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FULL PAPER

Molecular docking and in silico drug-likeness studies of *Garcinia prainiana* King bioactive compounds as pancreatic lipase inhibitors

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Abstract

Garcinia prainiana King is an underutilized local fruit possessing high value in numerous therapeutic uses. Unlike other *Garcinia* species such as *G. cambogia* and *G. atroviridis*, the anti-obesity effect of *G. prainiana* has never been evaluated. Thus, in the present study, the inhibitory potential of bioactive compounds from *G. prainiana* towards pancreatic lipase, an enzyme involved in fat digestion that caused obesity was evaluated. A molecular docking study of eleven *G. prainiana* bioactive compounds against pancreatic lipase was performed followed by *in silico* drug-likeness prediction using the SwissADME tool. The docking study demonstrated that amentoflavone is the top compound showing the highest inhibition activity towards pancreatic lipase compared to other compounds. Two hydrogen bonds were formed between amentoflavone and two catalytic residues, Ser152 and His263 of pancreatic lipase. The formation of hydrophobic interactions with the lid residues, Ala260 and Ala259, may also contribute to the inhibitory effect of this compound. Other than amentoflavone, 4‴-methylamentoflavone and naringenin 7-o-β-D-glucuronide also exhibited high inhibition activities against pancreatic lipase by interacting with the catalytic and lid residues through hydrogen bonds. However, in the context of drug developability, naringenin 7-o-β-D-glucuronide was predicted to have a higher potential to be an oral drug candidate compared to amentoflavone and 4‴-methylamentoflavone. In conclusion, this study indicated the potential of *G. prainiana* compounds, particularly amentoflavone, 4‴-methylamentoflavone and naringenin 7-o-β-D-glucuronide as new pancreatic lipase inhibitors. However, naringenin 7-o-β-D-glucuronide has a higher drug-likeness potential that could serve as a drug candidate for the development of an anti-obesity agent.

1. Introduction

Plants are valuable sources for the exploration and development of natural drugs in maintaining human wellness and treating numerous illnesses. Plants contain essential vitamins and powerful bioactive compounds with proven therapeutic efficacy against many diseases. Up to date, 50% of approved drugs in the market derive from natural or plants (Veeresham, 2012). Furthermore, these plant compounds are cheaper with less-lethal side effects than synthetic drugs (Nisar *et al*., 2017). Hence, the screening and exploitation of beneficial plants and their bioactive compounds for drug development are recently inactive execution.

Garcinia prainiana King, locally known as cerapu or mencupu, is native to Malaysia possessing high value in therapeutic uses but it has been underutilized and neglected. This plant is used among local folks for cooking and as a traditional remedy. Previous studies have reported that fruits and leaves exhibit high antioxidant activities and high total phenolic and flavonoid content (Asang *et al*., 2018). Flavonoids and triterpenes were mainly found in the leaves and stem barks (Klaiklay *et al.*, 2011; On *et al*., 2016; Jabit *et al*., 2019). It is proven that these compounds exhibited anti-tyrosinase, anti-inflammatory and anti-diabetic effects (On *et al*., 2016; Jabit *et al*., 2019). However, unlike

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other *Garcinia* sp. such as *G. cambogia* and *G. atroviridis*, this plant has never been evaluated for anti-obesity activity.

Obesity is one of the medical concerns involving excessive fat accumulation in the body that may cause adverse effects on health. This disease is associated with the imbalance of energy metabolism leading to excessive fat deposition in the adipose tissue. Thus, researchers have aimed to reduce dietary fat absorption as one of the ideal approaches to treating obesity. To target this, the inhibition of pancreatic lipase, an enzyme responsible for the hydrolysis of total dietary fats obtained from food consumption, is proven effective (Lunagariya *et al.,* 2014). Pancreatic lipase inhibitors prevent the digestion of triglycerides into monoglycerides and fatty acids leading to reduced fat absorption. Undigested fats will be discharged through the faeces. This approach has been employed for orlistat, an existing anti-obesity drug where it interacts with one of the catalytic residues of pancreatic lipase and inhibits the enzyme activity (Liu *et al.*, 2020). However, this drug exerts gastrointestinal side effects such as abdominal pain, fatty or oily stool, diarrhoea and increased defecation (Filippatos *et al.*, 2008). Therefore, the development of new and efficient inhibitors with less or no side effects is highly needed for the treatment of obesity.

