© March 2026 | IJIRT | Volume 12 Issue 10 | ISSN: 2349-6002

Comparative Study of Different Preservatives Used in Pharmaceautical Preparations

Ms.Chanchal N. Nigal[1], Ms. Tejaswi M. Paikrao[2], Ms. Pundkar Ashwini[3], Mr. Kamble Kaushik[4], Dr. Payghan Santosh[5]

[1,2,3,4,5]*Rajesh Bhaiyya Tope College of B. Pharmacy Nipani, Bhalgaon, Chh. Sambhajinagar-431136*

***Abstract*—The global market of food, cosmetics, and pharmaceutical products requires continuous tracking of harmful ingredients and microbial contamination for the sake of the safety of both products and consumers as these products greatly dominate the consumer's health, directly or indirectly. The existence, survival, and growth of microorganisms in the product may lead to physicochemical degradation or spoilage and may infect the consumer at another end. It has become a challenge for industries to produce a product that is safe, self-stable, and has high nutritional value, as many factors such as physical, chemical, enzymatic, or microbial activities are responsible for causing spoilage to the product within the due course of time. Thus, preservatives are added to retain the virtue of the product to ensure its safety for the consumer. Nowadays, the use of synthetic/artificial preservatives has become common and has not been widely accepted by consumers as they are aware of the fact that exposure to preservatives can lead to adverse effects on health, which is a major area of concern for researchers. Naturally occurring phenolic compounds appear to be extensively used as bio- preservatives to prolong the shelf life of the finished product. Based on the convincing shreds of evidence reported in the literature, it is suggested that phenolic compounds and their derivatives have massive potential to be investigated for the development of new moieties and are proven to be promising drug molecules. The objective of this article is to provide an overview of the significant role of phenolic compounds and their derivatives in the preservation of perishable products from microbial attack due to their exclusive antioxidant and free radical scavenging properties and the problems associated with the use of synthetic preservatives in pharmaceutical products. This article also analyzes the recent trends in preservation along with technical norms that regulate the food, cosmetic, and pharmaceutical products in the developing countries.**

***Index Terms*—antimicrobials, antioxidants, sodium benzoate, potassium sorbate, parabens, and natural preservatives like rosemary extract, vinegar, and salt.**

I. INTRODUCTION

Shelf life refers to the duration between manufacturing and expiry date, during which the product is expected to retain its original characteristics and remain acceptable for consumers as far as its quality is concerned. During this duration, the product is susceptible to chemical, biological, and physical deterioration, which ultimately degrade the qualitative characteristics of the product [1]. Therefore, preservatives have been extensively used in various pharmaceuticals, cosmetics, and food products to prevent them from deterioration [2,3]. Many factors are responsible for governing the mean life of the product such as the growth of microorganisms, heating, inappropriate temperature, long storage, change in moisture content, reaction with light and oxygen, fermentation, acidification, enzymatic changes, etc., which result in the loss of important properties of the finished product. Pharmaceutical preparation consists of a diverse range of structures and moieties that are susceptible to deterioration. Deterioration is the result of chemical reactions that occur between the various ingredients present in the formulation and the external environment. The deterioration of a product generally occurs during longer storage, affecting its stability, ultimately resulting in the product's decline in its intended natural quality due to microbial contamination and rendering the product harmful to the consumer. In general, there are three processes by which the product degrades [4]. Chemical breakdown includes chemical incompatibilities, such as hydrolysis, oxidation, photolysis, polymerization, hydration, dehydration, and decarboxylation. [5,6]. A change in temperature, particle size, evaporation, vaporization, efflorescence, hygroscope, deliquescence, etc. are all examples of physical degradation. Everywhere we look,there are microbes that assault the product once it is opened. The product starts losing its quality quickly on a microbiological level

II. COMPARATIVE ANALYSIS OF COMMON PHARMACEUTICAL PRESERVATIVES

- Parabens: (Methyl/Propyl): These are widely used, effective against molds and yeast, particularly in oral suspensions, but their effectiveness decreases at higher pH levels.
- Benzalkonium Chloride (BAK): Highly effective cationic surfactant, commonly used in nasal and ophthalmic formulations due to its low binding affinity and efficacy at 0.01%.
- Benzyl alcohol: Commonly used in parenteral and oral formulations (0.5–10%), it also offers anesthetic properties. It should be avoided in neonates due to toxicity risks.
- Benzoic acid: Suitable for oral products at low pH (<5.0), with the sodium salt providing better aqueous solubility.
- Phenolic compound: (e.g., Chlorocresol, m-Cresol): Effective over a wider pH range, often used in injections, though they can be more toxic.

