Scientific Foundation SPIROSKI, Skopje, Republic of Macedonia
Open Access Macedonian Journal of Medical Sciences. 2022 Nov 17; 10(A):1624-1629.
https://doi.org/10.3889/oamjms.2022.10457
eISSN: 1857-9655
**Category:** *A - Basic Sciences*
***Section:*** *Pharmacolgy*





# New Cholesteryl Ester Transfer Protein from Indonesian Herbal Plants as Candidate Treatment of Cardiovascular Disease

Ratih Dewi Yudhani[1,2]*, Khariz Fahrurrozi[3], Dono Indarto[2,4]

*[1]Department of Pharmacology, Faculty of Medicine, Universitas Sebelas Maret, Surakarta, Indonesia; [2]Biomedical Laboratory, Faculty of Medicine, Universitas Sebelas Maret, Surakarta, Indonesia; [3]Undergraduate Student, Faculty of Medicine, Universitas Sebelas Maret, Surakarta, Indonesia; [4]Department of Physiology, Faculty of Medicine, Universitas Sebelas Maret, Surakarta, Indonesia*

**Edited by:** Sinisa Stojanoski
**Citation:** Yudhani RD, Fahrurrozi K, Indarto D. New Cholesteryl Ester Transfer Protein from Indonesian Herbal Plants as Candidate Treatment of Cardiovascular Disease. OpenAccessMacedJMedSci.2022Nov17;10(A):1624-1629. https://doi.org/10.3889/oamjms.2022.10457
**Keywords:** Cardiovascular disease; Cholesterol ester transfer protein inhibitor; Molecular docking; Indonesian plants; Phytochemical screening; *In silico*
***Correspondence:** Ratih Dewi Yudhani, Department of Pharmacology, Faculty of Medicine, Universitas Sebelas Maret, Surakarta, Indonesia.
E-mail: ratihyudhani@staff.uns.ac.id
**Received:** 18-Jun-2022
**Revised:** 31-Oct-2022
**Accepted:** 07-Nov-2022

**Funding:** This study was supported by PDD Grant 2021-2022 from Universitas Sebelas Maret
**Competing Interests:** The authors have declared that no competing interests exist


**Abstract**

**BACKGROUND:** There is a strong negative relationship between high-density lipoprotein cholesterol (HDL-C) and the risk of cardiovascular disease (CVD). Cholesterol ester transfer protein (CETP) is a glycoprotein transporter that transfers cholesterol esters to very low-density lipoprotein and low-density lipoprotein cholesterol (LDL-C). The CETP inhibitor is a new strategy against CVD because of its ability to increase HDL-C. Various Indonesian plants have not been optimally used, and *in silico* phytochemical screening of these plants showing potential as CETP inhibitors is still limited.

**AIM:** This study for exploring Indonesian phytochemicals as CETP inhibitors for new CVD treatments.

**METHODS:** We screened 457 phytochemicals registered in the herbal database and met Lipinski's rule of five. Their molecular structures were downloaded from the PubChem database. The three-dimensional structures of CETP and dalcetrapib (the CETP inhibitor standard) were obtained from a protein data bank (http://www.rcsb.org/pdb/) with the 4EWS code and ZINC database with the ZINC03976476 code, respectively. CETP–dalcetrapib binding complexes were validated 5 times using AutoDock Vina 1.1.2 software. Interactions between CETP and phytochemicals were molecularly docked with the same software and visualized using Pymol 1.8× software.

**RESULTS:** Dalcetrapib had a docking score of −9.22 kcal/mol and bound to CETP at $Ser^{230}$ and $His^{232}$ residues. The 11 phytochemicals had lower binding scores than dalcetrapib, but only L-(+)-tartaric acid, chitranone, and oxoxylopine could interact with CETP at the $Ser^{230}$ residue. These are commonly found in *Tamarindus indica*, *Plumbago zeylanica*, and *Annona reticulata*, respectively.

**CONCLUSION:** L-(+)-Tartaric acid, chitranone, and oxoxylopine show potential as CETP inhibitors *in silico*.

## Introduction

Cardiovascular disease (CVD) is a major non-communicable disease and is the leading cause of mortality worldwide. Epidemiological studies from 1990 to 2013 documented an increasing pattern of premature deaths associated with CVD in low-and middle-income countries. In 2017, more than 17 million people worldwide died from CVD, which is 50% higher than the rate in 1990 [1], [2]. CVD is a major burden, as it is the main cause of morbidity and mortality, contributing to a third of deaths in Indonesia [3].

