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ORIGINAL ARTICLE / ÖZGÜN MAKALE

ACTIVE COMPOUNDS FROM MEDICINAL PLANTS AS NOVEL APPROACHES FOR ASTHMA THERAPY: *IN SILICO* DOCKING ANALYSIS

ASTIM TEDAVİSİNDE YENİ YAKLAŞIMLAR İÇİN TIBBİ BİTKİLERDEN ELDE EDİLEN AKTİF BİLEŞİKLERİN İN SİLİKO DOCKING ANALİZİ

Muhammet Zahit ÇELİK[1], Fatma UYSAL[1]*, Nuriye Hilal TAŞTEKİN[2], Ahmet Cenk ANDAÇ[3], Seyfullah Oktay ARSLAN[1]

[1]Ankara Yildirim Beyazıt University, Faculty of Medicine, Department of Medicinal Pharmacology, 06800, Ankara, Türkiye
[2]Ankara Medipol University, Faculty of Pharmacy, Department of Pharmacognosy, 06050, Ankara, Türkiye
[3]Yeditepe University, Faculty of Medicine, Department of Medicinal Pharmacology, 34755, İstabul, Türkiye

ABSTRACT

Objective: *Pharmaceutical molecules have historically drawn inspiration from natural substances. Nowadays, research on natural compounds is escalating, particularly on phytochemicals. In this context, asthma, characterized by airway constriction and inflammation, occupies a significant place in the search for effective herbal treatments. Nonetheless, the bronchodilatory efficacy of the bioactive phytochemicals remains ambiguous. This study explores plant-derived compounds proposed for asthma treatment, focusing on their bronchodilator effects mediated through β2-adrenergic and M3-muscarinic receptors. These receptors facilitate muscle relaxation respectively by increasing intracellular cAMP levels and reducing intracellular calcium release from the endoplasmic reticulum.*

Material and Method: *A comprehensive literature search was performed on phytochemicals tested on asthmatic animal models. A total of 898 articles were assessed in this manner. Following the elimination of duplicates, 100 bioactive plant compounds in 3D format, demonstrating potential bronchodilator effects, were assessed in silico for their impact on β2 and M3 receptors. The receptors were obtained from the Protein Data Bank. Compounds and references were docked to specific proteins by the PyRx program to facilitate the docking, and high-scored molecules were visualized by the DSV program. Besides, in silico pharmacokinetic parameters were evaluated via SwissADME tool and toxicity parameters were determined using ADMETLab 3.0 platform.*

Result and Discussion: *In the docking experiments, 34 out of the 100 compounds were demonstrated to have a potentially high affinity to β2 and/or M3 receptors. Several molecules like cryptotanshinone, paeoniflorin and rottlerin were found to have high binding affinities for the β2 receptor. On the other hand, it has been demonstrated that tetrandrine, fisetin, and cryptotanshinone have strong affinities for the M3 receptor. Considering the findings, these bioactive substances could benefit bronchodilation, particularly through the β2 and M3 receptor pathways. This in silico study highlighted the potential of plant compounds for bronchodilation in respiratory diseases and suggested avenues for future research and experimental validation in asthma therapy.*

* **Corresponding Author / Sorumlu Yazar:** Fatma Uysal
e-mail / e-posta: fatmauysal1989@gmail.com, **Phone / Tel.:** +905066446056

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ÖZ

Amaç: *İlaç molekülleri tarihsel olarak doğal maddelerden ilham alagelmektedir. Günümüzde doğal bileşikler ve özellikle fitokimyasallar üzerinde yapılan araştırmalar giderek artmaktadır. Bu bağlamda, solunum yolu daralması ve enflamasyonu ile karakterize astım hastalığı, etkili bitkisel tedavilere yönelik araştırmalarda önemli bir yer tutmaktadır. Bununla birlikte, biyoaktif fitokimyasalların bronkodilatör etkinliği belirsizliğini korumaktadır. Bu çalışmada astım tedavisi için önerilen bitkisel kaynaklı bileşiklerin, β2-adrenerjik ve M3-muskarinik reseptör aracılı bronkodilatör etkilerine odaklanılmıştır. Bu reseptörler, sırasıyla hücre içi cAMP seviyelerini artırarak ve endoplazmik retikulumdan hücre içi kalsiyum salınımını azaltarak kas gevşemesini sağlar.*

Gereç ve Yöntem: *Astımlı hayvan modelleri üzerinde çalışılmış bitkisel bileşikler hakkında kapsamlı bir literatür araştırması yapılmıştır. Toplamda 898 makale bu şekilde değerlendirmeye alınmıştır. Tekrar eden literatürlerin çıkarılmasının ardından, potansiyel bronkodilatör etkinlik gösteren üç boyutlu yapıdaki 100 farklı bitkisel bileşik, β2 ve M3 reseptörleri üzerindeki etkileri açısından in silico olarak değerlendirilmiştir. Reseptörler Protein Data Bank'tan elde edilmiştir. Bileşikler ve referanslar, kenetlenmeyi kolaylaştırmak için PyRx programı tarafından belirli proteinlere kenetlenmiş ve yüksek puanlı moleküller DSV programı tarafından görselleştirilmiştir. Ayrıca, in silico farmakokinetik parametreleri SwissADME aracılığıyla değerlendirilmiş ve toksisite parametreleri ADMETLab 3.0 platformu kullanılarak belirlenmiştir.*

Sonuç ve Tartışma: *Docking deneylerinde, 100 bileşikten 34'ünün β2 ve/veya M3 reseptörlerine potansiyel olarak yüksek afiniteye sahip olduğu gösterilmiştir. Kriptotanşinon, paeoniflorin ve rottlerin gibi birkaç molekülün β2 reseptörü için yüksek bağlanma afinitesine sahip olduğu bulunmuştur. Diğer taraftan, tetrandrin, fisetin ve kriptotanşinonun M3 reseptörü için güçlü afinitelere sahip olduğu gösterilmiştir. Bulgular göz önünde bulundurulduğunda, bu biyoaktif maddeler özellikle β2 ve M3 reseptör yolları aracılığıyla bronkodilatasyona fayda sağlayabilir. Bu in silico çalışma, solunum yolu hastalıklarında bronkodilatasyon için bitki bileşiklerinin potansiyelini göstermiştir. Astım tedavisinin gelecekteki araştırmaları ve deneysel çalışmaları için yollar göstermiştir.*

Anahtar Kelimeler: *Astım, β2 adrenerjik reseptör, bitkisel bileşik, M3 muskarinik reseptör, moleküler yerleştirme*

INTRODUCTION

Asthma has become more prevalent and severe worldwide, particularly over the past ten years. Th2-mediated immune response to environmental allergens causes allergic asthma having hallmarks such as chronic inflammation, airway aggression, mucus hypersecretion, airway eosinophilia, elevated IgE levels and airway hyperresponsiveness [1]. These result in reversible airway obstruction and airway remodeling accompanied by several symptoms such as coughing, wheezing, increased sputum production and sleep disturbance [2].

The mechanism of occurrence and development of asthma has not been exactly elucidated yet, as well as there is no definite cure [3,4]. However, currently available asthma treatments are used to alleviate symptoms and diminish the underlying airway inflammation [5]. These include β2 receptor agonists, M3 receptor antagonists, corticosteroids and xanthine with its derivatives [6].

β2 receptors are cell surface receptors that are clinically utilized in the treatment of bronchospasm in patients with bronchial asthma or other bronchospasm-related diseases [7].They are bound to heterotrimeric G protein, especially Gs protein. The activation of the G protein-coupled receptors by an agonist promotes the dissociation of guanosine diphosphate (GDP) from the α subunit of the cognate G protein. Guanosine triphosphate (GTP) then binds to G protein, and the α subunit dissociates from the β-γ unit. Thus, α subunit stimulates adenylyl cyclase to catalyze the conversion of adenosine triphosphate (ATP) to cyclic adenosine monophosphate (cAMP) [8]. cAMP acts as a second messenger within the cell, and in turn, cAMP initiates processes leading to smooth muscle relaxation (Figure 1) [9]. β2 receptors are predominantly found in airway smooth muscle. Numerous β2 agonists are used to

treat bronchospasm caused by disorders like bronchial asthma, including albuterol [10]. New drug development studies on the β2 receptors are ongoing.

