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Dietary flavonoids against various breast cancer subtypes: a molecular docking study

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ABSTRACT: Breast cancer is female most frequent diagnosed cancer and the leading cause of cancer death. The consumption of dietary flavonoids is reported to cause significant breast cancer risk reduction. In vitro studies often used aglycone flavonoids rather than its conjugated form that actually present in human body. Thus its mechanism against breast cancer has not been elucidated completely. The present study aimed to investigate the possible mechanism of dietary flavonoids against breast cancer by in silico study. Conjugated flavonoids were docked to ER (estrogen receptor), HER2 (human epidermal growth factor receptor 2) and EGFR (epidermal growth factor receptor) kinase domains. The molecular docking of 22 flavonoid conjugates towards EGFR and HER2 kinase domain, and ER was successfully performed. Potential binders to proteins: epicatechin conjugates to ER (−8.7 kcal/mol), isoflavone conjugates to HER2 kinase domain (−10.7 kcal/mol), and epigallocatechin and epicatechin conjugates to EGFR kinase domain (−9.2 kcal/mol), were suggested. Supported by other studies, conjugated flavonoids may exert similar inhibitory and agonistic properties to their parent flavonoids. Taken together, the present study showed possible effects of dietary flavonoids against various breast cancer subtypes.

KEYWORDS: molecular docking simulation, diet, flavonoids, antineoplastic agents, breast neoplasms

INTRODUCTION

According to GLOBOCAN 2018 database, breast cancer is female most diagnosed cancer and the leading cause of cancer death[1]. Breast cancer is heterogenous disease, comprised of various subtypes observable by the presence of the predictive molecular markers. Breast cancer can be categorized into: Luminal A (ER^+, $PR^{+/-}$, HER^-), Luminal B (ER^+, $PR^{+/-}$, $HER2^+$), HER2 (ER^-, PR^-, $HER2^+$), basal like and claudin low (triple negatives)[2]. Each has a different prognosis and responds differently to cancer treatment. Luminal A has the best prognosis, while $HER2^+$ and triple negative breast cancer (TNBC) have the poorest[3]. Today breast cancer endorsed to be treated with endocrine theraphy, targeted theraphy, and cytotoxic chemotheraphy[4]. Breast cancer with high expression of estrogen receptor (ER) and progesterone receptor (PR) is sensitive against endocrine theraphy. ER inhibition treatment in Luminal A and B breast cancer was proven to be effective and safe[5]. While $HER2^+$ breast cancer was effectively treated using targeted theraphy with trastuzumab or lapatinib[6]. But different from previous subtypes, triple negative breast cancer is not responded very well to hormone treatment and HER2 antibody, and often treated with systemic chemotherapy. Previous study found that epidermal growth factor receptor (EGFR) kinase inhibitor, gefitinib, was able to halt the TNBC cell outgrowth in vitro[7]. Thus ER, HER2, EGFR served as important targets in breast cancer treatment. It is also possible other chemical compounds found in food may also interacts with these particular proteins. Flavonoid is the most common phytochemical compound found

ubiquitously in human diet[8,9] and has huge impact in human health. In vitro studies showed that flavonoids have wide range of biological activity antioxidant, anti-inflammatory, anti-microbial, anti-fungal, antiviral, and anti-cancer[9,10]. Consumption of flavonoids is related with less risk of cardiovascular diseases and stroke[11,12]. Other studies found that the intake of flavonoids improved the outcome of the gastric and lung cancer[13,14]. Human study on consumption of food rich in flavonoids, green tea, against breast cancer showed mixed results. Case studies has shown green tea intake was correlated with significant breast cancer risk reduction[15–17], while recent prospective cohort studies showed no correlation[18]. Soy products were rich in isoflavone and high soy intake was modestly associated with reduced breast cancer risk[19].

It is important to note that flavonoid is quickly metabolized in the body. After ingested, glycoside flavonoid found in plant materials is subjected to deglycosylation, releasing aglycone compound that readily absorbed by the intestine lining[20]. Once entered circulatory system, flavonoid is immediately transported to liver and undergoes extensive metabolism. Phase metabolism II transformed free aglycone onto flavonoid conjugates by adding glucuronides and sulphate moiety[21]. Because of this, aglycone flavonoids are rarely found in plasma. Previous in vitro studies often used aglycone flavonoids rather than its conjugated forms that present in human body. Thus its mechanism against breast cancer has not been elucidated completely, since conjugation may affect how the molecules behave. To address this, conjugated flavonoids found in plasma after ingesting food rich in flavonoid was subjected to molecular docking against ER, HER2, EGFR. The present study describes possible mechanism how the dietary flavonoids may contribute against breast cancer.