Hence, this study aimed to determine the inhibitory potential of bioactive compounds from *G. prainiana* against pancreatic lipase through a molecular docking approach. The interaction of compounds and pancreatic lipase was predicted and elucidated. In addition, the compound's ability as an oral active drug was also evaluated using *in silico* drug-likeness analysis. To the best of our knowledge, this is the first report discussing the potential of *G. prainiana* compounds as pancreatic lipase inhibitors. This study is crucial in revealing the therapeutic potential of these compounds that eventually aids in providing potential candidates for the development of pancreatic lipase inhibitors.

2. Materials and methods

2.1 Preparation of ligands and receptor

The information on the bioactive compounds from *G. prainiana* leaf and bark was obtained from Jabit *et al.* (2019), Klaiklay *et al.* (2011) and On *et al.* (2016). A total of 11 compounds with structures available in the PubChem database (https://pubchem.ncbi.nlm.nih.gov/) and the standard drug, orlistat (CID: 3034010) were used in this study. The structures were minimized and converted into pdbqt format using Open Babel version 2.3 (O'Boyle *et al.,* 2011). The structure of pancreatic lipase colipase in complex with C11 alkyl phosphonate (PDB: 1LPB) at 2.46 Å was retrieved from Protein Data Bank (PDB) (http://www.rcsb.org). Water molecules, hetero atoms and inhibitors were removed whereas hydrogen atoms were added to the protein structure using Discovery Studio Visualizer *v19.1.0.*18287 (BIOVIA, San Diego, CA, USA).

2.2 Molecular docking

The grid box was set at the region within the catalytic site of pancreatic lipase with the size of 40×40×40 and a default spacing of 0.375 Å. The grid box was centred at coordinates of x = 4.448, y = 27.995 and z = 49.675 (Alias *et al.*, 2020). The tolerance of root mean square deviation (RMSD) was set to 2.0 Å. Docking simulation was carried out using Autodock Vina version 1.1.2 with an exhaustiveness of 100 (Trott and Olson, 2010). The docked complexes with the lowest binding energy (kcal/mol) were selected and their hydrogen and/or hydrophobic interactions were visualized using PyMOL version 2.4.0 (Schrodinger, LLC) and Discovery Studio Visualizer *v19.1.0.*18287 (BIOVIA, San Diego, CA, USA).

2.3 Drug-likeness prediction

The potential of compounds to be oral active drugs was evaluated using SwissADME (http://www.swissadme.ch/index.php). Drug-likeness properties of the compounds were assessed through Lipinski's rule of five where molecular weight, hydrogen bond donor and acceptor, and logP were measured. Topological Polar Surface Area (TPSA) measured the compound's ability to permeate cell membranes by defining the sum of the surface area of polar atoms including oxygen, nitrogen and attached hydrogens (Prasanna and Doerksen, 2009). Compounds with a TPSA value greater than 140 $Å^2$ is likely to be poor in permeating cell membranes whereas compounds with TPSA value lesser than 90 $Å^2$ could penetrate the blood-brain barrier (BBB) (Ertl *et al.*, 2000). Gastrointestinal (GI) absorption indicated the compound's ability to be taken by the gastrointestinal tract upon oral administration. The probability of compounds being a substrate of a drug transporter, P-glycoprotein (P-gp) was determined. In addition, Pan Assay Interference Compounds (PAINS) alerts were also assessed for all compounds to determine if the compounds may give false positives in the screening process.

3. Results

3.1 Molecular docking

All compounds from *G. prainiana* exhibited negative free binding energy indicating the energy released due to the interaction formed between the ligands and

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Table 1. Binding affinities of the bioactive compounds from *G. prainiana* against pancreatic lipase.