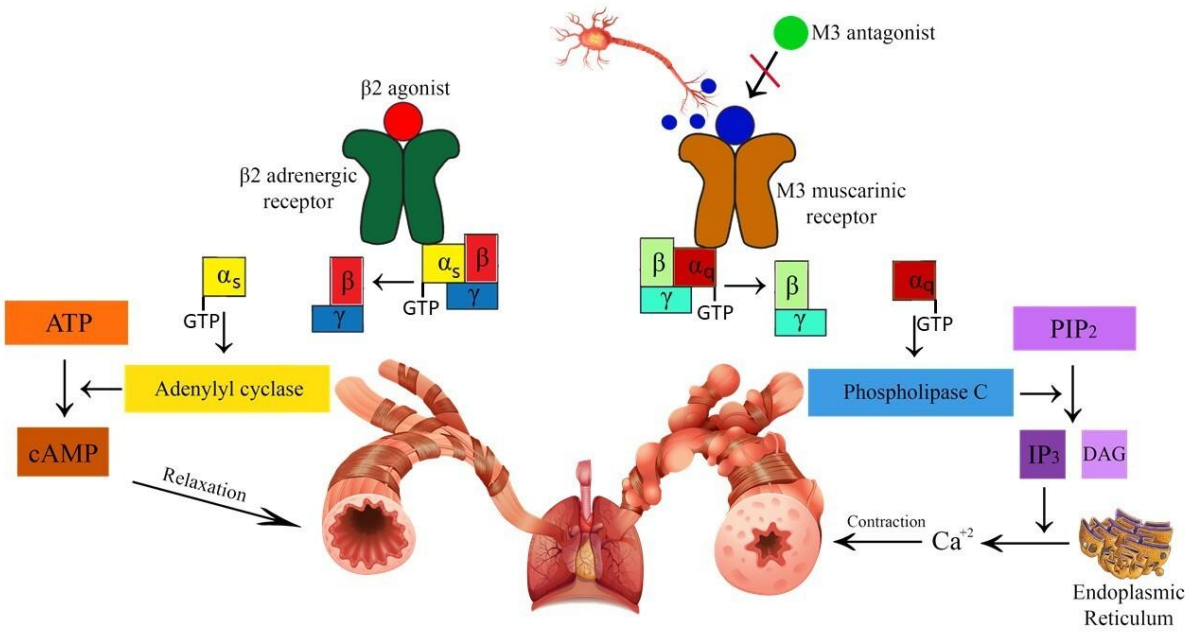

Figure 1. Mechanism of action of β2 agonists and M3 antagonists on bronchodilation
PIP_2: phosphatidylinositol 4,5- diphosphate, IP_3: inositol triphosphate, DAG: diacylglycerol

Through an asthmatic condition, elevated airway tone is seen primarily due to the activation of the vagus nerve that innervates the bronchi. The airway constriction is facilitated by the release of acetylcholine, which activates M3 receptors present throughout the bronchial system [11]. G proteins, specifically the Gq, are linked to the M3 receptors. Activation of the receptors by acetylcholine stimulates phospholipase C activity leading to membrane-derived phosphatidylinositol 4,5- diphosphate hydrolyzation. This results in the formation of inositol triphosphate (IP_3), which leads to the release of Ca^{+2} from the endoplasmic reticulum. That results in bronchial smooth muscle contraction and ultimately bronchoconstriction (Figure 1) [12]. Plants with anticholinergic effects, e.g. *Atropa belladonna*, have historically been used in the treatment of asthma, afterwards, their active compounds have led to therapeutics like muscarinic receptor antagonists, e.g. ipratropium bromide [13].

Molecular docking is an *in silico* structure-based method. Docking enables the identification of novel compounds of therapeutic interest, prediction of ligand-target interactions at the molecular level and determination of structure-activity relationships. Thus, docking has become an important component of the drug discovery process [14]. *In silico* technologies have had a tremendous influence on drug discovery, resulting in considerable savings in terms of time and cost. Utilization of cutting-edge technologies assists in selecting the appropriate chemicals for pre-clinical research [15]. Drug discovery frequently necessitates a comprehensive evaluation of numerous potential drug compounds on specific targets, in this regard, molecular docking serves as a broad screening approach to identify a wide array of potential compounds for therapeutic use [16].

Medicinal plants have been used worldwide for centuries, and in some cases, even for millennia, to promote and maintain good health, prevent diseases and treat various physical and mental ailments. These plants have garnered significant attention due to their substantial potential for addressing physiological disorders. Plants synthesize an extremely rich variety of secondary metabolites, including a large number of active or complementary compounds [17]. Although this diversity has many positive properties, it can also have certain undesirable consequences. The available empirical data regarding the

positive and negative impacts associated with the utilization of medicinal plants is currently insufficient. The field of ethnopharmacology has emerged to examine the effects of bioactive compounds derived from medicinal plants on biological systems, leading to further scientific research [6]. Indeed, many drugs in the market are derived from natural products. The application of plant extracts with hundreds of chemicals for medicinal purposes is growing day by day, and the mechanisms of action of their active compounds are being further investigated.

Numerous bioactive compounds extracted from medicinally important plants have been empirically demonstrated to possess therapeutic properties against asthma. Nonetheless, the precise mechanisms by which these substances exert their antiasthmatic effects remain ambiguous. The main objective of this study is to employ *in silico* analysis to assess the modulatory effects on β2 and M3 receptors of 100 plant-derived compounds experimentally shown to be potentially effective in treating asthma. The two receptors represent the most typically targeted molecules in the management of asthma.

MATERIAL AND METHOD

Construction of the Phytochemical Library

Plants have been employed as medicinal agents in traditional medicine for centuries. The pharmacological activities of the plants were generally attributed to the bioactive compounds, possessing a wide range of pharmacological activity. Therefore, a literature review was conducted to compile phytochemicals previously alleged to have anti-asthmatic effects. The search terms were chosen considering the sensitizing agents used to form/create asthma models on animals and the terms related to secondary metabolites since this research is focused on *in vivo* experimental studies and plant compounds. The keywords were as follows; ((asthma) OR (ovalbumin) OR (house dust mite)) AND ((medicinal plant) OR (phytotherapeutic) OR (herbal medicine) OR (bioactive compound) OR (phytochemistry) OR (essential oil) OR (secondary metabolite)).

For this review, PubMed, Scopus and Web of Science databases were searched for relevant articles in English published between 2013 and 2024. A total of 898 articles were retrieved from the databases. After removing duplicates, 653 studies remained. The primary selection criteria were that the experiments involved animals and employed a pure plant compound. The number of publications was reduced to 125 through implementing the requirements. 113 unique molecules were identified following the determination of the subjected molecules to the studies. Thirteen of these compounds lacked 3D structures in the PubChem database [18]. Ultimately, the *in silico* investigation encompassed 100 bioactive phytochemicals.

Protein Selection and Preparation

The X-ray crystallographic structures of the target proteins, i.e., M3 receptor (PDB code: 4U15) (resolution: 2.80 Å) and β2 receptor (PDB code: 6MXT) (resolution: 2.96 Å), were obtained from the Protein Data Bank (PDB) [19]. The 3D structures of two receptors were loaded to the chimera window and processed using the DockPrep tool in UCSF Chimera software. Water molecules were eliminated by the addition of polar hydrogens, and Gasteiger charges were accordingly calculated. In addition, all chains and residues except chain A were removed for simplicity and to ensure accuracy. Protein structures from X-ray crystallography may contain additional chains and residues due to crystal packing artefacts. These chains may not be biologically relevant in solution and can impede the docking investigations. Furthermore, the docking process is guaranteed to target the biologically relevant region by selecting the appropriate chain if the docking research focuses on a specific active site or interface. The PDBQT formats were ultimately obtained.

Ligand Preparation

Based on the comprehensive literature search, 100 of the natural compounds tested out *in vivo* to treat asthma were selected. Formoterol, a β2-receptor agonist, and tiotropium, an M3-receptor antagonist, were assigned as reference ligands based on their clinical use. These compounds were included in the docking process. Structures of the selected compounds were downloaded from PubChem in SDF format. The 3D SDF-formatted ligands were loaded into PyRx (software version 0.8) using the

OpenBabel graphical user interface [20]. The energy minimization of ligands was carried out using PyRx software. A total of 200 steps were performed using the conjugate gradient algorithm, with a step size of 1. The Universal Force Field (UFF) was employed during the minimization process, due to its well-suited for small-molecule ligand optimization. Following minimization, the ligands were converted to AutoDock-compatible PDBQT format using PyRx, ensuring the preservation of the minimized energy states for subsequent docking studies. Also, the protein was converted to PDBQT format using PyRx to prepare it for docking.

Molecular Docking

An *in silico* approach to ligand and receptor docking analysis has been used to investigate structural complexes. Therefore, PyRx virtual screening tool with Auto Dock Vina was employed in the current study. For each docking study, the grid box was determined based on the position of the ligand present in the X-ray structure. The grid box sizes were set to 24 × 24 × 24 and 25 × 25 × 25 for receptors PDB: 4U15 and PDB: 6MXT, respectively. Grid boxes were centered at x = 47.26, y = 92.48, z = 55.15 and x = -10.60, y = -3.93, z = 37.83 for the receptors, respectively. The other parameters were kept as default, besides, all of the bonds in the ligand were allowed to rotate freely, considering the receptor as rigid. The docking simulation was run with an exhaustiveness level of 8. The ligand with the most negative binding energy is meant to have the highest binding affinity [21]. The final visualization of the docked structures was performed using Discovery Studio Visualizer 3.0. The binding mode diagram between the target protein receptor and the compounds was drawn in 2D (two-dimensional).

The validation of the targeted active sites for both the β2-adrenergic receptor (6MXT) and the M3-muscarinic receptor (4U15) was performed by calculating the cluster Root-Mean-Square Deviation (RMSD) values. To ensure the reliability of the docking studies, the cluster RMSD values are required to fall within the range of 0–2 Å. For the validation of molecular docking, redocking was conducted within the predefined grid boxes created for the target regions of both 6MXT (including salmeterol) and 4U15 (including tiotropium). The cluster RMSD values for the ligand molecules, tested across 10 and 9 different conformations respectively, were determined to be 0.983 Å for 6MXT and 0.827 Å for 4U15. These results demonstrate that the ligand compounds docked to the designated target regions for both receptors exhibited RMSD values within the acceptable range, confirming the validity and consistency of the docking approach.

In silico ADMET

Pharmacokinetic parameters, including LogP, oral bioavailability, gastrointestinal absorption, blood-brain barrier permeability, skin permeation, cytochrome P450 enzyme inhibition, and drug-likeness (evaluated using the Lipinski Rule of Five), were calculated using the SwissADME tool [22]. Additionally, the potential toxicity of the substances was assessed utilizing the ADMETLab 3.0 platform [23].