MATERIALS AND METHODS

Molecular docking towards EGFR, HER2, and ER

Conjugated flavonoids found in plasma after ingesting food rich in flavonoids as previously reported from other studies were used[22–24]. Structural data of conjugated flavonoids were retrieved from PubChem database (Fig. 1) (pubchem.ncbi.nlm.nih.gov). Co-crystallized structures of ER-4-hydroxytamoxifen (PDB ID: 3ERT)[25], HER2-SYR127063 (PDB ID: 3PP0)[26], and EGFR-gefitinib (PDB ID: 4WKQ) were obtained from RCSB database (rcsb.org). Crystal structure data were prepared by removing solvent and extracting bound ligand. AutoDock vina was used in molecular docking under default settings. The docking methodology was validated by redocking the extracted bound ligand. Chimera was used on visualization in this study. Intramolecular analysis was performed using Pose View, available at Protein Plus (proteins.plus)[27].

Table 1 Predicted binding affinity (kcal/mol) of flavonoid conjugates and known inhibitors towards ER, HER2, and EGFR.

Flavonoid conjugate	Binding affinity		
	ER	HER2	EGFR
Gefitinib	–	–	−8.8
SYR127063	–	−11.0	–
4-hydroxytamoxifen	−9.7	–	–
(-)-Epicatechin-3-gallate	−8.7	−8.5	−8.6
(-)-Epigallocatechin-3-gallate	−7.0	−8.6	−9.2
(-)-Epigallocatechin-7-gallate	−7.4	−8.9	−8.0
4'-Methylepicatechin-5-sulfate	−7.2	−8.8	−7.7
4'-Methylepicatechin-7-sulfate	−7.9	−9.6	−7.2
4'-Methyl-epigallocatechin-3'-glucuronide	−7.9	−9.9	−9.1
4'-Methyl-epigallocatechin-7-glucuronide	−6.5	−9.0	−8.2
Daidzein-4'-sulfate	−7.1	−9.4	−8.5
Daidzein-7-sulfate	−6.6	−9.2	−8.4
Epicatechin-3'-glucuronide	−8.5	−9.5	−9.1
Epicatechin-3'-sulfate	−7.7	−9.1	−8.2
Epicatechin-5-sulfate	−7.1	−8.6	−8.4
Epicatechin-7-lucuronide	−7.5	−9.3	−8.3
Epigallocatechin-3'-glucuronide	−7.7	−9.7	−9.1
Epigallocatechin-7-glucuronide	−7.2	−8.3	−8.3
Genistein-4'-O-glucuronide	−8.3	−10.7	−8.0
Genistein-4'-sulfate	−7.3	−9.7	−8.3
Genistein-7-O-glucuronide	−6.8	−9.4	−7.7
Genistein-7-sulfate	−6.4	−9.1	−8.6
Isorhamnetin-3-O-glucuronide	−7.6	−8.3	−8.8
Quercetin-3'-glucuronide	−8.7	−8.8	−8.7
Quercetin-3'-sulfate	−8.1	−9.5	−8.4

RESULTS

Molecular docking analysis

Redocking was performed to evaluate software and docking parameters used. The root mean square deviation between docked and crystal compounds was less than 2Å except for EGFR bound ligand (gefitinib). This is due to the 6-propylmorpholino moiety of gefitinib sticking out to solvent and able to move freely[28]. Thus, AutoDock Vina has favourable accuracy and proceeds the docking of flavonoid-