Compound	PubChem ID	Free binding energy (kcal/mol)
Amentoflavone	5281600	-11
4‴-methylamentoflavone	136126988	-10.6
Naringenin 7-O-β-D-glucuronide	51136360	-10.1
Friedelin	91472	-10
Prainianonide	53465591	-9.9
Lupeol	259846	-9.5
(+)-Morelloflavone	12110448	-8.5
2″,3″-dihydromorelloflavone (GB-2a)	176988	-8.4
Volkensiflavone	5480834	-8.4
(–)-GB-1a	467746	-8.2
Squalene	638072	-7.7
Orlistat*	3034010	-6.2

*Standard drug

pancreatic lipase (Table 1). Interestingly, all of these compounds exhibited lower free binding energy than orlistat proposing that these compounds have higher affinity and greater intermolecular interaction as well as intermolecular bonds with pancreatic lipase compared to orlistat. Among all compounds, amentoflavone is the top compound showing the lowest free binding energy suggesting this compound possesses the highest inhibition activity towards pancreatic lipase. This compound formed hydrogen bonds with two important amino acid residues, Ser152 and His263 at a distance of 2.50 and 2.79 Å, respectively, which were involved in the pancreatic lipase activity (Figure 1). Hydrogen bonds were also formed with Gly76 and Phe215. Other than a hydrogen bond, Ile78, Ala260, Ala259, Tyr114, Pro180, Ala178 residues were in contact with this enzyme through hydrophobic interactions (Table 2).

In addition, 4‴-methylamentoflavone and naringenin 7-o-β-D-glucuronide also exhibited higher inhibition activity against pancreatic lipase compared to other compounds. 4‴-Methylamentoflavone and naringenin 7-o -β-D-glucuronide bound with one of the catalytic residues, Ser152 and His263, respectively, through hydrogen bonds. Other than catalytic residues, through hydrogen bonds, 4‴-methylamentoflavone also interacted with one of the lid residues, Arg256 whereas naringenin 7-o-β-D-glucuronide interacted with Phe77, His151 and Asp79. These compounds also came in contact with this enzyme through hydrophobic interactions. In orlistat-pancreatic lipase complex, orlistat formed a hydrogen bond and hydrophobic interaction with the catalytic residues, Ser152 and His263, respectively. Orlistat also interacted with Gly76 through a hydrogen bond. In addition, hydrophobic interactions were formed between orlistat and Phe215, Ala260, Ile209, Pro180.

3.2 Drug-likeness prediction

All the compounds were assessed for their potential to be oral active drugs. Of these, only five compounds (naringenin 7-O-β-D-glucuronide, friedelin, lupeol, squalene and prainianonide) obey Lipinski's rule where they violated only one criterion of the rule (Table 3). The other compounds were seen to violate more than one of Lipinski's rule criteria. All the compounds were predicted to have low GI absorption and zero permeant to BBB. Only naringenin 7-O-β-D-glucuronide and prainianonide can be P-gp substrates. All compounds are naturally specific as they possess no PAINS alert except for 2″,3″-dihydromorelloflavone (GB-2a) and (+)-morelloflavone where both have interferences with

Table 2. Molecular interaction of the top three hit compounds from *G. prainiana* with pancreatic lipase.

Compound	H-bonds interaction residue[a]	Distance (Å)	Hydrophobic interacting residue[a]
Amentoflavone	**His263**	2.50	Ile78, Ala260, Ala259, Tyr114,
	Ser152	2.79	Pro180, Ala178
	Phe215	2.00	
	Gly76		
4‴-methylamentoflavone	**Ser152**	3.04	Ala178, Tyr114, Phe215, Ala260,
	Arg256	4.43	Leu213, Ala259
Naringenin 7-O-β-D-glucuronide	**His263**	2.70	Tyr114,
	Phe77	3.43	Phe215
	His151	3.59	
Orlistat*	**Ser152**	2.29	Phe215, Ala260, **His263,** Ile209,
	Gly76	2.71	Pro180

