Biflavonoid compounds from *Selaginella doederleini* II Hieron as anticancer agents of hormone receptor-positive (HR+) breast cancer based on in silico study

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**Abstract.** *Selaginella doederleini* II Hieron is a wild plant that has long been used as a traditional anticancer drug in Indonesia. The majority of its anticancer activity comes from biflavonoids. However, the potency of the biflavonoids as anticancer agents for hormone receptor-positive (HR+) breast cancer, the most common type of cancer in Indonesia has never been identified. This study determined the potential of the biflavonoids to block ERα and CDK6 via molecular docking and identified the interactions of the two proteins with other oncogenic proteins via protein interaction network analysis. The results showed that 3',3'''-binaringenin, Hinokiflavone, and 2,3-dihydrohinokiflavone were the most potent compounds as ERα inhibitor. Hinokiflavone and Amentoflavone were the two best compounds that could inhibit CDK6 according to their high binding affinity. The presence of amino acid residues is vital in the binding process and the significant similarity with commercial drugs. ERα could interact with NCOA1, NCOA2, PELP1, CCND1, and AKT1, whereas CDK6 interacted directly with CCND1, CCND2, and CCND3. The upregulation of these proteins relates to the increase in cancer proliferation. These data indicated that the biflavonoids had a promising anticancer effect on HR+ breast cancer based on in silico studies. Additional researches are needed to validate the results.

**Keywords:** *Selaginella doederleini* II Hieron, biflavonoid, HR+ breast cancer, anticancer, molecular docking

**1. Introduction**

Breast cancer still becomes severe health that threat to women worldwide. This type of cancer ranks first for the total cases and the deaths of women, with percentages of 24.2% and 15.0%, respectively [1]. In Indonesia, breast cancer has the highest number of new cases [2]. Among all types of breast cancer, about 70% of them are classified as hormone receptor-positive (HR+) [3].

HR+ breast cancer treatment is not only achieved by using standard of care (SOC) therapy but also can be combined with plant-based bioactive compounds having anticancer activity. Besides reducing adverse side effects, the use of bioactive compounds from plants as a complementary therapy for
breast cancer can bring out synergy effects with anticancer drugs and diminish drug resistance [4].
One of the plants often used by Indonesian people as a traditional medicine is Selaginella doederleinii Hieron [5]. The majority of its anticancer activity comes from biflavonoids [6]. Biflavonoids are dimers of heterogeneous or homogeneous monoflavonoids, connected by C-C or C-O-C bonds [7]. Several studies revealed that biflavonoids had the same or higher biological and pharmacological potential than monoflavonoids [8–10]. Some biflavonoids from Selaginella doederleinii Hieron extract could inhibit the growth of various cancer cells, including breast cancer [11]. However, studies that specifically identify the potential of biflavonoids contained in Selaginella doederleinii Hieron as anticancer agents for HR+ breast cancer have never been conducted before.

The main target of HR+ breast cancer therapy is Estrogen Receptor-Alpha (ERα) because the rate of proliferation and growth of this type of cancer is influenced by estrogen [12]. Selective estrogen receptor modulators (SERM) are selective antagonist drugs to ERα, which can inhibit oncogenic signalling pathways transduction [13]. These drugs are often combined with CDK4/6 inhibitors in first-line metastatic HR+ breast cancer therapy [14]. CDK4/6 inhibitors inhibit cyclin D/CDK4 and 6/retinoblastoma signalling pathway so that the proliferation can be inhibited. The combination of the two was reported to increase the efficacy of hormone-resistant breast cancer therapy [15]. This study aimed to determine the anticancer potential of several biflavonoid compounds contained in Selaginella doederleinii Hieron to HR+ breast cancer through its inhibitory activity against ERα and CDK6 and to identify interactions of ERα and CDK6 with other proteins involved in the development of HR+ breast cancer by in silico study.

2. Materials and methods

2.1. Protein targets preparation

The crystal structure of ERα-4-hydroxytamoxifen (3ERT) with 1.9Å resolution and CDK6-Ribociclib (5L2T) with 2.37Å resolution were taken from RCSB Protein Data Bank (https://www.rcsb.org/). Protein preparation was done by removing water molecules, native ligands, and alternate conformations using BIOVIA Discovery Studio Client and Chimera1.14 software. Furthermore, the files were saved as .pdb.

