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Antiemetic activity of *trans*-ferulic acid possibly through muscarinic receptors interaction pathway: *In vivo* and *in silico* study

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ABSTRACT

Current study was conducted to assess the effectiveness of the polyphenol *trans*-ferulic acid (TFA) as an antiemetic agent using *in vivo* and *in silico* methods. To evaluate this, we induced emesis in 3-day-old chicks through the oral administration of copper sulfate ($CuSO_4{\cdot}5H_2O$) at a dose of 50 mg/kg. To ascertain the potential antiemetic mechanism of TFA, we employed various reference drugs such as domperidone (6 mg/kg), ondansetron (5 mg/kg), and hyoscine (21 mg/kg) as positive control groups, while the vehicle acted as a negative control group. TFA was administered orally at the doses of 25, 50 and 100 mg/kg body weight. Both the TFA and reference drug provided alone or in combined groups to assess their synergistic or antagonistic activity on the chicks. Molecular docking of TFA and the selected reference drugs was conducted against $5HT_3$, D_2, H_1, NK_1, and mAChRs (M_1-M_5) receptors for determining binding affinity to the receptors. Active binding sites and drug-receptor interactions were predicted with the aid of various computational tools. Various pharmacokinetic features and drug-likeness of all the selected ligands were determined through the SwissADME online server. The results suggest that TFA diminishes the mean number of retches and enhances latency in the chicks at lower doses. In the combined drug therapy, TFA exhibited better antiemetic effects with ondansetron and hyoscine. *In silico* ADME proposed that TFA retains preferable drug-likeness and better pharmacokinetic properties to be a reliable lead. Additionally, TFA revealed the elevated binding affinity against mAChRs and the ligand (TFA) expressed the highest binding affinity (−7 kcal/mol) with the M_5 receptor (6OL9). In conclusion, TFA demonstrated mild antiemetic effects in chicks, possibly through the mAChRs interaction pathway.

Introduction

Emesis commonly referred as vomiting is a protective reflex accommodating to animals and humans to eject typically noxious toxins or irritants from the stomach whereas nausea is an unpleasant subjective sensation and a feeling close to vomiting [1,2]. Toxins in the lumen or gastric irritation trigger vomiting via mucosal chemoreceptors in the gastrointestinal tract (GIT) [3]. Apart from consuming toxins or irritants, several traumatic events, post-traumatic incidents, negative responses to drugs, exposure to radiation, motion sickness, and various other medical conditions can also lead to nausea and vomiting in both humans and animals [4]. Moreover, certain microorganisms and their secretions are also able to induce GI disturbances and emesis [5,6]. It is also the most prevalent undesirable effect of cancer chemotherapy and

Abbreviations: TFA, *trans*-ferulic acid; $CuSO_4{\cdot}5H_2O$, copper sulfate; 6OL9, M_5 receptor; VC, vomiting centre; NTS, nucleus tractus solitaries; CTZ, chemoreceptor trigger zone; CSF, cerebrospinal fluid; H_1, histaminergic receptor; D_2, dopaminergic receptor; 5-HT_4, 5-HT_3, 5-HT_1A, serotoninergic receptors; NK_1, neurokinin type 1 receptor.

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radiation therapy [7].

The process of emesis is quite complicated. The stimulation of the vomiting centre (VC) in the medulla oblongata causes vomiting [8]. For afferent impulses coming from the GIT, the throat, and other visceral organs, the nucleus tractus solitaries (NTS) and the chemoreceptor trigger zone (CTZ) are the most important relaying regions [9]. Due to the proximity of the NTS to the CTZ, emetogenic chemicals in the blood or cerebrospinal fluid (CSF) might immediately induce a reaction at the CTZ. CTZ is also involved in regulating food consumption, conditioned taste aversion, and GIT motility [10]. VC can be triggered by afferent inputs from the GIT or by the CTZ during emesis, and it also synchronizes the activity of smooth muscles and skeletal processes associated with emesis [11,12]. Multiple pathways can elicit the stimulus. Among these is the activation of 5-HT_3 receptors on the vagal afferent pathway, which innervates the vomiting center in response to stimulation by various endogenous or external chemical insults [12]. The stomach muscle relaxes and HCl releasing is suppressed during emesis. A backward extensive contraction of the abdominal muscles, and the relaxation of the lower esophageal sphincter, allowing contents from the stomach to be expelled through the mouth and provoke retching [13]. Neurotransmitter receptors located in the brain's VC and CTZ regions, as well as in the peripheral neural pathways linked to the vomiting reflex, comprise various types, such as histaminergic (H_1), dopaminergic (D_2), serotoninergic (5-HT_4, 5-HT_3, 5-HT_1A), and neurokinin type 1 (NK_1) receptors, in addition to different types of endorphine, adrenergic (α_2), and muscarinic acetylcholine receptors (mAChRs) [14,15] and corticosteroids, $GABA_B$, and CB_1 receptor agonists [11], which could be the target of antiemetic action.

Long-term usage of synthetic antiemetic medicines is also associated with adverse effects. Hence, the production of natural products has become a remarkable necessity in the present [16]. The search for novel antiemetic medicines derived from natural sources continues to focus on mechanism-based methods that involve distinct cellular and molecular targets. Flavonoids, cannabinoids, chalcones, glucosides, hydroxycinnamic acids, diarylheptanoids, lignans, phenylpropanoids, saponins, polysaccharides, and terpenes are some of the bioactive chemicals that fall under this group for searching for novel antiemetic drug candidates [10].

Trans-ferulic acid (TFA: *trans*-4-hydroxy-3-methoxycinnamic acid) is an organic phytochemical and a stereoisomer of ferulic acid which is extensively dispensed in nature and is obtainable in various foods of the human diet such as eggplant, tomato, peanuts, rice, wheat, banana, and pineapples, etc. [17]. TFA has a number of pharmacological activity including antimicrobial, antioxidant, anti-inflammation, antifungal, anticancer, antiallergic, antithrombotic, anticarcinogenic, hepatoprotective, nueroprotective (Alzheimer's disease), cardioprotective, and antidiabetic activities as well as used in skin disease [18–20]. Due to its potent antioxidant property, it provides a significant protective effect [21]. It has been asserted that by increasing the natural immune defense, it protects against chemotherapy-induced side effects [22]. An *in vivo* study reported that ferulic acid can be beneficial in diminishing cisplatin-mediated emesis and developing GI symptoms such as abdominal discomfort induced by cytotoxic agents [23]. In another study, ferulic acid as an isolated compound demonstrated a mild antiemetic effect in apomorphine hydrochloride induced emesis [24]. Therefore, TFA is a potential phytochemical for developing and designing as an antiemetic agent.