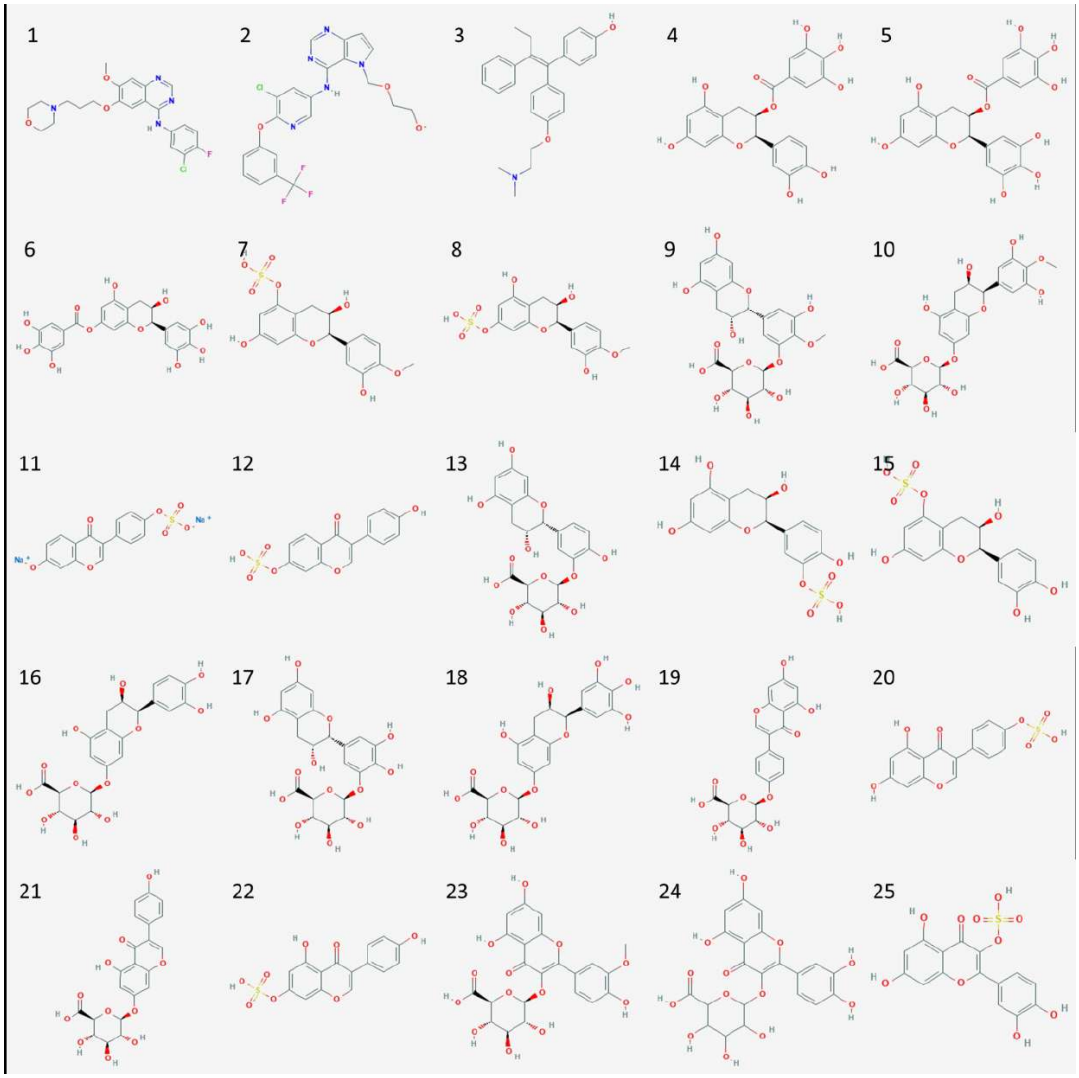

Fig. 1 The 2 dimensional structure of all studied ligands: (1) gefitinib, (2) SYR127063, (3) 4-hydroxytamoxifen, (4) (-)-epicatechin-3-gallate, (5) (-)-epigallocatechin-3-gallate, (6) (-)-epigallocatechin-7-gallate, (7) 4'-methylepicatechin-5-sulfate, (8) 4'-methylepicatechin-7-sulfate, (9) 4'-methyl-epigallocatechin-3'-glucuronide, (10) 4'-methyl-epigallocatechin-7-glucuronide, (11) daidzein-4'-sulfate, (12) daidzein-7-sulfate, (13) epicatechin-3'-glucuronide, (14) epicatechin-3'-sulfate, (15) epicatechin-5-sulfate, (16) epicatechin-7-glucuronide, (17) epigallocatechin-3'-glucuronide, (18) epigallocatechin-7-glucuronide, (19) genistein-4'-O-glucuronide, (20) genistein-4'-sulfate, (21) genistein-7-O-glucuronide, (22) genistein-7-sulfate, (23) isorhamnetin-3-O-glucuronide, (24) quercetin-3'-glucuronide, (25) quercetin-3'-sulfate.

conjugates. The molecular docking was performed to assess possible binding conformation of flavonoid conjugates towards receptors and possible biological actions of these compounds. The molecular docking of 22 flavonoid conjugates towards EGFR and HER2 kinase domain, and ER was successfully performed. The predicted binding affinity value of flavonoid conjugates was compared to each other and receptor bound ligand (Table 1).

In the present study, based on molecular docking, epichatehin and quercetin conjugates ((-)-epicatechin-3-gallate, quercetin-3'-glucuronide, and epicatechin-3'-glucuronide) were predicted as a potential binder towards estrogen receptor. HER2 kinase domain was predicted to interact strongly towards genistein and epigallocatechin conjugates (genistein-4'-O-glucuronide, genistein-4'-sulfate, epigallocatechin-3'-glucuronide,

Table 2 Hydrogen bond formed by flavonoids conjugates and known inhibitors towards EGFR, HER2, and ER.

Flavonoid conjugate	Receptor	Hydrogen bond
4-hydroxytamoxifen	ER	Asp394 Glu353 Leu346 Thr347 Asp351 Leu387 Glue419 Gly420
(-)-Epicatechin-3-gallate		
Quercetin-3'-glucuronide		Asp351 Glu353
SYR127063	HER2	Met801 Asp863
Genistein-4'-O-glucuronide		Ser783 Thr798
Gefitinib	EGFR	Met793
(-)-Epigallocatechin-3-gallate		Glu762 Leu788 Met793 Arg841