2.2. Ligands preparation

Ligands that would be docked to protein targets were biflavonoids contained in Selaginella doederleinii Hieron according to the research of Yao et al. and their 3D molecular structures had been available in the PubChem database [16]. The biflavonoids were stated in table 1. The files were downloaded from PubChem (https://pubchem.ncbi.nlm.nih.gov/) in SDF format. Energy minimization and conversion to PDB format were conducted by open babel on PyRx-Virtual Screening Tools. Native ligands of ERα and CDK6, namely 4-hydroxytamoxifen and Ribociclib, were obtained from each crystal structure of the protein-ligand complex used.

Table 1. List of biflavonoids and the PubChem IDs.

| No. | Ligand                  | PubChem ID |
|-----|-------------------------|------------|
| 1.  | Amentoflavone           | 5281600    |
| 2.  | Robustaflavone          | 5281694    |
| 3.  | 3′,3″-binaringenin      | 54582531   |
| 4.  | 2′,8″-biapigenin        | 11958336   |
| 5.  | Heveaflavone            | 15559724   |
| 6.  | Hinokiflavone           | 5281627    |
| 7.  | Bilobetin               | 5315459    |
| 8.  | Isoginketin            | 5318569    |
| 9.  | Robustaflavone-7,4″-dimethyl ether | 10816812 |
| 10. | 2″,3″-dihydroheveaflavone | 91884905 |
2.3. Molecular docking of ligand to a protein
Protein-ligand docking was performed by Autodock Vina in PyRx to predict binding affinity score and ligand orientation as bound its target protein [17]. This software used a maximum grid box and an exhaustiveness value of 8. The docked ligand-protein complex was formed by PyMol. Visualization of the ligand-protein complex and analysis of non-bond interactions were carried out by BIOVIA Discovery Studio Client [18].

2.4. Protein interaction network analysis
Oncogenic proteins that interacted with each of ERα and CDK6 were determined based on predictions and assessments from the STRING database (https://string-db.org/) [19]. The minimum required interaction score was set to the highest confidence (0.900) with the maximum number of interactions to show was no more than 10 interactions.

3. Result and discussion

3.1. Molecular docking and protein interaction network of ERα
The binding affinity of ligands docked to ERα ranged from -7.7 kcal/mol to -10.8 kcal/mol. There were three compounds which sequentially had higher binding affinity than 4-hydroxytamoxifen, as a native ligand (-9.6 kcal/mol), namely 3',3''-binaringenin (-10.8 kcal/mol), Hinokiflavone (-10.0 kcal/mol), and 2,3-dyhidrohinokiflavone (-9.9 kcal/mol) (table 2). 4-hydroxytamoxifen is a drug from the selective estrogen receptor modulator (SERM) class.

| Ligand                          | ERα binding affinity (kcal/mol) | CDK 6 binding affinity (kcal/mol) |
|--------------------------------|---------------------------------|-----------------------------------|
| 4-hydroxytamoxifen             | -9.6                            | -                                 |
| Ribociclib                     | -                               | -6.8                              |
| Amentoflavone                  | -9.0                            | -9.4                              |
| Robustaflavone                 | -9.3                            | -9.3                              |
| 3',3''-binaringenin            | -10.8                           | -9.0                              |
| 2',8''-biapigenin              | -7.7                            | -7.9                              |
| Heveaflavone                   | -8.4                            | -8.9                              |
| Hinokiflavone                  | -10.0                           | -9.7                              |
| Bilobetin                      | -8.6                            | -9.0                              |
| Isoginketin                    | -8.1                            | -8.0                              |
| Robustaflavone-7,4'-dimethyl ether | -8.1                            | -9.2                              |
| 2''',3''-dihydroheveaflavone   | -8.2                            | -9.8                              |
| 2,3-dyhidrohinokiflavone       | -9.9                            | -9.8                              |

