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Carbon-based nanomaterials and medicinal herbs for immune booster to countermeasure for COVID-19: A Mini Review

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Abstract: Carbon-based nanomaterials have much emerging roles for many industrial applications with potential biocompatibility and antiviral properties. In this review, graphene quantum dots/carbon dots or other carbon based composites are subject to antibacterial activity. The nanomaterials are also used as platform of functional molecules for specific antiviral activity with various medicinal herbs for immune system. At present, human beings often find themselves helpless arising from the emergence of the COVID-19 outbreak due to lack of tools to fight virulent infections and/or a slow down its outbreak that affect almost economic impacts and social implications. For new normal life, face masks against COVID-19 have been applicable with various potential utilities in association with instant hand hygiene. Besides, physical distancing, antiviral face masks, eye protection, and/or even work from home or stay home would be a better choice for the main systematic prevention policies in everyday life.

Keywords: Carbon based nanomaterials, Graphene, Face mask, Hand sanitizer, Medicinal herbs, Virus, COVID-19

1. Introduction

Daily news for the Covid-19 outbreak worldwide is now presented for the first priority in many visual media like by smart phone and home television. However, we may seek any progress information and/or recent research insights about the virus in CORONAVIRUAS UPDATES, particularly from ACS publications or other related sources i.e. the Graphene Newsletter. It is the fact that chemistry research is essential in understanding how to control the spread of coronaviruses and in the development of vaccines. List of the progress of the Covid-19 researches has been published in Journal of Proteome Research [1,2]. In the world map and the running records of the Covid-19 pandemic can be daily updated in terms of coronavirus case, death, and recovered. For active cases, currently infected patients are divided into mild condition and serious or critical condition. The other ones are reported with closed cases and cases which had

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an outcome like recovered/discharged case and deaths. Thus, it would say in such the way that chemistry is rationale background theory/concepts which has a key role to play in understanding everything from viral structure to pathogenesis, isolation of vaccines and therapies, as well as in the development of materials and techniques used by basic researchers, virologists and clinicians, for instant [3]. This review will therefore aim to provide a brief overview of the important contributions of chemistry and related fields to understanding and controlling the spread of coronaviruses.

For the following reviews, there are numerous issues to be concerned including the world situation of the Covid-19 outbreak as a daily news report, the non-medical treatment and prevention of the Covid-19, the chemistry insights their biological functions of drugs and/or vaccines development, and the on-going further required aspects of the "New Normal Life" for our human being at present.

Face mask

For virus protection, people recognize to wear a mask in the first priority and need to know how it spreads. Currently there is no effective vaccine to prevent the Covid-19. So, the best way to prevent illness is to avoid being exposed to this virus. Since the virus is thought to spread mainly from person-to-person, particularly between people who are in close contact with one another (within about 6 feet) through respiratory droplets produced when an infected person coughs, sneezes or talks. These droplets can land in the mouths or noses of people who are nearby or possible be inhaled into their lungs. So, some recent studies have suggested that the Covid-19 may be spread by people who are not showing symptoms [4-6]. In Thailand people get familiar with using known N95 or other cloth masks since before the Covid-19 outbreaks to Bangkok, we face an annual air pollution of aerosol particulates matter (PM) 2.5 micron, especially those are deemed in the Northern and the Southern parts of Thailand including in cloud areas of Malaysia and Indonesia, and also in Bangkok and other large cities are under influent respiratory condition of the PM 2.5 as well. In USA, they are strictly informed to wear face masks to stop the spread of Covid-19 as reported by the American Lung Association [7]. However, there is difference in between cloth masks and medical masks, i.e. N95 mask. It has a filtering ability down to or below the size of SARS-CoV-2, the virus that causes COVID-19. So, the coronavirus is about 0.12 microns in diameter and N95 protect down to 0.1 microns with 95% efficiency.

Besides, in parallel with using face protection masks, transmission of Covid-19 via respiratory droplets has been studied. Previous reports highlighted the role of respiratory droplets that enter the air when a person infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) cough, sneezes, and speaks, in the transmission of the virus [8]. Briefly, the droplets that measure less than 5 μm are known as aerosols. The average size of droplets is rather larger than that of viruses (30-200 nm) and other microorganisms (200 nm to lager) [8]. Thus, they can also dissolve all those of viruses and some bacteria in the air. These smaller droplets can remain suspended in the air for long periods leading to the virus's airborne transmission, particularly in indoor settings

with poor ventilation. That why aerosols have recently been emphasized as a potential route of transmission of the SARS-CoV-2. Then recent publication by the World Health Organization (WHO) highlighted research that supports the role of aerosols in spreading the virus, drawing attention to the need for more research to elucidate the mechanisms underlying this route of infection [9,10].