Natural preservatives are derived from natural sources (plants, animals, minerals, or fermentation) like salt, sugar, and rosemary extract, focusing on safety and cleaner labels but often having shorter shelf lives. Synthetic preservatives are lab-created (e.g., sodium benzoate, BHA), providing superior, long-lasting, and cost-effective antimicrobial protection but may carry higher risks of allergic reactions and health concerns.

III. KEY DIFFERENCES

- Source: Natural preservatives are derived from natural sources such as herbs, spices, minerals, or fermentation. Synthetic preservatives are artificially synthesized in a laboratory, sometimes from chemical compounds.
- Effectiveness & Shelf Life: Synthetic preservatives are generally more effective and provide a longer shelf life. Natural preservatives may have limited efficacy and, in some cases, shorter product stability.
- Cost: Natural preservatives (e.g., rosemary extract) can be more expensive, while synthetic alternatives (e.g., BHT) are generally cheaper.
- Health Impact: Natural preservatives are often perceived as healthier and safer with fewer side effects. Synthetic preservatives are linked to potential health concerns, including allergic reactions, skin irritations, and other sensitivities.
- Mechanism: Natural preservatives often work by changing the pH or reducing water content (e.g., salt, sugar, acid). Synthetic preservatives are designed to be broad-spectrum, inhibiting specific mold and bacterial growth.

IV. EXAMPLES

- Natural: Salt, sugar, vinegar, rosemary extract, citric acid, lemon juice, clove, cinnamon.
- Synthetic: Sodium benzoate, potassium sorbate, calcium propionate, BHA, BHT, nitrates.

Fig.1- Natural vs. Synthetic Preservatives

V. NATURAL MATERIALS

1. Salt (Sodium Chloride): Dehydrates microbes through osmosis.
2. Sugar (Sucrose): Acts as a humectant, reducing water activity to prevent bacterial growth in jams and jellies.
3. Vinegar (Acetic Acid): Lowers pH to create an acidic, unfriendly environment for microorganisms.
4. Lemon Juice (Citric Acid): Acts as an antioxidant and acidulant.

5. Spices/Herbs: Rosemary (contains carnosic acid), oregano, cloves, thyme, and sage (contain antimicrobial terpenoids like thymol and carvacrol).
6. Oils: Olive oil and coconut oil (provide a protective barrier). Microbial Agents: Nisin (produced by Lactococcus lactis) used in dairy.
7. Animal-Based: Chitosan (from crustacean shells), Lysozyme (from egg white).

VI. DEFINE: NATURAL

A natural preservative is a substance derived from plants, animals, or microbes that extends a product's shelf life by preventing spoilage from mold, bacteria, or oxidation, acting as a healthier alternative to artificial additives, with examples including salt, sugar, vinegar, rosemary extract, citric acid (lemon juice), and spices like cloves and garlic. They work by creating unfavorable conditions (like high acidity or low water activity) or by disrupting microbial cells.
preserving flavor and texture.
Direct antimicrobial action: Essential oils in spices like thyme and oregano disrupt microbial cell functions.

Fig. 1- Natural preservatives technique.

Methods
1. Fermentation: Produces natural alcohol or lactic acid, acting as a preservative.
2. Pickling: Soaking in acid (vinegar) or brine (salt)
3. Smoking: Exposes food to phenols that inhibit bacteria and prevent lipid rancidity.
4. Extraction & Application: Steam distillation of oils (rosemary, oregano) or solvent extraction of phenolic compounds.

Edible Coatings: Using chitosan or alginate-based films.

Advantages Of Natural Preservatives
1. Healthier Profiles: They are generally considered safer and non-toxic, with fewer reported side effects compared to chemical alternatives.
2. Antioxidant & Nutritional Benefits: Many natural preservatives (like tocopherols or rosemary extract) provide antioxidant properties that not only preserve food but also offer health benefits.
3. Consumer Demand: Increasing demand for organic, "clean label," and minimally processed products makes them highly desirable for marketing.
4. Flavor Enhancement: Some natural options can improve the overall flavor and aroma of the product.
5. Improved Safety: They offer a, and in some cases, more effective, way to inhibit microbial growth in food without relying on synthetic chemicals.

Disadvantages Of Natural Preservatives
1. Lower Effectiveness: Natural preservatives often require higher concentrations to be effective, and they generally provide a shorter shelf life compared to synthetic alternatives.
2. High Cost & Limited Availability: They are typically more expensive and harder to source in large, consistent quantities.
3. Variability in Quality: As they are derived from natural, biological sources, their potency can vary based on harvest season, soil, or country of origin.

Sensory Impact: Some natural preservatives can negatively affect the taste, color, or texture of the food or cosmetic product.

