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Preservation of Personal Care and Cosmetic Products: Effectiveness and Safety During the COVID-19 Pandemic

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Synopsis

The global beauty industry has been shocked by the COVID-19 pandemic. Currently, with increased hygiene habits, the choice of preservatives can be impacted by consumers opting for safe products. Products without preservation system could quickly become contaminated with mold, fungi, and bacteria, resulting in spoilage and increased risk of infection. This review explores the possible impacts of COVID-19 in the preservation of cosmetics from the perspective of effectiveness and safety. The preservatives included benzalkonium chloride, benzoic acid, sodium benzoate, benzyl alcohol, chloroxylenol, chlorphenesin, methylparaben, ethylparaben, propylparaben, butylparaben, phenoxyethanol, sorbic acid, potassium sorbate, as well as the multifunctional/booster agents ethylhexylglycerin, caprylyl glycol, and natural antimicrobials. First, we highlight the current scenario of cosmetic preservation, the mode of action, and the maximum concentration allowed for preservatives; then examines overexposure to preservatives. Unexpectedly, the COVID-19 pandemic paralyzed the world market, and cosmetic industries had to adapt to a new reality. Due to the widespread use of cosmetic products, the prevalence of allergies, microbiological resistance, the need for proper prevention of product contamination, and concerns over the safety of preservatives, further investigations into the modes of action of traditional or alternative preservatives are needed to create successful safety products.

INTRODUCTION

The global beauty industry (comprising skin care, color cosmetics, hair care, fragrances, and personal care) has been shocked by the COVID-19 crisis, due to which the beauty market is expected to decline 20–30% (1,2). In addition, approximately 17% of women stopped wearing makeup on account of COVID-19, and 30% of the beauty industry market was closed due to the COVID-19 pandemic (2).

The COVID-19 pandemic has deeply influenced many aspects of life, especially influencing sanitary restrictions (e.g., bans on leaving the house and the avoidance of direct social contact). People suddenly had more time which they could potentially devote to their

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appearance, the use of cosmetics, and hygiene. The COVID-19 pandemic's creation of additional time has undoubtedly changed hygiene and cosmetic habits (3).

Preservatives are added to cosmetics to maintain their microbiological purity during manufacturing, packing, and storage; during the entire period of use, they ensure user safety. Even though preservatives are usually used in small concentrations, they are considered one of the main factors causing allergies in users (4). The cosmetic preservative market size exceeded US $975 million in 2019 and is estimated to grow at over 7% compound annual growth rate (CAGR) between 2020 and 2026. The growing incorporation of preservatives in cosmetics, owing to the importance given to increased shelf life along with upgrading product quality and increasing beauty awareness among populations, has resulted in rising skin care product sales, thereby driving global market growth (5).

The contamination of cosmetic products is a risk for consumer health. According to the Rapid Alert System of the European Commission, 62 cosmetic products were recalled due to contamination by microorganisms between 2008 and 2014. The recalled products were found in 14 different countries, and their numbers were higher in 2013 and 2014. This data are often underreported, making it more difficult to access more realistic data. The most frequently found microorganism was pathogenic *Pseudomonas aeruginosa* (35.48%), and other microorganisms found were mesophilic aerobic microorganisms (bacteria, yeast and molds), *Burkholderia cepacia*, *Klebsiella oxytoca*, *Serratia marcescens*, *Enterobacter gergoviae*, *Enterobacter cloacae*, *Staphylococcus aureus*, *Achromabacter xylosoxidans*, *Rhizobium radiobacter*, *Candida albicans*, *Pantoea agglomerans*, *Citrobacter freundii*, *Pseudomonas putida*, *Enterococcus faecium,* and *Klebsiella pneumoniae* (6).

Currently, with increased hygiene habits, the choice of preservatives can be impacted by consumers opting for safe products. The nutrient- and moisture-rich environments afforded by many cosmetics support the growth of microorganisms. As such, preservatives are added not only to protect the product from spoilage and inadvertent contamination, but also to protect the consumer. The emergence of novel pathogens, viral or bacterial, has always posed serious challenges to public health worldwide (7).