Statin therapy to the lower low-density lipoprotein (LDL) cholesterol can reduce CVD events as primary or secondary prevention. However, significant cardiovascular risk still remains, even after the achievement of optimal LDL concentration. Moreover, in major statin trials, the maximum relative risk reduction did not exceed 47% [4].

A decreased level of high-density lipoprotein (HDL) cholesterol is another crucial risk factor for CVD events, independent of LDL-C levels. In addition, epidemiological data clearly demonstrate an inverse relationship between high-density lipoprotein cholesterol (HDL-C) levels and the risk of CVD [4], [5]. Higher levels of HDL-C are associated with both reduced plaque progression and frequency of CVD events. Therefore, raising HDL-C is considered an attractive target for strategies to the lower cardiovascular risk. Niacin reduces the risk of CVD through its role in reducing LDL-C levels while increasing HDL-C by 25%–35% when administered at the highest doses. However, niacin fails to suppress vascular events, such as strokes [5], [6]. Moreover, the use of atorvastatin (a statin or HMG-CoA reductase inhibitor), which became the best-selling drug in the United States is considered a major concern, given that the number of patients who suffer from heart disease in 2011 remained high, with health-care expenditures reaching $312.6 billion [5], [6].

Extensive research has been conducted to identify new HDL-raising drugs to further reduce CVD risk. Cholesteryl ester transfer protein (CETP) inhibitors are being actively studied for this purpose [4], [5].

CETP is a plasma–glycol protein that plays a crucial role in lipid metabolism and has an effect in reducing HDL-C levels. HDL plays an important role in relocating cholesterol from macrophages to the liver and increasing cholesterol excretion, thereby supporting its cardioprotective effect. Increased HDL levels are negatively correlated with the incidence of CVD. Inversely, either high CETP levels or its activity reduces HDL levels because it facilitates cholesterol ester (CE) transport and triglyceride exchange between various lipoprotein fractions [7].

CETP is mainly bound to HDL particles and specifically transfers CE from HDL to LDL and VLDL. Moreover, complementary triglyceride transfer occurs in the opposite direction. This results in CE depletion and triglyceride accumulation in HDL, which promotes HDL catabolism and reduces circulating HDL-C levels [7], [8]. CETP inhibitors are the most attractive candidates for raising HDL-C. The inhibition of CETP with a small compound promotes the increase of HDL-C levels and decreases LDL levels in plasma [5], [8], [9].

Small molecules or bioactive compounds for certain targets can be identified by high-throughput screening (HTS) methods to find drug candidates, although these methods are time consuming and require high costs. Virtual screening (VS) overcomes this limitation by applying computer-based methods to drug discovery pipelines that are mostly conducted prior to HTS. It is critical for eliminating unlikely drug–target pairs so that only potential drug–target pairs will pass for further testing. This minimizes HTS failures and makes drug discovery pipelines more effective and efficient [10]. One of them is a computational program called molecular docking, which can predict and evaluate optimal interactions between two molecules, especially a ligand and a receptor target [11].

Various Indonesian herb plants have not been optimally used, and *in-silico* phytochemical screening of those with potential as CETP inhibitors is still limited. Therefore, this study aims to explore Indonesian phytochemicals as CETP inhibitors that have the potential to be developed as new candidates for CVD treatment.

## Methods

### *Preparation of the target protein*

The three-dimensional (3D) structure of CETP was obtained from the Protein Data Bank (http://www.rcsb.org/pdb/) with PDB ID 4EWS. The CETP crystal structure has a 2.59 Å resolution and interacts with torcetrapib at $Ser^{230}$ and $His^{232}$ residues [12]. To maximize interaction between the CETP and its inhibitor or phytochemicals, we used AutoDock Tools 1.5.6 (available in http://autodock.scripps.edu/resources/adt) to remove torcetrapib and water molecules from the CETP. A hydrogen ion was then added to increase its polarity. The X-Y-Z axis in the grid box was set up to accommodate the target binding sites of CETP at $Ser^{230}$ and $His^{232}$.

### *Preparation of the standard ligand*

The 3D structures of the torcetrapib and dalcetrapib ligands were obtained from the ZINC database (http://zinc.docking.org), identified as ZINC98092268 and ZINC3976476, respectively. These molecular structures were downloaded and saved in *sdf format and converted into pdbqt files using OpenBabel in PyRx 0.8 software to molecularly dock these ligands into CETP. This validation process was then performed 5 times using AutoDock Vina 1.1.2 version (available in https://pyrx.sourceforge.io/) to obtain their average binding affinity values (Table 1). Ligand–CETP binding complexes were visualized using Pymol ×1.8. version, which is freely downloadable from https://pymol.org/2/.

