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In Silico Study to Estimate the Impact of Pollutants Resulted from Generators Emissions on ACE2 Receptor in the Respiratory System

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ABSTRACT

Pollution by greenhouse gases is a serious problem nowadays, especially those who are emitted by diesel generators. The angiotensin-converting enzyme-2 (ACE2) is a common enzyme with active receptor included on the alveoli surface in mammalians. This study used the software of molecular docking tools for turning out the interaction between ACE-2 receptor and generators emission gases and particulate matter, which are other important trace components in air. Molecular docking has been performed for many gases which might bind to chain (A) in ACE-2 receptor. Tools included the version 0.8 of the docking program (PyRx 2021) followed by analysing the binding by the program (discovery studio visualizer 2021) to show the amino acids and chemical bonds among gases and ACE-2 respecter. Results showed that the highest affinity of binding was the highest (- 9.9 kcal/ mol) of PM 2.5 to ACE-2 receptor, while the lowest was (- 0.7 kcal/ mol) of H2S to the same target. For the other gaseous pollutants the affinity to be docked with ACE-2 receptors fluctuated around (- 9 kcal/ mol) till less than (-2 kcal/ mol) with different bond types. In unexpected way, neither CO2 and CO nor CH4 recorded affinity or binding degrees towards ACE-2 receptor. In short, the most dangerous gaseous emissions of generators to human alveoli were PM molecules among the emissions of diesel generators.

1. Introduction

Angiotensin - converting enzyme -2 (ACE- 2) is a common enzyme with active receptor included on the alveoli surface in mammalians (Miftode, *et al*. 2023). Respiratory system is considered as the first line which can receive the immediate effect of atmospheric molecules (Jallul *et al*., 2022), like dust and greenhouse gases, according to the dose and time to exposure to such air pollutants especially for recurrent conditions, depending on the type of pollutant, the exposure time and the dose of the air pollutants (Iraqi Ministry of Planning, 2020; Bortman, *et al*. 2023).

ACE-2 molecules are mainly present on the surface of alveoli in mammalian respiratory system, including human, which are represent a receptor of inhaled gaseous substances or particles which are considered as ligands in biochemistry and bioinformatics (Al-Khafagy

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and Ibrahim, 2012). The structure of ACE-2 receptor expresses striking conformational changes in the active sites which impact many surrounding residues, including the ACE-2 residues, implicated in binding to ligands specifically by chain A in particular; as described by x-ray crystallography (Cambridge Crystallographic Data Centre, 2023). Researchers suggested that respiratory receptors are potential main targets of air pollutants and dust (Abed, *et al.* 2018). The ligands which bind to this receptor may affect negatively on human health. Apart of resources depletion and degradation of natural spaces of creatures, the emitted greenhouse gases into the atmosphere like carbon dioxide, methane and nitrous oxide which are generated from agricultural activities and diesel generators (IGES Institute, 2017); they are also considered the main three greenhouse gases (Mohamed, 2020). Gradually these gases were admitted to the atmosphere in huge amounts even they are necessary to trap sun's energy to keep some of heat so we can live and thrive on the earth planet; in addition to hazardous effects on human respiratory system and general body health which might be mitigated in order to keep the air pollutants within the acceptable limits for helath and proper air quality (EPA, 2005, Zuhair, *et al*. 2020).

By bioinformatics, ACE-2 receptor binding to some biosphere molecules results in investigation of which kind of emissions is more harmful for long exposure as the main aim of the current study. When the affinity of air pollutant binding with the receptor is highly negative, that would refer to the most potent binding with less demand binding energy with huge hazardous impact on human health.

2. Material and methods

In silico approach was used aided by PubChem website (www.pubchem.com) and Protein bank database (PBD) databases to get the information about each one of the emitted gases which is supposed to be a pollutant, and its strength to bind with the respiratory receptor ACE-2 was tested by using the software programs such as (PyRx 2021) for molecular docking; and (Discovery Studio Visualizer 2021) for visualization of docked compounds.

The programs were downloaded by the links available on network for free in order to perform the virtual binding of the pollutant gases and emissions with the ACE-2 receptor (Miftode, *et al*. 2023).

The supposed gases which are generated from diesel generators are listed in (Table 1) besides the fine particulate matters are also included in this study as PM1, PM7, PM2.5 and PM10 (IGES Institute, 2017).