Continuing attacks against most preservatives have kept formulators scrambling to find something that will not bring forth the dreaded "free-of" or "free-from" label claim, as demanded by marketing (8). This discussion has continued and is intensified by the COVID-19 pandemic leading to increased use of antimicrobial ingredients as active substances. Two paths may arise: (1) the return of traditional preservatives that have proven efficacy; (2) or new product formats and the search for natural alternatives.

Considering the changes in post-pandemic habits among cosmetic consumers, this review aims to evaluate the possible impacts of COVID-19 on the preservation of cosmetic products from the perspective of effectiveness and safety of the antimicrobial preservatives addressed in this study.

METHODS

SEARCH STRATEGY

The PubMed, Scopus, and Google Scholar databases were searched for articles and search terms including: "COVID-19," "SARS-CoV-2," "antimicrobial agents," "antimicrobial preservatives," "cosmetic preservation," "benzalkonium chloride," "benzoic acid," "sodium benzoate," "benzyl alcohol," "caprylyl glycol," "chloroxylenol," "chlorphenesin," "ethylhexylglycerin," "methylparaben," "ethylparaben," "propylparaben," "butylparaben," "natural antimicrobial agents," "phenoxyethanol," "sorbic acid," "potassium sorbate," "mode of action," "safety assessment," "irritant contact dermatitis," "natural antimicrobial agents," "contact dermatitis," and "antimicrobial resistance."

INCLUSION AND EXCLUSION CRITERIA

Selection criteria included articles that examined antimicrobial ingredients; antimicrobial preservatives; the relationship between COVID-19 and personal care products and cosmetics; market trends that directly impact cosmetic preservatives; the mode of action of antimicrobial agents; safety assessment of preservatives; irritant contact dermatitis (ICD) and allergic contact dermatitis (ACD) to preservatives; and antimicrobial resistance to preservatives. Articles that evaluated only other cosmetic ingredients that were not included in this study were excluded.

COSMETIC PRESERVATION

The COVID-19 pandemic has enhanced personal hygiene habits with products focused on sanitization, and this new scenario is also impacting cosmetic products. A study to evaluate hygienic and cosmetic care habits in Polish women during the COVID-19 pandemic demonstrated a change in the frequency of handwashing before and during the pandemic. Noticeable increases in frequency compared to the time before the pandemic were recorded after using public transport (from 53.6% to 80.7%) and after coming back home (from 80.0% to 100.0%). Other results demonstrated that the frequencies of taking showers and the use of hand cream increased, the number of people who washed their face only once a day decreased, while for most people, the frequency of hair washing did not change. The frequency of using antibacterial products has increased; however, excessive handwashing with detergents or disinfectants can damage the hydrolipid mantle of the skin surface and may also be responsible for irritation and even the development of contact dermatitis (CD) (3).

Cosmetic products without preservation system rapidly become contaminated with molds, fungi, and bacteria, resulting in spoilage and increased infection risk. Particularly problematic microbes include the Gram-positive *S aureus* and the Gram-negative *Escherichia coli* (9). Even though preservatives are usually used in small concentrations, they are considered one of the main factors causing allergies in users (4). The number of cosmetic products available on the market continues to increase together with the rates of adverse cutaneous reactions. Approximately 6% of the population is sensitized to the ingredients of cosmetics, especially to preservatives and fragrances (10,11).

The amount of antimicrobial agent to be used in a product depends on the agent's intended role; high concentrations are used for active substances in antimicrobial products (topical antimicrobials), and low concentrations are used for preservative purposes in cosmetic products (12), such as benzalkonium chloride (BAC) and chloroxylenol (CX). Currently, with the COVID-19 pandemic, antibacterial and antiviral agents have gained a fundamental role in personal care and cosmetic products. Until recently, we used a small amount of antimicrobial agent, while new products have emerged with these ingredients as leading features of the formulation. Table I describes the preservatives used in this study, as well as their modes of action and the maximum concentrations allowed.