VII. SYNTHETIC PRESERVATIVES (CLASS II)

Synthetic preservatives are manufactured in a laboratory to specifically target bacteria, molds, or fungi, or to act as antioxidants.
Materials
1. Benzoates (e.g., Sodium Benzoate): Used in

acidic foods like sodas and pickles to inhibit yeast and molds.
2. Sorbates (e.g., Potassium Sorbate): Highly effective against fungi in cheese, wine, and baked goods.
3. Nitrates/Nitrites (e.g., Sodium Nitrite): Used in cured meats to prevent Clostridium botulinum and maintain red color.
4. Sulfites (e.g., Sulfur Dioxide): Used in dried fruits and wine as both antimicrobial and antioxidant.
5. Propionates (e.g., Calcium Propionate): Used to prevent mold in bread.
6. Antioxidants (BHA/BHT): Used to prevent oxidation of fats in snacks and oils.
7. Chelating Agents (EDTA): Binds metal ions to prevent color and flavor deterioration.


fig. 1-Sodium Benzoate


fig. 2- food preservatives.

Methods
1. Direct Addition: Mixed directly into food products during manufacturing.
2. Spraying/Dipping: Commonly used for sulfite treatment on dried fruits.

Incorporation in Packaging: Releasing agents (e.g., sulfur dioxide) from packaging material

Synthetic Preservatives Define

Synthetic preservatives are lab-created chemical compounds added to food, cosmetics, and pharmaceuticals to extend shelf life by inhibiting microbial growth (bacteria, mold, yeast) and preventing oxidative spoilage. These additives maintain product quality, safety, and texture over time. Common types include sodium benzoate, potassium sorbate, and butylated hydroxytoluene (BHT).

VIII. CHARACTERISTICS AND EXAMPLES

Purpose: To prevent degradation, maintain color, and prevent illness.

Common Examples
1. Benzoates (e.g., Sodium Benzoate): Used in acidic foods like drinks and salad dressings.
2. Sorbates (e.g., Potassium Sorbate): Used in cheese, wine, and baked goods.
3. Nitrates/Nitrites (e.g., Sodium Nitrite): Used in cured meats to prevent botulism.
4. Antioxidants (e.g., BHA, BHT): Prevent fats and oils from turning rancid.

Advantages of Synthetic Preservatives:
1. Extended Shelf Life: Significantly slows spoilage, reducing food waste and making products last longer.
2. Effective Pathogen Control: Highly efficient at inhibiting the growth of dangerous bacteria and fungi.
3. Cost-Effective: Generally cheaper to produce and use than natural alternatives.
4. Broad Spectrum & Stability: Effective against a wide range of microorganisms and often stable in products with varied pH levels.
5. Maintains Appearance/Texture: Prevents rancidity and keeps food looking fresh (e.g., color retention).

Disadvantages of Synthetic Preservatives
1. Health Concerns: Linked to long-term health issues, including potential carcinogenicity (e.g., BHA/BHT), allergies, and skin irritation.
2. Behavioral Issues: Some studies suggest links to hyperactivity in children.
3. Negative Public Perception: Consumers are increasingly wary of artificial ingredients and prefer "clean label" products.
4. Petroleum-Based: Many are derived from petroleum, which is undesirable for natural-focused consumers.
5. Potential Toxicity: While regulated, cumulative effects of consuming various artificial additives are still a concern.

Conclusion on Preservative Use Natural Preservative Offer consumer-preferred, healthier, and eco-friendly solutions with strong antimicrobial/antioxidant properties, but face challenges in standardization, higher cost, and lower efficacy in some applications.

IX. SYNTHETIC PRESERVATIVES

Provide high-performance, cost-effective, and long-lasting protection against spoilage, but are associated with potential, though often regulated, health risks like allergies or long-term issues.

Future Direction: The market is heavily shifting toward natural options, often using technologies like encapsulation or blending with other natural methods to overcome efficacy limitations.

fig. - Natural vs. Synthetic Preservatives

X. FACTORS MONITORING THE EFFECTIVENESS OF PRESERVATIVES

Every product in the market, whether food, cosmetic, or pharmaceutical, comes with a shelf life. During this period, the product is expected to remain stable retaining its qualitative characteristics, but what if the effect of the preservative is lost? The effectiveness of a preservative depends upon its concentration, solubility, partition coefficient, nature of surfactants used in the formulation having antimicrobial activity, pH, etc. Consumers themselves can easily monitor the loss of effectiveness of a preservative or tarnished product by considering several factors such as the appearance of a greyish-green layer on the top surface of the product, loss of texture, bad taste and odor, change in pH, cloudiness, dryness, bleaching/fading, formation of separation layers, rancidity, staleness, etc. Additionally, some biochemical modifications that affect the organoleptic qualities of foods include hydrolysis, non-enzymatic browning (Maillard reaction), enzymatic browning, lipid oxidation, lipolysis, and proteolysis [13,14,15,16,17]. Therefore, the purpose of adding preservatives is to provide stability and protection against microbial attack, prolong the shelf life, and enhance the efficacy of the product. Before incorporation into miscellaneous products, preservatives have been investigated by researchers worldwide for their decontamination efficacy. The sorting of preservatives attributed to their mechanism of action and sources [18] is depicted below in