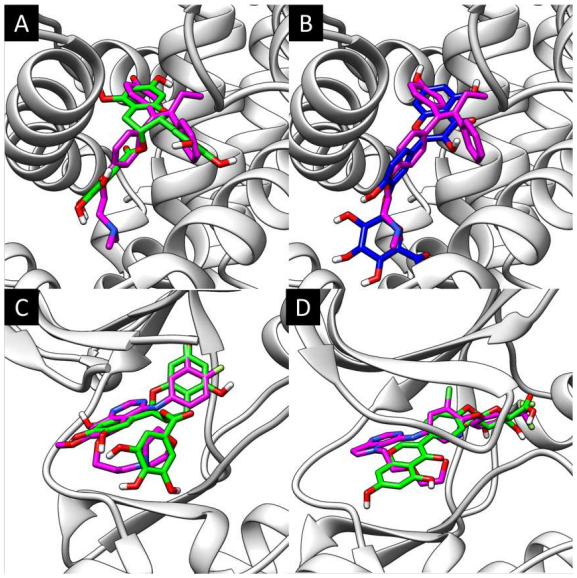

Fig. 2 Superimposed binding mode between flavonoid conjugate and known inhibitor towards ER, HER2, EGFR. (A) and (B) the binding mode of (-)-epicatechin-3-gallate (green), quercetin-3'-glucuronide (blue), and 4-hydroxytamoxifen towards (magenta) ER (light gray). (C) the binding mode of genistein-4'-O-glucuronide (green) and SYR127063 (magenta) towards EGFR kinase domain (light gray). (D) the binding mode of (-)-epigallocatechin-3-gallate (green) and gefitinib (magenta) towards HER2 kinase domain (light gray). The protein represented as ribbon, the compound as stick, and heteroatom represented in a different color from the carbon atom.

and 4'-methyl-epigallocatechin-3'-glucuronide) compared to other compounds. While several catechin derivatives ((-)-epigallocatechin-3-gallate, 4'-methyl-epigallocatechin-3'-glucuronide, epicatechin-3'-glucuronide, and epigallocatechin-3'-glucuronide) were predicted with a high affinity toward EGFR kinase domain as these compounds surpassed known inhibitor binding score.

Binding mode of the compound with the highest predicted binding affinity was visualized and superimposed with the receptor known inhibitor (Fig. 2). All compounds were found to occupy the active site of the protein. (-)-Epigallocatechin-3-gallate resembled similar binding mode with gefitinib, whereas its core structure aligned with the quinazoline and aniline moiety. While genistein-4'-O-glucuronide, (-)-epicatechin-3-gallate, quercetin-3'-glucuronide only shared small geometrical similarity when compared with the bound ligand. Furthermore, hydrogen bond inferred by Pose View was compared and presented in (Table 2). Similar to gefitinib, (-)-epigallocatechin-3-gallate formed hydrogen bond with Met793. SYR127063 and genistein-4'-O-glucuronide shared no similar intermolecular interaction. Quercetin-3'-glucuronide had similar interaction with 4-hydroxytamoxifen at Glu353. (-)-Epicatechin-3-gallate had the most hydrogen bond towards ESR1.

DISCUSSION

In present study, predicted binding affinity and binding mode of conjugated flavonoids present in plasma after ingestion of dietary flavonoids against ER, EGFR kinase domain, and HER2 kinase domain were characterized *in silico*. The result shows that most compounds with predicted high binding affinity were glucuronide flavonoid conjugates. It is interesting to point out that the predominant flavonoid metabolite found in plasma after an hour ingestion of radiolabelled epicatechin was its glucuronide conjugates[29]. Thus, the potential compounds found in this study were likely exist in large concentration in plasma after consumption of dietary flavonoids.

More than 70% diagnosed breast cancer was the overexpressed ER[3]. ER plays important role in development and progression of breast cancer, since ER drives proliferation of mammary cells upon binding with estrogenic hormone[30]. ER^+ breast cancer is sensitive against endocrine therapy and is effectively treated using selective estrogen receptor modulators such as tamoxifen[31]. This study found that (-)-epicatechin-3-gallate was a potential inhibitor of ER, because of its high predicted binding affinity and similar binding mode when compared to active metabolite of tamoxifen (4-hydroxytamoxifen). Tamoxifen interacts with several amino acid residues inside the binding pocket, including Leu346, Thr347 and Leu387, forming a van der walls interaction that stabilize the com-

plex[25]. Epicatechin conjugates was predicted to be interacted with similar manner. This finding confirmed by other studies whereas epicatechin gallate was able to hamper ER activity through direct inhibition[32,33]. Quercetin conjugates also have high predicted binding affinity towards ER. But quercetin conjugates may act as an agonist rather than antagonist, since previous study found that aglycone quercetin induced cell proliferation of ER-positive breast cancer cell line through ER stimulation[34].

HER2 is a receptor tyrosine kinase which is overexpressed in 30% human breast cancer[3]. $HER2^+$ breast cancer characterized by its aggressive phenotype: high tumorigenicity and invaseness[35]. The treatment involved is either by targeting the extracellular domain using trastuzumab or its kinase domain using lapatinib[4,36]. Previous study showed that flavonoid compounds were able to inhibit human kinases[37]. Molecular docking study reported that genistein-4'-O-glucuronide had predicted binding affinity close to SYR127063. SYR127063 itself is a potent HER2 kinase domain inhibitor at IC50 of 11 nM[26]. From the experimental study, genistein was able to attenuate HER2 phosphorylation in BT474 cell line through tyrosine kinase inhibition, thus supported present finding[38].

