Summary Report

Salicylic acid

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Clinical use of bulk drug substances nominated for inclusion on the 503B Bulks List
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Frequently Used Abbreviations

AAD	American Academy of Dermatology
API	Active Pharmaceutical Ingredient
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
5-FU	5-Fluorouracil
IRB	Institutional Review Board
OTC	Over-the-counter
ROA	Route of administration
SME	Subject matter expert
UK	United Kingdom
US	United States

INTRODUCTION

This report was created to assist the Food and Drug Administration (FDA) in their evaluation of the use of salicylic acid (UNII code: O414PZ4LPZ), which was nominated for use as a bulk drug substance in compounding by outsourcing facilities under section 503B of the Federal Food, Drug, and Cosmetic Act.

The aim of this report was to describe how salicylic acid is used in clinical research and practice to diagnose, prevent, or treat disease. Due to the broad, exploratory nature of this aim, scoping review methodology was used. Following the scoping review framework, a systematic literature review was conducted and healthcare practitioners were consulted to identify how salicylic acid has been used historically and currently.[1-3] Assessment of study quality and risk of bias were not performed because the aim of this report was not to make specific recommendations on the use of this substance in clinical practice.[1,4,5] Rather, the aim was to summarize the available evidence on the use of salicylic acid and thereby assist the FDA to determine whether there is a need for the inclusion of this substance on the 503B Bulks List.

REVIEW OF NOMINATIONS

Salicylic acid was nominated for inclusion on the 503B Bulks List by the Outsourcing Facility Association (OFA) and the Specialty Sterile Pharmaceutical Society (SSPS). Salicylic acid was nominated for use in combination with additional Active Pharmaceutical Ingredients (API) (refer to Table 8).

Salicylic acid was nominated for treatment of various skin conditions, including acne, dandruff, psoriasis, seborrheic dermatitis, warts, eczema as a keratolytic or antifungal agent via a topical cream, gel, lotion, body wash, shampoo, and solution, up to 60% in strength.

Nominators provided references from published peer-reviewed literature to describe the pharmacology and support the clinical use of salicylic acid.[6-14]

Reasons provided for nomination to the 503B Bulks List included:

- Compounded products may be the only product to effectively treat the indication for which it is intended.
- Patient need for dosage form or strength, including greater concentration, that is not available commercially.
- Patient sensitivities to dyes, fillers, preservatives, or other excipients in manufactured products.
- Manufacturer backorder.
- Prescriber or hospital preference for various strengths, combinations with other drugs, volumes and/or final product containers for administration
- Unsafe to expose the direct compounding area to hundreds of vials or ampoules and hundreds of aseptic manipulations during the compounding of a typical size batch for outsourcing facilities; a single vessel compounded from bulk API is safer and more efficient than unmanageable amounts of small vials.
- As required by Current Good Manufacturing Practices, bulk API powders can be formulated to 100 percent potency, but finished products cannot; commercially available finished products have an inherent variance in potency, creating an uncertain final concentration for the new product.
- According to SSPS, in order to utilize the most advanced technology available to provide the greatest level of sterility assurance and quality, bulk starting material is required; it is not feasible financially, nor from a processing standpoint, to use finished pharmaceutical dosage forms with advanced isolated robotic equipment or other advanced aseptic processing equipment.

METHODOLOGY

Background information

The national medicine registers of 13 countries and regions were searched to establish the availability of salicylic acid products in the United States (US) and around the world. The World Health Organization, the European Medicines Agency (EMA), and globalEDGE were used to identify regulatory agencies in non-US countries. The medicine registers of non-US regulatory agencies were selected for inclusion if they met the following criteria: freely accessible; able to search and retrieve results in English language; and desired information, specifically, product trade name, active ingredient, strength, form, route of administration (ROA), and approval status, provided in a useable format. Based on these criteria, the medicine registers of 13 countries/regions were searched: US, Canada, European Union (EU), United Kingdom (UK), Ireland, Belgium, Latvia, Australia, New Zealand, Saudi Arabia, Abu Dhabi, Hong Kong, and Namibia. Both the EMA and the national registers of select EU countries (Ireland, UK, Belgium, and Latvia) were searched because some medicines were authorized for use in the EU and not available in a member country and vice versa.

