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NATUROPATHY, NANOTECHNOLOGY, NUTRACEUTICALS, AND IMMUNOTHERAPY IN CANCER RESEARCH (H LATHA, SECTION EDITORS)

Green Synthesis–Mediated Nanoparticles and Their Curative Character Against Post COVID-19 Skin Diseases

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Abstract

Purpose of Review This article provides the explanatory manuscript regarding the SARS-Corona virus 2. Sub-titled as the history of single-stranded RNA, internal characters of COVID-19, resource, the life cycle of COVID-19, reservoir of the disease, secondary infections of COVID-19 and nano herbal remedy.

Recent Findings The skin is not the main target of the SARS-corona virus 2 infections but somehow directly or indirectly, it causes exacerbating eruptions on the skin. Recent research shows that curcumin–mediated synthesized AgNPs show its potential character in the entry of respiratory syncytial virus (RSV), blocks interaction with the viral surface, and damages the viral protein. In modern days, molecular docking studies fabricated copper iodide flower extract (CuI-FE) which shows tough inhibitory action against COVID-19. Many articles show green synthesis–mediated nanoparticles like silver, gold, zinc, copper, iron, titanium dioxide, selenium, and cadmium which possess high anti-viricidal activity.

Summary The anti-oxidant, anti-viral, anti-inflammatory, anti-hive rich plant–mediated nanoparticle synthesis might be an alternative betterment, cost-effective, and eco-friendly medication for the skin disease caused by SARS-corona virus 2 (the viral clinical signs are itchy, hives, rashes, papules, psoriasis, and inflammation) and (non-viral clinical signs-pressure urticaria, contact dermatitis, and acne) that occurred as the result of COVID-19.

Keywords Pandemic · Cuticular · Phytotherapeutic · Coronavirus · Reservoir · Anti-hives

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Introduction

The word virus is derived from the infectious fluid which is entitled "contagium vivum fluidum" by the inventors in 1930. A ubiquitous, pleomorphic, plasma membrane–wrapped surface with positive-sense RNA showing coronet texture, enclosing membrane proteins (M, E, N, and spiker) is known as coronavirus. In China, pneumonia patients isolated the severe acute respiratory syndrome coronavirus 2 which is a new zoonotic RNA virus and the causative agent of the coronavirus disease-19. The name was entitled by the public health international conference and WHO on February 11, 2020. This disease is menacing and prevailing throughout the world at a lurching speed [1••]. Genotypically, coronavirus is divided into four types of genera alpha, beta, delta, and gamma. This B.1.1.7 variant (alpha) was first documented in the UK, B.1.351 (beta) variant was documented in South Africa, P.1 variant (gamma) documented in Brazil, and B.1.617.2 (delta)

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variant was first documented in India [2]. At the end of World War I, the Spanish flu or great influenza epidemic or influenza pandemic caused by H1N1 created a menacing to public health. This virus increased the mortality rate in China, Hongkong, and Vietnam. This ubiquitous obligatory intracellular parasite affected all states of India by the travelers and tourists from China and other parts of Asia in the mid of March 2019 resulting in the sudden shoot of sickness and death. The researcher says this CoV binds to the cells in the mucous membrane through angiotensin II receptor blockers; it narrows the blood vessels, increases the blood pressure, and makes the heart function harder. Then in the mucous membrane, the sputum secretion is boosted up and then through cilia, the CoV is moved out of the nose which is trapped in the mucus [3]. Studies say the deposition of the sputum is more in the nasal cavity than in the throat so the liquid containing the infectious agent of 1–2 mm is transmitted by free-floating aerosol via sneezing and settling on a surface. By liquid sterilization using chemical agents like hypochlorite which is sensitive to the lipid layer of the RNA-packed enveloped virus which results in the destruction of the cell wall in a fraction of a second. The survival of the coronavirus on various surfaces and objects is hiked from hours to days or weeks because it remains for a long time in an unfavorable environmental condition. The invasion and growth of the CoV in the mucous membrane of the respiratory tract is acquired through the mouth, nose, and eyes after touching the surface or object soiled by the sputum droplets of CoV, and the moment of exposure of the onset of signs, symptoms of the disease from 2 to 14 days. The mild and moderate symptoms of CoV are fever, cough, headache, fatigue, myalgia, conjunctivitis, and untreated condition leads to breathlessness and in the fatal stage leads to death. Primary detection of the virus through multiplex PCR in blood and stool samples and the secondary stage of the CoV is identified through CT scan. In the case of skin, SARAS-CoV2 played a vast role from infant to adult. In pediatrics, characteristic mucocutaneous findings are identified in half of the children who are affected by multisystem inflammatory syndrome caused by SARS-Cov2 and the cutaneous findings differ from Kawasaki disease or multi lymph node syndrome [4]. The healthcare workers and dermatologists in hospitals due to prolonged exposure to personal protective equipment like eyeglasses, PPE, gloves and wearing a long-time N95 mask, and maintaining excess personal hygiene by washing hands frequently with a disinfectant like 60% ethanol/detergents leads to severe skin problems like allergic contact dermatitis, pressure ulcers, pressure hives, Sebopsoriasis, acne, and exacerbation of pre-existing skin diseases. The distinctive viricidal and physicochemical properties of the nanoparticle enrich its therapeutic efficacy and enhance intra and extracellular levels of drug delivery to the target site. Nanosize, targetability, easy responsiveness to the stimulus, and large surface area are all these remarkable properties of the nanoparticles that make them more effective against the antiviral agent [5]. In the present paper, we discuss the efficacy of the phyto compounds of the medicinal plant–mediated nanoparticles that might act as a potential viricidal agent against skin ailments caused by SARS-CoV-2.

