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Review Article

Role of Plant Based Hand Sanitizers During the Recent Outbreak of Coronavirus (SARS-CoV-2) Disease (Covid-19)

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Abstract

This literature review paper highlights the recent updates on the use of herbal extracts or essential oils of medicinal plants in the preparation of hand sanitizers. In India, Covid-19 patients with the development of black fungus infections, mucormycosis is another major health issue. Recent outbreak of coronavirus (SARS-CoV-2) with mucormycosis has promoted the hand hygiene so as to achieve a full recognition among healthcare workers, public and particularly elderly people for controlling the cross contamination of the pathogen. Hand hygiene can be achieved either through hand washing, or hand disinfection. Human health hazards are linked with the frequent use of alcohol-based hand sanitizers is a major health issue. The range of available hand sanitizers and their effectiveness as well as the formulation aspects, adverse effects, and recommendations to enhance the formulation efficiency and safety. Adaptation of alternative preparations of hand sanitizers based on natural and plant resources are the possible solution to get rid off toxicity problem. Washing hands is one of the simplest, most effective ways to get rid of germs and avoid infection. Aromatic plants with essential oils have been used because of their many different biological properties, including antimicrobial properties. Therefore, herbal based hand sanitization has been promoted during the recent outbreak of SARS- CoV-2.

Keywords: Antimicrobial; Aromatherapy; Coronavirus; Hygiene; Hand washing; Medicinal plants

Abbreviations: SARS-CoV-2: Severe Acute Respiratory Syndrome-2; ARDS: Acute Respiratory Distress Syndrome; MERS-CoV: Middle East Respiratory Syndrome Coronavirus; ABHS: Alcohol-Based Hand Sanitizers; NABHS: Non-Alcohol Based Hand Sanitizers; NBRI: National Botanical Research Institute; CSIR: Council of Scientific and Industrial Research; WHO: World Health Organisation; LAS: Linear Alkylbenzene Sulfonates

Introduction

Coronavirus is a very serious respiratory illness caused by Severe Acute Respiratory Syndrome-2 (SARS-CoV-2) [1-7]. The emergence of the coronavirus-2 (SARS-CoV-2) pandemic has risen to be a significant global public health concern and led to the extensive use of hand disinfectants as a promotive factor for controlling the cross contamination of this deadly viral disease (Covid-19). In view of the COVID-19 outbreak, the entire human race across the globe is perturbed. Coronavirus is zoonotic in nature infecting both animal and human, and therefore, a serious global health problem [1,2,8-13]. Further, coronavirus-2 (SARS-CoV-2) has caused a Public Health Emergency of International Concern [3,14,15]. Elderly people and children are more susceptible to viral infections and prone to serious outcomes, which may be associated with Acute Respiratory Distress Syndrome (ARDS) and cytokine storm [1,2,16,17]. The virus can infect cells of the lungs, kidneys, heart and intestine, resulting in the organ damage leading to the multiple organ dysfunction syndrome [1,2,8,9,16,17]. Coronavirus-2

(SARS-CoV-2) which is genetically similar to SARS-Co-V and Middle East Respiratory Syndrome coronavirus (MERS-CoV) is an enveloped, single and positive-stranded RNA virus with a genome comprising 29,891 nucleotides, which encode the 12 putative open reading frames responsible for the synthesis of viral structural and nonstructural [8,9,16,17]. Transmission of COVID-19 is mainly caused by respiratory droplets, direct human to human contact and fecal to oral transmission might also be associated. COVID-19 prominently affect the respiratory tract (both lower and upper respiratory tract), with the initial symptoms of common cold, fever, dry cough, fatigue, nasal congestion, sore throat and diarrhoea to severe pneumonia, difficulty in breathing and ends with the patient death [1-3,8,9,16,17].

The reservoir hosts of the disease are bats and Himalayan palm civets. Mutation is very common with RNA based viruses and led to the development of many mutants [3,8,9,16,17]. There are also reports of double mutants in the SARS-CoV-2 which is very infectious and transmission rate is also very fast. COVID-19 pandemic has created both economic and health crisis which has affected the negative GDP growth of many developed countries including India too. This COVID-19 pandemic crisis inevitably led to the increase in anxiety levels of general public in India [18]. In this critical situation, medical facilities are totally hampered in India. Indian hospitals are overwhelmed, and health care workers are exhausted and becoming infected. Social media is full of desperate people (doctors and the public) seeking medical oxygen, hospital beds, and other necessities. This new variant (B.1.167) with double mutation in the spike protein followed by fungal infections, mucormycosis is believed to be largely responsible for India's current second wave of the COVID-19 pandemic, with the highest infection rates and hospitalisations on the rise once again [6,7,19].

India has a very long, safe and continuous usage of many herbal drugs in the officially recognized health care systems viz. Ayurveda, Yoga, Unani, Siddha, and Homeopathy [20]. Evidence-based herbal based hand sanitizers are widely used in the diverse systems and manufactured, as per the pharmacopoeial guidelines, by a well-organised industry. Indian traditional herbal medicine is very famous since India is leading in the medicinal systems of Ayurveda and Siddha [3,20-40]. These medicinal plants are also important source of other type of beneficial compounds including the ingredients for functional foods. These functional foods promoted the better health to prevent the chronic illness [20,33]. Plant based hand sanitizers are very common in India and this literature review paper highlights the comparison between herbal hand sanitizers and chemical-based hand sanitizers. There are many advantages of herbal hand sanitizers as compared to chemical-based hand sanitizers which are toxic and there are many health issues have been discussed.