[a]**Bold** indicate catalytic triad residues (His263, Ser152 and Asp176)
*Standard drug

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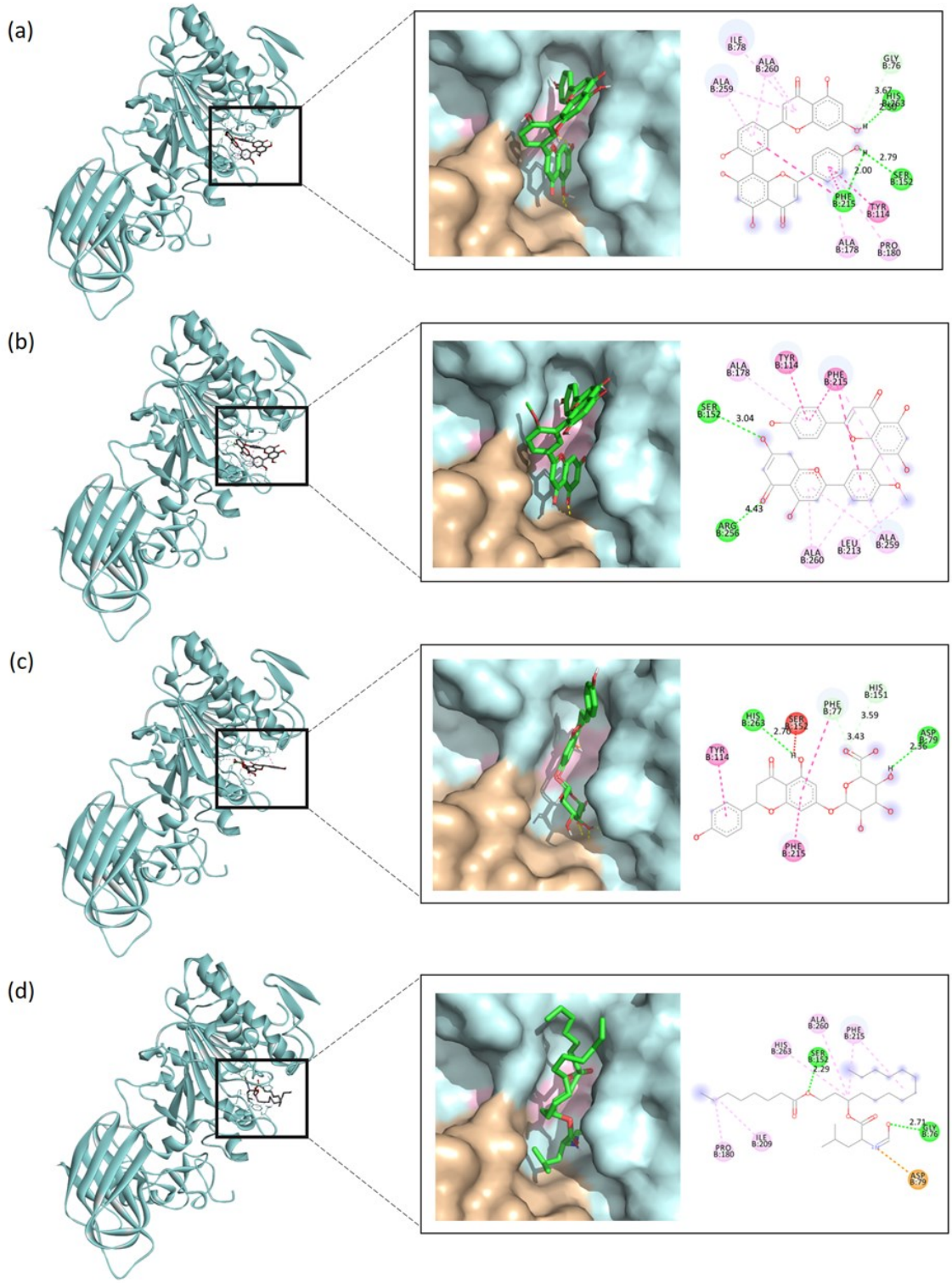