Table I
Modes of Action and Maximum Concentrations Allowed for Antimicrobial Preservatives

Substance	CAS number	Mode of action	Maximum concentration allowed[a]	Other	Reference
Benzalkonium chloride (BAC)	8001-54-5	• Decreases surface tension • Inactivates enzymes • Degrades cell-proteins	0.1%	Avoid contact with eyes	(16–18)
Benzoic acid (BEC) Sodium benzoate (SB)	65-85-0 532-32-1	• Acidifies the external environment, making it unfavorable to microbial growth • Inhibits enzymes from the cellular metabolism	2.5% (acid) – rinse-off products, except oral care 1.7% (acid) – oral care 0.5% (acid) – leave-on products		(19,20)
Benzyl alcohol (BA)	100-51-6	• Induces membrane lysis in bacteria • Denatures the structure of proteins by binding to amino acid residues	1%		(12,21)
Caprylyl glycol (CG)	1117-86-8	• Destabilizes and disrupts the microbial cell membrane and may inhibit DNA synthesis	0.5–1%	Up to 5%	(22,23)
Chloroxylenol (CX)	88-04-0/ 1321-23-9	• Causes membrane damage, resulting in leakage of cytoplasmic constituents	0.5%		(18,24)
Chlorphenesin (CP)	104-29-0	• Denatures proteins • Inhibits protein synthesis	0.3%		(12,25)
Ethylhexylglycerin (EEG)	70445-33-9	• Disrupts membrane integrity • Affects the interfacial tension at the cell membranes of microorganisms	0.5–2%	Up to 2% - sprayed products Up to 8% - maximum in rinse-off products	(4,26–28)

Methylparaben (MP) Ethylparaben	99-76-6 120-47-8	• Acts by disrupting membrane transport processes • Inhibits protein synthesis (ATPases/phosphotransferases) • Inhibits DNA and RNA synthesis • Causes leakage of cytoplasmic contents • Inhibits oxygen consumption of mitochondria in fungi	0.4% (acid) for a single ester 0.8% (acid) for a mixture of esters		(12,17,29)
Propylparaben (PP) Butylparaben	94-13-3 94-26-8		0.14% (acid) for the sum of the individual concentrations 0.8% (acid) for a mixture of methyl and ethylparaben, but not exceeding 0.14%	Not to be used in leave-on products designed for application on the diaper area of children under three years of age	
Natural antimicrobial agents		• Denatures membrane proteins • Inactivates enzymes • Destabilizes the proton motive force and electron flow • Mediates active transport and coagulation of the cell content • Causes breakdown of the permeability barrier • Inhibits the synthesis of DNA, RNA, proteins, and polysaccharides • Effects metabolic pathways and cell division			(4,30–38)
Phenoxyethanol (PE)	122-99-6	• Causes membrane damage, resulting in leakage of cytoplasmic constituents • Prevents cell growth by inhibiting DNA and RNA biosynthesis • Acts on energy metabolism through inhibition of malate dehydrogenase • Disrupts the proton gradient	1%	Intended for leave-on products designed for application on the diaper area of children under three years of age	(28,39–43)
Sorbic acid (SA) Potassium sorbate	110-44-1 246-376-1	• Acidifies the cytoplasm by the penetration of uncharged organic acids • Changes the fluidity of the plasma membrane	0.6% (acid)		(44,45)

[a]Maximum concentration according to Annex V of Regulation European Commission No. 1223/2009 or usual concentration for unregulated.

Clean beauty is having a moment, with an estimated global growth from US $5.4 billion in 2020 to US $11.6 billion by 2027, growing at a CAGR of 12.07% (13). The U.S. Food and Drug Administration (FDA) and other global institutions have failed to define clean which is sometimes confused with natural, leaving these labels open to interpretation by nondermatologist retailers, bloggers, and celebrities. Clean beauty products often claim to be safe, nontoxic, and has transparent labeling of ingredients. However, clean beauty is not necessarily natural and natural is not necessarily clean. The clean beauty and natural movements have demonized hundreds of compounds, while products with a clean or natural claim are not necessarily safer for consumers (14).

Prior to COVID-19, natural consumers avoided ingredients such as preservatives and artificial ingredients in their beauty products due to perceived health risks. With more concern surrounding shelf stability and sanitation across consumer-packaged goods categories, consumers will be more willing to accept these ingredients as long as brands provide evidence of their efficacy and safety from both health and environmental perspectives. As consumers become more aware about viruses and germs living on surfaces, packaging for cosmetic and personal care products may change. Spray and stick formats in both cosmetics and facial skincare have been increasing in popularity, and with the arrival of COVID-19, "touchless" beauty products will see increased demand (15).

