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NANOTECHNOLOGY AND ITS PROSPECTIVE ROLE IN USING BIOACTIVE COMPOUNDS TO FIGHT COVID 19 INFECTION IN THIS ERA

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RTIs or pneumonia, which account for 15% of all pediatric fatalities under the age of five and cause significant morbidity, continue to be a serious global health issue. The most dangerous infection lately COVID-19 associated with bacterial superinfections, which results in a fatal acute respiratory infection marked by shortness of breath. Scientists continue to face significant challenges in the development of vaccines and antiviral or antibacterial medications to treat these diseases. Recently, Bioactive natural products from a variety of plants and organisms, such as bacteria, fungi, and algae, hold promise as treatments for cancer, bacterial infections, inflammatory diseases, and other medical conditions. To facilitate the transport of these bioactive compounds to a particular target, nanoparticles drug delivery system can be adopted. Nanotechnology has been recognized as an essential tool in vast human medical fields. The goal of this review is to highlight prior and ongoing research on naturally occurring active nanomaterials as antiviral or antimicrobial agents, particularly for diseases of the modern era like COVID-19, and to suggest potential new research methodologies based on the nanotechnology platform.

Keywords: bioactive compounds, green synthesis, nano-drug delivery, COVID-19, foods and herbs

INTRODUCTION

Respiratory tract infections (RTIs) continue to be a major worldwide health problem, accounting for 15% of all pediatric fatalities under the age of five and causing significant morbidity. RTIs are generally classified as either upper or lower respiratory tract infections (URTI or LRTI). Lower respiratory tract infections (LRTIs) like pneumonia are far worse than URIs, such as the common cold (Thapa et al., 2017). Pathogens invade the respiratory tract; they cause common respiratory diseases and affect sterile areas of the respiratory tract such as the lungs, trachea, and bronchi, making LRTIs more severe (Prescriber, 2007). Pneumonia is a potentially fatal acute respiratory infection that primarily causes shortness of breath. The lungs are normally terminated by small air-filled sacs called alveoli, but when pneumonia develops, the alveoli become blocked with secretions, and breathing becomes difficult due to a limitation of oxygen intake (Dasaraju and Liu, 1996). Pandemics that count as catastrophic events, have taken place in the twenty-first century, including old infections such as cholera, plague, and yellow fever, as well as emerging diseases such as severe acute respiratory syndrome (SARS), Ebola, Zika, the Middle East respiratory syndrome (MERS), the human immunodeficiency virus (HIV), despite being technically endemic, influenza A (H1N1), and most recently, COVID-19 (Ong et at., 2020). Developing vaccines and antiviral or antibacterial drugs to treat these diseases remains a major challenge for scientists. Herbal medications continue to be the most common source of pharmaceuticals, and their side effects are far less severe than those of standard medicine, but they have considerable limitations. The most essential technique for addressing this issue is nanotechnology, which is an extremely talented technique for boosting the use of herbal medicine or, more particularly, re-discovering its potential as a pharmaceutical formulation (Abbas et al., 2021).

1. Respiratory Tract Infections (RTIs)

A respiratory tract infection (RTI) is a term used to describe any infectious condition affecting the upper or lower respiratory tract as described by the National Institute for Health and Clinical Excellence (NICE) (2008). The term "upper respiratory tract" is frequently used to describe the airflow that occurs above the larynx or vocal cords. The following portions, including the larynx, pharynx, sinuses, nose, and other structures, also belong to URT. Examples of URT infections include tonsillitis, pharyngitis, laryngitis, sinusitis, otitis media, and certain influenza strain infections that cause the common cold. URI symptoms include a cough, runny nose, nasal and throat congestion, headache, and an elevated body temperature (Presseau et al., 2014). While lower respiratory infections are more serious than upper respiratory infections and are the largest cause of death. Bronchitis and pneumonia are the most frequent LRIs. Moreover, influenza influences both the upper and lower respiratory tracts and causes more dangerous strains, such as the zoonotic H5N1, to attach to lung receptors (Wang et al., 2022).

Airways, lung function, and specific standards are estimated during pulmonary function testing (PFT), which can detect a variety of respiratory tract issues. The two methods that can assist in determining functional and total lung capacity are gas dilution and plethysmography. Based on the results of the previous examinations, it can be determined whether there is a need for lung function tests or not (Gu et al., 2021). Respiratory infections frequently follow seasonal patterns, with the winter months being more problematic in temperate regions. Various factors, such as alterations in human behavior and environmental factors, contribute to the seasonal increases in respiratory infections. The relative humidity and temperature of the environment influence viruses that cause respiratory issues. Winters in temperate climates feature decreased relative humidity, which enhances influenza transmission.

1.1. Viral infections

The majority of viruses that cause human respiratory infections show seasonal variations in their incidence. In winter, influenza, human orthopneumovirus (RSV), and human coronaviruses are more common (Moriyama et al., 2020).

Viruses can be transmitted directly from one person to another through droplets or aerosols, whether small or large, in the form of secretions loaded with viral particles, or by contact with contaminated surfaces (Tellier, 2022). Large droplets are mostly produced by coughing, sneezing, and talking, as well as by techniques such as suctioning and bronchoscopy, which also produce droplet nuclei. Droplets holding bacteria from one patient are released into the air and land on the conjunctiva, nasal mucosa, or mouth of another (Palombieri et al., 2022). Larger droplets spread quickly onto surfaces near the patient, raising the possibility of airborne transmission. Furthermore, viral infections can be transmitted by small aerosol particles (5-10 m) that can be infectious from a distance of several meters (Lewis, 2020). The SARS coronavirus 2 (SARS-CoV-2) was isolated from contaminated surfaces exposed to disease carriers, and the virus was found to be active for several hours on those surfaces. Additionally, coronavirus can be present in the air while carriers breathe or speak (Van Doremalen et al., 2020a).

Respiratory infections can be grouped either clinically, based on the clinical signs, or according to the virus type that caused them. Possible symptoms include fever, coughing, rhinorrhea, sneezing, and shortness of breath, chronic fatigue, and exhaustion (Arnold and Fuqua, 2020). Asymptomatic infections can cause pneumonia or acute respiratory distress, and systemic infections are all seen in the clinical stages of either (URTI or LRTI) (Jain, 2017). The severity of a viral infection of the respiratory system varies significantly as the disease progresses in the elderly, whether they have complications or not, and the same situation exists in children. The death rate rises as a result of a viral infection, the presence of other chronic diseases, or a bacterial infection in conjunction with a viral infection. The prevalence of respiratory viral infection varies by country and region, owing to geographical distribution, climate, prevention methods, and socioeconomic status (Varga et al., 2020).

1.2. Bacterial super infections

High rates of morbidity and mortality are associated with the possibility of bacterial infections associated with viral infections, otherwise known as secondary bacterial infections (Manohar et al., 2020 and Wang et al., 2018), as shown in Fig. (1).

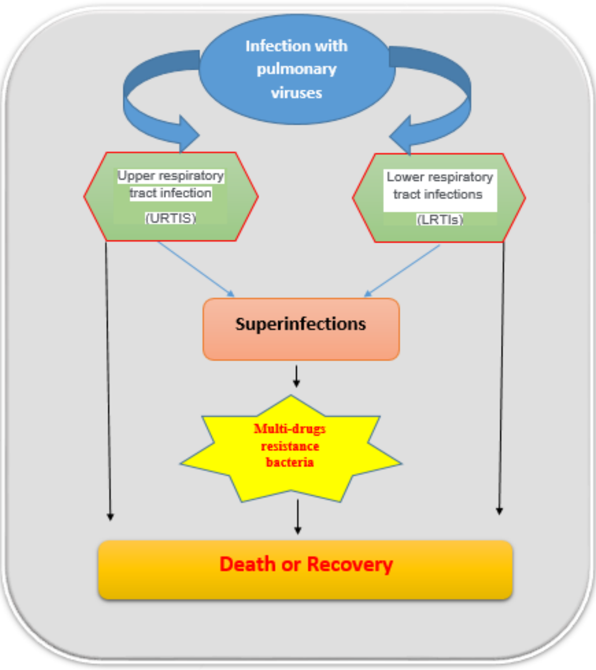

Fig. (1). Clinical development of patients with a respiratory virus infection.