All compounds had the same binding position with 4-hydroxytamoxifen, except 2',8''-biapigenin and 2''',3''-dihydroheveaflavone (data not shown). Based on the identification of interacting amino acid residues, the three compounds also had the best amino acid residues similarities with 4-hydroxytamoxifen among other compounds (data not shown). The binding position of the three compounds could be seen in figure 1. 3',3''-binaringenin formed three hydrogen bonds with GLU380, ASP351, and GLU353 as well as eight hydrophobic interactions with LEU525, LEU346, MET522, ALA350, and LEU387 (table 3). Hinokiflavone bound ERα through three hydrogen bonds with ASP351, GLU380, and LEU536 as well as through 10 hydrophobic interactions with LEU525, LEU346, THR347, LEU536, and ALA350. 2,3-dyhidrohinokiflavone interacted with ERα via three hydrogen bonds (GLU353, ASP351, LEU536) and eight hydrophobic interactions (LEU525, THR347,
A hydrogen bond is a key of molecular recognition to biological systems that can facilitate interactions between ligands and proteins by increasing binding affinity [20,21]. Hydrophobic interaction is the most common type of interaction in a ligand-protein complex that can raise the efficiency, stability, and affinity of ligand binding [22,23]. Besides these two categories of bonds, each of the three compounds also established another bond called Pi-Sulfur interaction with MET343. The interaction was not available in the 4-hydroxytamoxifen-ERα complex but was known to contribute to ligand binding to protein [24]. 3′,3‴-binaringenin and 2,3-dyhydrohinokiflavone could interact with the same amino acid residues of ERα via hydroponic bond in hydrophobic interactions, 3′,3‴-binaringenin had the most similarities with 4-hydroxytamoxifen (LEU525, LEU346, ALA350, and LEU387), whereas two other compounds only had three (LEU525, LEU346, ALA350). However, the Hinokiflavone-ERα complex had an unfavorable bump. The existence of unfavorable bumps causes a decrease in binding stability, but the fewer number of bumps are considered to be negligible [25]. Therefore, the three compounds were the best binders of ERα based on this study.

Figure 1. Interaction of ERα with ligands. (a) 4-hydroxytamoxifen, (b) 3′,3‴-binaringenin, (c) Hinokiflavone, and (d) 2,3-dyhydrohinokiflavone. At the top, the red, green, and blue ribbons represent ERα while yellow spheres represent ligand. At the bottom, the 3D structure of ligand interacting with amino acid residues of ERα.

| Compound                  | Interactions                                      |
|---------------------------|---------------------------------------------------|
| 4-Hydroxytamoxifen        | Hydrogen bonds: GLU353, ARG394, ASP351            |
|                           | Hydrophobic interactions: MET421 (4.97Å, 5.24Å), ALA350, LEU525 (4.77Å, 4.93 Å), LEU346 (5.08Å, 4.88Å), LEU387 |
| 3′,3‴-binaringenin        | Hydrogen bonds: GLU380, ASP351, GLU353            |
|                           | Hydrophobic interactions: LEU525 (3.70Å, 3.59Å, 5.38Å), LEU346, ALA350 (4.49Å, 4.91Å), MET522, LEU387 |
|                           | Other: MET343                                      |
| Hinokiflavone             | Hydrogen bonds: ASP351, GLU380, LEU536            |
|                           | Hydrophobic interactions: LEU525, LEU346 (4.94Å, 4.60Å, 4.67Å), THR347, LEU536 (4.84Å, 5.32Å), ALA350 (4.13Å, 4.55Å, 5.10Å) |
|                           | Other: MET343                                      |
|                           | Unfavorable bump: ARG394                           |
| 2,3-dyhydrohinokiflavone  | Hydrogen bonds: GLU353, ASP351, LEU536            |
Hydrophobic interactions: **LEU525** (3.93Å, 3.94Å), **LEU346** (5.11Å, 4.11Å), **THR347**, **ALA350** (4.33Å, 4.91Å), LEU536
Other: MET343

Nevertheless, ERα agonist and antagonist compounds can bind at the same place in the ligand-binding domain (LBD) [26]. In contrast to agonists, binding of antagonists to LBD can inhibit receptor activation due to changes in the position of Helix12 (residue 536-544)[27]. Helix 12 will transform into an inactive conformation when an antagonist compound binds LBD [26]. It can be characterized by no hydrogen bond formed with HIS524 residue due to the binding instability [28]. The residue plays a significant role in recognition of agonist compounds to LBD but is not very important for SERM compounds binding [29]. Besides, MET343, THR347, LEU346, and ASP351 residues are considered to have a key role in antagonists binding to ERα [30]. 3′,3″-binaringenin, Hinokiflavone, and 2,3-dihydrohinokiflavone did not interact with HIS524 but interacted with MET343, THR347, LEU346, and ASP351 residues (Table 3). Therefore, the three compounds had the potential role to become ERα antagonists. However, further tests such as in vitro and in vivo testings are required to validate the results.