Covid-19: Hygiene Science

Hygiene is the science of the health. Washing hands with soaps or using hand sanitizer is the first line of defensive mechanism against COVID-19 [41-44]. Proper hand hygiene is the single most important, simplest, and least expensive means of reducing the spread of disease [43-47]. Hand washing should become an educational priority and is the most important practice for controlling the pathogenic infections. Hand hygiene can be achieved either through hand washing, or hand disinfection [41-49]. The skin harbours mainly two types of microorganisms, the resident and the transient or contaminant flora [50]. The resident flora has a low pathogenic potential [50]. On the other hand, the transient flora has a short-term survival rate on the skin, but with a high pathogenic potential, and is responsible for the most nosocomially acquired infections resulting from the cross-transmission [50]. The aim of hand hygiene is to decrease hand colonization with transient flora [49,50]. Hand hygiene reduces the risk of cross-transmission of infections. Hygiene is the first priority for the healthy lifestyle and hand sanitizers will protect from many microorganisms and common germs [41,47,50]. Avoid unnecessary touching of surfaces in close proximity during travelling, particularly when visiting hospitals [41,43,46,47,50]. Soaps or detergents (chemical surfactants) are surface-active agents and are synthesized from petrochemicals [41-50]. Linear Alkylbenzene Sulfonates (LAS) are the most used surfactants in soaps, detergents, shampoos, and personal care products [44,47-50]. Hand sanitizers are not expensive, can be carried in the travelling, since small bottles could be easily accommodated. However, hand sanitizers are useful only when water facility is not readily available. The WHO declared that "Clean Care is Safer Care" as a prime agenda of the global initiative on patient safety programmes [42-50]. A range of hand sanitizers are available with various combinations of ingredients and modes of delivery [41-50].

Coronavirus: Hand Hygiene Sanitizers

An effective and simple method for reducing the transmission of viral or any type of infections in public or healthcare settings is hand hygiene. Hand sanitizers were used only when there is no availability water and soap. In general, hand sanitizers are classified into two main categories**:** (1) Alcohol-based hand sanitizers (ABHS), and 2) non-alcohol-based hand sanitizers (NABHS) [41-50]. The non-alcohol-based hand sanitizers (NABHS) are made up of various chemicals similar to the component found in the alcohol-based type with the exclusion of alcohol. The most common primary active ingredient of non-alcohol-based hand sanitizers (NABHS), benzalkonium chloride, a quaternary ammonium, is a commonly used as disinfectant [41,44,47,50]. Disinfectants with benzalkonium chloride are generally less irritating than those with alcohol, though more recent evidence suggests that benzalkonium chloride may cause contact dermatitis. However, benzalkonium chloride, the primary ingredient of Non-Alcohol-Based Hand Sanitizers (NABHS), is generally not effective against non enveloped viruses [41,44,47,50]. Although Alcohol-Based Hand Sanitizers (ABHS) are less user-friendly on skin than Non-Alcohol Based Hand Sanitizers (NABHS). Alcohol-Based Hand Sanitizers (ABHS), predominate in health care settings given their low cost and efficacy of reducing infectious transmission. The Non-Alcohol-Based Hand Sanitizers (NABHS), however, are less worrisome regarding

their flammability and abuse potential [41,44,47,50]. However, antimicrobial or disinfecting agents such as triclosan (TCS), triclocarban, sodium hypochlorite, chlorhexidine, benzalkonium chloride and benzithonium chloride are often added [41,44,47,50]. As far as Alcohol-Based Hand Sanitizers (ABHS) is concerned, they are included with either ethanol, isopropyl alcohol, n-propanol, or a combination of these chemicals, and diluted with water [41,44,47,50]. Solutions containing 70 to 95% alcohol in volume are very effective disinfectants even in the hospital and laboratory settings [41,44,47,51]. Humectants are included to prevent skin dehydration and moisturizing agents help to stabilize the product as well as to prolong the time needed for the evaporation of alcohol, thereby increasing its biocidal activity [41,44,52]. Further, WHO has recommended the use of Alcohol-Based Hand Sanitizers (ABHS) since not all the hand sanitizers are effective [41,44,47,51].

The composition of WHO-recommended hand sanitizer formulations contains, either ethanol (96%; final concentration 80% v/v) or isopropyl alcohol (99.8%; final concentration 75%) along with hydrogen peroxide (0.125% v/v as a preservative to inactivate bacterial spores) and glycerol (1.45% v/v as a humectant-moisturizing agent) diluted with sterilized distilled water or boiled water. Therefore, water is thus critical in the protein denaturation process [41,44,47,51]. Most Alcohol-Based Hand Sanitizers (ABHS) are effective at inactivating enveloped viruses, including coronaviruses [41-51]. Currently, strategies to deal with COVID-19 are purely supportive and preventative, aimed at reducing the viral transmission [41,44,47]. The World Health Organization recommends Alcohol-Based Hand Sanitizer (ABHS) formulations against bovine viral diarrhea virus, hepatitis C virus, Zika virus, murine norovirus, and coronaviruses as shown with the effective inactivation in quantitative suspension tests [41,44,47]. Further, *in vitro* studies using sputum cultures of SARS-CoV infected patients with four different Alcohol-Based Hand Sanitizer (ABHS) formulations were all able to inactivate the virus below the limit of detection [41,44,47]. When hand washing with soap and water is unavailable, a sufficient volume of hand sanitizer is necessary to ensure complete hand coverage, and compliance is critical for the appropriate hand hygiene [41,44,47].

