REVIEW ARTICLE

Binding Sites of Anticancer Drugs on Human Serum Albumin (HSA): A Review

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Abstract: ***Background***: To recognize the action of pharmacologically approved anticancer drugs in biological systems, information regarding its pharmacokinetics, such as its transport within the plasma and delivery to its target site, is essential. In this study, we have tried to collect and present complete information about how these drugs bind to human serum albumin (HSA) protein. HSA functions as the main transport protein for an enormous variety of ligands in circulation and plays a vital role in the efficacy, metabolism, distribution, and elimination of these agents.

Methods: Therefore, this study includes information about the quenching constant, the binding constant obtained from Stern-Volmer and Hill equations, and molecular docking.

Results: Molecular docking was carried out to detect the binding models of HSA–anticancer drugs and the binding site of the drugs in HSA, which further revealed the contribution of amino acid residues of HSA in the drug complex binding.

Conclusion: This review study showed that site I of the protein located in domain II can be considered the most critical binding site for anticancer drugs.

1. INTRODUCTION

In the blood circulation, several proteins and peptides are present. Human serum albumin (HSA) is distinctive in over 50% of the plasma proteins, it is also the most abundant protein with a concentration of ~35-50 mg/ml, while, the concentration of other major plasma proteins is much lower [1, 2]. HSA is critical in the colloid osmotic pressure process and has an anticoagulant character. Synthesis and secretion of albumin are feasible in the liver, where it is manufactured at almost 0.7 mg/h for every gram of liver (10-15 g daily). Albumin is secreted into the portal circulation as soon as it is manufactured and is not saved by the liver [3, 4]. The protein is heart-shaped in X-ray crystallography. HSA is composed of 585 amino acids (66.5 kDa) rich in lysine and aspartic acid. They are arranged in a single-chain α-helical structure with 17 disulfide bonds. Moreover, HSA has a free cysteine-derived thiol group at Cys-34, contributing to 80% of its redox activity. Three domains form its structure. Domain I consists of residues 5–196, domain II includes residues 197–383, and domain III is formed from residues 384-582 [5]. Each domain comprises two subdomains termed A and B (IA: residues 5–107, IB: residues 108–196, IIA: residues 197–297, IIB: residues 298–383, IIIA: residues 384–497, IIIB: residues 498–582). Among the subdomains, regions IIA and IIIA are called Sudlow's site I and site II, respectively [6, 7].

HSA is a conserved protein in various animals; fish serum albumins show morphological variety and play essential functions in plastic and osmotic transport. Mammalian and fish albumin genes are members of one superfamily demonstrating analogous motifs [8]. Serum albumin exhibits binding activity to metal ions and is involved in the storage and transport of fatty acids, bilirubin, amino acids, steroid hormones, and nanoparticle [9, 10]. Furthermore, albumin binds lipophilic compounds, such as steroid hormones, xenobiotics, and phytochemicals, with binding ability to receptors for other lipophilic hormones [11, 12]. Any drug, whether applied intramuscularly, sublingual, subcutaneous, intravenously or orally, is transported by the flowing of blood and its first encounter is not diverse cellular components but plasma proteins. Although the human body contains a number of essential carrier proteins, such as globulins, glycoproteins, and lipoproteins, HSA is primarily responsible for drug-protein interactions [13, 14]. Anticancer drugs can have different functions, including inducing tumor cells to emit signals that stimulate dendritic cell maturation, apoptosis, *etc.* [15-17]. HSA is a powerful carrier for the delivery of small molecule anticancer drugs. The interaction of anticancer drugs with HSA may cause a decrease or increase in the concentration of free biologically active parts of drugs. The strong binding of the drugs to this protein can decrease the

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concentration of the free drug in plasma, whereas weak binding can lead to a short lifetime or poor distribution of the drug. Determining the binding site of the drugs on HSA increases our knowledge to comprehend better the potential competition of such anticancer drugs with other medicinal compounds in the same place [18]. Fluorescence spectroscopic and molecular docking are two techniques to identify the binding sites. Thus, this study focuses more on collecting the results of those two methods. Therefore, the interactions of 46 anticancer drugs with HSA have been studied, all of which have been included in Table **1**.

Furthermore, the chemical structures of the anticancer drugs are shown in Table **2**.

2. FLUORESCENCE SPECTROSCOPY

Fluorescence spectroscopy has been widely used to characterize the interaction of a fluorescent macromolecule (protein) with other small molecules of clinical relevance. The potential conformational changes of protein upon the binding of drugs could also be characterized by fluorescence spectroscopy [19]. Two exciting wavelengths of 280 and 295 nm are commonly used to study HSA fluorescence intensity. Excitation of the protein sample at 280 nm will excite both Tyr and Trp residues of the protein, while the excitation at 295 nm is related to a single Trp (Trp214) residue. The phenomenon of ligand-induced protein fluorescence quenching mainly involves either collisional or static quenching mechanisms. Collisional quenching, a type of dynamic quenching process, results from random encounters between the excited fluorophores and the quencher (ligand) molecules, In contrast, static quenching involves the formation of a nonfluorescent ground-state complex between the protein and the quencher. The Stern–Volmer equation is widely used to determine the quenching constant (KSV) and the quenching rate (Kq) of binding between protein and ligand. It was employed as follows [20]:

$$F_0/F = 1 + KSV \, [Q] = 1 + Kq\tau_0[Q]$$

$$Kq = KSV \, /\tau_0$$

where F_0 and F are the fluorescence intensities in the absence and presence of the quencher, respectively, KSV is the Stern–Volmer quenching constant, Kq is the quenching rate, τ_0 is the average lifetime of the fluorophore without the quencher (10^{-8} s), and [Q] is the concentration of the quencher. By considering Kq for binding systems, which shows a value greater than 2.0×10^{10} $M^{-1}s^{-1}$, it leads to the conclusion that fluorescence quenching for HSA-anticancer drug is a result of static quenching.

Furthermore, the binding constant (Ka) for the complex of HSA-drug could be calculated using the Hill equation, which is as follows [12]:

$$\log (F0 - F/F) = \log Ka + n \log [Q]$$

Where F0, F, and [Q] are already mentioned above. K_a is the binding constant, and n equals the number of binding sites in HSA. The values of Ka for HSA-anticancer drug complexes are presented in Table **3**.

2.1. Molecular Docking

Docking studies can provide a further understanding of the interactions between the macromolecule and ligand to confirm the experimental results. Molecular docking is a suitable way to predict the exact binding sites and the amino acids around the drug [62, 63]. There are two major sites on each HSA structure; a large hydrophobic cavity reflected in subdomain IIA that many drugs can also bind. During docking, the HSA structure remains rigid, while the drug structure is flexible. Finally, the least free energy is selected as the best interactive energy, and the results are analyzed accordingly [9, 64].

2.2. Anticancer Drugs

Cancer is a multifactorial deficiency that results from cellular abnormalities and multiple genetic alterations. The complexity of the mechanism of cancer progression and heterogeneity lead to the aggressive growth of cancer cells, leading to significant death in cancer patients [65, 66]. There are several ways to control and treat cancer including surgery, radiotherapy, and treatment with drugs and chemotherapy compounds. The use of anticancer drugs and chemotherapy methods to kill cancer cells may be used alone or in combination with other drugs [67]. The anticancer drugs that were studied in this review are divided into alkylating agents [68], antimetabolite anticancer drugs [69], biological and targeted agents [70], mitotic inhibitors [71, 72], antibiotics, anticancer drugs [73], topoisomerase inhibitors [74] and hormonal agents [75] in terms of the mechanism of action (Table **4**).

2.3. Alkylating Agents

Alkylating agents, as an important treatment for some malignancies, including brain tumors, are the main group of pioneer chemotherapeutic drugs. These types of anticancer drugs can have different functions during all phases of the cell cycle, including directly on DNA structure, DNA double-strand breaks, crosslinking between N-7-guanine residues, mismatch base pairing, suppression of cell division, and the major mechanism of action of in these agents consisting of a disturbed structure of DNA and induced programmed cell death. It also affects various cellular pathways, including direct DNA damage, mismatch repair (MMR), and base excision repair (BER) [68, 76, 77].

Cyclophosphamide (CYC), an alkylating agent belonging to the group of oxazaphosphorines, is one of the oldest anticancer drugs. CYC was approved and introduced into cancer treatment as early as 1958 and 1959, respectively [78, 79]. It is known as a prodrug and is converted to 4-hydroxycyclophosphamide (HCP) by cytochrome P450 (CYP450). It remains a mainstay in the therapy of hematological malignancies, including lymphoma and leukemia, as well as of various epithelial tumors, including breast, ovarian and small-cell lung carcinomas (SCLC) [80, 81]. CYC has a significant antitumor function by repressing the activity of the immune cell and inducing the sensitivity of chemotherapeutic drugs toward the tumor cells. CYC is involved in critical cellular processes, such as apoptosis, by interacting with NF-κB, IL-6, TNF-α, and many caspases [82-84]. CYC was situated within the binding pocket of subdomain IIA. CYC was surrounded through amino acid residues Ala291, Leu238, Trp214, Leu260, Ile290, Ala215, and Val241 *via* hydrophobic interaction [21].

