Repurposing of FDA Approved Alkaloids as COVID 19 Inhibitors; In Silico Studies

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ABSTRACT

Background: Alkaloid drugs were permitted for using as a treatment of numerous diseases. Colchicine, codeine, piperine, papaverine, ergometrine, theophylline, theobromine and caffeine are recognized safe alkaloids and used for many human disfunctions. The chemical structures of alkaloids have flexible chemical moieties with various electronic and chemical characters. COVID-19 is a horrible disease as result from that the discovering of potent drugs from previously FDA approved drugs is the main objective of this study. Methods: docking studies were used for discovering the interactions of alkaloids with protease proteins. The nature of selected alkaloids structures was utilized for advance insights studies to predict new medical applications. Results: Docking studies for alkaloids were completed and the obtained outcomes, displayed that all tried alkaloids have great attraction with the five protease proteins, the energy docking score ranged from -2.9516 (for colchicine with 5R82) to -24.7449 (for ergotamine with 5R80) kcal/mol with 1-5 variable interactions bond. Conclusion: Among the tested drugs, papaverine and ergometrine revealed high docking scores for all five proteins (score ranged from -14.1058 to 23.1619 for papaverine and, -4.7900 to 24.7449 for ergometrine) and number of interactions with all tested proteins are two to three for papaverine but for ergometrine are two to five. Key words: Alkaloids, COVID-19, Docking study, FDA, Natural drugs.

INTRODUCTION

Coronavirus (COVID-19) is represented one of the main challenges affected the world population in now day and infected melons of people over the world[1,2]. This pandemic is reflected the greatest hazardous epidemics that diseased and threatened all the human inhabitants at the end of 2019 and till now[3,4]. As a result of this pandemic infection at latent stages, is respiratory system dysfunction and hypoxia. It was progressively spread to all territories of the world in spite of that it firstly distinguished in Wuhan, China[5,6]. According to World Health Organization classification, the COVID-19 is considered the greatest transmittable epidemic disaster which newly criticized the world populations, and the highest spreadable pandemic disease up till now[7]. Millions of peoples were infected with hirable pandemic crisis along with elevated death rate more than 115000 death case[8]. Regarding who reports, From the starting of that disaster, the number of affected people is constantly risen till the instant of article written. Since there is no approved and effective treatments for this epidemic crisis yet, utmost of the drug discovers and scientists, have engrossed their exertions to reach and discover an auspicious treatment, either by repurpose drugs, synthesis, semisynthesis, and natural occurring drugs which are predictable to own a optimistic effect on such epidemic type[9,10]. Alkaloids are naturally occurring organic nitrogenous compounds and can be detected in certain plant families[11,12]. It has been reputed for their medicinal values either as FDA approved drugs or in folk medicine[11]. They have been used as anti-inflammatory, analgesics, stimulant, antimicrobial, anticancer, antifungal, antispasmodics, neuropharmacologic and others[13-15]. Certain alkaloid individuals have been selected for theoretically testing their potentiality as antiviral drugs against the newly spread COVID-19[16,17]. The selected alkaloid members are FDA approved and possess safe and therapeutic uses at certain and calculated doses[18]. The two enzymes transcriptase and protease are vital key factors for reproduction and existence of RNA virus in host cell. COVID-19 is RNA virus type as a consequence, protease enzyme signifies as an one of most important targets for discovering of new antiviral drugs[19]. So, insight, in silico, or virtual docking studies aiming protease proteins of COVID-19, is considered as a new entry for discovering or repurposing new inhibitory drugs for COVID-19[20-22]. In this study, FDA safe alkaloids drugs were selected for research using docking program and the study were applied at five positions of protease targeting different proteins[22,23]. The main objectives of this virtual studies are discovering natural safe, and effective within short time which is essential factor in this epidemic crisis and to validate the affinity and binding types for the selected drugs with protease proteins.