RESULT AND DISCUSSION

Since β2 agonists and M3 antagonists are involved in the relaxation of airway bronchoconstriction as part of current therapeutic strategies, the receptors were identified as the targets for the plant-derived compounds [24].

Table 1 displays the docking study results for each of the receptors. The results are expressed as the docking scores (kcal/mol). Herein, low docking scores (kcal/mol) suggest high binding energies [25]. The reference compounds formoterol and tiotropium have docking scores of -9.297 and -9.312, respectively. It is noteworthy that plenty of the natural compounds have higher binding energies than the reference compounds like robustaflavone-4'-dimethyl ether, -10.5; cryptotanshinone, -10.2; rottlerin, -9.9 macelignan, -9.7; paeoniflorin, -9.7 for β2 receptor, and cryptotanshinone, -9.9; tetrandrine, -9.8; fisetin, -9.7; ovatodiolide, -9.5; columbianadin, -9.5 for M3 receptor.

Table 1. Assessment of the antiasthmatic activity of selected active compounds by molecular docking on β2 and M3 receptors

No	Compound's name	IUPAC name	Docking score (-) (kcal/mol)		References
			β2	M3	
1	(2'S,7'S)-O-(2-methylbutanoyl)-columbianetin (OMC)	(E)-3-(2-methylphenyl)prop-2-enamide	-7.8	-9.4	[26]
2	4-carvomenthenol	4-methyl-1-propan-2-ylcyclohex-3-en-1-ol	-6.6	-6.7	[27]
3	6-shogaol	(*E*)-1-(4-hydroxy-3-methoxyphenyl)dec-4-en-3-one	-8.8	-8.0	[28]
4	Acteoside	[(2*R*,3*R*,4*R*,5*R*,6*R*)-6-[2-(3,4-dihydroxyphenyl)ethoxy]-5-hydroxy-2-(hydroxymethyl)-4-[(2*S*,3*R*,4*R*,5*R*,6*S*)-3,4,5-trihydroxy-6-methyloxan-2-yl]oxyoxan-3-yl](*E*)-3-(3,4 dihydroxyphenyl)prop-2-enoate	-8.9	-8.5	[29]
5	Apigenin	5,7-dihydroxy-2-(4-hydroxyphenyl) chromen-4-one	-8.7	-9.0	[30]
6	Baicalein	5,6,7-trihydroxy-2-phenylchromen-4-one	-8.5	-9.2	[31]
7	Baicalin	(2*S*,3*S*,4*S*,5*R*,6*S*)-6-(5,6-dihydroxy-4-oxo-2-phenylchromen-7-yl)oxy-3,4,5-trihydroxyoxane-2-carboxylic acid	-9.4	-9.3	[32]
8	Berberine	16,17-dimethoxy-5,7-dioxa-13-azoniapentacyclo[11.8.0.0^{2,10}.0^{4,8}.0^{15,20}]henicosa-1(13),2,4(8),9,14,16,18,20-octaene	-9.6	-7.7	[33]
9	Bruceine D	(1R,2R,3R,6R,8S,12S,13S,14R,15R,16S,17R)-2,3,12,15,16-pentahydroxy-9,13,17-trimethyl-5,18-dioxapentacyclo[12.5.0.01,6.02,17.08,13]nonadec-9-ene-4,11-dione	-8.8	-9.3	[34]
10	Calcaratarin D	(3E,4S)-4-Hydroxy-3-{2-[(1S,4aS,8aS)-5,5,8a-trimethyl-2-methylenedecahydro-1-naphthalenyl]ethylidene}dihydro-2(3H)-furanone	-8.7	-9.2	[35]
11	Calycosin	7-hydroxy-3-(3-hydroxy-4-methoxyphenyl)chromen-4-one	-9.0	-8.8	[36]
12	Carvacrol	2-methyl-5-propan-2-ylphenol	-7.0	-7.0	[37]
13	Casticin	5-hydroxy-2-(3-hydroxy-4-methoxyphenyl)-3,6,7-trimethoxychromen-4-one	-8.1	-7.2	[38]
14	Cedrol	(1*S*,2*R*,5*S*,7*R*,8*R*)-2,6,6,8-tetramethyltricyclo[5.3.1.0^{1,5}]undecan-8-ol	-7.5	-8.9	[39]
15	Celastrol	(2*R*,4*aS*,6*aR*,6*aS*,14*aS*,14*bR*)-10-hydroxy-2,4*a*,6*a*,6*a*,9,14*a*-hexamethyl-11-oxo-1,3,4,5,6,13,14,14*b*-octahydropicene-2-carboxylic acid	-5.5	-5.2	[40]
16	Chrysin	5,7-dihydroxy-2-phenylchromen-4-one	-8.8	-9.3	[41]
17	Columbianadin	2-[(8*S*)-2-oxo-8,9-dihydrofuro[2,3-h]chromen-8-yl]propan-2-yl (*Z*)-2-methylbut-2-enoate	-9.3	-9.5	[42]
18	Cryptotanshinone	(1*R*)-1,6,6-trimethyl-2,7,8,9-tetrahydro-1*H*-naphtho[1,2-g][1]benzofuran-10,11-dione	-10.2	-9.9	[43]
19	Cycloastragenol	(1*S*,3*R*,6*S*,8*R*,9*S*,11*S*,12*S*,14*S*,15*R*,16*R*)-15-[(2*R*,5*S*)-5-(2-hydroxypropan-2-yl)-2-methyloxolan-2-yl]-7,7,12,16-tetramethylpentacyclo[9.7.0.0^{1,3}.0^{3,8}.0^{12,16}]octadecane-6,9,14-triol	-8.7	-4.9	[44]
20	Daphnetin	7,8-dihydroxychromen-2-one	-8.3	-7.3	[45]
21	Dehydrodieugenol	2-(2-hydroxy-3-methoxy-5-prop-2-enylphenyl)-6-methoxy-4-prop-2-enylphenol	-7.3	-7.4	[46]
22	Dehydromatricarin	[(3*aR*,4*S*,6*S*,6*aS*,9*aR*,9*bR*)-6,9-dimethyl-3-methylidene-2,7-dioxo-4,5,6,6*a*,9*a*,9*b*-hexahydro-3*aH*-azuleno[4,5-b]furan-4-yl] acetate	-8.7	-9.1	[47]
23	Deoxyvasicine	1,2,3,9-tetrahydropyrrolo[2,1-b]quinazoline	6.5	7.4	[48]

Table 1 ***(continue).*** Assessment of the antiasthmatic activity of selected active compounds by molecular docking on β2 and M3 receptors

No	Compound's name	IUPAC name	Docking score (-) (kcal/mol)		References
			β2	M3	
24	Dihydromyricetin	(2*R*,3*R*)-3,5,7-trihydroxy-2-(3,4,5-trihydroxyphenyl)-2,3-dihydrochromen-4-one	-8.0	-8.3	[49]
25	Diosgenin	(1*S*,2*S*,4*S*,5'*R*,6*R*,7*S*,8*R*,9*S*,12*S*,13*R*,16*S*)-5',7,9,13-tetramethylspiro[5-oxapentacyclo[10.8.0.0^{2,9}.0^{4,8}.0^{13,18}]icos-18-ene-6,2'-oxane]-16-ol	-9.3	-3.6	[50]
26	Dmp-butenol	(E)-4-(3',4'-dimethoxyphenyl)but-3-en-1-ol	-6.6	-6.7	[51]
27	Ellagic acid	6,7,13,14-tetrahydroxy-2,9-dioxatetracyclo[6.6.2.0^{4,16}.0^{11,15}]hexadeca-1(15),4,6,8(16),11,13-hexaene-3,10-dione	-8.4	-8.5	[52]
28	Estragole	1-methoxy-4-prop-2-enylbenzene	-6.0	-6.1	[53]
29	Ethyl p-methoxycinnamate	ethyl (*E*)-3-(4-methoxyphenyl)prop-2-enoate	-6.8	-6.9	[54]
30	Eucalyptol	1,3,3-trimethyl-2-oxabicyclo[2.2.2]octane	-6.0	-6.6	[55]
31	Farnesol	(2*E*,6*E*)-3,7,11-trimethyldodeca-2,6,10-trien-1-ol	-7.6	-7.5	[56]
32	Fisetin	2-(3,4-dihydroxyphenyl)-3,7-dihydroxychromen-4-one	-8.2	-9.7	[57]
33	FLLL31	(1*E*,6*E*)-1,7-bis(3,4-dimethoxyphenyl)-4,4-dimethylhepta-1,6-diene-3,5-dione	-9.4	-8.1	[58]
34	Fucoidan	[(2*S*,3*S*,4*S*,5*S*,6*R*)-4-hydroxy-5-methoxy-2,6-dimethyloxan-3-yl] hydrogen sulfate	-5.7	-6.8	[59]
35	Fucoxanthin	(3S,3'S,5R,5'R,6S,6'R,8'R)-3,5'-Dihydroxy-8-oxo-6',7'-didehydro-5,5',6,6',7,8-hexahydro-5,6-epoxy-β,β-caroten-3'-yl acetate	-7.5	-0.7	[60]
36	Geniposide	methyl (1*S*,4*aS*,7*aS*)-7-(hydroxymethyl)-1-[(2*S*,3*R*,4*S*,5*S*,6*R*)-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]oxy-1,4*a*,5,7*a*-tetrahydrocyclopenta[c]pyran-4-carboxylate	-7.6	-7.6	[61]
37	Guggulsterone	(8*R*,9*S*,10*R*,13*S*,14*S*,17*Z*)-17-ethylidene-10,13-dimethyl-1,2,6,7,8,9,11,12,14,15-decahydrocyclopenta[a]phenanthrene-3,16-dione	-8.9	-8.9	[62]
38	Citronellol	3,7-dimethyloct-6-en-1-ol	-6.2	-5.8	[63]
39	Hypophyllanthin	(7*R*,8*R*,9*S*)-9-(3,4-dimethoxyphenyl)-4-methoxy-7,8-bis(methoxymethyl)-6,7,8,9-tetrahydrobenzo[g][1,3]benzodioxole	-8.0	-6.8	[64]
40	Icariin	5-hydroxy-2-(4-methoxyphenyl)-8-(3-methylbut-2-enyl)-7-[(2*S*,3*R*,4*S*,5*S*,6*R*)-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]oxy-3-[(2*S*,3*R*,4*R*,5*R*,6*S*)-3,4,5-trihydroxy-6-methyloxan-2-yl]oxychromen-4-one	-9.0	-5.8	[65]
41	Imperatorin	9-(3-methylbut-2-enoxy)furo[3,2-g] chromen-7-one	-8.2	-9.2	[66]
42	Isoliquiritigenin	(*E*)-1-(2,4-dihydroxyphenyl)-3-(4-hydroxyphenyl)prop-2-en-1-one	-8.7	-8.5	[67]
43	Isoquercitrin	2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-3-[(2*S*,3*R*,4*S*,5*S*,6*R*)-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]oxychromen-4-one	-7.4	-8.8	[68]
44	LicochalconeA	(*E*)-3-[4-hydroxy-2-methoxy-5-(2-methylbut-3-en-2-yl)phenyl]-1-(4-hydroxyphenyl)prop-2-en-1-one	-8.2	-8.4	[69]
45	Ligustrazine	2,3,5,6-tetramethylpyrazine	-5.3	-5.8	[70]
46	Linalool	3,7-dimethylocta-1,6-dien-3-ol	-6.0	-6.0	[71]

