A Computational Approach in the Search of New Biologically Active 9,10-Anthraquinone Derivatives

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Abstract

The results of using a computer approach in the search for new potential biologically active compounds in a series of 9,10-anthraquinone derivatives using free online programs *PASS Online, CLC-Pred (Cell Line Cytotoxicity Predictor), Acute Rat Toxicity* and determining the level of binding of the studied structures of anthraquinones with target proteins using the *Schrodinger* software package are generalized. The directions of experimental primary assessment of antimicrobial, antiplatelet, antioxidant, antiviral, anticonvulsant, antitumor action for selected objects of research are determined. Molecular docking shows the prospects for studies of the mechanisms of anticancer and antiplatelet agents.

Keywords 1

9,10-anthraquinone derivatives, *in silico* prediction, biological action

1. Introduction

Despite the significant achievements of modern medical chemistry and pharmacology, the search for new more effective and safer medicinal substances remains an actual problem [1]. The number of biological activities studied by modern pharmacology is more than three thousand, and the number of potential molecular targets of drugs is tens of thousands [2]. Experimental verification of tens / hundreds of millions of chemical substances for thousands of types of pharmacological effect is practically not implemented. The basis of modern search and development of new drugs is the data analysis of the mechanisms of disease development, protein targets and compounds with pharmacological activity, the effect of which allows to remove the pathological process [3].

The structural formulas of molecules of studied substances using computer prediction allow to find new biologically active compounds with necessary properties [4]. The most promising substances for chemical synthesis are selected by researchers on the basis of *in silico* prediction and determine the priorities of their experimental testing, which significantly reduces the cost of experimental research and eliminates unpromising substances in the earliest stages of research.

Computer investigations are widely used to analyze the relationships "structure - biological effect" of organic compounds [5]. Search and designing materials with desired properties and optimization of pharmacodynamic and pharmacokinetic characteristics of the basic structures of new biologically active compounds is carried out using them. Most computer programs designed for this purpose are distributed on a commercial basis by specialized firms (*Accelrys, Tripos, ACD Labs, ChemSoft*, etc.).

There are a relatively small number of computer programs available for free over the Internet and predicting pKa (http://vcclab.org/lab/alogps/start.html), some physicochemical properties (http://www.molecularknowledge.com/Online/Estimation/online1.htm), solubility, lipophilicity, and some types of biological activity (http://www.organic-chemistry.org/prog/peo/index.html, http://www.molinspiration.com/cgi-bin/properties). In recent years, foreign web services have appeared on the Internet that allow predicting the interaction of chemical compounds with target macromolecules

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based on structural similarity (http://bioinformatics.charite.de/superpred/, http://cpi.bio-x.cn/drar/). The information available on these websites does not allow us to assess the quality of the prediction provided by these web services.

The computer program *PASS Online* [6] became the first of the free online services in the world, which allows you to predict 5066 types of pharmacological effects based on the structure of the molecule. Its effectiveness in finding new bioactive substances is constantly confirmed by the numerous works of more than 23,000 researchers from more than 100 countries, and the training sample is updated as new data on biologically active compounds for each type of biological activity. In recent years, *PASS Online* has been added by a number of free online web services on the *Way2Drug* platform that predict more than 4,000 types of biological activity, including acute toxicity to rats with four routes of administration, effects on tumor and non-tumor cell lines interacting with antytargets and etc..

Molecular docking (molecular modeling) is actively used to solve virtual screening problems [7]. Its essence is to model the relative position of the studied molecule and the target protein. The spatial structure of the molecular target and the spatial structure of the ligand (studied structure) make it possible to explain at the molecular level the mechanism of interaction of the ligand with the protein. The docking program tests the studied structures using a special scoring function (affinity), which roughly describes the energy of interaction of the molecule with the target protein. It is possible to reject from further consideration a substance with poor values of the scoring function using the results of docking. Modeling of ligand-receptor interactions is carried out using a variety of different software packages (*AutoDock, AMBER, eHiTS, Surflex-Dock, Schrödinger, etc.*) [8-11], each of which has its own advantages and disadvantages, including accessibility via the Internet.

Considering the above, an *in silico* approach was used in the search for new derivatives of 9,10-anthraquinone using the latest resources to determine the experimental directions of research on their pharmacological activity.

