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The Battle with COVID-19: Insight on External Intervention and Future Vaccination

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Authors' contributions

This work was carried out in collaboration among all authors. Author ASH designed and wrote the first draft of the manuscript. Authors ASH and SMS managed the literature searches. Author MMS collected drugs data while author ATAS collected plasma therapy and medicinal plants data. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

The battle against the pandemic novel coronavirus infection (namely COVID-19) that gravely hurts human health is a global mission for all humanity. Currently, there are no specific COVID-19 therapies; immune-suppressors as corticosteroids, protease inhibitor antivirals, monoclonal antibody analogues as well as prospective plasma therapy. Because of the possible adverse effects and continuous emerging doubts about the drugs combating COVID-19; certain medicinal plants and dietary herbs are potentially used to prevent or cure COVID-19. Nowadays investigations and clinical trials focused on development of safe and effective either drugs or vaccines to control even stop COVID-19 in near future. Providing comprehensive spotlights on virus pathogenesis, host cell interaction, immunological response, potential therapy, and vaccine emergence for COVID-19 is discussed in this article.

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1. INTRODUCTION

The novel coronavirus disease 2019 (COVID-19) is caused by "severe acute respiratory syndrome coronavirus 2" (SARS-CoV-2) which belonged to beta coronary virus. More than 10 million people have been infected with deaths exceed half million individuals globally by July 2020. In spite of that in the most infected cases, the disease goes mildly, about 10%–15% progress to severe pneumonia and respiratory failure, needing intensive care unit (ICU) hospitalization and mechanical ventilation. Therefore suggestion to applying host-directed immunotherapies as an accompanied therapy in severe cases to not only diminish inflammation-associated lung damage but also to prohibit ICU hospitalization and dependency on mechanical ventilation that exhaust the limited resources in the context of SARS-CoV-2 pandemic. So, several immunotherapeutic approaches that target either inflammatory cytokines mediators, passively neutralize SARS-CoV-2 through plasma administration, or hinder viral entry are under appraisal at various centers [1].

Moreover, another complementary COVID-19 prevention direction, the promotion to use of dietary therapy and herbal medicine to overcome the current absence of an efficient drug and/or vaccine against COVID-19/SARS-COV-2 or restrain the side effects of the present used drugs [2].

Global efforts are continuous to emerge efficient vaccines to curb then prevent the COVID-19 infection among human populations [3].

This review gives some extent to the ongoing status of virus pathogenesis, host cell interaction, immune response, prospective treatment, and vaccine development for COVID-19.

2. IMMUNOTHERAPY OF COVID-19

2.1 Intravenous Immunoglobulin

An immunotherapy that could be considered for COVID-19 is the intravenous immunoglobulin (IVIG) therapy which obtained from the pooled plasma of several thousand healthy donors which have broad anti-inflammatory and immunomodulatory effects and widely used for a large number of autoimmune and inflammatory diseases [4-9].

2.2 Convalescent Plasma

Investigations on COVID-19 patients' sera declared the presence of seroconverted antibodies, such as IgG, IgM and IgA, with varying kinetics and sensitivities [10,11]. So there are other passive immunotherapies concepts may be successfully applied on COVID-19 patients as using convalescent plasma (containing high concentrations of neutralizing antibodies obtained from the pooled plasma of numerous recovered patients), or neutralizing monoclonal antibodies [12,13,14].

3. DRUG TREATMENT

3.1 Dexamethasone

Based on the bad pathogenesis consequence of novel corona virus which associated with cytokine storm and production of harmful inflammatory response; the first thinking directed to administration of anti-inflammatory and immune-suppressants as corticosteroids.

Dexamethasone is a corticosteroid (9-fluoro-glucocorticoid) developed in 1957, FDA approved in 1958 for treatment of different local and systemic inflammatory illnesses as well as acquired hemolytic anemia, and as a soothing treatment in leukemia and lymphoma [15,16]. Dexamethasone binds to glucocorticoid receptor; enhancing short term anti-inflammatory signals with low therapeutic dose, while higher doses induces long term changes in gene expression and act as immunosuppressive [17].

