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RESEARCH ARTICLE

EFFECTS OF DRUGS ON SPIKE GLYCOPROTEIN OF SARS-COV-2 IN CONTROL OF COVID-19

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Abstract

The spike glycoprotein of SARS-CoV-2 is 3849 bp length present from 21536 to 25384 location in genome as per the prediction from FGENSEV0 server and is related to mutated SARS genome. The tiny molecular key on SARS-CoV-2 that gives the virus entry into the cell is called a spike glycoprotein, or S-glycoprotein. The docking results have shown that compounds like Curcumin (Enol form) and anti-viral drugs like Ombitasvir with SARS-CoV-2 has shown best results. Apart with these compounds Curcumin (Keto form), Cholecalciferol (Vitamin D), Ascorbic acid (Vitamin C), 3-isobutyl-1-methylxanthine (in tea), Chloroquine, Eugenol, Theophylline and Caffeine are also shown better results. The compounds provide support for the development of immune system and control SARS-CoV-2. The results have shown that turmeric powder, tea and sun light can treat COVID-19 in natural way.

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Introduction:-

New infectious diseases from several microbes emerged from past 50,000–100,000 years till modern humans (Kidgell et al., 2002; Stringer, 1990). Several viral diseases like smallpox, mumps, rubella, polio, influenza, herpes viruses, poliovirus, rabies, yellow fever, dengue fever, HIV and Severe Acute Respiratory Syndrome (SARS) are effected to humans from about 10,000 years ago (Grabenstein and Nevin, 2006). Some of the diseases are epidemics or pandemic of viral diseases effected on large number of people worldwide. The rare epidemics of viral diseases that are originating in animals will be short-lived as the emerged viruses were not fully adapted to humans. Measles was so common in children but COVID-19 is most common in people of all ages that destroys respiratory system. Some infectious diseases may play a major role in the development of Parkinson's disease (Vlajinac et al., 2003).

In recent decades several antiviral drugs and anti-inflammatory compounds (Chattopadhyay et al., 2009) have been developed to specifically target viruses for quicker recovery although vaccines are still the most powerful weapon against viruses. Ayurveda is perhaps originated 5,000 years ago in India for the treatment of diseases. Treatment of new emerging viral diseases is challenges for medical scientists from ancient times. Neem (*Azadirachta indica*) is a commonly grown medicinal herb that helps in the recovery from chicken pox. The Neem is brewed together with chrysanthemum used to drink as herbal tea for development of immune system and keeping away of acne, chicken pox and measles. Turmeric mixed with boiled milk or water is used to be taken for the treatment of intestinal disorders, viral fevers, cold and sore throats. An ancient Ayurvedic text Charaka Samhita provided information on illness from smallpox, with a recommended treatment of a poultice of neem leaves and turmeric (Nene, 2007).

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COVID-19 pandemic was emerged in December 2019 in Wuhan, China (Han et al., 2020), was spread to many countries that may have millions of confirmed cases/ deaths by the end of year 2020. Coronaviruses infect birds and mammals and primarily target epithelial cells that are associated with gastrointestinal and respiratory infections. Asian leopard cat, Chinese ferret badger, rodents, birds and bats play a vital role in coronavirus ecology and evolution especially from regions of China. Members of the family Coronaviridae generally contain two envelope proteins, the membrane (M) and spike (S) glycoproteins. The progenitors of the M and S glycoproteins were encoded from the common ancestor of the Corona- and Toro- virinae lineages (Sánchez et al., 1992). The particles are sensitive to lipid solvents, heat, non-ionic detergents, oxidizing agents, formaldehyde and UV irradiation (King et al., 2012). The S-glycoprotein is major inducer of virus-neutralizing antibodies that are drawn out mainly by several epitopes in the amino terminal half of the molecule.

Methodology:-

Genome retrieval and structure prediction of spike Glycoprotein from SARS-CoV-2:

The SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) complete genome sequence has been retrieved from the NCBI database (Accession number NC_045512.2) that is an isolate from Wuhan-Hu-1 of China. The gene prediction (Kaladhar and Krishna, 2011) for SARS-CoV-2 complete genome was predicted using FGENESV0. The gene identification for the protein sequences has been submitted to BLASTp and selected spike glycoprotein. The protein sequence was submitted to swissmodel and 3D model (Figure 1) was obtained for docking studies.