History of Single-Stranded RNA Evolution

In molecular biology, single-stranded RNA plays a dominant role [6]. RNA molecules do not code proteins and act themselves as proteins. Viruses have genetic material RNA and it may be single-stranded or double-stranded. The origin of RNA replicase or RNA-dependent RNA polymerase is tracked down from t-RNA fore-bearers. The fingers, palm, and thumb are the three functional subdomains of RNA replicase. Two conserving residues of catalytic aspartate and RNA recognizing Motif belonging to the subdomain of palm mingle with divalent metal ions which pave the way for the nucleophilic attack resulting in a chain formation of the emerged ribonucleotide. The interaction between the nucleotide and template occurs at the fingers of the subdomain [7]. The most inconsistent part of the protein is sited at the N terminal part of the enzyme which is situated at the thumb subdomain. In that, A-Fmotifs are sited in the palm subdomain and the A-Emotifs and Fmotifs are sited in the finger subdomain. The activation of Motifs is necessitated by substrate binding and cofactors which is close to the catalytic site. A twin role activity was played by RNA molecules by storing all genetic information in the sequences and also, they act as a catalyst that is decisive for all biological information. RNA replicase plays a vital role in the synthesis of proteins if RNA is the genetic material, replication, and continuous storage of genetic information in the initial genome [8]. The core hypothesis suggests that the tRNA is the ancient and the basic genetic material for the organization of life which gives rise to messenger RNA (mRNA) ribosomal RNA (rRNA), and also, the former ribonucleic acid (RNA) structural authentication is done. First proteins are synthesized after the advent of rRNA and mRNA from the ancient translation method. The transformation from RNA to RNA/protein world and then to RNA/DNA/Protein world is entertained from the basic primeval translation system.

Internal Characteristics of Coronavirus

Coronavirus belongs to the Coronaviridae family and is a + ve sense RNA and the genome is packed in a helix capsid surrounded by nucleocapsid protein. The average size and its diameter vary from 80 to 120 nm and in larger exceed 50 to

200 nm [9]. The membraneprotein (M), envelopeprotein (E), glycoprotein spike (S), and nucleoprotein (N) are the structural proteins surrounding the virus envelope. Being the central organizer of coronavirus assembly, the membrane protein (M) ensures an imperative role in determining the shape of the viral envelope. The binding of the host cell receptor in a critical state and paving the way for the host cell are the effective functions of spike glycoprotein (S). Envelope protein (E) forms the viral envelope after interaction with M (membrane protein); these are activities of the envelope protein. The nucleocapsid is formed after binding with the RNA genome which is the property of nucleocapsid protein (N). Club-shaped projections called spikes to surround the viral envelope [10]. In the case of membrane protein, it constitutes three domains N- terminal ectodomain, a transmembrane domain, and C- terminal Endodomain. Among these domains, the C terminal domain forms a thick envelope with the addition of matrix lattice because it contains 218 to 263 amino acid residues. Envelope protein consists of two domains: transmembrane domain and the C-terminal extra membrane domain. Then, five molecular ionic channels are formed in the lipid bilayer. Spike protein consists of two subunits S1 and S2 in which S1 forms the spikes head and also contains the receptor-binding domain. The S2 subunit enables stem formation, anchoring the spike, protease activation, and cell membrane fusion. The two subunits are non-covalently linked and studded on the viral envelope and exposed to the host cell membrane. Then later on, the two subunits separate after they bind to the host cell and work under the action of protease belonging to the transmembrane protease serine 2 and cathepsin. A small spike surface protein called haemagglutinin esterase protein appears as a tiny projection in between the spikes helping in the attachment and detachment from the host cell [11]. In recent microscopical view that says that the strand of viral genes coil up with proteins studded on the surface and suddenly, they are twisted into the cellular factories and built to form new viruses. The virus easily slips inside by fastening the spike proteins to hold on to the cells in the airways. Suddenly, the spike proteins break and join together and give a structure that resembles the tulip shape and also a three-part flower. In scanning electron, microscopic study shows how much atoms pushed and pulled each other in the proteins that are calculated. The success of the coronavirus is the flexibility of its spike proteins. The spikes whirl around the proteins and protect them from antibodies. The Cov2 fuse with the cell membrane when the spike protein experienced a series of reactions after it met a protein on the cell surface and, later on, innoculate its genes [12]. The genome of this virus is larger than a compendium. The strand untidily twisted together pleats devilishly. The genes are read and ejected extra new-fangled viral proteins by the cell's ribosomes [13]. Viral cell surfing, morphogenesis, and internal cell structures are cleanly observed and studied through a high-content screening microscope [14]. The viral replication and transcription take place in the cytoplasm.

Resource

Economical burden and morbidity is the significant result of this respiratory tract infection. Broadly divided into four main genus sub-groups known as *Alpha coronavirus*, *Beta coronavirus*, *Gamma coronavirus*, and *Delta coronavirus*, which are capable of infecting the immunosuppressed host suffering from upper respiratory infections [15]. Climatic parameters play an important in the spread of the coronavirus. In subtropical climates, the virus transmission is very effective and hikes in low temperature and humidity because the surveillance of the virus retains up to 14 days. The causative factors for the disease transmission may be changes in weather conditions, susceptibility in the host physiology, immunity function, and at last, communal etiquette [16]. The above shows the climatic factors pave the way for transmission of the disease because the virus survives in the ecological condition before emerging into the host.