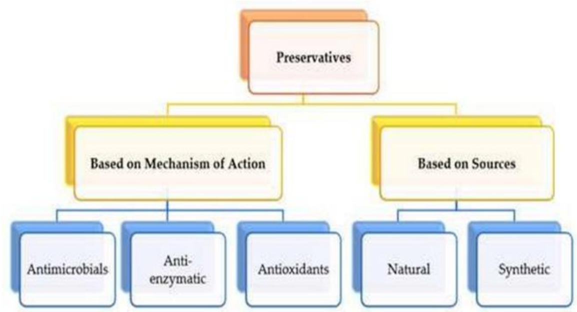

Fig.no.1

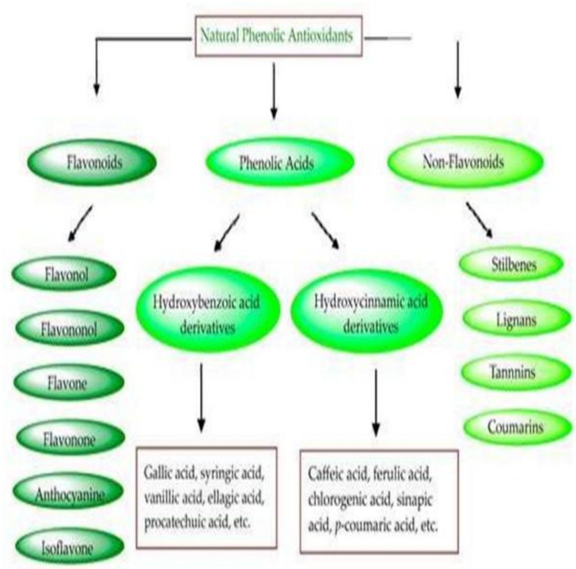

Fig.no.2

XI. DISCUSSION

Chemically synthesized in a laboratory; used for broad, reliable protection. Mechanism: Highly effective at destroying or inhibiting bacteria, yeast, and molds.

Examples: Sodium benzoate, potassium sorbate, calcium propionate, sodium nitrites, BHA (butylated hydroxyanisole), and BHT (butylated hydroxytoluene).

Pros: Very effective, long shelf life, cost-effective, require lower concentrations.

Cons: Potential health risks (e.g., allergies, carcinogenicity concerns), consumer scrutiny.

REFERENCES

[1] A. N. Martin and P. J. Sinko, Martin's Physical Pharmacy and Pharmaceutical Sciences: Physical Chemical and Biopharmaceutical Principles in the Pharmaceutical Sciences. Philadelphia, PA, USA: Lippincott Williams & Wilkins, 2006.

[2] D. Attwood and R. I. Poust, “Chemical kinetics and drug stability,” in Modern Pharmaceutics, vol. 1. Boca Raton, FL, USA: CRC Press, 2009, pp. 221–270.

[3] N. Gokoglu, “Novel natural food preservatives and applications in seafood preservation: A review,” J. Sci. Food Agric., vol. 99, no. 5, pp. 2068–2077, 2019.

[4] S. Pezeshk, S. Ojagh, and A. Alishahi, “Effect of plant antioxidant and antimicrobial compounds on the shelf-life of seafood—A review,” Czech J. Food Sci., vol. 33, no. 3, 2015.

[5] F. Zani, A. Minutello, L. Maggi, P. Santi, and P. Mazza, “Evaluation of preservative effectiveness in pharmaceutical products: The use of a wild strain of Pseudomonas cepacia,” J. Appl. Microbiol., vol. 83, no. 3, pp. 322–326, 1997.

[6] P. Rathee et al., “Polyphenols: Natural preservatives with promising applications in food, cosmetics and pharma industries; problems and toxicity associated with synthetic preservatives; impact of misleading advertisements; recent trends in preservation and legislation,” Materials, vol. 16, no. 13, p. 4793, 2023.

[7] R. Gyawali and S. A. Ibrahim, “Natural products as antimicrobial agents,” Food Control, vol. 46, pp. 412–429, 2014.

[8] C. R. Loss and J. H. Hotchkiss, “Inhibition of microbial growth by low-pressure and ambient pressure gases,” in Control of Foodborne Microorganisms, V. K. Juneja and J. K. Sofos, Eds. Boca Raton, FL, USA: CRC Press, 2001, pp. 245–281.