Table 1. **Molecular weight, half-life, percentage of protein binding, molecular formula, and solubility of the anticancer drugs (extracted from the DrugBank and PubChem).**

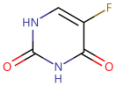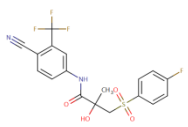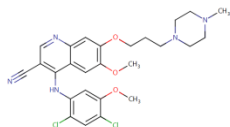| Drug	Molecular Weight (g/mol)	Half-life (h)	Protein Binding (Percent)	Molecular Formula	Solubility
Cyclophosphamide	261.08	6.5	20	C7H15Cl2N2O2P	Soluble in water
Oxaliplatin	395.3	~1	≥90	C8H12N2O4Pt	Soluble in water
Busulfan	246.3	2.6	32	C6H14O6S2	Insoluble in water
Temozolomide	194.15	1.8	15	C6H6N6O2	Soluble in DMSO
Thiotepa	189.22	1.5-4.1	Not available	C6H12N3PS	Soluble in water and organic solvents (Ethanol)
Capecitabine	359.35	~1	< 60	C15H22FN3O6	Soluble in water and organic solvents (Ethanol)
5-Fluorouracil	130.08	0.3	Not available	C4H3FN2O2	Soluble in DMSO
Methotrexate	454.4	8-15	46.5-54	C20H22N8O5	Insoluble in water soluble in organic solvents, such as DMSO and dimethyl formamide
Fludarabine	285.23	20	19-29	C10H12FN5O4	Sparingly soluble in water
Thioguanine	167.19	1-2	Not available	C5H5N5S	Insoluble in water soluble in ethanol
Clofarabine	303.68	5.2	47	C10H11ClFN5O3	Soluble in DMSO
Cytarabine	243.22	2	13	C9H13N3O5	Soluble in water
Gemcitabine	263.2	1.2	<10	C9H11F2N3O4	Soluble in organic solvents (Ethanol)
Bosutinib	530.4	22	94-96	C26H29Cl2N5O3	Soluble in organic solvents (Acetone); sparingly soluble in water
Axitinib	386.5	2.5 to 6	≥99	C22H18N4OS	Soluble in DMSO
Dabrafenib	519.6	8	99.7	C23H20F3N5O2S2	Soluble in organic solvents (Ethanol); sparingly soluble in water
Dasatinib	488	3-5	96	C22H26ClN7O2S	Soluble in organic solvents (Dimethyl formamide)
Ibrutinib	440.5	4-6	97.3	C25H24N6O2	Practically insoluble in water; soluble in organic solvents, such as ethanol, DMSO, and dimethyl formamide
Ponatinib	532.6	24	> 99	C29H27F3N6O	Soluble in organic solvents (DMSO); sparingly soluble in water
Trametinib	615.4	96-144	97.4	C26H23FIN5O4	Soluble in DMSO
Vandetanib	475.4	4-10	~90	C22H24BrFN4O2	Soluble in DMSO
Crizotinib	450.3	42	91	C21H22Cl2FN5O	Soluble in DMSO
Lapatinib	581.1	14-24	>99	C29H26ClFN4O4S	Soluble in organic solvents (DMSO)
Erlotinib	393.4	36	93	C22H23N3O4	Very slightly soluble in water; soluble in organic solvents, such as ethanol, DMSO, and dimethyl formamide
Gefitinib	446.9	48	90	C22H24ClFN4O3	Soluble in organic solvents (Ethanol)
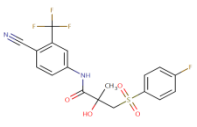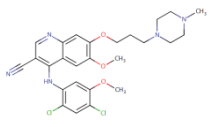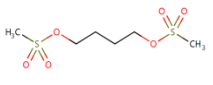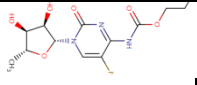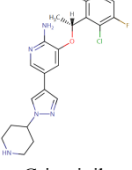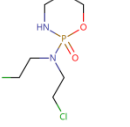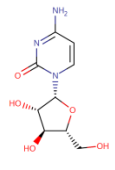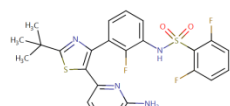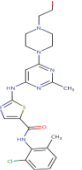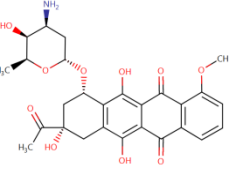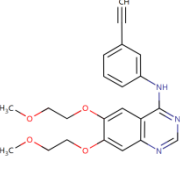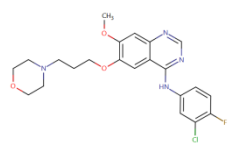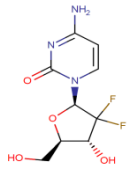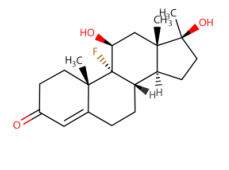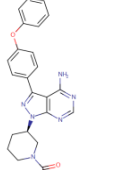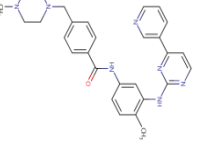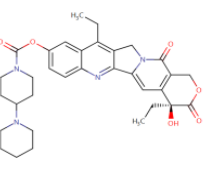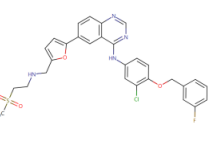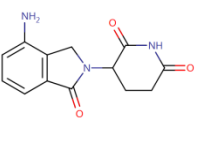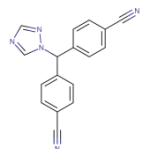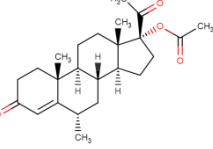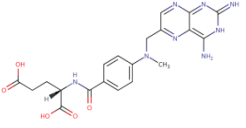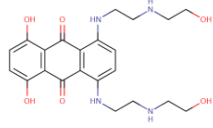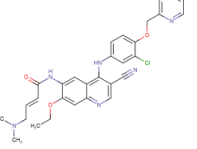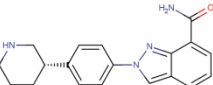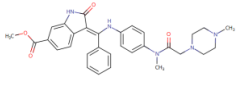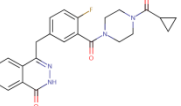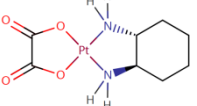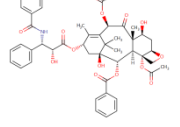
Drug	Molecular Weight (g/mol)	Half-life (h)	Protein Binding (Percent)	Molecular Formula	Solubility
Imatinib	493.6	18-40	95	C29H31N7O	Soluble in water, DMSO, DMF and PBS
Nintedanib	539.6	10-15	97.8	C31H33N5O4	Soluble in water
Sunitinib	398.5	40-60	95	C22H27FN4O2	Soluble in DMSO
Neratinib	557	14.6	> 99	C30H29ClN6O3	Soluble in organic solvents (DMSO)
Sorafenib	464.8	25-48	99.5	C21H16ClF3N4O3	Soluble in DMSO
Niraparib	320.4	36	83	C19H20N4O	Low solubility in water
Temsirolimus	1030.3	17	87	C56H87NO16	Practically insoluble in water, soluble in alcohol
Lenalidomide	259.26	3-5	30	C13H13N3O3	Soluble in organic solvent (DMSO)/ water mixtures
Olaparib	434.5	5-11	82	C24H23FN4O3	Soluble in organic solvents (Dimethyl formamide)
Acyclovir	225.2	2.5-3	9-33	C8H11N5O3	Slightly soluble in water
Paclitaxel	853.9	~53	89-98	C47H51NO14	Soluble in organic solvents (Ethanol)
Mitomycin	334.3	0.2-0.8	Not available	C15H18N4O5	Soluble in water
Daunorubicin	527.5	18.5	97	C27H29NO10	Soluble in methyl alcohol, insoluble in chloroform, and benzene
Mitoxantrone	444.5	75	78	C22H28N4O6	Sparingly soluble in water; slightly soluble in methanol; practically insoluble in acetonitrile chloroform, and acetone
Irinotecan	586.7	6 - 12	30-68	C33H38N4O6	Soluble in organic solvents (DMSO)
Bicalutamide	430.4	144	96	C18H14F4N2O4S	Practically insoluble in water and soluble in chloroform, ethanol, methanol, and acetone
Fluoxymesterone	336.4	9.2	19	C20H29FO3	Practically insoluble in water; soluble in acetone and chloroform
Tamoxifen	371.5	120-168	98	C26H29NO	Soluble in organic solvents (Ethanol)
Medroxyprogesterone acetate	386.5	40-60	86	C24H34O4	Insoluble in water; soluble in DMF and ethanol
Letrozole	285.3	42	55	C17H11N5	Practically insoluble in water; soluble in organic solvents such as DMSO

