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RESEARCH ARTICLE

Potential Anti-osteoporosis compounds from *Zingiber officinale*: A Molecular Docking and Pharmacokinetics Prediction

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ABSTRACT:

Osteoporosis is a systemic skeletal disease characterized by low bone mass, that can result in fracture when injury, for example, due to a traffic accident. This study aimed to identify secondary metabolites from *Zingiber officinale* that potentially inhibit cathepsin K, a critical enzyme that caused osteoporosis. In this study, a molecular docking of 102 bioactive compounds from *Zingiber officinale* against cathepsin K (PDB ID: 4X6I) was conducted. Ligand preparation was performed using JChem and Schrödinger's software, and virtual protein was elucidated using AutoDockTools version 1.5.6. Cocrystal ligand was carried out as a positive control ligand. Pharmacokinetics of the compounds was predicted with SwissADME online tool. Based on the results, nine compounds had good binding affinity against cathepsin K. The compounds were shogasulfonic acid C, (-)-beta-sitosterol, shogasulfonic acid D, shogasulfonic acid B, shogasulfonic acid A, isogingerenone B, (S)-8-gingerol, gingerenone A, and hexahydrocurcumin, with binding affinities of -7.2, -7.0, -6.9, -6.8, -6.8, -6.7, -6.7, -6.6, and -6.4 kcal mol^{-1}, respectively. Most compounds had great pharmacokinetic profiles and also drug-likeness properties. In conclusion, bioactive compounds from *Zingiber officinale* are potentially used as anti-osteoporosis agents targeting cathepsin K. However, *in vitro* and *in vivo* studies are needed to prove the anti-osteoporosis activity of these compounds.

KEYWORDS: Traffic accident, Osteoporotic, *In silico* study, Cathepsin K, Shogasulfonic acid.

INTRODUCTION:

Osteoporosis is a disease characterized by low bone mass, microarchitectural deterioration of bone tissue, and reduced bone strength[1–3]. Despite being a preventable disease, the prevalence of osteoporosis increases every year as the population ages, affecting more than 75 million people in the United States, Europe, and Japan[4,5]. Osteoporosis is highly associated with fracture risk, causing 8.9 million fractures worldwide annually[4]. Moreover, this disease also affects the quality of life and economic burden[1].

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In addition, the number of osteoporotic fractures is certain to increase by more than 3-fold over the next 50 years[4], making osteoporosis prevention and treatment a global concern.

Drugs used to treat osteoporosis are classified as antiresorptive and anabolic. Antiresorptive inhibits osteoclast's activity to resorb bone matrix, while anabolic acts in inducing osteoblasts to synthesize bone matrix. Bisphosphonates are one of the most used antiresorptive to treat bone disorders related to increased bone resorption[6]. However, it has been reported that bisphosphonates are linked to severe side effects such as necrosis of the jaw that is primarily found in patients with bone metastases[7,8]. Besides, bisphosphonate also caused upper gastrointestinal tract and ocular adverse events, as well as renal toxicity[7]. Considering the severe

adverse effects of the current drugs, there should be a safe yet effective agent to prevent and treat osteoporosis that will help in reducing the incidence rate of this disease.

Several proteins are required for bone cells to perform normal bone metabolism[9]. Cathepsin K is one of the essential enzymes that synthesized by osteoclasts. This enzyme degrades collagen type 1 (COL1), the most abundant protein in bone tissue. Due to its prominent role in bone resorption, cathepsin K and COL1 are sensitive measures of osteoclast-mediated bone resorption[10]. Several cathepsin K inhibitor has been shown an excellent selectivity against human cathepsin K, with IC_{50} ranging from 0.04 to 1.4 nM. However, most of the compounds are still in development, and there is still no clinical evidence regarding their safety[11].

Medicinal plants and phytochemicals are recognized to have minimal side effects and beneficial bone metabolism results[12]. It is reported that traditional medicine *Rehmanniae Radix* was proved to have anti-osteoporotic activity by regulating kidney and liver function as well as improving blood circulation[13]. In addition, Abdel-Naim *et al*. reported that paradol, a phenolic isolated from *Aframomum meleguta,* increased osteoblasts-like cells proliferation and differentiation while suppressed the osteoclast-related markers[14]. This indicated that medicinal plants and their bioactive compound are potentially used as osteoporosis drugs.