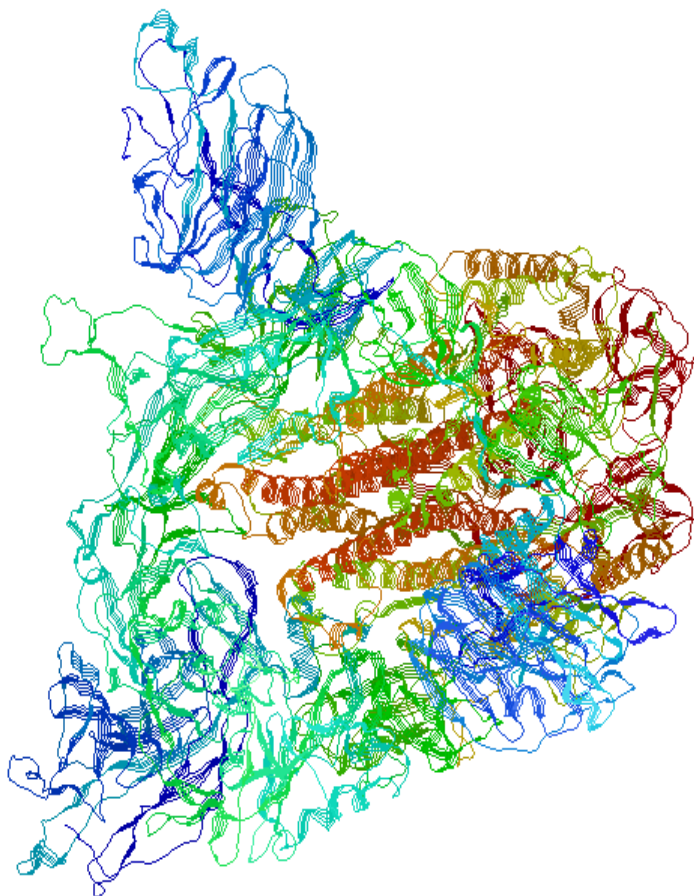


Figure 1:- Spike Glycoprotein of SARS-CoV-2.

Retrieval and design of Ligands:

The ligands like Caffeine, Theophylline, Metformin, Chloroquine, Coumarin, 3-isobutyl-1-methylxanthine, Ombitasvir, Vitamin C and Vitamin D were retrieved from Drugbank database. The ligands Camphor, Cineole, Curcumin and Eugenol were designed and optimized using ACDLABS 10.0 (ChemSketch) software. The molecules (Figure 2) are selected for testing activity against spike glycoprotein of SARS-CoV-2.