The mechanism of killing the microorganisms by soaps or detergents relies on the fact that they disrupt the lipophilic membrane of the cell wall of bacteria and other microorganisms including enveloped viruses. Similarly, alcohol also dissolves the lipid membrane of microorganisms [41,44,47]. Review of literature confirmed that ethanol is highly effective (within 30s) against almost all clinically relevant enveloped viruses including coronaviruses, Severe Acute Respiratory Syndrome (SARS-CoV) and Middle East Respiratory Syndrome (MERS-CoV), which belong to the same class of viruses as (SARS-CoV-2), and influenza viruses [41,44,47]. Alcohol-based disinfectants have also been shown to effectively inactivate the SARS-CoV and MERS-CoV (Middle East Respiratory Syndrome-Related Coronavirus) on inanimate surfaces, such as metal, glass, and plastic [41,44,47]. Alcohol-Based Hand Sanitizers (ABHS) have been utilized as an effective alternative to hand washing to prevent the spread of viral infections [41,44,47]. Alcohol-based hand sanitizers (ABHS) also contains additives such as colorants, stabilizers, fragrance and sometimes preservatives which may include formaldehyde, parabens among other chemicals [41,44,47,53]. Some other chemicals were also used in hand sanitizers for various purposes include polyacrylic acid, glycerin, carbomer, propylene glycol, triethanolamine (trolamine), chloroxyphenol B, triclosan, tetraethylammonium chloride, dichlorodimethylphenol, chlorine, deionized water, and extract of plants [41,44,47-56].

Many Alcohol-Based Hand Sanitizers (ABHS) carry a lot of risks since they are classified as Class I Flammable Liquid substances. Hence, Alcohol-Based Hand Sanitizers (ABHS) increases the risk of fire accidents, compared to choices like the towelettes [47,57]. The risk associated with the use of the Alcohol-Based Hand Sanitizers (ABHS) includes accidental poisoning via ingestion, fire hazard, organ toxicity via absorption through the skin among others particularly children [41,44,47,57]. In addition, alcohol-alcohol dilution is a major contamination in the industry. If the ethanol for instance, is adulterated with other toxic alcohols such as methanol, irreversible blindness, coma or even death could result [47,57]. Methanol is known to be more lethal than ethanol, and methanol is reportedly more toxic when inhaled, or exposed to human orally or through the skin [47,57]. The use of isopropanol-based hand sanitizers carries equal or even greater risk than ethanol-based counterparts [44,47,57]. Other adverse health effects that could result from both Alcohol-Based Hand Sanitizers (ABHS) and Non-alcohol-based hand sanitizers (NABHS) include ocular irritation, vomiting, conjunctivitis, oral irritation, cough, and abdominal pain [47,57]. In some rare scenario, adverse effects could include acidosis, respiratory depression, headache, hypoglycemia, irreversible blindness, central nervous system depression, seizure, coma and death [47,58].

The continuous use or overuse of hand sanitizers can cause chronic irritation and severe skin breakdown among other effects especially in children [47,59]. Furthermore, the continuous topical application of ethanol on the skin was reported to lower skin barrier functions, thereby rending the membrane highly susceptible to harmful chemicals in soaps and cosmetics [47,60]. Hand sanitizers usually end-up being deposited in high concentrations of the constituting chemical residues (contaminants) in the environmental soil and water bodies. Higher concentrations of these chemicals released in the environment could trigger multi-drug resistance [47,60]. Alcohol-based products achieve rapid and effective inactivation of various bacteria, but their efficacy is generally lower against non enveloped viruses [41,44,47,59]. The general safety issues associated with Alcohol-Based Hand Sanitizers (ABHS) are flammability of alcohol and toxicity due to the accidental ingestion of the sanitizer [41,44,47,59,60].

Therefore, washing hands with ordinary soap solution is very effective at killing and eliminating the virus and other germs in the hand [41,44,47,59-61]. The fatty outer surface of the virus is denatured by the soap molecule and this process leads to the destruction of the virus which is washed away by water [44,47,59-

61]. Hence hand washing with soap solution and rinsing with water (preferably warm water) will kill and eliminate the germs from the surface [41,44,47,59-61]. However, the use of Alcohol-Based Hand Sanitizers (ABHS) will kill the organism without eliminating them from the surface. The use of soap and water must be a preferred choice when the hand is visibly or grossly contaminated [41,44,47,59-61]. The use of Alcohol-Based Hand Sanitizers (ABHS) in the global markets have several potential adverse health effects on human such as dehydrated skin, irritation, poisoning, and cancer among others [41,44,47,59-62]. Thus, the careful adoption of hand washing with selected safe liquid soap should be encouraged [47,59-62]. Improvement in hand hygiene is akin to the containment of the spread of germs, including the ravaging viral infection, COVID-19 [47,59-62]. However, when the use of hand sanitizer is inevitable, consumers should be cautious of the chemical constituents as well as the concentration of each constituent [41,44,47,59-62].