Secondary infection, or "superinfection," occurs during viral epidemics; it is believed to be responsible for approximately 50 million deaths during the 1918-1919 Spanish flu pandemic (MacIntyre et al., 2018). Secondary infection usually occurs concurrently with the primary infection, considering the various pathogens that can be viral, bacterial, or fungal (Shen et al., 2022). Some of the most typical isolated bacteria during secondary infections include *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Neisseria meningitides*, *Haemophilus influenzae*, *Klebsiella pneumoniae*, and members of the genera *Proteus*, *Enterobacter*, and *Citrobacter* spp. (Ameen et al., 2021). The prevalence of tuberculosis (TB) in individuals who survived influenza or pneumonia, even without a clear differentiation between the two illnesses, was described as early as 1919 (Liu et al., 2020). Influenza increases the susceptibility to bacterial infections for a short period of time, as evidenced by the common incidence of bacterial pneumonia after viral pneumonia (McQuaid et al., 2021). Because influenza affects the immune system, it is possible that influenza might encourage the progression of active TB in individuals with dormant TB infection (LTBI) (Zürcher et al., 2016). On the other hand, TB can appear much later than influenza, making the temporal relationship hard to confirm.

1.3. Body's response to infection

Various types of innate defenses serve as the primary defense barrier against respiratory viral infections. Viruses are able to penetrate epithelial cells after these barriers are disrupted by camouflaging viral components with Toll-like receptors and intracellular receptors, resulting in an increase in the inflammatory response (Hendaus, 2019). All of these innate cells aid in the development of adaptive responses and support the antiviral response. Additionally, these inflammatory cells might contribute to the tissue damage caused by the innate immune system in TB (Miow et al., 2021). T-cells participate in cell-mediated immunity and the B-cell response, which clears the virus. B cells, in particular, have the ability to form antibodies that directly neutralize respiratory viruses by binding to viral surface proteins or stimulating the complement chain (Saeland et al., 2022). A crucial part of acquired immunity is played by T-follicular helper cells, a subset of CD4+ T cells that assist B cells in producing antibodies against foreign pathogens. In the removal of viruses, CD8+ T-cells with cytostatic activity also play a role (Siggins et al., 2021). A balance between pathological changes and viral clearance is achieved by T-cell regulatory mechanisms such as cytokine production, activation of inhibitory receptors, or expansion of the T-regulatory cell subset. All of these responses are also carefully regulated to prevent lung tissue damage. Neonates, infants, children, and adults all have different immune systems in terms of their structural makeup and functional reactivity to infectious diseases (Olin et al., 2018), as shown in Fig. (2).

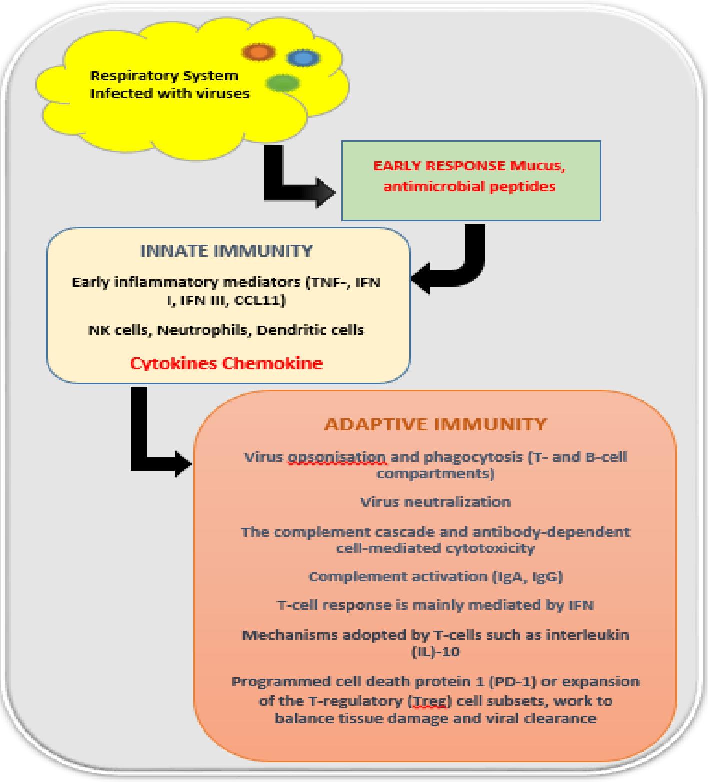

Fig. (2). Immune responses against virus infection.

Secondary infections, known as nosocomial pathogen infections, are common in hospitals because antibiotics are frequently used, and as a result, many have developed resistance to a variety of antibiotics. The overuse or abuse of antibiotics has led to the creation of multi-drug-resistant organisms (MDR). MDR is the most serious global health issue in many environments because there are few synthetic antibiotics available to treat such infections, which are mostly secondary infections (Loh and Leptihn, 2020). Secondary bacterial infections are made easier when a patient is exposed to a pathogen and his immune system is unable to respond correctly to both kinds of pathogenic organisms as a result of the first viral infection. The solitary choice for such individuals is to build up their immune systems and avoid infection developments that might lead to death, such as septic shock. Antibiotic treatment used as a "last resort" or with extremely high dosages of antibiotics frequently results in poor outcomes (Kumar and Chordia, 2017). Methicillin-resistant *Staphylococcus aureus* (MRSA), multidrug-resistant *Streptococci*, vancomycin-resistant *Enterococci* (VRE), *Mycobacteria*, carbapenem-resistant *Enterococci* (CRE), colistin-resistant *Klebsiella*, and carbapenem-resistant *Pseudomonas* are among the most important antibiotic-resistant species. But the situation became complicated due to the escalation by the big pharma companies towards ending efforts to develop chemical antibiotics by themselves (Loh and Leptihn, 2020). As a result, it is necessary to discover and develop new lead-beneficial natural product drugs to overcome MDR infection.

1.4. COVID-19 and respiratory diseases

SARS and MERS, two unknown zoonotic respiratory tract diseases with pandemic potential, have arisen in recent decades. Human coronaviruses are commonly divided into two categories: low-pathogenic and high-pathogenic. Low-pathogenic coronaviruses infect the upper respiratory tract and produce "flu-like" moderate respiratory disease, whereas extremely pathogenic coronaviruses (SARS and MERS) invade the lower airways and frequently cause deadly pneumonia (Zhou et al., 2021). Acute lung damage and acute respiratory distress syndrome (ARDS) are frequently accompanied by severe coronavirus pneumonia, which is marked by rapid virus multiplication, extensive inflammatory cell penetration, and enhanced pro-inflammatory cytokine and chemokine responses. Recent research in experimentally infected animals clearly suggests that virus-induced immune-pathological processes play a critical role in the development of lethal pneumonia after coronavirus infection (Hui et al., 2021). Coronaviruses are enclosed, sphere-shaped viruses with a single-stranded RNA genome; they fit into the Coronavirinae subfamily (order: Nidovirales, family: Coronaviridae) (Goodman-Davis et al., 2021 and El-Sayed et al., 2021). The beta coronavirus that causes COVID-19 first spread in Wuhan in late December 2019. Since then, it spread rapidly and turned into a global pandemic, affecting nearly 5 million confirmed cases of COVID-19 by May 2020, with about more than 6 million according to WHO in May 2023 deaths worldwide, according to the World Health Organization. Surprisingly, there was a high match between the genome of the newly sequenced COVID-19 virus (named SARS-CoV-2) and the genome of the bat coronavirus 96.2% (Teixeira et al., 2021).