Zingiber officinale is a widely spread medicinal plant that has long been known for several pharmacological activities such as antioxidant and anti-inflammatory[15–19]. Best of our knowledge, there is no report regarding the activity of this plant in bone cells or bone tissue. This study aimed to investigate the bioactive compounds from *Zingiber officinale* that potentially developed as Cathepsin K inhibitors by using *in silico* approach to search for effective anti-osteoporotic drugs with minimum side effects.

MATERIALS AND METHODS:

Ligand and protein preparation:

One hundred two secondary metabolites from *Zingiber officinale* were obtained from http://www.knapsackfamily.com. Ligand and protein preparation was performed based on Gani *et al*.[20] and Nurhan *et al*.[21]. Briefly, ligand structure was generated using JChem software and optimized using the LigPrep module from Schrodinger's software. Epic was used to adjust atomic protonation to pH 7.0, and the OPLS 2005 force field was used for geometry optimization.

Human cathepsin K (PDB ID: 4X6I) was downloaded from Protein Data Bank (https://www.rcsb.org/) and used as the target protein (Fig 1). Chain A of protein was prepared using AutoDockTools version 1.5.6. by removing water molecules and specific solvent residues, adding Kolman charge, and repairing the missing atoms in certain protein parts. The prepared protein was saved in PDBQT.

Molecular docking:

The molecular docking was performed using Inter(R) Celeron (R) 2955U @ 1.40GHZ processor, RAM 2.00 GB System type 64-bit Operating System with targeted docking method based on Gani *et al*.[22] and Nurhan *et al*.[23]. The grid box used was based on the co-crystalline ligand-binding site on the protein (40 Å x 40 Å x 40 Å centered at 18.05, 7.518, -19.401). The binding site was also reconfirmed with DoGSiteScorer (https://proteinsplus.zbh.uni-hamburg.de/#dogsite) using the converted PDB file from the prepared protein. Molecular docking was performed by using AutoDock Vina. The validity of the docking method was assessed based on the root mean square deviation (RMSD) using PyMOL software version 2.3.4. The docking method was considered valid when the RMSD of the co-crystalline ligand is less than 2 Å in at least after three times of docking. The molecular interaction between ligand and protein was visualised using Discovery Studio Visualiser v17.2.016349 software (Dassault Systèmes, San Diego).

Pharmacokinetics prediction:

The pharmacokinetic properties of the compounds were predicted using the SwissADME online tool (http://www.swissadme.ch/). The parameters for these pharmacokinetics predictions were gastrointestinal (GI) absorption, blood-brain barrier (BBB) permeability, P-glycoprotein (Pgp) substrate, logarithmic skin permeation coefficient (log Kp), Lipinski violations, bioavailability score, and cytochrome P450 (CYP) inhibitors (CYP1A2, CYP2C19, CYP2C9, CYP2D6, and CYP3A4).

RESULT:

Molecular docking analysis:

The *in silico* molecular docking study of 102 bioactive compounds from *Zingiber officinale* against cathepsin K was conducted. The protein that used in this study is present in Figure 1. Based on the DoGSiteScorer online tool, the protein's binding pocket volume was 421.12 $Å^3$ with a drug score of 0.71 (pocket P>0). Drug score is a drug's tendency to occupy in a binding pocket, scales from 0–1; the greater the score, the greater the tendency. Moreover, based on the binding affinity of the compounds, nine bioactive compounds potentially

inhibit cathepsin K (Figure 2). This is because these compounds had the same or lower binding affinity as the co-crystalline ligand (-6.4 kcal mol^{-1}). The compounds were shogasulfonic acid C, (-)-beta-sitosterol, shogasulfonic acid D, shogasulfonic acid B, shogasulfonic acid A, isogingerenone B, (S)-8-gingerol, gingerenone A, hexahydrocurcumin, with binding affinities of -7.2, -.7.0, -6.9, -6.8, -6.8, -6.7, -6.7, -6.6, and -6.4 respectively. Most of the chemical bonds presented between compounds and amino acids in the binding pocket were hydrogen bonds and van der Waals interactions (Figure 3).