There are a variety of in vivo and in vitro models for evaluating the antiemetic activity of a compound or plant extract. The chick emesis model is one of them [11]. In this model, copper sulfate induces emesis in young chicks (Gallus gallus domesticus) when administered orally. The test sample or standard is administered before 30 min of copper sulfate ($CuSO_4$), either orally or peritoneally. The antiemetic activity of the test sample is evaluated by comparing the number of retches with control groups [25]. On the other hand, computational drug discovery is an efficient method for speeding up and diminishing the cost of the drug research and development process. As a result of a significant increase in the availability of data on biological macromolecules and small molecules, computational drug discovery has become applicable to almost every stage of the drug discovery and development process. This includes target identification and validation, lead discovery and optimization, and preclinical testing [26]. Docking applications must promptly and precisely evaluate protein–ligand complexes, i.e., estimate the interaction energy [27]. During early drug discovery, activity and specificities of candidate medications are often tested at an early stage, but pharmacokinetic features and toxicity are assessed at a comparatively late time [28]. However, ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) features were mostly responsible for the unfavorable efficacy and safety of several candidate therapeutics in the terminal stage [29,30]. And the failure will discourage the investigators and result in a huge loss of investment. However, this problem may be reduced through an *in silico* strategy, it has become a cost-efficient and high-throughput alternative to experimental measurement methods for predicting ADMET characteristics [31]. This study seeks to determine how effective TFA is as an antiemetic, as well as predict how it works and assess its pharmacokinetic properties using computational methods.

Materials and methods

Chemical reagents and standards

TFA (*trans*-4-hydroxy-3-methoxycinnamic acid), 99%, mixture of isomers (CAS No.537–98-4) was purchased from Sigma-Aldrich (USA), while copper sulphate pentrahydrate ($CuSO_4{\cdot}5H_2O$) was purchased from Merck (India). Reference drugs, domperidone, ondansetron and hyoscine butyl bromide were collected from Beximxo Pharma Ltd., Incepta Pharma Ltd., and Opsonin Pharma Ltd., Bangladesh, respectively.

Animals

Young chickens (Gallus gallus domesticus) of either sex, 3 days old, weighing about 40–48 gm (Grade-A) were collected from Nourish Poultry & Hatchery Ltd., Sonargaon Janapath Road, Uttara, Dhaka-1230, Bangladesh. The chickens were placed in stainless steel cages, which were opened in the upper hood and kept at room temperature with a twelve-hour light and dark cycle. They were permitted to access standard feeds and water as much as they wanted. This was done for an additional day before the experiment began and after the collection from suppliers. After 12 h of fasting, the antiemetic test was conducted. This experiment was granted by the Department of Pharmacy and approved by the Ethical Committee of Bangabadhu Sheikh Mujibur Rahman Science and Technology University (#bsmrstu-phr-t5-22).

In vivo protocols

The study was conducted with minor adjustments to the methods described by Akita et al. (1998). All the chicks were distributed into ten groups with five in each. Before being given the treatments, each bird was maintained in a large transparent plastic container for 10 min. Three doses (25, 50 and 100 mg/kg) of the test sample (TFA) were prepared by dissolving in distilled water (DW) and administered orally with the aid of a literature review. Domperidone (DOM), ondansetron (OND) and hyoscine butyl bromide (HYS) were administered orally as reference drugs at the doses of 6, 5 and 21 mg/kg b.w., respectively. Three combined doses of the reference drugs were prepared by combining with TFA (50 mg/kg) and administered orally to animals to evaluate their synergistic effect. DW was considered as negative control (NC) and given orally at a dose of 150 mg/kg b.w. After 30 min of treatment, emesis was induced through $CuSO_4{\cdot}5H_2O$ at the dose of 50 mg/kg, b.w. by administering orally to every bird. Then the latency (first

retch after giving $CuSO_4{\cdot}5H_2O$ treatment) and number of retches (within 10 min, after having $CuSO_4{\cdot}5H_2O$ treatment) were recorded carefully. The percentage increase in latency and decrease in retches inspect of NC were calculated according to the following equations:

$$\%\text{increase in latency} = \frac{P - Q}{P} \times 100$$

$$\%\text{decrease in retches} = \frac{X - Y}{X} \times 100$$

where, P = Mean of latency in seconds in standard and test groups, Q = Mean of latency in seconds in NC group, X = Mean of retches in NC group, Y = Mean of retches in standard and test groups

Statistical analysis

The values of the antiemetic activity are reported as the mean value along with the standard error of the mean (SEM). A statistical software program called Graph Pad Prism (version 6.0) was used to calculate the difference's statistical significance, which was determined using a 95% confidence interval. P values of < 0.05 were considered significant and $p < 0.0001$ was highly significant.

In silico analysis

Homology model and preparation of receptors

We have targeted 9 receptors liable for inducing emesis based on literature to conduct molecular docking and ligand-receptor visualization. Due to the unavailability of the 3D structure of the human $5HT_3$ receptor in the RCSB Protein Data Bank [32], we performed a homology model. The SWISS-MODEL was utilized to perform homology model and get human $5HT_3$ receptor [33]. The sequence of the protein (UniProt ID: P46098) was collected form the UniProt database (http://www.uniprot.org/) [34], then a BLAST assessment was conducted using the NCBI BLAST [35] tool to choose the template. The $5HT_3$ homology modeling structures were assessed by GMQE [36] and a Ramachandran plot via ProCheck [37,38]. The other receptors such as D_2 (PDB ID: 6LUQ) [39], H_1 (PDB ID: 3RZE) [40], M_1 (PDB ID: 6WJC) [12], M_2 (PDB ID: 5ZK8) [12], M_3 (PDB ID: 8EA0) [12], M_4 (PDB ID: 7V6A) [12], M_5 (PDB ID: 6OL9) [12] and NK_1 (PDB ID: 6HLO) [41] sources of *Homo sapiens* were collected from the RCSB Protein Data Bank (https://www.rcsb.org/). After collection and developing homology modeling, the receptors were optimized to avoid docking interference by deleting all unnecessary molecules, e.g., lipids, water molecules, and heteroatoms from the sequence of proteins via the PyMol software package (v2.4.1) [42,43]. Finally, energy minimization and geometry optimization of the receptors were carried out through the SwissPDB Viewer software package by appealing to the GROMOS96 force field and saving the PDB file to perform molecular docking.

Selection and preparation of ligands

With the aid of literature, we select several established and marketed antiemetic drugs as reference ligands to compare the binding affinity and molecular interaction with our test ligand (TFA) and to understand the underlying antiemetic mechanism targeting various receptors liable for inducing emesis. After selection to perform molecular docking and predict pharmacokinetic features the 3D conformers of aprepitant (APT) (Compound CID: 135413536) of NK_1 receptor blocker [44], cinnarizine (CIN) (Compound CID: 1547484) of H_1 antihistamine [45], domperidone (DOM) (Compound CID: 3151) of D_2 receptor antagonist [46], hyoscine butylbromide (HYS) (Compound CID: 3000322) of mAChRs antagonist [47], ondansetron (OND) (Compound CID: 4595) $5HT_3$ receptor antagonist [48], and *trans*-ferulic acid (TFA) (compound CID: 445858) as test ligand were collected in SDF format from the PubChem chemical database (https://pubchem.ncbi.nlm.nih.gov/). Then, the energy of the 3D conformers of the chemical agents were minimized and saved in SDF files and converted into MOL files through the Chem3D 16.0 program package for predicting pharmacokinetics. Finally, all the ligands were optimized utilizing Gaussian view software (v5.0). The 2D structures of chemical agents are exhibited in Fig. 1.