According to current research, SARS-CoV-2 and SARS-CoV can infect host cells via the angiotensin-converting enzyme 2 (ACE2) receptor in collaboration with SARS-CoV-2 S proteins. Furthermore, cells with ACE2 but not the enzymes aminopeptidase N or human dipeptidyl peptidase-4, are more susceptible to SARS-CoV-2 infection (Kumar et al., 2022). Referring to a recent Chinese study, COVID-19 disease, has SARS-CoV-2 virus symptoms which are divided into three clinical patterns: asymptomatic, mild to moderate symptoms, and severe pneumonia that may necessitate intensive care (Yang et al., 2020). The duration between symptomatic onset of COVID-19 and intensive care admission is only 5 days which is considered a rapid onset when compared to other types of infections. The majority of

COVID-19 patients, according to the data, suffer chronic diseases such as chronic obstructive pulmonary disease (COPD), diabetes, hypertension, coronary heart disease, cardiovascular disease, and malignant tumors. Children infected with COVID-19 typically have less severe symptoms, making them easier to diagnose and/or treat than adults (Kumar et al., 2022). A combination of computed tomography scan (CT) test results, respiratory measurements (such as arterial oxygen tension/inspiratory oxygen ratio and peripheral capillary oxygen saturation), and blood tests (such as C-reactive proteins, lymphocyte counts, lactate dehydrogenase, triglycerides, ferritin, and fibrinogen) can help identify patients who are at high risk and should be transferred to the intensive care unit (ICU). It is important to note that the D dimer and interleukin (IL)-6 tests are critical in identifying cases that require intensive care (Wang et al., 2020). Edema, protein secretions, focal reactive hyperplasia of pneumococci with patchy inflammatory cell infiltration, and multinucleated giant cells with fibrous plugs in the airspace were all found in anatomic sections of samples taken from the lungs of deceased COVID-19 patients (Polak et al., 2020).

1.5. Cytokine storm as an immune system response to COVID-19

Viruses act as antigens, triggering human immune responses through T and B cells. One of the main mechanisms for acute respiratory distress syndrome (ARDS) is antibody formation against SARS-CoV-2, particularly immunoglobulins, the decline in CD4 and CD8 T cell numbers, and the release of large amounts of pro-inflammatory mediators by immune mediators such as IFN-a, IL-1b, IL-6, 12, 18, and 33, TNF-a, TGF-b, and chemokines. Patients infected with MERS-CoV had higher amounts of pro-inflammatory mediators in their blood than those infected with SARS-CoV and the immune system will trigger a cytokine storm, resulting in ARDS and organ failure, which could lead to death in severe cases infected with both mentioned viruses. Cytokines have an impact on all blood cells as well as other cells that support the body's inflammatory and immune responses by transmitting signals that cause abnormal cells to die while normal cells live longer, and they also support anti-cancer action (Yan et al., 2022). The cytokine storm caused by SARS-CoV-2 virus causes a faulty immunological response in some individuals, disrupting the cytokine secretion pattern. Hyper-cytokinemia is the primary reason for the hyper-inflammatory state that leads to lung invasion by neutrophils and macrophages and damage to vascular endothelial cells and alveolar epithelial cells (Pelaia et al., 2020). In such a pathogenic environment, interleukin-6 (IL-6) and other cytokines and chemokines play an important pro-inflammatory role, where potential therapeutics aim to reduce the severe load of the cytokine storm, which target cytokines and their receptors, as well as cytokine-dependent intracellular signaling pathways. Tocilizumab, a monoclonal antibody targeting the IL-6 receptor, is one of the most promising pharmacologic therapies (Kalra et al., 2021).

2. Ways to treat COVID-19

2.1. Vaccine

Treatment with vaccines or various antivirals is one of the most well-known treatment strategies applied in cases of viral infections, as antibiotics are ineffective at this stage. When a secondary infection with bacteria or fungi arises as a result of a compromised immune system, antibiotics are frequently applied. Vaccination may still be the fastest and most economical manner to provide broad-spectrum immune protection globally. When a sufficient section of the population becomes immune, the virus has inadequate opportunity to propagate locally, which is known as "herd immunity" (Borah et al., 2021). Due to the urgent need to make vaccines available to billions of people, the first priority must be to fully focus on vaccines that can be made cheaply and are known to be readily available or marketed. Viruses in their various forms (attenuated or inactivated) can be used to create vaccines; these can include viral vectors, nanoparticles, virus-like particles, protein or peptide fragments, RNA, DNA, or living cells (Hong et al., 2021).

On February 15, 2020, dendritic cells genetically engineered with SARS-CoV-2 structural and enzymatic proteins were used to perform the first vaccination trial against COVID-19 in China. A similar vaccination was combined with antigen-specific T-cell infusion in a second study conducted in China. The majority of vaccines are tested on healthy volunteers, but both mentioned vaccines were tested on COVID-19 patients. The first trial, funded by Moderna and the National Institute of Health, began in March 2020, employing lipid-coated messenger RNA particles expressing spike protein(s). Inovio Pharmaceuticals and CEPI began a DNA vaccination experiment utilizing a plasmid expressing the S protein in early April 2020. By mid-April 2020, China tested many vaccines containing an inactivated SARS-CoV-2 virus (Van Doremalen et al., 2020b). The first viral vector vaccine COVID-19, based on a chimpanzee adenovirus and encoding the S protein, was created at Oxford University in the United Kingdom. Adenovirus-5-based vaccines have also been tested in Wuhan, China. Almost all of these vaccinations were approved after receiving positive results from several clinical trials. Research on non-human mammals that received an inactivated virus vaccination showed significant levels of specific antibodies, excellent levels of protection, and no negative symptom development (Choi and Kim, 2022).

Even so, in the past, results revealed that using some inactivated coronavirus vaccines increased disease severity in animals. The reason is most likely due to a high mutation rate (such as at the S1/S2 junction) that occurs *in vitro* during the manufacturing process of inactivated viruses, which necessitates careful selection of vaccine strains (Goławski et al., 2022). According to a long and rich history of developing effective vaccinations and new genetic methodologies that boost the possibility of producing superior vaccine strains, attenuated viruses may be promising. Finding strains with the right combination of attenuation and production of sufficient immune responses, on the other hand, takes a long time. Furthermore, the manufacture of this type of vaccine will be in high demand in order to meet the rising global demand for Biosafety Level 3 viruses. The use of inactivated, attenuated viruses, which can multiply more easily than wild-type viruses, is an attractive possibility (Kang et al., 2020).

2.2. Antiviral and allopathic therapies

It seems that antiviral, immunomodulatory, anti-inflammatory, and other treatments, including herbal remedies, are mainly based on natural substances that make up most of the drugs currently available for the treatment of viral infections (CDC COVID-19 Response Team, 2020). Herbal medicine cannot be overstated in its ability to prevent and treat diseases, as numerous plants have antiviral properties. While medications are still being developed, using functional foods and herbal medication to avoid SARS-CoV-2 infections could be a supplemental COVID-19 therapy (Gautret et al., 2021). Treatments categorized as epidemic-resistant were used to control COVID-19 during the SARS-CoV-2 outbreak. On 99 patients, Wuhan Jinyintan Hospital used the protocols for these therapies at a rate of 76% for antiviral therapy, 71% for antibiotic therapy, 75% for oxygen therapy, and 27% for intravenous immunoglobulin therapy. The US Food and Drug Administration has not, however, approved these medications to treat COVID-19 (Grein et al., 2020). Among those drugs that were used for COVID-19 in clinical trials with another therapeutic effect were hydroxychloroquine and remdesivir; when combined with azithromycin, an effective therapeutic effect is achieved in reducing viral load in patients with COVID-19 (Frediansyah et al., 2021). Likewise, for remdesivir, an improvement in clinical outcomes was observed, which indicates its efficacy against COVID-19. Preventive medicine still needs more clinical trials to find a possible effective drug for COVID-19. Therefore, an important direction has been the use of herbal remedies with known antiviral efficacy as a dietary supplement that stimulates immune activity to prevent SARS-CoV-2 (Chen et al., 2020).

So far, no authorization has been obtained from the concerned authorities for certain drugs to combat (COVID-19), because the development of antivirals needs many pre-clinical and clinical studies, which are difficult to provide in the current epidemiological situation, so currently available antiviruses are used. The anti-SARS-CoV-2 influences of current antiviral drug categories such as fusion inhibitors, protease inhibitors, neuraminidase inhibitors, and M2 ion channel protein blockers have been evaluated. Even though clinical trials to determine the efficacy of these antiviral drugs are still ongoing, several studies such as docking analysis, modeling, *in vitro* investigations, and clinical data confirm the basic facts in recommending their use as antivirals against the COVID-19 pandemic (Singh et al., 2017). Although the US Food and Drug Administration has not yet approved specific antivirals for COVID-19, their use aids in targeting particular phases of the SARS-CoV-2 life cycle and may offer an alternative method of combating this pandemic.