Oxaliplatin (Eloxatin), a platinum analog to cisplatin and carboplatin, is a chemotherapeutic drug that has been used against colorectal cancer. It was approved by FDA in 1999. Oxaliplatin inhibits DNA synthesis and has been significantly accepted as potentially useful to treat cisplatin-resistant cases [22, 85, 86]. Oxaliplatin is involved in disrupting two main intracellular processes of replication and transcription, through the generation of extra DNA strands [87]. A molecular docking study showed that oxaliplatin binds to residues located in subdomain IIA. Based on recent studies, the C-ring of oxaliplatin was nearby the Trp214 residue of HSA [22].
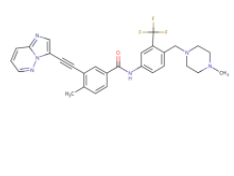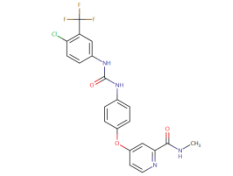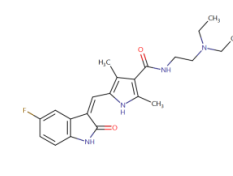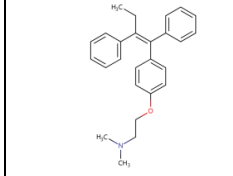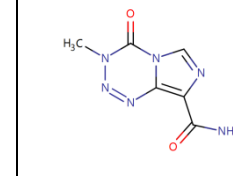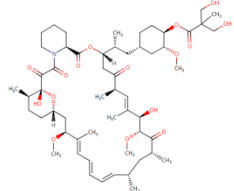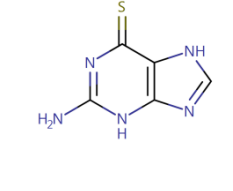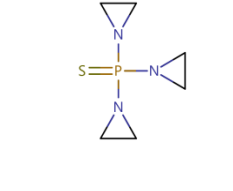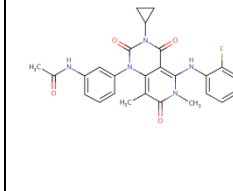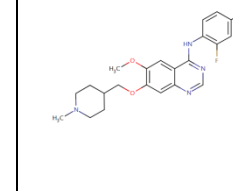
Busulfan (BN), approved by FDA in 1954, is used as an antineoplastic alkyl sulfonate agent for the treatment of myeloproliferative neoplasms (MPNs). It is applied currently by physicians as an alternative treatment in patients with BCR-/ABL1-negative MPNs that are intolerant to hydroxyl-urea [23, 88-90]. BN affects DNA-DNA as well as DNA-protein linkages, which ultimately control vital cellular processes such as replication, repair, and transcription. Also, BN has a cytotoxic effect on hematopoietic stem cells [91-93]. Based on an investigation by site-specific markers and molecular modeling methods, the locus binding of BN is the vicinity of site II (subdomain IIIA) of HSA. Two main forces involved in this interaction are hydrophobic and hydrogen bonding. The amino acid residues that are present in the interaction between BN and HSA are Thr420, Arg428, Lys190, Val424, Pro421, Thr527, Asn429, Ile523, and Glu425 [23].

Table 2. The chemical structures of the anticancer drugs.

5 fluorouracil	Acyclovir	Axitinib	Bicalutamide	Bosutinib
Busulfan	Capecitabine	Clofarabine	Crizotinib	Cyclophosphamide
Cytarabine	Dabrafenib	Dasatinib	Daunorubicin	Erlotinib
Fludarabine	Gefitinib	Gemcitabine	Halotestin	Ibrutinib
Imatinib	Irinotecan	Lapatinib	Lenalidomide	Letrozole
Medroxyprogesterone acetate	Methotrexate	Mitomycin	Mitoxantrone	Neratinib
Niraparib	Nintedanib	Olaparib	Oxaliplatin	Paclitaxel

Ponatinib	Sorafenib	Sunitinib	Tamoxifen	Temozolomide
Temsirolimus	Thioguanine	Thiotepa	Trametinib	Vandetanib

Table 3. **The Stern–Volmer quenching constants (KSV), binding constants (Ka), and quenching rate (Kq) values of HSA-anticancer drug systems.**

Drugs	T(K)	KSV (l mol^{-1})	Ka (l mol^{-1})	Kq (l mol^{-1} $^{s-1}$)	Refs.
Cyclophosphamide	298	4.08×10^{10}	1.84×10^{10}	4.08×10^{18}	[21]
Oxaliplatin	298	1.480×10^3	Not measured	1.480×10^{11}	[22]
Busulfan	298	1.83×10^3	1.84×10^3	3.27×10^{11}	[23]
Temozolomide	298	5.20×10^3	5.10×10^3	5.20×10^{11}	[24]
Thiotepa	298	2.84×10^3	1.05×10^3	2.84×10^{11}	[25]
Capecitabine	298	1.97×10^4	1.82×10^4	1.97×10^{12}	[26]
5-Fluorouracil	298	5.22×10^3	0.759×10^4	5.22×10^{11}	[27]
Methotrexate	298	4.81×10^4	5.92×10^4	4.81×10^{12}	[28]
Fludarabine	298	1.48×10^4	1.637×10^4	1.48×10^{12}	[29]
Thioguanine	298	8.69×10^4	3.67×10^5	1.52×10^{13}	[30]
Clofarabine	298	4.20×10^3	3.60×10^3	5.98×10^{12}	[31]
Cytarabine	298	0.925×10^3	2.141×10^3	1.54×10^{11}	[32]
Bosutinib	298	4.69×10^4	2.03×10^5	4.69×10^{12}	[33]
Axitinib	298	0.91×10^5	1.08×10^5	0.91×10^{13}	[34]
Dabrafenib	298	0.976×10^5	Not measured	0.976×10^{13}	[34]
Dasatinib	298	3.50×10^4	4.45×10^3	3.50×10^{13}	[35]
Ibrutinib	298	4.64×10^4	7.05×10^4	4.64×10^{12}	[36]
Ponatinib	298	4.57×10^4	4.93×10^4	4.57×10^{12}	[37]
Trametinib	298	6.70×10^4	6.82×10^4	1.321×10^{13}	[38]
Vandetanib	303	7.70×10^3	7.63×10^3	7.70×10^{11}	[39]
Crizotinib	298	3.23×10^4	3.60×10^4	3.23×10^{12}	[40]
Lapatinib	303	1.24×10^5	1.49×10^5	1.24×10^{13}	[41]
Erlotinib	298	4.49×10^4	8.13×10^4	4.49×10^{12}	[42]
Gefitinib	298	8.22×10^5	1.63×10^5	8.22×10^{12}	[5]

(Table 3) contd….

Drugs	T(K)	KSV (l mol^{-1})	Ka (l mol^{-1})	Kq (l mol^{-1} s^{-1})	Refs.
Imatinib	290	6.9×10^4	1.89×10^5	6.9×10^{12}	[43]
Nintedanib	298	2.55×10^3	1.04×10^3	4.4×10^{11}	[44]
Sunitinib	298	2.94×10^4	3.04×10^4	2.94×10^{12}	[45]
Neratinib	298	6.54×10^4	8.10×10^4	6.54×10^{12}	[46]
Sorafenib	298	3.67×10^4	5.32×10^4	6.12×10^{12}	[47]
Niraparib	298	3.38×10^4	4.40×10^4	3.38×10^{12}	[48]
Temsirolimus	298	4.9×10^4	2.90×10^4	8.40×10^{12}	[49]
Lenalidomide	298	2.55×10^4	2.33×10^4	9.44×10^{12}	[50]
Olaparib	298	2.90×10^3	Not measured	2.90×10^{11}	[51]
Acyclovir	298	2.84×10^4	2.89×10^4	2.98×10^{12}	[52]
Paclitaxel	298	1.26×10^5	4.57×10^4	1.26×10^{13}	[53]
Mitomycin	298	2.12×10^4	2.71×10^4	2.12×10^{12}	[54]
Daunorubicin	295	3.58×10^4	9.17×10^4	3.58×10^{12}	[55]
Mitoxantrone	298	3.17×10^4	1.55×10^5	3.17×10^{12}	[56]
Irinotecan	298	4.47×10^4	3.23×10^4	8.31×10^{12}	[57]
Bicalutamide	298	Not measured	1.95×10^4	0.853×10^{12}	[58]
Fluoxymesterone	298	10.53×10^{10}	4.39×10^{10}	10.53×10^{18}	[21]
Tamoxifen	310	1.05×10^3	2.45×10^6	5.75×10^{12}	[59]
Medroxyprogesterone acetate	298	1.07×10^4	2.50×10^4	1.77×10^{12}	[60]
Letrozole	298	6.74×10^5	6.74×10^5	3.16×10^{13}	[61]
Estradiol	310	7.35×10^5	1.02×10^4	4.60×10^{13}	[59]

Temozolomide (TMZ), a second-generation alkylating agent approved by the FDA in 1999, has anti-tumor activity against resistant malignancies such as metastatic melanoma and glioblastoma multiforme [88, 94]. The mechanism of action of TMZ is based on the deposition of methyl groups in guanine bases. As a result, it causes a nick in DNA structure, stimulating apoptosis and the inability of the cell repair system [95]. Docking and molecular dynamics methods revealed that TMZ is located in the subdomain IIA. In this complex, three amino acid residues (Cys34, Trp214, and Tyr138) are involved in this interaction through hydrogen bonds [24].

Triethylenethiophosphoramide (Thio, TEPA), a tri-functional alkylating agent, was approved by the FDA in 1994 as a combination therapy for relapsed or refractory leukemia, breast, ovarian, and bladder cancers. Thiotepa, as an alkylating agent, is involved in disrupting the cell repair mechanism by increasing cytotoxicity [88, 96, 97]. Based on both static and dynamic approaches, it was found that the interaction of the Thiotepa -HSA complex through a quenching mechanism is at domain I of HSA. There are 15 amino acid residues that stabilize Thiotepa in its binding site by hydrogen bonding interactions (Tyr161, Ala143, Ser193, Arg145, Phe157, Arg186, Phe149, Asp108, Lys190, Glu141, Leu185, Ile142, Gly189, Leu154, and Glu188) [25].

2.4. Antimetabolite Anticancer Drugs

Antimetabolite agents, as the first generation of targeted drugs, are the most useful group for the treatment of many cancers. There are various new antimetabolite drugs in clinical development. Antimetabolites are the most widely used and the oldest anticancer drugs and inhibit nucleic acid metabolism [98]. Antimetabolite agents and biologic molecules are structurally similar, and these agents participate in critical biochemical processes that require native metabolites [99].

Capecitabine (CAP), a classical cytotoxic agent, is a target-specific oral fluoropyrimidine that is activated in tumor tissue by high intra-tumoral concentrations of thymidine phosphorylase (TP). CAP had accelerated approval in 1998 to treat metastatic breast cancer resistant to paclitaxel [100-102]. It was specifically designed to reduce systemic exposure of normal tissues to fluorouracil and increase fluorouracil concentrations in tumor cells [100, 101]. Based on NMR studies, it was found that CAP is effectively bound to subdomain IIA. Discovery showed that the CAP molecule was mainly surrounded by the residues of Lys195, Leu198, Ala210, Trp214, Arg218, and Leu347 with a binding energy of -6.01 kcal.mol^{-1}. The docking studies of the system showed that the electrostatic energy was -0.13 kcal/mol and had potential interactions with Trp214 [26].