2. Relates works

The computer program *PASS Online* and a number of free online web services such as *CLC-Pred (Cell Line Cytotoxicity Predictor), Acute Rat Toxicity* of the *Way2Drug* platform [12] are widely used by the researchers from different countries for the search of new biologically active compounds among synthetic and natural compounds and predicted results had and have many examples of experimental verification. In particular, these programs have shown their effectiveness in the search for antimicrobial substances [13, 14], determination of toxicity level [15], search of new anticancer drugs and evaluation of their cytotoxicity [16, 17], etc. For 40 known natural anthraquinone derivatives *PASS Online* was used for evaluation of antiviral potential against different types of viruses like Herpes, Hepatitis B and C, Cytomegalovirus, Adenovirus, Hepatitis, HIV, Parainfluenza, Influenza, Picornas-, Pox-, Rhino-, and Coronavirus (Covid-19) and molecular docking using SWISS-MODEL was carried out in [18]. In work [19] molecular docking study of anthraquinone compounds extracted from *Anethum sowa L*. root was used for estimation of the their pharmacological potential targeted towards anticancer activity.

3. Materials and methods

In silico evaluation of the biological properties of new functionalized 9,10-anthraquinone derivatives (Fig. 1) was performed by the online services *PASS Online, CLC-Pred, Acute Rat Toxicity* of web portal *Way2Drug*. As an initial information, the structural formula of the substance in MOL or SDF file format was used to obtain prediction data in each of the mentioned programs. The connection table containing data of the molecule valent bonds and table of atoms types of the loaded structure of compound are basis for generation of the set of multilevel neighborhoods of atoms (MNA) structure descriptors [6]. The Bayesian mathematical approach is used as an algorithm for estimation of results of predicted biological activity [6]. This algorithm provides stable in the static sense of the dependence "structure-activity" and, accordingly, the results of the forecast. The work of the online services is based on the analysis of the "structure-activity" relationship for substances from the training set, which contains more than 40,000 different biologically active substances (substances of known drugs and physiologically active compounds), i.e. the result of prediction of biological activity is compared with known

experimental data [6]. A list of possible types of pharmacological effect shows two probabilities - the presence of Pa activity and the absence of Pi activity as the result of prediction (Fig. 2-4). Pa values range from 0.000 to 1.000. When Pa>0.7, the compound has a similar effect to the experimental one and in this case the chance of this compound being an analog of a known pharmacological drug is very high. If 0.5<Pa<0.7, the compound has a similar effect to the experimental one, but this probability is less and the compound is not similar to the known pharmacological drug. When Pa<0.5, the compound does not correspond to the experimental activity; however, the presence of this activity confirmed by experimental data, can become a new object for investigation.

CLC-Pred service allow to predict the cytotoxic action for non-transformed and cancer cell lines based on loaded molecular structure in comparison with the training set obtained from ChEMBLdb Database (https://www.ebi.ac.uk/chembldb/) [20]. Results of prediction using *CLC-Pred* are also presented as a list of Pa/Pi values of probable cancer cell lines (Fig. 2). *Acute Rat Toxicity* online service [21] allow *in silico* estimate probable level of toxicity using a rat model for four different routes of administration: intravenous, intraperitoneal, oral, subcutaneous (Fig. 3). Results of prediction are compared with the training sets of known compounds with determined experimental toxicity LD_{50} values obtained from Toxicity Database of SYMYX MDL (http://www.akosgmbh.de/accelrys/databases/symyx_dbs.htm). Output data show probable LD_{50} value in log10 (mmol/kg) or mg/kg and class of acute rodent toxicity.