3. COVID-19 and Utilization of Foods and Herbs

There are potential alternatives for treating COVID-19 with nutrients and herbs used for therapy in the current literature: (1) utilization of foods and herbs as a diet or supplement to avoid infection and enhance immunity; (2) use as an antiviral agent on masks; (3) use as an air-disinfectant essential oil to prevent airborne particle transmission; and (4) use as a surface sanitizing agent. Surgical masks are helpful in preventing viral transmission to humans, but once the mask is removed, the virus remains on it and is most likely re-aerosolized. Although the use of chemical antivirals to cover the mask may be beneficial, the toxicity of these materials and their effects on humans must be taken into account. Cleaning detergents are commonly used to disinfect surfaces in restaurants, but their safety and disinfection efficacy must be further evaluated. To improve anti-SARS-CoV-2 efficacy, detergents must contain natural antiviral compounds derived from herbs that are safe for humans (Panyod et al., 2020).

Researchers have recently focused their attention on the development of broad-spectrum antiviral medicines; however, new drug medication development is delayed due to the extended regulatory requirements needed to verify efficacy and safety. To address these restrictions, scientists are turning their attention to nanotechnology, which is gaining popularity and has previously been studied for application in the prevention of viral infections and/or their treatment (Chen et al., 2020). Due to their distinctive qualities, which include tiny size, enhanced solubility, surface adaptability, and multi-functionality, nanotechnology has been extensively used and studied in the medical field. Enabling the creation of safer medications, tissue-targeted therapies, tailored nanomedicines, as well as the early detection and treatment of diseases (Singh et al., 2017). As a result, nano-based techniques shall be the top option for developing the most efficient therapeutics for a variety of disorders, including COVID-19, in the near future. Nanotechnology could help in fighting COVID-19 by (a) designing safe personal protective equipment (PPE) to increase the safety of healthcare workers and (b) Developing surface coatings with potent antiviral properties that can inactivate the virus and stop it from spreading. (c) The development of very sensitive nano-based markers for detecting infection or an immune response rapidly (d) Development of novel medications with improved action, lower toxicity, longer half-lives, and tissue targets (e) The invention of a nanotechnology vaccine to increase cellular and humoral immune responses. Nano-based formulations have been proven to increase target drug delivery and therapeutic effectiveness of antiviral medications (Gera et al., 2017).

Furthermore, efforts have been created for the investigation of natural antiviral metabolites from plants. Though, most plant bioactive materials have minimal water solubility and availability, which means they have little therapeutic impact. Plant bioactive materials have been coupled together with various techniques based on nanotechnology to boost the therapeutic impact (Watkins et al., 2015). Indeed, plants may be the unique platform capable of producing such compounds at scale in a couple of weeks, as opposed to months or even years for cell-based systems. Plants may be useful in three areas: diagnostic reagents for identifying infected and recovered people, vaccinations to prevent infection, and antivirals to treat symptoms. Researchers are looking into the use of plant extracts in coronavirus management and prevention and may want to start with a number of naturally occurring substances derived from plants (polyphenols). Coronavirus enzymes (proteases) can be inhibited by antiviral polyphenolic compounds, where these enzymes are necessary for viral infection and replication (Praditya et al., 2019). The development of inventive anti-COVID-19 formulations can benefit from an understanding of the pharmaceutical structures of bioactive compounds due to their high safety for patients and lack of side effects**.**

Metallic nanoparticles (AuNPs or AgNPs) have significant relevance in biomedical, drug delivery, biomarker, antioxidant, and anticancer applications due to their biocompatibility, finely defined form, size, stability, and ease of synthesis. Additionally, due to their eco-friendliness, non-toxicity, low biohazards, cost effectiveness, and ease of scalability, green synthesis of herbal gold nanoparticles (AuNPs) and the improvement over their extracts, they have their extracts sparked a lot of interest**.** According to some studies, AuNPs may be regulated with a biodegradable polymer and serve as an efficacious antiviral operator contra H1N1, H3N2, and HIV-1, H5N1, and other viruses, and positively charged AuNPs can detect H3N2 and H1N1 by emulating, the enzymatic response of peroxidase assay. Several other modifications to metallic nanoparticles, such as tannic acid-modified silver nanoparticles, curcumin-modified silver nanoparticles, silver nanoparticle/chitosan composites, gallic acid-functionalized gold nanoparticles, and multivalent gold nanoparticles, have been investigated as potential antiviral agents (Yang et al., 2016). These effective metal-based nanoparticles block viral infection by preventing virus entrance into the host cell. Data from Mori et al. (2013) show that green syntheses of mineral nanoparticles have potent antiviral effects, showing that AuNPs can reduce the incidence of the H1N1 influenza pandemic. Therefore, more research is required to determine the potential benefits of these nanoparticles in combating the COVID-19 virus and its side effects, as was done with the H1N1 virus**.**

Other hypotheses hold that metal nanoparticles, such as silver, zinc, or other nano-metals, are not environmentally friendly due to their potential cytotoxicity. For these reasons, natural herbs such as licorice, neem, turmeric, honey, black seed, and others are environmentally friendly ingredients that have a significant impact due to their intrinsic biomedical properties. As a result, the generation of nano-fibrous membranes from natural polymers using an electrospinning process is regarded as a revolutionary strategy for biomedical applications such as wound dressing, tissue engineering, and drug administration, resulting in a novel area of investigation (Mori et al., 2013). According to previous research, the extracted licorice is treated with a polyvinyl alcohol (PVA) solution to generate an antiviral nano-film. The hydroxyl groups (OH) in the nanocomponents extracted from natural plants react chemically to disable the active sites of the virus by the esterification process, and this activity is attributed to licorice-containing compounds glycyrrhizin, glyceric acid, liquiritin, and isoliquiritin, which can neutralize the activity of COVID-19 and use it as an antiviral drug (Shahid et al., 2021).

4. Natural Products Nanoparticle Synthesis and Uses in Drug and Food Nanotechnology

Nanoscience and its practical applications are the novel era's science, with applications in electronics, agriculture, defense, medication creation and distribution, fermentation technologies, food processing and industry, chemical engineering, and other fields. "Nanotechnology is the study of science, engineering, and technology at the nanoscale, which ranges from 1 to 100 nanometers". It is characterized as "the capacity to observe and regulate single atoms and molecules (Woolley et al., 2016). One of the main industries with a considerable impact is the drug delivery and food industries. Nanoparticles, colloidal rigid particles (NP), are described as "a unique object with at least one dimension of 100 nm or less". On the other hand, the majority of drug delivery particles are 100–200 nm in size. Because of their small size, NPs have varying surface-to-volume ratios, emphasizing surface qualities. When compared to the bulk material or individual molecules, these characteristics give NPs their unique and potentially dangerous properties (Kashyap et al., 2020). Nanotechnology has various applications in food and agriculture systems, including food safety, packaging materials, disease management, and novel tools for molecular and cellular biology (Nowack and Bucheli, 2007).

Natural products, which include thousands of organic compounds that a living organism produces, may be present in different pharmaceutical forms in consumer items including dyes, additive agents that improve flavor and taste, and home detergent products. A lot of these items contain organic substances that have been dissolved or chemically changed to increase their effectiveness. If a substance is not soluble in the liquid necessary for formulation, its activity and application are restricted. Pharmaceutical drugs, for example, frequently have limited bioactivity and effectiveness due to their insolubility in water (Salvioni et al., 2021). Also, nutraceuticals, biocides, and a variety of other potentially helpful substances are included in the same boat. Insoluble materials can be more effective by producing tiny particles of organic compounds, which eliminates the need for new chemicals or the usage of flammable, poisonous, or volatile solvents. Because the range of chemical substances that become accessible gives enormous possibilities for creative and competitive product design, nanoparticles are an essential tool for creating and developing new items (Matos, 2017).