ANTIMICROBIAL AGENTS

BENZALKONIUM CHLORIDE (BAC)

Since 1935 a quaternary ammonium compound, BAC, has been used as a preservative in medical preparations, cosmetics, and over the counter products. Benzethonium chloride and cetyl peridium chloride are part of the same chemical group. They act by adsorbing to the cytoplasmic membrane, thus causing leakage of the constituents. They are more active against Gram-positive bacteria. The activity against fungi, mycobacteria, and Gram-negative bacilli is comparatively weak (16,18).

BAC is the most common primary active ingredient of non-alcohol-based hand sanitizer (46). The Cosmetic Ingredient Review (CIR) expert panel concluded that BAC may be safely used as an antimicrobial agent at concentrations up to 0.1%. Nevertheless, the panel noted that it might enhance the dermal penetration of other chemicals, thereby increasing the risk of sensitization and/or irritation (47).

BENZOIC ACID (BEC) AND SORBIC ACID (SA) AND ITS SALTS

Decreased use of traditional preservatives (e.g., parabens, isothiazolinones, formaldehyde releasers, and organic halogens) has boosted interest in alternative means of preservation with other antimicrobial choices, including organic acids such as BEC, SA and its salts (48).

BEC and its salt, sodium benzoate (SB), are reported to function as fragrance ingredients, pesticides, pH adjusters, preservatives, and/or viscosity-decreasing agents in cosmetic products (49). In general, BEC and SB have the broadest spectra of antimicrobial activity and are useful against many spoilage bacteria, fungi, and yeasts. As preservatives are used in a wide range of cosmetic product types, they can be applied to the skin, nails, or hair and may come into contact with the eyes and mucous membranes (12,49,50). The

Scientific Committee on Consumer Products ensures that BEC and SB are safe for use for preservative purposes in cosmetic rinse-off and leave-on products at the current maximum concentrations allowed (49,51).

SA and its salt, potassium sorbate (PS), have broad spectrum of fungistatic activity but are less active against bacteria. Their antimicrobial activity depends upon the amount of undissociated acid, which is determined primarily by the dissociation constant (1.73×10^5 for sorbic acid) and the pH of the system (up to 6.5). While sorbic acid occurs naturally in some berries, virtually all the world's supply of sorbic acid (which PS is derived) is manufactured synthetically (50,52).

PS and SB are listed among compounds that are generally regarded as safe (GRAS) by the United States FDA (50). PS and SB were classified as safe (Margin of Safety: 619.58 and 743.50, respectively) according to Canavez et al. (7) but should be used with caution for cosmetic products that may come into contact with the eyes, as they were classified as highly and moderately irritating to the eye, respectively, in hazard assessments.

CHLOROXYLENOL (CX)

CX is a commonly used preservative agent in cosmetics or as an antimicrobial agent in personal care products. The mechanism of action of CX is commonly assumed to be similar to those of other phenol and halophenol antimicrobials, specifically perturbing membranes and causing cell leakage. CX is bactericidal, good at killing Gram-positive bacteria, but less active against *P aeruginosa* (18,24).

With the recent ban of triclosan and triclocarban from some personal care products (53,54), many replacements antimicrobial compounds have been used. Nonetheless, the potential health risk and environmental impacts of these replacement compounds are largely unknown. The commonly used replacement antimicrobials are BAC, benzethonium chloride, and CX (55).

CHLORPHENESIN (CP)

CP functions as a biocide in cosmetics. Reportedly, CP has bactericidal activity against Gram-positive and Gram-negative bacteria as well as fungicidal activity against *Aspergillus niger* and *Penicillium pinophilum* (fungi) and is also active against *C albicans* and *Saccharomyces cerevisiae* (yeasts). It is used in hair, foot, and suntan sprays and could possibly be inhaled (56).

CP is considered safe in the present practices of use and concentration (56). The margin of safety (MoS) value calculated by Canavez et al. (7) in exposure assessment was 123.92, and a similar MoS value (120.00) was also calculated by the Scientific Committee on Cosmetology, which does not represent a systemic risk in normal conditions of use (57).

PARABENS

Parabens are esters of p-hydroxybenzoic acid, which are widely used as broad-spectrum antimicrobial preservatives (particularly against molds and yeast) in cosmetics, beverages, foods, and pharmaceuticals for more than 70 y. Methylparaben (MP) and propylparaben (PP) are by far the most used (9). Generally, they are considered synthetic compounds, but in recent years, many natural sources have been found (29,58,59). Despite the misguided apprehension about and public fear of preservatives being “bad for you” or “not natural,” parabens have been classified by the United States FDA as GRAS (60).

