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Review Article

SARS-CoV-2 Pandemic: A Review on Current Evidence and Unani Perspective

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A B S T R A C T

In December 2019, a novel coronavirus has emerged from the city Wuhan, China when cluster of pneumonia cases similar to viral pneumonia appeared, later named as SARS-CoV-2 virus, its symptomatology bears resemblance to *Nazla-e-Wabāiya* (epidemic influenza) in various treaties of Unani scholars. WHO on January 30, 2020 declared this outbreak as a public health emergency of international concern. To date, there are no specific vaccines or medicine for COVID-19 and the treatment is simply symptomatic. Therefore, prompt recognition of positive cases and rapid patient isolation may be needed to contain the disease spread to ensure timely management.

Unani System of Medicine aims at preservation of health, management of diseases with a holistic approach. As per Unani classical literature, during epidemics prevention of disease and maintenance of health was achieved by strengthening the *Ṭabī'at* (Medicatrix Naturae) and modifications in *Asbāb Sitta Darūriyya* (Six Essential Factors).

Keywords: COVID-19, Pandemic, Immunity, Immuno-Modulators, Unani

Introduction

Coronavirus disease (COVID-19) is an infectious disease caused by a newly discovered coronavirus which is distinct from both SARS-CoV and MERS-CoV, yet closely related, first identified in Wuhan, China in December 2019, later named 2019 novel coronavirus (nCOVID-19) by WHO.[1-4] Most people infected with the coronavirus experienced mild to moderate symptoms and recovered without requiring hospitalization. Common symptoms of COVID-19 include fever, dry cough, and fatigue, in severe cases, severe pneumonia, severe respiratory distress, multi-organ failure may occur.[5-7]

The Government of India imposed a complete lockdown in the country but despite taking timely counter measures to break the chain of spread of virus such as screening and isolation of infected individuals, social distancing, mandatory wearing of masks in public places and frequent hand sanitization or washing are being propagated, the number of positive cases of COVID-19 infection in India are increasing continuously. Till date, there are no available vaccines or specific medicines for the treatment of COVID-19. In light of the outbreak, various treatment modalities have been considered, including traditional medicine.

Though there is no direct reference in the classical Unani literature regarding the current disease, but its clinical manifestation are identical to *Nazla-e-Wabāiya* (epidemic influenza),[8] such as fever, sore throat, sneezing, nasal

irritation and malaise, sometimes cough, diarrhoea and delirium sets in and when the diseases worsens, pleurisy or pneumonia may occur in elderly, immunocompromised, and with underlying health conditions.[9]

Unani medicine lays great emphasis on the preventive, promotive and curative aspects through Six Essential Factors (*Asbāb Sitta Darūriyya*) of life to maintain a proper ecological balance and on keeping air, water and food free from all possible pollution and pathogens. As per Unani classical literature, improving immunity with immune enhancing plants is one of the key approaches for prevention of disease and maintenance of health.[10]

Methodology

For this study, the authors hand searched the library resources for relevant papers, and referred Unani classical books *Kitab al-Hawi, Kitab al-Mansoori* by *Zakariyā al-Rāzī* (865-925 AD), *Al-Qānūn fī al-ṭibb by Ibn Sīnā* (980-1035 AD), *Kitab al-Kulliyat* by *Ibn Rushd* (1126-1198 AD), *Kitab al-Mukhtarat fil-Tib* by *Ibn Hubal Baghdadi* (1121-1213 AD) and *Haziq* by *Hakim Ajmal Khan* (1868-1927 AD) along with other published books and journals. The electronic databases searched for the current review on SARS-CoV-2 pandemic were PubMed, Science Direct, Google Scholar, CENTRAL (Cochrane Central Register of Controlled Trials and Springer using keywords SARS-CoV-2, coronavirus, COVID-9, pandemic. Various scientific databases websites namely World Health Organization (WHO), Centers for disease Control and Prevention (CDC) and Indian Council of Medical Research (ICMR), India were also used to gather latest information on COVID-19.