Generally, a brief note besides using face masks can be seen elsewhere that everyone should wash their hands often, avoid close contact, cover their mouth and nose with a mask when around others, cover coughs and sneezes, clean and disinfect, and also monitor their health daily. The coronavirus pandemic has been having a significant impact on the graphene market and industry [11]. Even before the pandemic, graphene has already received much attention due to promising antimicrobial properties and demonstrated antiviral efficacy. Recently, ZEN Graphene Solutions develops a graphene with 99% virucidal activity against Covid-19. It is a novel graphene-based virucidal ink with 99% effectiveness against Covid-19, and also 99% effective a minimum of 35 days after application to N95 mask material [12]. The other work is also the development of anti-bacterial graphene face masks [13]. The initial tests showed very promising results in the deactivation of two species of coronaviruses.

The graphene masks are easily produced at a low cost, and can help resolve the problems of sourcing raw materials and disposing of non-biodegradable masks, since commonly used surgical masks are not anti-bacterial ones. This may lead to the risk of secondary transmission of bacterial infection when people touch the contaminated surfaces of the used masks of discard them improperly. The research team tested their laser-induced graphene with *E.coli*, and it achieved high anti-bacterial efficiency of about 82%. In comparison, the anti-bacterial efficiency of activated carbon fiber and melt-blown fabrics, both commonly-used materials in masks, were only 2% and 9%, respectively. In addition, some graphene-enhanced applications to battle the Covid-19 are listed as following [15]:

1) 2AM-branded graphene-enhanced antibacterial face masks (UK-based planarTECH and Thailand-based IDEATI).
2) New washable functionalized graphene-enhanced fabric mask (Haydale Graphene Industries & its partner RPC).
3) Graphene-enhanced protective face mask, which utilizes Polygrene, Versarien's graphene-enhanced polymer (Versarien).
4) Graphene mask for Covid-19 (Flextrapower).
5) New efficient prophylactic facemasks to combat the COVID-19 (Consortium of Spanish scientists and companies, in which the University of Granada)
6) Graphene masks (Research team from City University of Hong Kong (CityU)).
7) Development of a graphene oxide based sensor platform to detect acute infections (Researchers at the Fraunhofer Institute for Reliability and Microintegration IZM).

8) Development of a new type of multiplexed test with a low-cost sensor that may enable the at-home diagnosis of a COVID infection (Caltech researchers).

9) Development of a graphene-based virus testing platform to help combat COVID-19 (Grolltex has teamed up with Sanford Burnham Prebys Medical Discovery Institute).

10) Development of a graphene-based air purification tech that could help fight the virus (G6 Materials).

11) Using graphene to develop a rapid, ultrasensitive test using a paper-based electrochemical sensor (University of Illinois researchers).

Moreover, a trial of new graphene-based Covid-19 testing technology at Edmonton airport, Canada, is also practical. The test takes a saliva sample from a person and is expected to tell if someone has Covid-19 in within a minute. This test promises many advantages, from its ease of use to the elimination of the nasal swab to direct virus detection [16,17]. Briefly, the person being tested provides a saliva sample into the testing unit. The graphene surface inside the testing unit is designed to bond to the spike protein in the virus. This binding event changes the electronic characteristics of the graphene. Then, the device will show a red or green light in under one minute to indicate if a person is virus-free of not. Recently, graphene was used to develop a rapid, ultrasensitive test using a paper-based electrochemical sensor that can detect the presence of the virus in less than five minutes (Fig.1). The main advantages of graphene-based biosensors are their sensitivity, low cost of production and rapid detection turnaround [18,19]. In addition, using a carbon based TiO_2 nanocomposite can be a new platform for an evaluation of curcumin assistance in the antimicrobial and photocatalytic activity as well. It was tested against *S. aureus*, *E. coli* and *Candida* species [20].

