Advances in Bioresearch
Adv. Biores., Vol 14 (5) September 2023: 180-185

Print ISSN 0976-4585; Online ISSN 2277-1573
Journal's URL:http://www.soeagra.com/abr.html
CODEN: ABRDC3
DOI: 10.15515/abr.0976-4585.14.5.180185

Advances in Bioresearch

ORIGINAL ARTICLE

Black Tea and Peppermint as Possible Binding Compounds to Severe Acute Respiratory Syndrome Coronavirus-2 Major Protease

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ABSTRACT
Coronavirus disease 2019 is an exceptionally contagious respiratory illness coming from a dangerous novel coronavirus occur in December 2019, the world is facing unprecedented crises in the coronavirus disease 2019 pandemic. Amongst the uncertainty, many are left questioning what we can do to fight this virus; viral proteins have been approved to be a target for treatment especially that responsible for viral reproduction. To assessment the interaction between the bioactive constituents of black tea and peppermint aqueous extract against the main protease of severe acute respiratory syndrome coronavirus-2 using molecular docking method. Experiments including raw material plants like black tea was purchased from local Iraqi markets and the peppermint was cultivated from Iraqi farms at January to March 2021, then it was dried, grounded by electric mortar and stored in dark place at 20ºC until analyzed the bioactive constituents using GC-Mass. Molecular docking was achieved and re-rank score was used to compare the data. High concentration of thearubigins 59.2% was extracted from black tea followed by (-)-Epigallocatechin-3- gallate10.9%, (-)- Epigallocatechin 9.8% and (-) -Epicatechin-3-gallate7%. While the catechin was recorded as only 2% of the extract. As well as, high percentage of menthol 27%, menthone 16%, menthofuran 4.5% and menthylacetate 4.4% were extracted from peppermint. Cineole and Menthol extracted from peppermint had highest re-rank -100 and -99.2 respectively among the other extracted compounds. Followed by promising four compounds identified in black tea extracts and these were (-)-Epigallocatechin-3-gallate -98.77, Theaflavin -3-gallate -96.21, Quercetin -95.6 and Thearubigins -94.42. High interaction between the plant extract Mallotojaponin with Re-rank scored the highest value -140 and curcumin scored with re- rank -112 in comparison with other plant components from black tea and peppermint under investigation. Aqueous extraction of black tea and peppermint contained several bioactive compounds and the molecular docking ensured the interaction capability between ligand and M^{pro}. Incorporating few cups of black tea and peppermint into daily hot drink is an incredibly simple and cost-effective intervention, and it may help people to fight this pandemic-causing virus as well as aqueous extract could use as a mouth and tonsil wash several times at a day without any adverse effects.
Keywords: *Molecular docking, main protease (Mpro), black tea, peppermint, curcumin, Mallotojaponin, remdesivir and tenofovir*

Received 14.05.2023 Revised 24.06.2023 Accepted 23.07.2023

How to cite this article:
Thuraya K. AL-W, Raghad S. M, Areej A. H, Khlood A. Al-K, Mohammed W T. Black Tea and Peppermint as Possible Binding Compounds to Severe Acute Respiratory Syndrome Coronavirus-2 Major Protease. Adv. Biores. Vol 14 [5] September. 2023. 180-185.

INTRODUCTION

Severe acute respiratory syndrome coronavirus-2 (SARS-COV-2) is the third fatal coronavirus that has emerged in the past two decades, following sever acute respiratory syndrome coronavirus-1 (SARS-CoV-1) and the Middle East respiratory syndrome (MERS-CoV) [1]. More than 160 million persons were infected worldwide with mortality reached to 3320000 persons. Iraq is one of the Middle East Country that faced the pandemic of coronavirus disease 2019(COVID 19), more than 1120000 infected Iraqi people with 15430 deaths at May 13, 2021 [2].

Severe acute respiratory syndrome coronavirus-2 is a single-stranded RNA virus and shares 78% genetic similarity with SARS-COV-1, that emerged the outbreak at 2003 [3]. Six major open reading frames (ORF) exist in SARS-CoV-2, ORF1ab occupies the two-thirds length of the whole genome and sub genome RNA to play roles in viral pathogenesis excluding its replication function as well as involving in cellular signaling and modification of cellular gene expression [4]. It can be transmitted thought respiratory droplets and direct contact; while the main transmission route of SARS-CoV-2 is aerosols the virus was also found in stool of recover's patient [5]. The disease initiates through the interaction of its binding domain on the spike- like protein with the target host cell via angiotensin- converting enzyme 2(ACE2) that known to lying in different organs such as lung, intestine, adipose tissues cardiac cell[4]. There have also been geographic disparities in the frequency of specific COVID-19 clinical symptoms[6]. Sever acute respiratory syndrome - corona virus-2 infection is characterized by flu-like symptoms such as cough, fever, weakness, and myalgia. Patients may experience diarrhea and nausea for a few days before developing a fever, meaning that fever is the most frequent but not the most severe symptom of infection. A small percentage of patients can experience headaches or hemoptysis [7].

