In Silico Assessment for Asthma Bronchodilator Potency of Ginger Essential Oils

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ABSTRACT

Ginger has been recognized as a traditional medicine ingredient with a powerful anti-allergic and anti-inflammatory effects, particularly in respiratory conditions such as bronchospasm, an indication for asthma. This research aims to correlate the phytochemicals in ginger essential oils with their bronchodilator activities using *in silico* assessment. Phytocomponents were generated through GC-MS analysis. The suppression of bronchoplasm was assessed through molecular docking of ginger's phytocomponents to inhibit β-adrenoceptor (5X7D). Molecular docking against the human consensus olfactory receptor OR52c (8HTI) was also assessed, since those volatile components may enter through inhalation. β-Eudesmol is the best molecule, showing various interactions, particularly hydrogen-bond formation toward 5X7D and 8HTI, with the closest binding energies to carazolol and octanoic acid, the native ligands, respectively. The ADME properties of ginger's phytochemicals also show that β-eudesmol and other components, including cis-farnesol, caryophyllene oxide, β-phellandrene, camphene, *z*-citral, and eucalyptol, are PGP-non-substrates and presented in the yolk region of the BOILED-Egg graphic. These facts suggest that these phytochemicals are potentially bronchodilators, as they are pharmacokinetically stable and able to cross the blood-brain barrier, consistent with their potential to affect the central nervous system, which is responsible for various physiological effects. Nevertheless, further investigation through *in vitro* and animal models is necessary to confirm the bronchodilator potency.

KEYWORDS

ginger, essential oil, bronchodilator, in silico, olfactory

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INTRODUCTION

Asthma is a chronic disease of the airways of the lungs, characterized by narrowed, swollen airways that produce mucus, leading to difficulty breathing. Asthma is defined as airway inflammation characterized by heightened responsiveness of the tracheobronchial system to stimuli.[1] There are several drug classes used to treat asthma: β2-agonists, anticholinergics, methylxanthines, and chromones. An orthosteric β-adrenergic receptor antagonist is also known as a beta-blocker. However, the use of β-blockers shows some weaknesses or side effects, including bradycardia, hypotension, fatigue, dizziness, nausea, and bronchospasm in asthmatic patients.[2,3]

Herbal medicine is traditionally used a treat common conditions, such as bronchospasm associated with asthma. Indigenous knowledge has developed a popular natural-heritage formula for promoting bronchodilation and recovery. Some herbal medicines used to treat asthma are *Ginkgo biloba*, *Boswellia serrata*, *Ganoderma lucidum*, *Glycyrrhiza uralensis*, and *Perilla frutescens*.[4–6] These herbal medicines are included in formulations in Traditional Chinese Medicine, Ayurveda, and Kampo. In Indonesia, traditional medicine called Jamu also employs herbal remedies, primarily containing rhizomes of the Zingiberaceae, such as ginger, to relieve breathing difficulties associated with asthma.[7] Indigenous people in Indonesia have traditionally used ginger root to treat headaches, colds, nausea, and emesis. From a scientific standpoint, the various bioactive mechanisms of ginger, including antioxidant and anti-inflammatory activities, have been documented in prior research.[8]

The potential of ginger oil and extract in treating asthma has been tested *in vitro* and in clinical trials at therapeutic doses (1-4 grams of ginger), which can reduce asthma symptoms but do not alter the disease stage.[9] Thus, it is assumed that the chemical components of ginger may inhibit the protein receptor implicated in asthma. Although some *in silico* studies on the β2-adrenergic receptor have been conducted, the interaction of compounds from ginger oil with β2-adrenergic receptors has not yet been reported.[10–14]

This article examines the volatile components of ginger essential oil at different distillation temperatures and correlates their main phytocompounds with β-agonist receptors using *in silico* studies. Since flavor and aroma are also becoming significant motivations for seeking medical treatment, investigating the molecular mechanisms underlying them is expected. This paper also investigates the olfactory perception of ginger oil components relative to the human consensus olfactory receptor OR52c, which is referenced by several odor markers. Therefore, the structure-odor relationship assessment can be derived to represent sensory profile characters preserved in the ginger essential oils. Furthermore, the ADME (absorption, distribution, metabolism, and excretion) of phytocomponents in ginger essential oil is also explored to investigate their pharmacokinetic properties upon entry into the human body.

MATERIALS AND METHODS

Materials

The ginger rhizomes were obtained from the community medicinal plant garden (TOGA) Sari Hutani in Meru Betiri National Park. It was identified as *Zingiber officinale* by the Botany Laboratory at Universitas Jember.[15] The ligand and protein structures for molecular docking were obtained from PubChem (https://pubchem.ncbi.nlm.nih.gov/) and the Protein Data Bank website (https://www.rcsb.org/), by searching the compound names and ligand ID/sequence in the search box, respectively.

Distillation

Ginger was cleaned, air-dried, and crushed using a chopper. A 500 grams of ginger powder was distilled in a laboratory glassware steam distillation set-up for 5 hours. The distillation temperature in the sample

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flask was maintained at two conditions: below 120 °C (100-118 °C) and above 120 °C (125-140 °C). The oil was separated from the distillate and then added to magnesium sulfate to adsorb moisture. The ginger essential oil was stored in the refrigerator before analysis.

Chromatography Analysis

The Gas Chromatography system was a GCMS-QP2010S Shimadzu equipped with a DB-5MS column (30 m x 0.25 mm, 0.25 µm). The gas carrier was Helium with ionization EI 70 Ev. GC-2010 has a column oven temperature of 70 °C and an injection temperature of 300 °C. The MS started at 3.20 minutes and lasted 70 minutes. The scanned molecular weight/charge (m/z) range was 28 to 600. Spectra and their fragmentations obtained from GC-MS analysis were matched to the spectra in the Mass Spectral Libraries of WILEY229 and NIST62. The instrument is regularly standardized using a reference mass of PEG-PPG-Raffinose.

Molecular Docking Details

The ligands were prepared by drawing the structures in ChemDraw Ultra 8.0 to produce MDL Molfile *.*mol* format, then processed in Avogadro 1.2.0 to produce MDL SDfile *.*mol* format, and Open Babel 3.1.1 to obtain optimized 3D chemical structures in *.pdbqt* format.[16–18] The protein structures were retrieved from the PDB website (https://www.rcsb.org/); accession codes 5X7D (https://www.rcsb.org/structure/5X7D) and 8HTI (https://www.rcsb.org/structure/8HTI) correspond to the X-ray crystal structures of the 2-adrenoceptor and human consensus olfactory receptor OR52c, respectively. They were prepared directly in AutoDockTools-1.5.7.[19,20] The docking simulation was adjusted based on the docking parameters: number of GA runs (200), population size (300), and number of evaluations (2,500,000). The grid box was centered on the ligands in dimensions of *x* x *y* x *z* (specific coordinates): 40 x 40 x 40 (2.240 x 4.748 x 51.335) and 20 x 20 x 20 (171.310 x 173.964 x 141.445) for carazolol and octanoic acid toward 5X7D and 8HTI, respectively. This parameter was tabulated in Table S1 and verified during the redocking procedure, where it was optimized to an RMSD of less than 2.0. The PyMOL Molecular Graphics System v2.5.8 and Biovia Discovery Studio v24.1.0.23298 were used to visualize the conformation of the ligand-protein complex.[21,22]

Statistical Analysis

Data on chemical components of ginger essential oils were analyzed statistically using Principal Component Analysis (PCA) and a Venn diagram. This analysis builds on a previously presented approach, but employs different samples and newly generated data.[23,24]

ADME Pharmacokinetic

The major phytochemicals in ginger essential oils were analyzed using ADME (Absorption, Distribution, Metabolism, and Excretion) pharmacokinetics via the SwissADME web server (https://www.swissadme.ch/).[25] The canonical SMILES inputs of these phytochemicals are tabulated in Table S2. Evaluation of the ADME parameters includes Lipinski's Rule of Five, blood-brain barrier (BBB) permeability, human intestinal absorption (HIA), and P-glycoprotein (PGP), which are simply illustrated using the BOILED-Egg graph.