TNBC occurs approximately 10% in breast cancer cases3. TNBC is biologically aggressive and has the poorest prognosis when compared to other subtypes[3]. Previous study reported that EGFR is a potential target for TNBC[7]. In this work, epigallocatechin and epicatechin metabolites had notable predicted binding affinity towards EGFR kinase domain. This finding supported by another study where epigallocatechin-3-gallate was able to inhibit EGFR activity[39]. Inhibition of EGFR by epigallocatechin conjugate may also affect HER2 activation, since both proteins are able to form heterodimeric complex and activate each other.

CONCLUSION

Binding affinity and binding mode between conjugated flavonoids found in plasma against ER, HER2, EGFR had been characterized in silico. Supported by other studies, conjugated flavonoids may exert similar inhibitory and agonistic properties to their parent flavonoids. Our study thus confirm and offer possible explanations how dietary flavonoids act against various breast cancer subtypes.

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Re: Revision 1 of MS 2019-0552
Dear Dr. Wahyu Widowati,

Your manuscript (code 2019-0552) entitled **Dietary Flavonoids Against Various Breast Cancer Subtypes: A Molecular Docking Study** by **Wahyu Widowati,Diana Krisanti Jasaputra,Yusuf Heriady,Ahmad Faried,Rizal Rizal,Wahyu Setia Widodo,Satrio Haryo Benowo Wibowo,Hanna Sari Widya Kusuma,Ermi Girsang,I Nyoman Ehrich Lister**, submitted on July 14, 2019 for consideration for publication in *ScienceAsia*, has been sent for review and comments from the reviewers received are given below for your consideration. You are required to clarify these queries and comments in your revised version by copying and pasting the reviewers queries into your reply, and answer each of the points one by one. To expedite the publication process, please make sure that the references are in the correct format by checking the following points:

- the author or editor surname must precede the initials, e.g., Smith B;
- et al is only used if the reference has more than 8 authors;
- the year of publication in brackets follows the list of authors;
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- for journal articles the abbreviated journal name (or full journal name, if you are unsure of what abbreviation to use or the journal is an unusual one) is in italics and follows the title, and the volume number in bold font follows the journal name;
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- details of articles in press at the time of submission are updated;
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- titles of books and proceedings are in italics and Capitalized, e.g., Proceedings of the Siam Congress on Physics;
- the book publisher precedes the location of the publisher and is not in italics, e.g., Academic, New York;
- the edition (if applicable) is between the book title and publisher and is not in italics, e.g., 4th edn;
- for chapters in edited books, the editor names are given between In: and (eds) after the chapter title and before the book title;
- If you cite more than 3-4 references at one point in the manuscript, you need to reduce by selecting only the most important references. The number of references should be less than 40 in total.
- Web pages should not be given as references unless there is really no alternative.

If your manuscript contains figures, please check that:

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- writing (axis labels, numbers, etc.) in plots and diagrams is about the same size as the figure caption writing when the figure is the width of a single column when the document is in two-column mode;
- different line styles or plotted point styles on the same plot are clearly distinguishable;
- subplot labels (a) (b) etc. are inside the plot region (rather than outside the axes) in the top left if there is enough empty space;
- plot axes are labeled with the quantity (in the correct font - italics if a single letter symbol, etc.) followed by a space and then the units (if any) in brackets.
- zipped the figure files together with the .doc file (non-mathematic manuscript), or LaTeX file (mathematic manuscript).

For a non-mathematic manuscript, please send the revised version (with line numbers) of your .doc file, renamed 2019-0552.doc (or .odt) and the figure files in vector format as a separate file for each figure (JPG for photos; PDF or EPS for plots and diagrams). These should be zipped together with the .doc file. Any figure captions and tables should be included in the .doc file and not sent separately.

For a mathematic manuscript, this has to be in LaTeX (with line numbers). Please send the revised version of your LaTeX file, renamed 2019-0552.pdf and the figure files in vector format as a separate file for each figure (if any).

Re-submit the revised manuscript, with a document indicating responses or changes in the manuscript against the referees amendments to ScienceAsia within 1 week. Kindly visit www.scienceasia.org, click the Author login menu and use the MS Code No. and password provided at the top-right corner of this email to submit your revised manuscript.

Looking forward to receiving the revised manuscript and the reply to the referees from you soon. Thank you again for considering *ScienceAsia* as a journal to publish your works.

Note: To avoid problem due to typing error, please use Copy and Paste functions to copy and paste MS Code No. and password.