Survival in Temperature and Humidity

The predominance of coronavirus disease 2019 (COVID-19) is less in countries nearer to mid-latitude and shows high in the place having elevated temperature and humidity predicted visually after having a look at the world map. Warm weather hikes sunlight in the climate of the northern hemisphere; there is a rapid spread of this disease according to the study of 2020/2021 [17]. The weather-dependent seasonal infections and their causative agents are adenoviruses, rhinovirus, influenza A and B, meta pneumonia virus, and coronavirus. The lack of Vitamin D during winters makes healthy individuals immunosuppressors and easily prone to the disease. Coronavirus can easily withstand minimal temperature, humidity, and UV radiation environments. The national academies of science, engineering, and medicine and the European Respiratory society together held in the USA on April 7, 2020, reported [18] that coronavirus survives in hike temperature, humidity, and their transmission rates; ecological hypothesis all these are inversely related. Due to high temperature and UV-radiation, the coronavirus show that its susceptibility is concluded by many laboratory studies.

Survival in Acidity and Alkalinity

Coronavirus persists in body fluids like serum, sputum, urine, and stool for 4 days. The surveillance of the virus depends on the nature of the stool and its pH which may alter [19]. The rate of infection efficacy is less in urine. In the same way in an infant stool, it survives only for 3 h; in the case of a fresh normal stool of an adult in which both are acidic, the virus will not survive more than a day. But

Table 1 Variants of SARS-CoV-2

S. no	Alpha	Beta
1	Human coronavirus 229E (HCoV-229E)	HCoV-HKU1 (subgroup-A)
2	Humancorona virus (HCoV-NL63)	Human coronavirus OC43, SARS-CoV Severe acute respiratory syndrome coronavirus (subgroup-B)
3	-	Middle East respiratory syndrome-related coronavirus (MERS-CoV) (subgroup-C)

in a diarrheal stool whose pH is 9 and alkaline, it survives for 4 days. It may survive for a long time about 1 week in the infected secretions such as saliva, sputum, and sweat because all have a slightly acidic and alkaline pH that reaches up to 6.3 to 9.

Life Cycle of COVID-19

The coronavirus using its flexible spike projections holds on to the angiotensin-converting-enzyme-2 receptor of the host cell; from here, the life cycle proceeds. The binding of the receptor with the cell membrane via endosome pathway at this spot, the S protein emerged. Interactivity between receptor and protein was triggered by the contact between the host cell and the virion. Usually, the receptor-binding domain (RBD) is present in the S1 region within the virus but the position of RBD changes to C-terminal according to the infection severity. Peptidase cellular receptor is also involved in many strains of coronavirus as per the study [20]. Ejection of the RNA genome which has the replicase property into the host cell is the initial stage of the coronavirus cycle. Two open reading frames of this replicase protein are rep 1a and rep 1ba and then they also bear two common proteins pp1a and pp1ab. After protein synthesis cleave to produce functional two distinct polypeptides are conveyed to the harmful inherited sequences (5′-UUUAAAC-3′), this incident made a shift in ORF from rep1a to rep1b. Then, pp1a and RNA-dependent RNA polymerase is received by the genomic RNA which is broken into pieces by viral proteases. Subgenomic mRNAs positioned by liner transposition generated by polymerases are later converted into suitable infected proteins. The replicase structure of the virus is translated and distributed which is the result of RNA production. Sub genomic RNA which is packed as the mRNA is the result of the binding synthesis of viral RNA and this subgenomic RNA is situated in a part of the sequence of the genetic material towards the point of transcription of multifunction protein or replicase protein. The distinctive property of the viral genome of coronavirus is it bears a 3′ common end finalized length of the viral genome and stable RNAs. Through positive and negative sense RNA intermediates, the genomic and sub-genomic RNA is produced. The harmful interference of the RNA chain holds 1% positive sense strands. Then, the first synthesized RNA (produced at the time of minus-strand synthesized from genomic RNA is the subgenomic RNA) prepares the pack of basic viral proteins like S, M, and E; after amplification, they are pushed into the endoplasmic reticulum (ER). After crossing the epithelial pathway in the endoplasmic reticulum (ER) and Golgi apparatus (GIA), this infectious protein and genomic RNA are finally collected and mature in the matrix of (ERGIA). Later, they travel in the organelles and are expelled out as a very effective infectious, completely matured virion to attack another immunosuppressed host to begin its life cycle from the starting point.

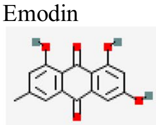
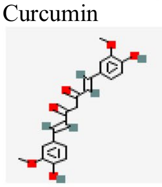
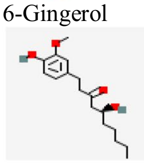
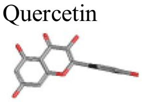
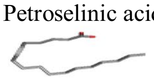
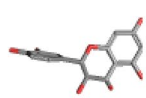
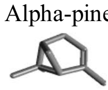
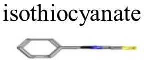
The Reservoir of Disease (COVID-19)

The epidemiological investigation first started at a wholesale seafood stall in Hua Nan of Wuhan city China. Later, it was identified that this stall might be the causative factor for the novel SARS-CoV-2 because nearly 100 patients show positive and were exposed to this infection [21]. The SARS-CoV-2 is procured directly from fauna or indirectly from fauna-based products via home delivery persons, restaurants, meat factories, poultry farms, and other industries in and around the Wuhan market to Beijing in China that act as the disease reservoirs. The edible faunal-based products are used up as resources by humans which highly transmit this disease and also act as the reservoirs of disease in China and Southeast Asia as reported in the Chinese Academy of engineering report of 2017. SARS coronavirus-2 which belongs to β genera shows 96% similarity with *Rhinolophus affinis* isolated from horseshoe bats and 91% similarity with *Manis javanica* isolated from Malayan pangolin in China. Scientist says the reservoir of disease for coronavirus is also pangolins but through bioinformatics, a study says that a special peptide present in the spike protein of coronavirus is not observed in pangolin, so through contamination in the faunal trade work, it might be directly transmitted from Sunda pangolin (Manisjavanica). Through zoo carriers, keepers, and rangers, the tiger and lion show COVID-19-positive and affected. The involvement of multiple strains of SARS-CoV2 due to rapid mutation made it widespread and exists for long periods on this planet [22••]. The fauna is an essential tale and plays a multi-task as a reservoir of disease in COVID-19. This disease is 99% transmitted via domesticated fauna, foodborne infection, and less by vector-borne disease.