Dexamethasone is administered either orally or intramuscular, bioavailability reaches 70-78%, binds to plasma proteins, especially, albumin by 77%. The half-life of orally or intramuscular dose is 6.6±4.3h, and 4.2±1.2h respectively. Dexamethasone is metabolized by hydroxylation, and excreted via urine with clearance rate 9-15 hours [17-19].

There are numerous significant side effects of continuous administration of high doses of dexamethasone; water retention, moon face, hypertension and glaucoma, hyperlipidemia,

myopathy, osteoporosis, hypocalcaemia, hypophosphatemia besides the immune-suppression and decreased resistance to infection [20].

Regarding Covid-19 pandemic, there was a clinical trial started on 8 June to investigate the benefit from using dexamethasone as supportive treatment with COVID-19 Patients in the UK. The data obtained from the trial will encourage the use of dexamethasone as it aid in decreasing the mortality rates of intensive care infected patients which frequently happened at day 28 [21].

3.2 Chloroquine

Chloroquine was derived from quinine, an alkaloid compound, whose therapeutic effects for febrile diseases were noticed centuries ago; it was proved to be effective against malaria during USA antimalarial research efforts in World War II [22].

Chloroquine (CQ) is 4-aminoquinoline, while the equally effective hydroxyl derivative of chloroquine 'Hydroxychloroquine (HCQ)' has a hydroxyl group attached to C_1 atom in the carbon chain. Hydroxychloroquine sulfate, was first synthesized in 1946 and was demonstrated to be much less (~40%) toxic than CQ in animals [23].

Chloroquine and hydroxychloroquine (CQ/HCQ) are therapeutically used in many diseases; because of its versatile pharmacological and physiological effects on human body. Also, CQ/HCQ have anti-infective properties, especially on parasites and viruses. The antiviral properties were noticed against wide range of viruses: RNA viruses like HIV [24], hepatitis A and C [25], and influenza A H5N1 virus [26]. Furthermore, CQ / HCQ were reported to be effective against coronaviruses as SARS-CoV and MERS virus via different ways as demonstrated in Fig. (3) [27-30].

In *vitro*, CQ showed a potent inhibition effects; lowered viral load, 100% viral clearance rather than inhibition of the infection spread when treated the Vero E6 cells before or post be infected by SARS CoV [31,32]. Based on the genetic relationship between novel corona virus epidemic and SARS-CoV and MERS viruses, CQ / HCQ were clinically tested to fight COVID-19. In a *vitro* study, Chloroquine proved effectiveness at both entry and post entry phases of 2019-nCoV in Vero E6 cells [33].

Quick clinical trials were conducted in China during the outbreak tested chloroquine phosphate on about 100 patients and showed improvement in symptoms of pneumonia associated with the infection as well as decreased mortality rate due to thrombosis. It shortened the disease course and many patient virus identification tests turned negative [34].

In addition to antiviral effects, CQ / HCQ have immunomodulatory effects; promoting antigen presentation, enhancing CD8+ cytotoxic T cells, interfere with virus cell signaling and finally reducing the production of pro-inflammatory cytokines [35].

Both CQ and HCQ have semi similar pharmacokinetic pathway Table 1 but almost have the same side effects and toxicity profile, however risk margin and side effects severity are lower in HCQ than CQ. The side effects include ocular, cardiovascular, nervous, psychiatric, dermatological, musculo- skeletal and others [36-39].

3.3 Favipiravir

Favipiravir (Toyama Chemical Co., Ltd., Japan) was discovered and approved by Japanese authorities in 2014 to be used as a promising treatment for neuramidase inhibitors resistant influenza A and B cases as well as Ebola virus [40,41]. Favipiravir (6-fluoro-3-hydroxy-2-pyrazinecarboxamide) is a pyrazine analogue derivative which is a prodrug undergoes intracellular phosphorylation and ribosylation and be converted into an active form, tagged favipiravir RTP which interacts with RNA dependent RNA polymerase (RdRp) but how kill the target virus wasn't fully distinguished. There are three possible supposed hypotheses as in Fig. 2 [42,43].