MATERIAL AND METHOD

Molecular modeling was employed as a valuable technique for estimating the interaction of...
medication-receptor macromolecule. This software aids to increase the achievement rate of an experiment and reduces the experimental fees. Through the molecular docking analysis, the possible binding presence of drugs can be estimated on the active sites of the objective enzyme. Molecular docking has been done to show some naturally FDA-approved biologically active alkaloids with the SARS-CoV2 protease in our research. The PDB has been downloaded with the isolated crystal structures of protease enzymes active sites (5R7Y, 5R7Z, 5R80, 5R81 and 5R82). Virtual studies have been carried out using the London dG force and the results have been sophisticated with the application of force field energy. The 3D structure built up by the MOE program was developed for the production of natural medication, colchicine, codeine, piperine, papaverine, ergotamine, theophylline, theobromine, and caffeine for the study (Molecular Operating Environment, Version 2008.06, Chemical Computing Group Inc., QC, Canada). Described techniques were employed before docking which incorporate, running conformational analysis using systemic search, 3D protonation of the structures, applying the same docking protocol was used with ligands and selecting the least energetic conformer (Figure 1-5). Alkaloids docking experiments, have been used. Interactions, arene cation, and hydrogen connection with amino acid, have been summarized in (Tables 1-5).

RESULTS AND DISCUSSION

Five proteins of protease were used and downloaded from PDB in this analysis. The five-crystal structures (5R7Y, 5R7Z, 5R80, 5R81 and 5R82) were modified for the docking analysis. These five proteins play an important role in the construction, configuration, and conformation of protease enzymes. Some safe natural alkaloids FDA approved drugs have been used in docking studies. The five proteins were used to confirm their activity, to prove binding modes and to predict the SAR of the tested compounds. The docking energy score(s) for the compounds tested ranged from -2.9516 to -24.7449 kcal / mol. (Tables 1-5). Various drug-protein interactions have been observed, ranging from one to five interactions, including H-bond acceptor, H-bond donor, and arene cation interactions (Tables 1-5, Figures 1-5).

Binding interactions of alkaloid with 5R7Y

The docking scores of tested alkaloids with 5R7Y ranged from -19.2769 for papaverine and -4.8801 for colchicine. Gln 189 amino acid formed H bond acceptor with C=O colchicine, with methoxy group, and furan oxygen of codeine, N-atom and methoxy group of papaverine, while formed H bond donor alcoholic OH of codeine, amidic N and alcoholic OH of ergotamine. Arene cation interactions were observed between

**Table 1: Interactions and docking score of alkaloids with 5R7Y.**

| No. | Drug Name   | Docking score | Number of interactions | Type of interaction | Amino acid | Function group |
|-----|-------------|---------------|------------------------|--------------------|------------|----------------|
| 1   | Colchicine  | -4.8801       | 3                      | Arene cation       | His 41     | Phenyl ring    |
|     |             |               |                        | H bond acceptor    | Thr 25     | Methox of heptene |
|     |             |               |                        | H bond acceptor    | Gln 189    | C=O of amide   |
|     | Codeine     | -11.0815      | 3                      | H bond acceptor    | Gln 189    | Methox phenyl  |
|     |             |               |                        | H bond acceptor    | Gln 189    | O of furan     |
|     |             |               |                        | H bond donor       | Gln 189    | OH alcohol     |
|     | Piperine    | -13.1326      | 1                      | H bond acceptor    | Asn 142    | C=O           |
|     | Papaverine  | -19.2769      | 2                      | H bond acceptor    | Gln 189    | N atom         |
|     | Ergotamine  | -18.0130      | 2                      | H bond donor       | Gln 189    | 4-methoxyphenyl|
|     | Theophylline| -9.5423       | 1                      | Arene cation       | His 41     | Imidazole ring |
|     | Theobromine | -8.6920       | 1                      | Arene cation       | His 41     | Imidazole ring |
|     | Caffeine    | -13.4502      | 1                      | H bond acceptor    | Gln 189    | 4-C=O         |