The decreased use of parabens has led, in part, to an increase in the use of isothiazolinones, botanicals, and other newer chemistries that may show higher incidence of allergic response due to their increased use, which is responsible for high medical bills, time away from work and family, and a diminished quality of life (14).

The American Contact Dermatitis Society named parabens the “2019 nonallergen of the year” (9). Parabens are some of the least allergenic preservatives available, with rates of contact sensitization between 0.5% and 1.4% – rates that have been stable since the 1990s (61).

The CIR Expert Panel has reviewed the safety of parabens several times, most recently in 2019. From the latest results, the panel issued a tentative amended report with the conclusion that 20 ingredients, including MP, ethylparaben, PP, and butylparaben, are safe in cosmetics under the present practices of use and concentrations described in their safety assessments (62).

Will COVID-19 encourage consumers to change their mind about parabens? This question is still unanswered, but a deeper understanding of hygiene and contamination brought about by the novel coronavirus disease outbreak may validate their usage (63).

PHENOXYETHANOL (PE) AND BENZYL ALCOHOL (BA)

Phenols and alcohols are substances with effective antimicrobial properties. Their action is bactericidal, especially with acid-resistant bacilli. At low concentrations, PE and BA may induce membrane lysis in bacteria. Thus, they can denature the structure of proteins by binding to amino acid residues (12).

PE has a large spectrum of antimicrobial activity and is effective against various Gram-negative (e.g., *P aeruginosa*) and Gram-positive (e.g., *S aureus*) bacteria and against yeasts (e.g., *C albicans*) (64). According to the Scientific Committee on Consumer Safety, phenoxyethanol is safe for all consumers—including children of all ages—when used as a preservative in cosmetic products at a maximum concentration of 1% (65,66). According to Grand Review Research, phenol derivates accounted for 35.7% of the total cosmetic preservative market revenue in 2015. In addition, growing demand for PE is expected to spur the highest market growth in this ingredient category: a 6.4% CAGR from 2016 to 2024 (67).

PE could be the next “free-from” ingredient because some researchers suggest it could be irritating due to impurities and when tested at 100% concentration, which are not relevant to the levels used in cosmetic products. Recently, safety reviews confirmed that PE is safe at the maximum concentration allowed, a rare sensitizer, and can be considered one of the most well-tolerated preservatives used in cosmetic products (7,64). Nevertheless, with more concerns surrounding product safety, PE and parabens may be better tolerated by consumers.

BA is active against Gram-positive bacteria and has some weak activity against Gram-negative bacteria, yeasts, and molds. It is classified as an allergen and frequently causes allergic reactions; for example, it has been found to cause allergic reactions in 1.2 to 15% of patients with eczema from cosmetic products (12). In a hazard assessment carried out by

Canavez et al. (7), BA was classified as highly eye-irritant and moderate skin-sensitizing. However, the MoS was 148.70, which does not represent a systemic risk, considering the concentrations currently used. Special attention should be considered mainly if the product´s fragrance contains the allergen, which may increase the dose–response relationship.

PRESERVATIVE BOOSTERS

Each ingredient is added to the cosmetic formulation for a well-defined function, but it can simultaneously contribute to another effect (e.g., antimicrobial activity), thus acting as a multifunctional ingredient. Chelating agents, surfactants, humectants, and phenolic compounds are examples of multifunctional ingredients (12).

Preservative boosters are defined as cosmetic ingredients with antimicrobial properties that can significantly reduce (or even replace) the concentration of synthetic preservatives used in cosmetic products and minimize the likelihood of allergic reactions or irritation of the skin. Moreover, preservative boosters can be considered multifunctional ingredients and show not only antimicrobial activity but also other desirable properties useful in cosmetic products (e.g., moisturizing, antioxidant, etc.) (4).