Viral proteins have been authorized to be a target for treatment; they are spike protein, RNA dependent RNA polymerase (Rd^{Rp}), the main protease (M^{pro}), chymotrypsin-like protease and papain-like protease that almost encodes by all coronavirus. Proteases enzymes used for proteolysis processing during virus maturation [8, 9]. This basically means that the virus needs these specific protein breaking enzymes in order to mature and function. Also, the chymotrypsin-like protease ($3CL^{pro}$) has been considered a very important molecular target for a novel anti-SARS-CoV drug [10-11].

Other approaches were applied in COVID19 treatment or prophylaxes and the most non-toxic without side effects is the based on the plant materials or their active ingredients such methods are called Unani and Ayurvedic medicines. Different parts of several plants were having antiviral activity [12-14]. A search of the Natural Product Libraries found that 720 pure natural products were investigated for compounds that could lead to a potential drug that has anti-COVID-19 efficacy. This was later narrowed down to 10 different compounds and mixtures that had strong potential for anti-COVID-19 efficacy. Most of these compounds come from different type of tea plant the *Camelia sinensis.* The compounds that have been found to have an anti-COVID 19 effect are the polyphenols that are found in teas [15]. The current study design to assessment the interaction between the bioactive constituents of black tea and peppermint aqueous extract against the main protease of severe acute respiratory syndrome coronavirus-2 using molecular docking method.

MATERIAL AND METHODS

Plants and preparation of extracts

Experiments including raw material plants were designed as previously described. Black tea was purchased from local Iraqi markets; peppermint was cultivated and then collected on Iraqi farms at January- March 2021. Meanwhile, it was dried in a paper bag, grounded by electric mortar and stored in dark place at 20ºC. Aqueous extraction of black tea and peppermint were done according to [16]. Then the bioactive constituents were analyzed using GC-Mass.

Structural analyses

To probe the molecular architecture of SARS-CoV-2 $3CL^{pro}$, comparative homology modeling was performed using Modeler version 9.11. To select closely-related templates for modeling, PSI-BLAST was performed against all known structures in the protein databank (PDB). Chimera v1.8.1 and PyMOL educational version were used for initial quality estimation, energy minimization, mutation analyses, and image processing.

Ligand database preparation and molecular docking

The bioactive constituents from aqueous extract of black tea and peppermint were docked against the predicted SARS-CoV-2 M^{pro} structure. Molecular operating environment (MOE) was used for molecular docking, ligand-protein interaction and drug likeness analyses. All analyses were performed using the same protocols that are already described in previous studies; re-rank value was used to identify the interaction between ligand (plant compound) and its receptor (M^{pro}) [17].

RESULTS AND DISCUSSION

Different strategies can be participating in the control or prevent the severity of COVID19 disease outcome; such strategies could apply separately or together such as vaccines, peptides, small molecules drugs, monoclonal antibodies and interferon therapies. Designing of new methods linking between computational and other structural biology have facilitate the discovery of new drugs against COVID-19. One of the main COVID-19 viral virulence factors is the M^{pro} protein that denote a critical role in disease outcome through

its involvement of virus replication and maturation. Studying its structure provides a new insight to treat disease by identify potential drugs or supplements to prevent or reduce the infection outcome. Our scope to follow the structure of M^{pro} protein and its interaction with plant-based compounds using docking and computational soft-wares.

The result of current study indicated that aqueous extracts of black tea and peppermint contained different bioactive ingredients, so high concentration of Thearubigins 59.2% was extracted from black tea followed by (-)-Epigallocatechin-3- gallate10.9%, (-)- Epigallocatechin 9.8% and (-) -Epicatechin-3- gallate7%, while high percentage of menthol 27%, menthone 16%, menthofuran 4.5% and menthylacetate 4.4% were extracted from peppermint. However, the catechin was recorded as only 2% of the extract. This related with fact, the secondary metabolites produced by tea plant, which play multiple essential roles in plant physiology and have potential health properties on human health, mainly as antioxidants, anti-allergic, anti-inflammatory, anticancer, antihypertensive and antimicrobial agents [18, 19].