Favipiravir was used in some finished clinical approach in China (6) as the incidences of dyspnea during the treatment was lower (3.45%), furthermore other current investigations in Italy (7), USA (8), (9), Egypt (10) is conducted to determine the efficacy and safety [44-46].

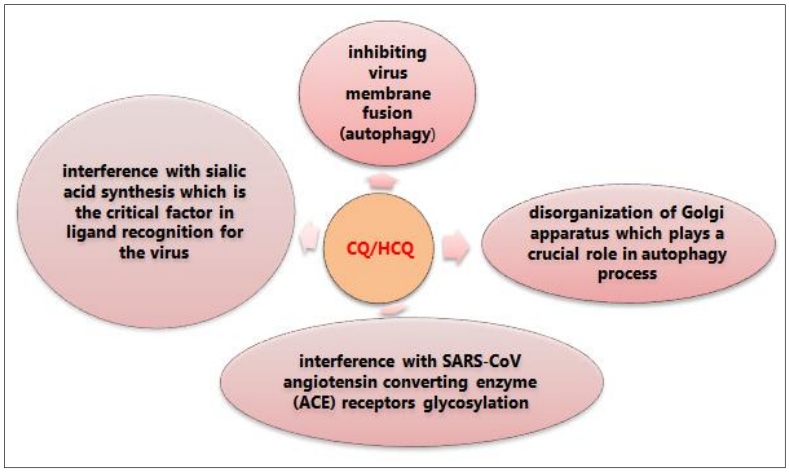

Fig. 1. The different anti -SARS mechanisms induced by CQ / HCQ

Table 1. The pharmacokinetics of both CQ and HCQ

	CQ	HCQ
Absorption % in oral administration	(52% - 102%)	(67%-74%)
Absorption in intravenous administration	the maximum concentration (C_{max}) reaches (650- 1300µg/L)	(C_{max}) reaches (1918 ng/mL)
plasma protein binding	(46%-74%)	(50%)
half-life	20-60 days	2 2 days in blood -123 days in plasma with oral route while in intravenous route reaches 40 days
metabolism	in the liver to three active forms; desethylchloroquine, bisdesethylchloroquine and 7-chloro-4 aminoquinoline	in the liver to the active form; desethylchloroquine
excretion	urine	urine

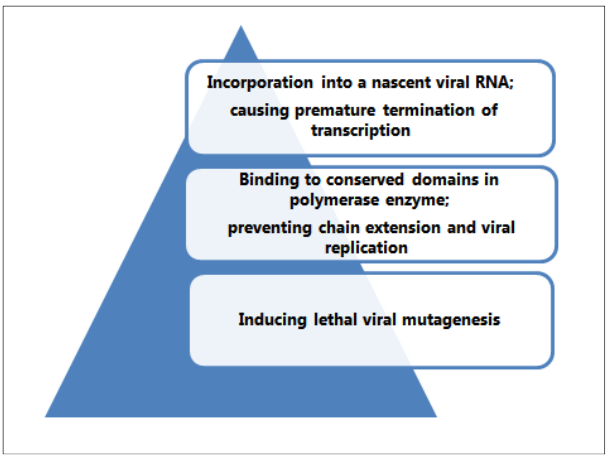

Fig. 2. The supposed hypotheses of Favipiravir antiviral mechanism

Bioavailability of Favipiravir is 97.6% and the mean C_{max} for the recommended dosing is 51.5 ug/mL with (54%) binding to plasma proteins and 65% fraction bound to serum albumin. It is metabolized by hydroxylation, to inactive metabolites and excreted mainly through urine [47,48].