Table 1 ***(continue).*** Assessment of the antiasthmatic activity of selected active compounds by molecular docking on β2 and M3 receptors

No	Compound's name	IUPAC name	Docking score (-) (kcal/mol)		References
			β2	M3	
47	Luteolin	2-(3,4-dihydroxyphenyl)-5,7-dihydroxychromen-4-one	-8.5	-9.3	[72]
48	Macelignan	4-[(2*S*,3*R*)-4-(1,3-benzodioxol-5-yl)-2,3-dimethylbutyl]-2-methoxyphenol	-9.7	-9.0	[73]
49	Magnolol	2-(2-hydroxy-5-prop-2-enylphenyl)-4-prop-2-enylphenol	-8.4	-8.4	[74]
50	Mangiferin	1,3,6,7-tetrahydroxy-2-[(2*S*,3*R*,4*R*,5*S*,6*R*)-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]xanthen-9-one	-8.7	-6.4	[75]
51	Menthone	(2*S*,5*R*)-5-methyl-2-propan-2-ylcyclohexan-1-one	-6.0	-6.6	[76]
52	Morin	2-(2,4-dihydroxyphenyl)-3,5,7-trihydroxychromen-4-one	-8.2	-8.4	[77]
53	Myrtenol	(6,6-dimethyl-2-bicyclo[3.1.1]hept-2-enyl)methanol	-6.4	-6.6	[78]
54	Narciclasine	(2*S*,3*R*,4*S*,4*aR*)-2,3,4,7-tetrahydroxy-3,4,4*a*,5-tetrahydro-2*H*-[1,3]dioxolo[4,5-j]phenanthridin-6-one	-8.2	-8.4	[79]
55	Nepetin	2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-6-methoxychromen-4-one	-8.3	-8.4	[80]
56	Nujiangexanthone A	1,2,5,6-tetrahydroxy-3-methoxy-4,7,8-tris(3-methylbut-2-enyl)xanthen-9-one	-8.2	-5.3	[81]
57	Oleanolic acid	(4*aS*,6*aR*,6*aS*,6*bR*,8*aR*,10*S*,12*aR*,14*bS*)-10-hydroxy-2,2,6*a*,6*b*,9,9,12*a*-heptamethyl-1,3,4,5,6,6*a*,7,8,8*a*,10,11,12,13,14*b*-tetradecahydropicene-4*a*-carboxylic acid	-5.6	-0.9	[82]
58	Oleic acid	(*Z*)-octadec-9-enoic acid	-7.3	-7.1	[83]
59	Oroxylin A	5,7-dihydroxy-6-methoxy-2-phenylchromen-4-one	-8.0	-8.2	[84]
60	Osthole	7-methoxy-8-(3-methylbut-2-enyl)chromen-2-one	-7.4	-8.9	[85]
61	Ovatodiolide	(1*S*,3*E*,5*R*,9*S*,12*E*)-3,12-dimethyl-8-methylidene-6,18-dioxatricyclo[14.2.1.$0^{5,9}$]nonadeca-3,12,16(19)-triene-7,17-dione	-8.2	-9.5	[86]
62	Oxyresveratrol	4-[(*E*)-2-(3,5-dihydroxyphenyl)ethenyl]benzene-1,3-diol	-9.3	-8.2	[87]
63	Paeoniflorin	[(1*R*,2*S*,3*R*,5*R*,6*R*,8*S*)-6-hydroxy-8-methyl-3-[(2*S*,3*R*,4*S*,5*S*,6*R*)-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]oxy-9,10-dioxatetracyclo[4.3.1.$0^{2,5}$.$0^{3,8}$]decan-2-yl]methyl benzoate	-9.7	-9.0	[88]
64	Phyllanthin	4-[(2*S*,3*S*)-3-[(3,4-dimethoxyphenyl)methyl]-4-methoxy-2-(methoxymethyl)butyl]-1,2-dimethoxybenzene	-8.0	-6.8	[89]
65	Piscroside A	[(1*R*,4*R*,5*S*,6*R*,7*R*,8*S*,9*S*)-5-chloro-3-hydroxy-9-[(2*S*,3*R*,4*S*,5*S*,6*R*)-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]oxy-2,10-dioxatricyclo[5.3.1.$0^{4,8}$]undecan-6-yl] 4-hydroxy-3-methoxybenzoate	-9.2	-9.2	[90]
66	Praeruptorin E	[(9*S*,10*S*)-8,8-dimethyl-10-(3-methylbutanoyloxy)-2-oxo-9,10-dihydropyrano[2,3-f]chromen-9-yl] (*Z*)-2-methylbut-2-enoate	-9.0	-8.3	[91]
67	Protocatechuic acid	3,4-dihydroxybenzoic acid	-7.1	-6.3	[92]
68	Protostemonine	(5*Z*)-4-methoxy-3-methyl-5-[(1*S*,2*R*,3*S*,6*R*,11*S*)-3-methyl-11-[(2*S*,4*S*)-4-methyl-5-oxooxolan-2-yl]-5-oxa-10-azatricyclo[8.3.0.$0^{2,6}$]tridecan-4-ylidene]furan-2-one	-8.8	-2.9	[93]
69	Puerarin	7-hydroxy-3-(4-hydroxyphenyl)-8-[(2*S*,3*R*,4*R*,5*S*,6*R*)-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]chromen-4-one	-8.9	-7.2	[94]

Table 1 ***(continue).*** Assessment of the antiasthmatic activity of selected active compounds by molecular docking on β2 and M3 receptors

