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Preparation of Copper/Aloe Vera-Based Hand Sanitizer: A Mini Overview

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Abstract

New hand sanitizer designs with eco-friendly components such as aloe vera and copper can allow pharmaceutical companies to bring enhanced applications onto the market while demonstrating simple and inexpensive preparations associated with improved microbial effectiveness. Alcoholic or non-alcoholic hand rubs are distinctively major classes of hand sanitizer platforms that can be prepared into hydrogels to address solutions for improved formulations. The innovative-utility of these hydrogels seems to be limited only by their ingredients and thus novel materials like copper or aloe vera can lead to optimization of anti-bacterial and anti-viral properties of sanitizers, and therefore a diversified product that may aid further research related to high demands of safe and sustainable materials to combat the current pandemic of COVID-19. The customized designs of starch or cellulosic hydrogels may ensure the diversity and right quality of incorporating these components needed for biocidal activity against microbes in the suggested hand sanitizers. Furthermore, the discussed sanitizer of copper and aloe vera combined in starch or cellulosic hydrogels are believed to exert enhanced texture, tone, and elasticity upon topical application due to their properties that may delve into the enzymatic activities required for less prevalence of skin lesions commonly known in traditional hand sanitizers.

Keywords: Copper; Aloe vera; Formulation; Hydrogel; Free radical(s); Wound healing; Hand sanitizer

Introduction

Hand sanitizers are increasingly being used worldwide to limit spreading of infection outbreaks such as COVID-19. However, combining information at the desired antipathogenic effect and preferred method of application is vital for developing hand sanitizer that achieve best therapeutic performance to supplement hand washing. In this context, hand sanitizers as gel rubs are shown in the preferred form to achieve skin hygiene compliance with instant or immediate effect, which are broadly classified into two types of alcohol-based or alcohol-free rubs [1,2]. In term of effectiveness, these types are almost similar even for coronavirus; however, while non-alcoholic preparations appear more eco-friendly that is highly demanded by consumers to have green products to alleviate human and environmental safety concerns [3-5], alcoholic rubs are currently considered as international standard and frequently used in homes and communities [6,7]. Alcoholic sanitizers could eliminate microbes relatively quickly and can be bio-sustainability produced; however, excessive application of alcoholic sanitizers is highly associated with irritation and skin damage through causing dryness, cracking, and changing the skin normal flora [8]. It is therefore suggested that using herbal non-alcoholic sanitizer could overcome these issues and produce more benefits to the skin, while being as effective in eliminating microorganisms.

In this article, we will briefly review and collate potential extension that can be introduced to the two-common hand-sanitizer types, with possible composition combinations as major feat to look for adding trending natural agents such as copper or ingredients derived from aloe vera plant (mainly leaf gel extract) to mitigate potential adverse skin and environmental impact while maintaining bio-inactivation of the targeted microorganisms. A focus has been placed on gel rubs in form of natural and biodegradable hydrogels to achieve the highest value of this hand sanitizer, while minimizing waste considering excessive use of sanitizing products in the coronavirus pandemic. Hydrogel is often recommended as an effective approach in obtaining stable formulations, which is easy to disperse and present a feasible product to have an acceptable skin feeling [2,9]. The biocidal properties and contribution to impaired skin wound healing of the suggested green components of this sanitizer in form of copper and aloe vera gel extract will be also highlighted.

Hydrogel: starch and cellulosic derivatives-based

The concept behind hydrogels involves production of three dimensional, hydrophilic, cross linked polymeric network that swells with water [10,11]. The hydrogel propagates to include natural and synthetic polymeric ingredients, which could be used fundamentally for its classification, though iterative classification may include properties of these polymers such as, configuration, electrical charge, and physical appearance. In particular, natural hydrogels based on starch or cellulosic derivatives potentially point to a significant increase in the versatility of hosting novel ingredients with an adaptive capacity to form homogenous products, and thereby these types are equally important for possible incorporation of the suggested ingredients in this review of copper or aloe vera components.

Starch hydrogels

While synthetic hydrogels may appear more reproducible, natural hydrogels and especially starch derivatives are more abundant, relatively inexpensive, and can show better biocompatibility and biodegradability with an acceptable consistency [12,13]. Recent studies of Starch hydrogel showed that this preparation may contribute to anti-microbial effect against both gram-negative and gram-positive bacteria [14-16]. For example, gelatinized starcare network offered oxidation stability of the used metal ion in copper nanoparticles (Cu NPs), which is essential for its biocidal activity [16]. Versatility by design can be applied to starch using different innovative yet green technologies to impart the desired functionalities [17]. For example, dry heating of starch used for hydrogel preparation might result in improved textural properties necessary for patient compliance upon applying the targeted hand sanitizer [18]. However, oxygen barrier activity of starch with limited water permeability, which are required for antimicrobial functionality, should be assessed during these modifications, and can be linked to the amorphous fractions of the processed or resourced starch [19,20].