Each medicine register was searched for salicylic acid; name variations of salicylic acid were entered if the initial search retrieved no results. The following information from the search results of each register was recorded in a spreadsheet: product trade name; active ingredient; strength; form; ROA; status and/or schedule; approval date. Information was recorded only for products with strengths, forms, and/or ROA similar to those requested in the nominations.

In addition to the aforementioned medicine registers, the DrugBank database (version 5.1.5) and the Natural Medicines database were searched for availability of over-the-counter (OTC) products containing salicylic acid. The availability of OTC products (yes/no) in the US and the ROA of these products were recorded in a spreadsheet. Individual product information was not recorded.

Systematic literature review

Search strategy

A medical librarian constructed comprehensive search strategies for Ovid MEDLINE and Embase. The search strategies used a combination of controlled vocabulary terms and keywords to describe three concepts: salicylic acid, topical administration or form, and therapeutic use (refer to Appendix 1 for full search strategies). Keywords for brand or proprietary products were not included in the search strategy because studies that utilized such products were excluded. Results were limited to original research articles and conference abstracts in English language. Searches were conducted on December 4, 2019. The reference lists of relevant systematic reviews and meta-analyses, retrieved in a separate search of Ovid MEDLINE on November 12, 2019, were reviewed to identify additional studies. In addition, the ECRI Guidelines Trust® repository was searched on November 12, 2019 for clinical practice guidelines that recommended the use of salicylic acid and provided sufficient information on dosing and administration.

Results were exported to EndNote for Windows version X9.2 (Clarivate Analytics), and duplicates were removed. The de-duplicated results were uploaded to Covidence (Veritas Health Innovation) for screening.

Study selection

Studies in which salicylic acid was used in the nominated dosage form, ROA, and/or combination product to diagnose, prevent or treat the nominated disease or condition, or other conditions not

specified in the nomination, were included. Studies were excluded if they were: written in a language other than English; reviews or meta-analyses; surveys or questionnaires (cross-sectional design); designed to evaluate cost-effectiveness, mechanism of action, pre-clinical use, safety, or toxicity; or any study design other than a randomized controlled trial conducted in a non-US country. Studies were also excluded if salicylic acid was used as: a brand or proprietary product; an FDA-approved product in the nominated dosage form, ROA, or combination; or a dosage form, ROA, or combination that was not nominated. Studies in which salicylic acid was used to diagnose, prevent, or treat autism were excluded due to a separate project examining the use of compounded substances in individuals with autism. Studies that did not meet the inclusion criteria but provided valuable information about the pharmacological or current or historical use of the substance were noted and put in a separate group in the EndNote library. Two reviewers independently screened titles and abstracts and reviewed full-text articles. A third reviewer reconciled all disagreements.

Data extraction

The following information was recorded in a standard data extraction form: author names; article title; journal; year of publication; country; study type; historical use of salicylic acid; setting; total number of patients; number of patients who received salicylic acid; patient population; indication for use of salicylic acid; dosage form and strength; dose; ROA; frequency and duration of therapy; use of salicylic acid in a combination product; use and formulation of salicylic acid in a compounded product; use of salicylic acid compared to FDA-approved drugs or other treatments; outcome measures; authors' conclusions. One reviewer extracted data from the included studies; a second reviewer checked the data extraction.

Interviews

Semi-structured interviews with subject matter experts (SMEs) were conducted to understand how and in what circumstances salicylic acid was used in a clinical setting. The systematic literature review and indications from the nominations were reviewed to identify the following medical specialties that would potentially use salicylic acid: dermatology. Potential SMEs within the relevant medical specialty were identified through recommendations and referrals from professional associations, colleagues' professional networks, and authors of relevant literature. In addition, the American Society of Health-System Pharmacists (ASHP) and select outsourcing facilities were contacted for interviews and referrals to additional SMEs. SMEs provided oral informed consent to be interviewed and audio recorded. Interviews lasting up to 60 minutes were conducted via telephone, audio recorded, and professionally transcribed. The transcriptions and notes were entered into NVivo 12 (QSR International) for qualitative data analysis. Several members of the research team independently coded the transcriptions of two representative interviews for themes. The team members discussed the codes that emerged from their independent analysis, as well as those codes that were determined a priori. The code book was developed out of the integration of these coding schemes.