RESULTS AND DISCUSSION

Chemical Profile of Ginger Essential Oils

The ginger essential oil was extracted by steam distillation at heating temperatures below and above 120 °C, yielding a 1.45% pale yellow and 1.55% dark brown oils, respectively. Heating the ginger sample above 120 °C causes thermal degradation, but it is common to occur in the steam distillation reactors whose heat is not controlled, especially in small industries. As a result, the aroma of fresh ginger (citrus, spicy) is reduced, while a roasted or caramel aroma develops from the Maillard reaction. Ginger samples heated above 120 °C become charred, resulting in a brownish color of the oil as some chemical components are oxidized. Therefore, it is important to study the different heating temperatures of the samples during steam distillation and their effects on the oil's chemical composition and potential bioactivity.

There are two character components in ginger oil: fragrant and pungent. Fragrant components are present in the essential oil, which contains zingiberene, camphene, citral, β-sesquiphellandrene, among others.[26] The pungent components of ginger oleoresin/extract are phenolic alkanones, including 6-gingerol, 6-shogaol, and zingerone. Volatile components responsible for the fragrance of ginger oil are shown in GC-MS analysis in Figure 1, with the detailed list of

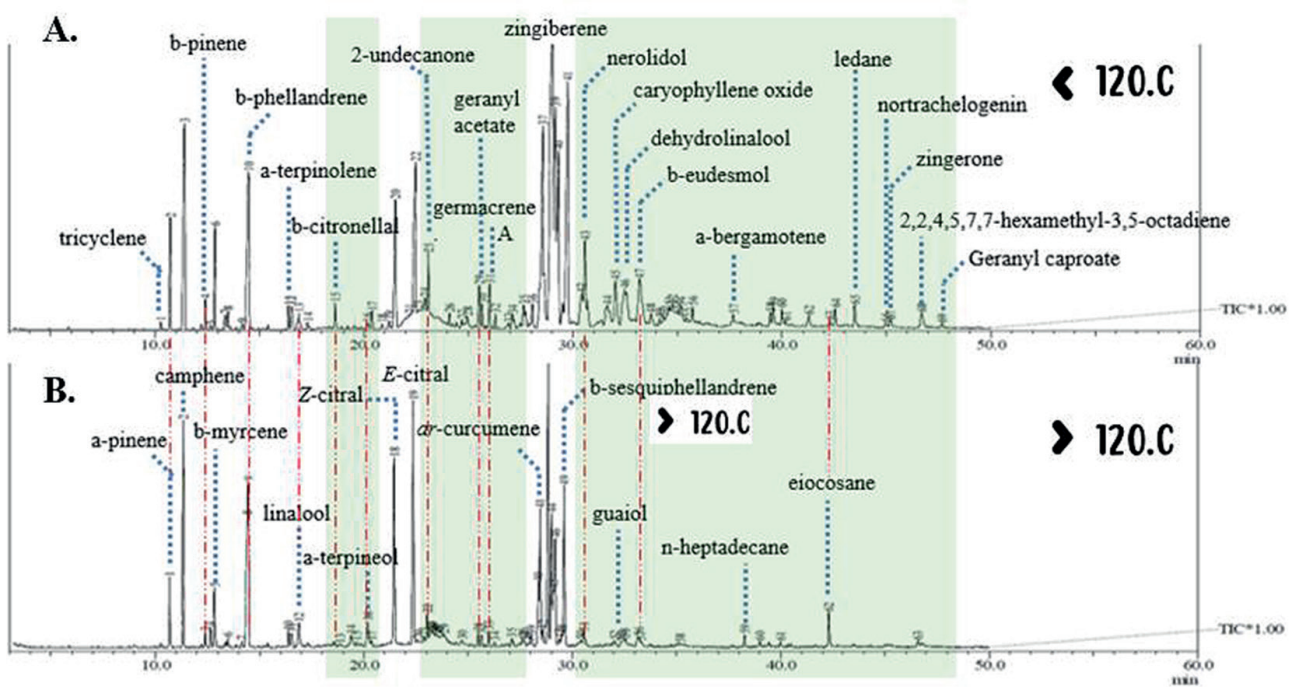


Figure 1: The GC chromatograms of ginger essential oils obtained from distillation processes below 120 °C (A) and above 120 °C (B). Green areas indicate significantly different components, as listed.

components tabulated in Table S3. However, the pungent component detected in the ginger oils in this study is zingerone alone.

Figure 1 represents the distribution of phytocomponents in their interactions with a non-polar column as the stationary phase and hydrogen gas in a GC-MS instrument. Green-blocked areas in Figure 1 contain specific peaks that differ significantly among the ginger essential oils. Compounds β-citronellal, 2-undecanone, geranyl acetate, germacrene-A, nerolidol, caryophyllene oxide, dehydrolinalool, α-bergamotene, ledane, nortrachelogenin, zingerone, 2,2,4,5,7,7-hexamethyl-3,5-octadiene, and geranyl caproate are components found specifically in ginger essential oil obtained by distillation at temperatures below 120 °C (Figure 1A). Meanwhile, α-terpineol and guaiol are found only in another ginger essential oil (Figure 1B). These data are also supported by information in the Venn diagram in Figure 2, which shows that 31 volatile components are distributed in both ginger essential oils, including zingiberene, *Z*-citral, α-pinene, β-bisabolene, α-farnesene, cis-farnesol, β-sesquiphellandrene, β-phellandrene, *ar*-curcumene, β-eudesmol, and camphene. Meanwhile, each temperature treatment during distillation also produced oil with characteristic components (Table S4). It contains 28 and 30 specific compounds for ginger oils from distillation above and below 120 °C, including eucalyptol and caryophyllene oxide, respectively. It is also important to note that nortrachelogenin, a lignan derivative, is found in ginger essential oil obtained by lower-temperature distillation.

The graph in Figure 3 shows that ginger oil distilled at temperatures above 120°C contained approximately 50% of hydrocarbons and oxygenated monoterpenes. Another ginger oil, obtained at a different distillation temperature, contained hydrocarbons and oxygenated sesquiterpenes, which together accounted for more than 60% of the total components (Table S5). It may be assumed that a higher temperature of distillation resulted in an easier and faster release of monoterpenoids compared to sesquiterpenes from ginger cells. Meanwhile, a gradual increase in distillation temperature to 120 °C produced essential oil with higher sesquiterpenoid content, as the cellular vacuole is gently opened to release high-molecular-weight terpenoids.

The PCA analysis in Figure 4 also strengthens the fact that both heating conditions show a significant difference in major components, such as zingiberene, *ar*-curcumene, and β-sesquiphellandrene, which are dominant in ginger oil from distillation below 120 °C (Table S6). On the other hand, β-citral, camphene, and β-phellandrene are major compounds found in significant amounts after heating treatments above 120 °C. The figure also showed that monoterpenoid components, such as eucalyptol, myrcene, pinene, and camphene, were predominantly present in high-temperature-distilled ginger oil. In contrast, sesquiterpenoids, such as nerolidol and β-eudesmol, were highly concentrated in low-temperature distilled ginger oil.