[9] I. Himoudy, “Preservatives and their role in pharma and clinical research,” Int. J. Pharm. Sci. Scient. Res., vol. 2, pp. 68–85, 2016.

[10] F. Remize, “The microbiological quality of food: Foodborne spoilers,” in Woodhead Publishing Series in Food Science, Technology, and Nutrition. Cambridge, U.K.: Elsevier, 2017, pp. 99–120.

[11] A. S. Bauer et al., “Cereal and confectionary packaging: Background, application and shelf-life extension,” Foods, vol. 11, no. 5, p. 697, 2022.

[12] E. Díaz-Montes and R. Castro-Muñoz, “Edible films and coatings as food-quality preservers: An overview,” Foods, vol. 10, p. 249, 2021.

[13] S. M. Shaikh, R. C. Doijad, A. S. Shete, and P. S. Sankpal, “A review on preservatives used in pharmaceuticals and impacts on health,” PharmaTutor, vol. 4, no. 5, pp. 25–34, 2016.

[14] S. Brul and P. Coote, “Preservative agents in foods: Mode of action and microbial resistance mechanisms,” Int. J. Food Microbiol., vol. 50, pp. 1–17, 1999.

[15] B. K. Meyer, A. Ni, B. Hu, and L. Shi, “Antimicrobial preservative use in parenteral products: Past and present,” J. Pharm. Sci., vol. 96, no. 12, pp. 3155–3167, 2007.

[16] R. Varraso and C. A. Camargo Jr., “Processed meat consumption and lung health: More evidence for harm,” Eur. Respir. J., vol. 43, no. 4, pp. 943–946, 2014.

[17] A. Etemadi et al., “Mortality from different causes associated with meat, heme iron, nitrates, and nitrites in the NIH-AARP diet and health study,” BMJ, vol. 357, p. j1957, 2017.

[18] N. Halla et al., “Cosmetics preservation: A review on present strategies,” Molecules, vol. 23, no. 7, p. 1571, 2018.

[19] A. O. Barel, M. Paye, and H. Maibach, Handbook of Cosmetic Science and Technology. Boca Raton, FL, USA: CRC Press, 2014.

[20] A. C. de Groot, I. R. White, M. A. Flyvholm, G. Lensen, and P. J. Coenraads,

"Formaldehyde-releasers in cosmetics: Relationship to formaldehyde contact allergy," Contact Dermatitis, vol. 62, no. 1, pp. 2–17, 2010.

[21] K. Russell and S. E. Jacob, "Sodium hydroxymethylglycinate," Dermatology, vol. 21, no. 2, pp. 109–110, 2010.

[22] L. Borisova-Jan, S. Jönsson, D. Fransson, M. Tammela, and M. Johansson, Screening Procedure for Determination of Preservatives in Commercial Skin-Care Products. Uppsala, Sweden: Swedish Medicines Agency (Läkemedelsverket), 2011.

[23] S. Zulaikha, "Hazardous ingredients in cosmetics and personal care products and health concern: A review," J. Public Health Res., vol. 5, p. 7, 2015.

[24] C. Y. Ho, M. C. Wu, M. Y. Lan, C. T. Tan, and A. H. Yang, "In vitro effects of preservatives in nasal sprays on human nasal epithelial cells," Am. J. Rhinol., vol. 22, no. 2, pp. 125–129, 2008.

[25] R. Świercz, T. Hałatek, W. Wąsowicz, B. Kur, Z. Grzelińska, and W. Majcherek, "Pulmonary irritation after inhalation exposure to benzalkonium chloride in rats," Int. J. Occup. Med. Environ. Health, vol. 21, no. 2, pp. 157–163, 2008.

[26] S. Mullapudi, R. M. Siletzky, and S. Kathariou, "Heavy-metal and benzalkonium chloride resistance of Listeria monocytogenes isolates from the environment of turkey-processing plants," Appl. Environ. Microbiol., vol. 74, no. 5, pp. 1464–1468, 2008.

[27] A. Dracopoulos, D. G. Dixon, L. W. Jones, J. G. Sivak, and V. Bantseev, "In vitro assessment of medical device toxicity: Interactions of benzalkonium chloride with silicone-containing and p-HEMA–containing hydrogel contact lens materials," Eye Contact Lens, vol. 33, no. 1, pp. 26–37, 2007.

[28] P. Rathee et al., "Polyphenols: Natural preservatives with promising applications in food, cosmetics and pharma industries; problems and toxicity associated with synthetic preservatives; impact of misleading advertisements; recent trends in preservation and legislation," Materials, vol. 16, no. 13, p. 4793, 2023.

[29] C. Baudouin, A. Labbé, H. Liang, A. Pauly, and F. Brignole-Baudouin, "Preservatives in eyedrops: The good, the bad and the ugly," Prog. Retin. Eye Res., vol. 29, no. 4, pp. 312–334, 2010.