No	Compound's name	IUPAC name	Docking score (-) (kcal/mol)		References
			β2	M3	
70	Pyrroloquinoline quinone	4,5-dioxo-1*H*-pyrrolo[2,3-f]quinoline-2,7,9-tricarboxylic acid	-8.8	-8.3	[95]
71	Quercetin	2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxychromen-4-one	-8.2	-8.6	[96]
72	Robustaflavone-7,4'-dimethyl ether	5,7-dihydroxy-6-[5-(5-hydroxy-7-methoxy-4-oxochromen-2-yl)-2-methoxyphenyl]-2-(4-hydroxyphenyl)chromen-4-one	-10.5	-2.5	[97]
73	Roseoside	(4*S*)-4-hydroxy-3,5,5-trimethyl-4-[(*E*,3*R*)-3-[(2*R*,3*R*,4*S*,5*S*,6*R*)-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]oxybut-1-enyl]cyclohex-2-en-1-one	-8.4	-8.1	[98]
74	Rosmarinic acid	(2*R*)-3-(3,4-dihydroxyphenyl)-2-[(*E*)-3-(3,4-dihydroxyphenyl)prop-2-enoyl]oxypropanoic acid	-9.2	-8.9	[99]
75	Rottlerin	(*E*)-1-[6-[(3-acetyl-2,4,6-trihydroxy-5-methylphenyl)methyl]-5,7-dihydroxy-2,2-dimethylchromen-8-yl]-3-phenylprop-2-en-1-one	-9.9	-6.9	[100]
76	S-allyl cysteine	(2*R*)-2-amino-3-prop-2-enylsulfanylpropanoic acid	-5.1	-4.8	[101]
77	Safranal	2,6,6-trimethylcyclohexa-1,3-diene-1-carbaldehyde	-6.6	-6.6	[102]
78	Sarsasapogenin	(1*R*,2*S*,4*S*,5'*S*,6*R*,7*S*,8*R*,9*S*,12*S*,13*S*,16*S*,18*R*)-5',7,9,13-tetramethylspiro[5-oxapentacyclo[10.8.0.0^{2,9}.0^{4,8}.0^{13,18}]icosane-6,2'-oxane]-16-ol	-7.9	-4.0	[103]
79	Schisandrin B	3,4,5,19-tetramethoxy-9,10-dimethyl-15,17-dioxatetracyclo[10.7.0.0^{2,7}.0^{14,18}]nonadeca-1(19),2,4,6,12,14(18)-hexaene	-7.2	-7.6	[104]
80	Schisandrol A	3,4,5,14,15,16-hexamethoxy-9,10-dimethyltricyclo[10.4.0.0^{2,7}]hexadeca-1(16),2,4,6,12,14-hexaen-9-ol	-7.0	-6.5	[105]
81	Sesamol	1,3-benzodioxol-5-ol	-6.4	-5.7	[106]
82	Silymarin	3,5,7-trihydroxy-2-[3-(4-hydroxy-3-methoxyphenyl)-2-(hydroxymethyl)-2,3-dihydro-1,4-benzodioxin-6-yl]-2,3-dihydrochromen-4-one	-9.2	-9.3	[107]
83	Sinapic acid	(*E*)-3-(4-hydroxy-3,5-dimethoxyphenyl)prop-2-enoic acid	-7.4	-7.1	[108]
84	Sinigrin	potassium;[(*E*)-1-[(2*S*,3*R*,4*S*,5*S*,6*R*)-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]sulfanylbut-3-enylideneamino] sulfate	-6.3	-6.9	[109]
85	Solasodine	(1*S*,2*S*,4*S*,5'*R*,6*R*,7*S*,8*R*,9*S*,12*S*,13*R*,16*S*)-5',7,9,13-tetramethylspiro[5-oxapentacyclo[10.8.0.0^{2,9}.0^{4,8}.0^{13,18}]icos-18-ene-6,2'-piperidine]-16-ol	-9.0	-3.6	[110]
86	Sophoraflavanone G	(2*S*)-2-(2,4-dihydroxyphenyl)-5,7-dihydroxy-8-[(2*R*)-5-methyl-2-prop-1-en-2-ylhex-4-enyl]-2,3-dihydrochromen-4-one	-8.5	-9.0	[111]
87	Sophoricoside	5,7-dihydroxy-3-[4-[(2*S*,3*R*,4*S*,5*S*,6*R*)-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]oxyphenyl]chromen-4-one	-9.6	-8.2	[112]
88	Spilanthol (SP)	(2*E*,6*Z*,8*E*)-*N*-(2-methylpropyl)deca-2,6,8-trienamide	-7.4	-7.2	[113]
89	Synephrine	4-[1-hydroxy-2-(methylamino)ethyl]phenol	-7.0	-6.2	[114]
90	Syringin	(2*R*,3*S*,4*S*,5*R*,6*S*)-2-(hydroxymethyl)-6-[4-[(*E*)-3-hydroxyprop-1-enyl]-2,6-dimethoxyphenoxy]oxane-3,4,5-triol	-7.4	-6.9	[115]
91	Tetrandrine	(1*S*,14*S*)-9,20,21,25-tetramethoxy-15,30-dimethyl-7,23-dioxa-15,30-diazaheptacyclo[22.6.2.2^{3,6}.1^{8,12}.1^{14,18}.0^{27,31}.0^{22,33}]hexatriaconta-3(36),4,6(35),8,10,12(34),18,20,22(33),24,26,31-dodecaene	-4.8	-9.8	[116]

Table 1 ***(continue).*** Assessment of the antiasthmatic activity of selected active compounds by molecular docking on β2 and M3 receptors

No	Compound's name	IUPAC name	Docking score (-) (kcal/mol)		References
			β2	M3	
92	Thymol	5-methyl-2-propan-2-ylphenol	-6.4	-6.8	[117]
93	Tomatidine	(1*R*,2*S*,4*S*,5'*S*,6*S*,7*S*,8*R*,9*S*,12*S*,13*S*,16*S*,18*S*)-5',7,9,13-tetramethylspiro[5-oxapentacyclo[10.8.0.0^{2,9}.0^{4,8}.0^{13,18}]icosane-6,2'-piperidine]-16-ol	-8.4	-4.8	[118]
94	Trans-anethole	1-methoxy-4-[(*E*)-prop-1-enyl]benzene	-6.2	-6.2	[119]
95	Vasicine	(3*S*)-1,2,3,9-tetrahydropyrrolo[2,1-b]quinazolin-3-ol	-6.6	-8.0	[120]
96	Vasicinone	(3*S*)-3-hydroxy-2,3-dihydro-1*H*-pyrrolo[2,1-b]quinazolin-9-one	-7.2	-8.2	[120]
97	Vicenin-2	5,7-dihydroxy-2-(4-hydroxyphenyl)-6,8-bis[(2*S*,3*R*,4*R*,5*S*,6*R*)-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]chromen-4-one	-8.3	-1.5	[121]
98	Vitexin	5,7-dihydroxy-2-(4-hydroxyphenyl)-8-[(2*S*,3*R*,4*R*,5*S*,6*R*)-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]chromen-4-one	-8.5	-8.7	[122]
99	Withaferin A	(1*S*,2*R*,6*S*,7*R*,9*R*,11*S*,12*S*,15*R*,16*S*)-6-hydroxy-15-[(1*S*)-1-[(2*R*)-5-(hydroxymethyl)-4-methyl-6-oxo-2,3-dihydropyran-2-yl]ethyl]-2,16-dimethyl-8-oxapentacyclo[9.7.0.0^{2,7}.0^{7,9}.0^{12,16}]octadec-4-en-3-one	-9.3	-5.7	[123]
100	Wogonin	5,7-dihydroxy-8-methoxy-2-phenylchromen-4-one	-8.9	-9.2	[124]

The intra-receptor positions of the three significant compounds with the highest binding affinities in the molecular docking for each target protein are shown in Figures 2 and 3. Obtained 2D diagrams via Discovery Studio Visualization regarding the amino acids present in the ligand binding sites and chemical bonds are also given in the figures. The chemical bonds include carbon-hydrogen bonds, π-sigma bonds, alkyl bonds and van der Waals forces. Among these, hydrogen bonds in particular contribute far more to the strength of the interaction.

Inevitably, there is presently no radical treatment for every disease including asthma. However, there exist some approaches to alleviating the symptoms of asthma by medical therapy [125].

One of the strategies is the activation of β2 receptors that promote the relaxation of smooth muscle. Although the mechanism of smooth muscle relaxation is uncertain, it may involve the phosphorylation of myosin light-chain kinase to an inactive form [8]. On the other hand, the release of acetylcholine by the vagus nerve activates M3 receptors, triggering an increase in intracellular Ca^{+2} concentration. Eventually, smooth muscle contraction occurs and airway tone increases. Thereby, β2 agonists and M3 antagonists contribute to relaxing airway bronchoconstriction (Figure 1) [6]. Apart from bronchoconstriction, asthma also possesses an immunological involvement. Even though the inflammatory basis of asthma is not entirely understood, the Th-2-mediated immune response is known to be associated. Thus, either lessening inflammation or bronchodilation are among the most valuable therapeutic strategies in asthma [5].

In addition to their therapeutic benefits, pharmaceuticals prescribed for asthma entail a variety of negative side effects. Hence, novel effective natural alternatives with minimal side effects are required. In this context, the effects of many plant-derived substances on the treatment of asthma have already been investigated in previous studies [126–130]. Once evaluating the effects of plant compounds on the immunopathological aspects, it has been depicted that the phytochemicals inhibit certain mediators involved particularly in asthma, such as Ig E, IL-4, IL-5 and eosinophils [126,127]. On the other hand, not much is known about the capacity of phytochemicals to alleviate bronchoconstriction. That is why,

the current study is focused on B2 and M3 receptors due to their involvement in bronchodilation, which aids asthma treatment.