**Table 1: Binding affinity score of dalcetrapib and torcetrapib to CETP docked using AutoDock Vina 1.1.2**

| CETP Inhibitor | Docking binding affinity (kcal/mol) | | | | | Average binding affinity (kcal/mol) | Binding site |
|---|---|---|---|---|---|---|---|
| | 1st | 2nd | 3rd | 4th | 5th | | |
| Dalcetrapib | −9.3 | −9.2 | −9.2 | −9.2 | −9.2 | −9.22 ± 0.04 | $Ser^{230}$, $His^{232}$ |
| Torcetrapib | −10.2 | −10.2 | −10.2 | −10.1 | −10.2 | −10.18 ± 0.04 | $Ser^{230}$, $His^{232}$ |

*The experiment was conducted 5 times, and the binding affinity scores are presented as mean ± SD.

Four CETP inhibitors (torcetrapib, dalcetrapib, anacetrapib, and evacetrapib) have recently been tested in large-scale randomized clinical trials [13], but we only compared torcetrapib and dalcetrapib as standard ligands. Torcetrapib, the first CETP inhibitor, was evaluated in phase 3 clinical trials. It has been shown to increase HDL-C by 60% and suppress LDL-C by 20% relative to statins. However, it also increases the risk of mortality. In contrast to torcetrapib, dalcetrapib is a modest CETP inhibitor, given that it only increases HDL-C levels by 30% and has a minimal effect on LDL-C levels. Interestingly, dalcetrapib administration does not increase vascular inflammation or endothelial dysfunction [14]. Thus, in the present study, we used dalcetrapib to validate molecularly with the CETP to screen selected phytochemicals.

### *Preparation and visualization of phytochemicals*

From a total of 6776 phytochemicals from Indonesian herbal plants, which were registered at HerbalDB http://herbaldb.farmasi.ui.ac.id/, 835 phytochemicals had 3D structures, which were available at the PubChem database https://pubchem.ncbi.nlm.nih.gov/. Lipinski's rule of five criteria was used to further select among these Indonesian phytochemicals [15]. Finally, we obtained 477 phytochemicals. However, 20 phytochemicals had similar molecular structures, so only 457 phytochemicals remained. The structures of

these selected phytochemicals were downloaded using the Open Babel in the PyRx 0.8 program and saved in *.pdbqt format.

Interactions between CETP and selected phytochemicals were assessed 5 times using AutoDock Vina 1.1.2, and their average binding affinity values (kcal/mol) were obtained. CETP–phytochemical binding complexes were visualized using Pymol software. A phytochemical that interacted with CETP at a binding energy lower than that of dalcetrapib and CETP was considered as a potential new candidate CETP inhibitor. Furthermore, the location of binding sites between dalcetrapib and residues of CETP was used to compare the binding sites between the selected phytochemicals and CETP. Subsequently, the molecular conformation of the phytochemicals was compared to dalcetrapib when interacting with CETP.

Lipinski's rule of five has been widely accepted as a basic approach for synthesizing or screening new compounds. The candidate should meet the following criteria: A molecular weight below 500 Dalton, a number of hydrogen-bond donors and hydrogen-bond acceptors <5 and <10, respectively; and a calculated octanol–water partition coefficient <5 [15].

## Results

### *Standard ligand validation*

The average binding affinities of dalcetrapib and torcetrapib are shown in Table 1. Dalcetrapib has a weaker binding affinity (−9.22 kcal/mol) than torcetrapib (−10.18 kcal/mol). Both CETP inhibitors interact with CETP at the same residues (Ser$^{230}$ and His$^{232}$) (Table 1 and Figure 1). The amino acid binding affinities of torcetrapib are similar to those in a previous study conducted by Liu *et al*. [12]. However, the determined binding sites of dalcetrapib to CETP are different from those in Okamoto's study, which suggested Cys$^{13}$ as the residue for interaction between dalcetrapib and CETP [16]. Molecular interaction showed that hydrogen bonds were detected in both Ser$^{230}$ and His$^{232}$ residues. In addition, these CETP inhibitors had similar molecular conformations.