Figure 5 presents possible chemical transformations during distillation under two different heating temperatures. The presence of heat during distillation increases the collision rate of water molecules, thereby lysing cellular vacuoles in ginger and extracting more volatile components. Indeed, several chemical compounds remain stable and constant, even though they were extracted at higher distillation temperatures. β-Pinene is one of those that does not increase significantly in the presence of heating since it undergoes a slow decomposition. The increased amount of camphene and β-phellandrene was suspected to result from the decomposition of β-pinene.[27,28] The conversion of α- dan β-pinene into myrcene has also been predicted, which causes myrcene content to increase slightly in ginger oil from higher temperature distillation (above 120 °C). Naturally, β-pinene is available in less abundance than its alpha isomers, as shown in this research.

Zingiberene is a major thermolabile component that determines the quality of ginger essential oil. This compound might explain the special flavor of ginger. Previous research mentions that zingiberene is the major component of ginger oil.[29,30] However, low zingiberene content resulting from conventional distillation is common, as it decomposes at high temperatures.[31,32] They suggested that zingiberene is converted to curcumene during steam distillation. Curcumene may be a significant compound in ginger oil after three years of storage at room temperature in the presence of air and light.[33] It is suggested that applying low temperatures during the extraction process could yield zingiberene in bulk quantities. Indeed, our research found that zingerone was obtained from low-temperature-distilled ginger oil as a decomposition product of ar-curcumene via the formation of vanillin.[34] Zingerone can also be obtained from gingerol, a product of retro-aldol reaction. This compound exhibited a slightly pungent aroma of ginger oil from distillation at a temperature below 120 °C.

(Z)-citral or neral, is a major component in ginger oil obtained from distillation above 120 °C. Citral might be produced from the oxidation

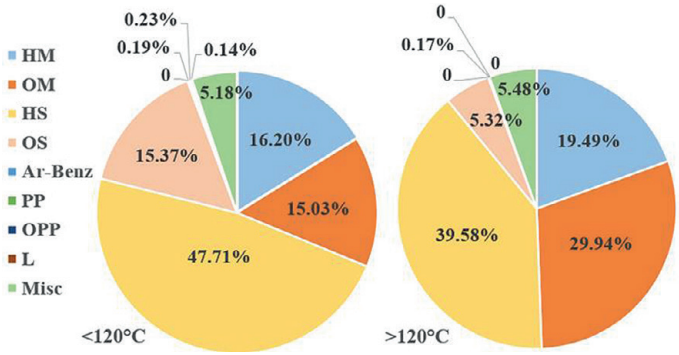


Figure 3: Phytochemical distributions of the essential oils obtained from distillation processes below 120 °C and above 120 °C. HM: hydrocarbon monoterpenes; OM: oxygenated monoterpenes; HS: hydrocarbon sesquiterpenes; OS: oxygenated sesquiterpenes;. Ar-Benz: aromatic-benzene derivatives; PP: phenylpropanoid; OPP: oxygenated phenylpropanoid; L: lignan; Misc: miscellaneous.

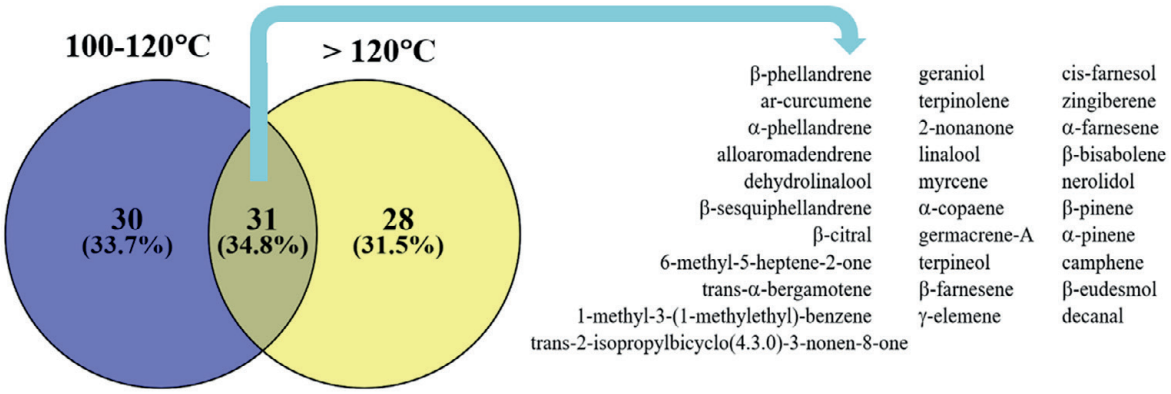


Figure 2: The Venn diagram of ginger essential oil phytocomponents obtained from distillation processes at 100-120 °C and above 120 °C.

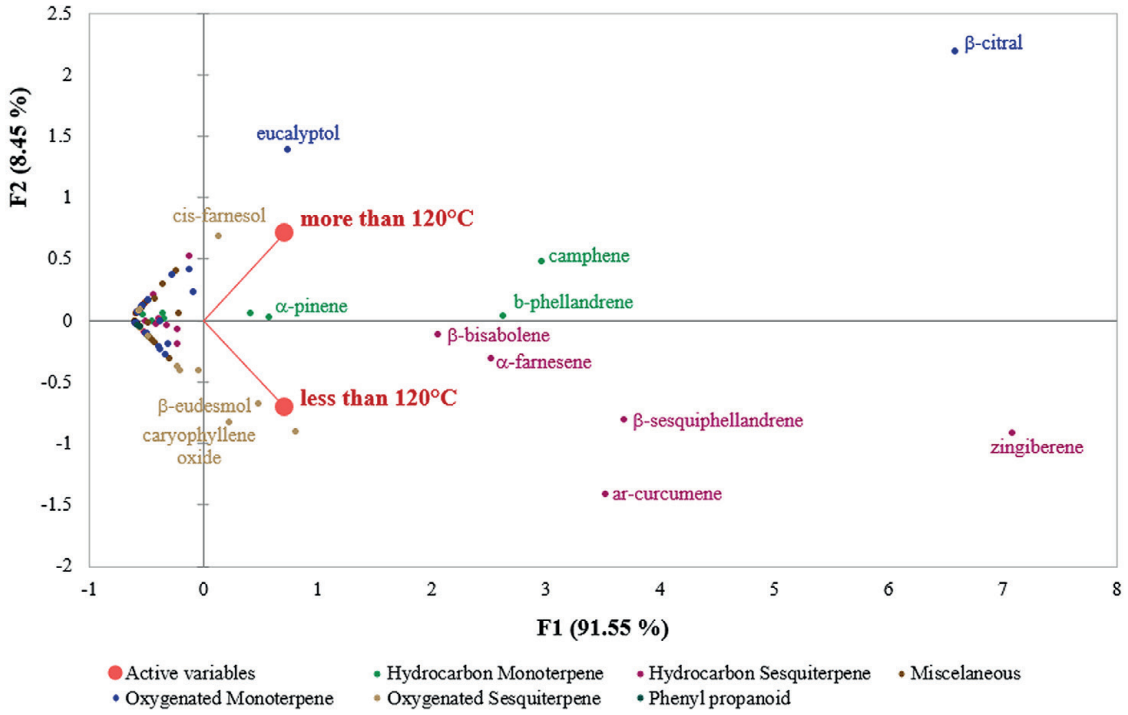


Figure 4: PCA of volatile components of ginger oils from both temperature distillations: biplot (axes F1 and F2: 100%).