According to protein network analysis by STRING shown by figure 2, ten proteins interacted with ERα, but six proteins had an interaction score of above 0.990, namely NCOA1, NCOA2, PELP1, AKT1, and CCND1, and SRC. The higher the interaction score, the higher the level of truth of the interaction according to STRING analysis. Nuclear receptor co-activators (NCOAs), also known as steroid receptor co-activators (SRCs) are members of a protein family that can act as co-activators of ERα, to facilitate the regulation of various genes transcription [31]. NCOA1, NCOA2, and NCOA3 are overexpressed in breast cancer [32]. NCOAs can directly bind the ERα-estrogen complex to interact with the estrogen response element in the nucleus [33]. Previous studies revealed that NCOA1 mediated the activation of metastatic genes and repressed the expression of particular genes associated with cell differentiation and apoptosis, while NCOA2 mediated EMT-related gene regulation in HR+ breast cancer [34,35]. However, if an antagonists bind ERα, the orientation of the helix-12 of LBD will change so that it blocks the binding of the co-activator, but facilitates the binding of the co-repressor [36]. Almost like NCOAs, Proline, glutamic acid, and leucine-rich protein 1 (PELP1) are co-activators for ERα in genomic and non-genomic signalling pathways and play an essential role in various oncogenic processes in breast cancer [37]. Meanwhile, cyclin C1 (CCND1) is a member of the cyclin family that is known as one of the downstream targets of ERα involving in a cell cycle [38]. Akt is a part of the PI3K/Akt/mTOR signalling pathway associated with the ER membrane and has a role in suppressing ER-dependent transcription (genomic pathway) but leads to cell proliferation and oncogenesis via non-genomic pathway [39]. Therefore, the inhibition of ERα by an antagonist is predicted to stop oncogenic signalling pathways involving these proteins.
Figure 2. Interaction of ERα with oncogenic proteins.

3.2. Molecular docking and protein interaction network of CDK6
This study revealed that the binding affinity of ligands docked to CDK6 varied from -7.9 kcal/mol to -9.8 kcal/mol. All compounds had a higher binding affinity than Ribociclib, as native ligands (-8.6 kcal/mol), except 2’,8”-biapigenin as well as isoginketin (table 2). Ribociclib is a selective CDK4/6 inhibitor commonly used with endocrine therapy to treat metastatic HR+ breast cancer [40]. The three compounds with the highest binding affinity were 2”,3”-dihydroheveaflavone (-9.8 kcal/mol), 2,3-dyhydrohinokiflavone (-9.8 kcal/mol), and Hinokiflavone (-9.7 kcal/mol).

All compounds had the same binding position with Ribociclib, except 2’’,8”-biapigenin (data not shown). However, according to the identification of interacting amino acid residues, Hinokiflavone and Amentoflavone had the most similarities with Ribociclib among other compounds (data not shown). The binding position of Hinokiflavone and Amentoflavone could be seen in figure 3. Hinokiflavone had two hydrogen bonds with VAL101 and GLN149, an electrostatic bond with ASP163, as well as 13 hydrophobic interactions (table 4). Amentoflavone had a hydrogen bond with GLN149, an electrostatic bond with ASP104, and five hydrophobic interactions with VAL27, ILE19, and ALA41. Identification of interacting amino acid residues similarities with Ribociclib revealed that Hinokiflavone had three interacting amino acid residues similarities with Ribociclib, namely GLN149, ASP163, and ILE19. Amentoflavone also had three interacting amino acid residues similarities with Ribociclib (GLN149, ASP104, and ILE19). GLN149 bound with two compounds through a hydrogen bond. ILE19 formed three hydrophobic interactions with each of the two compounds. ASP163 and ASP104 established an electrostatic bond (Pi-Anion type) with Hinokiflavone and Amentoflavone. A previous study reported that ILE19, VAL27, ALA41, PHE98, and ASP163 involved in the interaction of two biflavonoid-CDK6 complexes played a vital role in the formation of efficient and stable flavonoid-CDK6 complex due to their low decomposition energy [41]. There was no unfavorable bump observed.