Survey

A survey was distributed to the members of professional medical associations to determine the use of salicylic acid in clinical practice. The online survey was created using Qualtrics® software (refer to Appendix 2 for complete survey). A Google™ search was conducted to identify the professional associations in the US for the relevant medical specialties. An association's website was searched to identify the email of the executive director, regulatory director, media director, association president, board members, or other key leaders within the organization to discuss survey participation. If no contact information was available, the "contact us" tab on the association website was used. An email describing

the project and requesting distribution of the survey to the association's members was sent to the identified person(s). Associations that declined, did not respond, or did not provide significant data in project Year 1 were not contacted to distribute the project Year 2 surveys.

The survey was posted on the project website and the survey link was distributed to the associations that agreed to participate (refer to Appendix 3 for associations that participated and those that did not).

Participation was anonymous and voluntary. The estimated time for completion was 15 minutes with a target of 50 responses per survey.

The University of Maryland, Baltimore Institutional Review Board (IRB) and the FDA IRB reviewed the interview and survey methods and found both to be exempt. The Office of Management and Budget approved this project.

CURRENT AND HISTORIC USE

Results of background information

- Salicylic acid is not available as an FDA-approved product in the nominated dosage forms and ROA.
- Salicylic acid is available as an OTC product in the US.
- There is a current United States Pharmacopeia (USP) monograph for salicylic acid.
- Salicylic acid is available in the nominated dosage form and ROA in Abu Dhabi, Australia, Canada, Ireland, Saudi Arabia, and UK.

Table 1. Currently approved products – US

No approved products in the US

Table 2. Currently approved products – select non-US countries and regions[a]

Active Ingredient	Concentration	Dosage Form	ROA	Approved for Use		
				Country	Status	Approval Date[b]
Salicylic acid / Cantharidin / Podophyllin	30% / 1% / 2%	Liquid	Topical	Canada	Prescription	12/31/1984
Salicylic acid / Lactic acid	16.7% / 16.7%	Collodion		Ireland	Pharmacy[c]	2/19/1981
				UK		5/2/2001
		Lotion		Abu Dhabi	Active	–
		Solution		Saudi Arabia	Prescription	
	16.7% / 15%			Australia	Schedule 2	9/12/1991
				Ireland	Pharmacy[c]	1/21/1977
				UK		2/14/1990
	12% / 4%	Gel		Ireland		11/21/1989
				UK		7/29/2008

Abbreviations: "– ", not mentioned.

[a]Medicine registers of national regulatory agencies were searched if they met the following criteria: freely accessible; able to search and retrieve results in English language; and desired information (product trade name, active ingredient, strength, form, ROA, and approval status) provided in a useable format. Information was recorded only for products with strengths, forms, and/or ROA similar to those requested in the nominations. See Methodology for full explanation.

[b]If multiple approval dates and/or multiple strengths, then earliest date provided.

[c]Pharmacy-only medications may only be sold in a pharmacy, and a pharmacist must make or supervise the sale.

Results of literature review

Study selection

Database searches yielded 2204 references; 0 additional references were identified from searching ECRI Guidelines Trust® and the references of relevant systematic reviews. After duplicates were removed, 1761 titles and abstracts were screened. After screening, the full text of 291 articles was reviewed. Finally, 38 studies were included. Two hundred fifty-three studies were excluded for the following reasons: wrong study design (59 studies); salicylic acid used as brand or proprietary product (58); wrong dosage form or ROA (55); salicylic acid only mentioned briefly (22); wrong indication (21); foreign, non-RCT (20); wrong substance (8); duplicate study (5); salicylic acid not used clinically (4); unable to obtain (1).

Refer to Figure 1 for the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

Characteristics of included studies

The 38 included studies were published between 1960 and 2019. There were 37 experimental studies, 0 observational studies, 1 descriptive study, and 0 clinical practice guidelines. The 38 studies were conducted in the following countries: Austria, Australia, Belgium, Canada, Egypt, Germany, India, Iran, Israel, Italy, Lebanon, the Netherlands, Pakistan, Russia, Spain, Sweden, Turkey, UK, and US.