Ethylhexylglycerin (EEG) and caprylyl glycol (CG) are recognized for their antimicrobial activity and as boosters of traditional preservatives (i.e., increasing the microbiological spectrum). EEG is used for its surfactant, emollient, mild humectant, perfume solubilization, and antimicrobial properties based on its surfactant-like structure. EEG used at a 0.1% to 0.5% concentration can enhance the antimicrobial activity of synthetic preservatives (e.g., 1,2-pentanediol, phenoxyethanol or MP). CG has moisturizing properties and humectants can influence water activity and consequently preserve cosmetic formulations (4,28,68,69). These ingredients have antimicrobial properties but are not classified as preservatives in Annex V of Regulation No. 1223/2009.

An evaluation of the antimicrobial efficacy of CG and EEG was carried out by Lawan et al. (2009). The minimum inhibitory concentration (MIC) of CG for *S aureus*, *P aeruginosa*, *E coli,* and *C albicans* within 1 d and *A niger* within 28 d was 0.5%. EEG under the same conditions obtained an MIC of 1.5%. A mixture of CG and EEG at a proportion of 1:3 (0.5%:1.5%) was further prepared at concentrations of 0.5%, 1.0%, 1.5%, and 2.0%. The MIC of the preservative system for *S aureus* within 3 d, *P aeruginosa*, *E coli,* and *C albicans* within 1 d, and *A niger* within 28 d was 1.0%.

The CIR Expert Panel concluded that EEG and CG are safe in the present practices and concentrations (EEG: 0.000001–8%; CG: 0.00003–5%) described in their safety assessments (23,27). Nevertheless, the Expert Panel noted the potential for CG to be a penetration enhancer. Some cosmetic ingredients have been regarded as safe since they do not penetrate the skin. The impact of the penetration-enhancing activity of CG on the safety of other ingredients in formulations should be considered (23).

"GREEN PRESERVATIVES": NATURAL ANTIMICROBIAL AGENTS

In recent years, the use of natural ingredients in the cosmetic industry, focusing on sustainability and formulations free of synthetic preservatives, has increased. Recent advances have led to the production of antimicrobial agents obtained via green processes. Natural products (e.g., plant extracts, purified isolates, and essential oils) have been proposed as germ killers in hand sanitizers, soaps, and other cosmetics and body care products (70). These natural substances are often sold in mixtures with CG or EEG (4).

Natural compounds comprise the most comprehensively studied group of antimicrobial agents as alternatives to synthetic preservatives (4). The cosmetic industry adapts to the needs of consumers seeking to limit the use of preservatives and to develop preservative-free or self-preserving cosmetics, where preservatives are replaced by raw materials of plant origin (32). However, most of these substances are not recognized as preservatives by cosmetic regulation. Nevertheless, their effectiveness is well established.

Several studies have reported the antimicrobial activities of essential oils and plant extracts. The use of 3% *Thymus vulgaris* essential oil inhibited the growth of *S aureus*, *P aeruginosa,* and *E coli* in formulations O/W and W/O and *C albicans* only in formulations W/O, but not against *A niger* (34). The addition of 1 and 2% (v/v) *Calamintha officinalis* essential oil to O/W cream and shampoo inhibited the growth of the tested bacteria and fungi alone and in mixed culture (71). *Lavandula officinalis* and *Rosmarinus officinalis* oils (1.5%) in an O/W cream displayed marked antimicrobial activities against all common test microorganisms (including bacteria and fungi) and environmental isolates (35). The antimicrobial efficiency of 0.9% *Calendula officinalis* extract was sufficient to preserve the formulation against microorganism contamination (30).

The antimicrobial activity of *Anacardium occidentale* (cashew) leaf extracts at a concentration of 2.5 g (v/v) was shown to be as effective as 0.1% MP in cream formulations (31). Carvacrol, thymol, and eugenol are naturally occurring phenolic compounds known to possess antimicrobial activity against a range of bacteria, along with antioxidant activity. These antimicrobial agents, incorporated into biodegradable poly(anhydride esters) composed of an ethylenediaminetetraacetic acid backbone, have the capability to promote preservation in personal care products (72).

Certain consumers have the misunderstanding that raw materials of natural origin are safer than synthetic ones. However, these substances are more complex due to the phytochemical characteristics of their composition and may be unstable in cosmetic formulations, thus generating precursors of product degradation, increasing the potential for dermal sensitization, and/or photosensitization if exposed to UV radiation. These plant-based products also have sensitizing properties and potentially cause ACD. Sensitizing plants in cosmetics include tea tree oil, arnica, chamomile, yarrow, citrus extracts, common ivy, aloe, lavender, peppermint, and others. Case reports of CD and positive patch-test reactions to cucumber, eucalyptus, rosemary, sage, witch hazel, and chamomile have been reported (33,36–38).