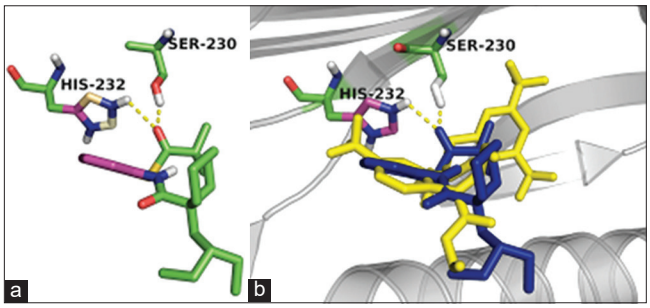


*Figure 1: Visualization of dalcetrapib–CETP binding complexes using PyMol ×1.8 software. (a) Dalcetrapib's interaction with Ser$^{230}$ and His$^{232}$ residues, similar to torcetrapib [12]. (b) Comparison of dalcetrapib's (blue) and torcetrapib's (yellow) positions relative to CETP*

### *Phytochemicals and CETP docking*

A total of 457 selected phytochemicals that complied with Lipinski's rule were molecularly docked with CETP 5 times. Table 2 indicates that 11 phytochemicals possessed stronger binding affinities and lower molecular weights than those of dalcetrapib. Interestingly, the strongest binding affinity was found in palmarumycin CP1 (−10.8 kcal/mol) and (+)-sesamin (−10 kcal/mol), but they had differently binding sites. The palmarumycin did not interact with the binding sites of CETP, whereas (+)-sesamin had molecular interaction through Val$^{198}$ and Arg$^{201}$ residues. Although L-(+)-tartaric acid, chitranone, and oxoxylopine had a weaker binding affinity than previous phytochemicals, they were able to bind to CETP at a polar residue (Ser$^{230}$). Further analysis revealed that only L-(+)-tartaric acid and oxoxylopine had hydrogen bonds at the binding site.

After visualization with Pymol 1.8, (+)-sesamin, tartaric acid, chitranone, and oxoxylopine were found to be located in the binding pocket of CETP (Figure 2). A similar molecular conformation to dalcetrapib was observed in L-(+)-tartaric acid and chitranone, that is, close to the Ser$^{230}$ side.

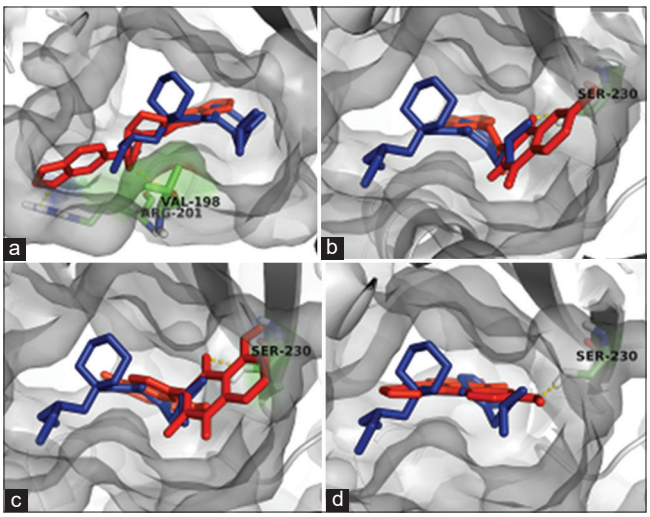


*Figure 2: Visualization of phytochemical–CETP blinding complexes. Phytochemicals (red) overlaid with dalcetrapib (blue), which were visualized using the PyMol ×1.8 program. (a) (+)-Sesamin's interaction with Val$^{198}$ and Arg$^{201}$, (b) L-(+)-Tartaric acid's interaction with Ser$^{230}$, (c) Chitranone's interaction with Ser$^{230}$, (d) Oxoxylopine's interaction with Ser$^{230}$*

## Discussion

In recent years, *in silico* method has allowed the screening of millions of compounds virtually in a short period of time, thus reducing the initial costs required for the hit identification process and increasing the chances of finding the desired drug candidate. Several molecular modeling techniques are