Figure 3. Interaction of CDK6 with ligands. (a) Ribociclib, (b) Hinokiflavone, and (c) Amentoflavone. At the top, the red, blue, and green ribbons represent CDK6 while yellow spheres represent ligand. At the bottom, the 3D structure of ligand interacting with amino acid residues of CDK6.

Table 4. Interactions of top three biflavonoids and control with CDK6
Compound | Interactions
--- | ---
Ribociclib | Hydrogen bonds: GLN149, THR107, ASP163, ASP102, GLN103
 | Hydrophobic interactions: ILE19
 | Other: ASP104
Hinokiflavone | Hydrogen bonds: VAL101, GLN149
 | Hydrophobic interactions: ILE19 (3.49Å, 3.65Å, 5.13Å), PHE98, ALA41, LEU152 (5.11Å, 4.90 Å), ALA162 (4.64Å, 5.23Å), ALA17 (4.56Å, 4.43Å), VAL27, LYS43
 | Other: ASP163
Amentoflavone | Hydrogen bonds: GLN149
 | Other: ASP104
 | Hydrophobic interactions: VAL27, ILE19 (4.71Å, 4.94Å, 5.15Å), ALA41

Based on the analysis of protein networks in STRING shown in figure 4, ten proteins interacted with CDK6 with an interaction score of above 0.995. However, only three proteins could interact directly with CDK6, namely cyclin D1 (CCND1), cyclin D2 (CCND2), and cyclin D3 (CCND3). The three types of cyclin D are recognized to be allosteric regulators of CDK6 at the G1 to S phase transition, which usually are overexpressed in cancer cells [42]. The formation of CDK6-cyclin D complex phosphorylates tumor suppressor retinoblastoma (RB) proteins so that E2F transcription factors can promote gene expression related to cell proliferation and DNA synthesis [43]. Therefore, like Ribociclib, the two compounds are predicted to be able to inhibit the formation of the complex by binding the ATP-competitive binding site of CDK6 [44]. Thus, the cancer cell cycle can be arrested at the G1 phase.

Figure 4. Interaction of CDK with oncogenic proteins.