Molecular docking and prediction of ligand-receptor interactions

Molecular docking was accomplished by utilizing the PyRx software package to estimate the active binding potential of the drugs against the active sites of receptors [49]. For carrying out the docking, the grid box dimensions were set as $76.37 \times 55.95 \times 83.32$ Å along x-, y- and z-axes, respectively and the calculation was run at 200 steps [50]. The result of the docking potential is saved in '.csv' format and the complex of ligand–protein is collected in PDB format for collecting the ligand in PDBQT format. The interactions of ligand-receptors and the receptor's active site were observed under the Discovery Studio Visualizer (v21.1.020298) and PyMol (v2.4.1) program packages, and then amino acid residues, bond types, number of hydrogen bonds and the length of hydrogen bonds of every ligand-receptor interaction are listed [51,52].

Prediction of drug-likeness and pharmacokinetics

"Drug-likeness" is a qualitative measure of a molecule's potential for discovery and development into an orally bioavailable medication. For compounds far enough along in research to be considered oral medication candidates, similarity to existing drugs was shown through structural or physicochemical analysis [53,54]. Drug-likeness and pharmacokinetics of a chemical agent can be estimated through various online servers and software. In this study, we described various factors for assessing the selected molecule's physicochemical properties important in drug development with the aid of SwissADME (https://www.swissadme.ch/index.php) [54]. The SMILES file of the ligands gathered from PubChem was submitted to SwissADME (https://www.swissadme.ch) to determine grouped characteristics to assess the physicochemical qualities, lipophilicity, pharmacokinetics, and drug-likeness.

Results

In vivo investigation

In our experiment, different doses of TFA significantly diminished the number of retches and latent period of retch in the bird. The lowest dose (25 mg/kg) of TFA exhibited first retch at 74.25 s (values are mean), where the latency gradually decreased with the increased of dose in the test sample such as highest dose (100 mg/kg) demonstrated first retch at 10.33 s. Very rapid retching was observed in the vehicle group, in this group first retch was observed at 7.5 s. The combined drug therapy (reference drug plus test sample) expressed higher latent period than the drug (reference) administered alone, such as first retching was observed in the DOM + TFA-50 group at 76.67 s where the DOM group exhibited first retch at 60.4 s. The onset of retch in other groups observed at 15.67, 11.00, 36.67 and 34.00 s for OND, HYS, OND + TFA-50 and HYS + TFA-50 groups respectively (Fig. 2).

The highest number of retches was observed in the vehicle group (mean value: 63.75). The number of retches gradually diminished in the test sample with increasing doses, such as TFA-25, TFA-50 and TFA-100 exhibited 25.00, 20.33 and 17.00 retches, respectively. Combination drug therapy also demonstrated a reduction in the number of retches in comparison with administering it alone. The lowest number of retches revealed in TFA-50 + DOM group (mean values: 9.33). The number of retches of all the treatment groups is exhibited in Fig. 3.

The percentage increase in latency compared to the NC group for the test groups was calculated as 89.90, 47.66 and 27.40 % for the TFA-25, TFA-50 and TFA-100 groups, respectively. Though a reduction of % increase in latency observed in the test sample with the elevation of dose, the combination therapy demonstrated a remarkable elevation in the % increase in latency. The highest percentage increase in latency

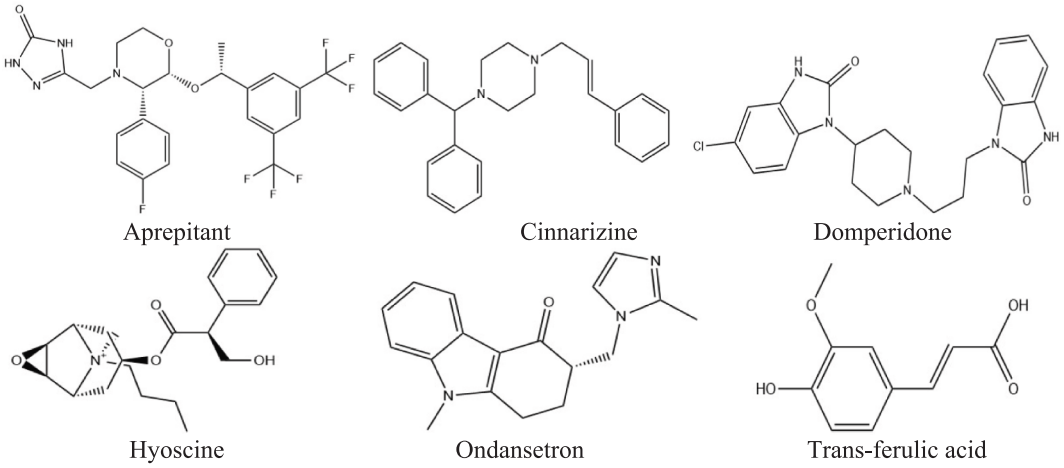

Fig. 1. Structures of *trans*-ferulic acid and selected reference drugs screened against the emesis inducing receptors.

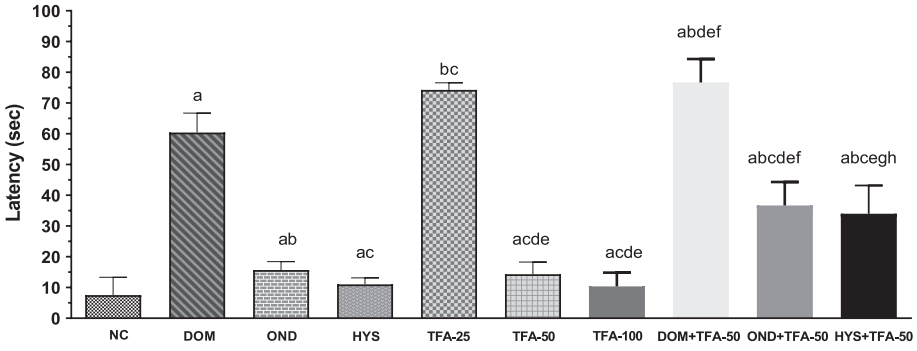

Fig. 2. Latency (sec) of retches observed in test sample, controls and combinations [Values are mean ± S.E.M. (n = 5). [a]compared to the NC (vehicle), [b]compared to the DOM (positive control: Domperidone); [c]compared to the OND (positive control: Ondansetron); [d]compared to the HYS (positive control: Hyoscine hydrobromide); [e]compared to the *trans*-ferulic acid (TFA)-25; [f]compared to the TFA-50; [g]compared to the TFA-100; [h]compared to the DOM + TFA-50; $p < 0.05$ (DOM vs DOM + TFA-50, OND vs HYS + TFA-50, TFA-50 vs HYS + TFA-50); $p < 0.01$ (OND vs OND + TFA-50, HYS vs HYS + TFA-50, TFA-50 vs OND + TFA-50, TFA-100 vs HYS + TFA-50); $p < 0.001$ (NC vs HYS + TFA-50, DOM vs OND + TFA-50, DOM vs HYS + TFA-50, HYS vs OND + TFA-50, TFA-100 vs OND + TFA-50); $p < 0.0001$ (NC vs DOM, NC vs TFA-25, NC vs DOM + TFA-50, NC vs OND + TFA-50, DOM vs OND, DOM vs HYS, DOM vs TFA-50, DOM vs TFA-100, OND vs TFA-25, OND vs DOM + TFA-50, HYS vs TFA-25, HYS vs DOM + TFA-50, TFA-25 vs TFA-50, TFA-25 vs TFA-100, TFA-25 vs OND + TFA-50, TFA-25 vs HYS + TFA-50, TFA-50 vs DOM + TFA-50, TFA-100 vs DOM + TFA-50, DOM + TFA-50 vs OND + TFA-50, DOM + TFA-50 vs HYS-TFA-50).