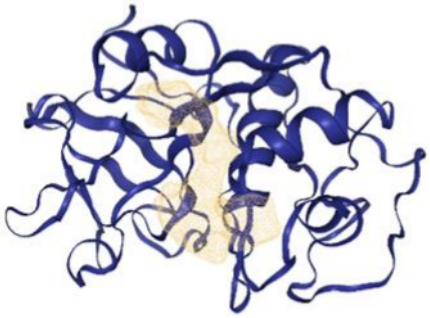


Figure 1. Cartoon representation of human cathepsin K and its binding site. The binding site was determined with DoGSiteScorer

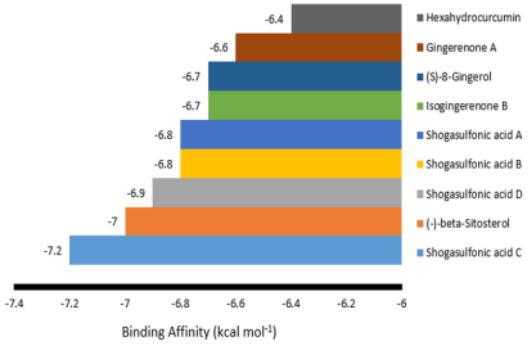


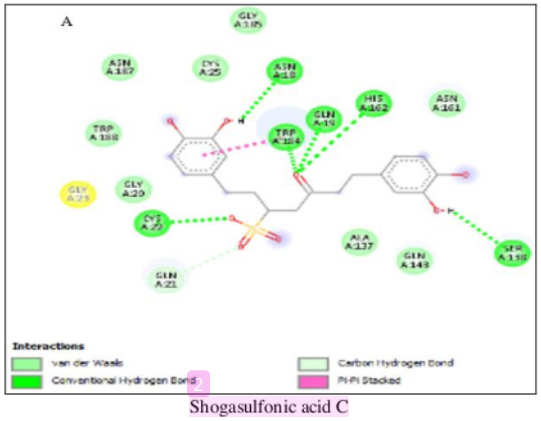
Figure 2. Binding affinity of potential cathepsin K inhibitors

Pharmacokinetics prediction analysis:

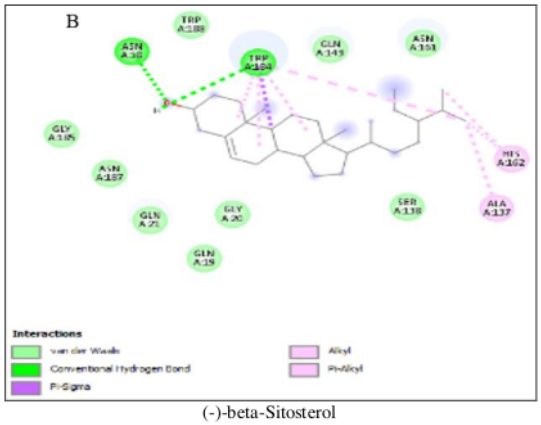
The prediction of the pharmacokinetic properties of 102 compounds from *Zingiber officinale* was conducted using SwissADME online tool. Most compounds had a great pharmacokinetics prediction profile, including nine potential anti-cathepsin K (Table 1). The top five compounds were predicted to have low GI absorption, while the other four were visualized to have the opposite. Six top compounds were predicted to be not permeant to the BBB. Some of the compounds were conceived to be Pgp substrate and CYP inhibitors (Table 1). Log Kp of the compounds varied from -8.06 to -2.2 cm s^{-1}. One compound named (-)-beta-Sitosterol violated one of the Lipinski rules by having Moriguchi octanol-water partition coefficient (MLOGP) more than 4.15. Moreover, most of the compounds had bioavailability scores of 0.55 or 0.56, indicating a good bioavailability.