4. Conclusion
Anticancer mechanism of biflavonoids from Selaginella doederleinii Hieron to HR+ breast cancer can occur through inhibition of ERα and CDK6 activity. The strongest ERα antagonist candidates were 3’,3”-binaringenin, Hinokiflavone, and 2,3-dihydrohinokiflavone, while the most potent compounds as CDK6 inhibitors were Hinokiflavone and Amentoflavone. NCOA1, NCOA2, PELP1, AKT1, and CCND1 were oncogenic proteins that could interact with ERα directly or indirectly, while cyclin D1, cyclin D2, and cyclin D3 interacted directly with CDK6. Nevertheless, the results of this study still need to be validated using more comprehensive studies to ascertain their anticancer activity against each of the target proteins.
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References
[1] World Health Organization 2018 Asian Pacific J. Cancer Prev. 4 3–4
[2] World Health Organization 2019 Int. Agency Res. Cancer 256 1–2
[3] Murphy C G and Dickler M N 2016 Endocr. Relat. Cancer 23 R337–52
[4] Li Y, Li S, Meng X, Gan R Y, Zhang J J and Li H Bin 2017 Nutrients 9 1–38
[5] Mustarichie R, Udin Z, Levita J, Musfiroh I and Zulfricar I 2011 Med. Heal. Sci. J. 9 47–57
[6] Li S, Zhao M, Li Y, Sui Y, Yao H, Huang L and Lin X 2014 Phytochem. Anal. 25 127–33
[7] Ogunwa T H 2018 J. Syst. Biol. Proteome Res. 2 10–20
[8] Tabares-Guevara J H, Lara-Guzmán O J, Londoño-Londoño J A, Sierra J A, León-Varela Y M, álvez-Quiniero R M, Osorio E J and Ramirez-Pineda J R 2017 Front. Immunol. 8 1-17
[9] Thapa A, Woo E R, Chi E Y, Sharoor M G, Jin H G, Shin S Y and Park IS 2011 Biochemistry 50 2445-55
[10] Li X, Ouyang X, Chai R, Chen D 2019 Molecules. 24 1–10
[11] Zou Z X, Tan G S, Zhang G G, Yu X, Xu P S and Xu K P 2017 Chinese Chem. Lett. 28 931–4
[12] El Sayed R, El Jamal L, El Iskandarani S, Kort J, Abdel Salam M and Assi H 2019 Front. Oncol. 9 1-23
[13] Devulapally R, Sekar T V, and Paulmurugan R 2015 Mol. Pharm. 12 2080–92
[14] Brufsky A M and Dickler M N 2018 Oncologist 23 528–39
[15] Wardell S E et al. 2015 Clin. Cancer Res. 21 5121–30
[16] Yao H, Chen B, Zhang Y, Ou H, Li Y, Li S, Shi P and Lin X 2017 Molecules 22 1-17
[17] Trott O and Olson A J 2009 J. Comput. Chem. 31 455-461
[18] BIOVIA, Dassault Systèmes, Discovery studio modelling environment, Version 4.5, San Diego: Dassault Systèmes, 2015
[19] Szklarczyk D et al. 2015 Nucleic Acids Res. 43 D447–52
[20] Chen D, Oezgun N, Urvil P, Ferguson C, Dann S M and Savidge T C 2016 Sci. Adv. 2 1-16
[21] Bulusu G and Desiraju G R 2020.J. Indian Inst. Sci. 100 31–41
[22] Ferreira De Freitas R and Schapira M 2017 Medchemcomm 8 1970–81
[23] Varma A K, Patil R, Das S, Stanley A, Yadav L and Sudhakar A 2010 PLoS One 5 1-10
[24] Arthur D E and Uzairu A 2019 J. King Saud Univ. - Sci. 31 1151–66
[25] Zainab B, Ayaz Z, Munir A, Hassom Mahmoud A, Soliman Elsheikh M, Mehmoood A, Khan S, Rizwan M, Jahangir K and Mehmood Abbasi A 2020 J. King Saud Univ. - Sci. 32 1793–811
[26] Puranik N V., Srivastava P, Bhatt G, John Mary D J S, Limaye A M and Sivaraman J 2019 Sci. Rep. 9 1–11
[27] Bruning J B, Parent A A, Gil G, Zhao M, Nowak J, Margaret C, Smith C L, Afonine P V, Adams P D, Katzenellenbogen J A and Nettles K W 2010 Nat.Chem.Biol. 6 837–43
[28] Muchtaridi M, Yusuf M, Diamentini A, Choi S B, Al-Najjar B O, Manurung J V., Subarnas A, Achmad T H, Wardhani S R and Wahab H A 2014 Int. J. Mol. Sci. 15 7225–49
[29] Ekena K, Weise K E, Katzenellenbogen J A and Katzenellenbogen B S 1997 J. Biol. Chem. 272 5069–75
[30] Li W M, Li X B, Sun S X, Liang J, Wang R L and Wang S Q 2013 Mol. Simul. 39 228–33
[31] Rollins D A, Coppo M and Rogatsky I 2015 Mol. Endocrinol. 29 502–17
[32] Wagner M, Koslowski M, Paret C, Schmidt M, Türeci Ö and Sahin U 2013 BMCCancer 13 1-9
[33] Conzen S D 2008 Mol. Endocrinol. 22 2215–28
[34] Walsh C A et al. 2014 Cancer Res. 74 2533–44
[35] Bozickovic O et al. 2019 J. Steroid Biochem. Mol. Biol. 185 57–70
[36] Katzenellenbogen B S, Sun J, Harrington W R, Kraichely D M, Ganessunker D and Katzenellenbogen J A 2006 Ann. N. Y. Acad. Sci. 949 6–15
[37] Flageng M H, Knappskog S, Gjerde J, Lønning P E and Mellgren G 2015 PLoS One 10 1–12
[38] Wang L and Di L J 2014 Int. J. Biol. Sci. 10 563–73
[39] Vasan N, Toska E and Scaltriti M 2019 Ann. Oncol. Off. J. Eur. Soc. Med. Oncol. 30 3–11
[40] Spring L M, Wander S A, Zangardi M and Bardia A 2019 Curr. Oncol. Rep. 21 1–14
[41] Zhang J, Zhang L, Xu Y, Jiang S and Shao Y 2018 PLoS One 13 1–18
[42] Qie S and Diehl J A 2016 J. Mol. Med. 94 1313–26
[43] Hamilton E and Infante J R 2016 Cancer Treat. Rev. 45 129–38
[44] Xiong Y, Li T, Assani G, Ling H, Zhou Q, Zeng Y, Zhou F and Zhou Y 2019 Biomed. Pharmacother. 112 1-12