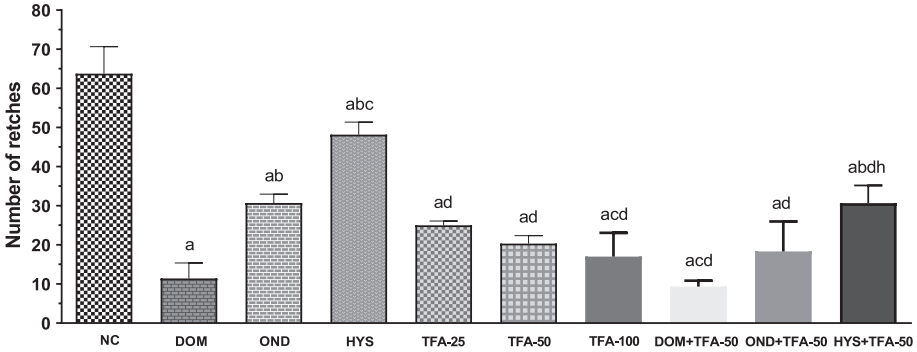

Fig. 3. Number of retches observed in test sample, controls and combinations [Values are mean ± S.E.M. (n = 5). [a]compared to the NC (vehicle), [b]compared to the DOM (positive control: Domperidone); [c]compared to the OND (positive control: Ondansetron); [d]compared to the HYS (positive control: Hyoscine hydrobromide); [e]compared to the *trans*-ferulic acid (TFA)-25; [f]compared to the TFA-50; [g]compared to the TFA-100; [h]compared to the DOM + TFA-50; $p < 0.05$ (NC vs HYS, OND vs TFA-100); $p < 0.01$(DOM vs HYS + TFA-50, HYS vs HYS + TFA-50, DOM + TFA-50 vs HYS + TFA-50); $p < 0.001$(OND vs HYS, OND vs DOM + TFA-50); $p < 0.0001$ (NC vs DOM, NC vs OND, NC vs TFA-25, NC vs TFA-50, NC vs TFA-100, NC vs DOM + TFA-50, NC vs OND + TFA-50, NC vs HYS + TFA-50, DOM vs OND, DOM vs HYS, HYS vs TFA-25, HYS vs TFA-50, HYS vs TFA-100, HYS vs DOM + TFA-50, HYS vs OND + TFA-50).

(90.22%) was observed in the DOM + TFA-50 group. On the contrary, the highest %decrease in retching in comparison to the NC group was determined in the same group. A significant elevation occurred in % decrease in retches of the test groups compared to the NC groups with enhancing of dose. We observed the % decrease of retches in the test groups at 60.78, 68.11 and 73.33 % for TFA-25, TFA-50 and TFA-100 groups, respectively. The number of retches revealed that TFA provided protective and antiemetic effect against copper sulfate-mediated emesis in chicks in a dose-dependent manner. The values of % decrease in retches and % increase in latency of all the treatment groups were exhibited in Table 1.

In silico analysis

Homology modeling of human 5HT$_3$ protein

The result of homology modeling indicates the sequence similarity between the target sequence and the template sequence of 4PIR (PDB ID) which is an X-ray crystallographic structure of the mouse serotonin

Table 1
Percentage increase in latency and decrease in retches in treatment groups.

Name of group	%Decrease in retches	%Increase in latency
NC (vehicle)	–	–
DOM	82.12	87.58
OND	51.84	52.14
HYS	24.44	31.82
TFA-25	60.78	89.90
TFA-50	68.11	47.66
TFA-100	73.33	27.40
DOM + TFA-50	85.36	90.22
OND + TFA-50	71.25	79.55
HYS + TFA-50	51.89	77.49

NC: Distilled water (Dose: 150 mg/kg); DOM: Domperidone (Dose: 6 mg/kg); OND: Ondansetron (Dose: 5 mg/kg); HYS: Hyoscine hydrobromide (Dose: 21 mg/kg); TFA-25: *Trans*-ferulic acid (Dose: 25 mg/kg); TFA-50: *Trans*-ferulic acid (Dose: 50 mg/kg); TFA-100: *Trans*-ferulic acid (Dose: 100 mg/kg); DOM + TFA-50: Domperidone + *Trans*-ferulic acid (Dose: 6 mg/kg 50 mg/kg); OND + TFA-50: Ondansetron + *Trans*-ferulic acid (Dose: 5 mg/kg + 50 mg/kg); HYS + TFA-50: Hyoscine hydrobromide + *Trans*-ferulic acid (Dose: 21 mg/kg + 50 mg/kg).

5-HT_3 receptor. The target protein sequence shows 86.95% identity and 58% sequence similarity with the template sequence and the template shares 95% coverage with the target protein. Therefore, the homology model of human 5-HT_3 was designed with QMEAN of −3.91 and GMQE score of 0.72 proposing good quality and reliability. The Ramachandran plot was evaluated to validate the precision and dependability of the residues' Psi and Phi angles. The plot demonstrated 91.65 % Ramachandran favored and 1.81% Ramachandran outliers (Fig. 4).

Molecular docking study

Molecular docking was performed to predict the probable binding affinity and interactions between drugs and receptors. The docking result of our *in silico* study demonstrated that TFA showed a moderate binding interaction with the emesis inducing various receptors. NK_1 receptor antagonist APT revealed the binding affinity −12.6 kcal/mol whereas, the ligand TFA exhibited lower binding values (−6.4 kcal/mol) against the NK_1 receptor. The antihistamine CIN expressed binding affinity of −8.1 kcal/mol. The dopamine receptor inhibitor DOM revealed docking scores of −9.6 kcal/mol against the D_2 receptor. The docking score varies for HYS against different subtypes of mAChRs receptors. HYS showed binding values of −6.8, −7.4, −6.4, −5.8 and −7.4 kcal/mol against M_1, M_2, M_3, M_4, and M_5 receptors respectively, whereas TFA expressed an elevated binding interaction against different subtypes of mAChRs than the other emesis inducing receptors. The highest docking scores (-7 kcal/mol) of TFA was observed against the M_5 receptor and −6.7, −6.6, −5.9, and −5.4 kcal/mol against the M_1, M_2, M_3, M_4 receptors respectively. The binding energy of TFA against the serotonin receptor (5HT_3) is −6.2 kcal/mol, whereas the reference OND scored −6.9 kcal/mol. The binding affinity of all the drugs against the selected receptors is exhibited in Table 2.

