquercetin	-8.5±0.05	10,5	-9.7±0.05	11,7
Quercetin 3-*O*-rhamnoside	-8.6±0.05	10,7	-9.7±0.05	11,7

Table 4

Ligand	Glioma cells (Hs683)	Keratinocytes (HaCaT)
Aspirin	0.450	0.234
Celecoxib	-	-
Quercetin	0.458	0.205
3-methylquercetin	0.399	0.177
Quercetin 3-*O*-rhamnoside	0.405	0.194

It follows from the results that quercetin and its derivatives are characterized by low cytotoxicity for untransformed cells, and the interaction with targets- COX-1 and COX-2 is stronger than with Aspirin and Celecoxib.

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