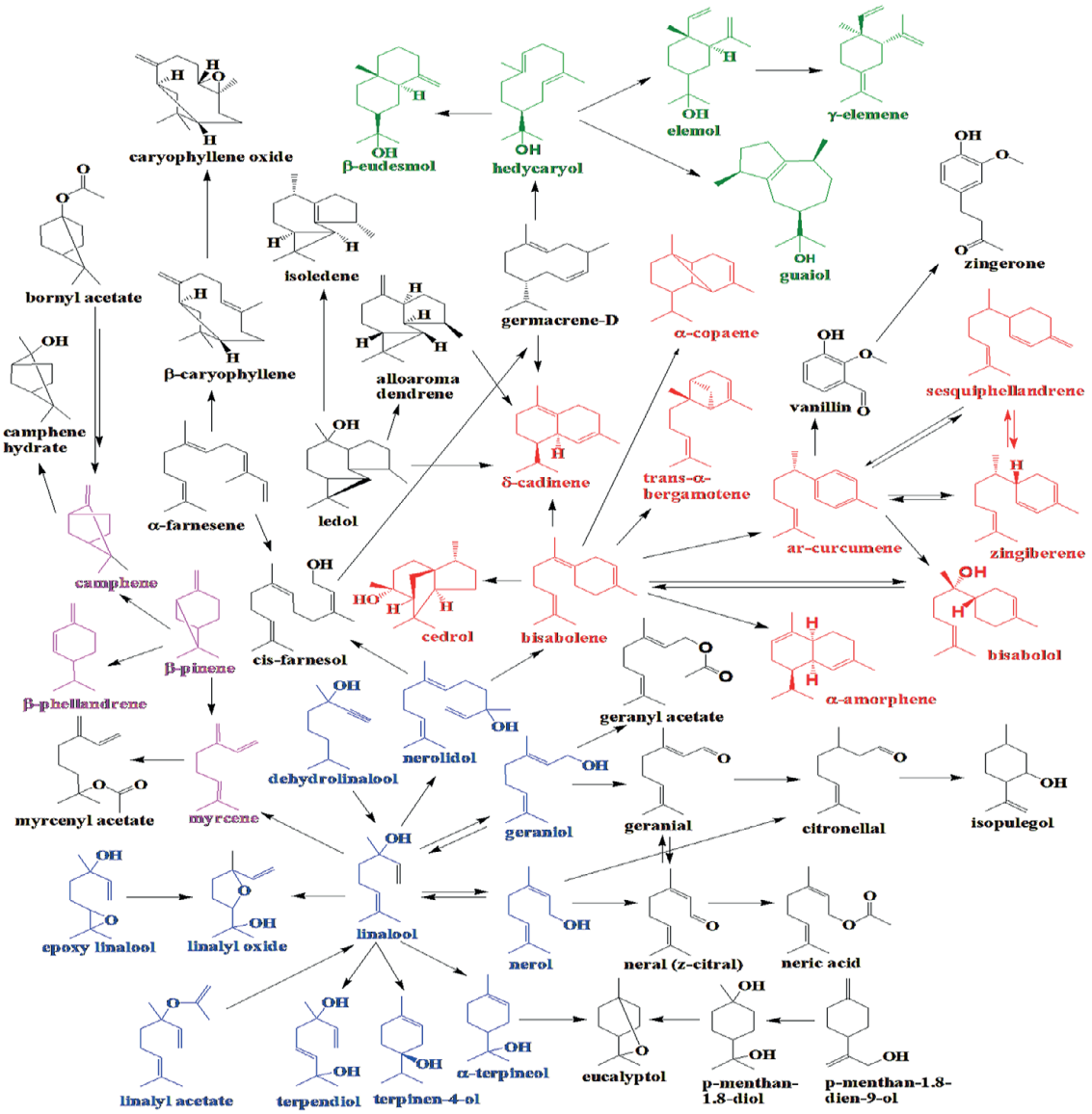


Figure 5: Metathesis reactions occurred during the distillation heating of the chemical components of ginger oils.

of geraniol and nerol, which led to the decrease of geraniol and nerol concentrations in ginger oil distilled above 120 °C compared to those below 120 °C.[35,36] Previous research shows that various extraction methods and the ginger origin can affect the chemical composition of ginger oil. Distillation of ginger also yields oils with higher citral than zingiberene.[37] An important thing to note is that citrus-like aroma oils can be obtained from a distillation process conducted at a mild heat level.[33]

Linalool is a secondary metabolite found in increased amounts inside ginger oil from distillation above 120 °C. Linalool is often found in combination with linalyl acetate in some plants.[38,39] However, linalyl acetate was not obtained in this ginger oil. Linalyl acetate is rapidly metabolized and hydrolyzed into linalool and acetic acid.[40] Linalool is also hydrated to β-myrcene, which can be further derivatized to myrcenyl acetate.[27] These reasons might be the causes of the unavailability of linalyl acetate, but there were slightly increased amounts of linalool and β-myrcene in the two ginger oils obtained in this research. Furthermore, dehydrolinalool was converted to linalool as the distillation temperature increased.[41] It leads to an increase in linalool in ginger oil during distillation above 120 °C. In fact, linalool content does not increase significantly in ginger oil from higher-temperature distillation. It might be caused by several factors, mainly the further decomposition of linalool into linalyl oxide, which is detected at higher levels in ginger oil distilled above 120 °C than below 120 °C.[42] Additionally, epoxy linalool is present at higher levels in ginger oil distilled at higher temperatures.[43] Previous research shows that epoxy linalool is also naturally obtained from papaya fruit pulp.[44] At pH 7.0, 6,7-epoxy linalool was also obtained in the pulp as the rearrangement of linalool. This 6.7-epoxy linalool is a precursor to the formation of linalyl oxides. In addition, a low-acidity environment in the pulp suggested partial decomposition of linalool to α-terpineol. Partial ring closure in the linalool structure converts it to α-terpineol, resulting in a higher α-terpineol concentration in ginger oil during distillation above 120 °C.[45] Further oxidation of α-terpineol in the presence of heat resulted in 1.8-cineole or eucalyptol.[46] In this study, terpenediol and terpinene-4-ol were also found only in ginger oil from high-temperature distillation, as degradation products of linalool.[47] These facts indicate a relatively constant amount of linalool relative to other linalool derivatives, with a 0.83% difference between the ginger oils obtained by distillation above and below 120 °C.

Conversely, geraniol and nerol were found to decrease following higher-temperature distillation of ginger. It was suspected that unstable geraniol and nerol were converted into linalool by rearrangement reactions.[48,49] Further decomposition of geraniol to geranyl acetate and isopulegol via citronellal formation also supports the decrease in geraniol content in ginger oil observed during higher-temperature distillation. Nerol was also converted into neral and neric acid at distillation above 120 °C.[50]

Bisabolene, as one of the big families of sesquiterpenes, also supports a range of chemical components inside ginger oil. Some appeared to be stable components obtained by distillation across both temperature variations. Trans-α-bergamotene and α-copaene are two examples.[51–54] Meanwhile, δ-cadinene, α-amorphene, and cedrol were obtained only from ginger oil distilled at higher temperatures.[55–58] Interestingly, bisabolol was a hydrated form of bisabolene found only in low-temperature-distilled ginger oil. Other bisabolene derivatives, such as zingiberene, *ar*-curcumene, and sesquiphellandrene, showed a significant decrease in the distillation of ginger at higher temperatures.[55]

Germacrene-D was detected only in ginger oil obtained by high-temperature distillation. It may be obtained from the degradation of farnesol. It is also a precursor of hedycaryol, which was further converted into elemene, β-eudesmol, and guaiol.[59] Elemene was oxidized to elemol under heat. Germacrene-D, together with β-elemene, alloaromadendrene, and ledol, can be converted into δ-cadinene and γ-muurolene via cyclization and rearrangement.[60,61]

Autooxidation of β-caryophyllene also generally occurs since it is unstable to oxidize into caryophyllene oxide.[62–65] However, the results show that β-caryophyllene was present in the ginger oil at a stable level across both distillation temperatures. Surprisingly, caryophyllene oxide was found only in ginger oil distilled at temperatures below 120 °C. Nerolidol, with a woody aroma reminiscent of fresh bark, is a precursor to farnesol.[66] Therefore, it may cause nerolidol to decrease, whereas farnesol may increase in ginger oil obtained at higher distillation temperatures.