Cellulosic derivatives hydrogels

Low cost and flexibility of performance modulation from principal and natural types of cellulosic derivatives-based excipients provide a large literature on their ample number of applications. Therefore, progressive attention is received towards their ability to host complex and new materials for potential innovative pharmaceutical products. Indeed, cellulosic derivatives have been used widely to produce stable natural hydrogels [21-23]. Two are the common ways to support stability in cellulosic-based hydrogel systems: sorption up to a certain extent of the embedded ingredient, for instance, this was utilized for the purpose of preserving the active metal forms towards a certain application, and finally reinforcing as a shear thickening material [24,25]. As an efficient bio-sorbent, cellulosic derivatives have been investigated to host the biocidal active form of copper metal of cupric ions (Cu^{2+}) into their hydrogel network. The accessibility of these Cu^{2+} ions onto the active sites of the hydrogel were facilitated and preserved, thus enhancing its antimicrobial activity and adsorption performance [26,27]. Therefore, it is a viable option for the innovation of developing an effective hand sanitizer based on copper, or cupric ions.

Hydrogels in handrub sanitizers: Benefits and considerations for alcohol and non-alcohol-based sanitizers

In response to customer compliance, hydrogel hand sanitizers are now often used. Unlike liquid sanitizers, their semi-solid characteristics have been reported with high covering, better dispensing control, and less handling difficulties [28]. Hydrogels can be used for alcohol-based or alcohol-free sanitizers. In these two types of sanitizers, alcohol-free is more favorable or safe for children, with limited irritation level to the skin. On the other hand, the return for using alcohol-based sanitizer is more, in terms of broader spectrum antimicrobial efficacy [29,30]. Percentage, type of alcohol and its contact time highly affect the efficacy and expected biocidal effects of alcohol-based sanitizer [31]. Therefore, hydrogel could be used for this type to ensure better safety through reduction of the evaporation rate of alcohol and thus lower the needed amount of alcohol, in addition to offering a relatively prolonged contact time [32]. Hydrogels could also contribute to better performance of non-alcoholic sanitizer. This may be achieved through hydrogel versatility or ability to integrate diverse chemical compounds, which are the major determinant of this sanitizer performance [2].

Copper: re-framing into hydrogels for potential hand sanitization

Foresight studies suggest future focus on copper as a vital resource that develops a sustainable strategy to meet high demands for topical antimicrobial products, such as hydrogel hand sanitizers [33]. Copper ions or complexes have been investigated widely in their potential to disinfect various media including solids, liquids, and human tissues [34]. It is hypothesized that copper could induce elimination of microorganisms via contact killing and lipid peroxidation. Decrypting how copper affects microbes negatively relies on its oxidation state or ion form, in addition to the available concentration. For example, copper is found at low concentrations in bacterial cells because it is an integral part of the cuproenzymes necessary in their life cycle. However, a relatively higher concentration of copper will cause an ionic imbalance leading to an excessive production of reactive oxygen species (ROS), which could initiate the bacterial cell death through damaging their cell membranes, DNA, and proteins [35]. This mechanism is referred to as contact killing in which copper starts to leach into ions when in contact with a surface, thus accumulating small aqueous space between the surface and bacterial membrane usually in the mM range that facilitates reactive oxygen species (ROS) production causing lipid peroxidation, hindrance of the respiratory chain, DNA degradation, and discharging of iron-sulfur cluster by inactivation of metalloproteins [34,35]. The extent of copper ability to eliminate microorganisms depends on several factors such as bacterial physiology, physiochemical properties of copper (size, shape, and surface preparation), and environmental conditions (presence of moisture or buffering agents) [34-36].

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Although both ions of copper can show broad-spectrum antimicrobial materials against bacteria, viruses and fungi, cuprous ion (Cu^{1+}) is the most effective form in comparison to the cupric ions (Cu^{2+}) [37]. The redox cycle between these ions catalyzes the production of short-lived hydroxyl radicals, which contributes to higher biocidal activity [38]. Therefore, a depletion of thiol and glutathione is expected and results in minimal ability to repair the cellular membranes, DNA and proteins damaged from this oxidative stress [35]. The mechanism of membrane damaged by copper involves the ability of both cuprous and cupric ions to bind into its components of the lipopolysaccharides, carboxylic groups, and peptidoglycans. This binding will induce membrane depolarization, which enables the leakage of cytoplasmic content and thereby causing cell rupture within of less than one minute of exposure [39,40]. It is worth to mention that this mechanism peaks in the presence of unsaturated fatty acids, such are the ones exist in mutant strains of E. coli bacteria, and thus make them more susceptible to contact killing through lipid peroxidation with copper [16,41].