A total of 3410 patients participated in the 38 included studies. The number of patients in each study ranged from 1 to 470.

Outcome measures differed among the included studies. For acne, outcome measures included: number of comedones, total number of lesions, acne grade, acne severity (Investigator's global assessment, Acne Severity Index, Michalson Acne Score, Global Acne Grading System), tolerability, patient satisfaction, skin tone, Global Physician Evaluation Score, clinical features of acne, scarring, and hyperpigmentation/erythema post inflammation.

For psoriasis, outcome measures included: Psoriasis Area and Severity Index score (PASI), clinical presentation (scaling, induration, erythema, pruritus), tolerability, and cosmetic properties of the product.

For seborrheic dermatitis, outcome measures included: corneocyte counts, clinical grading scale, surface lipids and free fatty acid to triglycerides ratio, clinical improvement, and dandruff score.

For warts, outcome measures included: size and number of warts, response rate, lesion clearance and recurrence rates.

For dandruff, outcome measures included: corneocyte counts, changes in clinical grading scale, severity score, scaliness, and *Malassezia spp.* count.

For actinic keratosis, photodamaged facial skin, and scalp dermatoses, outcome measures were clinical clearance of the keratoses, clinical grading, and symptom grading, respectively.

Refer to Appendix 2 for summary of study country, design, patient population, intervention and comparator, and outcome measures.

Use of salicylic acid

Eight hundred fifty-one patients received salicylic acid as a treatment for acne, administered topically in concentrations ranging from 1% to 2%. Duration of treatment ranged from 6 days to 20 weeks.

One hundred sixty-one patients received salicylic acid as a treatment for dandruff, administered topically in concentrations ranging from 2% to 3%. Duration of treatment ranged from 28 to 35 days.

Four hundred seventy patients received salicylic acid as a treatment for actinic keratosis, administered topically as a 10% concentration. Duration of treatment was 12 weeks.

Thirty-seven patients received salicylic acid as a treatment for photodamaged facial skin, administered topically in concentrations ranging from 1% to 2%. Duration of treatment ranged from 6 days to 20 weeks.

Two hundred ninety-nine patients received salicylic acid as a treatment for psoriasis, administered topically. Duration of treatment was 4 sessions.

Twenty-eight patients received salicylic acid as a treatment for scalp dermatoses, administered topically in a 2% concentration. Duration of treatment was 3 weeks.

Three hundred eighty-six patients received salicylic acid as a treatment for seborrheic dermatoses, administered topically in concentrations ranging from 2% to 3%. Duration of treatment ranged from 4 weeks to 35 days.

Four hundred thirteen patients received salicylic acid as a treatment for warts, administered topically in concentrations ranging from 10% to 17%. Duration of treatment ranged from 4 weeks to 6 months.

Refer to Tables 6 and 7 for summaries of dosage by indication.

Salicylic acid was not used as a compounded product but was used in a combination product (refer to Table 8).

Refer to Appendix 2 for summary of authors' conclusions.

Pharmacology and historical use

In addition to the 38 included studies, several studies were identified that did not meet the inclusion criteria but provided valuable information about the pharmacology and historical use of salicylic acid.

Salicylic acid is an O-hydroxybenzoic acid that is used to treat a variety of dermatologic conditions, including acne, warts, actinic keratosis, psoriasis, molluscum contagiosum, and seborrheic dermatitis (dandruff).[15,16] Although the exact mechanism of action of salicylic acid in the treatment of dermatologic conditions is not fully known, salicylic acid does act as a keratolytic agent by decreasing cohesion between keratinocytes and lowering the pH of the stratum corneum.[15,17-19] At concentrations >5%, salicylic acid exerts an increasingly potent, rapid, and deep keratolytic effect on the stratum corneum.[19] These actions increase hydration and softening, allowing other drugs to penetrate, and through chemical debridement and the resulting mild irritation, may boost the patient's immune response.[16,18,20] Salicylic acid also has anti-inflammatory properties through the arachidonic acid pathway.[16]