DISCUSSION:

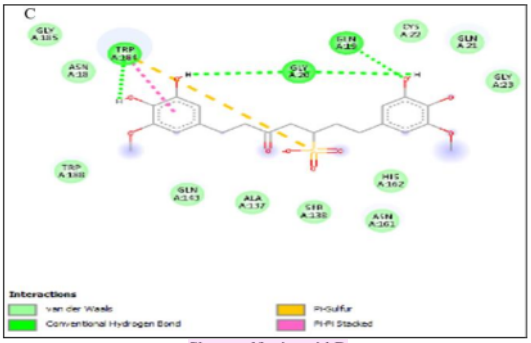
Ginger (*Zingiber officinale*) is a plant that belongs to the Zingiberaceae family that has long been used as a spice and herbal medicine. In Asia countries including China and Indonesia, ginger has been used as a traditional medicine to treat a variety of ailments such as vomiting, indigestion, joint and muscular pain, and common cold[15,19,24–26]. The reported pharmacological effects of ginger are anti-obesity and metabolic syndrome[24], weight-lowering agent[25], anticancer[27], gastroprotective effects[28], and antiemetic[29]. Moreover, ginger contains volatile oils, terpenoids, phenolics, and flavonoids[16,24,25]. Gingerols and shogaols are the primary metabolites in ginger that are known to have a variety of biological activities such as antioxidant and anti-inflammatory[18,30]. These activities also contributed to the use of ginger as a medicinal plant[24,31].