Secondary Skin Infections of COVID-19

Due to substantial immune response and the presence of primary receptor angiotensin-converting enzyme 2, SARS-corona virus2 enters the skin cells and causes lesions directly and also implied vasculitis and thrombotic vasculopathy due to vascular dysfunction. According to the

Table 2 Plant-mediated nanoparticles synthesize help in the viral skin problems. Different therapeutic plants and their three-dimensional structure, synthesized nanoparticles, size, shape, and characterization study show their efficacy on skin ailments are described in detail

S. No	Therapeutic plants	Plant parts	Phytochemical compound	Nano particles synthesis	Size and shape	Instrumental analysis	Mechanism of action	Reference
1.	*Aloe Barbadensis*	Latex	Emodin 	Ag, Se, Au	50 nm triangle	SEM, TEM, and UV-Visible spectrophotometer	Treat viral hives and warts and also inhibit the spike proteins	[28]
2	*Curcuma longa*	Tubers	Curcumin 	Ag, Zn, Au	445 nm, spherical	SEM, TEM	Hypertonic scars treating property and block the virus entry and penetration	[29]
3.	*Zingiber* officinale	Rhizome	6-Gingerol 	Ag, Zn, AU	18.93 nm	TEM, FESEM	Help in skin repairing damage due to viral hives	[30]
4.	*Allium sativum*	Cloves	Allicin 	Ag, Zn	22.73–60.61 nm	TEM, SEM	Helps to treat rashes and inflammation due to COVID-19 and also helps in inhibition of the virus to enter the host cell	[31]
5.	*Nelumbo nucifera*	Petals	Quercetin 	Ag	410 nm	TEM, SEM	Anti-acne and anti-hives property and interference with viral attachment.	[32]
6	*Coriandrum sativum*	Fruit	Petroselinic acid 	Ag	300-600 nm	UV–Vis spectrophotometer	It possesses anti-inflammatory, antihives property.	[33]
7.	*Musa acuminata*	Flower	Leucocyanidin 	Ag, Au	12.6 to 15.7 nm for Ag and 10.1 to 15.6 nm for Au nano particles	SEM, TEM	It possesses anti-ulcer activity and anti-hives properties and also inhibits the virus to enter the host cell.	[34]
8	*Citrus lemon*	Leaf	Alpha-pinene 	Ag	405–425 nm	SEM, TEM	It possesses the anti-inflammatory and anti-viricidal property	[35]
9.	*Carica papaya*	Leaf	Benzyl isothiocyanate 	Ag	400–435 nm	UV-Visible spectrophotometer	It possesses the anti-inflammatory property	[36]
10	*Syzygium aromaticum*	Leaf	Sesquiterpenoid 1	Ag, Au	4 to 150 nm.	UV-Visible spectrophotometer	It possesses anti-inflammatory and antiulcer activity and also inhibits virus cell entry.	[37]

researchers after exposure to the disease and completing its incubation period, the immunosuppressive persons show primary symptoms like cough, fever, myalgia, headache, breathlessness, and finally loss of smell and taste. In the moderate stage, slight discoloration develops on the toes and fingers. Soon after appears elevated fever, itchy rashes, and flat or red bumps with lymph nodal enlargement all over the trunk which resembles Grover disease. After showing elevation in WBC, reactive protein and ESR–hospitalized immunosuppressive host shows painful, red, and papules with or without vesicles. Pre lesions erupted 3 days before the diagnosis of COVID-19 and post lesions erupted after 13 days later and their time of healing and scar formation varies and depends on the disease severity [23]. The Chair of Dermatology at Northwestern Feinberg School of Medicine reports infectious disease like measles, scarlet fever, meningococci, and their histological findings and skin display reports differ from the skin manifestations of COVID-19. Infants show patchy rash and itchy bumps which also mimick diaper rashes. Reservoirs for nonviral skin infections are N95 mask, gloves, face shield, PPE, eyeglasses, wearing long time gowns, heat stress, and protective boots; all these cause direct or indirect blisters, eruptions, hives, folliculitis, vasculitis, and thrombotic vasculopathy for the health workers, attenders, and volunteers. Due to frequent hand washing with disinfectant, soaps also cause itching and contact dermatitis. Sometimes in the worst stage, itching continues for a long time and makes the patient difficult to take a rest. Asymptomatic persons show some clinical signs like papules, red or pink eruptions, and painful lesions which mimic keratosis pilaris. Hydroxychloroquine is the medication responsible for COVID-19 which causes multiple skin lesions like hair whitening, Stevens-Johnson syndrome (SJS), and acute generalized exanthematous pustulosis (AGEP), and exacerbation of psoriasis occur in patients of COVID-19 who consumed heavy doses [24]. In severe cases, high levels of interleukin, cytokines, chemokines, and platelet- circulating in the blood lead to inflammation in COVID-19 patients.