These measures are important to the prevention of avoidable implications such as unintentional or deliberate ingestion or chemical absorption through the skin which could lead to incidences such as irreversible blindness, depression, intoxication, liver cirrhosis, acidosis, headache, central nervous system depression, seizure, hypoglycemia, coma and death [41,44,47,59-62]. Alcohol and isopropyl alcohol spills in the water bodies are toxic to aquatic animals, while a large amount of isopropyl alcohol spill at soil may contaminate the groundwater [44,47]. There is a concern of skin damage due to excessive use of hand sanitizers, which can lead to an inability of the skin to protect against other microorganisms or viruses [41,44,47,59-62]. Methanol contamination has also been found in hand sanitizers probably due to the high demand for ethyl alcohol and isopropyl alcohol during this pandemic. FDA (U.S. Food & Drug Administration) found methanol contamination in several tested hand sanitizers (77 products as on July 23, 2020) and advises consumers not to use hand sanitizers from certain manufactures [44,47,63]. Therefore, there is a dire need to replace alcohol-based hand sanitizers with non-toxic or low-toxic hand sanitizers for human and environmental safety [44,47,63]. However, hand washing with soap removes the body's own fatty acids from the skin, which may result in cracked skin that ultimately provides a potential entry portal for pathogens [41,44,47].

To overcome the limitations of plain hand washing, hand sanitizers were introduced claiming to be effective against those pathogenic microorganisms as well as to improve the skin conditions due to the addition of emollients [41,44,47]. Plain soap with water can physically decrease the pathogens to a certain level, but antiseptic agents are necessary to obtain a significantly stronger reduction or elimination [44,47,50]. Hand disinfection is significantly more efficient than standard hand washing with soap and water or water alone [44,47,50]. The major risk factor is the skin irritation by hand hygiene agents probably constitutes an important barrier to appropriate compliance [44,47,53]. The superficial skin layers contain water to keep the skin soft and pliable, and lipids to prevent dehydration of the corneocytes [41,44,47,50]. However, more hand cleansing can increase skin pH, reduce lipid content, increase transepidermal water loss, and even increase microbial shedding [44,47,56].

Due to frequent hand washing during the COVID-19 pandemic, the concentrations of surfactants in the wastewater generated from the household and other institutions are expected to increase by several times [44,47,56]. Their impact on the performance of the wastewater treatment plants and environment during and the post-COVID-19 pandemic is yet to be quantified [44,47,52]. The detergents and alcohol cause skin irritation and dryness and are hazardous to the environment [44,47,50]. Therefore, there is a need for eco-friendly soaps and hand sanitizers for human and environmental safety [44,47,50]. Various nature-based compounds such as microbial bio-surfactants and plant secondary metabolites have been reported to have antimicrobial and virucidal activities [44,47]. These natural plant compounds are usually non-toxic and easily biodegradable [44,50,62]. The plant natural compounds are biodegradable, non-toxic to the environment, and usually biocompatible to humans. Therefore, plant-based hand sanitizers are safe, protective, and play a major role in controlling coronavirus cross contamination during recent outbreak of SARS-CoV-2.

Plant Based Hand Sanitizers

India is called as the land of pharmacy and the Indian traditional herbal system of medicine Ayurveda is one of the oldest systems of medical practice in the world [3,20-40,64-78]. Therefore, Indian herbal medicine has played an essential role in providing the health care services to human civilization [3,20-40,64-78]. Plant extracts and products have been used for centuries in the traditional medicine, functional food, natural dyes, cosmetics, and in the treatment of diseases. India has the exclusive distinction of its own recognized traditional medicine; Ayurveda, Yoga, Unani, Siddha, and Homoeopathy (Ministry of AYUSH, Government of India) [3,20-40,64-78]. The basic treatment approach of all these systems is holistic and the pharmacological modalities are based on the natural products of plants, animals, or mineral origin [3,20-40,64-78]. India is the leading country in the world for using many indigenous herbal plants in the Indian subcontinent for controlling human health disorders [3,20-40,64-78,79-84]. Many safe traditional herbal formulations of Ministry of AYUSH (Government of India), which are well known immunity modulators, have been used for centuries in the respiratory disorders and in allergic conditions [3,79-84]. The Ministry of AYUSH (Govt of India) has listed out such formulations and recommended their use as a prophylactic measure in red zones, containment zones, as well as for corona warriors. Many of them are now under clinical trial in COVID-19 patients [3,20-40,64-78,79-84].

There are many medicinal plants indigenous to India and used in the Indian Systems of Medicine which have been reported as potent antiviral with immunomodulatory and antiallergic/anti asthmatic activities [3,20-40,64-78,79-84]. Many of these medicinal plants are also an integral part of several traditional formulations that have been in use for a long time. Aromatic plants with essential oils have been used for thousands of years, not only as ingredients

of perfumes or as seasonings for the aromatization of food, but also in folk medicine, because of their many different biological properties, including antimicrobial properties [7,85]. Essential oils (EOs) are defined as volatile secondary metabolites of plants that give the plant a distinctive smell, taste, or both [7,85]. Essential oils are produced by more than 17,500 species of plants from many angiosperm families, e.g., *Lamiaceae, Rutaceae, Myrtaceae, Zingiberaceae,* and *Asteraceae*, but only about 300 of them are commercialized [7,85-87].

In India, during the recent outbreak of coronavirus (SARS-CoV-2), there are many medicinal plant extracts and essential oils have been successfully used in preparing the hand sanitizers, liquid soaps, surface cleaners, and toilet cleaners. Plant based hand sanitizers were already in the Indian market by many pharmaceutical and herbal drug companies in India [88,89]. Herbal hand sanitizers have antimicrobial property, antioxidant activity, and considerable microbial load [88,89]. When compared to alcohol-based hand sanitizers, herbal hand sanitizer is more effective against microbes, non toxic, formulate hand soft and makes the hand hygienic. As plants are rich in the wide variety of secondary metabolites such as tannins, terpenoids, alkaloids, and flavonoids etc., they possessed antimicrobial properties. Plants have been used by many traditional healers to prevent or cure infectious conditions [20,40,88,89]. The lead advantage of herbal hand sanitizers is that they are easily available, cheap and harmless without any side effect products. Hand hygiene of vital thing to avoid the transmission of harmful germs and prevent the infections [88,89].