5-fluorouracil (5-FU), which inhibits RNA and DNA synthesis, was approved by the FDA in 1962 [102]. The binding interaction of this anticancer drug with HSA was reported by a combination of molecular docking method and spectroscopic techniques. Several studies showed that the nature of the forces involved in the binding interaction between HSA and FU molecules were hydrogen bonding and van der Waals force interactions. These interactions make the local microenvironment in subdomain IIA of HSA more hydrophobic than its native state. Besides, the interaction at a low concentration of FU caused considerable conformation alterations of the protein, leading to the increase of the compact α-helix structure. Nevertheless, the high concentration of FU made the compact α-helix structure decrease. Based on the molecular docking study, FU could enter inside Sudlow's site I, a hydrophobic cavity of subdomain IIA, in the closeness of Trp214 residue with the configuration of specific hydrogen bonding with Lys199 and Trp214 residues, causing the fluorescence quenching of Trp214 through a static quenching mechanism [27].

Methotrexate (MTX), an inhibitor of tetrahydrofolate dehydrogenase that prevents the formation of tetrahydrofolate, acts as an antineoplastic, anti-inflammatory, and antimetabolic drug. MTX was approved by the FDA in 1972 [28, 103, 104]. MTX has many advantages including antiviral molecules, bactericidal, and promising therapeutic effects against the recurrence of malignancies, such as ovarian and breast cancer. Moreover, MTX can inhibit dihydrofolate reductase. Therefore, this enzyme is essential for the biosynthesis of tetrahydrofolate from folic acid. Thermodynamic parameter studies revealed that the binding reaction is spontaneous and that hydrogen bonds and van der Waals interaction play a significant role in the reaction. The molecular modeling approach and site marker competitive displacement experiments showed that MTX binds with appropriate affinity to the site I of HSA [28, 99, 104]. The results achieved by the molecular docking study demonstrated that the mean value of MTX interaction with HSA could be attributed to MTX hydrogen bonds with Gln196, Lys199, Arg218, Arg222, and Asn295 residues [105].

Fludarabine (FLU), approved by FDA in 2006, plays an important role in improving the condition of patients with CLL and indolent B-cell malignancies [88, 105, 106]. FLU in malignancies, by intercalating in the DNA structure inhibits transcription. Furthermore, FLU inhibits key enzymes in the process of cell growth and proliferation including ribonucleotide reductase, DNA primase, and DNA ligase [106, 107]. Molecular docking showed that HSA and FLU are more likely to act the site I *via* hydrogen bond interaction. This complex is surrounded by many amino acid residues such as Tyr452, Ala210, Gln194, Glu450, Ala196, Val455, Leu347, His242, Leu481, Lys199, Trp214, Leu198, Phe211, Lys212, and Ser202 [29].

Thioguanine (TG), as an anti-leukemic agent, was approved by the FDA in 1966. It is also used to treat various cancers such as glioblastoma, soft tissue sarcoma, melanoma, osteosarcoma, mesothelioma, neuroendocrine tumors, lymphomas, biliary tract cancer, pancreatic, and lung squamous cell carcinomas [88, 108, 109]. TG acts by integrating the single-stranded DNA and RNA to stop proliferation and transcription, respectively. It also inhibits the crosslinking and exchange of sister chromatids [110]. A molecular docking study determined that TG binds in the subdomain IIA through a hydrogen bond. The amino acid residues involved in the binding process are Lys195, Glu292, and Arg222 [30].

Clofarabine (Clolar) is a nucleoside analog for treating cancer. It was approved by the FDA in 2004, for the treatment of three important types of diseases including acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), and myelodysplastic syndrome (MDS). Its effectiveness consists of 3 mechanisms; incorporation into DNA, inhibition of ribonucleotide reductase, and induction of apoptosis [111, 112]. Molecular docking studies showed that Clolar binds nearby site II of HSA. Hydrogen bonding and hydrophobic interactions were the main bonding forces between them. Moreover, 16 amino acid residues are involved in the formation of Clolar-HSA complex (Gln29, Ala26, Phe149, Gln196, Ser192, Ser193, Tyr150, Cys245, Pro147, Cys246, Ala151, Tyr148, Leu250, Gly248, His146, and Lys106) [31].

Cytarabine, also known as cytosine arabinoside (ara-C), is an anticancer drug, which was approved in 1999 for the treatment of susceptible diseases including AML, CML, ALL, and non-Hodgkin's lymphoma [88, 113, 114]. After entering the body, cytarabine follows two paths; the first, rapid deamination by deoxycytidine deaminase (DCD), and the second, entering the cell through specific membrane transport proteins. Inside the cell, cytarabine acts only during phase S, which inhibits the DNA polymerase enzyme [115, 116]. Molecular modeling and spectroscopy approaches showed that the binding site of cytarabine was situated in subdomain IIA *via* hydrophobic interaction and hydrogen bonding. Cytarabine was surrounded by many amino acid residues such as Lys199, Arg222, Tyr150, Leu238, Ala291, His242, Leu260, Ser287, Arg257, and Ala261 [32].

Gemcitabine (GEM) was approved by the FDA to treat a wide range of solid tumors, including breast, lung, and pancreatic cancers. The molecule has an antimetabolite mechanism that its function is the enzymatic inhibitor such as DNA polymerase and ribonucleoside reductase. According to molecular docking studies, site 5 of subdomain IIIB is the location of the gemcitabine molecule in BSA. The molecule was surrounded by many amino acid residues such as Val599, Phe532, Val570, Leu598, Leu555, Leu552, Thr602, Lys548, Phe574, Met571 and Ala551. Among them, two amino acid residues, Lys548 and Thr602 have the most impact than the other residues [117-123].

2.5. Biological and Targeted Agents

Biological and targeted therapy methods for treating various cancers have increased in prominence due to their potential for reduced toxicity and improved efficiency. Generally, two major types of targeted agents are still under clinical examination. The first chemotherapeutic agents are critical for the survival and proliferation of pathologic cells. The second targeted agents include the use of tumor-specific ligands to deliver nonselective cancer drugs to malignant cells [124-126].

Bosutinib (BST), an oral Src/Abl tyrosine kinase inhibitor (TKI), was approved in 2012, is contributed to rationalized therapy in CML [88, 127, 128]. Based on biochemical and proliferation assays, BST could be active against Bcr-Abl and Src family kinases. The Bcr-Abl fusion gene product is critical for the progression of CML. Many studies have shown that Src kinases play a key role in causing cancer complications including malignant cell transformation, tumor progression, and metastatic spread [129-131]. Competitive and modeling studies showed that the binding site for BST was site II of BSA. At this site, BST was surrounded by 23 amino acid residues (Thr491, Leu406, Val432, Gln389, Gly430, Phe402, Ser488, Tyr410, Leu429, Gly433, Asn390, Leu452, Lys413, Arg409, Pro492, Arg412, Val408, Phe487, Leu386, Gly433, Asn390, Thr448 and Arg484) [33].

Axitinib (AXT) as a selective and potent second-generation inhibitor of vascular endothelial growth factor receptors 1-3 (VEGFRs), is approved by the FDA in 2012. AXT is used to treat patients with kidney cancer after failure of a prior systemic therapy [88, 132]. Based on the competitive drug displacement and molecular docking methods, the binding location of AXT to HSA was determined in the subdomain IIA. The drug was surrounded by several residues including Tyr-150, Lys195, Leu198, Lys199, Trp214, Arg218, Leu219, Arg222, Leu238, Val241, His242, Arg257, Leu260, Ala261, Ile264, Ser287, Ile290, Ala291, Glu292, Asp451 and Val455 [34].

Dabrafenib (Tafinlar®), approved by FDA in 2013, is a mutant BRAF kinase inhibitor for the treatment of solid tumors, especially malignant melanoma. The drug has a generally mild and manageable toxicity profile and was designed to target Val600 to replace glutamic acid, which is often seen in patients with melanoma [88, 133-135]. The situation of dabrafenib on HSA is subdomain IIIA. In this complex, the hydrophobic interaction has a significant function. The key residues related to interaction are Gln390, Lys414, Leu394, Arg410, Lys414, Arg485, Tyr411, Leu453, Ser489, and Asn391 [35].

Dasatinib (DAS), a tyrosine kinase inhibitor, was approved by the FDA in June 2006 to treat Philadelphia-chromosome-positive acute lymphoblastic leukemia (Ph-positive ALL) and CML with resistance to kinase inhibitors [88, 136]. The function of DAS is to inhibit the fusion protein BCR-ABL and the Src-kinase family. Moreover, DAS in combination with Erlotinib can prevent the acquired resistance *via* EMT [137, 138]. The molecular docking has revealed that DAS has a binding site in the subdomain IIA, surrounded by hydrophobic moieties. The amino acid residues involved in the interaction include the following: Leu302, Ala229, Pro224, Lys225, Ala226, Lys317, Pro3O3, Asp314, Phe228, Asn318, Lys313, Asp308, Ser232, Glu222, Ala307, Ala306, Cys316, Val315, and Phe309 [139].

Ibrutinib (IBR), an irreversible inhibitor of Bruton tyrosine kinase (BTK), was approved by the FDA in 2013 to treat patients with small lymphocytic lymphoma (SLL), CLL or B-cell malignancies (88, 140, 141). BTK, as a cytoplasmic tyrosine kinase, has a crucial function at all stages of B-cell maturation including development, activation, and differentiation [142]. Molecular docking studies determined

that IBR binds to HSA at the subdomain IIA. The drug IBR was simultaneously surrounded by some amino acid residues Cys245, Arg197, His247, Cys200, Gln196, Ala201, Cys246, His242, Leu203, Gln204, and Cys253 [36].