OVEREXPOSURE OF ANTIMICROBIAL PRESERVATIVES

The COVID-19 pandemic has introduced more concerns about the safety of cosmetics and personal care products from a microbiological point of view, though the indiscriminate use of these substances is also not desired. There are preservatives that may cause ACD and ICD (73). Moreover, it is very disturbing that some preservative-resistant bacterial strains isolated from cosmetic products show a degree of cross-resistance with antibiotics (74).

CONTACT DERMATITIS: COMMON FREQUENCY

CD is a common skin condition caused by contact with an exogenous agent that elicits an inflammatory response. Acute CD presents as a pruritic, erythematous rash with papules, vesicles, and crusted lesions, while chronic CD is typically associated with secondary skin changes (i.e., lichenification, fissuring, and scaling). The two main types of CD are ICD and ACD. ICD accounts for approximately 80% of CD cases, while ACD is less common (10,75). Since the 1950s, when formaldehyde was found to be the culprit responsible for several outbreaks of dermatitis from textiles and cosmetics, preservatives have been identified as a common cause of CD (76).

Some preservatives have long been recognized as important skin sensitizers and are common causes of both occupational and nonoccupational CD. Their impact is due not only to their sensitizing potency (most sensitizing preservatives are strong or extreme sensitizers) but also to their broad source of exposure. The most important preservatives, based on their frequency of use and the prevalence of sensitization, include isothiazolinones, methyldibromo glutaronitrile, iodopropynyl butylcarbamate, formaldehyde, and formaldehyde releasers (61).

According to the North American Contact Dermatitis Group, the most common primary geographic sites for CD are the hands, a scattered/generalized distribution pattern, and the face (77). ICD hand lesions involve the palms, the dorsal hand, and the distal dorsal digits but may also involve the interdigital web spaces, where irritants get caught. In contrast, ACD of the hand usually presents as well-demarcated plaques and vesicles involving the dorsal hands, fingers, and wrists. Common allergens include preservatives, fragrances, metals, rubber, and topical antibiotics (78).

The North American Contact Dermatitis Group's study showed that the most frequent specific allergens identified on patch testing in patients with suspected ACD were as follows: of the 10,983 positive allergic reactions, the top 10 most frequent allergens (and their respective prevalence rates) were nickel sulfate (17.5%), methylisothiazolinone (13.4%), fragrance mix I (11.3%), formaldehyde 2% (8.4%), the mixture of methylchloroisothiazolinone and methylisothiazolinone (7.3%), *Myroxylon pereirae*, Balsam of Peru (7.0%), neomycin (7.0%), bacitracin (6.9%), formaldehyde 1% (6.4%), and p-phenylenediamine (6.4%). The performance of the new allergens in order of frequency was as follows: ammonium persulfate (1.7%), chlorhexidine (0.8%), and hydroquinone (0.3%) (77).

ANTIMICROBIAL RESISTANCE

Some experts have warned of the link between COVID-19 and antimicrobial resistance (79–81). Several studies have reported outbreaks or an increase in infections with acquisition of multidrug-resistant bacteria during the COVID-19 pandemic (82–86). Increased use of hand sanitizers and other antimicrobial agents and their release in the environment may influence the levels of antimicrobial resistance during the COVID-19 pandemic (80,81,87,88). Antimicrobial agents used in hand sanitizers are also used as preservatives in cosmetic products as quaternary ammonium compounds.

Preservatives are used in cosmetics at low concentrations to minimize the risk of toxicity to consumers. However, this small quantity for some chemicals, represents the major factor in the appearance of the resistance phenomenon in microorganisms. In addition, contamination rate, target type, temperature, environmental conditions, and contact time are other factors affecting microbial resistance (12). Preservative resistance may be considered as the inactivation of the preservative agent, the reduction in preservative efficacy, or a tolerance of microorganisms (89). Generally, bacterial endospores (i.e., *Bacillus* and *Clostridium*) are the most resistant forms. In contrast, mycobacteria (due to cell wall composition) are more resistant than Gram-negative bacteria, while Gram-positive bacteria are most sensitive to preservatives (19).