Standardized ginger oil contains a high levels of zingiberene and low levels of pungent compounds. In this study, high zingiberene content was observed in lower-temperature-distilled ginger oil, whereas another ginger oil with a higher citral content exhibited no pungent aroma. Therefore, the distillation temperature can be customized to meet specific needs, as it determines the chemical composition and even the aroma of the ginger oil.

Molecular Docking of Ginger Phytochemicals Against the Protein Receptor of β2-Adrenoceptor

Chemical components in ginger oils will be correlated to their bioactivities. Previous research indicates that citral in ginger oil contributes to bronchodilatory activity.[67–69] Therefore, an analysis of ginger oil's biological activities based on its major components is required. To investigate the potency of ginger oil in overcoming asthma, molecular docking of several major chemical compounds in ginger oils was carried out against the protein receptor of 5X7D (Table 1), a protein receptor responsible for the interaction of the β2-adrenoceptor and ligand.[14] Carazolol, the native ligand in a crystal complex of 5X7D, has been redocked to form a superimposed ligand with RMSD less than 2Å (Figure 6A). Table 2 shows that the binding energy of the interactions between chemical components in ginger oil toward 5X7D did not compete with that of carazolol. However, the presence of chemical compounds with a binding energies closer to carazolol, i.e., β-eudesmol, caryophyllene oxide, zingiberene, etc., can be proposed as potential components that act synergistically to antagonize the β2-adrenergic receptor and suppress bronchospasm (Figure 6B). Therefore, a mixture of volatile compounds in ginger oil may retain its higher bronchodilator activity.

Possibility of Volatile Components Detected by Olfactory Receptor through the Respiratory Pathway

The major phytochemicals of ginger oils detected by GC-MS are volatile components from the terpenoid class. They evaporate readily due to their low boiling points and high vapor pressures. These properties enable their use in aromatherapy and as inhaler ingredients. The volatile components are inhaled directly by humans via the olfactory nerve or, after crossing the BBB, indirectly through the bloodstream. In the olfactory system, these chemicals interact with olfactory receptors and are then transported into the brain. As they reach the cerebellum, volatile components may influence human physiology and neurology. Therefore, the interaction between ginger phytochemicals, as ligands, and olfactory receptors warrants analysis.

Olfactory is related to the conscious perception of a smell in terms of perceived intensity and pleasantness, which is supported by molecular features of the components, including molecular weight, vapor pressure, and partial charge on the most negative atom. This research proposed an *in silico* study to correlate ginger phytochemicals with the human consensus olfactory receptor OR52c and to examine their influence on respiration and sniffing for medicinal purposes, such as a bronchodilator. The OR52c receptor (PDB ID: 8HTI) was docked against 28 reference odorant molecules (Table S7) to produce a standard molecule distribution in the PCA graph (Figure 7), containing four groups representing musk, woody, floral, and green odors (Table S8). Figure 7 shows that all phytocomponents of ginger essential oils are specifically close to green and floral odors (Figure S1).

Table 1. Interactions of protein residues of 5X7D with native ligand, and selected ginger phytochemicals.

Complex of ligand-protein	Residues of amino acids involved in the interactions
Native ligand (carazolol)	Hydrophobic interactions: Val114 (3.71 A°), Val117 (3.19 and 3.61 A°), Phe193 (3.53 and 3.84 A°), Tyr119 (3.63 A°), Phe208 (3.74 A°), Phe289 (3.53 A°). Hydrogen bonds: Asp113 (2.82 A°). π-stacking: Phe290 (4.60 and 4.57 A°).
zingiberene	Hydrophobic interactions: Asp113 (3.59 A°), Val114 (3.57 and 3.23 A°), Val117 (3.50 and 3.68 A°), Ile121 (3.98 A°), Phe193 (3.95 A°), Phe208 (3.38 A°), Phe289 (3.42 and 3.74 A°), Phe290 (3.37 and 3.12 A°).
(Z)-citral	Hydrophobic interactions: Val114 (3.64 and 3.61 A°), Val117 (3.36 and 3.40 A°), Phe208 (3.73 A°), Trp286 (3.32 A°), Phe290 (3.48 A°).
β-eudesmol	Hydrophobic interactions: Val114 (3.30 and 3.61 A°), Val117 (3.28 A°), Phe193 (3.99 A°), Phe208 (3.99 A°), Trp286 (3.65 A°), Phe289 (3.38 and 3.21 A°). Hydrogen bonds: Ser203 (2.73 A°), Ser207 (1.87 A°).

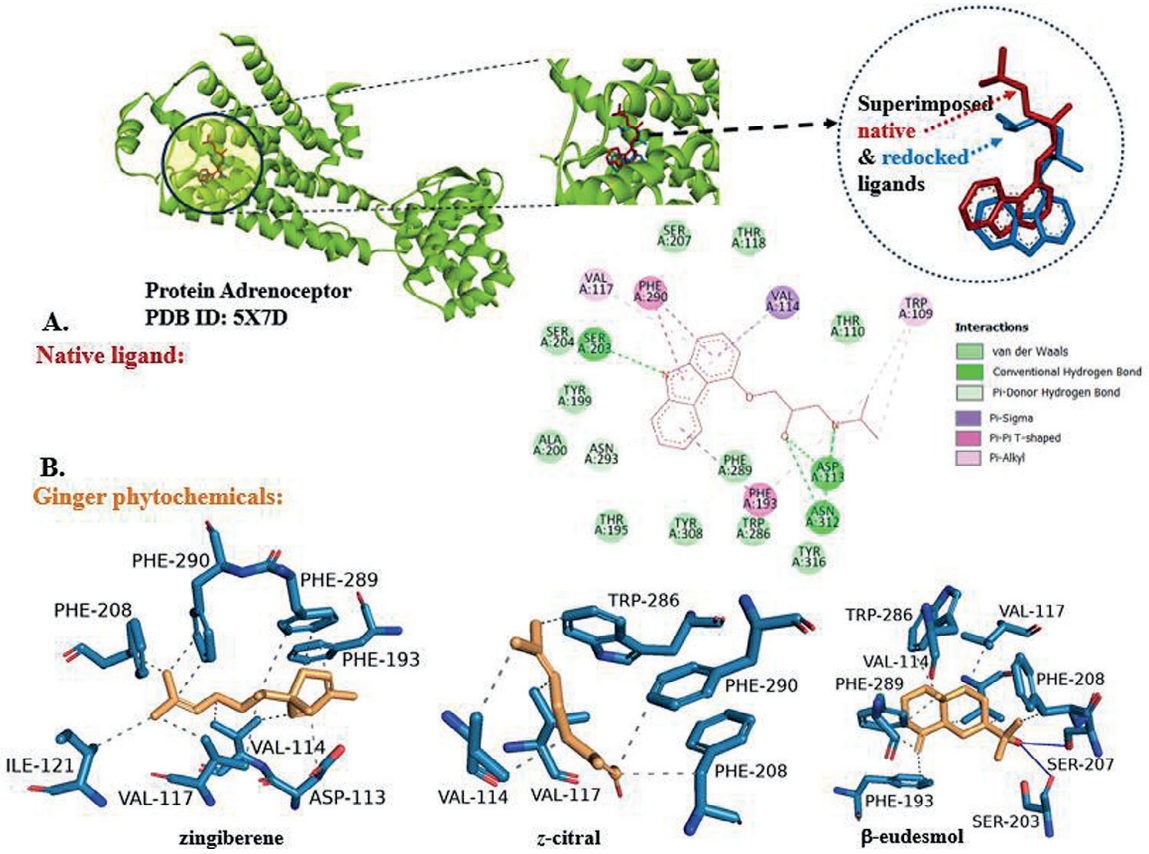


Figure 6: 2D and 3D interactions of superimposed ligands in the redocking process (A). 3D interactions between major compounds in ginger oil and specific amino acid residues of protein receptor PDB ID: 5X7D (B).