For the synthesis of NPs, several approaches have been utilized, but they are usually split into two classes: (1) the bottom-up method and (2) the top-down method, as illustrated in Fig. (3). These methods are additionally divided into subcategories according to the procedure and reaction state. In recent years, the pharmaceutical sector has been at the forefront of organic nanoparticle research. The development of nanomedicine has encouraged the discovery of novel materials as well as the improvement of well-established procedures. The "bottom-up" synthesis of nanoparticles capable of encapsulating or transporting active molecules, has resulted in dendrimer technologies, protein conjugates, DNA delivery vehicles, liposomes, and shell-cross-linked block co-polymer micelles. "Top-down" methods, such as wet nano-milling, have primarily relied on friction to grind large particles and produce particle ranges with sub-micron average particle sizes. There are numerous "wet" techniques for producing colloidal dispersions from liquid emulsions, most of which focus on removing the oil phase of an emulsion and then solidifying it via precipitation, crystallization, or encapsulation of any organic material dissolved within the solvent droplets. As a result, none of these methods have proven to be truly general, and they have been limited to specific groups of materials defined by chemical reactivity or physical properties (Kumar and Lal, 2014).

4.1. Synthetic techniques for organic nanoparticles

The production and uses of these organic nanoparticles, which are environmentally safe, cost effective, and better suited for biological applications, are detailed below:

a) emulsification-based method
b) Nano-precipitation
c) drying-based process
d) Green syntheses

The first technique consists of two processes, one of which is creating an emulsification system. In the first phase, specific-sized nano-droplets are created in which organic molecules (polymers, monomers, and lipids) are previously solubilized. The established emulsification techniques are distinct from their high- or low-energy stirring procedures. In the subsequent phase, several processes such as precipitation, gelation, or polymerization are used to create nanoparticles (Kumar and Lal, 2014). The second technique entails carrying out a single-step procedure wherein emulsification is not required before producing nanoparticles. The approaches typically rely on the precipitating of organic materials in solution, which can happen in a number of ways, including solvent displacement-induced nano-precipitation, ready-made processes brought on by ionic gelation, or by the creation of polyelectrolyte complexes. Other strategies based on techniques using spray-drying, supercritical fluid technology, or piezoelectric materials have also been thoroughly reported (Wright et al., 2010). As an alternative to chemical and physical synthesis, biological synthesis of NPs utilizing bacteria, enzymes, plants, and algae has been proposed. Biological extracts have been used to reduce metal ions using simple extracellular or intracellular approaches.

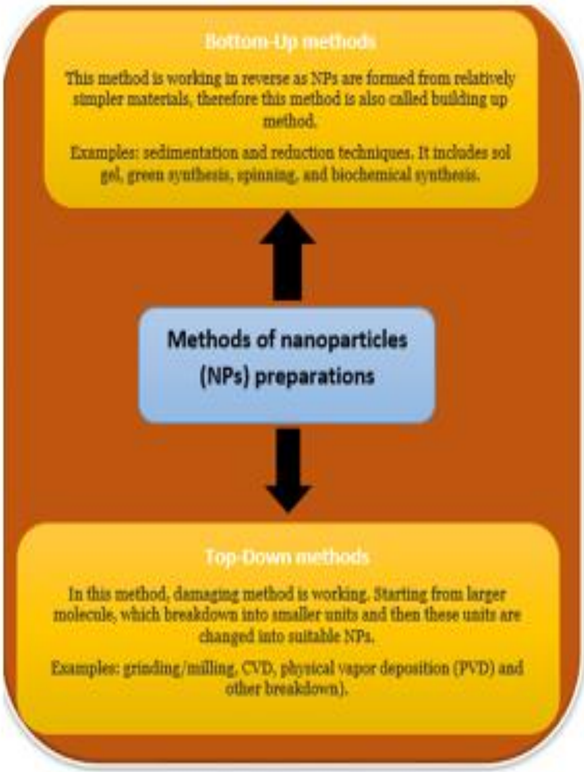

Fig. (3). Typical synthetic methods for NPs for the (a) top-down and (b) bottom-up approaches.

1. Emulsions: that is a mixture of two or more wholly or partially immiscible liquids that determines whether a surface-active substance is present or not. An o/w (oil in water) direct emulsion or a w/o (water in oil) inverse emulsion can be produced depending on the dispersed phase and the diffusion medium, but a more complex system such as an o/o (oil in oil) or several emulsions of various types (w/o/w, o/w/o, and w/o/o) can also be made. Based on the size of the droplets, the emulsion can be divided into three distinct groups: a micro-emulsion, which exhibits stable thermodynamic actions with droplet diameters between 10 and 100 nm, and a mini-emulsion or macro-emulsion system, which both exhibit thermodynamic instability with drop dimensions between 100 nm and 1 m and up to 1 m, respectively (Kumar and Lal, 2014). The following methods are used to generate nano-organic particles from emulsions: a) solvent-induced precipitation, b) evaporation of the solvent, c) solvent diffusion, d) salting-out, e) emulsion droplet gel-formation, f) polymer formation in emulsion, g) conventional emulsion polymerization, h) polymerization of emulsification without surfactants I) interfacial polymerization, and j) controlled/living radical polymerization (Wright et al., 2010).

2. Nanoprecipitation: Nanoprecipitation is also known as the interfacial deposition technique. It is the most elegant, efficient, and energy-efficient technique of producing nano-spheres by employing premade polymers in place of monomers. That approach is similar to the method of spontaneous emulsification that has already been reported in that it is built on the polymer surface deposition following the removal of a semi-polar solvent from a lipophilic solution that is miscible with water (Wright et al., 2010). This process involves three constituents: the polymer, the polymer solvent, and the non-solvent for the polymer. Ethanol, acetone, hexane, methylene chloride, or dioxin are the most used polymer solvents. Polymers might be artificial, semi-synthetic, or natural. High water solubility and simplicity of evaporation removal are two factors that influence the choice of the polymer solvent. Acetone is frequently used to meet these requirements, although a dual mix of solvents, such as acetone plus a little amount of water, or acetone and ethanol or methanol mixtures, may also be employed**.** This technique is mostly applicable to non-polymeric molecules like cyclo-dextrin and drugs. Finally, because of its simplicity, speed, and repeatability, the nanoprecipitation approach is frequently employed for polymeric or non-polymeric nano-spheres precipitation, even though the recovery output of nanoparticles is limited by the low polymer concentration needed (Dalpiaz et al., 2009).

3. Drying process for nanoparticles: In recent times, environmentally related concerns are motivating research into the nanoparticle manufacturing procedures evolution that do not require organic solvents usage**.** For this context, spray drying or supercritical technologies provide the capability of creating and developing nanoparticles free of restrictions associated with traditional approaches (Kumar and Lal, 2014). The two steps in the supercritical process are Rapid Expansion of both Supercritical Solution and Supercritical Solution into Liquid Solvent. To create submicron organic particles or turn nanoparticle dispersion into dry powder form, spray drying has lately been used in pharmaceutical and biomedical applications, particularly in delivery of drugs (Cheng et al., 2008). Using a hot drying gas to meet a small mist of droplets of liquid to evaporate the moisture and create a solid product, which is subsequently recovered with a cyclone machine, is a characteristic spray-drying technology. This method is used to prepare nanoparticles like whey protein, arabic gum, modified starch, polyvinyl alcohol, maltodextrin, and bovine serum albumin nanoparticles (Schuck et al., 2009).

4. Green syntheses: The green synthesis technique uses microbes and plants to make nanoparticles that are economical, good for the environment, and biologically secure. Inorganic metal ions from the environment can now be consumed and accumulated by plants and microorganisms. Both extracellular and intracellular nanoparticles are known to be synthesized by living entities**.** A previously unexplored area of biochemical research has been made possible by the biological organism's ability to transform elemental metallic ions to nanoparticles using its own organic chemistry processes. In nano-biotechnology, living entities of both prokaryotic and eukaryotic origin include cyanobacteria, bacteria, viruses, algae, actinomycetes, fungi, yeasts, and plants. The ability of each biological system to provide metallic nanoparticles differs (Abbas et al., 2021 and Arpagaus and Schafroth, 2009). However, because of their enzymatic activity and inherent metabolic activities, not all living species could create nanoparticles. As an outcome, living entities or their extracts are employed in the ecofriendly synthesis of metallic nanoparticles from metallic particles via bio-reduction, which enables the production of nanoparticles. These biosynthesized metallic nanoparticles can be applied to numerous pharmacological processes, such as the transport of drugs or genes, the detection of pathogens or proteins, and tissue engineering (Arpagaus and Schafroth, 2009).