**Table 2: Top 11 phytochemicals as CETP inhibitors**

| Phytochemicals compounds | Molecular Weight (g/mol) | Docking binding affinity (kcal/mol) | | | | | Average binding affinity (kcal/mol) | Binding site | The type of binding |
|---|---|---|---|---|---|---|---|---|---|
| | | 1st | 2nd | 3rd | 4th | 5th | | | |
| Dalcetrapib | 389.598 | −9.3 | −9.2 | −9.2 | −9.2 | −9.2 | −9.2 | $Ser^{230}$, $His^{232}$ | Hydrogen bond |
| Palmarumycin CP1 | 316.312 | −10.8 | −10.8 | −10.8 | −10.8 | −10.8 | −10.8 | – | – |
| (+)−Sesamin | 354.358 | −10.0 | −10.0 | −10.0 | −10.0 | −10.0 | −10.0 | $Val^{198}$, $Arg^{201}$ | Van der Waals ($Val^{19}$), Hydrogen bond ($Arg^{201}$) |
| L-(+)-Tartaric acid | 150.086 | −9.8 | −9.8 | −9.8 | −9.8 | −9.8 | −9.8 | $Ser^{230}$ | Hydrogen bond |
| Chitranone | 374.348 | −9.8 | −9.8 | −9.8 | −9.8 | −9.8 | −9.8 | $Ser^{230}$ | Van der Waals |
| Heliettin 3-O-Methylcalopocarpin | 314.381 | −9.6 | −9.6 | −9.6 | −9.6 | −9.6 | −9.6 | $Arg^{201}$ | Hydrogen bond |
| (−)-Sesamin | 338.403 | −9.5 | −9.5 | −9.5 | −9.5 | −9.5 | −9.5 | - | - |
| Licarin B | 354.358 | −9.4 | −9.4 | −9.4 | −9.4 | −9.4 | −9.4 | - | - |
| Oxoxylopine | 324.376 | −9.4 | −9.4 | −9.4 | −9.4 | −9.4 | −9.4 | - | - |
| Xylopine | 305.289 | −9.4 | −9.3 | −9.4 | −9.4 | −9.4 | −9.4 | $Ser^{230}$ | Hydrogen bond |
| Rutacridone | 295.338 | −9.3 | −9.3 | −9.4 | −9.3 | −9.3 | −9.3 | - | - |
| | 307.349 | −9.2 | −9.3 | −9.3 | −9.2 | −9.3 | −9.2 | - | - |

*Due to the high toxicity of torcetrapib, we only used dalcetrapib as a standard ligand for interaction with CETP.

currently available to facilitate the discovery of these drug candidates. Most of these techniques belong to structure- and ligand-based approaches. Molecular docking is one of the most widely used *in silico* structure-based methods. This method has been successful in predicting interactions that occur between molecules and biological targets. Molecular docking is initially performed with the identification of the binding structure of the ligand molecule at the receptor, followed by the estimation of complementarity between the molecule and the biological target through a scoring function [17].

Moreover, molecular docking is a computational method for predicting the interaction between a ligand and the receptor-active site by exploring various possible relative ligand–receptor binding configurations while simultaneously evaluating the intermolecular interactions that occur at each configuration position. This allows one to determine the most potent configuration of the ligand–receptor complex. Information on the 3D structure of the target molecule with high resolution is required in the molecular docking procedure. Interestingly, the 3D crystal structure of CETP has been elucidated as a long tunnel with four bound lipid molecules, each containing two CE and phosphatidylcholines. This 3D CETP structure contributes crucially to facilitating the exploration of CETP inhibitor candidates by assessing the complex binding between the 3D CETP structures and various CETP inhibitor candidates *in silico*. Hence, VS by molecular docking is widely implemented as the latest strategy for obtaining new active compounds through exploration from *in silico* chemical databases [18].

In the current molecular docking study, we documented that dalcetrapib can interact with CETP at the same binding site as torcetrapib *in silico* ($Ser^{230}$ and $His^{232}$). This finding is different from biochemical studies showing that $Cys^{13}$ has an important role in the interaction between dalcetrapib and CETP with disulfide bonds [16], [19]. Although flexibility of the target binding site is essential, it is frequently ignored in molecular docking. During the molecular recognition process, conformational changes can occur in the target protein. These changes may only be small, and the ligand may still fit in a binding site with little adjustment, whereas some proteins have significant changes that can involve elements of the secondary and tertiary structures [20]. CETP is a glycoprotein that may undergo significant conformational changes during the molecular recognition process, and this was ignored in the molecular docking analysis.

We also observed some differences in the complex binding sites between the phytochemicals and the CETP (Figure 2). Khalaf *et al*. elucidated the structure of CETP as a long tunnel, which is completed with the binding of two neutral lipids (hydrophobic cholesteryl esters) in the tunnel and two phospholipids (phosphatidylcholines) that plug in as two distinct openings at each end [21]. Moreover, CETP has many binding sites. Most are hydrophobic residues (e.g., $Ile^{11}$, $Cys^{13}$, $Arg^{201}$, $Ala^{20}$, and $Val^{198}$), and the others are polar residues (e.g., $Ser^{230}$, $His^{232}$, and $Gln^{199}$) [22]. Biochemical studies have demonstrated that CETP interacts with the phospholipid surface of HDL particles through hydrophobic or hydrophilic interactions [23].