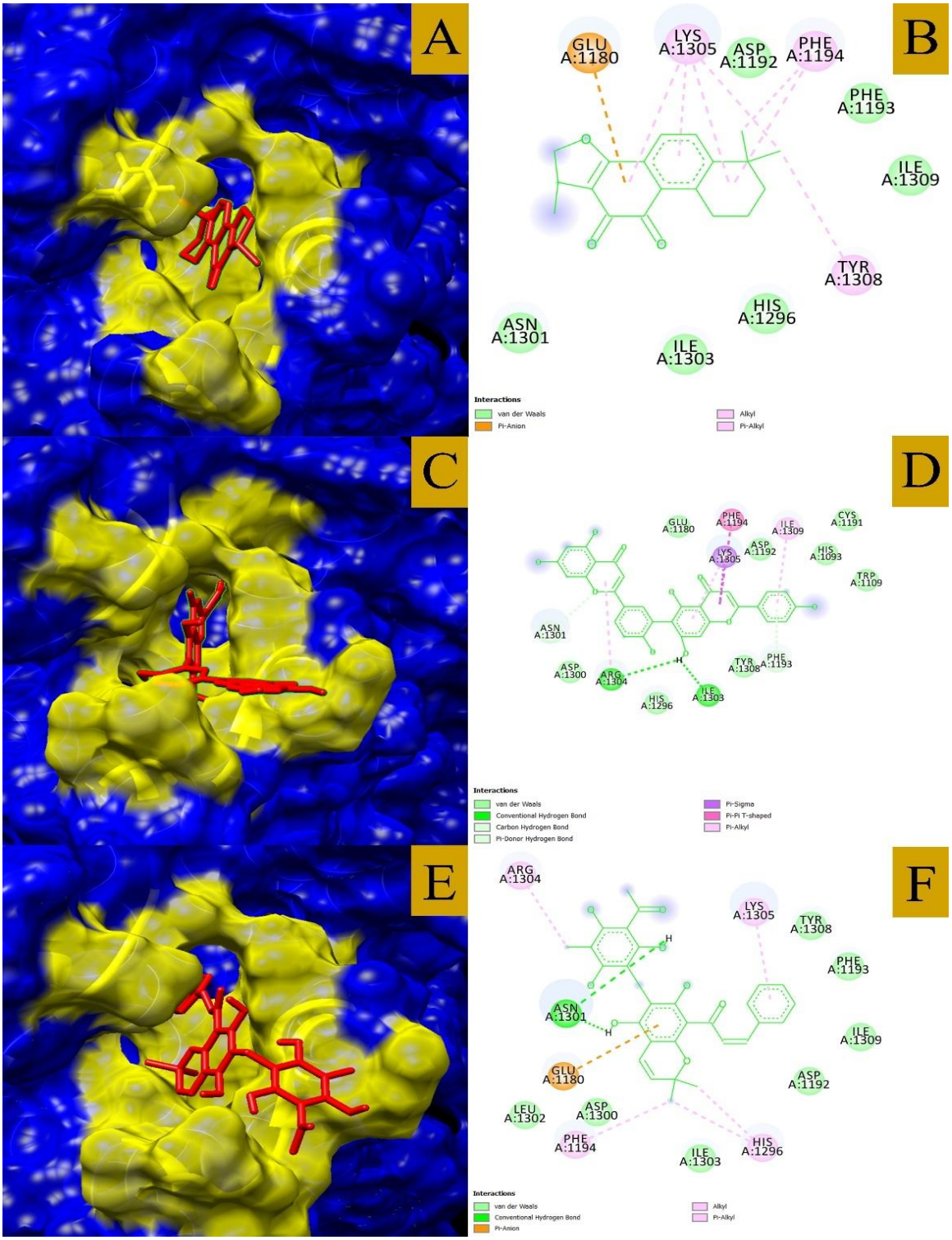

Figure 2. Molecular docking diagram of chemical composition to 6MXT (β2 receptor) and their 2D diagram of ligand binding site atoms of cryptotanshinone (A, B), robustaflavone-4'-dimethyl ether (C, D), rottlerin (E, F)

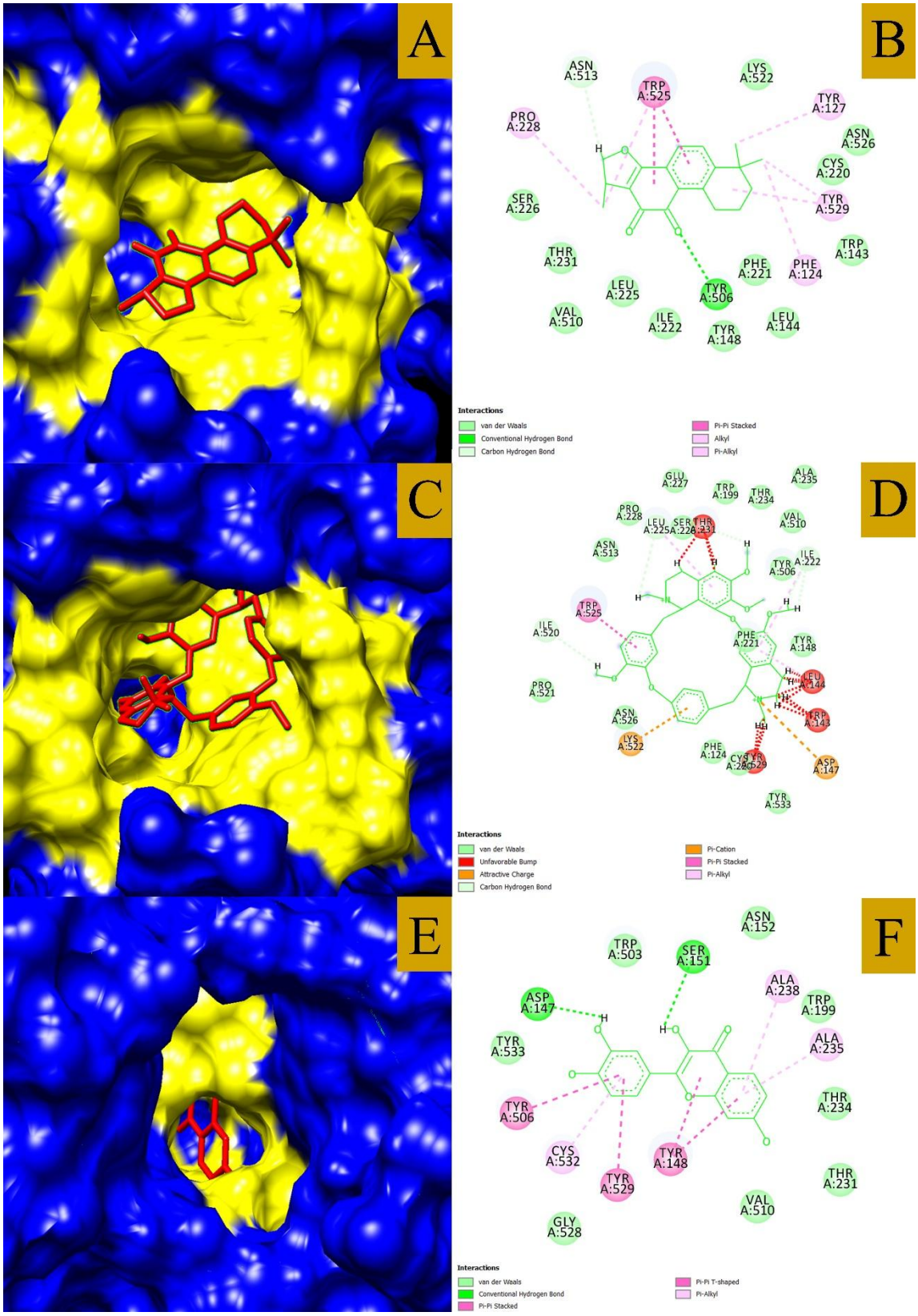

Figure 3. Molecular docking diagram of chemical composition to 4U15 (M3 receptor) and their 2D diagram of ligand binding site atoms of cryptotanshinone (A, B), tetrandrine (C, D), fisetin (E, F)

The docking score obtained is inversely proportional to the affinity of a molecule to a receptor. With the current *in silico* studies, comprehending the mode of action of 100 compounds that exhibit potential efficacy in asthma management was aimed. According to the results, the compounds have different affinities for β2 and M3 receptors. Considering the docking scores of formoterol (-9.297) and tiotropium (-9.312) -the established ligands for the target molecules β2 and M3 receptors, respectively- compounds with lower docking scores are encouraging.

Table 2. Molecular docking results of compounds with docking scores of -9 and above against each protein (β2 and M3 receptor)

Compounds	β2 receptor	M3 receptor	H-bond form with binding β2's residues	H-bond form with binding M3's residues
Baicalin	-9.4	-9.3	His1296, Ile1303, Asn1301, Phe1193	Tyr148, Ile222, Tyr506, Ala235
Berberine	-9.6	-7.7	Asn1301, Lys1305, Asp1192	Ser226, Pro228, Val510
Calycosin	-9.0	-8.8	Tyr1308, Cys1191	Asp147, Tyr529, Cys532
Columbianadin	-9.3	-9.5	Phe1193	Tyr539, Tyr148, Ala235
Cryptotanshinone	-10.2	-9.9	0	Tyr506, Asn513
Diosgenin	-9.3	-3.6	Phe1193, Cys1191	Tyr506
Flll31	-9.4	-8.1	Ser1207	Lys522, Cys220, Tyr127, Leu144, Thr234
Icariin	-9.0	-5.8	Asn1312, Thr1195, His1296, Val1297, Asn1301	Tyr148, Asn513,
Macelignan	-9.7	-9.0	Ser1207, Asn1293, Ser1203, His1093	Asp147
Oxyresveratrol	-9.3	-8.2	Thr1118, Ser1203, Asn1293, Val1114, Ser1204, Thr1110	Thr234, Asp147, Ala235
Paeoniflorin	-9.7	-9.0	His1296, Ile1303	Trp525, Tyr506, Leu225, Thr231
Piscroside A	-9.2	-9.2	Phe1193	Tyr506, Tyr148, Ile222, Asn526, Thr231
Praeruptorin E	-9.0	-8.3	Lys1305, His1296	Lys522,
Robustaflavone-4'-dimethyl ether	-10.5	-2.5	Arg1304, Ile1303, Asn1301, Phe1193	Leu225, Tyr148, Tyr506, Asn152, Asn526
Rosmarinic acid	-9.2	-8.9	Asn1312, Tyr1316, Trp1313, Phe1193, His1093	Trp199, Asn152, Ser151, Thr231, Asn507, Tyr529
Rottlerin	-9.9	-6.9	Asn1301	Asn507, Ile222
Silymarin	-9.2	-9.3	Asp1113, His1093, Asp1192, Lys1305, His1296, Asp1192	Trp525, Tyr506, Leu225, Thr231, Ala235
Solasodine	-9.0	-3.6	Cys1191	Tyr506
Sophoricoside	-9.6	-8.2	Gly1090, Asn1312, Phe1193	Ala238, Ile222, Tyr148, Asn152
Withaferin A	-9.3	-5.7	Asn1312, Asn1301	Ile222, Ser151
Omc	-7.8	-9.4	Phe1193	Ser151, Asn152
Apigenin	-8.7	-9.0	Tyr1316, Gly1090, Phe1193	Tyr529, Thr231
Baicalein	-8.5	-9.2	Tyr1316, Trp1313, Gly1090, Phe1193	Asn507, Thr231
Bruceine D	-8.8	-9.3	Ile1303, Glu1180, Phe1194	Tyr506
Calcaratarin D	-8.7	-9.2	His1296	Asp147
Chrysin	-8.8	-9.3	Phe1193, Trp1313	Asn507, Ala235
Dehydromatricarin	-8.7	-9.1	His1296, Asn1301	Lys522, Ile222, Phe221
Fisetin	-8.2	-9.7	Phe1193, Asp1113, Tyr1316,	Asp147, Ser151
Imperatorin	-8.2	-9.2	Asp1113, Phe1193, Trp1313	Tyr506
Luteolin	-8.5	-9.3	Ser1207, Val1114	Asp147, Ala235
Ovatodiolide	-8.2	-9.5	0	Tyr529, Tyr506
Sophoraflavanone G	-8.5	-9.0	Phe1193, Thr1195, Phe1194	Ser226, Leu225, Tyr529
Tetrandrine	-4.8	-9.8	Asn1301, Asp1192, Asp1300	Ile520, Leu225, Thr231, Ile222
Wogonin	-8.9	-9.2	Tyr1308, Thr1195, Val1114	Asn507, Tyr148, Thr234