Acne is a common inflammatory skin condition, affecting 85-90% of adolescents.[21] Acne manifests as non-inflammatory comedones (blackheads and whiteheads) and inflammatory pustules, papules, and nodules.[16,22] Topical therapy is the preferred first option for mild acne, and is also used for moderate to severe acne. First-line topical therapies for acne include retinoids, benzoyl peroxide, and

antibiotics.[16] Salicylic acid is available for the treatment of acne in a variety of topical OTC formulations in concentrations ranging from 0.5-3%. Salicylic acid is also used at higher concentrations in chemical peels to treat patients with acne. When used to manage acne, salicylic acid can be administered alone or in combination with other substances, such as benzoyl peroxide.[23] In 2016, an American Academy of Dermatology (AAD) guideline evaluated several therapeutic options for the management of acne vulgaris.[22] The authors of this guideline assigned topical salicylic acid a 'B' strength of recommendation for use in patients with acne vulgaris, indicating that the recommendation was based on inconsistent or limited quality patient-oriented evidence. Salicylic acid was the only substance amongst the topical therapies that the AAD guideline reviewed, including benzoyl peroxide, retinoids, and azelaic acid, that received a 'B' strength of recommendation; all other topical therapies received an 'A', indicating that the recommendation was based on consistent and good-quality patient-oriented evidence. Salicylic acid was not recommended in the treatment algorithm for mild, moderate, or severe acne vulgaris as either a first-line or alternative treatment. The guideline did suggest that using multiple topical therapies that act on different aspects of the acne pathway can be useful and that combination therapy should be used in the majority of patients with acne.

The AAD guideline provided prescribing information for all the therapies that were evaluated. This prescribing information indicated that topical salicylic acid was used alone or in combination with other drugs for the treatment of acne in concentrations of 0.5-2%, applied 1-3 times per day.[22] Possible side effects included excessive dryness or peeling, hypersensitivity reaction, erythema, and salicylate toxicity. The prescribing information warned that there was an increased risk of salicylate toxicity with prolonged or excessive use of topical salicylic acid in children <12 years of age. Higher concentration topical salicylic acid products (6% cream, lotion or gel and 15% plaster) were not recommended for use in children <2 years of age.

A 2012 evidence-based review on topical antimicrobial therapy for acne vulgaris also found limited evidence to demonstrate that salicylic acid, either alone or in combination with benzoyl peroxide, improved acne.[24] A 2010 meta-analysis showed that co-administration of benzoyl peroxide 5% and salicylic acid 2% was superior to benzoyl peroxide alone, clindamycin alone, or combination benzoyl peroxide/clindamycin at 2-4 weeks, but similar to the other substances at 10-12 weeks.[23] The authors of this meta-analysis noted that all included studies that used benzoyl peroxide and salicylic acid utilized the same solubilized benzoyl peroxide gel, which may have been the reason for the increased efficacy of benzoyl peroxide and salicylic acid, not their co-administration.

A 2020 Cochrane review evaluated topical azelaic acid, salicylic acid, nicotinamide, sulfur, zinc, and alpha-hydroxy acid for the treatment of acne.[16] Outcome measures included participants' global self-assessment of acne improvement (PGA), withdrawal from study, adverse effects, and quality of life. There was little difference between salicylic acid and tretinoin for PGA (low quality evidence). Due to the very low quality of the available evidence, a difference in PGA between salicylic acid and pyruvic acid could not be determined. PGA was not measured in the comparison between salicylic acid and benzoyl peroxide. Overall, the evidence available was very low to moderate quality for PGA, low quality for withdrawals, and very low quality for adverse effects. The authors of the review expressed concerns about the small size of the available studies and how these studies were conducted.

Chemical peels are also used in the management of acne, for their anti-inflammatory, antibacterial, keratolytic and comedolytic effects.[22] Chemical peels are a skin resurfacing procedure, which cause injury to the skin, leading to regeneration of the epidermal layer.[21] The depth of injury to the skin is

determined by the strength of acid used, vehicle for administration, buffering, and duration of contact. In their 2016 guideline, the AAD considered chemical peels, including salicylic acid peels, as a treatment method for acne, assigning a 'B' strength of recommendation for their use.[22] The authors commented that "glycolic acid and salicylic acid chemical peels may be helpful for noninflammatory (comedonal lesions)" but multiple treatments are necessary and the results are not persistent.[22] It was the opinion of the guideline work group that "chemical peels may result in mild improvement in comedonal acne."[22] The AAD guideline prescribing information for salicylic acid peels indicated that these peels are used for comedonal acne in concentrations of 20-30%, applied for 2-4 minutes. Possible side effects included stinging, burning, erythema and mild to intense exfoliation.