Prediction of drug-likeness and pharmacokinetics

The drug-likeness of a chemical agent is a crucial factor in the process of developing a medicine from it and in the evaluation of its pharmacokinetics. Molecular weight (MW), Log P, HBA, HBD, and MR are the main factors by which drug likeness can be evaluated. Our inquiry findings indicated that all drugs except for APT, which has 12 HBA, maintained their molecular weight below 500 Da (table 3). According to Lipinski's rule of five, except for APT, the values of HBA (≤10) and HBD (≤5) are within the limit. HYS, OND and TFA are soluble in water, and others are moderately soluble. All the ligands are highly absorbable through the GI membrane except APT which is slightly absorbable. There is a probability to pass through BBB barrier and producing CNS related effects for all the ligands excluding APT and HYS. The predicted values of several pharmacokinetic parameters are also provided in Table 3.

Prediction of non-bond interactions between drug-receptor complexes

TFA exhibited highest binding affinity (-7 kcal/mol) against M_5 receptor besides showing higher affinity to other muscarinic receptors than the other receptors liable for inducing emesis (Table 2). The strong binding potential of TFA toward muscarinic receptors is due to its ability to form HB (both conventional HB and carbon HB) with other types of bonds such as alkyl, pi-alkyl, pi-sigma, pi-pi T-shaped, pi-sulfur, pi-cation and pi-pi stacked. TFA formed two HB with ASP110, SER114 and several hydrophobic bond with CYS484, TRP455, TYR111 AA residues of M_5, on the other hand the reference drug HYS did not show any HB except some hydrophobic bond with the AA residues of TRP477, VAL474. TFA showed at least 2 HB with several other bonds, especially hydrophobic bonds against various subtypes of muscarinic receptors. Both the OND and TFA did not interact with 5HT_3 receptor through HB, but the ligand OND exhibited higher binding affinity by forming several hydrophobic bonds with the AA residues of PRO303, ALA297, LEU249, VAL291. The *in silico* investigation demonstrated that the strong binding potential of DOM against D2 receptor due to forming 5 HB with AA residues of GLU95, THR433, ASP114, HIS414, SER430 along with several hydrophobic bonds with the AA residues of LEU94, VAL115, PHE189, PHE410, CYS118. Though CIN did not interact with H1 receptor through HB, it formed a greater number of hydrophobic bonds with AA residues of PHE190, TRP158, LEU157, PRO161, ILE197, and VAL187. On the contrary, TFA formed 1 HB and 1 other bond with the AA residues of ASP183 and PHE190 respectively. The elevated binding affinity of APT against NK_1 receptor due to it formed 4 HB with AA residues of ASN89, GLN165, TRP184, HIS265 and other hydrophobic

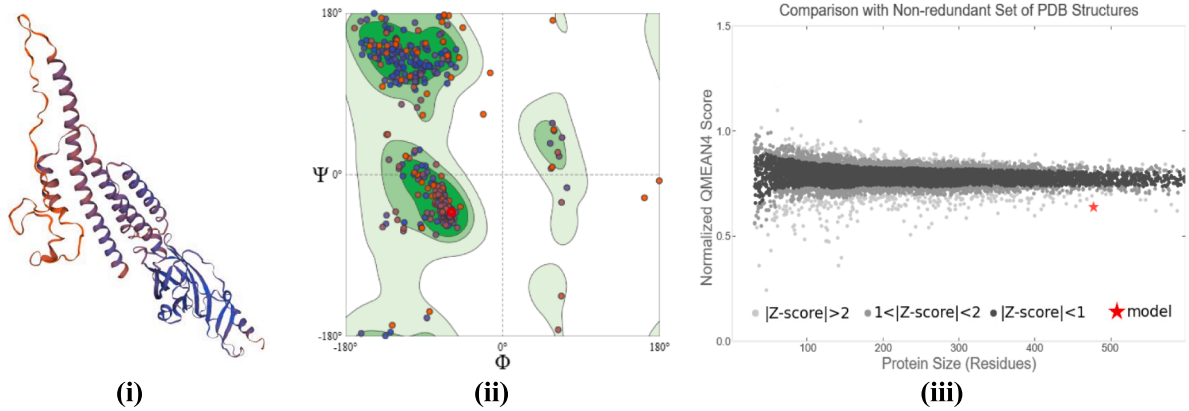

Fig. 4. I) 3d structure of human 5ht$_3$ receptor homology model build by SWISS MODEL, ii) Ramachandran plot of the homology modeled 5HT_3 protein for all non-glycine/proline residues, iii) Comparison between the modelled protein structure and a non-redundant set of PDB structures.

Table 2
Docking scores of *trans*-ferulic acid and different selected ligands against emesis inducing receptors.

Ligands	Receptors									
	Common Name	$5HT_3$	D_2	H_1	M_1	M_2	M_3	M_4	M_5	NK_1
	PDB ID	**–**	**6LUQ**	**3RZE**	**6WJC**	**5ZK8**	**8EA0**	**7V6A**	**6OL9**	**6HLO**
APT		–	–	–	–	–	–	–	–	−12.6
CIN		–	–	−8.1	–	–	–	–	–	–
DOM		–	−9.6		–	–	–	–	–	–
HYS		–	–	–	−6.8	−7.4	−6.4	−5.8	−7.4	–
OND		−6.9	–	–	–	–	–	–	–	–
TFA		−6.2	−6.7	−5.6	−6.7	−6.6	−5.9	−5.4	−7	−6.4

APT: Aprepitant; CIN: Cinnarizine; DOM: Domperidone; HYS: Hyoscine hydrobromide; OND: Ondansetron; TFA: *Trans*-ferulic acid.

Table 3
Different parameters of drug-likeness and pharmacokinetics of *trans*-ferulic acid and selected standards estimated by SwissADME.

Parameters	APT	CIN	DOM	HYS	OND	TFA
MF	$C_{23}H_{21}F_7N_4O_3$	$C_{26}H_{28}N_2$	$C_{22}H_{24}C_lN_5O_2$	$C_{17}H_{21}NO_4$	$C_{18}H_{19}N_3O$	$C_{10}H_{10}O_4$
MW	534.43	368.51	425.91	303.35	293.36	194.18
Log P	4.05	4.44	3.28	1.19	1.75	1.00
HBA	12	2	3	5	2	4
HBD	2	0	2	1	0	2
MR	118.82	125.86	124.08	83.48	87.39	51.63
Solubility (water)	Moderately soluble	Moderately soluble	Moderately soluble	Soluble	Soluble	Soluble
GI absorption	Low	High	High	High	High	High
BBB permeant	No	Yes	Yes	No	Yes	Yes
P-gp substrate	Yes	Yes	Yes	No	Yes	No
CYP2C19 int	No	No	Yes	No	Yes	No
BIO Score	0.55	0.55	0.55	0.55	0.55	0.85

MF = Molecular formula; MW = Molecular weight (g/mol) (optimum = ≤500); LogP = Log $P_{o/w}$ (MLOGP) (optimum = ≤5); HBA = Hydrogen bond acceptor, (optimum = ≤10); HBD = Hydrogen bond donor (optimum = ≤5); MR = Molar refractivity (optimum = ≤140); CYP2C19 int = CYP2C19 inhibitor; BIO Score = Bioavailability Score; APT = Aprepitant; CIN = Cinnarizine; DOM = Domperidone; HYS = Hyoscine hydrobromide; OND = Ondansetron; TFA = *Trans*-ferulic acid.

bonds with AA residues of PHE268, HIS197, PRO112, ILE113, ILE204, MET291, MET295, ILE182, TRP261 and PHE264, where the test ligand TFA exhibited 3 HB with AA residues of GLN165, ASN89, HIS108 and a hydrophobic bond with the AA residue of PRO112. The Bond types, HB number, HB length, and AA residues liable for ligand-receptor interactions of our selected ligand and receptors are provided in the Table 4 **and** Fig. 5.