Ponatinib (PTB or AP24534), a potent oral drug, is a tyrosine kinase inhibitor that blocks mutated and un-mutated BCR-ABL. It was approved by the FDA in 2012 to treat patients with Ph-positive ALL and CML. According to previous studies, ponatinib impaired the function of the respiratory chain, which was accompanied by increased ROS levels and decreased mitochondrial membrane potential [88, 143, 144]. Molecular modeling studies indicated that PTB was located in Sudlow's site I (subdomain IIA) of HSA. Seventeen amino acid residues were involved in the interaction, include: Ile264, Pro447, Tyr150, Ile190, Ser267, Cys448, His242, Arg222, Leu260, Lys436, Arg218, Asp451, Arg257, Lys199, Ala261, Gln196, and Ala291. Thus, it has been proven that hydrogen bonds and hydrophobic forces are mainly involved in stabilizing the interaction of PTB and HSA [37].

Trametinib (Mekinist), an orally bioavailable MAPK kinase inhibitor, was approved by the FDA in 2013 to treat patients involved with melanoma, NSCLC, and anaplastic thyroid malignancies. The drug has several functions that can be mentioned as follows: inhibiting cell proliferation in melanoma by blocking the activation of ERK1/2 and improving survival in melanoma patients [88, 145-147]. Site marker displacement experiments and molecular docking reveal that trametinib primarily binds to site I of HSA through hydrogen bonds and hydrophobic interactions. The complex was surrounded by some amino acid residues, including His242, Lys195, Gln196, Arg218, Ser192, Arg222, Leu219, Ala291, and Asp451 [38].

Vandetanib (VDB), an orally active antagonist of vascular endothelial growth factor (VEGF), (VEGFR-2), (EGFR or HER1 or ErbB1), and RET kinase, was approved by the FDA in 2011 to treat patients with metastasis of medullary thyroid carcinoma (MTC) [88, 148, 149]. Molecular docking analysis showed the location of the drug on HSA was subdomain IIA. The amino acid residues involved in the interaction of HSA and VDB were the following: Leu260, Tyr150, Ala261, Glu153, Ile264, Lys195, Ser287, Gln196, His288, Leu198, Ile 290, Lys199, Ala291, Trp214, Glu292, Arg218, Val343, Leu219, Asp451, Arg222, Ser454, Leu238, Val455 His242, and Arg257 [39].

Crizotinib (CRB), acts as an anaplastic lymphoma kinase (ALK) and c-ROS oncogene 1 (ROS1) inhibitor. CRB was approved by FDA in August 2011 for the treatment of some non-small cell lung carcinoma (NSCLC) [150]. Competitive experiments and molecular docking discoveries showed that the binding site of CRB is in subdomain IIA. Based on the computed thermodynamic parameters and molecular docking studies the main binding forces involved in the formation of the BSA-CRB complex were electrostatic and hydrophobic interactions. It was shown that CRB is related to residues of Try149, Glu152, Ser191, Arg194, Arg198, Trp213, Arg217, Arg256, His287, Ala290, Glu291, Ser343, and Asp450 [40].

Lapatinib (LAP) was approved on March 13, 2007, by the FDA to treat patients with HER2 over-expressing

metastatic breast cancer, who had received prior therapy such as taxane, anthracycline, and trastuzumab. LAP is a small hydrophobic drug molecule, an oral, dual tyrosine kinase inhibitor of ErbB-1 and ErbB-2 for use in the compound with capecitabine and is approximately 99% bound to HSA [151, 152]. Molecular docking studies showed that lapatinib is mainly located within site III in subdomain IB of HSA. The formation of the HSA-LAP complex at site III involves 25 residues, includes: Asn109, Pro110, Asn111, Leu112, Pro113, Arg114, Leu115, Val116, Arg117, Met123, Phe134, Lys137, Thr138, Glu141, Ile142, Arg145, His146, Phe149, Phe157, Tyr161, Leu182, Leu185, Arg186, Gly189 and Lys190 [39].

Erlotinib (ERL), orally available, is a reversible tyrosine kinase inhibitor of the EGFR and was approved by the FDA in November 2004 to treat advanced NSCLC, pancreatic, and colorectal cancer. The drug plays several roles that can suppress tumor cell proliferation, blocks the cell cycle process, and induces apoptosis in EGFR-overexpressing human tumor cells [153-156]. The mechanism of action of this drug is inhibition of the intracellular domain through the ATP binding site of the receptor [157, 158]. This medication's molecular docking studies demonstrate that erlotinib binds to site IIIA of HSA [42]. Gefitinib (GEF, Iressa) is a selective inhibitor drug of the tyrosine kinase domain of EGFR approved in 2003 to treat metastatic NSCLC [158, 159]. GEF affects the expression of HER2 and EGFR by reducing HER2, HER3, and EGFR phosphorylation in breast cancer cells, resulting in obstruction of the downstream signaling pathways of the STAT3, MAPK, and AKT pathways. It can also reduce glycogen synthase kinase 3β (GSK-3β) phosphorylation as a target of the AKT signaling pathway [160, 161]. The thermodynamic analysis displays gefitinib can bind to HSA by van der Waals and hydrogen interactions. Molecular docking discoveries showed that the binding site of GEF is subdomains IB, IIA, and IIIA in the center of HSA. Based on studies of the interactions of GEF-HSA complex at sites IIA, IIIA, and IB, including Arg218, Arg222, His288, Glu292, Val293, Glu294 from IIA, Pro447, Cys448, Tyr452 from subdomain IIIA, and Glu153, Phe157, Asp187, Glu188, Ala191, Ser192, and Lys195 from subdomain IB. Additionally, there are four hydrogen bonds between GEF and the residues of Glu188, Lys195, Arg218, and Glu292, demonstrating that the hydrogen bond plays a crucial function in this interaction [5, 162].

Imatinib (IMT) is an inhibitor of the Bcr-Abl tyrosine kinase, PDGFRα, β (platelet-derived growth factor receptor), and KIT receptor [163, 164]. IMT is the first targeted anticancer drug introduced in clinical development and is an effective drug used against two important malignancies, including gastrointestinal stromal and chronic myeloid leukemia [165, 166]. The molecule has a high affinity to bind to albumin, plasma proteins, and AGP (α1-acid glycoprotein) being the primary carrier. HSA is known as a secondary carrier, in critical states determined by low AGP levels, such as hyperthyroidism, hepatitis, hepatic cirrhosis, malnutrition, nephrotic syndrome, cachexia, and pancreatic cancer [163]. According to displacement studies and thermodynamic parameters, it was suggested that imatinib bound at subdomain IIA. It was reported that IMT is

surrounded by amino acid residues of Ala216, Leu348, Glu207, Ser328, Leu210, Ala341, Ser201, Cys476, Gly327, Ser343, Leu346, Phe205, Arg347, Gly206, Lys350, Leu330, Tyr352, Glu351, Lys204, Leu326, Trp213, Phe325, Val342, Arg208, Asp323, and Ala354 [33, 43].

Nintedanib (NIB) a triple angiokinase inhibitor, was evaluated in various cancers such as pancreatic cancer, NSCLC, ovarian, and colorectal [167, 168]. It can block PI3K/MAPK activity, inhibit *in vitro* proliferation of pancreatic ductal adenocarcinoma cell (PDAC), and lead to the induction of apoptosis [167]. The residues involved in the binding site, the forces involved in the HSA-NIB complex, and the energy ranking were estimated by molecular docking. So, It was found that NIB binds at close site II (subdomain III) of HSA. The molecule interacts *via* hydrogen bonding with two residues Val409, and Glu542. NIB-HSA complex is also stabilized by the hydrophobic interaction with some residues of Glu334, Glu390, Leu394, Asn405, Ala406, Thr540, Lys541, Leu544, and Lys545 [44].

Sunitinib (SU), an oral multi-targeted tyrosine kinase inhibitor, was approved by the FDA in 2011. SU has antitumor and antiangiogenic activities for the treatment of pancreatic neuroendocrine tumors [169, 170]. *In vivo*, its most important roles include inhibition of VEGFR-1, VEGFR-2, fetal liver tyrosine kinase receptor 3 (FLT3), platelet growth factor receptors α and β (PDGFR). *In vitro*, SU inhibited some factors involved in cell growth such as PDGF, VEGF, SCF, and induction of apoptosis [171]. Molecular docking suggested that SU binds to subdomain IIA. The amino acids involved in the binding site include: Arg222, Trp214, Leu219, Arg257, Ala291, Lys195, His288, Glu292, Lys199, Glu153, Tyr150, Phe157, Glu188, and Ser192 [45].

Neratinib (NRB) was approved by FDA, in 2017 to treat patients with amplified breast cancer with HER2 overexpression, colorectal, lung, and bladder cancers. In addition, this drug was used as adjuvant trastuzumab-based therapy. NRB, as an irreversible TKI, is an inhibitor that associates with the catalytic domain of various EGFR family molecules such as HER2, HER4, and EGFR and inhibits their downstream signaling pathways. Experimental findings and molecular modeling studies showed that the subdomain IIA was determined as the binding site of NER. Hydrogen bonds and van der Waals, contribute to the forming of the HSA-NER complex. Many amino acids appear in the interaction, including Trp214, Leu260, Arg222, Ser192, Phe223, Ser287, Arg257, Leu198, Gln196, Leu238, Ala291, Ala215, Ala261, Ile290, Tyr150, Lys199, Glu153, His242, Lys195, Leu219, Lys199, Phe211, Arg218, Ser202, and Ile264 [46, 172-174].