The interaction between olfactory receptors and the selected major ginger oil phytochemicals, together with the details of their binding energies, is presented in Figure 8 and Table 3. The protein cavity of 8HTI contains amino acid residues that are functionalized to interact with ligand molecules. Redocked ligand, octanoate, was superimposed with octanoic acid as the native ligand, to activate protein 8HTI sites of His107, Phe161, Val204, Ala205, and Phe261 by hydrophobic interactions. Three phytochemical markers in ginger oil, i.e., β-eudesmol, zingiberene, and *z*-citral, have also been linked to those amino acid residues of 8HTI active sites. However, the strong interaction of ligand and receptor 8HTI, which was supported by hydrogen bonding in cavities provided by Glu182, His183, and Met184, is also provided by in β-eudesmol and *z*-citral but in different amino acid residue cavities (Table 4). Meanwhile, salt bridges, which were formed from the residues of His107 and His183 with the native ligand, were not found in the interaction with ginger phytochemicals, unless through hydrogen bonding formation. Therefore, it resulted in a stronger binding interaction between the 8HTI protein and ginger phytochemicals compared to the native ligand.

The ADME properties of the ginger phytochemicals were calculated using SwissADME and are presented in Table S9. Since the

Table 2. Binding energy of the interactions between chemical components in ginger oil toward 5X7D

No	Ligand	Binding Energy (kcal/mol)
1	carazolol (native ligand)	-10.25
2	β-eudesmol	-8.87
3	caryophyllene oxide	-8.60
4	zingiberene	-8.31
5	cis-farnesol	-8.23
6	β-sesquiphellandrene	-7.91
7	β-bisabolene	-7.87
8	α-farnesen	-7.52
9	*ar*-curcumene	-7.46
10	β-citral	-6.50
11	eucalyptol	-6.00
12	β-phellandrene	-5.77
13	α-pinene	-5.76
14	camphena	-5.56

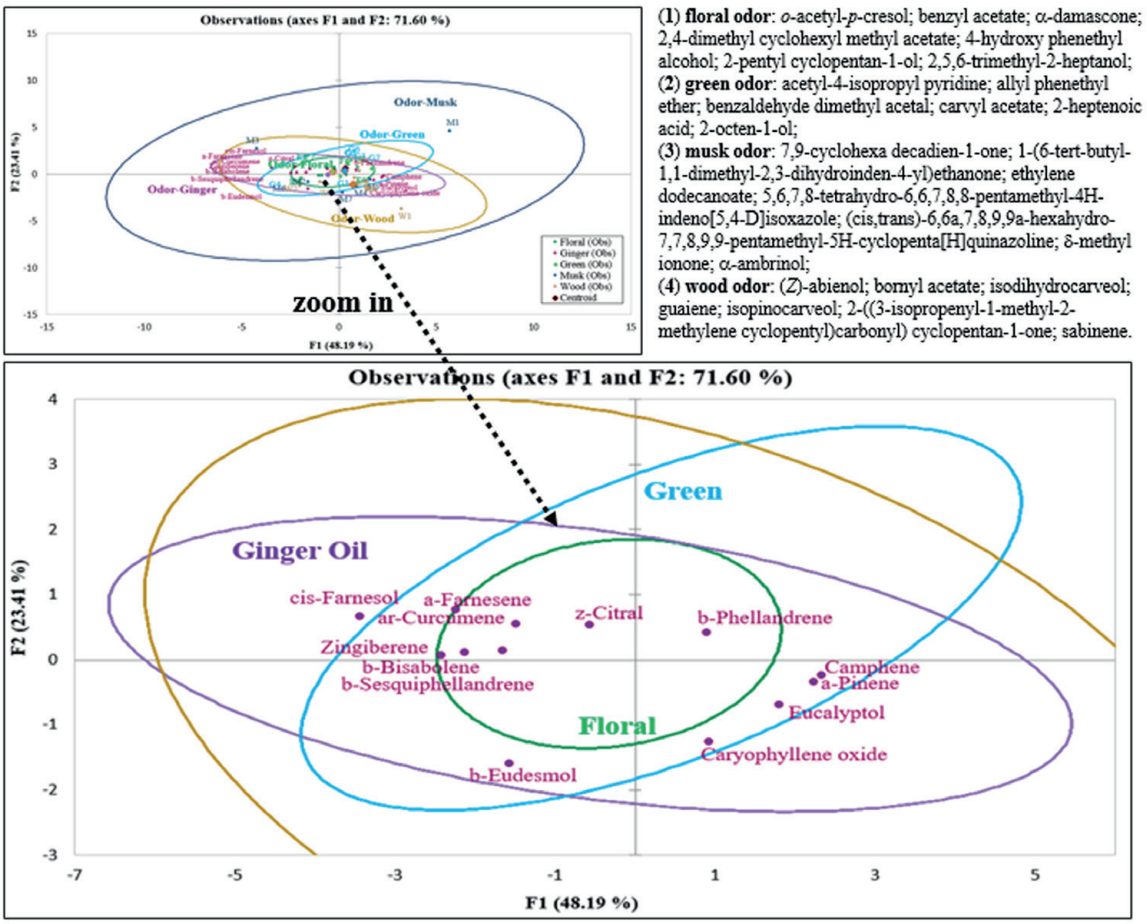


Figure 7: PCA of ginger oil's phytocomponents against selected reference odorant molecules (musk, wood, floral, and green).