One of the leading plant-based hand sanitizers in Indian market is Neem (*Azidarachta indica*; family *Meliaceae*) based 70% ethanol [27,40,89,90]. In this hand sanitizer, neem plant extract is mixed with 70% ethanol with glycerol since neem has antiviral properties [86,88-91]. Another herbal hand sanitizer is manufactured by one of the local pharma company is ARAR Neem care sanitizer (www.ararpharma.com; Belagavi, Karnataka, India) in which 0.20% v/v of neem (*Azidarachta indica*), 0.20% v/v *Citrus Medica* extract is used with 80% v/v ethanol, 0.125% v/v of hydrogen peroxide 1.45% v/v of glycerol. Citrus flavanoid has a large spectrum of biological activity including antibacterial, antifungal anti-diabetic, anticancer and antiviral activities [86,88-93]. This herbal hand sanitizer is very famous and extensively used by the local people during recent outbreak of coronavirus in Karnataka, Goa, and Maharashtra, India. Another best example of hand sanitizers is made from camphor tree (*Cinnamomum camphora* (L.) (Family *Lauraceae*) would have the greatest advantage because it is readily absorbed through the skin producing either a coolness or warmth sensation or could act as a local anesthetic and antimicrobial substance.

Currently a lot of anti-itch gels and cooling gels use camphor as the active ingredient. There are many herbal products in the Indian market for example is the pure hands gel (orange smell) hand sanitizer from Himalaya herbal products, Bangalore, Karnataka, India. This plant-based hand sanitizer also contains neem extract, *Coriandrum sativum* and other plant extracts with 60% ethanol (Himalaya herbal drugs, Bangalore, Karnataka, India). *Aloe vera* (*Aloe barbadensis*; Family *Asphodelaceae* (*Liliaceae*) gel is also used as hand sanitizer during the recent outbreak of coronavirus (SARS-CoV-2) in India [88,89,94-96]. *Aloe vera* has a versatile skin care properties due to its different hydrophilic components. However, the absorption of these hydrophilic components through the skin is limited due to the presence of the stratum corneum, a water impermeable outer layer of the skin [86,88-96]. *Aloe vera* is famous for its powerful healing activity even at the epithelial level of the skin, and thus provides a protective layer on the skin, which allows the skin to heal at a faster rate due to its nutritional contents and antioxidant properties [86,88-96]. The skin drying is prevented by the application of *Aloe vera* [86,88-92]. Its moisturizing effect makes it perfect for oily skin. Giberellin (present in *Aloe vera*) is a growth hormone which stimulates the growth of new cells and heals the skin with minimal scarring [86,88-92]. *Aloe vera* is also used in the Ayurvedic medicines to heal chronic skin problems such as psoriasis, acne and eczema [96]. Antioxidants including β-carotene, vitamin C and E present in *Aloe vera* leaves, improved the natural firmness of the skin and keep the skin hydrated [86,88-96]. In another study, coconut oil is mixed with turmeric (*Curcuma longa* L.) (*Haladi*; *Arashina* in Kannada belonging to the ginger family *Zingiberaceae*) is also used as homemade hand sanitizer in the rural parts of Karnataka, India during recent outbreak of coronavirus (SARS-CoV-2) for controlling the cross transmission of the virus [96,97]. The combination of coconut oil, and turmeric is very pleasant gel hand sanitizer with advantages such as smoothing the hand, antiviral property, maintain the hand moisture, remain effective for longer period, killing many fungi, bacteria and virus, leaving behind the gentle and rejuvenating freshness. This also avoid dryness of the skin surface and protects the texture of skin surface without any side effects [96,97].

Mysore sandal soap is very famous in Karnataka, India where Indian Sandal wood (*Santalum album*; Srigandha in Kannada, Family, *Santalaceae*) species of *Santalam album* oil is used in the soap. During recent Covid-19 outbreak*, Santalum album* oil is also used in the preparation of liquid hand sanitizer since the use of sandal wood oil gives a very good smell, fragrance, and antiviral activity. Hand sanitizers often smell unpleasant and leave hands feeling dry or sticky. Sandalwood oil is also a disinfectant and has emollient properties, which makes it ideal for things like lotions and deodorants. Therefore, sandal wood oil will remove harmful bacteria, virus from the surface of the skin while also soothing any irritations or breakouts. However, sandalwood oil is also toxic and should not be applied on skin directly. Sandalwood oil should be diluted with water. Therefore, very lower concentration of Sandalwood oil is used in the hand sanitizers and played an important role in controlling recent outbreak of Covid-19. Sandalwood**,** a special limited edition of plane-Aire hands with an ultra-silky texture and enticing sandalwood fragrance. Sandalwood is scented with notes of leather, musk, spice, cedarwood, smoke and cardamom, and is thoughtfully crafted with a unique blend of premium, nourishing ingredients like safflower oil, green tea extract, glycerin and inner leaf *Aloe vera*.