The drawback of Favipiravir is known to be teratogenic; inducing embryonic anomalies and early deaths. Decreasing in body weight, vomiting and lower locomotor activities were the signs associated with single-dose toxicity in mice, while the repeated dose toxicity resulted in decrease in red blood cells with increase in liver enzymes and total bilirubin. The same study supposed that the lethal dose for oral and intravenous administration in mice was >2000 mg/kg [49].

3.4 Ribavirin

Ribavirin RBV' (commercially named Virazole) approved as a broad spectrum antiviral compound with a major activity against DNA and RNA viruses *in vitro* and *in vivo*. Ribavirin is a synthetic purine nucleoside analogue with a structural similarity to guanosine (or inosine) [50,51]. RBV was used for the treatment of many viruses as severe respiratory syncytial virus (RSV) infection in children, [52] and has been used in the treatment of influenza A and B [53], Lassa fever virus infection [54]. The broad antiviral activity of RBV suggests several direct and indirect mechanisms of action Fig. (3) [55-57].

Absorption of Ribavirin after oral administration is reported to be quick and extensive. The average time needed after oral administration of 1200 mg ribavirin to achieve C_{max} is 2 hours. Oral bioavailability after a single oral dose of 600 mg ribavirin is 64% displaying large volume of distribution without any reported protein binding. RBV undergoes metabolism firstly for activation; intra cellular phosphorylation then, after activation and function, ribavirin undergoes two metabolic degrading pathways. RBV metabolites are excreted mainly via kidney; approximately 61% of the drug was detected in the urine and 12% in the feces [58].

Previous examined RBV activity against other coronaviruses showed a disappointing manner; as the *in-vitro* activity of RBV against SARS CoV was limited and required high dose levels (1.2 g to 2.4 g orally every 8 hours) to inhibit viral replication, and usually need a combination therapy with intravenous administration. In analysis of 26 out of 30 studies discussed the clinical experience with ribavirin for the treatment of SARS showed indecisive findings, with 4 trials suggested possible harm due to adverse effects including hematological and liver toxicity [59]. Also, in MERS treatment, ribavirin has shown no obvious effect on clinical outcomes or viral clearance alone, and usually need accompaniance with interferons [60,61].

All previous data result in lack of ribavirin clinical evidence for SARS CoV-2 and suggest that it has limited value for COVID-19 treatment; consequently the outcomes must be extrapolated from other coronaviruses results, therefore, combination therapy will likely provide the best chance for clinical efficacy if ribavirin is used for COVID-19 [62,63]. Ribavirin has numerous side effects and is also a known teratogen and contraindicated during pregnancy [64].

3.5 Lopinavir/ritonavir

Lopinavir/ ritonavir (LPV/r) (Kaletra®) is a drug combination that used as classical HIV treatment. The lopinavir/ritonavir co-formulation produces its antiviral effect by inhibiting the formation of infectious virions, thus preventing subsequent waves of cellular infection [65]. LPV/r was the only protease inhibitor (PI) approved by the US Food and Drug Administration (FDA) to be used for the treatment of human immunodeficiency viruses (HIV) infection in adults and children older than 6 months of age [66].

The antiviral activity of the combination is mainly contributed to the protease inhibition effect of lopinavir, [67], while, ritonavir inhibits the lopinavir metabolizer CYP3A4 isoenzyme in the human liver microsomes resulting in increased concentrations of lopinavir [68]. Regarding, the molecular dynamics simulations studies showed that the SARS-CoV 3CLpro enzyme could be inhibited by the combination of lopinavir and ritonavir with acceptable EC50 [69], however, the efficacy of lopinavir against SARS was poor [70]. On the other side, animal studies of lopinavir/ritonavir combination against MERS showed reduction in viral load and replication with improvement in pulmonary functions [71].