[30] D. Suzuki, "The 'Dirty Dozen' ingredients investigated in the David Suzuki Foundation survey of chemicals in cosmetics," David Suzuki Foundation, Vancouver, Canada, Backgrounder Report, 2010.

[31] D. Sasseville, "Hypersensitivity to preservatives," Dermatol. Ther., vol. 17, pp. 251–263, 2004.

[32] X. Fan, C. Kubwabo, P. Rasmussen, and H. Jones-Otazo, "Simultaneous quantitation of parabens, triclosan, and methyl triclosan in indoor house dust using solid phase extraction and gas chromatography–mass spectrometry," J. Environ. Monit., vol. 12, no. 10, pp. 1891–1897, 2010.

[33] P. D. Darbre, A. Aljarrah, W. R. Miller, N. G. Coldham, M. J. Sauer, and G. S. Pope, "Concentrations of parabens in human breast tumours," J. Appl. Toxicol., vol. 24, no. 1, pp. 5–13, 2004.

[34] R. S. Tavares, F. C. Martins, P. J. Oliveira, J. Ramalho-Santos, and F. P. Peixoto, "Parabens in male infertility—Is there a mitochondrial connection?," Reprod. Toxicol., vol. 27, no. 1, pp. 1–7, 2009.

[35] M. D. Lundov, L. Moesby, C. Zachariae, and J. D. Johansen, "Contamination versus preservation of cosmetics: A review on legislation, usage, infections, and contact allergy," Contact Dermatitis, vol. 60, no. 2, pp. 70–78, 2009.

[36] J. D. Lee et al., "Risk assessment of triclosan, a cosmetic preservative," Toxicol. Res., vol. 35, no. 2, pp. 137–154, 2019.

[37] N. Halla et al., "Cosmetics preservation: A review on present strategies," Molecules, vol. 23, no. 7, p. 1571, 2018.

[38] E. A. Silva, M. R. M. Bosco, R. R. Lozano, A. C. P. Latini, and V. N. B. de Souza, "High rate of sensitization to Kathon CG detected by patch tests in patients with suspected allergic contact dermatitis," An. Bras. Dermatol., vol. 95, pp. 94–99, 2020.

[39] T. Isaacs, "Skin hypersensitivity reactions to

preservatives: Allergies in the workplace," Curr. Allergy Clin. Immunol., vol. 25, no. 1, pp. 41–45, 2012.Burnett, C.L., Bergfeld, W.F., Belsito, D.V., Klaassen, C.D., Marks, J.G., Shank, R.C., Slaga, T.J., Snyder, P.W. and Andersen, F.A., 2010. Final report of the safety assessment of methylisothiazolinone. International journal of toxicology, 29(4_suppl), pp.187S-213S.

[40] M. A. R. Scherrer and V. B. Rocha, "Increasing trend of sensitization to methylchloroisothiazolinone/methylisothiazolinone (MCI/MI)," An. Bras. Dermatol., vol. 89, no. 3, pp. 527–527, 2014.

[41] B. N. Statham et al., "Concomitant contact allergy to methylchloroisothiazolinone/methylisothiazolinone and formaldehyde-releasing preservatives," Contact Dermatitis, vol. 62, no. 1, 2010.

[42] P. Rathee et al., "Polyphenols: Natural preservatives with promising applications in food, cosmetics and pharma industries; problems and toxicity associated with synthetic preservatives; impact of misleading advertisements; recent trends in preservation and legislation," Materials, vol. 16, no. 13, p. 4793, 2023.

[43]] J. Mutter and D. Yeter, "Kawasaki's disease, acrodynia, and mercury," Curr. Med. Chem., vol. 15, no. 28, pp. 3000–3010, 2008.

[44] D. Eke and A. Celik, "Genotoxicity of thimerosal in cultured human lymphocytes with and without metabolic activation," Toxicol. In Vitro, vol. 22, no. 4, pp. 927–934, 2008.

[45] R. F. Berman et al., "Low-level neonatal thimerosal exposure: Further evaluation of altered neurotoxic potential in SJL mice," Toxicol. Sci., vol. 101, no. 2, pp. 294–309, 2008.

[46] E. K. Park, S. K. Mak, D. Kültz, and B. D. Hammock, "Evaluation of cytotoxicity attributed to thimerosal on murine and human kidney cells," J. Toxicol. Environ. Health A, vol. 70, no. 24, pp. 2092–2095, 2007.

[47] S. I. Liu et al., "Thimerosal-induced apoptosis in human SCM1 gastric cancer cells: Activation of p38 MAP kinase and caspase-3 pathways," Toxicol. Sci., vol. 100, no. 1, pp. 109–117, 2007.