Table (1): Studied ligands and their chemical formula:

No.	Emitted Gas	Chemical Formula
1	Acetylene	C_2H_2
2	Benzene	C_6H_6
3	Benzopyridine	C_4H_8
4	Chromium trioxide	CrO_3
5	Carbon monoxide	CO
6	Carbon dioxide	CO_2
7	Formaldehyde	CH_2O
8	Hydrogen sulfide	H_2S
9	Methane	CH_4
10	Nitrogen monoxide	NO
11	Nitrogen dioxide	NO_2
12	Naphtha	Aliphatic hydrocarbons
13	PM 1, PM 7, PM 2.5 and PM 10	Dust, dirt, soot, smoke and liquid droplets
14	Sulphur dioxide	SO_2

-Preparing the ACE-2 receptor:

By PDB website, all information and chemical formula related to the ACE-2 receptor were obtained and saved. The receptor ACE-2 was initially visualized by (Discovery Studio Visualizer 2021) software and only chain A was kept from all structural configuration of this protein. Mainly, water molecule and non-essential residues were all deleted. The new configurationally shape of the ACE-2 protein was saved to be docked later with each of ligand, elsewhere gases or fine particulate matters.

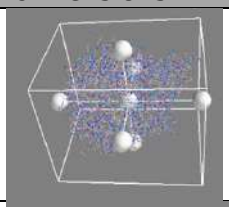
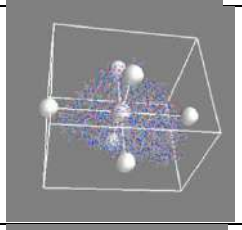
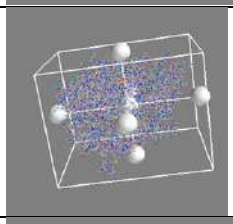
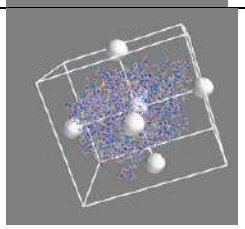
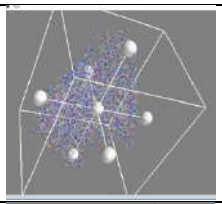
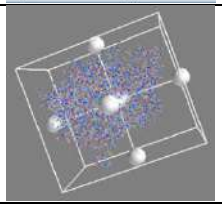
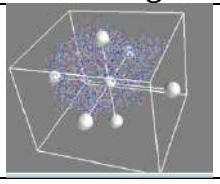
-Preparing the tested ligands:

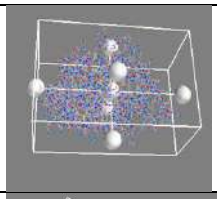
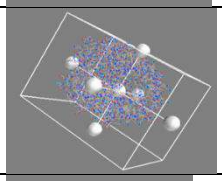
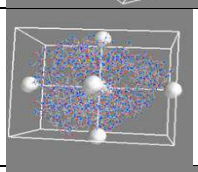
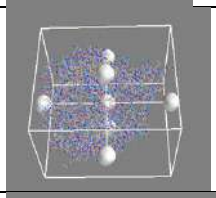
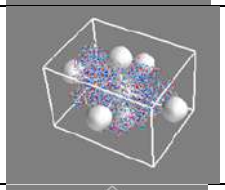
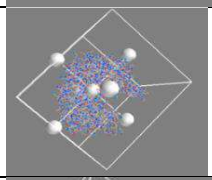
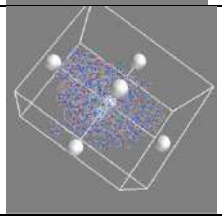
The chemical formula of generators-emitted gases and particulate matters were all downloaded as SDF formula by using pubchem.com website. In order to perform the virtual binding, the ligand should be prepared as special form to make it suitable to occupy the active site of the receptor. All the gases and PM formulas were modified by the option of (convert to ligand in PyRx 2021 software) then were saved after some chemical configurational changes to bind with the modified receptor in the earlier step above (Al-Shuhaib and Hashim, 2021).