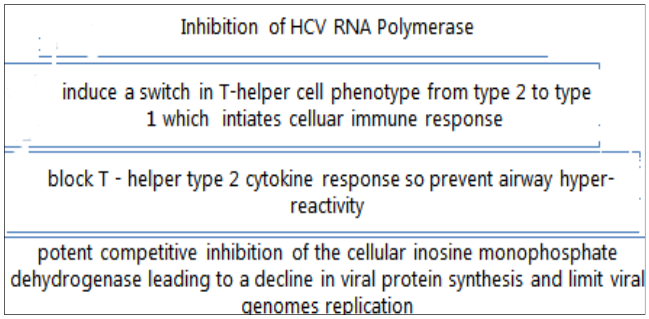

Fig. 3. Ribavirin antiviral mechanisms

Lopinavir/ritonavir is used as clinical trials for COVID-19 treatment and the results may be a promising [72]. The standard adult dose of lopinavir/ritonavir is 400 mg /100 mg twice daily. 9.8 ± 3.7 µg/mL is the mean peak plasma concentration (C_{max}) at this dose approximately 4 hours after a dose administration [73]. The lipid-soluble lopinavir passes the cerebrospinal barrier results in a significant lowering of the CSF viral load [74,75]. Lopinavir/ritonavir is mainly eliminated by the fecal route with urinary excretion about more than 2% of the eliminated drug [76].

As lopinavir is only available in combination with ritonavir, there is little experience with an acute sole overdose of lopinavir. In pediatric patients the risk associated with overdose appears more pronounced. One case report described a fatal cardiogenic shock in a 2,1 kg infant after an approximately 10-fold overdose of the combination oral solution, whereas other reported overdose reactions in infants include complete AV block, cardiomyopathy, lactic acidosis and acute renal failure [77].

3.6 Remdesivir

Remdesivir was produced in 2016 during the efforts to fight Ebola virus [78] and considered one of promising and efficient drugs that will be used for COVID-19, in 2017, its activity against SARS- CoV and MERS –CoV in *vitro* and in animal models was proved [79]. Remdesivir is a 1′-cyano-substituted adenine C-nucleoside ribose analogue, where the cyano group is responsible for its selectivity and efficacy against a wide range of RNA viruses. It is a pro-drug that exhibit intracellular biochemical conversion to its active triphosphate metabolite [78].

Remdesivir is a nucleoside analog that incorporates itself in the virus RNA transcript; result in its premature termination, acting as RNA-dependent RNA polymerase (RdRp) inhibitor, however, with high selectivity toward pathogen RdRp not the human version of RNA polymerase [80], in addition, remdesivir can act effectively, with higher, nontoxic doses, against pathogen resistance originated from ExoN proof reading activity [81].

Remdesivir showed promising efficacy against emergent COVID-19, preliminary data showed efficient inhibition of virus infection in human cell lines. The remdesivir activity was tested in three different stages of time; “full time”, “entry”, and “post entry” against SARS Cov-2 infection in Vero E6 cell. qRT-PCR was performed and results analyzed via Western blot which showed that remdesivir is effective against SARS Cov-2 infection and mostly in the “post entry” phase which agreed with its mechanism of action [82]. Clinical trials were established to estimate safety and efficacy of remdesivir in standard care receiving patients or hospitalized patients, positively tested with 2019-nCoV [83-85].

Remdesivir is of low bioavailability so preferred to inject intravenously a dose of 10 mg/kg; it will be activated to nucleoside triphosphate and reach a peak, with a survival rate of 100% [86]. It can pass through body barriers so reach to the testis, epididymis, eyes, and brain [78]. Unfortunately, there are no date records for remdesivir’s elimination, toxicity and side effects.

3.7 Tocilizumab

Tocilizumab is a recombinant humanized monoclonal antibody, which acts as interleukin-6 (IL-6) inhibitor. It was firstly mentioned in literature in 2003 for treatment of inflammatory and autoimmune diseases e.g. rheumatoid arthritis [87,88]. After COVID-19 pandemic, tocilizumab showed promising role in treating the

"cytokine storm" associated with the disease; lowering its morbidity and mortality rates [89,90].