In this bio-computional study, we demonstrated that L-(+)-tartaric acid, chitranone, and oxoxylopine are potential candidates that can be developed as CETP inhibitors *in silico* in terms of binding energy, binding sides, and molecular weight. A lower binding energy observed in L-(+)-tartaric acid, chitranone, and oxoxylopine will lead to a higher affinity of interaction with CETP compared with a standard CETP inhibitor (dalcetrapib). A more negative docking score is known to lead to a higher binding affinity [21]. Regarding the herbalDB database, Indonesian herbal plants that contain L-(+)-tartaric acid, chitranone, and oxoxylopine are *Tamarindus indica* (tamarind), *Plumbago zeylanica*, and *Annona reticulata*, respectively.

Tartaric acid is the main compound in the pulp of Tamarind, and this fruit extract has the potential to prevent atherosclerosis in humans, given its potent antioxidant activity [24]. Chitranone is an active compound of the flavonol group belonging to the flavonoid class. It can be found in *P. zeylanica* from the *Plumbanginaceae* family, which is known to have antioxidant activity [25]. Oxoxylopine, or lanuginosine, which belongs to the alkaloid class, is one of the phytoconstituents that has been isolated from the *Anonna* genus plants [26].

*T. indica* (tamarind) has an effect on reducing fat accumulation and improving hyperlipidemia in rats. The leaf extracts of tamarind have been proven to significantly reduce total cholesterol and triglyceride while improving

HDL-C levels in hypercholesterol-fed rats compared to the negative control group [27]. The fruit pulp extract of *T. indica* can decrease LDL-C, triglyceride, and total cholesterol levels in hamsters, either in the absence or presence of a high-cholesterol diet [28]. Moreover, the seed extracts of tamarind can lower blood glucose and serum cholesterol and enhance glycogen storage in rats [29]. A randomized controlled trial involving 40 obese and overweight participants showed that the consumption of 10 g of tamarind fruit pulp twice daily for 6 weeks significantly reduces body mass index, LDL-C levels, waist circumference, and blood pressure relative to pre-treatment measurements [30].

The effectivity of *P. zeylanica* in modulating lipid profiles was proven by Pai *et al*., who reported that plumbagin, a napthoquinone contained in the root of *P. zeylanica*, has properties in reducing triglyceride, total cholesterol, LDL-C, and very low-density lipoprotein levels while increasing HDL-C levels in rats induced by chronic fructose feeding. These effects are due to the ability of plumbagin to inhibit lipogenesis while promoting fat oxidation. It also possesses anti-inflammatory and anti-oxidant properties [31].

There is no evidence about the antilipidemic effect of *A. reticulata*, but another species of *Annona*, *Annona muricata*, has been proven to play an important role in ameliorating the lipid profile of a C57BL/6 adult male mice model of metabolic disorder induced by a high-fed diet. Treatment with aqueous leaf extracts of *A. muricata* significantly reduces serum triglyceride and LDL-C levels. Moreover, this extract also significantly increases HDL-C levels, especially at a dose of 150 mg/kg body weight [32].

## Conclusion

L-(+)-Tartaric acid, chitranone, and oxoxylopine show potential as CETP inhibitors *in silico*. The docking results in this study showed that these three phytochemicals had lower binding energy relative to dalcetrapib and interacted with CETP at the $Ser^{230}$ residue. Moreover, a molecular conformation similar to that of dalcetrapib was observed in L-(+)-tartaric acid and chitranone. *T. indica*, *P. zeylanica*, and *A. reticulata* are Indonesian herbal plants that contain L-(+)-tartaric acid, chitranone, and oxoxylopine, respectively. Further investigations should be performed to confirm this finding.

## Authors' Contributions

All authors have contributed significantly and approved the manuscript submission. RDY contributed in designing the general structure and drafting the manuscript. KF conducted the *silico* docking, and DI gave the molecular docking concept and critically revised the manuscript.