Figure 1. Interaction of top three compounds, (a) amentoflavone, (b) 4‴-methylamentoflavone and (c) naringenin 7-O-β-D-glucuronide from *G. prainiana* and (d) orlistat with pancreatic lipase (PDB ID: 1LPB). The interaction sites were enlarged in boxes where the compounds in sticks and the pancreatic lipase in cyan. The catalytic site and lid domain of pancreatic lipase were pink and brown, respectively. In 2D, hydrogen bonds were in dark and light green and hydrophobic interactions were in dark and light purple.

catechol A.

4. Discussion

Pancreatic lipase is a primary hydrolase that breaks down triglycerides into monoglycerides and fatty acids. The activity of this enzyme is assisted by the catalytic triad of His263, Ser152 and Asp176 which is enclosed in a hydrophobic lid domain (Winkler *et al.*, 1990). The lid domain, in a pure aqueous media, is mostly closed hence, it protects the catalytic site of pancreatic lipase from accessing substrates. However, under a hydrophobic environment, the lid partially opens and exposes the catalytic site that consequently activates the enzyme activity (Yang and Lowe, 2000; Khan *et al.*, 2017). In human pancreatic lipase (PDB ID: 1LPB), the lid domain

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Table 3. Structural and physicochemical properties of compounds from *G. prainiana*.

Compound name	Molecular weight[a]	H-bond donor	H-bond acceptor	LogP	Lipinski Violations	TPSA[b] (Å^2)	GI absorption[c]	BBB permeant[d]	P-gp substrate[e]	PAINS alerts[f]
Amentoflavone	538.464	6	10	5.134	3	181.8	Low	No	No	0
4‴-Methylamentoflavone	552.491	5	10	5.389	2	170.8	Low	No	No	0
Naringenin 7-O-β-D-glucuronide	448.38	6	10	0.075	1	183.21	Low	No	Yes	0
Friedelin	426.729	0	1	8.457	1	17.07	Low	No	No	0
Prainianonide	462.407	5	11	0.164	1	172.21	Low	No	Yes	0
Lupeol	426.729	1	1	8.025	1	20.23	Low	No	No	0
(+)-Morelloflavone	556.479	7	11	4.499	3	198.12	Low	No	No	1
2″,3″-dihydromorelloflavone (GB-2a)	558.495	7	11	4.433	3	194.21	Low	No	No	1
Volkensiflavone	540.48	6	10	4.794	2	177.89	Low	No	No	0
(–)-GB-1a	542.496	6	10	4.727	2	173.98	Low	No	No	0
Squalene	410.73	0	0	10.605	1	0	Low	No	No	0
Orlistat*	495.745	1	5	6.882	1	81.7	Low	No	Yes	0

[a] Molecular weight in g/mol, [b] Topological Polar Surface Area (TPSA), [c] Gastrointestinal (GI), [d] Blood Brain Barrier (BBB), [e] P-glycoprotein (P-gp), [f] Pan Assay Interference Compounds (PAINS); * Standard drug.

is located between the residues of Cys237 to Cys261 (Khan *et al*., 2017). Interaction of ligands with the catalytic site residues and the lid domain would be favourable for the inhibition of pancreatic lipase activity.

The compounds from *G. prainiana* which were mainly flavonoids exhibited inhibition potential towards pancreatic lipase. Amentoflavone has been the most potent compound in inhibiting the activity of pancreatic lipase. The interaction of this compound with two catalytic residues through hydrogen bonds may likely contribute to the strong inhibition of the enzyme. Moreover, hydrophobic interactions formed, particularly with lid residues, Ala260 and Ala259, may possibly influence the lid conformation that consequently aids in inhibiting pancreatic lipase activity (Thomas *et al.*, 2005). This is similar to those reported by Sridhar *et al*. (2017) where the formation of hydrophobic interactions between the ligands and lid domain contributed to the docking scores of the compounds. The inhibitory activity of amentoflavone towards pancreatic lipase has also been observed by Gök *et al.* (2020) through in vitro study.