Tocilizumab is a genetically engineered monoclonal antibody which the light chain consists of 214 amino acids while the heavy chain is made up of 448 amino acids. It is IL-6 antagonist; competes the IL-6 via binding and blocking the soluble and membrane bound IL-6 receptor, results in hindering the proinflammatory effects of IL-6 [91,92]. Consequently, it improves 2019-n-CoV patients' with clinical manifestations associated cytokine storm syndrome [93].

There are several clinical trials will evaluate the interaction between tocilizumab versus COVID-19; in China [94,95], Italy [96] and USA14 15 [59,97]. It is metabolized into smaller proteins and amino acids by the action of different proteolytic enzymes [98,99]. Unfortunately, there are no elimination data and no available date regarding safety of tocilizumab, however, upon overdosing cases of neutropenia was reported are not available [100].

3.8 Meplazumab

It is humanized anti-CD147 IgG2 monoclonal antibody and also be tested and evaluated for COVID-19 pneumonia. This antibody therapy was aimed at preventing CD147-mediated SARS-CoV-2 viral entry and T cell chemotaxis. Preliminary results obtained from a small number of patients demonstrated that meplazumab improved clinical course of the disease and normalized the peripheral lymphocyte count and CRP level [101].

4. MEDICINAL PLANTS AND SPICES

As the proteins of corona virus contain active carboxyl (-COOH) and amino (-NH2) groups, so one of virus deactivation strategies is to neutralize the effect of these functional groups to protect or minimize the adverse effects of corona virus on human body. It is clear that the extracted components of many natural plants, especially which contain hydroxyl (-OH) group have the ability neutralize the chemical and molecular bonding of amine (-NH2) and carboxyl (-COOH) functional groups of major corona proteins by esterification process [102-104].

4.1 *Salvadora persica* L. *(miswak)*

The miswak, also known as Peelu (in Urdu) and Arak (in Arabic) is one of the most popular medicinal plants, and the most common traditional source of tooth or chewing stick between Muslims. Its importance is contributed to bioactive compounds such as flavonoids, alkaloids and vitamin C with broad pharmacological properties; *S. persica* is used as sedative, analgesic, anti-inflammatory, antioxidant, antimicrobial [105-107].

Recent studies also exposed the potential of antiviral activity of *S. persica* and used against herpes simplex virus [108]. Therefore, *S. persica* was started to be tested as a natural weapon against COVID-19 through docking studies. Molecular docking simulation of identified flavonoid compounds resulted in interfering of SARS-CoV2 Mpro 'which is an important key for virus transcription and replication' more than the currently used COVID-19 main protease inhibitor Darunavir [109].

The freshly cut *S. persica* miswak had no cytotoxic effect, but the same plants may show harmful components if used after 24 h. the effect of direct administration of high doses of *S. persica* miswak extract to mice revealed minor side effects on reproductive systems and fertility of males and females [110].

4.2 *Glycyrrhiza glabra (Licorice)*

Licorice root extract of active compounds (glycyrrhizin, glycyrrhetic acid) has been investigated on virus replication of SARS Cov. [111,112]. Licorice extract when mixed with polyvinyl alcohol (PVA) solution at 50:50 ratio by electrospinning machine produce nano membrane which has antiviral activity [113].

4.3 *Nigella sativa* (Haba sawda)

Nigella sativa L. commonly known as black seed or black cumin (Haba sawda) is widely recommended in Middle East societies during the COVID-19 crisis for their probable antiviral effects [114]. *N. sativa* is cited by many research papers for its multiple benefits as antiviral, anti-inflammatory, anti-cancer, analgesic and immunomodulatory [115-119]. Docking of Nigellidine and α- hederin 'which are the main compounds of *N. sativa* ' showed that the energy scores of their complexes are better or as the complexes of antiviral drugs which are under clinical tests [120]. More investigations are required in *vitro* and in vivo to ensure and measure the *N. sativa* inhibitory action against COVID 19 and presentation of any side effects [121,122].