Discussion

Oral administration of toxic $CuSO_4$ has the potential to cause a specific vagal-induced vomiting response. This is because $CuSO_4$ acts as an oxidizing agent that can harm the mucous membranes in the GIT [55,56]. The act of vomiting is triggered by peripheral processes that stimulate the visceral afferent nerve fibers in the gastrointestinal tract, which then relay the stimuli to the vomiting center [57,58]. Additionally, it has been verified that the serotonin receptors located in the periphery, specifically the $5HT_3$ and $5HT_4$ receptors, are implicated in this process [59,60], NK_1 receptor [61] and H_1-histamine receptors [62] are engaged in emesis as well as D_2 within the CTZ are also stimulated at their own receptor sites and induce emesis [63]. And some other types of receptors are also liable for inducing emesis in response to various toxicants or irritants, such as opioid receptors in the CTZ [64], cannabinoid receptors [15] and muscarinic receptors (M_1-M_5). Muscarinic cholinergic receptors likely play a considerably more significant function in nausea and vomiting mediation [65]. These receptors produce vomiting by acting on the vomiting center and GI tract [66].

Our chosen standard medication (DOM) acted as a selective peripheral antagonist of dopamine receptors, particularly D_2 receptors, which resulted in alleviation of symptoms by inhibiting or counteracting the activity of these receptors at the CTZ located in the brain [67,68]. In our investigation, we observed that the group of chicks who received the DOM medication had an average of 11.4 retches, while the NC group had a much higher average of 63.75 retches. Furthermore, the $5HT_3$ receptors are involved in the process of inducing vomiting by processing information from the gastrointestinal tract. These receptors also play a major role in regulating bowel motility and peristalsis in the enteric nervous system [69]. And the $5HT_3$ antagonists such as OND block the function of the receptor and provide relief from vomiting.

In this experiment, OND and HYS (mAChRs antagonist) reduced the number of retches in the chick group compared to the vehicle group and exerted remarkable antiemetic activity. Based on the findings of the experiments, it can be postulated that TFA has a safeguarding effect against toxicity by diminishing or impeding nerve signals that are capable of triggering emesis. Because the results demonstrated that all TFA groups remarkably reduced the number of retches and increased the latency period compared to the NC group. Furthermore, when comparing the number of retches to the standard DOM group, the value was similar to that of the DOM group. Our test sample TFA reduced the number of retches from 63.75 to 17 (for 100 mg/kg dose), as well as increasing the latency compared to the OND and HYS groups. The result explained that TFA is more capable of reducing retches and enhancing latency compared to standard OND and HYS groups in copper sulfate-mediated emesis.

In the field of pharmacology, the term “synergism” refers to a phenomenon where the combined effect of two or more medications is greater than the effect produced by each drug administered alone. This is known as a synergistic effect [70]. According to the study, the concurrent use of multiple drugs had a synergistic effect as it resulted in a decrease in the number of retches and an elevation in the time it took for chicks to display symptoms of nausea. The study suggests that the use of antiemetic drugs delayed the occurrence of vomiting or nausea induced by chemotherapy for cancer or acute toxicity [71]. In our investigation, the latency of retching in seconds in the test groups was higher than that in the NC group, and the highest latency (sec) was observed in the combined group (DOM + TFA-50). The results of our *in vivo* study, demonstrated that TFA provided a more synergistic effect in combination with OND and HYS than the DOM group alone as DOM group

Table 4
Amino acid residues, number of hydrogen bonds and hydrogen bond length of non-bond interactions between the selected ligands and receptors.

Receptors	Ligands	No. of HB	HB residues	HB length (Å)	Other bond residues
$5HT_3$	OND	0	–	–	PRO303, ALA297, LEU249, VAL291
	TFA	–	–	–	TYR89
D_2	DOM	5	GLU95, THR433, ASP114, HIS414, SER430	2.22, 2.26, 2.99, 3.44, 3.54	LEU94, VAL115, PHE189, PHE410, CYS118
	TFA	2	ASP114, SER197	2.46, 2.37	TRP407, CYS118, VAL115
H_1	CIN	0	–	–	PHE190, TRP158, LEU157, PRO161, ILE197, VAL187
	TFA	1	ASP183	2.02	PHE190
M_1	HYS	1	TYR85	2.598	LEU183, TYR82, TYR85, TRP101, TYR404
	TFA	2	ASN382, SER109	2.24, 2.46	CYS407, TRP378
M_2	HYS	3	ILE178, CYS176, THR187	2.56, 3.74, 3.18	TYR83, THR187, TRP422
	TFA	2	ASP103, ASN404	2.12, 2.03	CYS429, TRP400
M_3	HYS	3	THR524, THR75, ASN527	2.29, 2.90, 2.35	TRP531, LEU74, ILE71, TRP531
	TFA	2	ASN527, THR126	2.22, 3.63	TRP531, ILE129
M_4	HYS	1	THR321	2.582	ASP337, TYR320, LYS330, ALA338
	TFA	3	THR329, THR190 GLN52	2.52, 1.74, 2.18	PHE191, LYS54, VAL332
M_5	HYS	0	–	–	TRP477, VAL474
	FTA	2	ASP110, SER114	2.59, 2.97	CYS484, TRP455, TYR111
NK_1	APT	4	ASN89, GLN165, TRP184, HIS265	2.67, 2.84, 2.29, 3.45	PHE268, HIS197, PRO112, ILE113, ILE204, MET291, MET295, ILE182, TRP261, PHE264
	TFA	3	GLN165, ASN89, HIS108	2.26, 2.48, 3.55	PRO112

AA: amino acid; HB: hydrogen bond; TFA: *Trans*-ferulic acid; OND: Ondansetron; DOM: Domperidone; CIN: Cinnarizine; HYS: Hyoscine hydrobromide; APT: Aprepitant.

expressed 82.12 % reduction in retches whereas combined therapy reduced 85.36%. But OND + TFA-50 and HYS + TFA-50 diminished more percentage of retches than they administered alone.

The study found that copper sulfate-induced emesis does not occur as a result of vagal nerve stimulation. It was observed that even after performing a vagotomy (which involves cutting the end of the vagus nerve in the gastrointestinal tract), emesis could not be prevented [72,73], the presence of chemoreceptor signaling, as shown in Fig. 6 for TFA, may play a role in this scenario (Fig. 6).