Docking by software *In silico* tools:

After preparing and saving all suitable forma of ligands and receptor that will be docked together, (PyRx 2021) tool was used. VINA box is a representative box which gave all angles and rotation capacity of the binding process for each ligand with the same ACE-2 receptor respectively and virtually (NAMD, 2023). Table (2) illustrates the configurational characteristics of VINA box search space of each studied ligand in docking process with ACE-2 receptors**.**

Table (2): The configurational characteristics of VINA box search space of each studied ligand in docking process with ACE-2 receptors

No.	Tested ligand	Centre (Angstrom)	Space (Angstrom)	VINA box dimensions
1	Acetylene	56.5254	81.7763	
2	Benzene	61.3471	79.3864	
3	Benzopyridine	58.4456	78.0680	
4	Chromium trioxide	58.019	76.7422	
5	Carbon monoxide			No docking
6	Carbon dioxide			No docking
7	Formaldehyde	58.3977	78.8767	
8	Hydrogen sulphide	59.7942	76.3357	
9	Methane			No docking
10	Nitrogen monoxide	60.7109	81.5701	

11	**Nitrogen dioxide**	**58.2868**	**81.1924**	
12	**Naphtha**	**58.7159**	**82.8906**	
13	**PM 1**	**55.7205**	**79.1850**	
14	**PM 2.5**	**58.3627**	**74.8521**	
15	**PM 7**	**56.6660**	**81.8457**	
16	**PM 10**	**58.3874**	**84.8716**	
17	**Sulphur dioxide**	**57.5318**	**80.5422**	

After accomplishing of docking of each pollutant with ACE-2, the affinity was calculate automatically and computationally by using python language by the same program, then the results of the binding strength were all written down for comparison of the hazardous affinity with the pollutant, measured by minus values as the bigger one in an inversive relationship.

The compounds resulted from docking were all saved and then displayed by (Discovery Studio Visualizer 2021) to show the binding sites among amino acids of both combined molecules; in addition to the bonds which binds them together.

-Visualizing amino acids and chemical bonds:

Each docked compound, which is resulted from molecular docking of ACE-2 receptor with each of mentioned ligands, was then displayed in (Discovery visualizer 2021) tool for getting more information about the bound amino acids and the bonds among them (Al-Shuhaib and Hashim, 2021).

3. Results and Discussion

As recorded below the affinity, which refers to the energy of the binding by minus, was listed in Table 3 from the highest to the lowest values, besides the type of the chemical bonds which bind each of the ligand to the ACE-2 receptor (NAMD, 2023).

Table (3): The strength and chemical bonds of each tested ligand with ACE-2 receptor

Ligand	Affinity (kcal/ mol)	Chemical bond/s
PM 2.5	**-9.9**	**Pi-Pi Vander Waals Pi-Alkyl**
PM 10	**-9.6**	**Pi-Pi Vander Waals Pi-Alkyl**
PM 1	**-9.4**	**C-O bonds**
PM 7	**-8.8**	**Pi-Pi Vander Waals Conventional hydrogen bond**
CrO_3	**-6.3**	**Pi-Pi Vander Waals Pi-Alkyl Pi-Sigma C-O bonds**
NO_2	**-5.7**	**Vander Waals Pi-Alkyl Conventional hydrogen bond C-H bonds**
Naphtha	**-4.6**	**Pi-Pi Vander Waals Pi-Alkyl Pi-Sigma**
Benzene	**- 4.5**	**Pi-Pi Vander Waals Pi-Alkyl Pi-Sigma**
SO_2	**-3.0**	**S-O bonds**
NO	**-2.9**	**O-H and O-N bonds**
Benzopyridine	**-2.2**	**Pi-Pi Vander Waals Pi-Alkyl**
Formaldehyde	**-1.8**	**C-H bonds Vander Waals Conventional hydrogen bond**
Acetylene	**-1.3**	**Pi-Pi Vander Waals Pi-Alkyl Pi-Sigma**
H_2S	**-0.7**	**S-H bonds**
CH_4, CO, CO_2	**No Affinity**	**----------**

In order to discuss the hazardous effects of generators emissions, they were categorized to three major groups as PM molecules, hydrocarbonic and non hydrocarbonic gases (Bortman, *et al*. 2023), and for each category here is a represented figure of 2D and 3D of the docked molecules.