Mode of Transmission of COVID-19

COVID-19 virus is primarily transmitted through respiratory droplets (diameter >5-10µm) in close contact (within 1 m) with someone who has respiratory symptoms; coughing or sneezing and potentially infective respiratory droplets or direct contact.[11-14] Airborne transmission may be possible in specific settings where procedures that generate aerosols are performed; endotracheal intubation, bronchoscopy, open suctioning, nebulization, manual ventilation before intubation, turning the patient to the prone position, disconnecting the patient from the ventilator, non-invasive positive-pressure ventilation, tracheostomy and cardiopulmonary resuscitation. There are no reports of faeco-oral transmission, however, a study claimed to culture the COVID-19 virus from a single stool specimen.[15,16] Viable virus has been isolated from specimens of pre-symptomatic and asymptomatic individuals, suggesting that asymptomatic may transmit the virus.[17-24]

Risk Factors: Mortality rate for 2019-nCoV is 2% which is however less than that of SARS (10%) and MERS (34%).[3] Age: No fatalities have been reported in the age group between 0-9 age groups. However, children and adolescents are just as likely to become infected as any other age group and can spread the disease but evidence to date suggests that they are less likely to get severe disease, fatality rate in the age group 10-19 years was 0.2%.[23] The age group of 75 and older had the highest case fatality rate of all age groups at 48.7%. Gender: Case fatality rate for males was 61.8% and less for females was 38.2%.[23] Comorbidity: Patients who reported no comorbidity had a case fatality rate of 0.9%. Patients with pre-existing medical (comorbidities) conditions had much higher rates: 13.2% for cardiovascular diseases, 9.2% for diabetes, 8.4% for hypertension, 8% for chronic respiratory disease and 7.6% for cancer.[23] At present there is no evidence that pregnant women are at higher risk of getting severe illness and also that virus can be transmitted through breast milk. Even lactating women infected with COVID-19 virus should continue breastfeeding by taking standard precautions to prevent transmission of infection in neonate. Some reports have indicated that people with no symptoms can also transmit the virus to others.[23]

Incubation Period: The Incubation Period (IP) is estimated to be 2-14 days, most commonly around 5 days based on reports by WHO, 2-10 days by CDC, 10-14 days by China's National Health Commission (NHC), or as long as 24 days (range: 0-24 days; median: 3.0 days), which could actually reflect a second exposure rather than a long IP of COVID-19.[18-19] However, a person may transmit the infection 24 to 48 hours before the symptoms appear and last for 7 to 12 days in case of moderate infection and 14 days in severe cases.[24-28]

Clinical Manifestation: COVID-19 affects different people in different ways, majority (80%) of people develop only mild to moderate symptoms, most commonly dry cough, sudden onset of high-grade fever and fatigue.[29-33] Less common symptoms include; nasal congestion, sore throat, productive cough, headache, myalgia, conjunctivitis, diarrhea, nausea, haemoptysis or vomiting. Recently olfactory and gustatory dysfunction or a rash on skin or discoloration of fingers or toes were also reported in few cases.[30] But one out of 5 patient becomes seriously ill and require critical care, death may occur if complications; acute respiratory failure, pneumonia, Acute Respiratory Distress Syndrome (ADRS), arrhythmia, shock, acute cardiac or kidney injury occurred. A study on 99 patients found that approximately 17% patients developed ARDS and of which 11% died of multiple organ failure.[29,30,33]

Laboratory Findings

A meta analysis showed that increased CRP (73.6%), ESR (61.2%), IL-6 (53.1%), LDH (46.2%) and decreased albumin (62.9%), eosinophils (58.4%), lymphocytes (47.9%) are the most prevalent laboratory findings. Patients with lymphopenia, elevated CRP and LDH were significantly

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associated with severity.[29] Notably, 56% had normal CT in early phase but after the onset of symptoms, CT findings became more frequent, hallmarks of COVID-19 infection includes; consolidative pulmonary opacities, ground-glass opacity and bilateral patchy shadowing, bilateral and peripheral disease, greater total lung involvement, linear opacities, 'crazy-paving' pattern and the 'reverse halo' sign.[31-33,35]

A combination of molecular and serological tests is needed to improve the diagnostic accuracy of COVID-19. Antibody IgM are produced within 5-7 days of infection suggesting recent infection, while IgG are produced within 10-15 days and may remain detectable for months or years. The presence of antibodies was <40% among patients within 1-week since onset, and rapidly increased to 100% (Ab), 94.3% (IgM), and 79.8% (IgG) 15 days after onset.[34-37]