In another development, Norden, USA Hand sanitizer spray (Sandalwood, Cardamom) were used with 70% alcohol, fragranced with 100% natural plant essential oils. This also contains Aloe leaf extract to help moisturize and hydrate skin (Norden hand sanitizer spray (sandalwood and cardamom). Hand Sanitizer Spray "Tangerine x Sandalwood: 70% Isopropyl alcohol, soothing raw *Aloe vera*, black Cumin seed, unrefined evening primrose for moisture. Tangerine sandalwood is a beautiful warm scent, with light citrus notes. Sandalwood essential oil: Sandalwood has natural healing properties that promotes relaxation in the mind and body. In Traditional Chinese medicine, tangerine scent is said to offer an energy boost (OCIN hand sanitizer spray-OCIN). Patanjali (Germi-X) hand sanitizer (India) is an instant germ protection formula which made from ethyl alcohol (70% v/v) and precious herbs. It kills 99.99% of germs without water and leaves hands soft and refreshed (Baba Ramdev Patanjali herbs, India). Alcohol is tough on skin, therefore, the most of the commercial hand sanitizers contain humectants to replenish moisture. The homemade hand sanitizer should hopefully contain glycerin, *Aloe vera*, or some other humectant to lock in moisture, essential oils' effects can also help to replenish lost nutrients and soothe dry, chapped skin. Furthermore, essential oils have antimicrobial properties. Hence the use of selected plant essential oils to homemade hand sanitizer, can improve its effectiveness [92-97]. Another advantage is the addition of plant essential oils in hand sanitizers provide aromatherapy benefits like boosting mood, relaxing tension in the body, and even helping to concentrate. Some of the best plant essential oils used in the preparation of hand sanitizers are Cinnamon, Tea tree, Oregano, Rosemary, Thyme, and Clove (Stephanie, Pollard, 2021, How to make hand sanitizer with essential oils (Updated with CDC recommendations) | Hello Glow) [92-97].

Alpine provisions hand sanitizer

This hand sanitizer is specially formulated with FDA-approved, plant-based alcohol that can effectively clean hands (and other surfaces) when soap and water are not available. Made without any synthetic fragrances, this hand sanitizer is antibacterial, antiviral, antimicrobial, and antifungal along with Aloe leaf juice, this hand sanitizer is infused with cedarwood essential oil, known for its calming properties; sandalwood essential oil, said to evoke feelings of serenity; lavender essential oil, thought to be a miracle worker that can heal delicate skin; and juniper essential oil, which is said to calm inflamed skin and promote restfulness (Alpine provisions-Hand sanitizer-Lavender Juniper. Vanila based hand sanitizers are also available in the market since vanilla is known for its pleasant smell that is found to be effectively kills the germs in a matter of seconds. It also provides the protection from 99.99% germs on hands and keeps it sanitized for the longer periods. On the other hand, Basil is commonly known everywhere for its cooling and medicinal properties. Basil helps to clean hands by killing 99.99% of germs on hands, thus provides a cool and fresh feel [92-98].

In one of the recent developments, Scientists of the National Botanical Research Institute (NBRI), Lucknow, UP, India, have developed the alcohol-based herbal hand sanitizer. The product is developed under the Council of Scientific and Industrial Research (CSIR)-Aroma Mission as per the World Health Organisation (WHO) guidelines. This sanitizer contains Tulsi (Tulsi (*Ocimum sanctum*) belongs to basil family *Lamiaceae* (tribe *ocimeae*) essential oil as herbal constituent, which is strong natural antimicrobial agent, and 60 percent of isopropyl alcohol for killing germs. Its impact lasts for about 25 minutes and it prevents the skin from dehydrating," In clinical trials done on the pathogen (*Staphylococus epidermidis*) harmful to human skin and found on surfaces, the herbal sanitizer has been found to be effective. The know-how of the product and the technology has been transferred to M/s. Sadguru Biologicals Pvt. Ltd, Lucknow, UP, India. This product will be available in the market soon under the brand name of 'Clean Hand Gel'. (NBRI) Scientists develop herbal hand-sanitizer. Grace and co-workers [98] reported the herbal hand wash by using some extracts of commonly available plants like *Andrographis paniculata*, ginger, lemon juice [98]. The formulation was evaluated for its physical parameters. It is sure that these ingredients on combination behave as an effective hand sanitizer [98].

The production of hand sanitizers from locally grown medicinal plants namely; wild spinach, turmeric, garlic) and camphor was achieved by obtaining the plants, grinding and performing ethanolic extraction for 72hrs on them [92-99]. This ethanolic extract in combination with glycerin and absolute ethanol were used for the final preparation [99]. Turmeric and garlic failed the hand sanitizer 's approval test based on their colour and pungent smell, but wild spinach and camphor were found to be good candidates for the hand sanitizers production in Nigeria and inclusion of such products could increase the hand hygiene compliance levels [99]. Hand sanitizers effectiveness starts with its formula. The base of all hand sanitizers is alcohol, added to vitamin E, and *Aloe vera* (or another softening ingredient), and glycerine [92-99]. The essential, and germ-killing ingredient in hand sanitizers is the alcohol, and the minimum amount that needs for a hand sanitizer is 60% [99]. Kalaivani and co-workers [100] reported the use of *Trachyspermum copticum* (Omum seed), *Coleus Aromaticus* (Karpooravalli), *Acorus calamus* (Sweet flag; Vasambu), *Mentha piperita* (Peppermint), *Piper nigram* (Milagu), *Elatteria cardamomum* (Ellam), and *Aloe barbadensis* (Aloe) for the preparation of the herbal hand sanitizers [100]. Guava (*Psidium guajava* L. belongs to family *Myrtaceae*) extract is effective against bacteria, fungi and virus [81-84,86-89]. Phenolic compounds are responsible to inhibit microbial growths and leaves of guava (*Psidium guaja*) possess strong antimicrobial properties due to enrichment of phenolic compounds. Guava leaves has the ability to heal the wound surface [81-84,86-89]. The ancient people of India, Iran (Persian) and China made a Guava (*Psidium guaja*) extract is effective against bacteria. Guava leaf extract showed good activity against intestinal microbes, Vibrio Cholera, etc., [81-84,86-89].