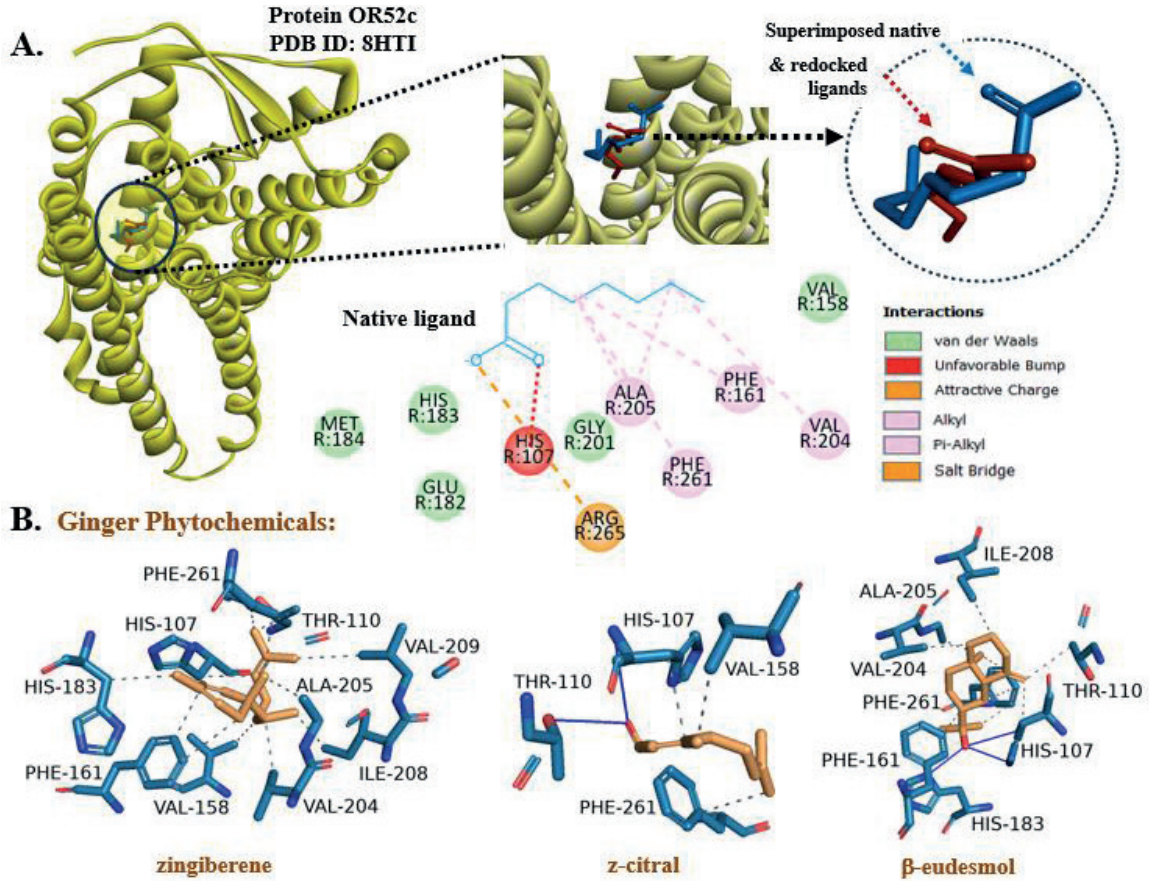


Figure 8: (A) The 2D and 3D interaction of superimposed native and redocked ligands toward the protein of OR52c (PDB ID: 8HTI). (B) Interaction of 8HTI with selected ginger phytochemicals: zingiberene, *z*-citral, and β-eudesmol.

β-adrenergic receptor is a β2-type, it is normally located in the lungs and cerebellum. The cerebellum modulates respiratory responses during challenges such as hypoxia and obstructed breathing. Thus, factors such as structure, polarity, and particle size may influence the transport of ginger compounds into specific tissues. These data correlate with derived properties that support ADME calculations, including molecular weight, the logarithm of polarity, the number of hydrogen-bond donors and acceptors, the number of rotatable bonds, the topological polar surface area, molecular refractivity, and the logarithm of aqueous solubility. Moreover, those ADME properties support a prediction of a molecule's drug-likeness, particularly for oral bioavailability, known as Lipinski's Rule of Five. However, many compounds that violate one or more of Lipinski's Rules may still be effective and approved for clinical use, because other factors, such as permeability and specific interactions with protein targets, can also influence their absorption. Further integration of ADME properties and reported biological activities related to the anti-asthma mechanism is shown in Table 5. This approach highlights z-citral and eucalyptol as compounds with favorable pharmacokinetic profiles and demonstrates a strong bronchodilatory effect. Other compounds with strong evidence of potential anti-inflammatory activity are β-eudesmol, cis-farnesol, and α-pinene. However, the other major compounds in ginger oil also exhibit anti-inflammatory activity, with distinct mechanisms that may involve bronchodilatory effects. The synergistic effect of these phytocomponents may make ginger oil an effective natural supplement for treating asthma.

The graphical output of ADME parameters in Figure 9, known as BOILED-Egg, illustrates a simple pharmacokinetic model for the provided chemicals based on physicochemical descriptors listed in Table S10. It enables easy evaluation of chemical distribution via passive brain access (if within the yolk), passive gastrointestinal lumen access (if within the white), and poor absorption (whenever in the grey region).[25] According to Figure 9, *cis*-farnesol, β-eudesmol, caryophyllene oxide, β-phellandrene, camphene, α-pinene, *z*-citral, and eucalyptol are molecules inside the yolk, predicted to be able to cross the Blood-Brain Barrier (BBB) and potentially reach the central nervous system. Meanwhile, zingiberene, α-farnesene, β-bisabolene, β-sesquiphellandrene, and ar-curcumene are predicted to have poor gastrointestinal (GI) absorption, as they fall within the grey region. Other molecules in the yolk region, b-phellandrene, a-pinene, and camphene, also have low GI absorption since they are close to the grey region. This pharmacokinetic model is influenced by the TPSA parameter, which is correlated to the topological polar surface area of the molecule. Whenever the molecule is a hydrocarbon only, it shows a value of 0 (zero) or is non-polar. In fact, all the studied molecules show TPSA values in the range of 0-60 Å (Table S10). They are predicted to cross the BBB and cell membranes via passive diffusion since they are lipid-soluble. However, it may pose a problem, as they can be trapped within lipid bilayers due to their extreme hydrophobicity. The permeability glycoprotein (PGP) is responsible for pumping many foreign substances out of cells. Figure 9 shows that carazolol is a PGP+ or a substrate of PGP (color coding blue). As a PGP-transported molecule, carazolol is susceptible to pharmacokinetic changes and may be more readily eliminated from the body, reducing its effectiveness. Meanwhile, phytochemicals in ginger essential oil are classified as PGP- or non-PGP substrates, and are color-coded red in Figure 9. Therefore, phytochemicals of ginger oil are not significantly affected by PGP actions in eliminating chemical uptake, particularly to and from the cytosol. Those reasons indicate that several chemicals with red color codes in the yellow region of the current BOILED-Egg graphic have potential medical applications, particularly for crossing the blood-brain barrier in the central nervous system. According to this mechanism, the appropriate medical treatment is the administration of drugs containing these ginger phytochemicals via the olfactory receptors.

Table 3. Binding energy of the interactions between chemical components in ginger oil toward 8HTI.

No	Ligand	Binding Energy (kcal/mol)
1	β-eudesmol	-8.41
2	zingiberene	-7.50
3	cis-farnesol	-7.30
4	β-bisabolene	-7.28
5	β-sesquiphellandrene	-7.16
6	caryophyllene oxide	-6.99
7	α-farnesen	-6.75
8	ar-curcumene	-6.70
9	eucalyptol	-6.21
10	*(Z)*-citral	-5.93
11	α-pinene	-5.76
12	camphena	-5.64
13	β-phellandrene	-5.46
14	octanoic acid	-5.10

CONCLUSION

Ginger has been widely used in traditional medicine to relieve inflammation and enhance the body's resistance to disease by warming and refreshing the body. Extracting ginger in hot water (decoction) has a similar process to distillation, producing extracts containing many beneficial volatile components which are further digested and absorbed in the gastrointestinal tract to cross the blood barrier and interact with several protein receptors present in the blood. The phytochemicals in ginger oil that enter the bloodstream may bind to β-adrenergic receptors, thereby triggering physiological effects, including changes in heart rate and blood pressure, as well as muscle relaxation. The *in silico* study of ginger's phytochemicals towards β-adrenoceptor (5X7D) shows that β-eudesmol has the closest binding energy to carazolol, the native ligand. However, the low binding energies of most major compounds in ginger oils to 5X7D suggest that the phytochemicals in ginger oil act synergistically,

Table 4. Interactions of receptor residues of OR52c (8HTI) with native ligands, and major ginger phytochemicals.