4.2. Characteristics of NPs

Numerous characterization approaches have been used to investigate different NPs' physiochemical properties. These methods include SEM, TEM, Brunauer-Emmett-Teller (BET), X-ray diffraction (XRD), X-ray photoelectron spectroscopy (XPS), infrared (IR), and particle size analysis.

1. Morphological properties: For shape examinations, several characterization techniques exist, although microscopic tools like scanning electron microscopy (SEM), polarized optical microscopy (POM), and transmission electron microscopy (TEM) are the most common (Zhang et al., 2020).

2. Structural properties: The main method used to study composition and material bonding is structural features. It provides a wealth of details regarding the bulk characteristics of the subject matter. Energy dispersive X-ray (EDX), XRD, Raman, XPS, BET, IR, and the Zeta size analyzer are popular techniques used to investigate the structural properties of NPs (Saeed and Khan, 2016).

3. Characterization of particle size and surface area: Zeta size analyzer Light scattering is a key analytical technique for the characterization of particulate materials, and it is most typically used to assess particle size and Zeta Potential in colloidal systems, nanoparticles, and macromolecules in solution or dispersion. Also, a variety of approaches can be employed to evaluate the diameter of NPs. TEM, SEM, AFM, XRD, and dynamic light scattering are among them (DLS) (Khan et al., 2017).

4. Optical characterizations: Since optical properties play a significant role in photocatalytic applications, photo-chemists realized how to apply this method to understand what their photochemical systems do. These explanations ~~are~~ based on the Beer-Lambert law and basic lighting principles. These methods can be used to determine the NPs' absorbance, reflectance, luminescence, and phosphorescence properties. It is common knowledge that NPs, especially metallic and semiconductor NPs, have unique kinds and are hence best suited for applications involving light. To investigate the optical properties of NPs materials, such a well optical instruments UV-visible (UV-Vis), photoluminescence (PL), and the null ellipso-meter can be utilized (Kestens et al., 2016).

4.3. NPs applications and types

Nanotechnology has opened the way for the manufacture of a variety of nanomaterials and nanoparticles, providing new possibilities for use in numerous applications. In this work, the use of organic nanoparticles for food and medicine delivery is investigated. Because they are in direct contact with humans when they are utilised in food, nanoparticles must be safe for both the environment and life. Generally, natural products are safer than their chemically derived equivalents. "Generally Recognized As Safe," or GRAS, organic nanoparticles made from natural ingredients are frequently used in food and medication delivery applications. Furthermore, they're split into: lipid-based, protein-based, and polysaccharide-based (Kestens et al., 2016).

1. Lipid Based GRAS System: GRAS systems made from lipids are one of the most optimistic formulation methods in the developing discipline of nano-biotechnology. Lipid based nano-encapsulation systems have various benefits over other encapsulation technologies. Examples of fat nanomaterials developed for delivery of drugs include lipid nanotubes, lipid nanospheres, and lipid nanoparticles **(Khan et al., 2017)**. Nano liposomes, nano-co-chelates, and archaeosomes are the three primary lipid-based nano-encapsulation systems that may be employed to preserve, distribute meals, nutraceuticals and sensory purpose. A recent study characterized how to employ submicron lipid transporters to diffuse insoluble -carotene in an aqueous solution as a component in drinks, despite the fact that their use in food technology has not yet been investigated (Kestens et al., 2016).

2. Protein-Based GRAS System: GRAS systems based on proteins have unique functional features, such as the capacity to form gels and emulsions, making them a suitable material for encapsulating bioactive chemicals. Because of their excellent nutritional value and GRAS status, dietary proteins are commonly employed in designed foods. In food applications, protein hydro gels are among the most practical and extensively utilized frequently used composite. To include nanoparticles into non-solid and semi-solid foods without changing their sensory properties, however, it is required to minimize their size (Liu et al., 2015). No organic solvents are required in the manufacture of protein NDSs, and encapsulation is done under gentle circumstances, reducing the degradation of sensitive nutraceutical ingredients. For example, glob proteins like milk's whey protein and gelatin NP, whose main advantage is their easy and repeatable manufacture along with affordability and many customization options. Over the coming decade, food protein-based materials are anticipated to have a major role in improving the efficacy of functional foods (Kosaraju, 2005).

3. Polysaccharide and Poly (lactic) Acid-Based GRAS System: Plants, mammals, algae, and microorganisms all produce polysaccharides naturally. These polymers, which are frequently large and branched, have a variety of roles in biological and life processes. These polymers are broken down by the colonic microflora to simple saccharides, which can shield nutritional supplements from unpleasant conditions of the small intestine and stomach. Once in the colon, hydrolysis of glycosidic linkages promotes the bound molecule's release. Chitosan and pectin, for example, are highly appreciated polysaccharides in biomedical sciences for drug delivery, owing to their permeability-enhancing properties (des Rieux et al., 2006). Active targeting systems and polysaccharide-based packaging are thought to hold potential for the advancement of food and nutraceutical formulations. Because of their biodegradability and biocompatibility, polymers made from poly (lactic acid) and poly (glycolic acid) are commonly utilized to provide sustained-release transporters for medicines and proteins. By highlighting considered advantages for drug delivery, micro, and NPs have enhanced their therapeutic beliefs (Tallury et al., 2010).

5. Examples of Natural Products Nanoparticles and Their Biological Roles

5.1. *Aloe vera*

Aloe vera is a plant widely utilized for its several actions, including antibacterial, antiviral, anti-inflammatory, immune-stimulant, and angiotensin-converting enzyme (ACE). Moreover, SARS-CoV-1 has been demonstrated to be affected by minerals like zinc. Finally, *Aloe vera* is taken orally in a variety of ways, including (soft gel, capsules, yogurt, toothpaste, ice cream, juice, tea, jam, tablets) (Chauhan and Kumar, 2020). The nano-crystalline (ZnO + *Aloe vera*) powders have antibacterial activity against *Pseudomonas aeruginosa*, which can cause blood infections, pneumonia, or affect other parts of the body after surgery. Although the presence of *Pseudomonas aeruginosa* in bronchitis is a symptom of significant lung infections, this is not associated with a quicker decline in pulmonary function metrics (Ayeshamariam et al., 2016). Also, bacterial pathogens such as *Pseudomonas aeruginosa* become increasing with the SARS-CoV-2 viral RNA load (Rhoades et al., 2021). With regard to pathogens including *Escherichia coli*, *Klebsiella pneumonia*, *Pseudomonas aeruginosa*, *Shigellaflexner*i, *Salmonella typhi*, and *Staphylococcus aureus*, causing pneumonia, *Aloe vera*-silver nanoparticles have demonstrated reasonable antibacterial potential (Singh et al., 2014). The AgNPs + *Aloe vera* gel have the highest antibacterial ability against *E. coli* -even at very low concentrations-causing a pulmonary infection that results from Internal bleeding from either the gastrointestinal or urinary tract or from thhase pharynx (Zhang et al., 2010). *Aloe vera* contains virucidal secondary metabolites such as anthraquinones/anthrones that have been shown to inhibit RNA and DNA of several virus species *invitro* and *invivo*. For example, Aloe-emodin effect on many viruses (Varicella (VZV), Herpes simplex (HSV) type 1 and 2, Pseudorabies, Zika, hereditary immuno-deficiency (HIV) and SARSCoV1 involves halting the cleavage of 3C-like protease, an enzyme that is crucial for viral replication, in order to limit nucleic acid biosynthesis as a result of protein synthesis termination. The viral envelope of hemorrhagic viral rhobda virus septicaemia is destroyed by alion compounds. Lectin chemicals prevent Cytomegalovirus (CMV) from spreading by getting in the way of CMV and Parvovirus (HPV) protein synthesis. Chrysophanic acid prevents the virus from entering the cell through diffusion, translation of the viral RNA, or early cleavage of the poliovirus protein. Molecular docking studies and ADME properties confirmed that, it is the best pharmaceutical choice. An anti-viral component in the coating hexadecyltrimethoxysilane (HDTMS) and *Aloe vera* extract prevents viruses from adhering to the surface. The coating may be an effective anti-COVID-19 covering due to its water-repellent properties and use of an antiviral substance, *Aloe vera* (Mpiana et al., 2020). *Aloe Vera*-silver nanoparticles (Ag-NPs) show an improved role as an antioxidant and anti-inflammatory. *Aloe vera* is also effective in improving the lung cytotoxicity caused by Ag-NPs. As a result, clinical trials are required to prove the effectiveness of *Aloe vera* on COVID-19.