Nanoherbal Remedy

"Creation," "exploitation," and "synthesis are the principles of nanotechnologies to produce a broad and wide range of products. The name "Nanos" is derived from the Greek word that means small, dwarf, or tiny. Prevention by nanotechnology-based therapeutic therapies against COVID-19 is an overwhelming gifted approach for skin manifestation. Inhibition of transcription, translation, membrane fusion, and virus

Table 3 Gram-positive and gram-negative bacteria, fungi, and algae-mediated nanoparticles are the precursors in the viral skin problem

S. no	Bacteria	Fungi	Algae	NPs	Characterization study	Mechanical action	Reference
1	*Staphylococcus aureus*	*Penicillium polonicum*	*Chetomorpha antennina*	Ag, Au, and ZnO	SEM, TEM, and UV spectroscopy	Inhibit the spike protein	[38]
2	*Escherichia fergusonii*	*Aspergillus sydowii*	*Galaxaura glangata*	Ag and Au	SEM and TEM	Inactivate the virus and block the virus entry	[39]
3	*Bacillus brevis*	*Fusarium oxysporum*	*Ulvafasciaba*	Ag, and Au	SEM and TEM	Competition for the binding of the virus to the cell	[40]
4	*Bacillus funiculus*	*Monascus*	*Turbiaria conoides*	Ag	TEM,SEM	Interference with viral attachment	[41]
5	*Pseudomonas aeruginosa*	*Botryosphaeria rhodina*	*Portieria hornemannii*	Ag, and Au	SEM, TEM	Inactivate the virus and block the virus entry	[42]
6	*Pseudomonas putida*	*Penicillium oxalicum*	Tubinaria Conoides	Au, Ag, and Zn	TEM	Block the virus entry and penetration	[43]
7	*Escherichia hermannii*	*Cladosporium*	*Sargassum plagiophyllum*	Ag and Au	TEM	Competition for the binding of the virus to the cell	[44]
8	*Bacillus cereus*	*Trichoderma harzianum*	*Cyanobacterium*	Ag and Au	SEM	Interaction with gp120	[45]
9	*Bacillus endophyticus*	*Trichoderma reesei*	*Bifurcaria bifurcate*	Ag	SEM	Inhibit the spike proteins	[46]
10	*Brevibacillus formosus*	*Trametes trogii*	*Oscillatoria limetoca*	Ag	TEM	Inhibit the virus-cell entry	[47]

replication in all these stages nanomaterial shows its effective role and protects the host from its vast effect [25]. The elevated surface area of the nanoparticles can mingle with RNA, antibodies, and peptides and enhance the contact of the analyte with the sensor and increase the detection limit and detection time. Due to the extreme surrounding mingled with elevated poisonous chemicals, the eco-friendly green method of synthesis using plants, fungi, and bacteria is also an efficient way to enhance the therapeutic potential to fight against the global threat. Viral skin ailments like hives, eruptions, boils, warts, molds, and inflammations all are treated by some plant-mediated nanomaterial applications in the form of cream, paste, powder plasters, and bandages which are obtained from the oil, leaf juice, twigs powder, and paste of the bark that are procured from some therapeutic flora. Nanoparticles act as a blocker and prevent the binding of S protein to the host cell in certain viruses such as HBV (hepatitis B virus), HCV (hepatitis C virus), Hu Nov (human Norovirus), and SARS coronavirus 2. Appropriate doses show differences in the characteristic of the cellular membrane and the physical character all these pave and deliver appropriate nano-drug to the target cells [26, 27•]. This section explores that the natural polymers like curcumin, 6-Gingerol, allicin, quercetin, and emodin isolated from the therapeutic plants might act as nanocarriers or nanomedicine. Low density, cheap, and ecofriendly are the characteristics of natural fibers such as cotton reinforced by the natural polymer mediated nanoparticles. For example in the case of HIV-1, the curcumin-loaded silver nanoparticles inhibit the entry, fusion, and infectivity at a non-toxic dose of 10–25 μg/ml at a size of 10 nm in a study against tacaribe virus (a new arenavirus). Green synthesized nanoparticles have the inhibitory action against many viral skin diseases. For external applications, the appropriate concentration of fibers composed of nanomedicines can be molded into non-allergic natural plasters which deliver the appropriate concentration of the nanomedicine to the infection site on the dermal layer. Different nanoparticles synthesized mediated therapeutic flora, microorganisms like bacterial, fungal, and algal their surface topology and their three-dimensional picture all are briefly sketched in the Tables 1 and 2 and also illustrate the life cycle of the virus along with that the route of pathogenicity causing skin infection as the result of COVID-19, and the green