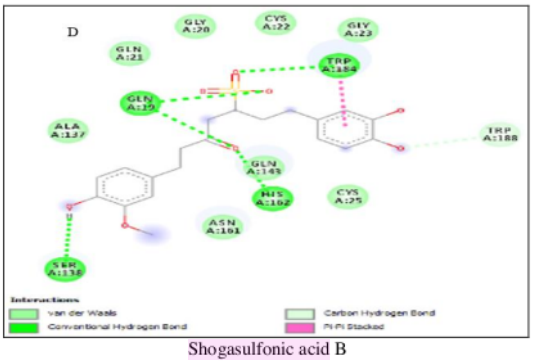
Shogasulfonic acid C



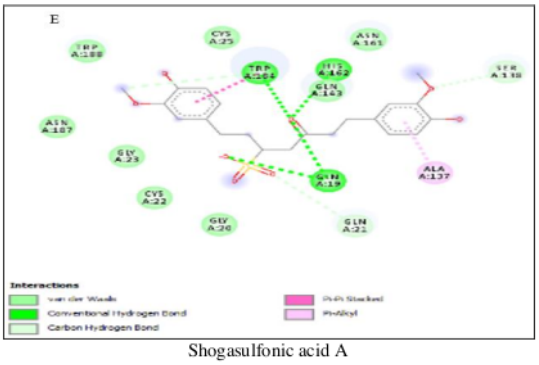
(-)-beta-Sitosterol



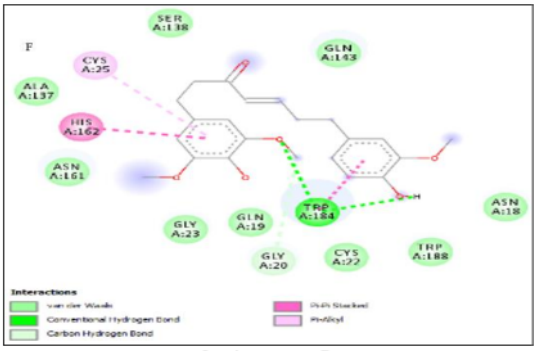
Shogasulfonic acid D



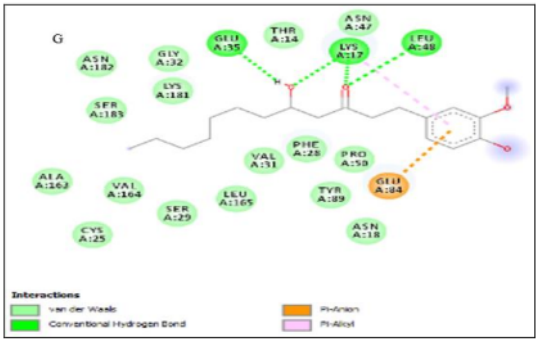
Shogasulfonic acid B



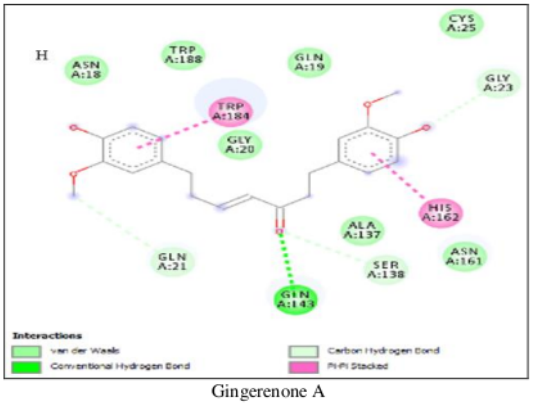
Shogasulfonic acid A



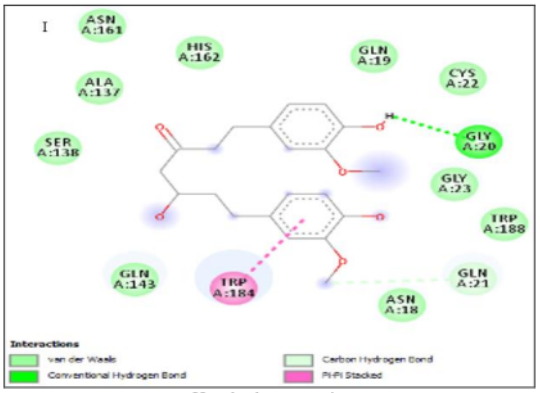
Isogingerenone B



(S)-8-Gingerol



Gingerenone A



Hexahydrocurcumin

Figure 3: Molecular interaction of potential cathepsin K inhibitors on the specific binding site

Bone diseases such as bone defects, osteoporosis, and osteoarthritis are challenging to treat [32–37]. Osteoporosis is a bone disease that occurs when the body constantly absorbs and replaces bone tissue, resulting in weak and brittle bone[1–3]. Overactivity of osteoclasts and lacking actions of osteoblasts may result in osteoporosis[3]. A variety of proteins are required in osteoporosis's pathogenesis[38,39], one of which is the cathepsin K.

Cathepsin K is a protease that belongs to the papain family of cysteine protease found in osteoclasts[10]. This enzyme degrades COL1 that is recognized as the most abundant protein in bone tissue[10,11]. Because of its central role in bone metabolism, drugs targeting cathepsin K is a promising method in managing osteoporosis.

Molecular docking of 102 bioactive compounds from ginger against cathepsin K was conducted in the current study. Nine compounds potentially inhibit human cathepsin K; this is because the binding affinity of these compounds was the same or less than the co-crystalline ligand that was designed as a cathepsin K inhibitor. In the present study, shogasulfonic acid A, B, C, and D are four of the nine compounds with the highest binding affinity. Shogasulfonic acids are sulfonated compounds that were previously isolated from ginger together with 4-gingesulfonic acid[40]. Shogasulfonic acid A also was isolated by the same research team from methanolic extract of *Zingiberis processum*[41], in line with study conduct by Li *et al*.[42]. There is no current report about the ADME and pharmacological activities of these compounds. However, based on our prediction, shogasulfonic acids may have low GI absorption. Shogasulfonic acid A was predicted to be CYP2C19 and CYP2D6 inhibitors, and Pgp substrate together with shogasulfonic acid D. Moreover, Shogasulfonic acid C and D had a predictional bioavailability score of 0.11. Considering these predictions, the delivery of shogasulfonic acids as an anti-osteoporotic agent should be well-design to improve its pharmacokinetic action *in vivo*.