Other than amentoflavone, its derivative, 4‴-methylamentoflavone and naringenin 7-O-β-D-glucuronide was also the top inhibitors against pancreatic lipase compared to other compounds from *G. prainiana*. Similar to amentoflavone, 4‴-methylamentoflavone and naringenin glucuronide interacted with the key residues, Ser152 and His263, respectively, through hydrogen bonds which could be the main contributors of the high inhibitory activities exhibited by these compounds. Naringenin, a flavonoid produced from the metabolism of naringin, has been reported to possess an anti-obesity effect through the inhibition of HMG-CoA reductase (Ahmed *et al.*, 2012). However, the inhibitory effect of this compound against pancreatic lipase has never been discussed. Hence, to our knowledge, this is the first report revealing the inhibitory potential of naringenin towards pancreatic lipase.

Orlistat is a synthetic derivative of lipstatin that is responsible for the irreversible inhibition of pancreatic lipase. This inhibitor reduces the systemic absorption of dietary fats by competing with the fats for active serine sites on lipase (Heck *et al.*, 2000). So far, orlistat has been the only pancreatic lipase inhibitor approved by FDA and no new molecule after orlistat has reached clinical use (Lunagariya *et al*., 2014; El-Korany *et al.*, 2020). Thus, orlistat has been utilized as a reference inhibitor in many studies (Sankar and Engels, 2018; Itoh *et al.*, 2019; Coronado-Cáceres *et al.*, 2020). Our docking study demonstrated I interaction of orlistat with Ser152 and His263 which possibly played a major role in its inhibitory activity against pancreatic lipase, similar to those observed by Alias *et al*. (2020) and Nguyen *et al* (2020). However, it is interesting that the compounds of *G. prainiana* possess higher inhibitory activities than orlistat suggesting that these compounds could be more potent inhibitors than orlistat. Hence, these compounds could be a good candidate for the development of anti-obesity drugs.

Prior to the development of the drug, the drug-likeness properties of compounds are initially analysed to predict their solubility and permeability which are important criteria to be qualified as a drug candidate. Lipinski's rule is one of the methods to estimate the physicochemical properties of the compound where the compound is classified as a potential drug when it has none or not more than one violation of the following criteria; molecular weight less than 500 g/mol, hydrogen bond acceptors less than 10, hydrogen bond donors less than 5 and logP value less than 5 (Lipinski et al., 1997). For *G. prainiana*, half of the compounds passed Lipinski's rule suggesting their potential to be candidate drugs. However, the rest violated more than one of Lipinski's rule criteria.

It is speculated that aromatic rings in the compounds' structures possibly affect the drug-likeness properties of the compounds. Compared to orlistat, the top compounds, amentoflavone and 4‴-methylamentoflavone have more aromatic rings in their structures (Figure 1). Although aromatic rings are crucial in increasing the compound potency, a large number of aromatic rings decreases the compound's solubility and permeability consequently reducing the drug-likeness potential of the compound (Ritchie and Macdonald, 2009). In contrast, naringenin 7-O-β-D-glucuronide exhibited higher compound developability than amentoflavone and 4‴-methylamentoflavone as it passed Lipinski's rule indicating this compound could be a potential oral drug candidate.

5. Conclusion

The present study revealed the inhibitory potential of compounds from *G. prainiana* against pancreatic lipase by interacting with the catalytic and lid residues which are crucial for enzyme activity. Amentoflavone, 4‴-methylamentoflavone and naringenin 7-o-β-D-glucuronide were the top hit compounds with the highest inhibitory effects towards pancreatic lipase. However, in the context of drug developability, naringenin 7-o-β-D-glucuronide exhibited the highest potential to be an oral drug candidate. Overall, this study provides potential candidates for the development of new pancreatic lipase inhibitors. *In vitro* and *in vivo* studies will be significant to validate further the inhibitory activity of these compounds against pancreatic lipase.

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Conflict of interest

The authors declare no conflict of interest.

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