**Table 2: Interactions and docking score of alkaloids with 5R7Z.**

| No. | Drug Name  | Docking score | Number of interactions | Types of interaction | Amino acids | Function group   |
|-----|------------|---------------|------------------------|----------------------|-------------|-----------------|
| 1   | colchicine | -22.1963      | 2                      | H bond acceptor      | His 163     | C=O of amide    |
|     |            |               |                        | H bond acceptor      | Gln 189     | Methox of heptene |
|     |            |               |                        | H bond acceptor      | Gly 143     | Methox phenyl   |
|     |            |               |                        | H bond donor         | His 163     | OH alcohol      |
| 2   | Codeine    | -17.4083      | 2                      | Arene cation         | His 41      | Phenyl ring     |
|     |            |               |                        | H bond acceptor      | Gln 189     | 7-methoxysquainoline|
| 3   | Piperine   | -17.2722      | 1                      | Arene cation         | His 41      | Phenyl ring     |
|     |            |               |                        | H bond acceptor      | Gln 189     | 4-imethoxyphenyl|
| 4   | Papaverine | -23.1619      | 3                      | H bond acceptor      | Gly 143     | Phenyl ring     |
|     |            |               |                        | Arene cation         | His 41      | 9-N            |
| 5   | Ergotamine | -19.2085      | 2                      | H bond acceptor      | Asn 142     | C=O of amide    |
|     | Theophylline| -7.4275       | 1                      | H bond donor         | Gln 166     | OH alcohol      |
|     | Theobromine| -7.7700       | 2                      | H bond acceptor      | Gln 166     | 4-C=O          |
|     | Caffeine   | -11.5933      | 1                      | Arene cation         | His 41      | Imidazole ring  |
Table 3: Interactions and docking score of alkaloids with 5R80

| No. | Drug Name   | Docking score | Number of interactions | Interaction types | Amino acid | Function group |
|-----|-------------|---------------|------------------------|------------------|------------|---------------|
| 1   | Colchicine  | -12.1316      | 2                      | H bond donor     | Glu 166   | N of amide    |
|     |             |               |                        | H bond acceptor  | Gln 189   | C=O of amide  |
| 2   | codeine     | -7.4168       | 1                      | H bond donor     | Glu 166   | OH of alcoholic group |
|     |             |               |                        | H bond acceptor  | Gln 189   | C=O          |
| 3   | Piperine    | -16.6878      | 1                      | H bond acceptor  | Glu 189   | C=O          |
| 4   | Papaverine  | -16.7969      | 2                      | Arene cation interaction | His 41 | Phenyl of isoquinoline |
|     |             |               |                        | H bond acceptor  | Gln 189   | 3-methoxy    |
| 5   | Ergotamine  | -24.7449      | 2                      | H bond acceptor  | Gln 189   | C=O of oxazole |
|     |             |               |                        | H bond acceptor  | Gln 189   | C=O of amide  |
| 6   | Theophylline| -6.0634       | 2                      | H bond acceptor  | Glu 189   | 9-N          |
| 7   | Theobromine | -9.3451       | 1                      | H bond acceptor  | Gln 189   | 2-C=O        |
| 8   | Caffeine    | -11.9342      | 1                      | H bond acceptor  | Gln 189   | 2-C=O        |

Table 4: Interactions and docking score of alkaloids with 5R81.

| No. | Drug Name   | Docking score | Number of interactions | Types of interaction | Amino acids | Function group |
|-----|-------------|---------------|------------------------|----------------------|------------|---------------|
| 1   | Colchicine  | -15.1191      | 3                      | Arene action interaction | His 41 | Phenyl ring |
|     |             |               |                        | H bond acceptor      | Gly 143   | Carbamide C=O group |
|     |             |               |                        | H bond acceptor      | Gln 189   | C=O of cycloheptene |
| 2   | Codeine     | -16.9709      | 2                      | Arene action interaction | His 41 | Phenyl ring |
|     |             |               |                        | H bond acceptor      | Asn 142   | Alcohol C=O  |
|     |             |               |                        | H bond acceptor      | Gln 189   | O of furan    |
| 3   | Piperine    | -16.7741      | 1                      | Arene action interaction | His 41 | Phenyl ring |
|     |             |               |                        | H bond acceptor      | Gly 143   | C=O of oxazole |
| 4   | Papaverine  | -18.5474      | 2                      | Arene action interaction | His 41 | Phenyl ring |
|     |             |               |                        | H bond acceptor      | Gly 143   | 6-methoxy of isoquinoline |
|     |             |               |                        | H bond acceptor      | Gln 189   | N of pyrrole  |
| 5   | Ergotamine  | -20.4813      | 5                      | Arene action interaction | His 41 | Phenyl ring |
|     |             |               |                        | H bond acceptor      | Gln 189   | C=O of amide  |
|     |             |               |                        | H bond acceptor      | Gln 189   | C=O of oxazole |
|     |             |               |                        | H bond acceptor      | Glu 166   | Alcohol C=O  |
| 6   | Theophylline| -9.6485       | 1                      | Arene action interaction | His 41 | Phenyl ring |
|     |             |               |                        | H bond acceptor      | Gly 143   | 7-N          |
| 7   | Theobromine | -9.2269       | 2                      | Arene action interaction | His 41 | Phenyl ring |
|     |             |               |                        | H bond acceptor      | Gly 143   | 7-N          |
| 8   | Caffeine    | -11.8040      | 2                      | Arene action interaction | His 41 | Phenyl ring |
|     |             |               |                        | H bond acceptor      | Gly 143   | 7-N          |