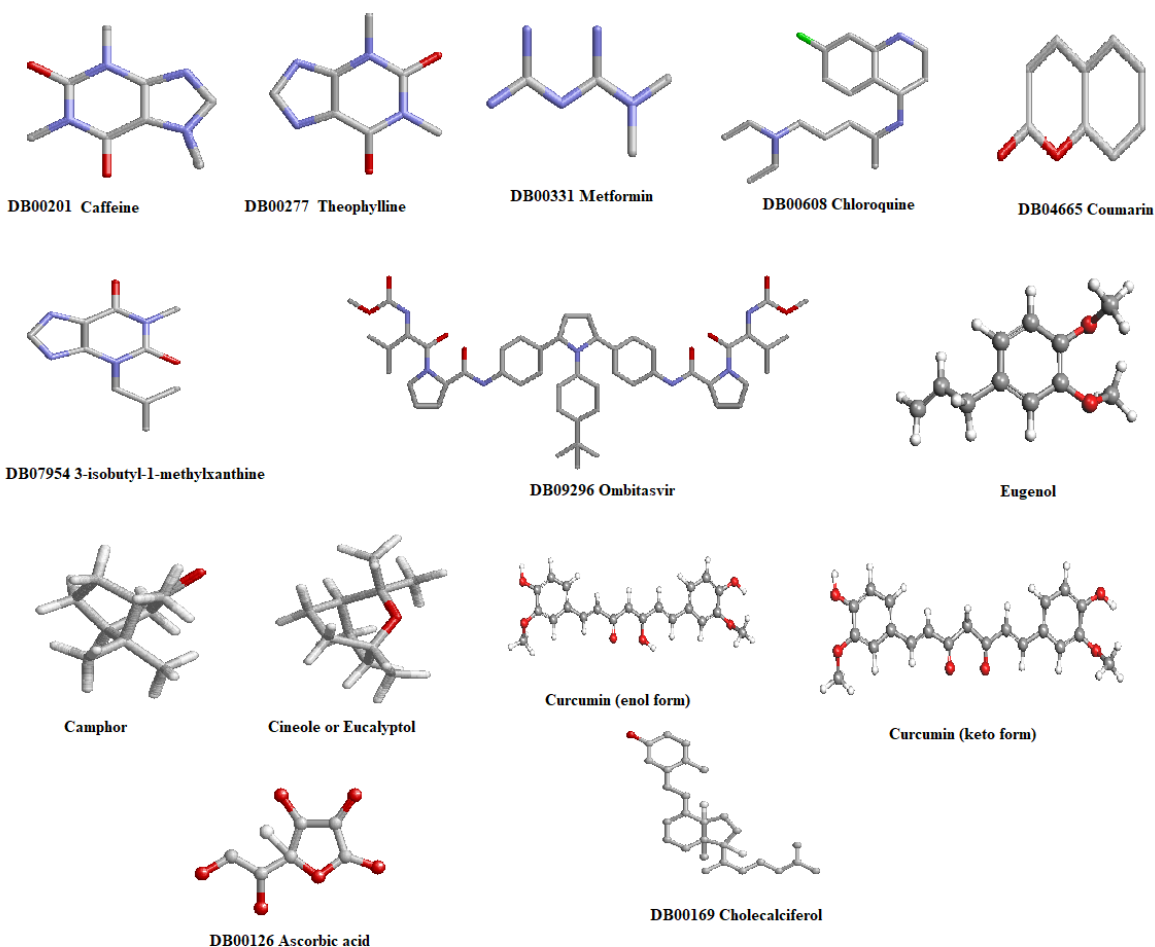


Figure 2:- Selected ligands tested for SARS-CoV-2.

Properties of computer:

The system properties in the present work are as follows:

Processor: Pentium (R) Dual-core CPU E5200 with 2.50 GHz, 2GB RAM and 32 bit Operating system.

Docking studies:

The modeled structure of spike glycoprotein of SARS-CoV-2 is selected as receptor in the present study. The docking studies of spike glycoprotein with selected ligands are conducted using iGEMDOCK v2.1 software.

Results:-

The SARS-CoV-2 genome sequence of NC_045512.2 related to severe acute respiratory syndrome coronavirus 2 isolate Wuhan-Hu-1, complete genome has been retrieved from NCBI. The complete genome has 29903 bp, ss-RNA with linear structure. The spike glycoprotein of SARS-CoV-2 is 3849 bp length that is present from 21536 to 25384 location, as per the prediction from FGENSEV0 server. The sequence is related to SARS genome based on the identification method used by BLASTp.

The structure of the identified SARS-CoV-2 was shown in Figure 3.

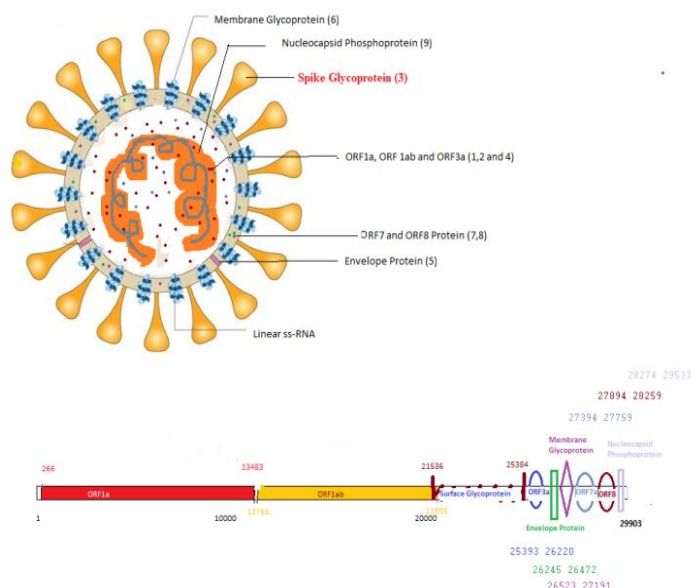


Figure 3:- Phenotypic and genomic structure of SARS-CoV-2.