Currently, SARS-CoV-2 can be detected in different clinical specimens but all had a different Positive Rate (PR). A Bronchoalveolar Lavage Fluid (BALF) specimen had the PR of 91.8%, followed by rectal swabs (87.8 %), Lower Respiratory Tract (LRT) specimens (71.3%), and then sputum (68.1%). Nasopharyngeal swab, a widely used specimen had a moderate PR of 45.5% also a low PR was observed in oropharyngeal swabs (7.6%) and blood samples (1%), Feces had a PR of 32.8% whereas no virus was detected in the urine and urinogenital specimens.[34,38]

Unani Concept of Health

Unani System of Medicine, provides preventive, promotive, curative and rehabilitative healthcare with holistic approach. Every person is supposed to have a unique temperament constitution depending upon predominance of humours; sanguine, phlegma, choleric or melancholic. Balance in the quality and quantity of these indicates health which is maintained by a special power of self-preservation called *Quwwat-e-Mudabbirah* (Medicatrix Naturae). If this power weakens or imbalance in humor occur, disease may occur. Unani medicine helps in regaining this power to an optimum level and thereby restore humoral balance.[40]

Concept of Epidemics (*Waba Umumi*), Contagion (*Ajsam-e-Khabisa*)

The term Epidemics, referred as *Wabā Umūmī* in Unani Medicine, since there is no direct description of microbes before the advent of microscope but Unani physicians were well acquainted with the concept of microbes which they referred as *Ajsam-e-Khabisa* (noxious substances), according to which these noxious substances when transferred from the diseased to healthy persons either by direct contact or through air, water may result into a disease.[40] And similar, theory of contagion is advocated by a number of Unani scholars. It is evident that despite the inability to observe microbes, Unani scholars could envision and comprehend their sources and reservoirs, modes of transmission of infections, and potential causes of infections turning into epidemics. The theories and observations closely resemble the contemporary knowledge of infections, which reinforce the fact that Unani Medicine can play a significant role in combating current health problems.[41,42]

Different Views of Unani Scholars about Infectious Diseases or Epidemics

Medicine was largely dominated by the traditions of Buqrat (Hippocrates), *Jalinus* (Galen), *Rāzī* (Rhazes) and *Ibn Sīnā* (Avicenna), *Ibn Khātima*.

Ibn Sīnā (Latinized Avicenna, 980-1037 AD)

- In *Al-Qānūn fī al-ṭibb* (The Canon of Medicine) an entire section is devoted to the effects of air on the human body, where air is one of the factors that affects human health and promote disease.[43]
- *Ibn Sīnā* observed that the putrefaction of air coincided with the appearance of diseases, in particular epidemics, this statement suggests, the presence of infectious agents occurs in the air of that epidemic area.[44]
- He stated that *Amrāḍ-e-Wabāiya* (Infectious Diseases) spread from one person to another, and to one city to another 'like a message', or by the *Ajsām Khabītha* (contagion) present in water or air.[43]
- He stated that people with an underlying diseases or weak constitution as being more susceptible to epidemic diseases or have poor prognosis during epidemics.[44]
- Though an ancient idea considered that air did not act as a medium for the spread of disease; rather air itself contained miasma (vapors, particles or smoke) but he proposed that some particles which cause diseases could be airborne.[45] Thus, he opened a new window in epidemiology and provided a major base for the diagnosis and treatment of many communicable disease including influenza and tuberculosis. He also hypothesized that tuberculosis and other diseases can be contagious.[45,46]
- He stated that changes in the air quality (excess of heat or cold) exerts a negative effect on the human body, placing them in a state of "disorder". He believed that disorder occurred when the body humors became putrid, and that the putrefaction of the humors was a direct effect of putrid air. Thus, *Ibn Sīnā* has concluded that abnormal warm and cold airs are not good for healthy persons.[47]
- Precaution suggested by *Ibn Sīnā* are equally relevant in modern days as the practice of quarantine for contagious diseases,[41] and he believed that the traveler is more exposed to illness from the diversity of drinking water rather than the foods consumed.[47]

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***Ibn Zakariyā al-Rāzī* (Latinized Rhazes, 865–925 AD)**