The method of molecular docking can be utilized to simulate the atomic-level interaction between a protein and a small molecule. This enables us to understand how small molecules behave within the binding site of target proteins, and to gain insight into the underlying biochemical processes [74]. In recent times, computational studies have provided a new means of screening, designing, and developing potential drug candidates. This approach not only helps to reduce the overall time required for evaluation but also minimizes the need for laboratory animals and associated costs [75]. The degree of interaction between a receptor and a ligand can be determined by assessing their binding affinity [76].

In this experiment, TFA expressed higher level of binding interactions with the different subtypes of muscarinic receptors than the other receptors responsible for inducing emesis. TFA exhibited the highest binding affinity toward the M_5 receptor, and blocked the response of the receptor which induces emesis by regulating dopamine release [77]. The binding energy of TFA required for interacting with M_5 is −7 kcal/mol, whereas the standard HYS expressed the value of −7.4 kcal/mol and the ligand also exhibited better docking scores with the other subtype of muscarinic receptors as well as a mild interaction with D_2 receptors (binding affinity of −6.7 kcal/mol). As a result, it's our view that TFA is more potent for muscarinic receptors than the other receptors liable for emesis as the docking scores of TFA for muscarinic receptors are higher than the other receptors as well as *in vivo* combined therapy with HYS demonstrated more activity than other combinations.

Drug-likeness is a crucial factor in the process of discovering and developing new drugs, as it helps to assess the likelihood of a chemical compound being suitable for oral administration based on its bioavailability. This is determined by analyzing the physicochemical properties of the drug, which can provide insight into the compound's pharmacokinetic characteristics [54,78]. Lipinski's rule of five is a commonly employed approach for predicting drug-likeness and pharmacokinetics. It outlines four criteria that a potential drug candidate should meet: a molecular weight of not more than 500 g/mol, not more than five hydrogen bond donors, not more than ten hydrogen bond acceptors, and a lipophilicity (LogP) within 5. The rule also allows for up to one violation of these criteria for a compound to be considered acceptable, with a range of 0 to 1 [79]. According to Lipinski's rule, all the ligands are within the limits of becoming drugs and predict better pharmacokinetic properties though except TFA all are established drugs. Our selected test ligand (TFA) fulfills all the criteria of Lipinski's rule of five and ascertains better pharmacokinetic features.

Among various subtypes of muscarinic receptors, the M_3 and M_5 receptors are strongly involved in emesis and GI disturbances [4,80–82]. M_3 receptors are rich in smooth muscle and GIT and are liable for GI and gallbladder smooth muscle contraction while acetylcholine is utilized to activate M_3 receptors, which are under sympathetic control [83,84]. Conversely, M_5 receptors are mostly found in the substantia nigra and ventral tegmental regions of the rat brain, which may indicate a role for these receptors in the regulation of the dopaminergic transmission [85].

The active site of M_5 is the region on the receptor where its ligand (e.g. the neurotransmitter acetylcholine) binds and initiates the receptor's activation. While the specific amino acid residues that make up the active site of M_5 have not been fully characterized, some important residues have been identified through studies. In our *in silico* visualization, if we compare the bonded amino acid residues of various receptors between the ligand TFA and the selected drugs then the amino acid residues of ASP114, CYS118, VAL115 for D_2, PHE190 for H_1, ASN527, TRP531 for M_3 and ASN89, GLN165, PRO112 for NK_1 are identical. That means they are coupled at the same location on the receptors by interaction with the indicated amino acid residues. The reason for the higher binding affinity against M_5 receptors is due to the formation of two HB and several hydrophobic bonds whereas the reference drug HYS did not form any HB other than hydrophobic bonds. Therefore we predict that ASN527, TRP531 of M_3 and ASP110, SER114, CYS484, TRP455, TYR111 of M_5 are the key residues involved in the antagonizing activity of TFA against M_3 and M_5 respectively.

So, the outcomes of this study revealed that the TFA expressed mild antiemetic activity against the $CuSO_4{\cdot}5H_2O$-induced emesis model, which is due to the possibility of antagonizing capability against muscarinic acetylcholine receptors. And the *in vivo* result also demonstrated that the antiemetic activity of TFA is consistent and reliable at its lowered dose. Various studies reported that the currently available synthetic antiemetic drugs have a number of side effects, such as diarrhea or constipation, fatigue, malaise, headache, dizziness, blurred