## References


1. Li Z, Lin L, Wu H, Yan L, Wang H, Yang H, *et al*. Global, regional, and national death, and Disability-Adjusted Life-Years (DALYs) for cardiovascular disease in 2017 and trends and risk analysis from 1990 to 2017 using the global burden of disease study and implications for prevention. Front Public Health. 2021;9:559751. https://doi.org/10.3389/fpubh.2021.559751
   PMid:34778156
2. Roth GA, Mensah GA, Johnson CO, Addolorato G, Ammirati E, Baddour LM, *et al*. Global burden of cardiovascular diseases and risk factors, 1999-2019. Update from the GBD 2019 study. J Am Coll Cardiol. 2020;76(25):2982-3021. https://doi.org/10.1016/j.jacc.2020.11.010
   PMid:33309175
3. Maharani A, Sujarwoto, Praveen D, Oceandy D, Tampubolon G, Patel A. Cardiovascular disease risk factor prevalence and estimated 10-year cardiovascular risk scores in Indonesia: The SMARThealth Extend study. PLosOne. 2019;14(4):e0215219. https://doi.org/10.1371/journal.pone.0215219
   PMid:31039155
4. Kosmas CE, DeJesus E, Rosario D, Vittorio TJ. CETP inhibition: Past failures and future hopes. Clin Med Insights Cardiol. 2016;10:37-42. https://doi.org/10.4137/cmc.s32667
   PMid:26997876
5. Shinkai H. Cholesteryl ester transfer-protein modulator and inhibitors and their potential for the treatment of cardiovascular diseases. Vasc Health Risk Manag. 2012;8:323-31. https://doi.org/10.2147/vhrm.s25238
   PMid:22661899
6. Farrer S. Beyond statins: Emerging evidence for HDL-increasing therapies and diet in treating cardiovascular disease. Adv Prev Med. 2018;2018:6024747. https://doi.org/10.1155%2F2018%2F6024747
   PMid:30112217
7. Chirasani VR, Senapati S. How cholesteryl ester transfer protein can also be a potential triglyceride transporter. Sci Rep. 2017;7(1):6159. https://doi.org/10.1038/s41598-017-05449-z
   PMid:28733595
8. Woudberg NJ, Pedretti S, Lecour S, Schulz R, Vuilleumier N, James RW, *et al*. Pharmacological intervention to modulate HDL: What do we target? Front Pharmacol. 2018;8:989. https://doi.org/10.3389/fphar.2017.00989
   PMid:29403378
9. Filippatos TD, Kei A, Elisaf MS. Anacetrapib, a new CETP inhibitor: The new tool for the management of dyslipidemias? Diseases. 2017;5(4):21. https://doi.org/10.3390/diseases5040021
   PMid:28961179
10. Rifaioglu AS, Atas H, Martin MJ, Atalay RC, Atalay V, Doğan T. Recent applications of deep learning and machine intelligence on *in silico* drug discovery: Methods, tools and databases. Brief Bioinform. 2019;20(5)1878-912. https://doi.org/10.1093/bib/bby061
    PMid:30084866