- *Zakariyā al-Rāzī* a great Arab clinician and epidemiologist who described all of the basic tools of modern epidemiology.
- He gave first scientific description for the recognition and differentiation of smallpox and measles in his scientific treatise, "*Kitab fi 'l-Jadari wa-'l-Hasaba* (On Smallpox and Measles)". *Rāzī* described the modes of spread, differential diagnosis and complications of the two highly contagious diseases of epidemics, smallpox and measles which were difficult to differentiate during the early stages as the skin rash and fever are common to both.[41,48]
- The direction of winds plays a significant role in the spread of the *Amrāḍ-e-Wabāiya* (Infectious Diseases), northern winds are colder and southern winds are warmer, this difference in temperature makes people more susceptible to respiratory infections.[41] In *Kitāb al-Manṣūrī*, he stated that most epidemics spread in the season of autumn, especially if the preceding summer season was humid and the wind was tranquil. In this context, the direction of winds is given utmost significance.[42]
- He stated that during epidemics patients have always something in common whether a place or food or drink or travel history.[41]
- In *Kitab al-Hawi, Rāzī* described that people who remain physically active and exercise regularly, have a lesser susceptibility to *Amrāḍ-e-Wabāiya* (Infectious Diseases).[41]

Similarly, *Ibn Hubal Baghdadi* (1121–1213 AD) mentioned in his treatise *Kitab al-Mukhtarat fil-Tib* (The Book on Choice of Medicine), if southern winds are replaced by northern winds, then catarrhal illnesses will occur in abundance.[40] Because, as stated by *Rāzī*, southern winds are warmer while the northern winds are colder, and this change of temperature makes people more susceptible to respiratory infections.[41]

The 13th-century Persian scholar *Najeebuddin Samarqandi* (1222 AD) mentioned about a type of epidemic influenza in his treatise *Al-Asbāb wa Alamat*, translated version is *Sharah Asbab*, the disease is mentioned by the name of *Nazla-e-Wabāiya*, which is associated with fever, sneezing, sore throat, nasal irritation, malaise and weakness sets in early in the disease. He further stated that these patients may also suffer from cough, diarrhea, and sometime delirium and disease progression of pleurisy or pneumonia may worsens the prognosis.[8]

Ibn Khātima (c.1324-c.1369) in his treatise *Taḥṣīl garaḍ al-qāṣid fī-tafṣīl al-maraḍ al wāfid* (Succeeding in clarify pest disease), described the Black Death, the pandemic that devastated Asia, Africa and Europe in the 14th century which clearly stated that when a healthy person became infected come in contact with the plague patient, showed the similar symptoms as of the diseased.[51]

Concept of *Ṭabī'at Mudabbira Badan* (Medicatrix Naturae)

Unani Medicine describes the concept of *Ṭabī'at*, which is a supreme planner of the body to create the healthy environment within the body and prepare to fight against the disease. If *Ṭabī'at* is strong, then person do not suffer from a disease easily: if it weakens, person becomes prone to disease easily. The *Ṭabī'at* may be defined as the sum total of structural, functional and psychological character of the human being. According to Hippocrates, there is a special ability hidden in every individual called the defensive mechanism of the body known as *Ṭabī'at-e-Muddabar-e-Badan*. This *Ṭabī'at* is the best physician, and maintains the equilibrium of four body humours. For the maintenance of health, the quantity and quality of these humours should be as per the natural composition of the body. Broadly speaking *Ṭabī'at* is considered as the real healer of the body and the role of the *Tabeeb* (physician) is to aid this *Ṭabī'at*.[52-54]