The molecular modeling of affinity (binding) with the corresponding target protein site was used to determine probable mechanisms of action using *Small-Molecule Drug Discovery Suite* of *Schrödinger* within the test access [22] and *AutoDock Vina* [23] was carried out in addition to the above-mentioned free online access programs for predicting the pharmacological effects of the studied structures. The conformation of the ligand (studied chemical structure) that best interacts with the protein binding site is the result of molecular modeling. The structure of biological targets for molecular modeling were taken from database RCBS Protein DataBank (https://www.rcsb.org). For the molecular docking as target proteins were selected: receptor proteins-tyrosine kinases cyclooxygenase-1 (*COX-1*) - *3N8X*, glycoprotein-IIb/IIIa (*GPIIb /IIIa*) - *2VDM*, glycoprotein-VI (*GP-VI*) - *2G17*, purine receptor *P2Y12* - *4PXZ*, prostacyclin receptor (*PG-I2*) - *4F8K*, protein-activated receptor-1 (*PAR-1*) - *3VW7*, antithrombin III (*ATIII*), factor-X (*FX*), factor-II (*F-II*), factor -IX (*F-IX*) and vitamin K-epoxy reductase (*VKOR*) - *1NQ9, 1KSN, 5JZY, 1RFN* and *3KP9*, *c-Kit*, *B-Raf*, *EGFR* (*1NQL, 1IVO, 1M17, 2GS6*) and *PDGF (1T46, AKT1, ERK2)*, non-receptor tyrosine kinases *SRC (1SKJ)*, nonspecific tyrosine kinases *ABL* (*3OXZ, 3QRJ, 2ABL*). Then, the target protein is prepared using the Protein Preparation Wizard with the removal of water molecules and the addition of missing hydrogen atoms in the structure of the target protein and the optimization of the structure of protein using the PROBKA subprogram. At the next stage, the protein structure is minimized by the OPLS-2005 subprogram. Preparation of ligand (studied chemical structure) is performed using LigPrep Wizard. Next, the ligand binding region to the receptor is generated using the Receptor Grid Generation module of the Glide Maestro and docking is performed in the XP phase. The result of docking is a set of structures in 3D with a set of numerical indicators describing their affinity G_{score} (scoring function) to the active site of the protein.

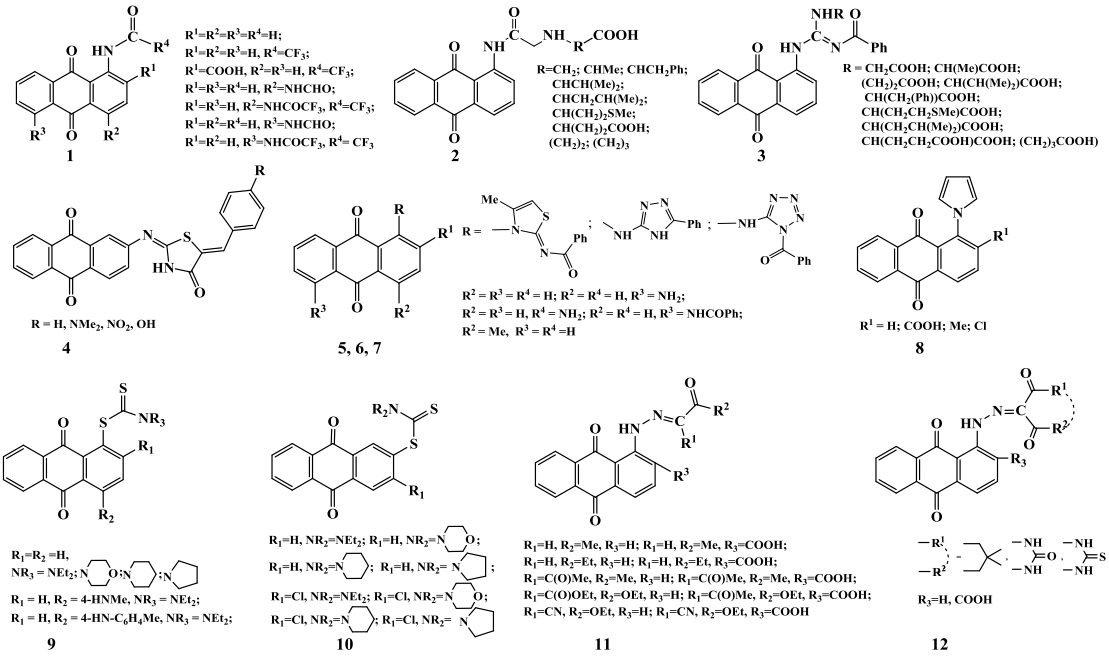

Figure 1: Objects *in silico* study

All ○ Pa>Pi ○ Pa>0,3 ○ Pa>0,7 ok

Pa	Pi	Activity
0,639	0,021	Neurotransmitter uptake inhibitor
0,631	0,025	Alkane 1-monooxygenase inhibitor
0,626	0,028	Aldehyde oxidase inhibitor
0,601	0,026	27-Hydroxycholesterol 7alpha-monooxygenase inhibitor
0,591	0,022	3-Hydroxybenzoate 6-monooxygenase inhibitor
0,585	0,021	Ovulation inhibitor
0,602	0,041	Nicotinic alpha4beta4 receptor agonist
0,582	0,033	Thioredoxin inhibitor
0,571	0,028	(R)-6-hydroxynicotine oxidase inhibitor