Table 5: Interactions and docking score of alkaloids with 5R82.

| No. | compound     | Docking score | Number of bonds | Type of interactions | Amino acids | Function group |
|-----|--------------|---------------|-----------------|----------------------|------------|---------------|
| 1   | Colchicine   | -2.9516       | 2               | H bond donor         | Glu 189   | N of amide    |
|     |              |               |                 | H bond acceptor      | Gln 166   | C=O of heptene |
| 2   | Codeine      | -14.0087      | 1               | H bond acceptor      | Glu 166   | OH of alcohol |
|     |              |               |                 | H bond acceptor      | Glu 166   | OH of alcohol |
| 3   | Piperine     | -13.9889      | 2               | H bond acceptor      | Glu 166   | C=O          |
|     |              |               |                 | H bond acceptor      | Glu 166   | C=O          |
| 4   | Papaverine   | -14.1058      | 3               | Arene cation interaction | His 41 | Phenyl ring |
|     |              |               |                 | H bond acceptor      | Glu 166   | Phenyl ring   |
| 5   | Ergotamine   | -4.7900       | 2               | H bond acceptor      | Asn 142   | N of amide    |
|     |              |               |                 | H bond acceptor      | Gln 189   | OH of alcohol |
|     |              |               |                 | H bond acceptor      | Gln 189   | OH of alcohol |
| 6   | Theophylline | -9.0847       | 3               | Arene cation interaction | His 41 | Phenyl ring |
|     |              |               |                 | H bond acceptor      | Glu 166   | C=O          |
| 7   | Theobromine  | -14.2779      | 2               | Arene cation interaction | His 41 | Phenyl ring |
|     |              |               |                 | H bond acceptor      | Glu 166   | 4-C=O        |
| 8   | Caffeine     | -11.8904      | 2               | Arene cation interaction | His 41 | Phenyl ring |
|     |              |               |                 | H bond acceptor      | Glu 166   | 4-C=O        |
|     |              |               |                 | Arene cation interaction | His 41 | Phenyl ring |
|     |              |               |                 | H bond acceptor      | Glu 166   | 4-C=O        |

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| No. | Name     | 2D Allosteric binding of drugs with protease, (PDB, ID; 5R7Y); | 3D Allosteric binding of drugs with protease, (PDB, ID; 5R7Y); |
|-----|----------|---------------------------------------------------------------|---------------------------------------------------------------|
| 1   | Colchicine | ![Colchicine 2D Structure](image1)                              | ![Colchicine 3D Structure](image2)                             |
| 2   | Codeine   | ![Codeine 2D Structure](image3)                                | ![Codeine 3D Structure](image4)                                |
| 3   | Piperine  | ![Piperine 2D Structure](image5)                               | ![Piperine 3D Structure](image6)                               |
| 4   | Papaverine, | ![Papaverine 2D Structure](image7)                            | ![Papaverine 3D Structure](image8)                            |
| 5   | Ergotamine | ![Ergotamine 2D Structure](image9)                             | ![Ergotamine 3D Structure](image10)                            |
amino acid his 41 with phenyl ring of colchicine, and imidazole of both theophylline and theobromine. colchicine and codeine had 3 interactions with 5R7Y, but the other alkaloids had only one or two interactions (Figure 1, Table 1).