[48] D. Q. Nguyen, S. Srinivasan, P. Hiscott, and S. B. Kaye, "Thimerosal-induced limbal stem cell failure: Report of a case and review of the literature," Eye Contact Lens, vol. 33, no. 4, pp. 196–198, 2007.

[49] J. G. Dorea, "Exposure to mercury during the first six months via human milk and vaccines: Modifying risk factors," Am. J. Perinatol., vol. 24, no. 7, pp. 387–400, 2007.

[50] J. Tuells et al., "About false beliefs and thiomersal in vaccines," Atencion Primaria, vol. 52, no. 6, pp. 439–440, 2019.

[51] I. Knezevic, E. Griffiths, F. Reigel, and R. Dobbelaer, "Thiomersal in vaccines: A regulatory perspective," Vaccine, vol. 22, no. 15–16, pp. 1836–1841, 2004.

[52] Y. S. Chang et al., "In vitro benzyl alcohol cytotoxicity: Implications for intravitreal use of triamcinolone acetonide," Exp. Eye Res., vol. 86, no. 6, pp. 942–950, 2008.

[53] C. Bitter et al., "Preservative-free triamcinolone acetonide suspension developed for intravitreal injection," J. Ocul. Pharmacol. Ther., vol. 24, no. 1, pp. 62–69, 2008.

[54] I. P. Kaur, S. Lal, C. Rana, S. Kakkar, and H. Singh, "Ocular preservatives: Associated risks and newer options," Cutaneous Ocular Toxicol., vol. 28, no. 3, pp. 93–103, 2009.

[55] S. Langsrud et al., "Ethylhexylglycerin impairs membrane integrity and enhances the lethal effect of phenoxyethanol," PLoS One, vol. 11, no. 10, p. e0165228, 2016.

[56] J. Wang et al., "Toxicity of the cosmetic preservatives parabens, phenoxyethanol and chlorphenesin on human meibomian gland epithelial cells," Exp. Eye Res., vol. 196, p. 108057, 2020.

[57] O. Aerts, L. Verhulst, and A. Goossens, "Ethylhexylglycerin: A low-risk but relevant sensitizer in hypoallergenic cosmetics," Contact Dermatitis, vol. 74, no. 5, pp. 281–288, 2016.

[58] R. A. Dorschner and D. W. Shaw, "Allergic contact dermatitis from ethylhexylglycerin," Dermatitis, vol. 23, pp. 134, 2012.

[59] L. E. Wineski and A. W. English, "Phenoxyethanol as a nontoxic preservative in

the dissection laboratory," Cells Tissues Organs, vol. 136, no. 2, pp. 155–158, 1989.

[60] Y. Chervona et al., "Nonclinical safety evaluation of Prevnar 13 in a multi-dose formulation containing the preservative 2-phenoxyethanol," Vaccines, vol. 13, no. 5, p. 486, 2025.

[61] M. A. Aranzabal et al., "Contact urticaria caused by phenoxyethanol in ultrasound gel," Contact Dermatitis, vol. 81, pp. 132–133, 2019.

[62] B. Dréno et al., "Safety review of phenoxyethanol when used as a preservative in cosmetics," J. Eur. Acad. Dermatol. Venereol., vol. 33, pp. 15–24, 2019.

[63] J. B. Leikin and F. P. Paloucek, Poisoning and Toxicology Handbook. Boca Raton, FL, USA: CRC Press, 2008.

[64] P. Lai, C. Coulson, D. D. Pothier, and J. Rutka, "Chlorhexidine ototoxicity in ear surgery: Review of the literature," J. Otolaryngol. Head Neck Surg., vol. 40, no. 6, 2011.

[65] K. Hirata and A. Kurokawa, "Chlorhexidine gluconate ingestion resulting in fatal respiratory distress syndrome," Vet. Hum. Toxicol., vol. 44, no. 2, pp. 89–91, 2002.

[66] I. Ahmad et al., "Photostability and interaction of ascorbic acid in cream formulations," AAPS PharmSciTech, vol. 12, no. 3, pp. 917–923, 2011.

[67] O. Shelke, K. P. C. Susarla, and M. Bankar, "Understanding the stabilization engineering of ascorbic acid," AAPS PharmSciTech, vol. 25, no. 6, p. 159, 2024.

[68] M. A. Sheraz et al., "Factors affecting formulation characteristics and stability of ascorbic acid in water-in-oil creams," Int. J. Cosmet. Sci., vol. 36, no. 5, pp. 494–504, 2014.

[69] S. A. V. Tfouni and M. C. F. Toledo, "Determination of benzoic and sorbic acids in Brazilian food," Food Control, vol. 13, no. 2, pp. 117–123, 2002.World Health Organization, 2000. Benzoic acid and sodium benzoate. In Benzoic acid and sodium benzoate.