Figure 1: Example of prediction results of *PASS Online*

Cancer cell line prediction result

Pa	Pi	Cell-line	Cell-line full name	Tissue	Tumor type
0.392	0.043	HeLa	Cervical adenocarcinoma	Cervix	Adenocarcinoma
0.235	0.007	U2OS	Osteosarcoma	Bone	Sarcoma
0.316	0.130	RKO	Colon carcinoma	Colon	Carcinoma
0.316	0.198	Hs 683	Oligodendroglioma	Brain	Glioma
0.243	0.128	HOP-18	Non-small cell lung carcinoma	Lung	Carcinoma
0.111	0.017	MEXF276L	Xenograft melanoma	Skin	Melanoma
0.111	0.017	MEXF989	Xenograft melanoma	Skin	Melanoma
0.111	0.017	PAXF546	Pancreatic carcinoma	Pancreas	Carcinoma

Figure 2: Example of prediction results of *CLC-Pred*

Rat acute toxicity predicted by GUSAR

Rat IP LD50 Log10(mmol/kg)	Rat IV LD50 log10(mmol/kg)	Rat Oral LD50 log10(mmol/kg)	Rat SC LD50 log10(mmol/kg)
0,307 in AD	-0,382 in AD	0,330 in AD	0,272 in AD

Rat IP LD50 (mg/kg)	Rat IV LD50 (mg/kg)	Rat Oral LD50 (mg/kg)	Rat SC LD50 (mg/kg)
717,400 in AD	146,500 in AD	755,000 in AD	661,200 in AD

Acute Rodent Toxicity Classification of Chemicals by OECD Project

Rat IP LD50 Classification	Rat IV LD50 Classification	Rat Oral LD50 Classification	Rat SC LD50 Classification
Class 5 in AD	Class 4 in AD	Class 4 in AD	Class 4 in AD

Figure 3: Example of prediction results of *Acute Rat Toxicity*

4. Results and Discussion

Analysis of prediction data for all new structures of functionalized 9,10-anthraquinone derivatives **1-12** (Fig. 1) showed that the main, expected, direction of experimental studies is the investigation of

the antitumor effect (Pa in the range 0.3-0.6). Since the studied structures **1-12** are new objects for the *PASS Online* training set, the Pa values for many structures are in the range 0.3-0.6. Taking into account results of anticancer activity prediction, cytotoxicity was evaluated *in silico* against cancer cell lines using the web service *CLC-Pred* [20]. The analysis of the obtained results showed that the most probable effect of the studied compounds **1-12** (Pa=0.3-0.8) is on cancer cell lines of the lungs, lymphoid tissue, glandular tissue of the breast, and for some compounds is on also tissues of the cervix, brain, and colon.

The introduction of new biophore fragments into the 9,10-anthraquinone molecule allowed to expand the range of experimental *in vitro* and *in vivo* studies, in addition to the study of the antitumor effect predicted using *PASS Online*, in the following areas. In particular, antimicrobial and antioxidant activities were predicted for *N*-acylamino-9,10-anthraquinones **1**, amino acid derivatives of 2-chloro-*N*-(9,10-dioxy-9,10-dihydroanthracen-1-yl) acetamide **2** (Pa=0.3-0.6). 1,2,3-Substituted guanidine **3** would be interesting subjects to test for antianginal (Pa=0.3-0.4), anti-ischemic (Pa=0.3-0.35), cardiotonic (Pa=0.3-0.45) effects. The direction of research on hypoglycemic activity would be interesting for 5-arylidene derivatives **4** (Pa=0.3-0.35). Iminothiazoles **5**, 1,2,4-triazoles **6** and tetrazoles **7** can be studied also for antimicrobial (Pa=0.3-0.4), anti-inflammatory (Pa=0.3), anti-allergic effects (Pa=0.3-0.4) and effects on vascular processes (Pa=0.3-0.33). An additional area of testing for pyrrolylantracenediones **8** is to determine the level of antibacterial and antifungal activity (Pa=0.4-0.5). The antitumor activity of the dithiocarbamate derivatives **9, 10** was supplemented by antimicrobial, antioxidant, antiplatelet, antiviral, anticonvulsant effects at Pa=0.3-0.55 according to Pa prediction data. Predicted Pa values (Pa=0.3-0.4) for the dithiocarbamates **9, 10** and hydrazone derivatives **11, 12** showed perspective for their further investigations for antiviral properties.