The following compounds have superior docking scores according to the reference value of -9.297 on the β2 receptors: robustaflavone-4'-dimethyl ether, -10.5; cryptotanshinone, -10.2; rottlerin, -9.9; paeoniflorin, -9.7; macelignan, -9.7; sophoricoside, -9.6; berberine, -9.6; FLLL31, -9.4; baicalin, -9.4; columbianadin, -9.3; diosgenin, -9.3; oxyresveratrol, -9.3; withaferin A, -9.3; rosmarinic acid, -9.2. Among them, paeoniflorin has been demonstrated to relax the airway via B2 receptors [127-133]. Besides, β2 receptor interaction of rosmarinic acid has been evidenced both *in vitro* and by molecular docking [134]. Consistency with the aforementioned literature data suggests that the other substances that have not been experimentally proven yet are likewise associated with the β2 receptors. On the other hand, experimental studies with berberine conducted in an organ bath indicates that the bronchodilation is not correlated with the β2 receptor [135,136]. This could be as a result of the fact that studies on molecular docking do not always accurately depict the practice. Another promising phytochemical rottlerin has been shown to be associated with the K channel, however, its association with β2 receptor has not been investigated [137]. Due to the fact that a molecule may have multiple mechanisms of action, hence, additional research is required to explore the relationship between the compound and the β2 receptors.

The molecules that yielded docking scores of -9.282 and lower on the M3 receptor are as follows: cryptotanshinone, -9.9; tetrandrine, -9.8; fisetin, -9.7; columbianadin, -9.5; ovatodiolide, -9.5; (2'S,7'S)-O-(2-methylbutanoyl)-columbianetin (OMC), -9.4; baicalin, -9.3; bruceine D, -9.3; chrysin, -9.3; luteolin, 9.3; silymarin, -9.3; paeoniflorin, -9.0. According to the literature, fisetin is involved in the relaxation of acetylcholine-precontracted airway smooth muscle by dual inhibition of PLCβ and PDE4 [138]. PLCβ is indirectly associated with the M3 receptor, suggesting that the efficiency of fisetin may be M3-related. Another active compound, luteolin relaxes the bronchi probably by inhibiting PDE activity and decreasing the amount of Ca^{+2} in the trachealis [139]. Although paeoniflorin has been documented to be active via β2, the effect on the M3 receptor has not been evaluated [133]. A comparison of the affinity of these compounds for β2 and M3 is displayed (Table 2). It should be highlighted that several compounds appear to have an affinity for both proteins, necessitating further research.

In silico approaches have been established as an efficient component of various drug development programs, from lead discovery to optimization. A variety of methodologies, including computational screening based on ligands or targets, are frequently implemented in this type of investigation. Docking results provide information about the binding energy and the interaction between the ligand and macromolecule. However, they do not state whether or not this is an agonist/antagonist interaction [140]. While image analysis allows us partially make predictions in this regard, it is not a quantitative approach. By conducting molecular dynamics, more trustworthy data may be obtained about the type of interaction.

X-ray crystallography was preferred in selecting the target protein since X-ray crystallography is an efficient process that yields high-resolution structural data at the atomic level. What is more, resolution rates were maintained low suggesting the study was trustworthy. The adequate length of the amino acid chain of the protein was also taken into consideration. The existence of a small molecule in the X-ray structure that represents the receptor's ligand, which was utilized as a reference to establish the grid box, was an important factor in the protein selection process. Despite the fact that the X-ray structure of the β2 receptor was derived from human cells, X-ray structure of the M3 receptor could be acquired only from rat cells due to the lack of literature. For the sake of data validity, comparability, and particularly public health, it would be ideal if both protein structures were of human origin.

The evaluation of drug-like properties is essential in drug discovery and development. Key parameters include molecular weight (MW), which should ideally be ≤500 g/mol to satisfy Lipinski's rule of five; hydrogen bond acceptors (HBA) and donors (HBD), with thresholds of ≤10 and ≤5, respectively. MLogP, representing lipophilicity, should be ≤5 for optimal bioavailability. Gastrointestinal (GI) absorption indicates the likelihood of intestinal uptake, while BBB permeability predicts a compound's ability to cross the blood-brain barrier. P-glycoprotein (P-gp) substrate status and CYP450 enzyme inhibition assess potential drug efflux and metabolism-related interactions, respectively.

Table 3. The pharmacokinetic properties of the 34 promising substances (the SwissADME platform)

	MW (g/mol)	H-Bond Acceptor/ Donor	MLogP	GI Absorption	BBB Permeant/ P-gp Substrate	CYP Enzymes inhibitor*	Skin Permeation (Log Kp. cm/s)	Druglikeness Lipinski Filter	Oral Bioavailability Score (F%)
Apigenin	270.24	5/3	1.89	High	No/No	a, d, e	-5.80	Yes	0.55
Baicalein	270.24	5/3	2.43	High	No/No	a, d, e	-5.70	Yes	0.55
Baicalin	446.36	11/6	1.75	Low	No/Yes		-8.23	No	0.11
Berberine	336.36	4/0	0	High	Yes/Yes	a, d, e	-5.78	Yes	0.55
Bruceine D	410.42	9/5	-0.49	Low	No/Yes		-10.52	Yes	0.55
Calcaratarin D	318.45	3/1	3.23	High	Yes/No	b, c	-5.27	Yes	0.55
Calycosin	284.26	5/2	2.40	High	No/No	a, d, e	-6.30	Yes	0.55
Chrysin	254.24	4/2	2.27	High	Yes/No	a, d, e	-5.35	Yes	0.55
Columbianadin	328.36	5/0	3.51	High	Yes/No	a, b, c, e	-5.68	Yes	0.55
Cryptotanshinone	296.36	3/0	2.81	High	Yes/Yes	a, b, c, e	-5.41	Yes	0.85
Dehydromatricarin	304.34	5/0	2.15	High	Yes/Yes		7.06	Yes	0.55
Diosgenin	414.62	3/1	4.49	High	Yes/No		-4.80	Yes	0.55
Fisetin	286.24	6/4	1.50	High	No/No	a, d, e	-6.65	Yes	0.55
Flll31	424.49	6/0	4.05	High	Yes/No	c, d, e	-5.50	Yes	0.55
Icariin	676.66	15/8	3.78	Low	No/Yes		-9.25	No	0.17
Imperatorin	270.28	4/0	3.05	High	Yes/No	a, b, c	-5.46	Yes	0.55
Luteolin	286.24	6/4	1.86	High	No/No	a, d, e	-6.25	Yes	0.55
Macelignan	328.40	4/1	3.82	High	Yes/No	b, c, d	-4.64	Yes	0.55
Omc	161.20	1/1	1.65	High	Yes/No		-6.09	Yes	0.55
Ovatodiolide	328.40	4/0	2.71	High	Yes/No	b, c	-6.61	Yes	0.55
Oxyresveratrol	244.24	4/4	1.44	High	No/No	a, c, e	-5.82	Yes	0.55
Paeoniflorin	480.46	11/5	2.49	Low	No/Yes		-9.96	Yes	0.55
Piscroside A	548.92	13/6	1.97	Low	No/No		-9.79	No	0.17
Praeruptorin E	428.47	7/0	3.88	High	No/No	b, c, e	-5.78	Yes	0.55
Robustaflavone-4'-dimethyl ether	566.51	10/4	4.11	Low	No/No	c	-5.72	Yes	0.55
Rosmarinic acid	360.31	8/5	1.48	Low	No/No		-6.82	Yes	0.56
Rottlerin	516.54	8/5	3.57	Low	No/No	b	-5.25	Yes	0.55
Silymarin	482.44	10/5	2.79	Low	No/No	e	-7.89	Yes	0.55
Solasodine	413.64	3/2	4.26	High	Yes/Yes		-5.00	Yes	0.55
Sophoraflavanone G	424.49	6/4	3.14	High	No/No	c, e	-4.79	Yes	0.55
Sophoricoside	432.38	10/6	2.21	Low	No/No		-8.33	Yes	0.55
Tetrandrine	622.75	8/0	5.23	High	No/No		-5.37	Yes	0.55
Withaferin A	470.60	6/2	3.24	High	No/Yes		-6.45	Yes	0.55
Wogonin	284.26	5/2	2.55	High	No/No	a, c, d, e	-5.56	Yes	0.55

*CYP enzymes correspond to a-CYP1A2, b-CYP2C19, c-CYP2C9, d-CYP2D6, e-CYP3A4.