11. Banchi L, Fingerhuth M, Babej T, Ing C, Arrazola JM. Molecular docking with Gaussian Boson sampling. Sci Adv. 2020;6(23):eaax1950. https://doi.org/10.1126/sciadv.aax1950
PMid:32548251
12. Liu S, Mistry A, Reynolds JM, Lloyd DB, Griffor MC, Perry DA, *et al*. Crystal structures of cholesteryl ester transfer protein in complex with inhibitors. JBC. 2012;287(44):37321-9. https://doi.org/10.1074/jbc.M112.380063
PMid:22961980
13. Shrestha S, Wu BJ, Guiney L, Barter PJ, Rey KA. Cholesteryl ester transfer protein and its inhibitors. J Lipid Res. 2018;59(5):772-83. https://doi.org/10.1194/jlr.R082735
PMid:29487091
14. Nicholls SJ, Bubb K. The mystery of evacetrapib-why are CETP inhibitors failing? Expert Rev Cardiovasc Ther. 2020;18(3):127-30. https://doi.org/10.1080/14779072.2020.1745633
PMid:32200670
15. Boyd NK, Teng C, Frei CR. Brief overview of approaches and challenges in new antibiotic development: A focus on drug repurposing. Front Cell Infect Microbiol. 2021;11:684515. https://doi.org/10.3389/fcimb.2021.684515
PMid:34079770
16. Okamoto H, Yonemori F, Wakitani K, Minowa T, Maeda K, Shinkai H. A cholesteryl ester transfer protein inhibitor attenuates atherosclerosis in rabbits. Nature. 2000;406(6792):203-7. https://doi.org/10.1038/35018119
PMid:10910363
17. Pinzi L, Rastelli G. Molecular docking: Shifting paradigms in drug discovery. Int J Mol Sci. 2019;20(18):4331. https://doi.org/10.3390%2Fijms20184331
PMid:31487867
18. Ta'rraga WA, Garda HA, Toledo JD, Gonzalez MC. Potential inhibitors of the activity of the cholesterol-ester transfer protein. J Comput Biol. 2019;26(12):1458-69. https://doi.org/10.1089/cmb.2018.0227
PMid:31356116
19. Ranaletta M, Bierilo KK, Chen Y, Milot D, Chen Q, Tung E, *et al*. Biochemical characterization of cholesteryl ester transfer protein inhibitors. J Lipid Res. 2010;51(9):2739-52. https://doi.org/10.1194/jlr.m007468
PMid:20458119
20. Ferreira L, Dos Santos R, Oliva G, Andricopulo A. Molecular docking and structure-based drug design strategies. Molecules. 2015;20(7):13384-421. https://doi.org/10.3390/molecules200713384
PMid:26205061
21. Khalaf RA, Sabbah D, Al-Shalabi E, Bishtawi S, Albadawi G, Sheika GA. Synthesis, biological evaluation, and molecular modeling study of substituted benzyl benzamides as CETP inhibitors. Arch Pharm (Weinheim). 2017;350(12):e1700204. https://doi.org/10.1002/ardp.201700204
PMid:29112287
22. Khalaf RA, Al-Rawashdeh S, Sabbah D, Sheikha GA. Molecular docking and pharmacophore modelling studies of fluorinated benzamides as potential CETP inhibitors. Med Chem. 2017;13(3):239-53. https://doi.org/10.2174/1573406412666161104121042
PMid:27823564
23. Zhang M, Lei D, Peng B, Yang M, Zhang L, Charles MA, *et al*. Assessing the mechanisms of cholesteryl ester transfer protein inhibitors. Biochim Biophys Acta Mol Cell Biol. 2017;1862(12):1606-17. https://doi.org/10.1016/j.bbalip.2017.09.004
PMid:28911944
24. Arshad MS, Imran M, Ahmad A, Sohaib M. Ullah A, Nisa MU, *et al*. Tamarind: A diet-based strategy against lifestyle maladies. Food Sci Technol. 2019;7(11):3378-90. https://doi.org/10.1002/fsn3.1218
PMid:31762991
25. Salamah NN, Aryati WD, Yanuar A. Virtual screening of Indonesian herbal database as adenosine $A_2A$ antagonist using AutoDock and AutoDock Vina. Pharmacogn J. 2019;11(6):1219-24. https://doi.org/10.5530/pj.2019.11.189
26. Nugraha AS, Damayanti YD, Wangchuk P, Keller PA. Anti-infective and anti-cancer properties of the *Annona* species: Their ethnomedicinal uses, alkaloid diversity, and pharmacological activities. Molecules. 2019;24(23):4419. https://doi.org/10.3390/molecules24234419
PMid:31816948
27. Aprilia CA, Ninditasari G, Walujo D. Hypolipidemic effect and antioxidant activity of tamarind leaves extract in hypercholesterol-fed rats. Indonesian J Cardiol. 2017;38(2):72-80. https://doi.org/10.30701/ijc.v38i2.730
28. Lim CY, Junit SM, Aziz AA, Jayapalan JJ, Hashim OH. The hypolipidemic effects of *Tamarindus indica* fruit pulp extract in normal and diet-induced hypercholesterolemic hamsters are associated with altered levels of serum proteins. Electrophoresis. 2018;39(23):2965-73. https://doi.org/10.1002/elps.201800258
PMid:30280388
29. Uchenna UE, Shori AB, Baba AS. *Tamarindus indica* seeds improve carbohydrate and lipid metabolism: An *in vivo* study. J Ayurveda Integr Med. 2018;9(4):258-65. https://doi.org/10.1016/j.jaim.2017.06.004
PMid:29203351
30. Asgary S, Soltani R, Barzegar N, Sarrafzadegan N. Evaluation on the effects of *Tamarindus Indica* L. fruit on body weight and several cardiometabolic risk factors in obese and overweight adult patients: A randomized controlled clinical trial. Int J Prev Med. 2020;11:24. https://doi.org/10.4103%2Fijpvm.IJPVM_558_18
PMid: 32175064
31. Pai SA, Munshi RP, Pancal FH, Gaur IS, Mestry SN, Gursahani MS, *et al*. Plumbagin reduces obesity and nonalcoholic fatty liver disease induced by fructose in rats through regulation of lipid metabolism, inflammation and oxidative stress. Biomed Pharmacother. 2019;111(2019):686-94. https://doi.org/10.1016/j.biopha.2018.12.139
PMid:30611993
32. Sasso S, Souza PC, Santana LF, Cardaso CA, Alves FM, Portugal LC, *et al*. Use of an extract of *Annona muricata* Linn to prevent high-fat diet induced metabolic disorders in C57BL/6 mice. Nutrients. 2019;11(7):1509. https://doi.org/10.3390/nu11071509
PMid:3126972