- **PM molecules:**

They included PM 1, 2.5, 7 and 10 according to the size of each of them. They are usually containing dust, smoke and dirt embedded in liquid droplets. Figure 1 represents both of 3D structure (at the left) and 2D structure (at the right) resulted from molecular docking of PM 2.5 with ACE-2 receptors, accompanied with the detailed amino acids and chemical bonds between them (displayed by studio visualizer program).

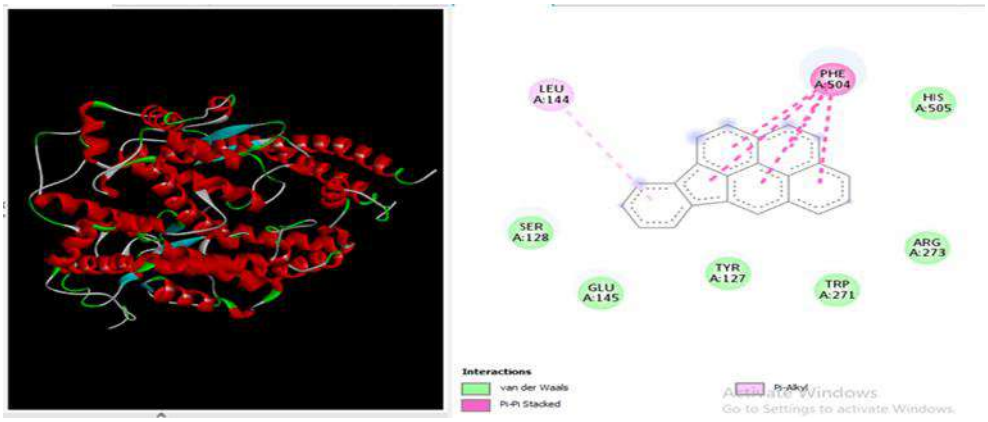


Figure (1): PM 2.5 molecules docked with ACE-2, with the 3D at the left and 2D at the right including amino acids and chemical bonds.

Restovski, *et al*. (2022) reported that PM impact on human health can be deadly and categorised to short term effects like asthma and allergies with dysfunction of lungs and alviolies, and long term exposure which may lead to liver and lung cancers to people and generators workers within emission areas.

IGES Institute (2017) and the reports of Iraqi ministry of planning (2023) also described that PM2.5 as the most emitted fine particulate matters to the atmosphere that can be causes tracheal infection, bronchitis, and subsequently lung cancer. The other harmful effects on human health might be brain strock and heart ischemic disease due to lower respiratory infections.

-Hydrocarbonic gases:

The hydrocarbonic emission including Acetelyne, benzene, benzobyredene naphtha and formaldehyde. They all have C and H atoms in their structure. The interaction between naphtha pollutants and ACE-2 receptor is a common and good example for docking among the suspected attached molecules (Miftode, *et al*. 2023). The representive figure of 2D and 3D illustrates the bonds and amino acids sharing the bonding process (Figure 2).

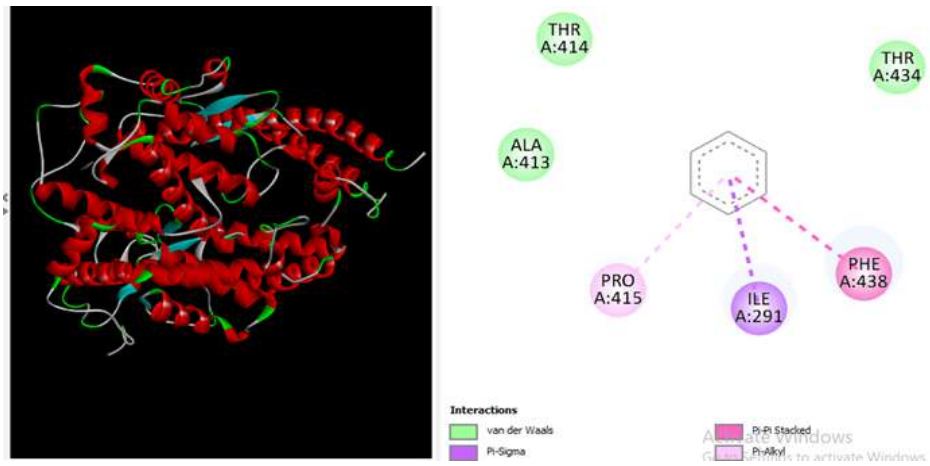


Figure (2): Naphtha molecules docked with ACE-2, with the 3D at the left and 2D at the right including amino acids and chemical bonds.