5.2. Curcumin

Curcumin is the most important polyphenol component from the rhizomes of *Curcuma longa*, a member of the Zingiberaceae family. It is used for numerous viral illnesses through different models like transcription and replication regulation, protease inhibition, prevention of the virus's invasion and binding to cells, or inactivation of the virus's structural components. It showed potent activity towards viruses like Human Immunodeficiency Virus (HIV), Epstein-Barr Virus (EBV), Respiratory Syncytial Virus (RSV), Hepatitis C Virus (HCV), and Bovine Herpes virus 1 (BHV1). While, Ebola Virus, Human Cytomegalovirus (HCMV), Chikungunya Virus, Entero Virus 71, Human Noro Virus (HuNoV), Influenza A Virus (IAV), Rift Valley Fever Virus (RVFV), and Fish Viral *Hemorrhagic Septicemia* Virus (VHSV) were affected by curcumin**.** Poor solubility combined with rapid metabolism of curcumin causes limitations in its use due to its low bioavailability. So, the development of the aqueous soluble nano-curcumin was necessary to get the most benefits from using it as a treatment. As a result, there are different developed nano-carriers for curcumin, such as nanoparticles, nano-emulsions, liposomes, micro-emulsions, nano-gels, and micelles (Yang et al., 2016 and Dourado et al., 2021). This nano-formulated curcumin could be administered in the form of dry powder, nebulizer, solution, nasal spray, or gel**.**It has been claimed that phospholipid vesicles containing curcumin can considerably increase the anti-inflammatory effects of curcumin, increasing its total therapeutic efficacy. So, it is employed to treat some respiratory ailments like asthma and chronic obstructive lung disease (Thimmulappa et al., 2021). Another developed glycerosome formula was used to deliver curcumin to the lungs through aerosol therapy, as it improved the effect of curcumin via preventing the synthesis of inflammatory cytokines (IL-6 and IL-8). Additionally, this formula protects A549 cells from oxidative stress, and increases curcumin deposition in the lower respiratory tract through *in vitro* and *in vivo* studies, respectively (Quispe et al., 2021). Curcumin liposomes with chitosan and hyaluronan coatings were also developed for pulmonary medication. Due to the capacity of these vesicles to connect with cells and release curcumin in the cytoplasm, it increased curcumin lung deposition and antioxidant potential, as well as reducing inflammatory indicators along with pro-inflammatory markers' production TNF, IL-1, IL-6 and IL-8 (Manca et al., 2015 and Manconi et al., 2017). In addition, another curcumin-loaded Chitosan-tripolyphosphate nanoparticles was applied as an antibacterial agent against *Staphylococcus aureus* and *Pseudomonas aeruginosa* infection (Ng et al., 2018). Curcumin liposome formulations have also been shown to lower (TNF-, IL-6, and IL-8) in human synovial fibroblasts in additional investigations (Mirnejad at al., 2014). Curcumin loaded on a-cyclodextrin (CD) functioned graphene oxide (GO) composite and curcumin- silver nanoparticles (cAgNPs) suppressed RSV, an RNA virus that infects the host cells in the tissue culture module and causes severe lung illness in new-borns' lower respiratory tracts, with no damage to the host cells. The virus was inactivated directly by preventing its attachment by previously mentioned nano-forms (Yang et al., 2017). There have been several reports of employing nano-curcumin to treat COVID-19 infection through viral suppression, inflammatory regulation, and/or immunological responses, it can cure pulmonary edema and pathways associated with fibrosis (Yang et al., 2016 and Dourado et al., 2021). In patients with lung damage, cytokine storm, or the enhanced release of cytokines such IL-1, IL-6, TNF-, and IL-18, is a sign of COVID-19 infection. As a result, a clinical experiment on COVID-19 patients verified the capacity of curcumin nano-micellar to lower mRNA expression and cytokine release, resulting in improved recovery (Thimmulappa et al., 2021). Another nanozyme Fe-curcumin nanoparticle was designed for intra-tracheal and intravenous injection to control oxidative stress and inflammation in acute lung damage. It's done by looking at inflammatory cytokines (including TNF- and IL-6), the NLRP3 inflammasome, and intracellular Ca2+-related signaling pathways that are suppressed. These findings imply that using Fe-curcumin nanoparticles to minimize COVID-19-related mortality is a viable option (Yuan et al., 2021). Today, Nano-technological curcumin products become obtainable on the market in the shape of polymeric nanoparticles like (Nanocurc™), liposomes (Lipocurc™), and nano-micelles (Sinacurcumin®) (Manohar et al., 2020).

5.3. Chia seed

Chia (*Salvia hispanica* Family Lamiaceae) seeds are rich in lipids (34.4%), fibers (23.7%), proteins (19.6%), vitamins (A, B, K, E, D), minerals and antioxidants. The amounts of A, B1, B2, B3, B6, and C vitamins found in chia seeds were 37 IU, 8.7 μg g^{-1}, 1.7 μg g^{-1}, 58 μg g^{-1}, 6.9 μg g^{-1} and 157 μg g^{-1}, respectively. Among the water-soluble vitamins determined, pantothenic was found at 9.40 μg g^{-1} (Ghena and Amany, 2020 and Coelho and Salas-Mellado, 2014). Furthermore, because of the presence of polyphenols, chlorogenic and caffeic acids, myricetin, quercetin, and kaempferol, chia seeds are a viable source of antioxidants (KnezHrnčič et al., 2019 and Reyes-Caudillo et al., 2008). Chia seed oil contains a variety of nutrients, including a significant proportion of polyunsaturated fatty acids.

Oleic acid is also the most common polyunsaturated fatty acid. Palmitic acid, a saturated fatty acid, is also present in significant concentrations. Omega-3, Omega-6, and omega-9 are all abundant in chia seed oil, accounting for 62, 17.4, and 10.5% of total lipids, respectively (Doaei et al., 2021). Taking omega-3 fatty acid as a supplement provides a variety of health advantages, including the ability to prevent viral entrance by modifying the fat content of the cell's bi-lipid membrane. Omega-3 fatty acids are absorbed into the cell membrane and stimulus the clustering of toll-like receptors, stopping signals from stimulating NF-B and aiding in the alleviation of COVID-19 problems by producing fewer pro-inflammatory mediators, as reducing pulmonary neutrophil recruitment, enhancing macrophage apoptosis, and decreasing broncho-alveolar IL-6 production, thereby reducing lung inflammation. Omega-3 fatty acids aid macrophages in increasing their phagocytic capabilities by causing changes in the configuration of the cell membrane bi-lipid layer, also play a function in influencing both the innate and acquired immune systems (Hathaway et al., 2020). The relationship between an omega-3 fatty acid-rich diet and clinical outcomes may be significantly more complicated than previously thought when treating COVID-19 patients. In addition, omega-3 is a natural, affordable supplement with numerous therapeutic qualities that could play a role as a healthy supplement. In severe COVID-19 cases, omega-3 treatment improved key measures of respiratory and renal function (Doaei et al., 2021 and Hathaway et al., 2020). A number of oils, including chia oil, can be used to create nano-emulsions. Nano-emulsions improve the bioavailability of chia oil's active biological components. Nano-emulsion-based delivery methods are being investigated for use in food, personal care, cosmetics, and pharmaceutical applications to encapsulate lipophilic bioactive components. The chia seed oil nano-emulsion delivery method allows chia seed oil to be used in drinks and functional foods where a slightly turbid or even transparent appearance is desired. Chia seed mucilage is a potential alternative to synthetic polymers for nano-encapsulation (Rocha-Filho et al., 2014). Recently, many studies have shown the importance of nano-encapsulation of chia seed extract, its impact on human health, and its use in the pharmaceutical and food industries. El-makawy et al. (2022) studied the effect of nano-encapsulated chia oil of inhibition against DMBA-induced breast cancer through tumor gene expression modulation and oxidative stress repression in rats. The results showed that chia oil nano-capsules improved the tissue architecture of breast tumors and inhibited cancer cells in the rat breast. Also, Shaer and Al-Abbas (2022) discussed the possible impact of nanoparticles of crude chia seeds extract on Mcf-7 breast cancer cell line, which explained that have a significant anti-migration effect on MCF-7 breast cancer cells in addition to significantly inducing apoptosis in MCF-7 breast cancer. Additionally, Hosseini et al. (2023) showed that the use of encapsulated chia seed extract during ricotta cheese production resulted in the retardation of oxidation and extended the shelf life of the cheese in addition to increasing its health benefits.