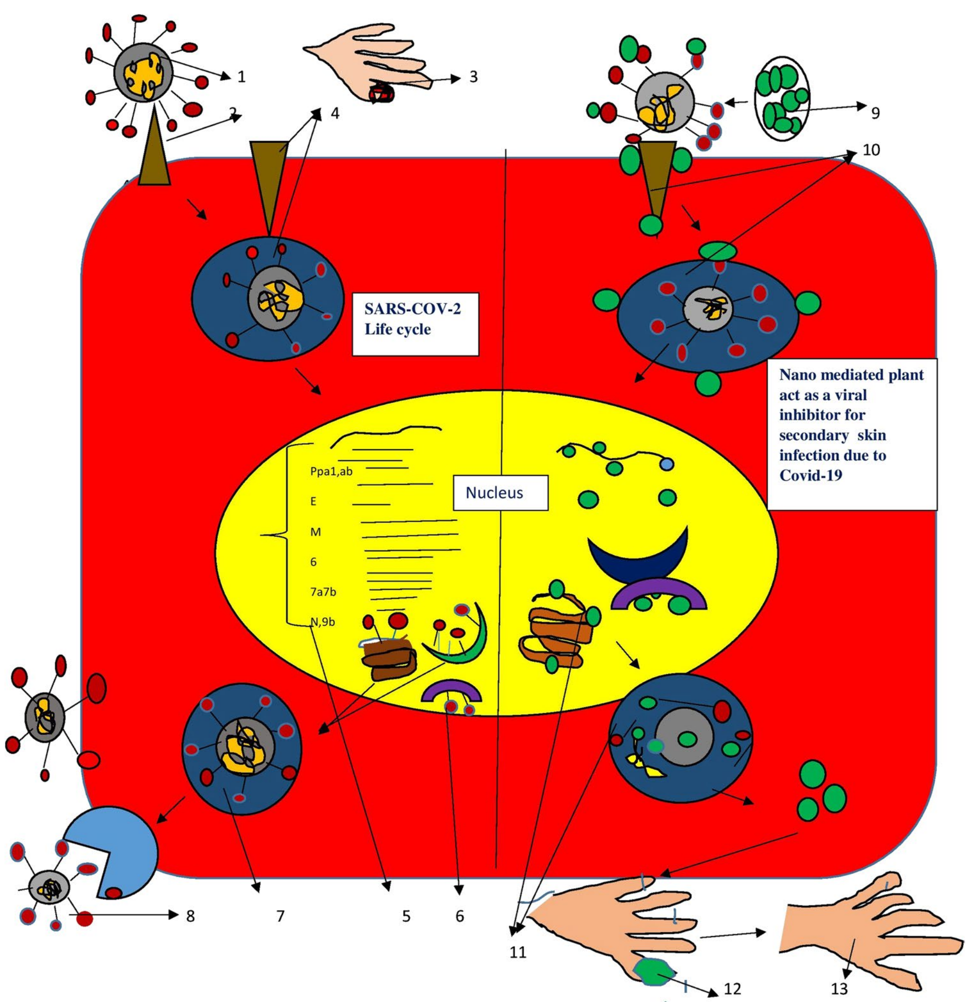


Fig. 1 Lifecycle of SARS-COV-2 and inhibition of skin infections by plant-mediated nanoparticles might act as an antiviral agent. (1) SARS-COV-2 virus. (2) ACE2 receptor (angiotensin-converting enzyme-2). (3) Pre inflammatory occurred due to ACE2 receptor. (4) Binding of the virus with ACE2 receptor. (5) mRNA synthesis of the viral genome. (6) Transcription and translation occur in the nucleus by the formation of virions in the endoplasmic reticulum, Golgi bodies, and mitochondria. (7) Assembly and budding of virions. (8) Exocytosis release of the mature viral progeny. (9) Plant-mediated metal nanoparticle (viral inhibitor). (10) Block the ACE2receptor and inhibit the virus entry by binding with the virus. (11) Block the transcription and translation, inhibit the formation of the virion in the cell organelles, and also inhibit the assembly of the virion. (12) Metal nanoparticles after playing the role of inhibitors and act as an anti-inflammatory agent. (13) Plant-mediated metal nanoparticles might act as an alternative medication in treating the skin infections caused by COVID-19

synthesis Table 3 nanoparticle acting as the inhibitor is shown in the Fig. 1.

Both gram-positive and negative organisms, fungi, and algae-mediated nanoparticle synthesis and their inhibitory action are clearly illustrated in the table.

Conclusion

Scientists focus on the etiology, pathogenicity, and detailed study about the host immune response to the virus-cell; all these together enhance to search for an effective therapeutic agent for the global threat pandemic. Increasing the efficacy of treatment controlled the release of the properties, reducing the period and dosage of the therapeutic agent against the treatment, and control of the infectious disease. Curcumin-like compounds possess many natural resources against many sensitive viruses. The attitude of the nanomaterials reaches the blood circulation of the body and inhibits the formation of the corona proteins. Different ways of mutation and elevated transfer rate made this virus more potent against the immunosuppressive host. COVID-19 acts as the greatest army for the scientist which molds them to gain knowledge about its nook and corner as fast as its speed.

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Declarations

Conflict of Interest The authors declare no conflict of interest.
Human and Animal Rights and Informed Consent.
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References

Papers of particular interest, published recently, have been highlighted as:
• Of importance
•• Of major importance