Ligand-protein complex	Interactive amino acid residues
octanoic acid	Hydrophobic interactions: His107 (3.54 A°), Phe161 (3.69 A°), Val204 (3.35 A°), Ala205 (3.58 A°), and Phe261 (3.50 A°). Hydrogen bond: Glu182 (2.95 A°), His183 (2.52 A°), and Met184 (2.53 A°). Salt bridges: His107 (3.69 A°) and His183 (5.06 A°).
β-eudesmol	Hydrophobic interactions: His107 (3.48 A°), Thr110 (3.86 A°), Phe161 (3.46 A°), Val204 (3.17 A°), Ala205 (3.09 A°), Ile208 (3.38 A°), Phe261 (3.10, 4.00, and 3.26 A°). Hydrogen bond: His107 (1.95 and 3.30 A°), and His183 (3.22 A°).
zingiberene	Hydrophobic interactions: His107 (3.38 A°), Thr110 (3.31 A°), Val158 (3.51 A°), Phe161 (3.33 and 3.94 A°), His183 (3.88 A°), Val204 (2.95 A°), Ala205 (3.24 A°), Ile208 (3.84 A°), Val209 (3.86 A°), and Phe261 (3.26 and 3.24 A°).
(Z)-citral	Hydrophobic interactions: His107 (3.68 A°), Val158 (3.31 A°), Phe261 (3.99 A°). Hydrogen bond: His107 (2.96 A°), and Thr110 (1.98 A°).

Table 5. Integration of ADME properties and anti-asthma activity of major phytochemicals from ginger essential oils.

Phytochemicals	MW (g/mol)	Log P	Log S	Lipinski violation	Biological Target	Anti-Asthma Mechanism	Model Study	Evidence Strength	Ref
zingiberene	204.35	4.47	-4.10	1 ⚠	Anti-inflammation	↑ FOXP3 gene expression ↓ inflammation	Clinic/ In vivo	Strong	70–73
(Z)-citral	152.23	2.71	-2.43	0 ☑	Bronchodilator & Anti-inflammation	Relaxing airway/ ↑ PPAr-γ activation	In vitro/ In vivo	Strong	67,74–77
α-farnesene	204.35	4.96	-4.57	1 ⚠	Antiinflammation	↓ neutrophil mobility	In vitro	Medium	78
α-pinene	136.23	3.44	-3.51	1 ⚠	Bronchodilator	↓ airway inflammation	In vivo	Strong	79–81
ar-curcumene	202.34	4.86	-4.52	1 ⚠	Anti-inflammation	↓ chemokine proinflammation	In vitro	Strong	81
β-bisabolene	204.35	4.83	-4.89	1 ⚠	Anti-inflammation & Antioxidant	↓ TNF-α, IL-1β proinflammatory cytokines ↓ ROS, COX2, Keap1, NO	In silico & In vitro	Medium	82–84
β-phellandrene	136.23	3.07	-2.79	0 ☑	Anti-inflammation	↓ NF-kB & proinflammatory cytokines	In vivo	Medium	81,85,86
β-sesquiphellandrene	204.35	4.56	-4.25	1 ⚠	Immunodulator & Antiviral	↓ IL-1β, TNF-α ↑ cytochrome c, activate caspases	In silico/ In vitro	Weak	87–89
camphene	136.23	3.43	-3.43	1 ⚠	Antioxidant	↓ ROS and NO ↑ cell viability and glutathione	In vivo	Strong	90–92
caryophyllene oxide	220.35	4.31	-4.08	1 ⚠	Anti-inflammation & Analgesic	↓ inflammatory mediator of pain ↓ efflux pump, cytochrome P450	In vivo/ In vitro	Medium	62,93–96
cis-farnesol	222.37	4.40	-3.32	0 ☑	Anti-inflammation	↓ airway inflammation	In vivo	Strong	97,98
eucalyptol	154.25	2.67	-2.52	0 ☑	Bronchodilator & Anti-inflammation	↓ airway & bronchial inflammation	Clinic	Very strong	99–103
β-eudesmol	222.37	3.61	-3.51	0 ☑	Anti-inflammation & Anti-allergic	↓ airway inflammation ↓ histamine	In vitro/ In vivo	Strong	104–107

MW: molecular weight; Log P: lipophilicity; Log S: solubility; FOXP3: forkhead box P3;PPAr-γ: peroxisome proliferator-activated receptor gamma; TNF-α: tumor necrosis factor-α; IL-1β: interleukin-1β; ROS: reactive oxygen species; COX2: cyclooxygenase-2; Keap1: Kelch-like ECH-associated protein 1; NO: nitric oxide.

thereby maintaining bronchoplasm suppression. Meanwhile, volatile components of ginger essential oils, when inhaled, enter the respiratory pathways via the human consensus olfactory receptor OR52c (8HTI). The primary interactions between ginger's volatile components and 8HTI receptors trigger a sense of smell and enhance the structure-odor relationship during sniffing. B-eudesmol is a phytocomponent producing the best binding energy against the 8HTI receptor. Based on the ADME properties of ginger phytochemicals, β-eudesmol, apart from other chemicals, including *cis*-farnesol, caryophyllene oxide, β-phellandrene, camphene, *(Z)*-citral, and eucalyptol, can pass the BBB and enter the central nervous system without any significant changes in their pharmacokinetics since they are PGP-non-substrate molecules. These conclusions support the continued use of ginger essential oils as bronchodilators that act via the olfactory pathway through inhalation of their volatile components.

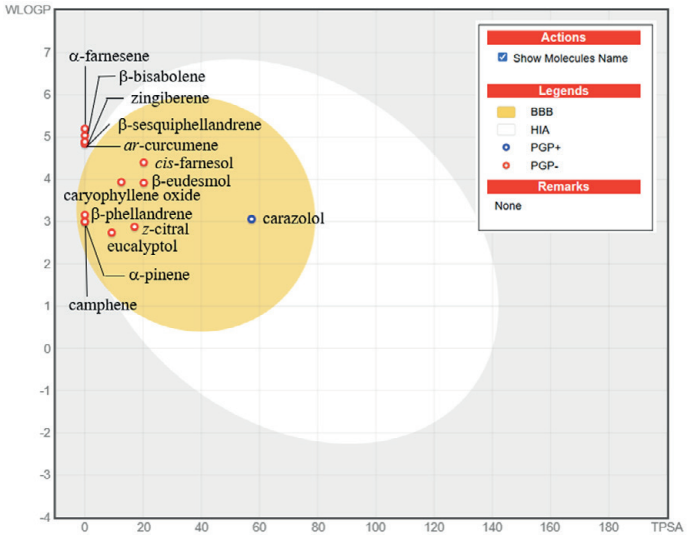


Figure 9: Graphical output (BOILED-Egg) of ADME parameters in Tables S9 and S10. HIA: passive human intestinal absorption; BBB: blood-brain barrier; PGP+: P-glycoprotein substrates; PGP-: P-glycoprotein non-substrate.

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CONFLICT OF INTEREST

The authors report no financial or any other conflicts of interest in this work.

DECLARATION OF GENERATIVE AI AND AI-ASSISTED TECHNOLOGIES

The authors confirm that no generative artificial intelligence or AI-assisted technologies were used for the purpose of the research conducted or for the preparation of the manuscript.

CREDIT AUTHORSHIP CONTRIBUTIONS STATEMENT

IO and ASN contributed to the conceptualization, drafting, and critical revision of the manuscript; supervision; and final approval. IO, DTF, AY, and MR contributed to methodology, software, formal analysis, data curation, and technical or material support. Funding was covered by a research grant for IO.

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