Table 4. The toxicological properties of the 34 promising substances (the ADMETLab 3.0 platform)

	hERG Blockers	Drug-Induced Liver Injury (DILI)	AMES Toxicity	Rat Oral Acute Toxicity	Skin Sensitization	Carcino-genicity	Respiratory	Human Hepato-toxicity	Drug-induced Nephro-toxicity	Drug-induced Neuro-toxicity	Oto-toxicity	Hemato-toxicity
Apigenin	(+)	(++)	(+)	(+)	(++)	(++)	(+)	(---)	(---)	(---)	(---)	(---)
Baicalein	(--)	(+++)	(++)	(+)	(+++)	(++)	(++)	(+)	(---)	(---)	(+)	(---)
Baicalin	(---)	(+++)	(+)	(---)	(+++)	(---)	(---)	(+)	(++)	(---)	(+)	(--)
Berberine	(-)	(---)	(+)	(+++)	(+++)	(++)	(+++)	(---)	(---)	(---)	(---)	(---)
Bruceine D	(---)	(+)	(++)	(+++)	(+++)	(---)	(+++)	(+)	(+++)	(---)	(+++)	(+)
Calcaratarin D	(--)	(-)	(+)	(+++)	(+++)	(+++)	(---)	(+++)	(+++)	(+)	(++)	(+)
Calycosin	(--)	(+)	(+)	(+)	(+)	(++)	(++)	(+)	(--)	(+)	(+)	(---)
Chrysin	(---)	(+++)	(+)	(+)	(+)	(++)	(++)	(+)	(---)	(---)	(---)	(---)
Columbianadin	(--)	(+++)	(+++)	(++)	(+++)	(+++)	(++)	(++)	(+)	(+)	(--)	(--)
Cryptotanshinone	(---)	(+++)	(+++)	(+)	(+++)	(+++)	(+)	(+++)	(+++)	(+++)	(+++)	(+++)
Dehydromatricarin	(---)	(+++)	(+++)	(-)	(+++)	(+++)	(-)	(+)	(+)	(-)	(-)	(+++)
Diosgenin	(--)	(++)	(---)	(---)	(+++)	(+++)	(+)	(++)	(+)	(---)	(+++)	(---)
Fisetin	(---)	(++)	(+)	(+)	(++)	(++)	(++)	(+)	(---)	(---)	(+)	(---)
Flll31	(-)	(+)	(+)	(---)	(++)	(++)	(+)	(++)	(+)	(+++)	(+)	(+)
Icariin	(---)	(+++)	(+++)	(---)	(+++)	(---)	(---)	(++)	(+++)	(---)	(+++)	(---)
Imperatorin	(--)	(++)	(+)	(+)	(---)	(++)	(+)	(+)	(+)	(+)	(++)	(+)
Luteolin	(---)	(+++)	(+)	(+)	(+++)	(++)	(++)	(---)	(---)	(---)	(+)	(---)
Macelignan	(-)	(+)	(+)	(---)	(+)	(++)	(++)	(++)	(++)	(++)	(+)	(++)
Omc	(--)	(+)	(++)	(---)	(++)	(++)	(++)	(++)	(---)	(++)	(---)	(---)
Ovatodiolide	(---)	(+++)	(+)	(+)	(+++)	(++)	(---)	(+++)	(+++)	(+++)	(+)	(+)
Oxyresveratrol	(--)	(---)	(+)	(+)	(+++)	(+)	(++)	(---)	(---)	(+)	(---)	(---)
Paeoniflorin	(---)	(--)	(+++)	(---)	(+++)	(---)	(---)	(++)	(+++)	(---)	(+++)	(+)
Piscroside A	(---)	(+++)	(+++)	(---)	(+++)	(---)	(---)	(++)	(++)	(---)	(+++)	(+)
Praeruptorin E	(---)	(+++)	(+)	(+)	(++)	(++)	(+)	(++)	(++)	(---)	(+)	(+)
Robustaflavone-4'-dimethyl ether	(--)	(+++)	(+++)	(+++)	(---)	(++)	(+++)	(++)	(---)	(---)	(---)	(---)
Rosmarinic acid	(---)	(+++)	(+)	(---)	(+++)	(---)	(---)	(+++)	(+)	(---)	(+++)	(---)
Rottlerin	(---)	(---)	(+)	(---)	(+++)	(---)	(+++)	(+++)	(+)	(---)	(--)	(---)
Silymarin	(---)	(---)	(+++)	(++)	(+)	(++)	(++)	(++)	(+)	(+)	(+++)	(---)
Solasodine	(--)	(---)	(---)	(---)	(+++)	(+++)	(+)	(++)	(+)	(---)	(+++)	(---)
Sophoraflavanone G	(---)	(+)	(+++)	(+++)	(+++)	(---)	(+++)	(++)	(++)	(+)	(++)	(---)
Sophoricoside	(---)	(+++)	(+++)	(---)	(+++)	(+)	(---)	(+++)	(+++)	(---)	(+++)	(---)
Tetrandrine	(+++)	(---)	(++)	(++)	(++)	(++)	(++)	(++)	(+)	(+++)	(+)	(---)
Withaferin A	(---)	(---)	(+)	(---)	(+++)	(+++)	(++)	(---)	(+++)	(---)	(++)	(++)
Wogonin	(---)	(+++)	(+)	(+)	(+)	(++)	(+++)	(++)	(---)	(---)	(---)	(+)

Skin permeation (Log Kp) measures transdermal absorption potential, and oral bioavailability score (F%) estimates the compound's suitability for oral administration. These parameters collectively aid in determining a compound's pharmacokinetic profile and drug-likeness. Among the substances with high docking scores for the β2-adrenergic receptor (as shown in Table 2, and detailed pharmacokinetic properties of the 34 key compounds are summarized in Table 3), cryptotanshinone and macelignan meet the fundamental pharmacokinetic criteria. However, the other substances, including paeoniflorin, rottlerin, and robustaflavone-4'-dimethyl ether, can be unsuitable as drug candidates due to their high molecular weights, which limit their drug-like potential. Similarly, for the M3 muscarinic receptor, compounds such as cryptotanshinone, fisetin, tetrandrine, ovatodiolide, and columbianadin demonstrate

promising docking scores. Upon further evaluation, all compounds except for tetrandrine may be considered as viable drug candidates, however, tetrandrine's high molecular weight renders it ineligible according to conventional drug-likeness standards.

The toxicity profiles of several molecules, as presented in Table 4, reveal diverse effects across different categories. Tetrandrine, for example, has been associated with hERG blockade, which can lead to arrhythmias, a potentially harmful effect in asthma patients. Similarly, substances such as robustaflavone-4'-dimethyl ether and rottlerin, which exhibit respiratory toxicity, may significantly impact individuals with asthma. While each drug can present distinct toxic effects, the selection of a therapeutic agent must be carefully evaluated in the context of the patient's specific condition. Considering the cardiovascular and pulmonary risks associated with asthma, drug candidates like cryptotanshinone, ovatodiolide, and paeoniflorin - which exhibit minimal or no detrimental effects on these systems - may offer valuable therapeutic options. Nonetheless, it is crucial to assess the patient's other medical conditions, as these factors may influence the selection of the therapeutic molecule. Ultimately, these findings underscore the variability in toxicity profiles and highlight the need for further research to ensure the safety and therapeutic viability of these molecules.

Asthma is a medical condition characterized by bronchoconstriction accompanied by an immunological base. In the treatment, therapeutic agents with anti-inflammatory or bronchodilator properties are preferred. Even while the primary focus of our research was the bronchodilator mechanism, it is noteworthy that nearly all compounds examined in silico have been demonstrated to have anti-inflammatory characteristics in previous experiments. The ability to show both a bronchodilator and the anti-inflammatory effect of a compound has significant potential regarding the enhancement of asthma therapy.

This study is the first to investigate *in silico* the effects of active compounds from medicinal plants on bronchodilator processes, which has been demonstrated experimentally to be potentially beneficial in the treatment of asthma. β2 and M3 receptors have already been the subject of attention in the treatment of asthma owing to their alleviating properties on airway constriction. Our results suggest that evaluated plant compounds might act as bronchodilators via activating β2 receptors and inhibiting M3 receptors. The compounds apparently show promise for the future of asthma treatment. Additional research is required to confirm the bronchodilator activity and therapeutic efficacy in the management of asthma. Accordingly, the findings might provide a basis for further research on the mechanisms of action of relevant compounds.

AUTHOR CONTRIBUTIONS

Concept: F.U., S.O.A.; Design: M.Z.Ç., S.O.A.; Control: F.U., S.O.A.; Sources: M.Z.Ç., A.C.A.; Materials: - ; Data Collection and/or Processing: M.Z.Ç., A.C.A.; Analysis and/or Interpretation: M.Z.Ç., N.H.T., S.O.A.; Literature Review: M.Z.Ç., F.U.; Manuscript Writing: M.Z.Ç., N.H.T.; Critical Review: M.Z.Ç, F.U., N.H.T., A.C.A., S.O.A.; Other: -

CONFLICT OF INTEREST

The authors declare that there is no real, potential, or perceived conflict of interest for this article.

ETHICS COMMITTEE APPROVAL

The authors declare that the ethics committee approval is not required for this study.

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