[70] C. Vargas, Organic Acids. New York, NY, USA: Nova Science Publishers, 2017.

[71] U. Marz, World Markets for Citric, Ascorbic and Isoascorbic Acids: Highlighting Antioxidants in Food. Norwalk, CT, USA: Business Communications Company, 2002.

[72] M. M. Silva and F. C. Lidon, "Food preservatives—An overview on applications and side effects," Emirates J. Food Agric., vol. 28, no. 6, p. 366, 2016.

[73] E. Richter, A. Wick, T. A. Ternes, and A. Coors, "Ecotoxicity of climbazole, a fungicide contained in antidandruff shampoo," Environ. Toxicol. Chem., vol. 32, no. 12, pp. 2816–2825, 2013.

[74] E. Richter, A. Wick, T. A. Ternes, and A. Coors, "Ecotoxicity of climbazole, a fungicide contained in antidandruff shampoo," Environ. Toxicol. Chem., vol. 32, no. 12, pp. 2816–2825, 2013.

[75] U. Bernauer et al., "SCCS opinion on Ethylzingerone— 'Hydroxyethoxyphenyl Butanone' (HEPB) (Cosmetics Europe No. P98)," Scientific Committee on Consumer Safety (SCCS), 2016.

[76] Y. Zhang et al., "Serum pharmacokinetics and coagulation aberration induced by sodium dehydroacetate in male and female Wistar rats," Sci. Rep., vol. 7, no. 1, p. 46210, 2017.

[77] C. Foti, P. Romita, G. Ettorre, G. Angelini, and D. Bonamonte, "Allergic contact dermatitis caused by resorcinol and sodium dehydroacetate in a patient with leg ulcers," Contact Dermatitis, vol. 74, no. 6, 2016.

[78] EFSA Panel on Food Additives and Nutrient Sources Added to Food (ANS), "Scientific opinion on the re-evaluation of erythorbic acid (E315) and sodium erythorbate (E316) as food additives," EFSA J., vol. 14, no. 1, p. 4360, 2016.

[79] M. M. Rahman, O. H. Rashid, S. Bhadra, and A. S. Rouf, "Development and validation of colorimetric and RP-HPLC methods for the determination of formaldehyde in cosmetics," Am. Chem. Sci. J., vol. 5, pp. 224–237, 2015.

[80] S. Sharma, "Food preservatives and their harmful effects," Int. J. Sci. Res. Publ., vol. 5, no. 4, pp. 1–2, 2015.

[81] S. K. M. S. Baig and S. S. Kasim, "Study of harmful effects of consuming food additives and public awareness," IJSRST, vol. 2, no. 4, pp. 1071–1074, 2018.

[82] Food Irradiation: A Technique for Preserving and Improving the Safety of Food. Geneva, Switzerland: World Health Organization, 1988.

[83] L. Kovanda et al., “In vitro antimicrobial activities of organic acids and their derivatives on several species of gram-negative and gram-positive bacteria,” Molecules, vol. 24, no. 20, p. 3770, 2019.

[84] M. Gómez-García et al., “Antimicrobial activity of a selection of organic acids, their salts and essential oils against swine enteropathogenic bacteria,” Porcine Health Manag., vol. 5, no. 1, p. 32, 2019.

[85] M. Gómez-García et al., “Antimicrobial activity of a selection of organic acids, their salts and essential oils against swine enteropathogenic bacteria,” Porcine Health Manag., vol. 5, no. 1, p. 32, 2019.

[86] J. Müller and A. Heindl, “Drying of medicinal plants,” in Frontis, 2006, pp. 237–252.

[87] K. Eichner and R. Heiss, Haltbarmachen von Lebensmitteln: Chemische, Physikalische und Mikrobiologische Grundlagen der Verfahren. Berlin, Germany: Springer, 1994.

[88] B. H. Kroes, “The legal framework governing the quality of (traditional) herbal medicinal products in the European Union,” J. Ethnopharmacol., vol. 158, pp. 449–453, 2014.

[89] General Guidelines for Methodologies on Research and Evaluation of Traditional Medicine. Geneva, Switzerland: World Health Organization, 2000.

[90] Quality Assurance of Pharmaceuticals: A Compendium of Guidelines and Related Materials, Vol. 2: Good Manufacturing Practices and Inspection. Geneva, Switzerland: World Health Organization, 2007.

[91] A. N. M. Alamgir, “Herbal drugs: Their collection, preservation, and preparation; evaluation, quality control, and standardization,” in Therapeutic Use of Medicinal Plants and Their Extracts: Vol. 1 Pharmacognosy. Cham, Switzerland: Springer, 2017, pp. 453–495.