Sorafenib (SOR), an oral kinase inhibitor, was approved by FDA to treat patients with hepatocellular carcinoma in 2005. This molecule directly inhibits the auto-phosphorylation of various receptor tyrosine kinases (RTKs) such as VEGFR1, 2, and 3, PDGFRβ, c-Kit, and RET [175-177]. Molecular docking discoveries showed that SOR binds within subdomain IIA of BSA. Based on studies, the interaction forces between SOR and HSA may involve hydrogen bonds, hydrophobic force, electrostatic, and van der Waals interaction [47, 178]. Moreover SOR is

surrounded by polar, charged and hydrophobic residues, such as Tyr173, Trp237, Ser238, Tyr286, Ser310, Tyr475, Glu176, Arg218, Arg222, Arg241, Lys245, Asp260, Asp279, Arg280, Asp282, Lys285, Glu315, Glu467, Arg468, Glu473, Asp474, Leu221, Leu257, Leu261, Val264, Ala281, Leu283, Ala284, Ile287, Lys309, Ile313, Ala314, Val316, Val366, Val456, Leu476, and Leu478 [47].

In March 2017, Niraparib (NIR) was approved by FDA for advanced malignancies such as peritoneal, fallopian tube, breast, prostate, and ovarian cancers. Also, its function was determined as a poly ADP-ribose polymerase (PARP) inhibitor. PARP inhibition is a key mechanism in treating cancers in which the repair system is impaired, especially in the BRCA1 and BRCA2 genes. These mutations increase the susceptibility to ovarian and breast cancers. Based on molecular docking and computational analysis, the binding site of NIR to HSA is site III. The binding interaction between NIR and HSA is hydrophobic, in which various amino acid residues are involved, including Ala158, Phe165, Arg186, Phe134, Leu115, Ile142, Tyr161, and Lys190 [48, 179, 180].

Temsirolimus (CCI-779) as an anticancer drug for patients with colon and renal cell carcinoma, was approved by the FDA in 2007. Temsirolimus inhibits the mammalian target of rapamycin (mTOR) kinase through binding to FKBP-12 and complexing with mTOR. Temsirolimus can reduce the transcription and increase degradation of cancerous inhibitors of protein phosphatase 2A (CIP2A) through autophagy. CIP2A is expressed in many cancers and plays an oncoprotein role [88, 181, 182]. Based on spectroscopy and molecular modeling studies, the situation of CCI-779 was located in Sudlow's site I of HSA. The residues of Lys199, Lys195, Lys432, Lys436, Lys439, Lys444, Arg218, Arg222, Asp187, Asp451, Asn429, Trp214, Tyr452, Gln221, Ala191, Leu198, Val343, Val433, and Pro447 stabilize CCI-779 in the binding site through hydrophobic interaction and hydrogen bonding [49].

Lenalidomide (LND), an oral immune-modulatory drug, was approved in 2005 to treat patients with multiple myeloma and lymphoma. Its mechanism of toxic action is through increases in the production of inflammatory cytokines and IL2 [88, 183-185]. Docking methods and site marker displacement assays indicated that the situation of LND on BSA was subdomain IIA. The amino acids involved in the interaction are including Val342, Trp213, Leu454, Leu197, Val481, Arg194, Asp450, Arg198, Leu346, Ser201, Leu480, Ala209, Ser453, Arg217 and Ser343 [50].

Olaparib (OLA), approved by the FDA in 2014, has antitumor activity in patients with ovarian, breast, and metastatic pancreatic cancer. OLA is known as a PARP inhibitor that targets DNA repair mechanisms during the destruction of the cellular repair system, especially for BRCA mutation-associated cancers [88, 186-188]. Dynamics simulations and molecular docking studies showed that OLA is stably bound to site I. In this situation, the drug is surrounded by several amino acids, including Lys195, Arg218, His288, Arg257, Ile264, Phe211, Ser287, His242, Leu238, Lys199, Gln196, Trp241, Ala291, Leu260, Glu292, and Ala261 [51].

Acyclovir (ACV), as a potent antiviral agent, was approved by the FDA in 1981 and has been generally used during the last few decades, especially for the treatment of viral infections, such as herpes simplex virus (HSV), varicella-zoster virus (VZV), Epstein-Barr virus (EBV), cytomegalovirus (CMV), and human herpesvirus 6 (HHV-6) [52, 189]. HSV infection due to induction immunosuppression, is common in patients undergoing cytotoxic therapy for cancer [190]. ACV by inhibition depends on interactions with DNA polymerase and thymidine kinase could suppress the synthesis of viral DNA [191]. The binding properties with HSA were analyzed using different advanced in silico and spectroscopic approaches. The results demonstrate that ACV binds within the hydrophobic pocket in the subdomains IIA and IIIA. The residues correlated with ACV in site I are Gln196, Lys199, Arg222, and Ala291 and in site II are Leu387, Asn391, Tyr411, Lys414, and Leu430 [52].

Penciclovir (PNV), an acyclic guanine nucleoside analog, is similar to acyclovir in the activity and potency against HSV. PNV was approved in 1996. The drug inhibits DNA synthesis through competitive inhibition of viral DNA polymerase [192]. The use of this drug can have several consequences, including: decreased cell growth and proliferation, over-expression of caspase-3 and induced apoptosis, inhibition of cell invasion and colony formation ability and finally upregulated level of E-cadherin protein [191, 193]. According to molecular modeling studies, the binding site of PNV at the protein level is similar to that of ACV at subdomains IIA and IIIA [52]. Discoveries demonstrated that PNV was mainly surrounded by the residues Glu153, Lys195, Lys199, His288, Ala291, and Glu292 in site I, and Asn391 and Tyr411 in site II [52].

2.6. Mitotic Inhibitors

The identification of anticancer drugs against endothelial cells is of considerable value for the treatment of patients with angiogenesis-related tumors. Most mitotic inhibitor compounds disrupt the basal function of mitotic spindles by two mechanisms, one being the major building blocks of microtubules and the other being the target tubulin. Based on previous studies, like other anticancer drugs, these types of anticancer drugs can stimulate apoptosis in tumor cells, which is considered the most important event in the treatment process [194-196].

Paclitaxel, approved by the FDA in 1991, is the first taxane in clinical trials and is also active against a broad range of malignancies that are commonly considered refractory to conventional chemotherapy. It is used to treat various cancers such as lung, ovary, and breast cancer. In the human body, two isoenzymes of cytochrome P450 are contributed to the biotransformation of paclitaxel by human liver microsomes. Paclitaxel reduces Bcl-2 expression and increases bax and Bcl-Xl expression, which in turn induces apoptosis [197-201]. A computational method was used to study the interaction of the potent paclitaxel with HSA. It was found that two binding sites were located in the cleft between domains I and III of HSA and at the interface of subdomains IIA and IIIA [53]. The studies showed that the paclitaxel molecule forms part of the wall in one of the two

main drug-binding cavities of HSA by binding to the surrounding area of Trp214 (subdomain IIA) [202].

2.7. Antibiotic Anticancer Drugs

Antibiotic anticancer drugs are an important class and are widely used to treat different tumors. Studies revealed that antibiotics, which inhibit mitochondrial biogenesis, can be used to eliminate cancer stem cells (CSCs). This group of drugs has significant effects in inhibiting melanoma, breast, DCIS (Ductal carcinoma *in situ*), prostate, glioblastoma, pancreatic, lung, and ovarian cancers [203, 204].

Mitomycin (MMC), approved by the FDA in 2002, has been used as a treatment approach against many malignancies, including bladder, gastric, pancreatic, breast, head, neck, cervical and NSCLC cancers [88, 205]. DNA alkylation is one of the key roles of mitomycin. In addition, it has several other roles, including inhibition of ribosomal RNA and subsequent suppression of the translation process, suppression of the enzyme thioredoxin reductase (TrxR), increase of P53 and P21 proteins and decrease of Bcl-2 expression in the induction of apoptosis in tumor cells [206-208]. Molecular docking investigation revealed that MMC was situated in the entrance of site I of HSA between subdomains IB and IIA. There are 11 amino acids surrounding MMC such as Lys195, His288, Gln196, Arg257, Ala191, Phe149, Tyr150, Ala291, Glu153, Tyr148, and Lys199 [54].

Daunorubicin (DNR), approved by the FDA in 1998, is one of the antitumor drugs widely used to treat AMLs [88, 209]. DNR damages DNA and induces apoptosis through its toxicity. Also, this drug is involved in apoptosis induced by TNFα, phosphoinositide 3-kinase (PI3K), NF-κB, and other cytotoxic agents. Furthermore, based on a novel study, DNR in combination with midostaurin inhibits the Aldo-keto reductase enzyme [209, 210]. Using modeling methods, the researchers found that the situation of DNR on HSA was site II. The amino acid residues involved in the interaction were Phe223, Arg222, Val216, Leu219, Arg218, Ile264, Phe211, Leu238, Leu266, Ala261, Trp214, Ile290, Glu292, Ala291, Lys256, Ser257, His288, Val241, Arg258, His242, Asp256, and Lys195 [55].

Mitoxantrone (Novantrone®), a doxorubicin analog, is an antineoplastic and immune-modulatory agent. It was approved by the FDA in 1987 to treat AML and prostate cancer [211, 212]. This small molecule passes through the cell membrane by the flip-flop mechanism. Inside the cell, MTX reduces the severity of the disease through various mechanisms, including: decreased B-cell, T-cell, and macrophage proliferation. As a result, it destroys the production of antibodies and IL-1, IL-6, and TNF-α cytokines [212-214]. Molecular modeling studies showed that MTX binds with HSA at subdomain IB. The drug was surrounded by many amino acid residues, including Leu115, Ala194, Phe149, Val456, Ile142, Ala191, Gln459, Gly189, His146, Arg114, Arg186, Arg197, Lys190, Lys196, Val116, Val455, and Ser193 [56].