Protein-damaging; however, is achieved by copper in a process called mismetallation of proteins/enzymes and this involves metal displacement reaction for native metals in metalloproteins of the microbial cells. This has been shown to occur predominantly when copper exist as a cuprous ion and consequently have an impact on iron-sulfur clusters within enzymes, such as dihydroxyacid dehydratase and isopropylmalate isomerase (IPM), a process leading to inactivation of the key metabolic enzymes [42]. Furthermore, copper has been shown to affect the gene expression involved in iron-sulfur scaffolding proteins, and therefore could result in permanent damage for the target enzymes of iron-sulfur cofactors and progressively eliminates more microbes [43]. On the other hand, potential antimicrobial action of copper through contact killing induces DNA damage as a secondary event. Copper-induced free radical products of hydroxyl groups (ROS), which bind to DNA and cause oxidative cleavage of its structure at the periplasmic site, thus leading to cell death [44,45]. With copper metal having proved its antimicrobial effectiveness, its skin cytotoxicity is a major aspect to be addressed for potential safe hand sanitization. Sparse data is found on this aspect, and a low prevalence of safety concern was proven in preclinical models. However, this safety is linked to the oxidation level of this metal, copper nanostructures, copper composites, its dose, in addition to the integrity of the outermost layer of the skin [46-48].

A perspective on the sanitization effectiveness of copper ions in the presence of aloe vera extract

Research currently is being conducted to retrieve the knowledge developed anciently for therapeutic applications of natural resources towards green and sustainable solutions and eco-friendly ingredients, such as copper metal and the herbal miracle of aloe vera. Copper is abundant earth transition metal and low-cost redox center; besides the antimicrobial activity it has proven to promote wound healing in dermatology for topical skin application through stimulation of collagen and elastin upregulation and improves growth of new blood vessels [38,49-51]. Similarly, aloe vera is naturally abundant and can offer a range of applications that consist of antimicrobial activity against bacteria, viruses, and fungi, in addition to the superior skin healing effects that have been utilized extensively in cosmetic products [52]. Aloe vera leaf gel is transparent, jelly-like, and biocompatible material that consists of two key molecules; namely aloin and aloe emodin, which belong to anthraquinones and are mainly responsible for its antiviral and antibacterial effect [53]. Interestingly, antiviral activity of this aloe emodin can extend to combat attack of enveloped and non-enveloped viruses, a unique property thereof on dealing with COVID-19 [54]. In fact, aloe vera contains several vitamins, enzymes, polymers, and minerals including copper. Copper and glucomannan polymer in aloe vera can play a role in its biocidal activity; however, this combination has been associated with wound healing effect and imparting flexibility to the skin. These were attributable to the stimulation of antibodies' production, release of growth factors and upregulation of collagen and elastin fibers [38,55-58]. Moreover, aloe vera leaf gel contains chlorophyllin's that can serve as generator for free oxygen radicals to kill microbes; mainly gram-positive bacteria, when exposed to visible light [59-61].

This photosensitized property may create a stimuli-response or smart system adequate for self-preserved formulation under light conditions. Therefore, hand sanitizer that combines copper and aloe vera extract is plausibly considered optimal to harness the capabilities of these ingredients into good adsorbing and preserving natural hydrogels, such as starch and cellulosic derivatives. This may entail a hand sanitizer that can be applied onto a contaminated cut with healing power, minimal skin irritation and antimicrobial properties. The preparation of novel sanitizers containing copper or aloe vera is still ongoing. Hand sanitizers containing one or both components are not readily available or limited. Recently, copper-containing sanitizers were investigated and have shown promising potential to disinfect viruses in vitro with prolonged time compared to alcohol containing sanitizers [62]. Whereas aloe vera gel in alcohol-free hand sanitizer has shown antimicrobial activity with stability concerns if considered as an alternative to alcohol-based sanitizers [63].

Conclusion

A precise knowledge of more compact and novel designs of hand sanitizers will provide new development opportunities and improve current therapeutic outcomes. This mini overview focuses on the preparation of hydrogels based and contain natural and green components that may impart dual functionalities suitable for injured skin and mainly eliminates bacteria and viruses within several seconds of exposure. This article presents a good first step towards advancement that can be introduced into one product (i.e., hand sanitizer), which is on a high demand for

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the current pandemic conditions and serves as a good medium towards reducing cost and supporting health system of an effective product while being non-toxic to the environment.

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