Yours sincerely,
Prof. Supa Hannongbua
Editor,
ScienceAsia

REVIEWERS COMMENT

Scientific validity :	not sound, in part
Scientific interest :	above average
Presentation :	not clear
Comment :	Comments for Dietary Flavonoids Against Various Breast Cancer Subtypes: A Molecular Docking Study This manuscript presents the computational study about the interactions between flavonoid conjugate compounds and breast cancer related proteins, ER, HER2 and EGFR by using molecular docking. COMMENTS TO THE AUTHORS: Comment 1: The abstract should be concise and clear. Comment 2: More details of docking protocol are required. PDB id of the structure EGFR-gefitinib (lines 87-88) should be provided. Comment 3: The sentence The 3-dimensional structure data for every compound was obtained from PubChem database (https://pubchem.ncbi.nlm.nih.gov) (lines 86-87) is a bit awkward and should be rewritten. Comment 4: The paragraph in lines 107-116 should be rewritten. Comment 5: (-)-Epicatechin-3-gallate showed binding energy with ER similar to 4-hydroxytamoxifen. More discussion on which amino acid residues interact with compound (lines 142-144) in comparison to 4-hydroxytamoxifen is required. Comment 6: For superimposed binding mode between flavonoid conjugate and known inhibitor in Figure 1, heteroatom should be presented in a different color from the carbon atom and figure caption should be rewritten for better understanding. In addition, the 2D structure of all studied ligands should be added. Comment 7: The reference format must be rechecked. Grammar and typo errors throughout the manuscript must be corrected.

EDITORS COMMENT

According to the comments from the reviewer, this manuscript can be accepted after minor revsion. Please inform the authors and ask them to response with clear indication about the revision. The generation of the line number can be done in order to making the clear response. Also, the authors shall follow the instruction for authors and follow the criteria of the journal. Figure and Table should be less than 8.

EDITORIAL OFFICE: c/o Science Society of Thailand, Faculty of Science, Chulalongkorn University
PhyaThai Road, Patumwan, Bangkok 10330, Thailand
Tel:+662 218 5245 Fax: +662 252 7987
E-mail: editor@scienceasia.org

Dear Author,

We are still waiting to hear from you after our email of 5 November 2019, please send back as soon.

Regards,

Mongkon Youngtanurat

Dr. Wahyu Widowati
Jl. Surya Sumantri No. 65 Bandung 40164, West Java, Indonesia
wahyu_w60@yahoo.com, wahyu@amubbrc.co.id
Re: Acceptance for MS 2019-0552
Dear Dr. Wahyu Widowati,

I am pleased to inform you that your manuscript (code 2019-0552) entitled **Dietary Flavonoids Against Various Breast Cancer Subtypes: A Molecular Docking Study** by **Wahyu Widowati,Diana Krisanti Jasaputra,Yusuf Heriady,Ahmad Faried,Rizal Rizal,Wahyu Setia Widodo,Satrio Haryo Benowo Wibowo,Hanna Sari Widya Kusuma,Ermi Girsang,I Nyoman Ehrich Lister**, submitted on July 14, 2019 has been considered to be accepted for publication in ScienceAsia. However, this letter is not an ACCEPTANCE LETTER. Prior to issuing a formal ACCEPTANCE LETTER, we would like to remind you that papers recommended to be published in ScienceAsia are required to pay for publication fee of 500 USD. The charge excludes printing of graphics or figures in full colour in the hard copy version which will cost an additional of 1,000 USD per paper. Printing of graphics in full colour is optional and is at the author's discretion. In all cases, the payment must be settled soon after the authors have been notified that the paper is recommended to be published.Delay in receiving the publication fee from you may mean that the journal will have to postpone the publication of your article.

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Thank you for choosing to publish with *ScienceAsia*.

Yours sincerely,
Emeritus Prof. Piamsook Pongsawasdi
Editor-in-chief, *ScienceAsia*

Dr. Wahyu Widowati
Jl. Surya Sumantri No. 65 Bandung 40164, West Java, Indonesia
wahyu_w60@yahoo.com, wahyu@amubbrc.co.id

Subject: Re: 2019-0552 proof of your article
Entitled: **Dietary Flavonoids Against Various Breast Cancer Subtypes: A Molecular Docking Study**
Author(s): **Wahyu Widowati,Diana Krisanti Jasaputra,Yusuf Heriady,Ahmad Faried,Rizal Rizal,Wahyu Setia Widodo,Satrio Haryo Benowo Wibowo,Hanna Sari Widya Kusuma,Ermi Girsang,I Nyoman Ehrich Lister**

Dear Dr. Wahyu Widowati,

The proof version of your manuscript is available at (http://scienceasia.org/manuscript/msfiles/2019-0552/2019-0552P1.pdf) Please read the proof very carefully. It is journal policy to edit manuscripts to ensure that they conform to the journal style and also in some cases to improve conciseness, clarity, and accuracy. These changes are based on the editors' interpretation of what was originally written -- it is possible that the editors have misunderstood some parts. Any sections highlighted in yellow indicate words that we have added, changed, or are unsure about that we would like you to check in particular. Sections highlighted in red definitely need a response from you -- e.g., the definition of an abbreviation is not given, or we couldn't understand at all what is meant. ??? signifies a missing value or word. If there is an error in a citation number in the text (not the references), give us the corrected citation number in terms of the existing numbers in the list of references. If necessary we will then reorder the list of references and make the corresponding adjustments to the citation numbers throughout.