2.8. Topoisomerase Inhibitors

Topoisomerase (Topo) proteins are essential for vital functions such as cell survival and DNA processing. The enzyme includes two types, I and II. They have different characteristics that make them different. Topo I is not a specific cell cycle enzyme, it only causes single-stranded fractures and its mechanism is ATP-independent, while Topo II is a cell-specific enzyme that causes single-stranded and double-stranded fractures and desperately needs ATP. Based on the mentioned characteristics, this enzyme was used clinically as a target in anticancer drugs. Topoisomerase inhibitors are one of the best stimulants for the apoptosis process. These inhibitors activate caspases by damaging DNA and releasing proapoptotic mitochondrial molecules. Protein kinases DNA-PK, ataxia-telangiectasia-mutated (ATM), and ataxia telangiectasia and rad3-related (ATR), which bind to DNA breaks, initiate the cell response to DNA damage caused by topoisomerase inhibitors. Cell death induced by these inhibitors is controlled by upstream pathways such as the proapoptotic SAPK/JNK, Chk2, and c-Abl pathways [74, 215, 216]. The mechanism of action of topoisomerase inhibitor I is that it allows Topo I to covalently bind to the end of 3'-P on the broken strand by forming a complex called "dead-end" [217]. Numerous malignancies are affected by topoisomerase II inhibitors. However, the multi-drug resistance produced by these inhibitors is an important consideration. Due to variable functions, topoisomerase II inhibitors have various mechanisms of action, including increased detoxification and decreased activation [74].

Irinotecan (CPT-11), a water-soluble analog of CPT, is a topoisomerase I inhibitor and was approved by the FDA in 1996 for the treatment of many types of human tumor cells, including SCLC, NSCLC, malignant lymphoma, cervical, ovarian and colorectal cancer [88, 218-221]. The drug is a chemotherapy agent, and has a significant function in S-phase-specific cell killing by poisoning Topo I in defective cells. Following this action, basic intracellular processes such as replication, transcription, and repair change. Another role of irinotecan is the inhibition of acetylcholinesterases [222, 223]. Docking results demonstrated that CPT-11 binds to subdomain IIA. The amino acids involved in the interaction include: Arg222, His146, Lys195, Ser193, Lys190, Tyr150, Arg145, Trp214, Ala191, Asp187, Ala194, and Arg218 [57].

2.9. Hormonal Agents

The last category of anticancer drugs discussed in this article is hormonal agents. Estrogen plays an essential role in the growth and survival of normal and cancer cells by activating the estrogen receptor (ER). Activation of these receptors has significant consequences in the cell, such as: cell division, formation of new blood vessels, suppression of apoptosis, and protease activity. These events play a role in the development of breast and prostate cancer. In these types of cancer, there has been a remarkable development in hormonal therapy, which includes various methods such as estrogen therapy, releasing hormone agonists, antiandrogen therapy, combined androgen blockade *etc.* [224-226].

Bicalutamide, a nonsteroidal antiandrogen, was approved by FDA in 1995 to treat patients with early prostate cancer. The key role of this drug is the inhibition of androgen receptors, which exerts its effect by blocking the G1/S phase of the cell cycle [227-229]. Molecular docking studies

Table 4.   **Proposed use/uses and mechanism of action of the anticancer drugs.**

Categories	Approved Drugs	Proposed Use/Uses	Mechanism of Action	Refs.
	Cyclophosphamide	Leukemia, lymphomas, and breast	Interaction with NF-κB, IL-6, TNF-α, and many caspases	[82-84]
	Oxaliplatin	Colorectal	Involved in replication and transcription	[87]
Alkylating agents	Busulfan	CML	Effect on DNA-DNA and DNA-protein interactions	[91, 92]
	Temozolomide	Glioblastoma and astrocytoma	Changes in DNA structure and induction of apoptosis	[95]
	Thio-TEPA	Breast, ovarian, and bladder	Destroying the cell repair mechanism	[97]
	Capecitabine	Breast and colon	Increasing the concentration of thymidine phosphorylase	[102]
	5-fluorouracil	Solid tumors	Suppression of RNA and DNA synthesis	[102]
	Methotrexate	Solid tumors	Enzymatic inhibition	[104]
Antimetabolites	Fludarabine	CLL	Inhibition of replication and transcription	[106, 107]
	Thioguanine	AML and CML	Inhibition of proliferation and transcription	[110]
	Clofarabine	ALL	Induction of apoptosis	[111, 112]
	Cytarabine	Leukemia	Inhibition of DNA polymerase enzyme	[115, 116]
	Gemcitabine	Liver	Inhibitor of DNA polymerase and ribonucleoside reductase	[117, 118]
	Bosutinib	Pc-CML	Tyrosine kinase inhibitor	[128]
	Axitinib	Advanced renal cell carcinoma	VEGFR inhibitor	[132]
	Dabrafenib	Malignant melanoma	Mutant-BRAF kinase inhibitor	[134, 135]
	Dasatinib	CML	Tyrosine kinase inhibitor	[136]
	Ibrutinib	CLL	Bruton tyrosine kinase inhibitor	[141]
	Ponatinib	Pc-CML	Tyrosine kinase inhibitor	[144]
Biological and targeted agents	Trametinib	Malignant melanoma	MAPK kinase inhibitor	[147]
	Vandetanib	Medullary thyroid	EGFR and RET kinase inhibitor	[149]
	Crizotinib	NSCLC	ALK and ROS1 inhibitor	[150]
	Lapatinib	Breast cancer	Tyrosine kinase inhibitor	[151]
	Erlotinib	Pancreatic and NSCLC	Reversible tyrosine kinase inhibitor	[156]
	Gefitinib	NSCLC	Tyrosine kinase inhibitor	[5]
	Imatinib	Pc-CML	Tyrosine kinase inhibitor	[43]
	Nintedanib	Pancreatic cancer, NSCLC, ovarian, and colorectal	Triple angiokinase inhibitor	[167]
	Sunitinib	Gastrointestinal stromal	Multi-targeted tyrosine kinase inhibitor	[169]
	Neratinib	Breast	Irreversible tyrosine kinase inhibitor	[161]

(Table 4) contd….

| Categories	Approved Drugs	Proposed Use/Uses	Mechanism of Action	Refs.
	Sorafenib	Renal cell, liver, and thyroid	Kinase inhibitor	[178]
	Niraparib	Ovarian	PARP inhibitor	[180]
	Temsirolimus	Renal-cell carcinoma	mTOR kinase inhibitor	[181]
	Lenalidomide	Multiple myeloma	Modulator of immune system	[185]
	Olaparib	Ovarian	PARP inhibitor	[188]
	Acyclovir	HSV	Suppression synthesis of viral DNA	[191]
	Penciclovir	HSV	Inhibition of viral DNA polymerase	[191]
Mitotic inhibitors	Paclitaxel	Ovarian, breast, and lung	Inducing apoptosis	[201]
	Mitomycin	Stomach and pancreas	Inducing apoptosis and suppression of the thioredoxin reductase	[208]
Antibiotic	Daunorubicin	AML	Inducing apoptosis through DNA damaging and triggering TNFα, PI3K, NF-κB & Aldo - keto reductase inhibitor	[209, 210]
	Mitoxantrone	Cute leukemia, lymphoma, prostate, and breast	Antineoplastic and immune-modulatory agent	[212]
Topoisomerase inhibitors	Irinotecan	Colorectal, ovarian, and NSCLC	Topoisomerase I and acetylcholinesterases inhibitor	[218, 223]
	Bicalutamide	Prostate	Cell cycle arresting	[229]
	Fluoxymesterone	Breast	Interaction with the glucocorticoid receptor	[21]
Hormonal agents	Tamoxifen	Breast	ER receptor inhibitor and modulator of the signaling pathways such as apoptosis	[234, 242]
	Medroxyprogesterone acetate	Kidney and womb	Anti-proliferative transcriptional effect	[236, 238]
	Letrozole	Breast	Aromatase inhibitor	[241]

revealed that the binding site of bicalutamide to HSA was located in the hydrophobic inner hub of site I. Hydrogen bonding and hydrophobic interactions are the main binding forces in forming of BIC-HSA complex. The residues involved in the interactions were Met123, Tyr138, Tyr161, Leu115, Pro118, Ala126, Phe134, Tyr161, Phe165, and Leu182 [58, 230].

Fluoxymesterone (Halotestin), a synthetic androgen, was approved by the FDA in 1956 to treat patients with resected early-stage breast cancer. The chemical structure of the drug is similar to 11β-hydroxyl, which increases the interaction with the glucocorticoid receptor. As a result, elevate the anti-glucocorticoid action of fluoxymesterone [88, 231, 232]. Spectroscopy and molecular docking approaches revealed that fluoxymesterone was located on subdomain IB in site III. More discoveries demonstrate that some amino acid residues have a major effect on interactions around ligands (Tyr161, Leu115, Ile142, Arg117, Tyr138, Leu182, Glu141, and Met123) [21].

Tamoxifen (TAM), an essential drug for the treatment of breast cancer, was approved by the FDA in 1977. The primary mechanism of action of TAM is the inhibition of the estrogen receptor (ER). Scientists later discovered that it was involved in other mechanisms of signaling proteins, such as protein kinase C (PKC), calmodulin, transforming growth factor-β (TGF-β), proto-oncogene c- Myc, mitochondrial permeability transition (MPT) and oxidative stress. Moreover, it has implicated the role of MAPKs including p38, JNK and caspases in TAM-induced apoptotic pathway [88, 233, 234]. Molecular modeling results showed that the drug binds in the vicinity of subdomain IIA. The amino acid residues that are involved in this complex include: Trp214, Ala291, Gln196, Glu292, Ile290, Leu260, Arg222, Lys199, His288, Phe157, Glu188, His242, Leu219, Arg257, Tyr50, Lys195, Arg218, Glu153, and Leu238 [59].