4.4 Thyme

Thymus species, 'specially *Thymus vulgaris* and *Thymus transcaspicus*' is native to the Mediterranean and surrounding countries, Northern Africa, and parts of Asia. The plant has been cultivated in Egypt, Morocco, Algeria, Tunisia, Libya [123]. *Thymus* species contain many monoterpene essential oils including thymol, carvacrol, γ-terpinene and P-cymene which exhibit antibacterial, antifungal, antiviral and antioxidant activities [124]. The extract of *T. vulgaris* has been shown a high antiviral activity against Herpes Simplex (HSV-1 and HSV-2), while *T. transcaspicus* essential oil extract has moderate antiviral activity so they are considered good candidates for testing against human viruses [125,126]. As the monoterpene essential oils especially thymol 'which is the main component of the oil (64%)' interacted in a dose-dependent manner with HSV-1 particles thereby inhibit viral infectivity [127]. Most of adverse events appear are dermatologic or allergic reactions. The essential oil of thyme should not be used orally because it has been associated with toxic reactions with range starts from nausea to respiratory arrest [128].

4.5 Ginger

Zingiber officinale Roscoe (ginger) is a tropical plant, rich in oils that both kill micro-organisms and stimulate the immune system [129]. Ginger rhizome is widely used as a folk medicine; treatment for colds and flu as a common cold remedy, it is a common ingredient of Chinese traditional prescriptions for airway infections. The ginger oil contains mainly zingiberene (18.9%), limonene/cineol (15.5%), b-sesquiphellandrene (6.8%), camphene (6.2%) and pinocamphene (6.8%) [130]. Ginger has been proved to be effective against various viruses [131,132]. Antiviral activity of ginger oil against Herpes simplex virus (HSV) type 1 [133] and (HSV) type 2 was studied [134]. It was found that ginger interfered with virion envelope structures, hindered the viral adsorption and entry into host cells resulted in reduction in virus infectivity.

Acute Toxicity studies of oil extract on albino rats declared that five out of the six treated animals at varying doses (0.02, 0.04, 0.06, 0.08 and 0.1 mL/kg body weight) of the fixed oil survived. However, at 0.2 mL/kg, mortality was reported. Also, there were no observable differences in the histology of the organs treated with essential oil of *Z. officinale* [135].

4.6 Anise

Anise (*Pimpinella anisum* L.), is common important spice native to Mediterranean region [136,137]. This spice plant has shown antimicrobial, antifungal, insecticidal, and antioxidtaive effect on human health [138,139]. Antiviral activity of anise oil against Herpes simplex virus (HSV) type 2 was studied [134]. Anethole and estragole content of anise are structurally related to safrole which is a known hepatotoxin and carcinogen. Both anethole and estragole have been shown to cause hepatotoxicity in rodents, however, anise seeds are not a risk to human health when consumed in amounts normally encountered in foods. Intoxication with the volatile oil of anise is not known so anise and oil of anise are generally regarded as safe for human consumption [140].

4.7 Chamomile

Chamomile (*Matricaria chamomilla* L.) is a well-known medicinal spice known as the “star among medicinal species.” Nowadays it is much used medicinal plant in folk and traditional medicine [141] chamomile has been used as herbal remedy for thousands of years, especially in ancient Egypt, Greece, and Rome [142]. It contains a lot of therapeutically interesting and active compound classes. Sesquiterpenes, flavonoids, coumarins, and polyacetylenes are considered the most important constituents of the chamomile drug [143]. Antiviral activity of chamomile oil against Herpes simplex virus (HSV) type 2 was studied [134].

Several toxicity studies have been carried out with the chamomile drug, there appeared to be no reports of any serious toxicity or allergenic caused either by the individual compounds or by the crude preparations of chamomile. However, chamomile drug has tolerable effects [144].