5.4. Thyme

Thyme (*Thymus vulgaris* L.) is a medicinal plant that is a member of the Lamiaceae family. It has a pleasant aromatic flavor and odor (Ahmadi and Jafarizadeh, 2021). The herb thyme and its volatile oil have long been used to treat sprains, parasite infections, bronchitis symptoms, and upper respiratory tract infections (URTIs). These days, it is frequently employed in dentistry as a disinfectant and as an expectorant for coughs brought on (Nilima et al., 2013). However, due to its lower aqueous solubility and increased susceptibility to oxidation, light, and heat, its essential oil (EO) as a natural preserving agent has limited applicability. Thyme EO can also interact with the primary ingredients of food such as proteins, carbohydrates, and lipids, and significantly alter their organoleptic characteristics (Barzegar et al., 2016). The two main chemical constituents of Thyme essential oil as mentioned before are thymol (5-methyl-2-propan-2-ylphenol) and carvacrol (2-methyl-5-propan-2-ylphenol) as isomer, each of which has distinct biological properties. Thymol, the main monoterpene phenol compound in thyme, has anti-inflammatory, immune-modulating, antibacterial, antioxidant, antiviral, antifungal and even anti-cancer (Quynh and Trang, 2019 and Schnitzler, 2019). Since the beginning of time, essential oils have been used for a variety of purposes, such as food preservation, medicine, and agricultural products. These substances have been found to have antibacterial properties against both gram-positive and gram-negative (Saranra and Devi, 2017 and Quynh and Trang, 2019). The essential oil of *T. vulgaris* has been shown to limit bacterial growth and possesses powerful bactericidal activities, including activity against antibiotic-resistant strains. Also, it has been shown to inhibit bacterial colonization and biofilm development on surfaces by uropathogenic *E. coli* (Flores-Encarnación, 2018). There are only a few reports on the bactericidal action of *T. vulgaris* essential oil. This essential oil, like other oils, is thought to modify membrane permeability. It also has an antiviral effect on human rhinoviruses, influenza viruses, HIV-1, and herpes simplex virus types I and II (HSV-1 and HSV-2) (Adam et al., 2020). For example, transcription and replication of the HIV virus were reported to be inhibited by *T. vulgaris* EO (Feriotto et al., 2018), and by boosting the immune system with its strong antioxidant components and antiviral activity, it decreased the respiratory symptoms in COVID-19 patients (Sardari et al., 2021). Thyme EO, like other plant oils, with poor dispersity in aqueous systems was provided in the nanoscale to overcome that and to increase its bioavailability, so Thyme EO nano-emulsions were made using different emulsifiers like xanthan gum and saponin to increase its antioxidant, and antibacterial activities. Additionally, the use of subcritical water facilitated the desolation of Thyme EO and lowered the need for emulsifiers in the production of the nanoemulsion (Omid and Hoda, 2021).

CONCLUSION

COVID-19 presents a significant barrier to human health and economic growth. Many natural compounds have gained a lot of attention as potential anti-SARS-COV-2 medications and have demonstrated some efficacy in this regard. The current evaluation concentrates on recent advancements in the application of a few key natural products. A significant range of phytochemicals has been found to have potential antiviral properties in several experimental investigations. The discovery of novel antiviral drugs from plants, on the other hand, is a difficult challenge. Nanotechnology has enormous potential for both diagnosing and treating viral diseases. According to several research, nanoparticles (whether metals or natural compounds) might be utilized as a diagnostic and therapeutic tool for viral infections. Finally, an analysis of the main anti-viral techniques suggests that nano-based approaches may be beneficial in detecting and curing COVID-19 viral infections worldwide.

Abbreviations

(RTIs)	Respiratory tract infections
(URI or URTI)	upper respiratory tract infection
(LRTI) (LRI or LRTI)	lower respiratory tract infection
(LRIs)	Upper and lower respiratory system infections are the two types of respiratory infections
(URTIS)	Upper respiratory tract infection
(LRTIs)	Lower respiratory tract infections
(TB)	Tuberculosis
(SARS)	severe acute respiratory syndrome
(MERS)	Middle East respiratory syndrome
(H1N1)	influenza A
(PFT)	Pulmonary Function Testing
(RSV)	human orthopneumovirus
(SARS-CoV-2)	SARS coronavirus 2
causal virus (virus type)	causal virus (virus type)
(LTBI)	TB in individuals with latent TB infection
(MDR)	multi-drug resistant
(MRSA)	Methicillin-resistant Staphylococcus aureus
(VRE)	vancomycin-resistant enterococci
(CRE)	carbapenem-resistant enterococci
Page=7	Acute lung damage and ARDS
(dubbed SARS-CoV-2)	the genome sequence of the new virus that causes COVID-19
Page=8	novel SARS-CoV-2 and SARSCoV infect host cells by using the same receptor (angiotensin-converting enzyme 2, ACE2)
(ICU)	the intensive care unit

(COPD)	chronic obstructive pulmonary disease
(IL)	interleukin
(IL-6)	Interleukin-6
(PPE)	personal protective equipment
(AuNPs or AgNPs)	metallic nanoparticles
(AuNPs)	herbal gold nanoparticles
(-OH)	The hydroxyl
(Arbidol)=page 18	Fusion inhibitor Umifenovir
(HA)	hemagglutinin envelope glycoprotein
Page=18	reverse transcription stage by blocking RdRp
(TNF-, IFN I, IFN III, CCL11)	Early inflammatory mediators
(T- and B-cell compartments)	Virus opsonization and phagocytosis
(PD-1)	Programmed cell death protein 1
(T-reg)	T-regulatory

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تقنية النانو ودورها المرتقب في استخدام المركبات النشطة لمكافحة COVID 19 عدوى هذا العصر

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التهابات الجهاز التنفسي أو الالتهابات الرئوية، التي تمثل ١٥٪ من جميع وفيات الأطفال دون سن الخامسة وتسبب أعراض مرضية كبيرة، ولا تزال تمثل مشكلة صحية عالمية خطيرة. فأخطر عدوى موجودة من وقت قريب هي COVID-19 المرتبط بالعدوى البكتيرية، والتي بدورها تؤدي إلى عدوى تنفسية حادة قاتلة تتميز بضيق في التنفس. ولا يزال العلماء يواجهون تحديات كبيرة في كيفية تطوير اللقاحات والأدوية المضادة للفيروسات أو المضادة للبكتيريا لعلاج هذه الأمراض. في الآونة الأخيرة، تعد المنتجات الطبيعية النشطة بيولوجيًا المستخلصة من مجموعة متنوعة من النباتات والكائنات الحية، مثل البكتيريا والفطريات والطحالب، بمثابة علاجات واعدة للسرطان والالتهابات البكتيرية والأمراض الالتهابية والحالات الطبية الأخرى. ومن أجل تسهيل نقل هذه المركبات النشطة بيولوجيًا إلى هدف معين بناءً على خصائص الدواء والأعضاء، تم استخدام تقنية النانو بحيث يمكن تحميل هذه المركبات الطبيعية النشطة بيولوجيًا على الجسيمات النانوية (كيميائيًا أو فيزيائيًا). إن تقنية النانو تعتبر أداة أساسية تساعد في الكشف عن مجموعة واسعة من الحالات الطبية البشرية وعلاجها. الهدف من هذه المراجعة هو تسليط الضوء على الأبحاث السابقة والجارية حول المواد النانوية النشطة التي تعمل بشكل طبيعي كعوامل مضادة للفيروسات أو مضادات الميكروبات، خاصة بالنسبة لأمراض العصر الحديث مثل COVID 19، واقتراح منهجيات بحثية جديدة محتملة تعتمد على منصة تكنولوجيا النانو.