The analysis of the prediction results showed that, in the overwhelming majority, the Pa values for the studied structures are in the range Pa=0.3-0.6. Taking into account the categorization of Pa values, such low Pa values can be explained by the novelty of molecular structures for the *PASS Online* training set. The predicted data became the basis for the experimental study of the above mentioned antraquinone derivatives **1-12.**

The probable acute toxicity of LD_{50} using the online resource *Acute Rat Toxicity* using *in silico* rat model with four different routes of administration: intraperitoneal, intravenous, oral and subcutaneous [21] for promising compounds, selected by the experimental tests, allows to estimate the level probable toxicity of anthaquinone derivatives **1-12**. The results showed that the studied structures of compounds can be classified as medium-, low- and non-toxic compounds.

As outcome result of the molecular docking, the values of G_{score} scoring functions were determined and the anthraquinone derivatives with high, medium and low levels of binding to a specific target protein *PDGF (1T46), VKOR (3KP9), c-Kit* and *B-Raf* associated with anticancer and antiplatelet actions with G_{score} in the range from -6.7 to -11.8 were found among the studied molecular structures **1-12** [24]. Examples of visualization of binding of hit compounds among triazole **6**, dithiocarbamate **9,10** and triazinone **7** anthraquinones in the corresponding active zone of the sites of previously mentioned proteins are given below (Fig. 2-7).

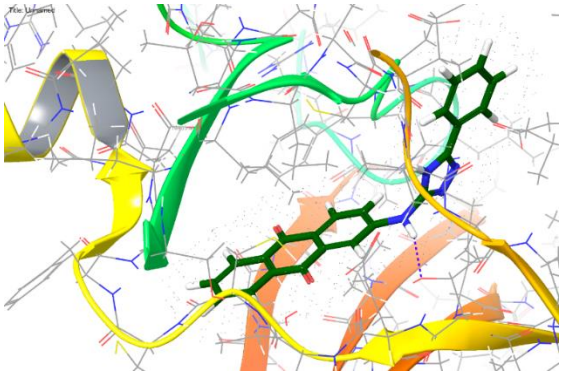

Figure 2: Visualization of the binding of the hit compound triazole anthraquinone in the active zone of the protein *1T46* (G_{score}= -10.7)

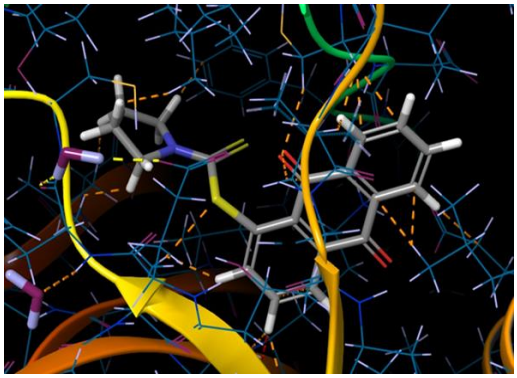

Figure 3: Visualization of the binding of the hit compound pyrrolidine dithiocarbamate in the active zone of the protein *1T46* (G_{score}= -10.92)

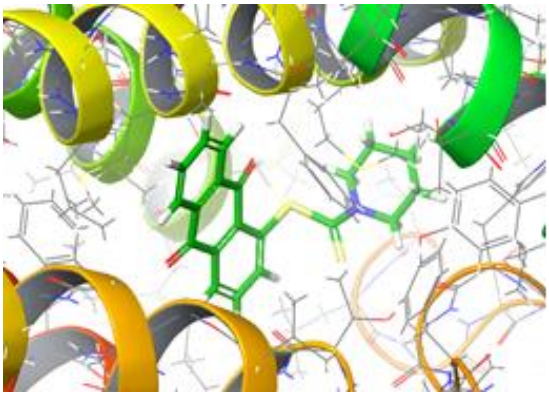

Figure 4: Visualization of the binding of the hit compound piperidine dithiocarbamate in the active zone of the protein *3KP9* (G_{score} = -10.39)