1.•• Guo YR, Cao QD, Hong ZS, Tan YY, Chen SD, Jin HJ, Tan KS, Wang DY, Yan Y. The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak–an update on the status. Mil Med Res. 2020;13(1):11. https://doi.org/10.1186/s40779-020-00240-0. **This article provides a comprehensive review of reservoir, transmission, and clinical signs and symptoms of coronavirus**.
2. Xia S, Zhu Y, Liu M, Lan Q, Xu W, Wu Y, et al. Fusion mechanism of 2019- nCoV and fusion inhibitors targeting HR1 domain in spike protein. Cell Mol Immunol. 2020;17:765–7. https://doi.org/10.1038/s41423-020-0374-2.
3. Lee PI, Hsueh PR. Emerging threats from zoonotic coronaviruses-from SARS and MERS to 20196-nCoV. J Microbiol Immunol Infect. 2020;53(3):365–7. https://doi.org/10.1016/j.jmii.2020.02.001.
4. Chen C, Zhang XR, Ju ZY, He WF. Advances in the research of cytokine storm mechanism induced by corona virus disease 2019 and the corresponding immunotherapies. Zhonghua Shaoshang Zazhi. 2020;36:5.
5. Wang H, Xiao X, Lu J, Chen Z, Li K, Liu H, et al. Factors associated with clinical outcome in 25 patients with avian influenza a (H7N9) infection in Guangzhou, China. BMC Infect Dis. 2016;16(1):53. https://doi.org/10.1186/s12879-016-1840-4.
6. Wells MF, Salick MR, Wiskow O, Ho DJ, Worringer KA, Ihry RJ, et al. Genetic ablation of AXL does not protect human neural progenitor cells and cerebral organoids from Zika virus infection. Cell Stem Cell. 2016;19(6):703–8. https://doi.org/10.1016/j.stem.2016.11.01.
7. Recalcati S. Cutaneous manifestations in COVID-19: a first perspective. J Eur Acad Dermatol Venereol. 2020;34(5):e212–3. https://doi.org/10.1111/jdv.16387.
8. Jimenez-Cauhe J, Ortega-Quijano D, Carretero-Barrio I, et al. Erythema multiforme-like eruption in patients with COVID-19 infection: clinical and histological findings. Clin Exp Dermatol. 2020;45(7):892–5. https://doi.org/10.1111/ced:14281 (Published online).
9. Tong JY, Wong A, Zhu D, Fastenberg JH, Tham T. The prevalence of olfactory and gustatory dysfunction in COVID-19 patients: a systematic review and meta-analysis. Otolaryngol Head Neck Surg. 2020;163:3–11. https://doi.org/10.1177/0194599820926473.
10. Struyf T, Deeks JJ, Dinnes J, Takwoingi Y, Davenport C, Leeflang MM, et al. Signs and symptoms to determine if a patient presenting in primary care or hospital outpatient settings has COVID-19 disease. Cochrane Database Syst Rev. 2020;7(7):Cd013665. https://doi.org/10.1002/14651858.Cd013665.
11. Munblit D, Nekliudov NA, Bugaeva P, Blyuss O, Kislova M, Listovskaya E, et al. StopCOVID cohort: an observational study of 3,480 patients admitted to the Sechenov University hospital network in Moscow city for suspected COVID-19 infection. Clin Infect Dis. 2021;73(1):1–11. https://doi.org/10.1093/cid/ciaa1535.
12. Lauretani F, Ravazzoni G, Roberti MF, Longobucco Y, Adorni E, Grossi M, et al. Assessment and treatment of older individuals with COVID 19 multi-system disease: clinical and ethical implications. Acta Biomed. 2020;91(2):150–68. https://doi.org/10.23750/abm.v91i2.9629.
13. Ludvigsson JF. Systematic review of COVID-19 in children shows milder cases and a better prognosis than adults. Acta Paediatr. 2020;109:1088–95. https://doi.org/10.1111/apa.15270.
14. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020;382(18):1708–20. https://doi.org/10.1056/NEJMoa2002032.
15. Korber B, et al. Tracking changes in SARS-CoV-2 spike: evidence that D614G increases infectivity of the COVID-19 virus. Cell. 2020;182:812-827.e19. https://doi.org/10.1016/j.cell.2020.06.043.
16. Worobey M, et al. The emergence of SARS-CoV-2 in Europe and North America. Science. 2020;370:564–70.
17. Zhu N, et al. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med. 2020;382:727–33. https://doi.org/10.1056/NEJMoa200101.