Medroxyprogesterone acetate (MPA), a progestin drug was approved by the FDA in 1992 to treat oral contraception and hormone replacement therapy in patients with breast and prostate cancer. MPA has an Anti-proliferative transcriptional effect in estrogen receptor-positive subsequent breast cancer. The molecular docking results showed that MPA is located at subdomain IIIA. Moreover, many residues are involved in surrounded of MPA, include: Glu176, Tyr173, Ala214, Arg220, Glu219, Ala217, His265,
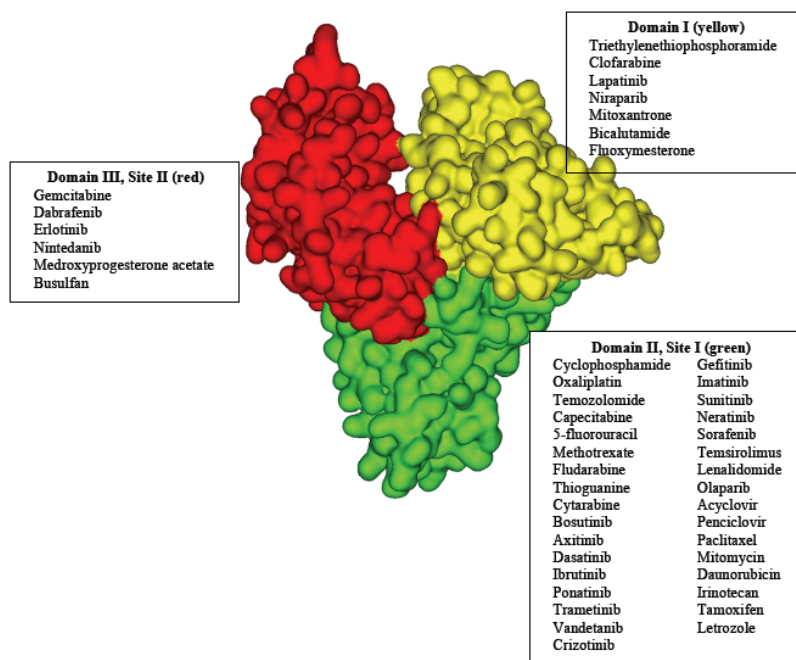
Figure 1. Structure of HSA (PDB ID: 1AO6). The domains were displayed in different colors (domain I in yellow, domain II in green, and domain III in red). The binding site of each drug is provided in the box. *(A higher resolution/colour version of this figure is available in the electronic copy of the article).*
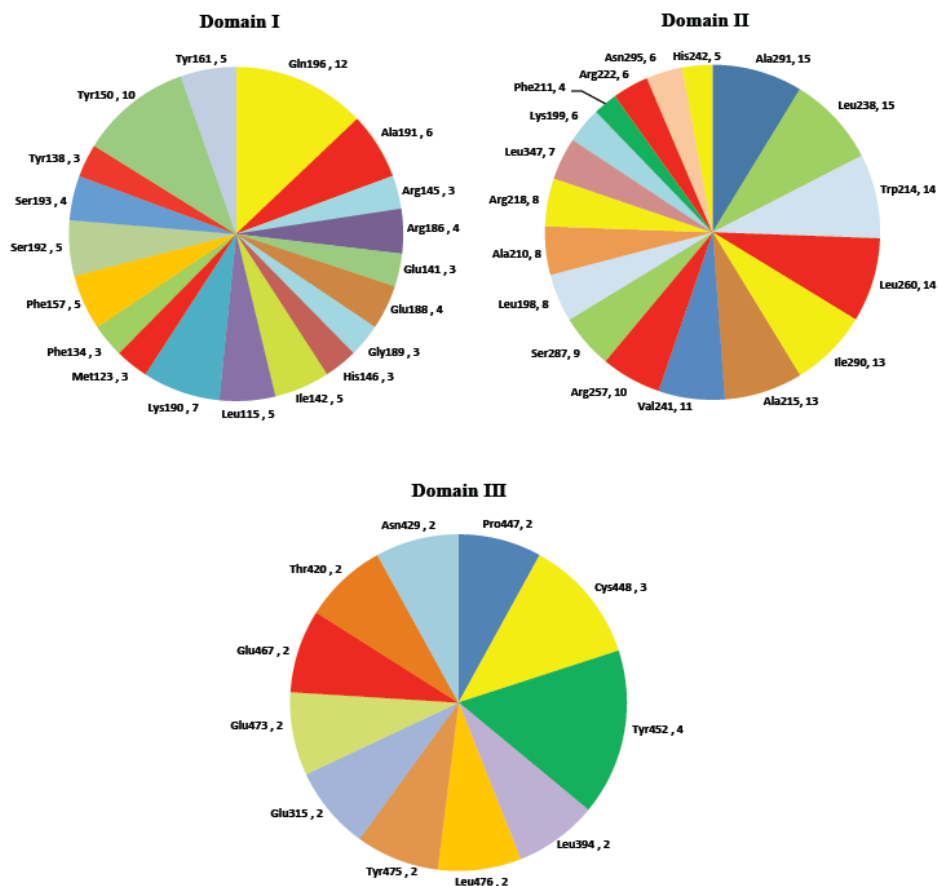
Figure 2. The amino acids that make the largest number of repetitions in the interaction are shown. For domains I, II, and III, residues that have been repeated more than three, four, and two times are presented, respectively. *(A higher resolution/colour version of this figure is available in the electronic copy of the article).*

Arg222, Arg218, Leu478, Leu221, Arg459, Leu476, Ser225, Tyr475, Glu315, Cys460, Thr472, leu261, Ala474, Ala314, Glu473, Cys471, Trp237, Ser367, Pro470, Arg241, Val366, Met469, Leu242, Leu370, Glu467, Lys318, and Lys245 [60, 235-238].

Letrozole (LET) was known as a nonsteroidal inhibitor of the aromatase enzyme, approved by the FDA in 1998. The molecule has shown efficacy in treating women with early-stage or advanced breast cancer. Aromatase expression is increased in the early stages of many cancers. Therefore, it is used as a suitable target for treating breast, ovarian, and liver cancers. According to previous research, LET causes inhibition of aromatase in peripheral tissues and subsequently disrupts the final stage of steroid synthesis and suppression of estrogen production. The molecular modeling studies demonstrated that the binding site of LET is subdomain IIA. As well as the amino acid residues involved in this interaction including Lys351, Arg209, Ala350, Glu354, Gly328, Leu331, Ala231, Val216, and Asp324 [61, 239-241].

CONCLUSION

In the present study, the binding sites of 46 anticancer drugs on HSA were collected. All drugs studied are FDA-approved, and also their interaction with HSA has been reported in various studies. The results showed the binding site for 7 drugs was domain I, for 33 drugs was domain II (site I) and 6 drugs bind to domain III (site II) (Figure **1**). Therefore, it can be said that the key site of HSA protein for anticancer drugs is site I, placed in the domain II of the protein. The results also showed that the amino acids of Ala291 and Leu238 in domain II have the highest frequency of interaction with 15 repetitions (Figure **2**). The drug–protein interactions, especially the interaction between HSA and anticancer drugs, can further be used in the development of biomedicines and assessment of safety-engineered drug delivery. In addition, this study enhances our knowledge of multi-drug combination therapy. Because the use of a combination of drugs has been promising for cancer therapy, major challenges accompany multi-drug combination therapy, including bioavailability, pharmaco-kinetics, and cellular uptake. These obstacles have limited the clinical success of combination therapy. To overcome these challenges, several drug delivery systems have been explored to simultaneously deliver multiple drugs at the site of action and improve anti-tumor activities [242]. Among them, human serum albumin (HSA)-based multi-drug systems are promising owing to HSA's unique properties relative to other drug carriers. We needed to consider two potential problems: (I) if the drug that is conjugated or bound to HSA is weak, the drug will be released from the HSA carrier into the bloodstream, leading to unexpected side effects *in vivo*; and (II) if the drug that is conjugated or bound to HSA is tight, the drug will not be released from the HSA carrier into the cancer cells. Thus, while we need rational designed HSA-based multi-drug systems to increase drugs' delivery efficiency, we should regulate their release from HSA *in vivo*. Therefore, we need to understand the binding constant and the binding site of anticancer drugs in HSA to better plan their use [243]. Furthermore, this study provides valuable information of clinical relevance to HSA-drug interaction. Because identifying the binding site of a drug at the protein level can help reduce drug interference. For example, if the binding sites of two drugs are the same on the protein, the first drug with a higher binding affinity has a better chance of drug delivery and the second drug with a weaker binding is removed from the circulatory system more quickly. Therefore, this study can provide physicians with appropriate information regarding the prescription of anticancer drugs and lead to increased drug efficacy and possibly more successful treatment.

LIST OF ABBREVIATIONS

HSA	=	Human serum albumin
KSV	=	Quenching constant
Kq	=	Quenching rate
BER	=	Base excision repair
SCLC	=	Small-cell lung carcinomas
ALL	=	Lymphoblastic leukemia
AML	=	Acute myeloid leukemia
MDS	=	Myelodysplastic syndrome
TKI	=	Tyrosine kinase inhibitor
VEGFRs	=	Vascular endothelial growth factor receptors 1-3
SLL	=	Small lymphocytic lymphoma
PDAC	=	Pancreatic ductal adenocarcinoma cell
RTKs	=	Receptor tyrosine kinases
ER	=	Estrogen receptor

AUTHORS' CONTRIBUTIONS

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