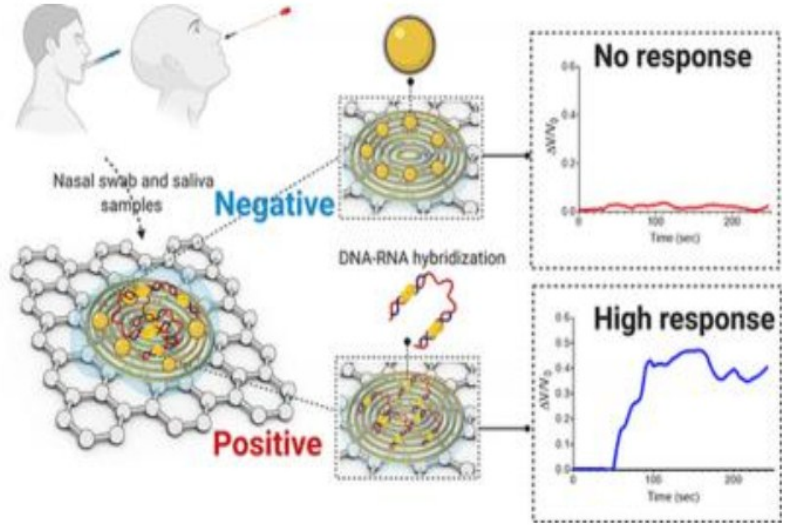

Fig. 1 Schematic route for using a paper-based electrochemical sensor detecting the presence of the virus [18]

Hand sanitizer and point of care system

Presently, human being of an individual prevention from the spreading of Covid-19, especially via aerosols air-borne transmission, it is said that hand sanitizers, i.e. 70-75% alcohol spray and/or liquid of premixed sol-gel alcohol, have never been in higher demand or seen more security [21]. Despite the relatively simple formulations and preparation protocols, it is critically important that proper quality assurance and control measures be in place to ensure the safety and efficacy of the hand sanitizer products. However, there is another way for rapid detection of the virus. One is point-of-care system based on photonic that could be deployed to detect SARS-CoV-2 [22]. Now it has real prototype of a sensing system based on photonic chips, and a measuring device, which is capable of detecting proteins in very low concentrations – inflammation and antibody biomarkers present in patients that are allergic to antibiotics. They will keep improving the optical sensitivity of the sensor and develop chemical protocols so that only a specific protein that expresses SARS-CoV-2, or the antibodies to such protein.

Role of SARS-CoV-2

This following way to understand the real effective mechanisms of killing virus is to take some basic details of chemistry and biological function/biochemistry of specific antibiotics used and/or improving human immune by vaccine trial development. Starting from the commonly frequent asked "What happen and fear of dead?" When SARS-CoV-2 spreading in air and easily infect through lung in our body (Fig. 2) [6]. For drug targets and potential treatments, in principle, all CoV enzymes and proteins involved in viral replication and the control of host cellular machineries are potentially druggable targets in the search for therapeutic options for SARS-CoV-2. For SARS-CoV-2, its structural proteins compose of spike S protein, membrane M protein, small envelope E protein, viral RNA and nucleocapid N protein. The virus can attack the human cell through ACE2 receptor, then within the cell via this receptor mediated endocytosis step through numerous active replication until attributing to exocytosis step forward to another cells.

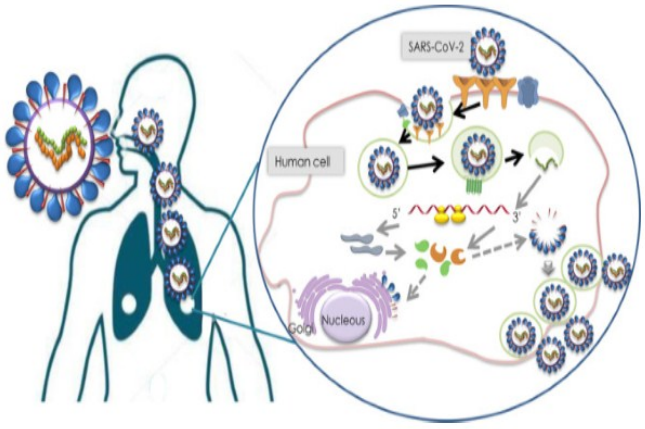

Fig. 2 The picture showing when SARS-CoV-2 spreading in air and easily infect through lung in our body [6]

Enzyme inhibitors

An enzyme inhibitor is a molecule that binds to an enzyme and decrease its activity. Since blocking an enzyme's activity can kill a pathogen or correct a metabolic imbalance, so many drugs are enzyme inhibitors. The SARS-CoV-2 macro domain protein bound to small molecule fragments that could be the basis of novel antiviral drugs (Fig. 3). Thus, binding to enzymes' active sites, inhibitors reduce the compatibility of substrate and enzyme and this leads to the inhibition of enzyme-substrate complexes' formation, preventing the catalyzation of reactions and decreasing the amount of product produced by a reaction.