A 2018 systematic review examined the use of chemical peels in the management of acne vulgaris.[21] Twelve studies were included in the review, 9 of which evaluated salicylic acid, Jessner's solution (a premixed formula of salicylic acid 14%, lactic acid 14%, and resorcinol 14%), or both. The authors found equivalent efficacy between salicylic acid and trichloroacetic acid peels, salicylic acid and pyruvic acid peels, salicylic acid and glycolic acid peels, salicylic acid and lipohydroxy acid peels, and Jessner's solution and glycolic acid. Salicylic acid peels were more effective than Jessner's solution for treatment of comedones but less effective than phototherapy for treatment of pustules. The combination of salicylic acid and mandelic acid in a peel was more effective than glycolic acid. All peels were well-tolerated, although some patients did experience burning, stinging, dry skin, scaling and erythema during or after application of the peel. The authors concluded that "Commonly used chemical peels appear to be similarly effective for mild-to-moderate acne vulgaris and well tolerated" but due to limited evidence, they could not draw "robust" conclusions about the superiority or equivalence of the agents commonly used in peels.[21] The authors mentioned the trend of using a combination of agents in chemical peels, such as salicylic acid, resorcinol, and lactic acid (Vitalize Peel®) or salicylic acid and glycolic acid (Micropeel® Plus), and suggested that future studies should investigate these premixed formulations.

Topical salicylic acid is also used to treat warts, which are common skin lesions caused by human papillomavirus.[18] Salicylic acid is considered a first-line therapy for cutaneous warts. The optimal concentration of salicylic acid for the treatment of warts has not been determined, but most studies have used formulations ranging from 11-40%.[18] A potential drawback to the use of salicylic acid for the treatment of warts is the need for daily application over a long period of time (up to 12 weeks) for complete resolution.[18,20] A 2012 Cochrane review of topical treatments for cutaneous warts found that when compared to placebo, salicylic acid significantly increased the chance of wart clearance at all sites.[20] Subgroup analysis suggested salicylic acid might be more effective for clearance of warts on the hands than those on the feet. Two of the included studies demonstrated that salicylic acid and cryotherapy were more effective when used together than they were when used alone. The authors of the review concluded that "Salicylic acid, a cheap and easily-available solution painted on to warts, had a definite but modest beneficial effect compared to placebo" with few adverse effects.[20] A 2011 meta-analysis on topical treatments for cutaneous warts had similar findings to those of the Cochrane review, namely, salicylic acid was superior to placebo and when used together, salicylic acid and cryotherapy had a higher cure rate than either salicylic acid or cryotherapy alone.[25] Pooled analysis showed a cure rate of 52% for salicylic acid, 58% for salicylic acid and cryotherapy together, and 23% for placebo. The authors of this meta-analysis found the quality of the available studies to be poor, concluding that "Aside from the use of salicylic acid and aggressive cryotherapy there is insufficient evidence from RCTs [randomized controlled trials] to support the use of other therapies."[25] In 2014, a systematic review on non-genital warts also found that topical salicylic acid increased the cure rate of warts compared to placebo.[26] Topical salicylic acid was the only

intervention that the authors considered beneficial. Some therapies, such as contact immunotherapy and cryotherapy, were considered likely to be beneficial while others, such as photodynamic therapy, intralesional bleomycin, and duct tape, were of unknown effectiveness.