The tiny molecular key on SARS-CoV-2 that gives the virus entry into the cell is called a spike glycoprotein, or S-glycoprotein. Hence spike surface glycoprotein is the main protein to be concentrated for understanding effects with anti-viral drugs and drugs. The lower the value of K_i , the more will be favorable is the binding. Hence, the docking studies with lower energies show better activity of ligands with receptor (Table 1).

Table 1:- Docking studies of selected ligands with S-glycoprotein of SARS-CoV-2.

Ligand	Energy in Kcal/mol	VDW/HBond/Elec	Active sites
Caffeine	-70.03	-60.65/-9.38/0	Thr439-Phe524-Phe438-Glu525-Leu526
Theophylline	-73.75	-50.16/-23.6/0	Phe842-Leu867-Thr 868 -Val869-Asp623-Arg655-Ala861
Metformin	-66.16	-33.75/-30.6/-1.82	Cys388-Val391-Ser392-Arg992-Glu997-
Chloroquine	-81.86	-74.86/-7/0	ASP839-Leu867-Phe842-Thr868-Val869-Leu968
Coumarin	-66.6	-54.18/-12.42/0	Asn773-Asn326Thr770-Arg774-Gln323-Thr324
3-isobutyl-1-methylxanthine	-82.3	-71.87/-10.43/0	Gln966-Thr970-Gln1019-Gln771-Gln966-Ala967
Ombitasvir	-124.97	-108.3/-16.67/0	Cys175-Thr176-Arg366-Asn369-Asn174-Phe177-Pro239-Asn403-Pro530-Thr532
Eugenol	-75.33	-75.33/0/0	Lys1047-Arg1048-Val1049 -Tyr1056-His1057
Camphor	-65.78	-56.34/-9.44/0	Ser1046-Lys1047-Arg1048
Cineole	-62.85	-60.38/-2.47/0	Lys1047-Arg1048
Curcumin (Enol form)	-112.37	-95.04/-17.34/0	Cys769-Arg774-Asn326-Thr748-Thr770-Asn773-Gln323-Thr324-Ser325-Arg328
Curcumin (Keto form)	-102.27	-81.68/-20.59/0	Arg774-Ser325-Asn326-Arg328-Thr748-Thr770-Gln323-Thr324
Ascorbic acid	-82.83	-38.22/-44.61/0	Asn108-Lys-196-Asn-197-Leu198-Arg199-His216-Thr217
Cholecalciferol	-88.38	-88.38/0/0	Ile1022-Ala1025-Glu1026-Ala1029-Leu1033-Ala1025-Arg1028-Ala1029-Leu1033

The docked poses of Curcumin (Enol form) and Ombitasvir with SARS-CoV-2 respectively has been shown in Figure 4.

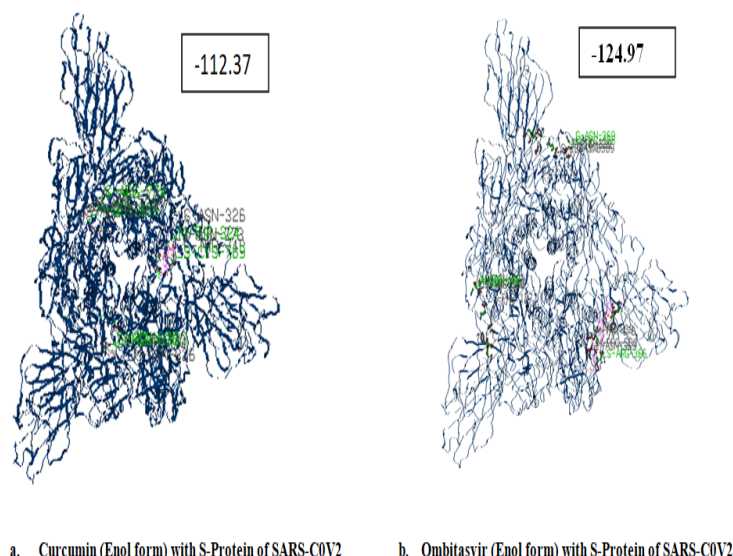


Figure 4:- Docked poses of Curcumin (Enol form) and Ombitasvir with SARS-CoV-2 respectively.