Microbiological contamination of cosmetic products is a matter of great importance to the industry and is potentially a major cause of both product and economic losses. The most common signs of microbial contamination are organoleptic alterations, (e.g., offensive odors), changes in viscosity, and color alterations (74). Moreover, in some cases, exposure to pathogenic microorganisms may cause human health problems (e.g., skin irritation, ACD, and infection, especially in the eyes, mouth, or wounds) (90,91).

The different types of microorganisms vary in their response to antimicrobial agents and have different cellular structures, compositions, and physiologies. Traditionally, microbial susceptibility to antimicrobials has been classified based on these differences (92).

The resistance of different types of bacteria (mycobacteria, nonsporulating bacteria, and bacterial spores) can be either a natural property of an organism (intrinsic) or acquired by mutation or acquisition of plasmids (self-replicating, extrachromosomal DNA) or transposons (chromosomal or plasmid integrating, transmissible DNA cassettes). Intrinsic resistance is demonstrated by Gram-negative bacteria, bacterial spores, mycobacteria, and, under certain conditions, *staphylococci*. Acquired, plasmid-mediated resistance is most widely associated with mercury compounds and other metallic salts. In recent years, acquired resistance to certain other types of biocides has been observed, notably in *staphylococci* (92,93).

In comparison with bacteria, little is known about the ways in which fungi can circumvent the action of antimicrobial agents (94). There are two general mechanisms of resistance: (1) intrinsic resistance, a natural property or development of an organism, in which the cell wall presents a barrier to reduce or exclude the entry of an antimicrobial agent; and (2) acquired resistance (95). Mold spores, although more resistant than nonsporulating bacteria, are less resistant than bacterial spores to antiseptics and disinfectants. The cell wall composition in molds may confer a high level of intrinsic resistance on these organisms (92).

Some examples of mechanisms of microorganism resistance are organic acids (e.g., BEC), sorbic acid and its salts, which can be related to (1) degradation of the organic acid, sorbic acid may be degraded to 1,3-pentadiene by some species of *Penicillium*, and BEC is metabolized by several species of *Pseudomonas* and by *Acinetobacter calcoaceticus* (96); and (2) adaptation of the microorganisms to the acidic medium (the yeasts only adapt to small-chain fatty acids) may be achieved by using the H^+-ATPase pump, by the accumulation of the anions to buffer acid pH, or by the synthesis of acid shock proteins (20). In the case of parabens, microorganisms are resistant due to (1) enzymatic inactivation after hydrolysis to 4-hydroxybenzoic acid by esterase; (2) super expression of efflux pump genes; and possibly (3) porin deficiency (97–99). The external membrane and lipopolysaccharides of Gram-negative bacteria can be responsible for the high intrinsic resistance to quaternary ammonium compounds (e.g., BAC). *Pseudomonas aeruginosa* modifies the outer membrane structure by changing its fatty acid composition and phospholipids, hindering the penetration of such antimicrobials (19,100).

Microorganisms are very versatile and adaptive and, to survive, they need to be capable of dealing with toxic substances. There are multiple components in microbial cells that may be targets of antimicrobial agents, and there are just as many targets that may be modified by microorganisms to enable resistance to those ingredients (93). Overexposure to preservatives can decrease the effectiveness of these ingredients, in addition to possible contribution to increased antimicrobial resistance. These problems can be reduced by conscious use of these ingredients by the cosmetic industry, accompanied by correct consumer use recommendations.

CONCLUSION

Attitudes and perception of cosmetic preservatives has changed significantly changed in recent years. Traditional safe preservatives (e.g., parabens) have been replaced by other ingredients of questionable safety. The use of antimicrobial alternatives and the "preservative-free" claim have become popular in the cosmetics market, due in part to current consumer beliefs that a product containing preservatives may pose a higher risk than "unpreserved" or "self-preserved" options.

Unexpectedly, the COVID-19 pandemic paralyzed the global market, and cosmetic industries had to adapt to a new reality. Due to the widespread use of cosmetic products, the prevalence of allergies, microbiological resistance, the need for proper prevention of product contamination, and concerns over the safety of preservatives, further investigations into the modes of action of traditional or alternative preservatives are needed to create successful safety products.

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