Several studies that did not meet the inclusion criteria utilized the nominated combination cantharidin/podophyllotoxin/salicylic acid for the treatment of warts.[9,27-32] According to Ghonemy,[28] the first report of the use of this combination was published in 1984 by Coskey,[27] who described the use of the cantharidin/podophyllotoxin/salicylic combination acid in 121 children with plantar warts, 81 of whom experienced clearance of their warts with treatment. In a 2008 retrospective study, 144 patients with plantar warts were treated with a compounded topical cantharidin 1%/podophyllotoxin 5%/salicylic acid 30% solution; 138 patients (95.8%) had complete clearance of their warts.[32] López-López et al described the use of the cantharidin/podophyllotoxin/salicylic acid combination in patients with plantar warts in two descriptive studies.[9,30] These authors applied a compounded topical cantharidin 1%/podophyllotoxin 5%/salicylic acid 30% preparation with flexible collodion to the wart, then covered it with a dressing. The wart was rechecked after 24-48 hours, at which time the vesicle that had formed was drained and the area debrided. If the wart persisted after 15-20 days, then the combination was applied again. In 1 study with 15 patients, warts were cleared after 1 application in 8 patients and after 2 applications in 7 patients.[30] In the second study with 75 patients, warts were cleared after 1 application in 54 patients and after 2 applications in 21 patients.[9] In both studies, the authors concluded that the cantharidin/podophyllotoxin/salicylic acid combination was a safe and effective treatment for cutaneous warts. A 2012 experimental studied compared the use of cantharidin 1%/podophyllotoxin 5%/salicylic acid 30% (14 patients) to cryotherapy (12 patients) in patients with plantar warts.[29] All patients (100%) in the cantharidin/podophyllotoxin/salicylic acid group had complete clearance of their warts; 5 patients (41.7%) in the cryotherapy group had complete clearance of their warts. The authors concluded that topical cantharidin/podophyllotoxin/salicylic acid was more effective than cryotherapy in the treatment of plantar warts. In a 2017 experimental study, 30 patients with plantar warts were treated with either cantharidin 1%/podophyllotoxin 20%/salicylic acid 30% or long-pulsed Nd:YAG laser.[28] Fourteen patients (93%) in the cantharidin/podophyllotoxin/salicylic acid group experienced complete clearance of their warts; 8 patients (53%) in the laser group experienced complete clearance of their warts. The author concluded that while both therapies were safe and effective, the cantharidin/podophyllotoxin/salicylic acid combination appeared to be more efficacious. A 2019 retrospective study utilized cantharidin 1%/podophyllotoxin 2%/salicylic acid 30% in 52 children and 83 adults with cutaneous warts.[31] Complete wart clearance occurred in 86.5% of the children and 62.7% of the adults. The concentrations of cantharidin (1%) and salicylic acid (30%) in the combination remain consistent amongst the preparations described in the literature, while the concentration of podophyllotoxin is 2%, 5%, or 20%. Cantharidin is a blistering agent produced by beetles that has been used as a single-agent for the treatment of warts and molluscum contagiosum since the 1950s.[28,29] Cantharidin triggers the release of proteases, which destroy desmosomal attachments, leading to acantholysis, intraepidermal blistering, and nonspecific lysis of the skin.[28,29] Podophyllotoxin is the purified, biologically active form of podophyllum, an herbal extract derived from the American mandrake plant or Indian podophyllum; it has been used in the treatment of anogenital warts since 1942.[29] Podophyllotoxin inhibits cell mitosis and therefore, cell division, leading to keratolysis and tissue necrosis.[28,29] In all of the aforementioned studies, the cantharidin/podophyllotoxin/salicylic acid combination was applied by a health professional in an office setting. The authors of 1 study stated that self-application of the cantharidin/podophyllotoxin/salicylic acid combination "was not allowed due to its toxicity and potential misuse, as it can be fatal if ingested."[31]