Table 1. Binding affinities and ADMET prediction of the top 50 compounds

S. No.	Compounds	Binding Affinity	GI absorption	BBB permeability	Pgp substrate	CYP1A2 inhibitor	CYP2C19 inhibitor
1	Shogasulfonic acid C	-7.2	Low	No	No	No	No
2	(-)-beta-Sitosterol	-7.0	Low	No	No	No	No
3	Shogasulfonic acid D	-6.9	Low	No	Yes	No	No
4	Shogasulfonic acid B	-6.8	Low	No	No	No	No
5	Shogasulfonic acid A	-6.8	Low	No	Yes	No	Yes
6	Isogingerenone B	-6.7	High	No	No	No	No
7	(S)-8-Gingerol	-6.7	High	Yes	Yes	Yes	No
8	Gingerenone A	-6.6	High	Yes	No	Yes	No
9	Hexahydrocurcumin	-6.4	High	No	Yes	No	No
10	[7]-Paradol	-6.3	High	Yes	No	Yes	No
11	beta-Cadinene	-6.3	Low	No	No	No	Yes
12	alpha-Muurolene	-6.2	Low	No	No	No	Yes
13	(-)-Zingiberene	-6.2	Low	No	No	No	Yes
14	Curcumene	-6.1	Low	No	No	No	No
15	[6]-Dehydroshogaol	-6.1	High	Yes	No	Yes	Yes
16	6-Gingesulfonic acid	-6.1	High	No	Yes	No	No
17	(S)-(+)-Curcumene	-6.1	Low	No	No	No	No
18	[6]-Shogaol	-6.1	High	Yes	No	Yes	Yes
19	Aframodial	-6.0	High	Yes	No	No	No
20	beta-Sesquiphellandrene	-6.0	Low	No	No	No	Yes
21	beta-Santalol	-6.0	High	Yes	No	No	Yes
22	4-Gingesulfonic acid	-5.9	High	No	No	No	No
23	[8]-Gingerdiol	-5.9	High	No	Yes	No	No
24	[7]-Gingerol	-5.9	High	Yes	Yes	Yes	No
25	[4]-Gingerol	-5.9	High	Yes	No	No	No
26	Zonarene	-5.9	Low	No	No	No	Yes
27	beta-Bisabolene	-5.9	Low	No	No	No	No
28	Safrole	-5.9	High	Yes	No	Yes	No
29	(S)-6-Gingerol	-5.9	High	Yes	No	Yes	No
30	Methyl [6]-Shogaol	-5.8	High	Yes	No	Yes	No
31	Diacetoxy-[4]-gingerdiol	-5.8	High	No	Yes	No	No
32	[9]-Paradol	-5.8	High	Yes	No	Yes	No
33	Sesquisabinene hydrate	-5.8	High	Yes	No	No	Yes
34	(-)-Germacrene D	-5.8	Low	No	No	No	No
35	Copaene	-5.8	Low	Yes	No	Yes	Yes
36	Cedr-8-ene	-5.8	Low	No	No	No	Yes
37	6-Dehydrogingerdione	-5.7	High	Yes	No	Yes	Yes
38	Dehydrogingerdione	-5.7	High	Yes	No	Yes	No
39	Acetoxy-[10]-gingerol	-5.7	High	No	No	No	No
40	[6]-Gingerdiol	-5.7	High	Yes	Yes	Yes	No
41	[4]-Isogingerol	-5.7	High	Yes	No	Yes	No

42	Zingiberenol	-5.7	High	Yes	No	No	No
43	1-Dehydro-[8]-gingerdione	-5.6	High	Yes	No	Yes	No
44	gamma-Cadinene	-5.6	Low	No	No	No	Yes
45	(+/-)-beta-Phellandrene	-5.6	Low	Yes	No	No	No
46	Terpinolene	-5.6	Low	Yes	No	No	No
47	[10]-Dehydroshogaol	-5.5	High	Yes	No	Yes	No
48	Methyl [8]-Shogaol	-5.5	High	Yes	No	Yes	No
49	1-Dehydro-[6]-gingerdione	-5.5	High	Yes	No	Yes	Yes
50	1-Dehydro-[10]-gingerdione	-5.5	High	Yes	No	Yes	No