Guava leaf extract also reduces the allergic reaction. The leaves were also used to reduce itching problem and Eczema of skin. These abilities in Guava leaves can make hand sanitizer effective [81-84,86-89]. Handwashing is critical in controlling

the cross contamination of covid-19. There are many problems of adverse effects like itching, irritation, dermatitis etc., has been reported using the synthetic hand wash formulations. Therefore, a poly herbal hand wash using extracts of *Sida cardifolia* (Family-*Malvaceae*), *Azadirachta indica*, *Aloe vera* gel and lemon juice has been reported. Hence this study supported the incorporation and utilization of herbs in the formulations to give a better effect [81-84,86-89,100]. These results suggested that the constituents of the various extracts of *Azadiracta indica, Sida cardifolia* and their combinations are capable of giving superior inhibition than the commercially available antiseptic soaps against the skin pathogens [81-84,86-89,100].

This might be rational basis for use of herbs in the preparation of hand wash and use of these compounds in making the antiseptic lotions or soaps in place of chemicals. The leaves of *Azadiracta indica* are widely used for medicinal purposes [101]. Plants are the rich source of vast variety of secondary metabolities such as tannins, terpenoids, alkaloids and flavonoids etc., which have been found to possess the antimicrobial properties [20-40,85-102]. Some of the herbs that were used to prepare the herbal hand sanitizers are *Ocimum sanctum* (Tulsi leaves), *Eugenia caryophyllus* (clove), *Cymbopogon flexuous* (lemon grass), *Aloe baarbadensis* (Aloe), *Mentha arvensis* (mint), *Azadirachata indica* (neem), *Eucalyptus globulus* (Eucalyptus) [98,101,103-105]. In the current era of Covid-19 pandemic outbreak, the applications of herbal hand sanitizers have become double fold and are much needed. Several herbal hand sanitizers are being introduced in the market such as puro herbal hand sanitizer gel, Himalaya pure hand sanitizer, and feel alive hand sanitizer etc., [98,101,103-105]. Vyas and coworkers [104] reported the use of *Panchavalkala,* is the combination of barks of five different plants viz. *Vata (Ficus bengalensis Linn.)*, *Udumbara* (*Ficus glomerata Roxb.)*, *Ashwattha* (*Ficus religiosa Linn.), Parisha* (*Thespesia populnea Soland*. ex Correa.), *Plaksha* (*Ficus lecor* Buch. Ham.). *Kwatha* (aqueous extract) of *Panchavalkala* was formulated into anti septic liquid and gel by using suitable excipients, which can be used as a ready-made herbal hand wash [98,101,103-105].

The composition of *Panchavalkala* has been attributed with properties like free radical scavenging, anti-helmintic, antimicrobial, anti inflammatory and analgesic etc., [98,101,103-105]. The traditional herbs are very useful antimicrobial agents that can be used as hand sanitizers with lesser side effects and long-lasting effects [105]. The herbal formulations have shown even better results than the commercially available alcohol-based sanitizers [105]. Some of the Indian herbs that can be used for hand sanitizer making are *Cuscuta reflexa, Eucalyptus globulus, Ocimum sanctum, Ocimum grarissum, Azadirachata indica, Aloe vera Mentha arvensis, Ocimum sanctum*, *Eugenia caryophyllus* and *Cymbopogon flexuous* [105]. Singla and Saini, [106] reported the antimicrobial proprieties of aqueous extract extracted from the leaves of some plants like Eucalyptus, Madagascar Periwinkle *(Catharanthus Roseus)* and Neem *(Azadirachta Indica*) [106]. The aqueous extract has more economical for commercial production than essential oil. Eucalyptus extract showed prominent antimicrobial properties therefore, along with the rose extract and glycerin was used to develop the hand sanitizer. These results showed that hand sanitizer effectively reduced bacterial load on hands to a varying degree [106].

Hand sanitizers are alternatives to hand washing with the soap and water for personal hygiene and are helpful when there is poor access to water [107]. Essential oil-based hand sanitizers are more effective than soap, as the essential oils contain compounds that are microstatic and/or microbicidal and stay longer after application [107]. Therefore, the formulation of an essential oil and alcohol-based hand sanitizer from fruit peel extract of *Citrus aurantifolia* has antimicrobial properties against known clinical isolates found on human hands. The antibacterial and antifungal potency of the hand sanitizer could be because of presence of antimicrobial compounds in the oils which showed high content percentage of β-bisabolene and caryophyllene that are known to have antimicrobial and antiviral effects [107]. Following is the list of plant essential oils or plant extracts with proven antiviral activity has been used in the home-made hand sanitizers or manufactured by the herbal company [33,85-108]. These plants with disinfecting properties were also used in the Indian traditional herbal medicine for controlling many human diseases [85-108].