Usūl-i 'Ilāj **(Principles of Treatment)**

Most people with COVID-19 don't become seriously ill but older people and those with pre-existing comorbid conditions is most likely to be serious. People who have moderate to critical severity would be treated in hospital. But if someone has mild symptoms of COVID-19, they can probably be looked after at home. Currently there's no proven treatment for COVID-19 but people with COVID-19 need supportive care to ease their symptoms. Worldwide people are looking towards traditional systems of medicine to fight against COVID-19. One area that is directly in our control is to help the body fight against infection by boosting our immune system. There are several ways of improving immunity, one such way includes abiding by six essential factors of life (*Asbāb-e-Sitta Zaruriyya*): (1) *Hawa'* (Air)–fresh, unpolluted air is effective in preserving health; (2) *Ma'kul-o-Mashrub (*Foods and Drinks) - nutritional deficiencies make us more susceptible to infections and taking water immediately after meal should be avoided; Oxymel with *Arq-e-Gulab* is advisable during epidemics[38] (3) *Harakat-o-Sukun Badani* (Bodily movement and Repose)- balanced rest and movement exert an optimistic effects on individual health, movement stimulate the innate heat (*hararat-e-ghareeziyah*) and dissolve the waste product of the body and Rest, after movement is indispensable for health preservation; according to *Rāzī*, people who are physically active and exercise have a lesser susceptibility to epidemic diseases[41] (4) *Harakat-o-Sukun Nafsani* (Psychic movement and Repose) - lower stress by meditating, exercising, yoga and controlled breathing exercises; (5) *Nawm-o-Yaqza* (Sleep and Wakefulness) - A healthy immune system can fight off infections more than a sleep-deprived immune system, *Rāzī* explains that 8 hours of sleep is good for health, it strengthens the vital faculty, pneuma and promotes digestion by retaining

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hararat-e-ghareeziyah.(6) *Istifragh wa Ihtibas* (Evacuation and Retention)–when elimination and retention take place at the time when they are needed, they are beneficial for maintenance of health.[40]

'Ilāj bi'l-Dawā' **(Pharmacotherapy)**

Concept of Immuno-modulators in Unani Medicine: Immuno-modulators are the medications used to help regulate or normalize immune system. Unani Medicine offers a number of drugs of plant, mineral and animal origin in single or compound form that have immuno-modulatory activity and effective to strengthen and increase or decrease the immunity system, hence such drugs can be safely used for the prevention as well as management of COVID-19.[55-57]

Compound Unani Formulations are recommended during epidemics *viz*. *Tiryaq-e-Arba*; a compound with *Dafae Sumoom* (antidote) and *Dafae Tashannuj* (anti-spasmodic) properties,[58] *Tiryaq-e-Wabai*; an antidote for epidemic[41,58] and *Khameera-e-Marwareed* with immunomodulatory and *Muqawwi-e-Aza Raeesa* (Tonic for vital organs) properties.[59] In case of fever- *Sharbat-e-Khaksi, Habb-e-Bukhar, Habb-e-Mubarak, Habb-e-ikseer Bukhar*, to relieve cough-*Habb-e-Surfa, Khamira-e-Banafsha, Laooq-e-Sapistan, Sharbat-e-Sadr, Sharbat Unnab*; sore throat -*Sharbat-e-Toot Siyah*; Breathlessness- *Sharbat-e-Zufa Murakkab, Laooq-e-Katan, Habb-e-Hindi Zeeqi, Sharbat-e-Nazla* orally, local application of *Roghan-e-Banafshan* in nostrils and fumigation of herbs like *Kundur, Kafoor, Loban, Izkhar, Qust, Mastagi*; if patient complains chest pain due to excessive cough, local application of *Roghan-e-Babuna, Qairooti Arde Karsna, Roghan Mom/ Kafoori Balm* may be beneficial.[41,42,45]

Single Unani Drugs Recommended for Use during Epidemics[42,59]