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Yours sincerely,
Asst. Prof. Dr. Khamron Mekchay
Managing Editor, *ScienceAsia*

LEMBAR HASIL PENILAIAN
SEJAWAT SEBIDANG atau *PEER REVIEW*

KARYA ILMIAH : JURNAL ILMIAH

Judul Karya Ilmiah (Artikel)	:	Dietary flavonoids against various breast cancer subtypes: a molecular docking study
Jumlah Penulis	:	10 orang
Nama-nama Penulis	:	**Wahyu Widowati**, Diana Krisanti Jasaputra, Yusuf Heriady, Ahmad Faried, Rizal Rizal, Wahyu Setia Widodo , Satrio Haryo Benowo Wibowo, Hanna Sari W Kusumad, Ermi Girsange, I Nyoman Ehrich Lister
Status Penulis	:	Penulis Pertama / ~~Penulis ke ....~~ / Penulis Korespondensi- **)
Identitas Jurnal Ilmiah	: a.	Nama jurnal : Science Asia
	b.	Nomor ISSN : 15131874
	c.	Vol., No., Bulan, Tahun : Vol. 45, 2019
	d.	Penerbit : Science Society of Thailand under Royal Patronage
	e.	DOI Artikel (jika ada) : 10.2306/scienceasia1513-1874.2019.45.452
	f.	Alamat Web Jurnal : http://www.scienceasia.org
	g.	Terindeks di : Scopus Q3, SJR 0.186

Kategori Publikasi Jurnal Ilmiah: *(beri tanda √ yang dipilih)*

- [√] ~~Jurnal Ilmiah Internasional~~ / Internasional Bereputasi **)
- [ ] Jurnal Ilmiah Nasional Terakreditasi
- [ ] Jurnal Ilmiah Nasional / Nasional terindeks ***)

HASIL PENILAIAN (*Peer Review*) :

No	Komponen Yang Dinilai		Nilai Maksimal JURNAL ILMIAH			Nilai Akhir Yang Diperoleh *)
			Internasional / Bereputasi [√]	Nasional Terakreditasi [ ]	Nasional ***) [ ]	
a.	Kelengkapan unsur isi karya	(10%)	4			3,7
b.	Ruang lingkup dan kedalaman pembahasan	(30%)	12			11,8
c.	Kecukupan dan kemutakhiran data/ informasi dan metodologi	(30%)	12			11,8
d.	Kelengkapan unsur dan kualitas penerbitan	(30%)	12			11,6
	Total	**100%**	**40**			38,9

Catatan Penilaian ARTIKEL oleh Reviewer :

a. Kelengkapan dan kesesuaian unsur.....
Paper ditulis dengan baik, unsur lengkap, hasil sesuai judul penelitian, untuk mengisi kaidah penulisan karya ilmiah internasional bereputasi

b. Ruang lingkup & kedalaman pembahasan .....
lingkup penelitian berbagai senyawa flavonoid mengatasi kanker payudara

c. Kecukupan & kemutakhiran data serta metodologi. Sumber pustaka mutakhir, metode penelitian molecular docking berbagai senyawa flavonoid yang memiliki binding affinity terhadap protein ER, HER 2, EGFR

d. Kelengkapan unsur dan kualitas penerbit .....

Science Asia terindeks Scopus Q3 SJR 0,19. Penerbit Science Society of thailand under Royal Patronage

e. Indikasi plagiasi
Tidak terdapat indikasi plagiarism atau self-plagiarism

f. Kesesuaian bidang ilmu
Paper bidang bioinformatika sedikit kurang sesuai dengan bidang ilmu peneliti

REVIEWER 1

(Prof. Dr. Chrismis Novalinda Ginting, M.Kes)
NIK : 0115127801
UNIVERSITAS PRIMA INDONESIA

LEMBAR HASIL PENILAIAN
SEJAWAT SEBIDANG atau *PEER REVIEW*

KARYA ILMIAH : JURNAL ILMIAH

Judul Karya Ilmiah (Artikel)	:	Dietary flavonoids against various breast cancer subtypes: a molecular docking study
Jumlah Penulis	:	10 orang
Nama-nama Penulis	:	**Wahyu Widowati**, Diana Krisanti Jasaputra, Yusuf Heriady, Ahmad Faried, Rizal Rizal, Wahyu Setia Widodo , Satrio Haryo Benowo Wibowo, Hanna Sari W Kusumad, Ermi Girsange, I Nyoman Ehrich Lister
Status Penulis	:	Penulis Pertama / ~~Penulis ke ....~~ / Penulis Korespondensi- **)
Identitas Jurnal Ilmiah	: a.	Nama jurnal : Science Asia
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Kategori Publikasi Jurnal Ilmiah: *(beri tanda √ yang dipilih)*

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- [ ] Jurnal Ilmiah Nasional Terakreditasi
- [ ] Jurnal Ilmiah Nasional / Nasional terindeks ***)