The docking results have shown that compounds like Curcumin (Enol form) and anti-viral drugs like Ombitasvir with SARS-CoV-2 is shown best results. Apart with these compounds Curcumin (Keto form), Cholecalciferol (Vitamin D), Ascorbic acid (Vitamin C), 3-isobutyl-1-methylxanthine (in tea), Chloroquine, Eugenol, Theophylline and Caffeine (in coffee) are also shown better results. The compounds provide support for the development of immune system and control SARS-CoV-2. The results have shown that turmeric powder, tea and sun light can treat COVID-19 in natural way.

Discussion:-

Coronaviruses appear as pleiomorphic, 120–160nm in diameter, roughly spherical, with a characteristic fringe of large (ca. 20nm), petal-shaped surface projections comprised of trimers of the spike (S) glycoprotein. The spike (S) glycoprotein of SARS-CoV-2 is responsible for receptor binding and a major antigenic determinant that is capable of inducing protective immunity. Receptor-binding domain (RBD) of S glycoprotein is an important immunogenic site in patients is a critical neutralization determinant of SARS-CoV-2 during viral infection and immunization (He et al., 2005).

Plants play important role in control of several viral diseases. The selected ligands in the present work and the availability from plant sources were shown in Table 2.

Table 2:- Selected ligands and the availability from plant sources.

Ligand	Plant /s	Disease	Reference
Caffeine	<i>Camellia sinensis</i> , <i>Coffea canephora</i> (<i>robusta coffee</i>), <i>C. brevipes</i> and <i>C. stenophylla</i>	Stimulant	Gramza-Michałowska, 2014; Clifford and Ramirez-Martinez, 1991
Theophylline	<i>Camellia sinensis</i>	Stimulant	Popa et al., 2010
Metformin	<i>Galega officinalis</i>	Diabetes	Bailey, 2017
Chloroquine	Cinchona bark	Anti-malarial	Kenyon et al., 1949
Coumarin	<i>Dipteryx odorata</i> ; vanilla grass (<i>Anthoxanthum odoratum</i>), sweet woodruff (<i>Galium odoratum</i>), sweet grass (<i>Hierochloe odorata</i>) and sweet-clover (genus <i>Melilotus</i>)	Oedemas; anticoagulant (blood thinner); prevent blood clots in the heart, lower body, and lungs	Bairagi et al., 2012

3-isobutyl-1-methylxanthine	<i>Camellia sinensis</i>	Stimulant	Popa et al., 2010
Ombitasvir	Cannabis Plant	Anti-viral	Dimond and Lorem, 2020
Eugenol	<i>Ocimum sanctum</i>	Anthelmintic activity, anti-inflammatory	Thakur and Pitre, 2009
Camphor	<i>Ocimum canum</i> Sims, <i>Ocimum urticifolia</i> Roth	Pesticides	Chagonda et al., 2000
Cineole	<i>Artemisia annua</i>	Antiinflammatory	Tripathi et al., 2001
Curcumin (Enol form)	<i>Curcuma longa</i>	Anti-inflammatory, anti-oxidant, and neuroprotective	Akram et al., 2010
Curcumin (Keto form)	<i>Curcuma longa</i>	Anti-inflammatory, anti-oxidant, and neuroprotective	Akram et al., 2010
Ascorbic acid (Vitamin C)	<i>Malus domestica</i> , <i>Citrus sinensis</i> , <i>Ananas comosus</i> and <i>Citrullus lanatus</i>	Wound healing. Antioxidant, lower blood cholesterol, treating the common cold	Nweze et al., 2015
Calciferol (Vitamin D-sunlight)	Microalgae	Hypertension, autoimmune diseases, diabetes, and cancer	Brown et al., 1999

The total number of cases is increasing and may have millions of confirmed cases/ deaths by the end of year 2020. The coronavirus COVID-19 was affected many countries and territories around the world and international conveyances. The experimentation has shown that turmeric powder, tea and sun light can treat COVID-19 in natural way.

Conclusion:-

Large number of viruses has been emerged for the ancient times from China. There is a need to control these new emerging viruses to several counties before spread. The development of immune system through natural sources, distance maintenance and isolation of people (Fast pandemic to slow pandemic), avoiding exchange of materials like plastics, utensils, etc, washing hands with soap solution, use of antiviral drugs, medicinal compounds like turmeric powder, tea, vitamin D (sitting in morning sun light) and vaccines are better methods to control COVID-19.

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Conflict Of Interests:

There is no known conflict of interest associated with the publication

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