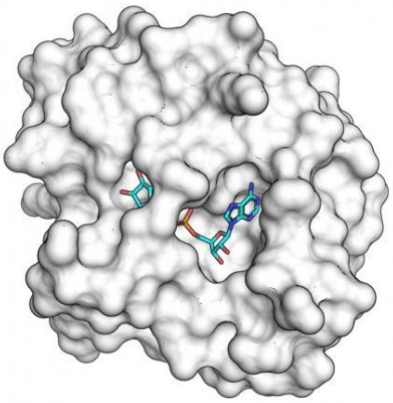

Fig. 3 The SARS-CoV-2 macro domain protein bound to small molecule fragments that could be the basis of novel antiviral drugs [23].

Some of SARS-CoV-2 protease inhibitors with their IC_{50} values (*data not shown*) have also been reported [6,11,12] including Lopinavir and Ritonavir, both being used as antiviral inhibitors, the most active drugs at present. Remdesivir and Favipiravir are both inhibitors active against SAR-CoV-2 under clinical trial. Another modulators having chemical structures with specific functional groups include Camostat, Bromhexine, and Nafamostat. Genistein, Estradiol, and Enzalutamide are found to be transcriptional inhibitors of the modulators. In addition, chemical probes targeting Cathepsin L with inhibitory activity against SARS-CoV-2 and SARS-CoV infection are metabolic involved. However, Fluphenazine, Pimozide, Raloxifene and Clomiphene & Tamoxifen are those of clinically used drugs. Glycyrrhizin, Nitazoxanide, and other related drugs are anti-IFV-A agents with potential therapeutic effects on SARS-CoV-2 [24-28]. Now, Umifenovir, Oseltamivir and Nelfinavir are also antiviral used in clinics as potential Covid-19 treatments. Therefore, many approved drugs in clinical trials for Covid-19 are almost synthetic and bioactive compounds with specific functional groups.

Inhibitory effects of medicinal herbs on SARS-CoV

Medicinal herbs can also be a potential subject to use for inhibitory effect on many SARS-CoV. In such case, cinnamon cortex extract and caryophylli flos extract showed their inhibitory activities against HIV/SAR-CoV pseudovirus. The 50% inhibitory

concentration (IC_{50}) of the former was lower than those of the later, both of them were less than 60 mg/mL [29]. Secondary metabolites from conventional medicinal plants were found as an inhibitory effect on Covid-19 virus protease by molecular docking analysis [23]. For chemical insights, an identification of natural compounds from more than 200 Chinese medicinal herb extracts with antiviral activities against SAR-associated coronavirus has been compiled.

In Thailand, there is a prominent natural plant found in Asia, namely the *Houttuynia cordata* Thunb., *Saururaceae* family. It is noted that four antiviral properties of the herbal plant include: prevent the virus entering into cells, reduce virus cell division, boot immune, and ameliorate lung inflammation from viral infection [30-35]. For medical uses of the herb, active compounds include phenolic compounds, flavonoids and alkaloids [36]. For viral inhibitory activities, they can direct to inhibit cell division to kill viruses or to reduce virus activity of acute inflammation of the body [37-40]. So, in this research the active substances are classified as protease inhibitors like Lopinavir and Ritonavir as mentioned earlier. Thus, these days' herbal medicine plays a major role in the prevention and treatment of many diseases also for the novel coronavirus. It is a long time known that Chinese medicine is the pioneer of the herbal medicine among all of the countries.