**Binding interactions of alkaloid with 5R7Z**

The docking scores of tested alkaloids with 5R7Z ranged from -23.1619 for papaverine and -7.4275 for theophylline. Glu 166 amino acid formed H bond acceptor with C=O of theobromine, while formed H bond donor with alcoholic OH of ergotamine. Glu 189 constricted H-bond acceptor with methoxy groups of colchicine and papaverine. Arene cation interactions were observed between amino acid his 41 with phenyl rings of piperine and papaverine and imidazole of caffeine (Figure 2, Table 2).

**Binding interactions of alkaloid with 5R80**

The number of interactions of alkaloids with 5R80 are 2 (colchicine, papaverine, ergotamine and theophylline) but codeine, piperine, theobromine and caffeine formed only one interaction. The docking scores of tested alkaloids with 5R80 ranged from -24.7449 for ergotamine and -6.0634 for theophylline. Glu 166 amino acid formed H bond donor with amidic N of colchicine and ergotamine, alcoholic OH of codeine, and N atom of theophylline while formed H bond donor with C=O of ergotamine. Gln 189 made H-bond acceptor with C=O groups of colchicine, piperine, theophylline, theobromine and caffeine but with methoxy group of papaverine (Figure 3, Table 3).

**Binding interactions of alkaloid with 5R81**

The docking scores of tested alkaloids with 5R81 ranged from -20.4813 for ergotamine and -9.2269 for theobromine. Gly 143 amino acid formed five H bond acceptor, with C=O groups of colchicine, piperine, caffeine and theobromine while with methoxy group of papaverine. Gln 189 made six H bond acceptor with C=O groups of colchicine, ergometrine (amidic and oxazole C=O), and theophylline but with furan of codeine, and methoxy of papaverine (Figure 4, Table 4).

**Binding interactions of alkaloid with 5R82**

The docking scores of tested alkaloids with 5R82 ranged from -14.2779 for theobromine and -2.9516 for colchicine. Papaverine formed three interactions, two H bond acceptor with gly 143 and one amine cation interaction with his 41. Also, theophylline formed three interactions, one is amine cation interaction with his 41 and two H bond acceptor with gly 143 and glu166 amino acids (Figure 5, Table 5).
| No. | Compound     | 2D Allosteric binding of drugs with protease, (PDB, ID: 5R7Z). | 3D Allosteric binding of drugs with protease, (PDB, ID: 5R7Z). |
|-----|--------------|---------------------------------------------------------------|---------------------------------------------------------------|
| 1   | Colchicine   | ![Colchicine 2D Binding](image1)                            | ![Colchicine 3D Binding](image2)                           |
| 2   | Codeine      | ![Codeine 2D Binding](image3)                                | ![Codeine 3D Binding](image4)                               |
| 3   | Piperine     | ![Piperine 2D Binding](image5)                               | ![Piperine 3D Binding](image6)                              |
| 4   | Papaverine   | ![Papaverine 2D Binding](image7)                             | ![Papaverine 3D Binding](image8)                            |
| 5   | Ergotamine   | ![Ergotamine 2D Binding](image9)                             | ![Ergotamine 3D Binding](image10)                           |
**Figure 2**: 2D Allosteric binding of drugs with protease, (PDB, ID; 5R7Z); 3D Allosteric binding of drugs with protease, (PDB, ID; 5R7Z).

| No. | Compound name | 2D Allosteric binding of drugs with protease, (PDB, ID; 5R7Z) | 3D Allosteric binding of drugs with protease, (PDB, ID; 5R7Z) |
|-----|---------------|-------------------------------------------------------------|-------------------------------------------------------------|
| 6   | Theophylline  | ![Image](image1.png)                                         | ![Image](image2.png)                                         |
| 7   | Theobromine   | ![Image](image3.png)                                         | ![Image](image4.png)                                         |
| 8   | Caffeine      | ![Image](image5.png)                                         | ![Image](image6.png)                                         |