Table No. 2 Metabolism and bioavailability prediction of the top 50 compounds

No.	Compounds	CYP2C9 inhibitor	CYP2D6 inhibitor	CYP3A4 inhibitor	log Kp (cm s-1)	Lipinski violations	Bioavailability Score
1	Shogasulfonic acid C	No	No	No	-7.65	0	0.11
2	(-)-beta-Sitosterol	No	No	No	-2.2	1	0.55
3	Shogasulfonic acid D	No	No	No	-8.06	0	0.11
4	Shogasulfonic acid B	No	No	No	-7.51	0	0.56
5	Shogasulfonic acid A	No	Yes	No	-7.36	0	0.56
6	Isogingerenone B	Yes	Yes	Yes	-6.02	0	0.55
7	(S)-8-Gingerol	No	Yes	Yes	-5.29	0	0.55
8	Gingerenone A	Yes	Yes	Yes	-5.82	0	0.55
9	Hexahydrocurcumin	No	Yes	Yes	-6.67	0	0.55
10	[7]-Paradol	No	Yes	No	-4.78	0	0.55
11	beta-Cadinene	Yes	No	No	-4.71	1	0.55
12	alpha-Muurolene	Yes	No	No	-4.65	1	0.55
13	(-)-Zingiberene	Yes	No	No	-3.88	1	0.55
14	Curcumene	No	Yes	No	-3.71	1	0.55
15	[6]-Dehydroshogaol	Yes	No	Yes	-4.7	0	0.55
16	6-Gingesulfonic acid	No	No	No	-6.59	0	0.56
17	(S)-(+)-Curcumene	No	Yes	No	-3.71	1	0.55
18	[6]-Shogaol	No	Yes	No	-5.15	0	0.55
19	Aframodial	Yes	Yes	No	-5.68	0	0.55
20	beta-Sesquiphellandrene	Yes	No	No	-3.71	1	0.55
21	beta-Santalol	Yes	No	No	-4.14	0	0.55
22	4-Gingesulfonic acid	No	No	No	-7.19	0	0.56
23	[8]-Gingerdiol	Yes	Yes	Yes	-4.65	0	0.55
24	[7]-Gingerol	No	Yes	No	-5.6	0	0.55
25	[4]-Gingerol	No	Yes	No	-6.73	0	0.55
26	Zonarene	Yes	No	No	-4.69	1	0.55
27	beta-Bisabolene	Yes	No	No	-2.98	1	0.55
28	Safrole	No	No	No	-5.19	0	0.55
29	(S)-6-Gingerol	No	Yes	No	-6.14	0	0.55
30	Methyl [6]-Shogaol	No	Yes	Yes	-5.05	0	0.55
31	Diacetoxy-[4]-gingerdiol	No	No	Yes	-6.08	0	0.55
32	[9]-Paradol	No	Yes	Yes	-4.19	0	0.55
33	Sesquisabinene hydrate	Yes	No	No	-4.76	0	0.55
34	(-)-Germacrene D	Yes	No	No	-4.18	1	0.55
35	Copaene	Yes	No	No	-4.37	1	0.55
36	Cedr-8-ene	Yes	No	No	-4.27	1	0.55
37	6-Dehydrogingerdione	No	No	Yes	-5.59	0	0.55
38	Dehydrogingerdione	No	No	No	-5.76	0	0.85
39	Acetoxy-[10]-gingerol	No	Yes	Yes	-4.55	0	0.55
40	[6]-Gingerdiol	No	Yes	No	-5.79	0	0.55
41	[4]-Isogingerol	No	Yes	No	-6.73	0	0.55
42	Zingiberenol	Yes	No	No	-4.63	0	0.55
43	1-Dehydro-[8]-gingerdione	No	Yes	Yes	-4.99	0	0.55
44	gamma-Cadinene	Yes	No	No	-4.49	1	0.55
45	(+/-)-beta-Phellandrene	No	No	No	-4.69	0	0.55
46	Terpinolene	Yes	No	No	-3.96	0	0.55
47	[10]-Dehydroshogaol	Yes	Yes	Yes	-3.5	0	0.55
48	Methyl [8]-Shogaol	No	Yes	Yes	-4.46	0	0.55
49	1-Dehydro-[6]-gingerdione	No	No	Yes	-5.59	0	0.55
50	1-Dehydro-[10]-gingerdione	Yes	Yes	Yes	-4.39	0	0.55

Another compound that potentially inhibits cathepsin K is (-)-beta-sitosterol. Beta-sitosterol is a phytosterol found in dietary and non-dietary plants[43]. This compound possesses a variety of biological activities, including antidiabetics and anticancer[43–45]. A study by Chauhan *et al*. reported that *Bombax ceiba* stem bark extract was able to increase osteoblasts proliferation and activity *in vitro* and ameliorated osteoporotic bone tissue *in vivo*. Moreover, quantification of phytoconstituents showed the extract contained beta-sitosterol[46]. This indicated that beta-sitosterol might have beneficial effects on osteoporosis. However, further study regarding this is needed.

Besides shogasulfonic acids and beta-sitosterol, our current study also showed that a compound called isogingerenone B was potentially inhibited human cathepsin K. This compound was isolated from ginger rhizomes and was also found in Chinese herbal medicine called Huang Lian-Gan Jiang[47,48]. There is no current report about the ADME of this compound. However, based on our *in silico* prediction, this compound may have high GI absorption and a bioavailability score of 0.55, indicating a good bioavailability.