4.8 Cinnamomum (Cinnamon)

There are two main types of cinnamon namely the ceylon or true cinnamon (*Cinnamon zeylanicum*) and cassia (*Cinnamom aromaticum*). Cinnamon/ cassia has a long history as a spice and remedy [145].

The anti-influenza activity of both aqueous extract cinnamon and its silver nanoparticles (Ag NPs) against highly pathogenic avian influenza virus subtype H7N3 was evaluated in Vero cells. After 24 h incubation, No cytopathic effects were

shown in examined cells under microscope with cinnamon-based AgNPs are more effective against the virus. Furthermore, MTT assay revealed that none of the tested concentrations of the cinnamon extract or its nanoparticles was toxic to cells. It showed that besides the direct effect on viral glycoproteins, NPs may entered into the cell and exhibited their antiviral activity through interactions with the viral genome (RNA or DNA), cellular factors, or pathways of host cells that are necessary for viral replication [146].

Safety information about cinnamon powder or cinnamon extract (aqueous or alcoholic) and for cinnamaldehyde has been studied with no observed adverse effect level (NOAEL) information with a good margin of safety following acute oral overdose [147].

5. VACCINATION

As over the past two decades, human coronaviruses (SARS-CoV and MERS-CoV) emerged worldwide, causing considerable threat to global health and unfortunately, there are still no approved vaccines for these human coronaviruses [148]. Current SARS-CoV-2 research groups around the world are working on acceleration the development of COVID-19 vaccines using different approaches. In general, the principles of vaccines relied on targeting the antigenic determinant of the virus as well as the immune response pathways [149].

5.1 Recombinant Subunit Vaccine

Subunit vaccines are advantageous over other types of vaccines in that they are highly safe and have minimal side effects by stimulating the immune system without introducing infectious viruses [150-152].

5.2 DNA Vaccine

DNA vaccines exhibit an innovative approach by direct electroporation of plasmids encoding the antigens, and can be applied as prophylactic vaccines and therapeutic vaccines [153,154]. mRNA vaccines have important advantages over conventional vaccines, by the absence of genome integration, the enhanced immune responses, the quick development, and the production of multimeric antigens [155].

Also there are other vaccine approaches developed; COVID-19 vaccine using hyleukin-7 platform technology [156-174].

6. CONCLUSION AND PERSPECTIVE

The development of specific therapeutics and vaccines for the treatment and holding of COVID-19 is up to this time in its early steps. Nevertheless, there has been some progress in this research area and clinical trials acting on the data obtained from the complete genome sequencing and proteomics of SARS-CoV-2.

Every day a new suggested drug is used to manipulate the disease but there are emerging retardants as the adverse reactions as well as un-specificity. There are many evidences that support the value of natural medicinal plants and dietary herbs in the combating of COVID-19 as an immunomodulatory and viral controlling therapy.

Nutrition may raise immunity against SARS-CoV-2 which behaves as other coronaviruses and influenza. Therefore, vitamin C may be effective, vitamin D intake and zinc supplement may reduce the risk of influenza and by similar COVID-19 infections and related deaths.

The prospective vaccine development researches and clinical trials are currently conducted by various technology and laboratory companies looking for dawn of COVID-19 containment.

Further studies are needed to investigate the molecular mechanism and overall clinical incidence of COVID-19–related death, as well as possible therapeutic interventions to reduce it.

7. EGYPT VS. COVID-19

Until now, by the first week of July 2020, the situation in Egypt is still under control and not bad as happen in other European countries and USA. According to the official announcement of the Egyptian Ministry of Health mentioned that the number of confirmed infected individuals about 75000 with cured 20000 (27%) and 3200 (4%) deaths.

There are many Egyptian clinical trials, researches and projects related to application of drugs, plasma of convalescence patients, nutrition on the novel corona virus cases among the Egyptian population under supervision of Egyptian authorities and universities.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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