Tea tree oil (*Melaleuca alternifolia*), the volatile essential oil is derived mainly from the Australian native plant *Melaleuca alternifolia* belong to the family *Myrtaceae.* Hand sanitizer formulations with around 70% alcohol and 5-10% Tea Tree Oil (TTO) are most common. The ethanol evaporates quickly while the Tea Tree Oil (TTO) remains much longer on the skin potentially providing additional protection through its antimicrobial efficacy. 2) Lemon balm (*Melissa officinalis*) (Family-*Lamiaceae*). **3**) Garlic oil (*Allium sativum*) (Family- *Amaryllidaceae*). 4) The essential oil of *Laurus nobilis* (Family-*Lauraceae*). **5**) Rosemary (*Rosmarinus officinalis*) (Family- *Lamiaceae*). 6) Thyme oil (*Thymus vulgaris*) (Mint Family-*Lamiaceae*). **7**) *Achillea clavennae* (Family-*Asteraceae*). 8) Cinnamon Oil (*Cinnamomum zeylancium* or *Cinnamomum vervun*) (Family**-***Lauraceae*) [33]. 9) *Copaifera officinalis* (Family**-** *Fabaceae*). 10) *Artemisia longifolia* (Family-*Asteraceae*). 11) *Artemisia Frigida* (Family-*Asteraceae*). 12) *Piper nigrum* (Family- *Piperaceae*). 13) *Salvia lavandulifolia* (Family- *Lamiaceae*). 14) *Thuja sp. (Thuja plicata*, *Thuja occidentalis*) (Family-*Cupressaceae*). 15) *Euphrasia rostkoviana* (Family-*Orobanchaceae*). 16) Fennel Oil (*Foeniculum vulgare)* (Family-*Apiaceae*). 17) Peppermint Oil (*Mentha piperita* or *Mentha balsamea*) (Family-*Lamiaceae*). 18) Clove oil (*Eugenia caryophyllata*) (also known as *Syzygium aromaticum*, *Eugenia aromatica*, *Eugenia caryophyllus*) (Family-*Myrtaceae*). 19) Oregano Oil (*Origanum vulgare*) (Family-*Lamiaceae*). 20) *Theileria Orientalis* Oil (Family-*Theileriidae*). 21) Ginger (*Zingiber officinale*) (Family-*Zingiberaceae*). 22) Sweet wormwood (*Artemisia annua*) (Family-*Asteraceae*). 23) Guduchi or Giloy (*Tinospora cordifolia*) (Amruthballi in Kannada) (Family-*Menispermaceae*). 24) Cloves (*Syzygium aromaticum*) (Family-*Myrtaceae*). 25) *Terminalia Bellerica* (Family-*Combretaceae*), and *Terminalia chebula* (Family-*Combretaceae*). 26) German Chamomile (*Matricaria Chamomilla*) (Family-*Aesteracea*) [80,86]. 27) Olive oil (*Olea Europeae*) (Family-*Oleaceae*) based hand sanitizer. 28) NOMAD Lemongrass

(*Cymbopogon Citratus*) (Family-Poaceae) hand sanitizer. 29) NOMAD Jasmine (Olive Family- *Oleaceae*) hand sanitizer. 30) *Galium odoratum* (Family-*Rubiaceae*). 31) *Hibiscus Sabdariffa* (Family- Malvaceae). 32) Butterfly pea (*Clitoria Ternatea*) (Family-*Leguminosae*). 33) Madagascar periwinkle (*Catharanthus Roseaus*) (Family-*Apocynaceae*). 34) *Acacia Caesia* (Family-*Mimosaceae*) (Kaadu siege in Kannada). 35) *Achyranthes bidentata* (Family-*Amaranthaceae*) (Aane hatti in Kannada). 36) *Argmone mexicana* (Family-*Papaveraceae*) (*Aarishina* datura in Kannada). 37) *Cassia Hirsuta* (Family-*Caesalpiniaceae*). 38) *Chenopodium Ambrosioides* (Family-*Chenopodiaceae*). 39) *Commelina Benghalensis* (Family-*Commelinaceae*). 40) East Indian lemon grass or Malabar or Cochin grass is native to India (*Cymbopogon Flexuosus*) (Family-*Poaceae*).

Conclusion

The use of traditional herbal extracts or essential oils of medicinal plants in the preparation of hand sanitizer played a significant role in controlling the cross contamination of recent outbreak of coronavirus (SARS-CoV-2). However, chemicals used in the hand sanitizers have several potential adverse health effects on human such as dehydrated skin, irritation, poisoning, and cancer among others. WHO and FDA (USA) has warned about the toxicity of hand sanitizers and is a major health issue. The action of hand washing can mechanically remove the microorganisms, but the removal of resident pathogens is more effective when hands are washed with preparations containing plant extracts as anti-microbial agents. Proper hand hygiene is one of the essential infection control strategies as it can undeniably lower the likelihood of direct or indirect transmission of microorganisms. Washing hands with soap and water is superior to sanitizer. However, when hand washing is unavailable or inconvenient, due to the lack of water facility, a sufficient volume of herbal hand sanitizer is important to ensure the complete hand coverage, and compliance is critical for appropriate hand hygiene. The liquid herbal hand sanitizer is very easy to prepare, convenient, portable, no side effects and inactivates the microorganisms within few seconds. Large number of medicinal plants were evaluated and screened for their antimicrobial properties for the preparation of herbal liquid hand sanitizers and found successful. Therefore, on the basis of literature survey, herbal hand sanitizers with 60% to 70% alcohol were found to be more effective during the recent outbreak of coronavirus disease (Covid-19). Therefore, all the above listed plants are strong enough to replace the commercial hand sanitizers and achieve a good personal hygiene in rural areas where the accessibility or affordability of commercial hand sanitizers are limited or absent. These plants are abundantly available in rural areas to be a promising source of commercial antimicrobial agent production for hand sanitizers.

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