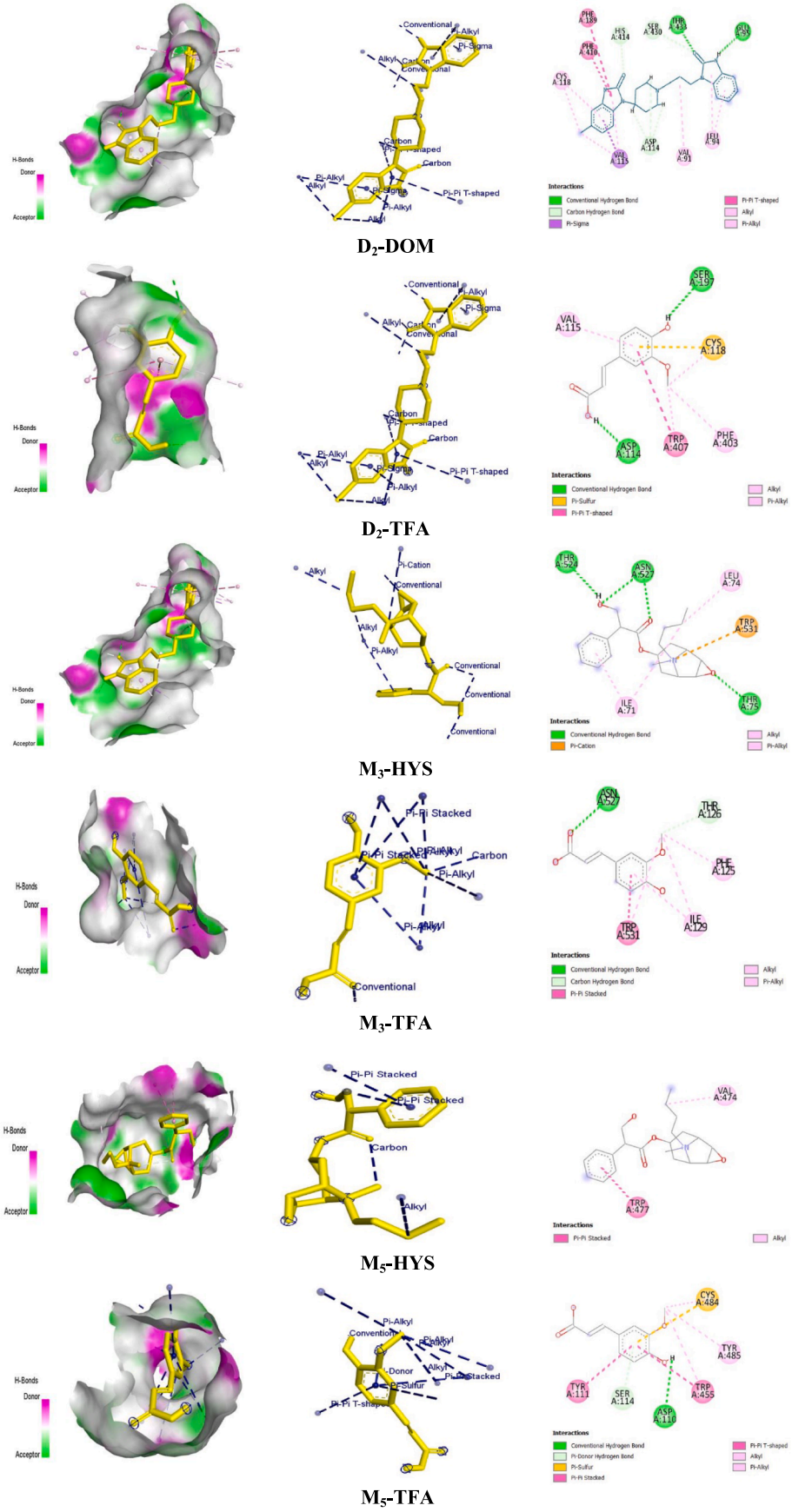

Fig. 5. 3D view of receptor binding site with names of non-bond interactions and 2D view of interacted amino acid residues between selected ligands and various emesis inducing receptors.

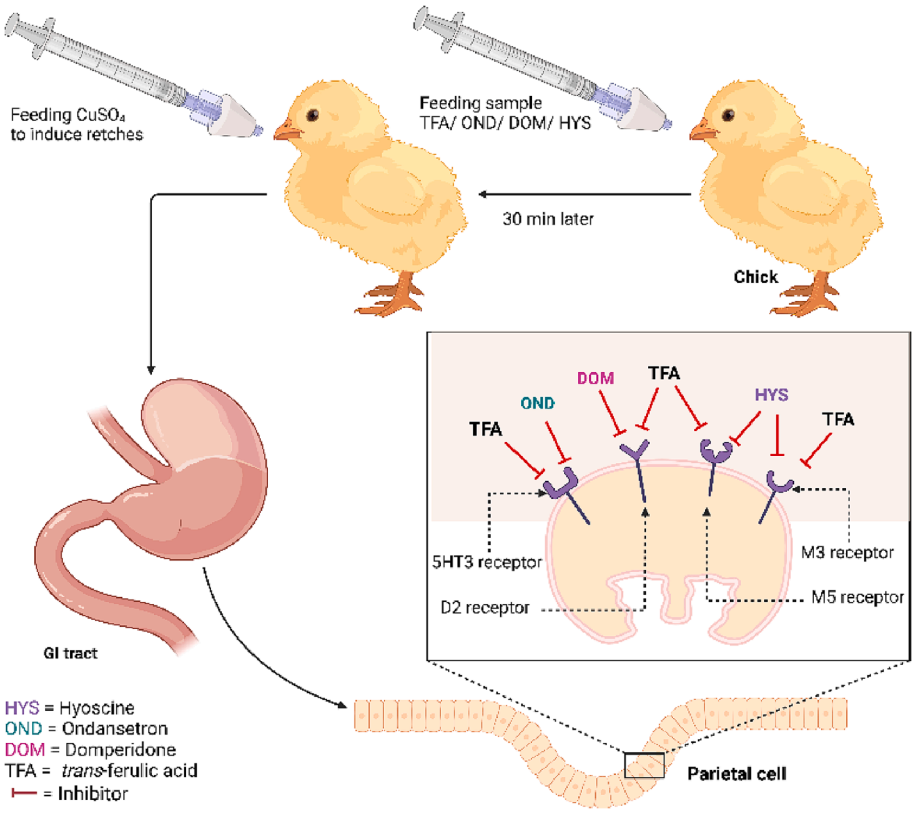

Fig. 6. Proposed anti-emetic mechanism of the test sample and reference drugs [This Fig. represents possible anti-emetic mechanisms of TFA, OND, DOM and HYS based on the binding affinity of these ligands with the $5HT_3$, D_2 and muscarinic receptors. Here, TFA acts as an inhibitor of $5HT_3$, D_2, M_3 and M_5 receptors, while OND, DOM inhibit $5HT_3$, D_2 receptors, respectively and HYS blocks the action of M_3 and M_5 receptors. Blocking these stomach receptors causes the vomiting center (medulla oblongata) to remain unstimulated, which means that there will be no muscle or gastrointestinal tract contraction, and as a result, there will be no vomiting].

vision, light-headedness, and dry mouth [81,86], whereas the alternative antiemetic drugs, especially natural compounds, revealed relatively fewer side effects and efficacious therapeutic benefits [87–89]. From the findings of our study, it is clear that TFA exerted mild antiemetic potentials in experimental animals without showing abnormal activities or adverse events, which was further confirmed by observing the animals for an additional 23 h after the study. During this period, we did not see any deaths among the TFA-treated animals. On the other hand, there was a normal recovery (without drug treatment) of $CuSO_4{\cdot}5H_2O$-induced emetic tendency within the observed period (test hours plus additional observation hours). Moreover, we have scope to modify the effects of lead compounds in various ways, such as structural modification and combinatorial synthesis. Therefore, the compound demonstrates clinical efficacy in the treatment of emesis.

Conclusion

In summary, the results of the *in vivo* investigation demonstrate that TFA has remarkable antiemetic activity and the chemical agent protects against $CuSO_4{\cdot}5H_2O$-mediated retching in chicks, perhaps by peripheral action. The *in silico* investigation ensured that TFA retaining drug-likeness and better pharmacokinetic property to be a reliable lead as well as the molecular docking predicts that TFA has an elevated binding affinity for muscarinic acetylcholine receptors, especially M_5 than the other receptor responsible for inducing emesis. The compound also expressed synergistic activity when administered in combination with different approved antiemetic drugs targeting various receptors. Taken together, TFA diminished $CuSO_4{\cdot}5H_2O$-mediated emesis in chicks in combination with HYS, proposing its antiemetic potential, possibly through interacting with the muscarinic acetylcholine receptor. It is possible that TFA belongs to a group of natural antiemetic substances obtained from plants. Additional research is required to establish the ideal dosage and precise mechanism of action for TFA in treating nausea and vomiting caused by various other factors.

CRediT authorship contribution statement

Md. Shimul Bhuia: Conceptualization. **Hossam Kamli:** Conceptualization. **Tawhida Islam:** Methodology. **Fatema Akter Sonia:** Methodology. **Md. Azim Kazi:** Methodology. **Md. Sajjad Hossain Siam:** Software. **Naimur Rahman:** Software. **Mehedi Hasan Bappi:** . **Md. Nayem Mia:** . **Md. Munnaf Hossen:** Supervision. **Daniel Luna Lucetti:** . **Paulo Leonardo Celestino Oliveira:** . **Henrique D.M. Coutinho:** Project administration. **Muhammad Torequl Islam:** Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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