HASIL PENILAIAN (*Peer Review*) :

No	Komponen Yang Dinilai		Nilai Maksimal JURNAL ILMIAH			Nilai Akhir Yang Diperoleh *)
			Internasional / Bereputasi [√]	Nasional Terakreditasi [ ]	Nasional ***) [ ]	
a.	Kelengkapan unsur isi karya	(10%)	4			3,8
b.	Ruang lingkup dan kedalaman pembahasan	(30%)	12			11,6
c.	Kecukupan dan kemutakhiran data/ informasi dan metodologi	(30%)	12			11,8
d.	Kelengkapan unsur dan kualitas penerbitan	(30%)	12			11,9
	Total	**100%**	**40**			39,1

Catatan Penilaian ARTIKEL oleh Reviewer :

a. Kelengkapan dan kesesuaian unsur
Kelengkapan unsur di artikel sudah cukup lengkap dan terdapat kesesuaian antara unsur dan isinya

b. Ruang lingkup & kedalaman pembahasan
Ruang lingkup bahasan sudah memadai dan lengkap serta terdapat kedalaman analisa data dan pembahasan.

c. Kecukupan & kemutakhiran data serta metodologi
Secara umum metodologi sudah memadai dan lengkap, kemutakhiran data sudah terpenuhi juga.

d. Kelengkapan unsur dan kualitas penerbit

Kualitas penerbit sudah memenuhi kaidah dan kualitas jurnal masuk kategori bereputasi yang baik

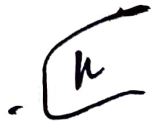
e. Indikasi plagiasi

Belum terlihat atas adanya unsur dindikasi plagiasi

f. Kesesuaian bidang ilmu

Jurnal ini sudah sesuai dengan bidang ilmu yang diteliti

REVIEWER 2



(Prof. Dr. Ermi Girsang, M. Kes)
NIK : 0117057501
UNIVERSITAS PRIMA INDONESIA

LEMBAR HASIL PENILAIAN
SEJAWAT SEBIDANG atau *PEER REVIEW*

KARYA ILMIAH : JURNAL ILMIAH

Judul Karya Ilmiah (Artikel)	:	Dietary flavonoids against various breast cancer subtypes: a molecular docking study
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- [ ] Jurnal Ilmiah Nasional / Nasional terindeks ***)

HASIL PENILAIAN (*Peer Review*) :

No	Komponen Yang Dinilai		Nilai Maksimal JURNAL ILMIAH			Nilai Akhir Yang Diperoleh *)
			Internasional / Bereputasi [√]	Nasional Terakreditasi [ ]	Nasional ***) [ ]	
a.	Kelengkapan unsur isi karya	(10%)	4			3,75
b.	Ruang lingkup dan kedalaman pembahasan	(30%)	12			11,7
c.	Kecukupan dan kemutakhiran data/ informasi dan metodologi	(30%)	12			11,8
d.	Kelengkapan unsur dan kualitas penerbitan	(30%)	12			11,75
	Total	**100%**	**40**			39,0

Catatan Penilaian ARTIKEL oleh Reviewer :

a. Kelengkapan dan kesesuaian unsur.....
Paper ditulis dengan baik, unsur lengkap, hasil sesuai judul penelitian, runtun mengikuti kaidah penulisan karya ilmiah internasional bereputasi

Kelengkapan unsur isi artikel sudah cukup lengkap dan terdapat kesesuaian antara unsur dan isinya

b. Ruang lingkup & kedalaman pembahasan .....

Lingkup penelitian berbagai senyawa flavonoid mengatasi kanker payudara

Ruang lingkup bahasan sudah memadai dan lengkap serta terdapat kedalaman analisa data dan pembahasan.

c. Kecukupan & kemutakhiran data serta metodologi

Sumber pustaka mutakhir, metode penelitian molecular docking berbagai senyawa flavonoid yang memiliki binding affinity terhadap protein ER, HER2, EGFR

Secara umum metodologi sudah memadai dan lengkap, kemutakhiran data juga sudah terpenuhi

d. Kelengkapan unsur dan kualitas penerbit

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kualitas penerbit sudah memenuhi kaidah dan kualitas jurnal masuk kategori bereputasi yang baik

e. Indikasi plagiasi

Tidak terdapat indikasi plagiarism atau self-plagiarism

Belum terlihat adanya unsur indikasi plagiasi

f. Kesesuaian bidang ilmu

Paper bidang bioinformatika sedikit kurang sesuai dengan bidang ilmu penulis

Jurnal ini sudah sesuai dengan bidang ilmu yang ditekuni

Medan,
Reviewer 2

(Prof. Dr. Ermi Girsang, M.Kes)
NIK : 0117057501
UNIVERSITAS PRIMA INDONESIA

Medan,
Reviewer 1

(Prof. Dr. Charismis Novalinda Ginting, M.Kes)
NIK : 0115127801
UNIVERSITAS PRIMA INDONESIA