Unani Drug (Scientific Name)	Pharmacological Properties	Chemical Constituents
Aab-e-Anar (*Punica granatum* L.)[60,62]	Anti-microbial, anti-bacterial, anti-fungal, anti-viral, antioxidant, anti-inflammatory, vasculo-protective	Anthocyanins, Phenolic compounds, flavonoids, anthocyanins, tannins, ascorbic acid, citric acid, malic acid, punicic acid
Amla (*Amla Emblica* officinalis L.)[62-64]	Immunomodulatory	Galic acid, ellagic acid, chebulinic acid, Ascorbic acid, citric acid, quercetin, chebulagic acid, chebulinic acid, Emblicanin-A, Emblicanin-B, Kaempferol
Amaltas (*Cassia fistula* L.)[65]	Immunomodulatory, anti-oxidant, hepatoprotective	Glycosides, tannins
Assalussus (*Glycyrrhiza glabra* Linn)[66-67]	Immunostimulating, Antithrombin activity, Antibacterial, Antimycobacterial, anti-inflammatory, antineoplastic, antioxidant, antiviral, Antimalarial activity, Antitussive, expectorant	Glycyrrhizin glycyrrhetic acid, Licochalcone, glabridin, Isoliquiritigenin, licocoumarin
Asgand (*Withania somnifera* L)[68]	General tonic, anti-inflammatory, immunomodulator	Steroidal Lactones (Withanolides), polysaccharides, lectins, proteins and peptides
Behi dana (*Cydonia oblonga*)[49,69]	Antioxidant, immunomodulator, antiallergic, anti-influenza	Kaempferol, Quercitin glycosides, galic acid, ascorbic acid, citric acid
Elwa (*Aloe barbadensis*)[72-73]	Immunomodulatory	Alkaloids, tannins
Gilo (*Tinospora cordifolia* L.)[72-75]	Immunomodulatory, anti-oxidant, anti-microbial	Alkaloids, diterpenoid lactones, glycosides, steroids, sesquiterpenoid, phenolics. 11- hydroxymustakone, N-methyl-2-pyrrolidone, N- formylannonain, cordifolioside A, magnoflorine, tinocordiside and syringin
Gul-e-Banafsha (*Viola odorata* L.)[76]	Anti-microbial, anti-fungal	Glycosides, phenolic comp, tannin, resins, sterols

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Haleela (*Terminalia chebula* Retz.)[77]	Anti-microbial	Glycoside, flavonoids, tannins
Haldi (*Curcuma longa*)[78]	Anti-oxidant, anti-inflammatory,	Curcuminoids
Imli (*Tamarindus indica* L.)[79]	Analgesic, anti-inflammatory, anti-oxidant, antipyretic, anti-atherosclerosis	citric acid, oleic acid, linoleic acid, volatile oils (geraniol, limonene), pipecolic acid, lupeol, orientin, vitamin B3 and C, vitexin, phenylalanine, leucine, potassium, Campesterol, β-amyrin, β-sitosterol, Tannins, saponins, glycosides
Karanjwa (*Caesalpinia bonducella*)[80-82]	Antipyretic, antimicrobial, anti-inflammatory, mmunomodulatory, antimalarial	Phenolic, flavonoid compound
Kalonji (*Nigella sativa*)[83]	Immunomodulatory, anti-inflammatory, anti-oxidant	Thymoquinone, nigellone and d-limonene
Musli safed (*Chlorophytum borivilianum*)[72,84]	Immunomodulatory, anti-oxidant	Steroidal saponins, fructans and Fructoligosaccharides (FOS), acetylated mannans, phenolic compounds, proteins
Revand Chini (*Rheum australe* D. Don)[85]	Anti-inflammatory, antifungal, antimicrobial, antioxidant, hepatoprotective, immune-enhancing activities, nephroprotective, improving renal function	Anthraquinones (emodin, chrysophanol, physcion, aloe-emodin, rhein), stilbenoids (piceatannol, resveratrol), flavonoids
Sapistan (*Cordia myxa*)[71]	Immunomodulator, tracheal smooth muscle relaxant, anti-oxidant	Phenolics, tannins, steroids
Turanjabeen (*Alhagi pseudalhagi*)[86-89]	Anti-microbial, anti-oxidant, anti-pyretic, hepatoprotective, anti-asthmatic	Flavonoids, phenol
Unnab (*Zizyphus jujube*)[8,89]	Anti-influenza, immunomodulator, antioxidant, anti-pyretic	Polyphenol, tannin, Glutathione (GSH), Kaempferol, total polyphenol
Za'fran (*Crocus sativus*)[8,91]	Immunomodulatory, anti-inflammatory, broncho-dilatory antioxidant, anti-inflammatory, analgesic, protective (hepatic, renal, CNS) effects	Carotenoid and flavonoid compounds, notably glycosides of crocin, kaempferol. Safranal (immunological, broncho-dilatory)
Zanjabeel (*Zingiber officinale*)[92-96]	Immuno-modulatory, anti-tumorigenic, anti-inflammatory, antiplatelet, anti-lipidemic	Sesquiterpenes and aromatic ketones, gingerols, [8]-Paradol (most potent antiplatelet aggregation agent and COX-1 inhibitor)

Conflicts of Interest: None

Refeerences

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