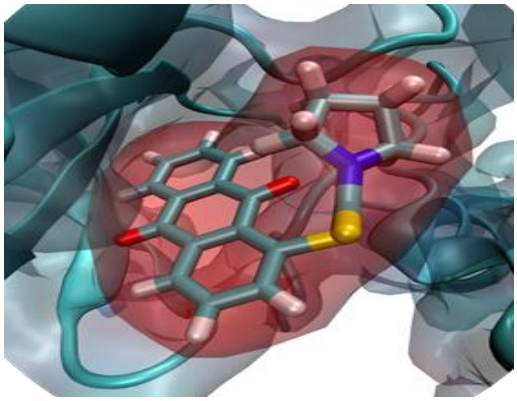

Figure 5: Visualization of the binding of the hit compound pyrrolidine dithiocarbamate in the active zone of the protein *c-Kit* (G_{score}= -9.1)

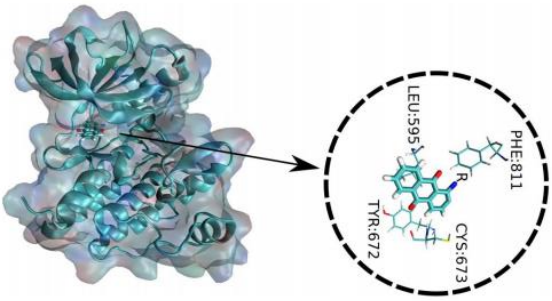

Figure 6: Visualization of the binding of the hit compound anthratriazinone in the active zone of the protein *c-Kit* (G_{score} = -11.8)

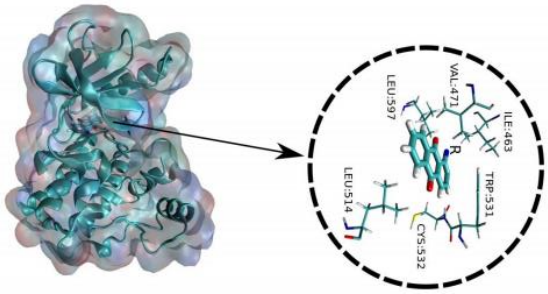

Figure 7: Visualization of the binding of the hit compound anthratriazinone in the active zone of the protein *B-Raf* (G_{score} = -11.3)

It should be noted that the dithiocarbamate derivatives of anthraquinone of type **9,10**, which had the highest values of the scoring function G_{score}= -10.92…-11.2 are promising objects for experimental study of the mechanisms their antioxidant, anticancer and antiplatelet action.

Therefore, the results of predicted by the online programs *PASS Online, CLC-Pred, Acute Rat Toxicity* regarding the probable manifestation of antimicrobial, antiplatelet, antioxidant, antiviral, anticonvulsant, antitumor actions and predicted values of acute toxicity, as well as molecular docking data obtained by *Small-Molecule Drug Discovery Suite Schrödinger* and *AutoDock Vina* have been verificated by experimental *in vitro* and *in vivo* investigations.

5. Conclusion

In this article, we present the generalized results of using in silico tools in the search for new potential pharmacologically active compounds in the series of 9,10-anthraquinone derivatives. The used computer approach carried out by free online programs *PASS Online, CLC-Pred, Acute Rat Toxicity* allowed to determine the directions of the experimental primary assessment of antimicrobial, antiplatelet, antioxidant, antiviral, anticonvulsant, antitumor action for the selected objects of study. Molecular docking data on biotargets of pathological processes allowed to define compounds with a high degree of affinity and showed the prospect of studying the mechanisms of anticancer and antiplatelet agents from this class of compounds by modifying the ligand with various pharmacophore fragments. The results of *in silico* approach allowed experimentally identify promising compounds in the series of 9,10-anthraquinone.

6. Acknowledgements

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7. References

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