This medicinal plant has been used for treatment of inflammation-related disorders [14,31] and protection against oxidative stress in Asian countries. The aerial parts of *H. cordata* contain various types of flavonoids and some alkaloids [15-18]. Twenty compounds were isolated from *H. cordata* using chromatographic and semi-preparative HPLC techniques, and found to be two harmala alkaloids, one phenolic acid, four chlorogenic acid derivatives, three phenolic glycosides, two phenylpropanoids derivatives and eight flavonoids. Chemical structures of these compounds were characterized by spectroscopic methods as 3a, 12a-dihydro-2*H*-furo[3,2-b]indolo[3,2,1-ij] [1,5] naphthyridine-1, 1 (4*H*)-diol, perlolyrine, 4-hydroxycinnamic acid, neochlorogenic acid, neochlorogenic acid methyl ester, cryptocholorogenic acid, cryptochlorogenic acid methyl ester, benzyl-β-D-glucoside, β-phenylethoxy-β-D-glucopyranoside, dopaol-β-D-glucoside, guaiacylglycerol, (+)-(7*S*,8*S*)-guaiacylglycerol-8-*O*-β-D-glucopyranoside, luteolin, quercetin, apigenin, afzelin, quercitrin, hyperoside, kaempferol-3-*O*-α-L-rhamnosyl-7-*O*-β-D-glucoside and quercetin-3-*O*-α-L-rhamnosyl-7-*O*-β-D-glucoside [30-33]. Also, its main active components consist of volatile oil and flavanoids. These active components, contents affected by cultured and preparing techniques, pharmacological and immunotoxicological effects, adverse effects, clinical application and immunotoxicological research development were discussed in order to recognize its pharmacological, edible values and immunotoxicity. [20,34,41].

Besides, other recently reported the detection of SARS-CoV-2 is as follows: In-silico molecular docking study of spike protein of the SAR-CoV-2 virus to develop a novel antiviral drug was investigated by young scientist [10,37]. She demonstrated the finding potential molecules with special structure that strongly bond at the apex side of proteins of SARS-CoV-19 and can inhibit its infective activity [26]. It is the AI method to develop a novel antiviral drug now a day [7,24,28,29]. Another news is the bioluminescent

method used in the assay provides clinical labs with a simple, scalable workflow that is easily automated, taking you from sample to answer within 1 hour. However, the colorimetric test for fast detection of SARS-CoV-2 in basal and throat swabs are still developed, recently published in ACS Sensors [30,42].

Vaccine development and production for COVID-19

Anyway, during the Flu season it would be better to protect your health, while getting a flu vaccine will not protect against Covid-19 there are many important benefits, such as: Flu vaccines have been shown to reduce the risk of flu illness, hospitalization, and death. Also, with getting a flu vaccine can be save healthcare resources for the care of patients with Covid-19. Recently, it is our pleasured to hear that AstraZeneca (Biological products company of England-Sweden) developed the vaccine AZD1222 against Covid-19 seeks Thailand as its production platform with Siam Bioscience and SCG companies, which was established by King Rama IX the Great, it is so-called "*the Present of our King Rama IX for Thai people*", to produce the Biological Products by Biological Technology, for serving next year trial in Thailand and Southeast Asian countries, besides it produces new screening test (RT-PCR) for Covid-19 pandemic used to be in Thailand since 2020. From the world news dated on November 10, 2020, Pfizer and BioNTech companies also reported that the Covid-19 mRNA vaccine has been successfully tested over than 90% with infected people of 43,500 in six countries including USA, Germany, Brazil, Argentina, South Africa and Turkey, demonstrating no side effects with safety one [42]. COVID-19 Vaccine Moderna dispersion for injection has also been approved. One dose (0.5 mL) contains 100 micrograms of messenger RNA (mRNA) (embedded in SM-102 lipid nanoparticles). Single-stranded, 5′-capped mRNA produced using a cell-free in vitro transcription from the corresponding DNA templates, encoding the viral spike (S) protein of SARS-CoV-2 [43]. Another vaccine developed will be choice of the COVID-19 immune booster including Sinopharm (BBIBO-CorV)/Sinovac and Gamaleya (Sputnik V).

New normal life against COVID-19

Actually it is quite difficult right now to get final conclusion to overcome the Covid-19 outbreak, except getting the effective target vaccines properly on time. However, the best way for keeping away from Covid-19 is pursued in the following ways: regular wash hands with alcohol-based hand rub or with soap, maintain at least 1-meter distance between yourself and others, avoid going to crowded places because when people come together in crowds, you are more likely to come into close contact with someone who has Covid-19, avoid touching eyes, nose, and mouth because you touch many surfaces and can pick up viruses, and stay home and self-isolate even with minor symptoms such as cough, headache, mild fever, until you recover. The world situation of the Covid-19 subsides as if the effective vaccines being now produced and applied to human with mostly satisfied outcomes and it also still be kept on-going research for other mutation species and once doing with clinical trials.

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