*Table showing various compounds with their corresponding 2D and 3D binding representations.*
|   | Compound       | 2D Allosteric binding of drugs with protease, (PDB, ID: 5R80) | 3D Allosteric binding of drugs with protease, (PDB, ID: 5R80) |
|---|----------------|-------------------------------------------------------------|-------------------------------------------------------------|
| 1 | Colchicine     | ![Colchicine 2D](image1)                                    | ![Colchicine 3D](image2)                                    |
| 2 | Codeine        | ![Codeine 2D](image3)                                      | ![Codeine 3D](image4)                                      |
| 3 | Piperine       | ![Piperine 2D](image5)                                     | ![Piperine 3D](image6)                                     |
| 4 | Papaverine     | ![Papaverine 2D](image7)                                   | ![Papaverine 3D](image8)                                   |
| 5 | Ergotamine     | ![Ergotamine 2D](image9)                                   | ![Ergotamine 3D](image10)                                  |
| 6 | Theophylline   | ![Theophylline 2D](image11)                                | ![Theophylline 3D](image12)                                |
| 7 | Theobromine    | ![Theobromine 2D](image13)                                 | ![Theobromine 3D](image14)                                 |
| 8 | Caffeine       | ![Caffeine 2D](image15)                                    | ![Caffeine 3D](image16)                                    |

**Figure 3:** 2D Allosteric binding of drugs with protease, (PDB, ID: 5R80); 3D Allosteric binding of drugs with protease, (PDB, ID: 5R80).
| No. | Name       | 2D Allosteric binding of drugs with protease (PDB, ID: 5R81) | 3D Allosteric binding of drugs with protease (PDB, ID: 5R81) |
|-----|------------|-------------------------------------------------------------|-------------------------------------------------------------|
| 1   | Colchicine | ![Colchicine 2D](image1) ![Colchicine 3D](image2)          | ![Colchicine 3D](image3) ![Colchicine 2D](image4)          |
| 2   | Codeine    | ![Codeine 2D](image5) ![Codeine 3D](image6)               | ![Codeine 3D](image7) ![Codeine 2D](image8)               |
| 3   | Piperine   | ![Piperine 2D](image9) ![Piperine 3D](image10)            | ![Piperine 3D](image11) ![Piperine 2D](image12)            |
| 4   | Papaverine | ![Papaverine 2D](image13) ![Papaverine 3D](image14)       | ![Papaverine 3D](image15) ![Papaverine 2D](image16)       |
| 5   | Ergotamine | ![Ergotamine 2D](image17) ![Ergotamine 3D](image18)       | ![Ergotamine 3D](image19) ![Ergotamine 2D](image20)       |
| No. | Name          | 2D Allosteric binding of drugs with protease, (PDB, ID; 5R81) | 3D Allosteric binding of drugs with protease, (PDB, ID; 5R81) |
|-----|---------------|-------------------------------------------------------------|-------------------------------------------------------------|
| 6   | Theophylline  | ![Image](338x70 to 451x153)                                  | ![Image](341x164 to 449x234)                                 |
| 7   | Theobromine   | ![Image](342x244 to 447x322)                                 | ![Image](360x356 to 476x514)                                |
| 8   | Caffeine      | ![Image](361x749 to 470x866)                                 | ![Image](363x640 to 469x743)                                |

*Figure 4:* 2D Allosteric binding of selected alkaloids with protease, (PDB, ID; 5R81); 3D Allosteric binding of drugs with protease, (PDB, ID; 5R81).
CONCLUSION

Gln 189 and his 41 amino acids represent a corner stone for binding of alkaloid with 5R7Y while papaverine has the highest docking score with 5R7Z with three interactions. Ergotamine has the highest docking score with 5R7Z with two H-bonds one acceptor and the another is donor. 5R81 amino acids, Gln 189 and Gly 143 formed six and five H-bond acceptors, respectively. While in 5R82, the amino acids Glu 166 formed five interactions with colchicine, codeine, piperine, theophylline and caffeine while his 41 formed arene cation interactions with papaverine, theophylline, theobromine and caffeine. Among the tested drugs, papaverine and ergometrine revealed high docking scores for all five proteins (score ranged from, -14.1058 to 23.1619 for papaverine and, -4.7900 to 24.7449 for ergometrine) and number of interactions with all tested proteins are two to three for papaverine but for ergometrine are two to five.

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Figure 5: 2D Allosteric binding of drugs with protease, (PDB, ID; 5R82); 3D Allosteric binding of drugs with protease, (PDB, ID; 5R82).
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GRAPHICAL ABSTRACT

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