Zuhair, *et al*. (2020) mentioed that the harmful impact of short or long exposure to naphtha and Hydrocarbonic gases that are emitted to the atmosphere from generators includes central nervous system, liver, lungs and respiratory diseases in addition to shortness of life span. CO, CO2 and CH4 are probably emitted from the solid waste materials of burning fuel, increase as temperature of the embedded air (Hammadi, *et al*. 2020). Therefore their receptors are not located on alviole particularily ACE-2 receptor.

Iraqi Ministry of Planning (2020) recorded high levels of air gaseous pollutants including aromatic hydrocarbonic group that have been emitted from vehicles, factories and diesel generators. The report of this ministry (2023) also listed a high consumption of diesel or gasoline which leads to the emission of hazardous substances to the air with huge health effects for prolonged inhalation for generator workers or people lived near the polluted areas (Iraqi Ministry of Planning, 2023).

-Non hydrocarbonic gases:

They are including CrO_3, NO, NO_2, SO_2 and H_2S. As an example of the doking between CrO_3 and ACE-2 receptor, the representive figure of 2D and 3D illustrates the bonds and amino acids sharing the bonding process (Figure 3).

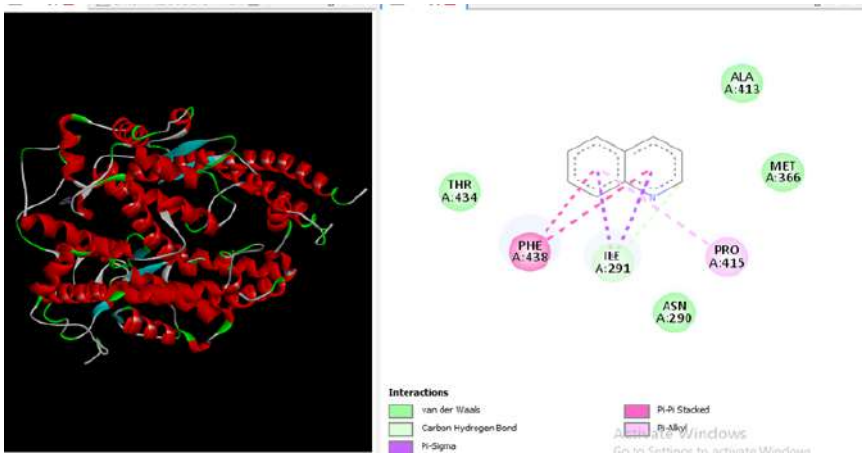


Figure (3): CrO_3 molecules docked with ACE-2, with the 3D at the left and 2D at the right including amino acids and chemical bonds.

Abed *et al*. (2018) had recorded the air pollutants of non hydrocarbonic gaseos emissions could be primary like those emitted directly to the atmosphere, or secondary pollutants that are formed from a reaction of primary pollutants like SO_2, NO_2, and volatile inorganic compounds. Mohamed (2020) documented the effects of them are generaly causes eye dryness, respiratory disorders, allergies, ccirculatory diseases and cancer for the long term of exposure.

In short, bioinformatics can provide deep information about life molecules and to which extent they can be affected, in other words the most biohazardous molecules for the health of the human respiratory system can be evaluated by *In silico* tools to investigate the lung injury and other vital organs of human body, in addition to the illness mechanism (Al-Khafagy and Ibrahim, 2012; Restovski, *et al.* 2022).

4. Conclusions

Although the CO, CO_2 and CH_4 are considered as the main greenhouse gases in emissions of generators, but they has no affinity to be bound with the respiratory receptor ACE-2; while PM particles were the most able to be docked with the same receptor as the strength of binding was much higher than those with other emitted gases of diesel generators, regardless the type of chemical bonds which bind them.

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[17]. Molecular Docking programs:
1- One of molecular visualization tools:
Biovia Discovery Studio Visualizer 2021 (https://www.3dsbiovia.com/products/collaborative-science/biovia-discovery-studio/visualization-download.php)
2- One of Molecular Docking software
PyRx 2021: for site specific docking which include AutoDock 4 and AutoDock Vina (https://pyrx.sourceforge.io/).

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