A Chinese research group studied these compounds in tea, and investigated whether they can inhibit chymotrypsin-like protease activity or not [20, 21]. They found that black tea significantly inhibited chymotrypsin-like protease activity. Furthermore, they dove deeper to specifically determine the molecule that is responsible for such activity and they reported that Theaflavin-3,3′ -digallate (TF3) was responsible for this activity. In-vitro study found that TF3 completely inhibited COVID virus replication in cell culture. Another study reported that theaflavins extracted from black tea were able to completely neutralize bovine coronavirus and rotavirus infections [22]. Molecular docking between ligand and the receptor M^{pro} in the present study illustrated in Figures (1, 2, 3) it demonstrated that more than one domain could candidate in the interaction of the bioactive compounds enhancing enzyme inhibition through different ligands such as hydrophobic interaction, ionic bonds, aromatic- aromatic interaction. One study demonstrated that protein structure of M^{pro} of SARS-CoV-2 shares almost 75-80% identity with other corona virus and described it as a good target for drug development; crystal structure of the M^{pro} stated three domains having cysteine protease with a chemotrypsin like two domain fold. Such structure could interact with different molecules that might inhibit its activity or denature its structure [23]. Recently Food and Drug administration authorities the use of Remdesivir at 1st May 2020; its function as a broad-spectrum antiviral drug that inhibits Rd^{Rp} enzyme from SARS-CoV-2 and another coronavirus [21, 22]. Other proposed drug target was the main protease Mpro which encodes for cysteine protease with a unique substrate containing glutamine residue at the P1 site; the inhibition of Mpro for almost coronavirus as well as enteroviruses rhinoviruses and noroviruses [12]. Recently reported that replication of picornaviruses and coronaviruses requires 3C protease (3Cpro) and 3C-like protease (3CLpro) respectively, which are structurally analogous with chymotrypsin-fold, but the former is a monomer and the latter is dimeric due to an extra third domain for dimerization, so the potential anti-coronavirus and anti-picornavirus therapeutic agents and a clue to convert 3CLpro inhibitors into 3Cpro inhibitors and vice versa[24]. So, the current study compared with two plant Mallotojaponin and Curcumin as well as two types of drugs it considered the first insight about the drugs remdesivir and tenofovir, they were able to interact with COVID19 M^{pro} protein with re-rank reached to -111 and -122 respectively. Earlier studies referred to the action of remdesivir as anadenosine nucleoside triphosphate analog in inhibition of viral RNA dependent RNA polymerase enzyme and evades proofreading by viral exoribonuclease (ExoN), causing a decrease in viral RNA production after only three nucleotide incorporation such medication [25, 26]. The other nucleotide analogue tenofovir that designed to inhibit the enzyme named as nucleotide reverse transcriptase decreasing the ability of viral replication through the inhibition of ATP- polymerization into the growing nucleic acid chain [27]. Additionally, the strong ligand-protein interactions of some conventional drugs such as Remdesivir and Tenofovir in addition to plant-based compounds such as Curcumin (*Curcuma longa*) and Mallotojaponin (*Mallotus versitifolius*) render these compounds promising and recommended for further studies [28, 29].

Based on docking results (Table 1), various extracts of black tea and peppermint exhibited a significantly strong interaction with the studied receptor. Re-rank used here to determine the strongest of simulated interaction between ligand and its target receptor, data referred to that Cineole and Menthol extracted from peppermint had highest re-rank -100 and -99.2 respectively among the other extracted compounds. Followed by promising four compounds identified in black tea extracts and these were (-)-Epigallocatechin-3-gallate -98.77, Theaflavin -3-gallate -96.21, Quercetin -95.6 and Thearubigins -94.42. The hydroxyl group, ketone group and ether group in cineole and menthol extracted from peppermint predicted to initiate an interaction with the amino acid residues in active site of M^{pro} causing an inhibition to its activity. The interactions might due to hydrophobic residues interactions, ionic interactions, hydrogen bonds, aromatic- aromatic interaction and sulfur bonds within the peptide-protein complexes. Such finding of oily extracted of 1,8 Cineole from eucalyptus exhibited high interaction with M^{pro} of Covid19 and inhibit viral reproduction. However, several studies conducted in different countries reported the essential role

for this material as therapeutic agent in treatment such as study predicted in vitro enzyme assays as well as animal models ensure the simulant studies regarding the pharmacological potentials against different respiratory infections [23]. Other study reported that 1,8-cineole is known for its mucolytic and spasmolytic action on the respiratory tract, with proven clinical efficacy, so 1,8-cineole has also shown therapeutic benefits in inflammatory airway diseases, such as asthma and chronic obstructive pulmonary disease (COPD) [30]. Menthol has been shown to reduce dyspnea in many respiratory conditions[31,32,33].