18. Volz E, et al. Evaluating the effects of SARS-CoV-2 spike mutation D614G on transmissibility and pathogenicity. Cell. 2020;184:64-75.e11.
19. Pinto D, et al. Cross-neutralization of SARS-CoV-2 by a human monoclonal SARS-CoV antibody. Nature. 2020;583:290–5.
20. Joob B, Wiwanitkit V. COVID-19 can present with a rash and be mistaken for dengue. J Am Acad Dermatol. 2020;82(5):e177. https://doi.org/10.1016/j.jaad.2020.03.036.
21. KamaliAghdam M, Jafari N, Eftekhari K. Novel coronavirus in a 15-day-old neonate with clinical signs of sepsis, a case report. Infect Dis. 2020;52(6):427–9. https://doi.org/10.1080/23744235.2020.1747634.
22. Gianotti R, Zerbi P, Dodiuk-Gad R. Histopathological study of skin dermatoses in patients affected by COVID-19 infection in the Northern part of Italy. J Cosmet Dermatol Sci Appl. 2020;98(2):141–3. **This article provides a comprehensive review of clinical and histological reports of the patients affected by CoV skin infections**.
23. Najarian DJ. Morbilliform exanthem associated with COVID-19. JAAD Case Rep. 2020;6(6):493–4. https://doi.org/10.1016/j.jdcr.2020.04.015.April19.
24. Droesch C, Hoang M, DeSancho M, Lee E-J, Magro C, Harp J. Livedoid and purpuric skin eruptions associated with coagulopathy in severe COVID-19. JAMA Dermatol. 2020;156(9):1022–4. https://doi.org/10.1001/jamadermatol.2020.2800.
25. Roca-Ginés J, Torres-Navarro I, Sánchez-Arráez J, et al. Assessment of acute acral lesions in a case series of children and adolescents during the COVID-19 pandemic. JAMA Dermatol. 2020;156(10):1134–6. https://doi.org/10.1001/jamadermatol.2020.2340.
26. Madigan LM, Micheletti RG, Shinkai K. How dermatologists can learn and contribute at the leading edge of the COVID-19 global pandemic. JAMA Dermatol. 2020;156(7):733–4. https://doi.org/10.1001/jamadermatol.2020.1438.
27. Galván Casas C, Català A, Carretero G, et al. Classification of the cutaneous manifestations of COVID-19: a rapid prospective nationwide consensus study in Spain with 375 cases. Br J Dermatol. 2020;183(1):71–7. https://doi.org/10.1111/bjd.19163. **This article provides a comprehensive review of CoV skin manifestation and shows the difference with other skin manifestation**.
28. Oryan A, Mohammadalipour A, Moshiri A, Tabandeh MR. Topical application of aloe vera accelerated wound healing, modeling, and remodeling. an experimental study with significant clinical value. Ann Plast Surg. 2016;77:37–46. https://doi.org/10.1097/SAP.0000000000000023.
29. Maghimaa M, Alharbi SA. Green synthesis of silver nanoparticles from Curcuma longa L and coating on the cotton fabrics for antimicrobial applications and wound healing activity. J Photochem Photobiol B Biol. 2020;204:111806.
30. Eptiyani R, Wibowo C. Identification of active compounds and testing the antioxidant properties of neem leaf extract. AIP Confer Proc. 2019;2094:0200341–7. https://doi.org/10.1063/1.509750.
31. Fernanda P, Vanessa E, Cueva V, Lorena M. Preparation of a degradable hydrocolloid film with silver nanoparticles synthesized with aqueous garlic extract (Allium sativum). Periodico Tche Quimica. 2018;15:263–327.
32 Zhu MZ, TLiu CY, Zhang C, Guo MQ. Flavonoids of lotus Nelumbo nucifera seed embryos and their antioxidant potential. J Food Sci. 2017;82(8):1834–41.
33. Sathishkumar P, Preethi J, Vijayan R, Mohd Yusoff AR, Ameen F, et al. (2016) Anti-acne, anti-dandruff and anti-breast cancer efficacy of green synthesised silver nanoparticles using Coriandrum sativum leaf extract. J Photochem Photobiol B. 2016;163:69–76.
34. Arumugam N, Thulasinathan B, Pasubathi R, Thangavel K, Muthuramalingam JB, Arunachalam A. Biogenesis of silver nanoparticles using selected plant leaf extract; characterization and comparative analysis of their antimicrobial activity. Nanomedicine Journal. 2017;4:208–17.
35. Jassim AMN, Mohammed MT, Farhan SA, Dadoosh RM, Majeed ZN, Abdula AM. Green synthesis of silver nanoparticles using Carica papaya juice and study of their biochemical application. J Pharm Sci Res. 2019;11:1025–34.
36. Yu J, Xu D, Guan HN, Wang C, Huang LK, Chi DF. Facile one-step green synthesis of gold nanoparticles using Citrus maxima aqueous extracts and its catalytic activity. Mater Lett. 2016;166:110–2.
37. Maciel MV, Almeida AD, Machado MH, Melo AP, Rosa CG, Freitas DZ, et al. Syzygium aromaticum L. (Clove) essential oil as a reducing agent for the green synthesis of silver nanoparticles. Open J Appl Sci. 2019;9:45–55.
38. Lee SH, Jun BH. Silver nanoparticles: synthesis and application for nanomedicine. Int J Mol Sci. 2019;20(4):865.
39. Long YM, Hu LG, Yan XT, Zhao XC, Zhou QF, Cai Y, Jiang GB. Surface ligand controls silver ion release of nanosilver and its antibacterial activity against Escherichia coli. Int J Nanomedicine. 2017;12:3193. https://doi.org/10.2147/IJN.S132327.
40. Shanmuganathan R, Mubarak Ali D, Prabakar D, Muthukumar H, Thajuddin N, Kumar SS, Pugazhendhi A. An enhancement of antimicrobial efficacy of biogenic and ceftriaxone-conjugated silver nanoparticles: green approach. Environ Sci Pollut Res. 2017;1:9.
41. Rónavári A, Igaz N, Gopisetty MK, Szerencsés B, Kovács D, Papp C, Vágvölgyi C, Boros IM, Kónya Z, Kiricsi M, et al. Biosynthesized silver and gold nanoparticles are potent antimycotics against opportunistic pathogenic yeasts and dermatophytes. Int J Nanomed. 2018;13:695–703. https://doi.org/10.2147/IJN.S152010.
42. Gunaseelan S, Balupillai A, Govindasamy K, et al. Linalool prevents oxidative stress activated protein kinases in single UVB-exposed human skin cells. PLOSOne. 2017;12(5):e0176699.
43. Partila AM. Microbial production of silver nanoparticles by Pseudomonasaeruginosa cell free extract. J Ecol Health Environ. 2015;3(3):91–8.
44. Wang C, Kim YJ, Singh P, Mathiyalagan R, Jin Y, Yang DC. Green synthesis of silver nanoparticles by Bacillus methyl trophicus, and their antimicrobial activity. Artif Cells Nanomed Biotech. 2016;44:1127–32.
45. Erdem B, Dayangaç A, Kıray E, YalçınDuygu D. Biosynthesis of silver nanoparticles ffonı Aeromonas sobria and antibacterial activity against fısh pathogens. Int J Environ Sci Tech. 2018;23:1–6.
46. Ajah HAK, Chandra H, Patel D, Kumari P, Jangwan JS, Yadav S. Phytomediated synthesis of zinc oxide nanoparticles of Berberis aristata: characterization, antioxidant activity, and antibacterial activity of with special reference to urinary tract infection. Mater Sci Eng C Mater Biol Appl. 2019;102:212–20.
47. Agrahari S, Dubey A, Nanoparticles in plant growth and development. In Biogenic Nano-Particles and Their Use in Agro-Ecosystems (eds Ghorbanpour, M. et al.) 2020;9:37