Furthermore, another compound predicted to have inhibitory action against cathepsin K is (S)-8-gingerol. Gingerols are the primary metabolites in *Zingiber officinale* and were reported to have many protective and therapeutic effects[49]. 8-Gingerol took 3.20% of white ginger and 4.64% of yellow ginger extract composition, while 6-gingerol was the most abundant, took up 27.56% and 33.96% of sample composition in white and yellow ginger extract, respectively[50]. This compound is widely known for its antioxidant and anti-inflammatory activity with IC_{50} values of 19.47, 2.5, and 1.97µM against DPPH, superoxide, and hydroxyl radicals, respectively[51]. 6-Gingerol was known to have osteogenic activity by increasing osteoblasts' transcription levels, alkaline phosphatase activity, and enhanced mineralized nodule formation *in vitro*[52]. In addition, 10-gingerol was reported to inhibit osteoclasts activity *in vitro*, marked with downregulated osteoclastic markers and cathepsin K activity[53]. 10-Gingerol was also found to inhibits osteoclastogenesis in prednisolone-induced osteoporosis in zebrafish animal models[53]. There is no current report about the effect of 8-gingerol on bone cells. Our prediction study paves new potential activity of 10-gingerol in osteoporosis. However, further investigation is required to prove this prediction.

Based on the present study, another compound that potentially inhibits cathepsin K is gingerenone A. Gingerenone A is a diarylheptanoid mainly presented in the rhizomes of ginger[48,54]. This compound was reported to have moderate anticoccidial activity compared to other metabolites from the same plant[48]. Besides, this compound was also reported to have antiviral[55] and anti-hyperglycemic activity[56]. there is no report regarding the activity of gingerenone A in bone cells or tissue. The present study proposed a new pharmacological action of gingerenone A against cathepsin K, which may improve the compound's anti-osteoporotic activity. However, further study regarding this should be conducted *in vitro* and *in vivo*.

A bioactive compound called hexahydrocurcumin was also predicted to have inhibitory activity against human cathepsin K. Besides being present in the rhizome of ginger[54,57], hexahydrocurcumin is also one of the secondary metabolites of curcumin[58]. This compound has been reported to have a variety of pharmacological activities, this includes antioxidant and anti-inflammatory[58], larvicidal[57], anti-angiogenic[59], and anticancer[60,61]. Based on our current *in silico* study, hexahydrocurcumin may also have anti-osteoporotic activities targeting cathepsin K. Considering its excellent pharmacokinetic properties, the development of this compound as an anti-osteoporotic agent is a promising aspect.

Furthermore, most of the chemical bonds that present between nine potential anti-osteoporotic compounds with cathepsin K were hydrogen bonds and van der Waals interactions. These bonds are essential in the docking mechanism, which helps strengthen the molecular interaction of the ligand with protein and plays a role in the accuracy of the docking score[62,63]. Therefore, based on the present *in silico* molecular docking and pharmacokinetics prediction, nine bioactive compounds from ginger is potentially used as cathepsin K inhibitor to prevent and treat osteoporosis.

CONCLUSION:

In silico study of 102 bioactive compounds from *Zingiber officinale* against cathepsin K was conducted. Based on its binding affinity value, nine compounds have great potential as cathepsin K inhibitors. These are shogasulfonic acid C, (-)-beta-sitosterol, shogasulfonic acid D, shogasulfonic acid B, shogasulfonic acid A, isogingerenone B, (S)-8-gingerol, gingerenone A, hexahydrocurcumin, with binding affinities of -7.2, -.7.0, -6.9, -6.8, -6.8, -6.7, -6.7, -6.6, and -6.4 respectively. All compounds have favorable chemical bound with the protein that beneficially contributed to the binding affinity value. Moreover, most of the compounds have great pharmacokinetic and drug-likeness properties. Thus, bioactive compounds from *Zingiber officinale* are potentially developed as drugs targeting cathepsin K to find safe and effective anti-osteoporotic therapy.

CONFLICT OF INTEREST:

The authors have no conflicts of interest regarding this investigation.

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