Compounds Ligand	Molecular Formula	PubChem CID	MolDock	Rerank	HB
Limonene	C10H16	22311	-43.27	-89.70	-7.75
Cineole	C10H18O	10106	-98.23	-100.00	-9.20
Menthone	C10H18O	26447	-46.71	-76.71	-4.75
Menthofuran	C10H14O	329983	-19.23	-84.98	-6.25
Isomenthone	C10H18O	6986	-94.80	-83.80	-4.50
Menthyl acetate	C12H22O2	27867	-39.84	-75.53	-4.00
Sopulegol	C10H18O	170833	-50.14	-90.88	-7.00
Menthol	C10H20O	1254	-91.36	-99.20	-9.10
Pulegone	C10H16O	442495	-36.40	-88.52	-6.50
Carvone	C10H14O	7439	-53.58	-77.90	-5.50
(-)-Epicatechin	C15H14O6	72276	-87.93	-82.62	-6.00
(-)-Epicatechin-3-gallate	C22H18O10	65056	-32.97	-74.35	-3.75
(-)-Epigallocatechin	C22H18O11	65064	-57.01	-92.06	-8.00
(-)-Epigallocatechin-3-gallate	C34H36O22	102025303	-84.49	-98.77	-8.70
(+)-Catechin	C15H14O6	9064	-29.53	-87.34	-6.75
(+)-Gallocatechin	C15H14O7	65084	-60.45	-79.08	-4.25
Theaflavin	C29H24O12	135403798	-81.06	-81.44	-5.00
Theaflavin-3,3' -digallate	C43H32O20	136277567	-63.88	-93.24	-7.25
Theaflavin-3'-gallate	C36H28O16	136825044	-26.10	-86.16	-5.25
Theaflavin -3-gallate	C36H28O16	169167	-77.62	-96.21	-8.50
Thearubigins	C43H34O22	100945367	-67.32	-94.42	-8.25
Kaempferol	C15H10O6	5280863	-74.19	-80.26	-5.75
Myricetin	C15H10O8	5281672	-22.66	-73.17	-3.50
Quercetin	C15H10O7	5280343	-70.75	-95.60	-7.50
Remdesivir	**C27H35N6O8P**	**121304016**	**-128.23**	**-111.00**	**-8.60**
Tenofovir	**C9H14N5O4P**	**464205**	**-144.25**	**-122.00**	**-9.50**
Mallotojaponin	**C24H28O8**	**122659**	**-180.20**	**-140.00**	**-11.23**
Curcumin	**C21H20O6**	**969516**	**-172.25**	**-112.00**	**-8.50**

Table 1: The Predicted Poses Scores of The Rest Inspected Antiviral Drugs

Recent finding also refer to the high interaction between the plant extract Mallotojaponin that extracted from *Mallotus versitifolius* plant, re- rank scored the highest value -140 and curcumin scored with re- rank -112 in comparison with other plant components from black tea and peppermint under investigation. compounds from the aqueous extract of peppermint and black tea as well as the extract of curcumine, all challenged against the main protease of COVID-19 to perform a binding simulation in the search for probable inhibitors.

CONCLUSION

In conclusion, it's important to note that this is preliminary data and it may help to fight against COVID-19; aqueous extraction of black tea and peppermint contained several bioactive compounds and the molecular docking ensured the interaction capability between ligand and Mpro. Consumption of black tea and peppermint could augment the chemical drug Remdesivir or Tenofovir against COVID-19. Incorporating few cups of black tea and peppermint into daily hot drink is an incredibly simple and cost-effective intervention, and it may help people to fight this pandemic-causing virus. Also, as a daily habit, aqueous extract could use as a mouth and tonsil wash several times at a day without any adverse effects.

ACKNOWLEDGMENT

The assistance provided by Dr. Michael Alabboud at University of Tehran was greatly appreciated.

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