Salicylic acid has also been used in combination with 5-fluorouracil (5-FU) to treat cutaneous and anogenital warts.[33,34] A 2004 systematic review and meta-analysis evaluated the efficacy of the topical 5-FU/salicylic acid combination for the treatment of warts.[33] The review found a 63.4% response rate (complete healing) for the 5-FU/salicylic acid combination versus a 23.1% response rate for 5-FU-free controls in patients with common warts, and a 63% response rate versus 11% response rate in patients with plantar warts. The authors concluded that "The combination of 5-FU and salicylic acid is an effective and beneficial therapy for common and plantar warts."[33] A 2014 randomized controlled trial compared the efficacy of a topical 5-FU 0.5%/salicylic acid 10% combination with topical potassium hydroxide 5% solution in 60 patients with anogenital warts.[35] After 12 weeks of treatment, excellent clearance according to the physician's global assessment index was achieved in 76.7% of patients who received 5-FU/salicylic acid and 70.0% of patients who received potassium hydroxide. The number of patients who showed complete or marked improvement was greater in the 5-FU/salicylic acid group, although there was no significant difference in the physician's global assessment index at the end of the study. Both treatments were well tolerated with no major side effects; mild and temporary burning and erosion were reported by patients in both groups. Recent articles in dermatology trade magazines have described one author's positive experiences treating cutaneous warts using a patented compounded product called Wartpeel®, a combination of 5-FU 2.5% and salicylic acid 17% delivered in a sustained release topical adhesive gel.[34,36] The 5-FU/salicylic acid combination is approved in Canada (Actikerall®), the UK (Actikerall®) several EU countries (Actikerall®, Verrumal®, Verrucutan®), Australia (Actikerall®) and Hong Kong (Verrumal®) for treatment of warts and/or hyperkeratotic actinic keratosis.

Actinic keratosis is a common skin condition, often associated with chronic skin exposure, that manifests as scaly macules, papules, or plaques.[37,38] Some lesions spontaneously resolve overtime while others, if left untreated, progress to invasive squamous cell carcinoma. The 5-FU 0.5%/salicylic acid 10% solution has been investigated for use in patients with grade I/II actinic keratosis lesions. 5-FU is "a cytostatic agent with antimetabolite effects that prevent the growth of AK [actinic keratosis] cells by inhibiting both DNA and RNA synthesis."[39] The keratolytic activity of salicylic acid decreases the thickness of the actinic keratosis lesions, allowing for better penetration of 5-FU. In a 2016 literature review, the authors found that the use of 5-FU/salicylic acid for the treatment of actinic keratosis was associated with "high rates of histologic clearance, reduction in lesion number/area, and sustained clinical response" and concluded that the combination is an effective and well-tolerated treatment for mild-to-moderate hyperkeratotic actinic keratosis. In 2017, the Canadian Agency for Drugs and Technologies in Health (CADTH) released their review of the use of Actikerall® (5-FU 0.5%/salicylic acid 10%) for the topical treatment of slightly palpable and/or moderately thick hyperkeratotic actinic keratosis (grade I/II) of the face, forehead and balding scalp in immunocompetent adults.[37] One double-blind randomized controlled trial met the inclusion criteria for the CADTH review. The 470 patients in this study were randomized to receive the 5-FU/salicylic acid solution, diclofenac gel, or placebo for topical treatment of actinic keratosis until lesion clearance or up to 12 weeks.[40] The primary outcome measure was histological clearance of actinic keratosis in a single pre-defined lesion 8 weeks post-treatment. Complete clearance of the pre-defined lesion was significantly higher in the 5-FU/salicylic acid group (72%) versus the diclofenac (59.1%) or placebo group (44.8%). Significantly more lesions were cleared in the 5-FU/salicylic acid group (74.5%) compared with patients in the diclofenac (54.6%) and placebo groups (35.5%). The authors of the study concluded that 5-FU/salicylic acid was an effective treatment for actinic keratosis.

In addition to warts, topical salicylic acid has been used in the treatment of another viral skin infection, molluscum contagiosum. This skin condition is caused by the molluscum contagiosum virus, which is in the pox virus family.[41] Molluscum contagiosum, which is seen most frequently in children, is characterized by single or multiple painless, shiny, pearly-white papules.[41] These lesions often spontaneously resolve over a period of months to years. A 2017 Cochrane review evaluating interventions for molluscum contagiosum found low quality evidence to show which treatments were superior for short-term clinical cure.[41] The only findings of note for salicylic acid were that salicylic acid 5% was more effective when applied with sodium nitrate 5% than when applied alone, and salicylic acid 50% plaster was more effective when used with povidone iodine 10% than when used alone. The authors of this review concluded that "No single intervention has been shown to be convincingly effective in the treatment of molluscum contagiosum."[41]

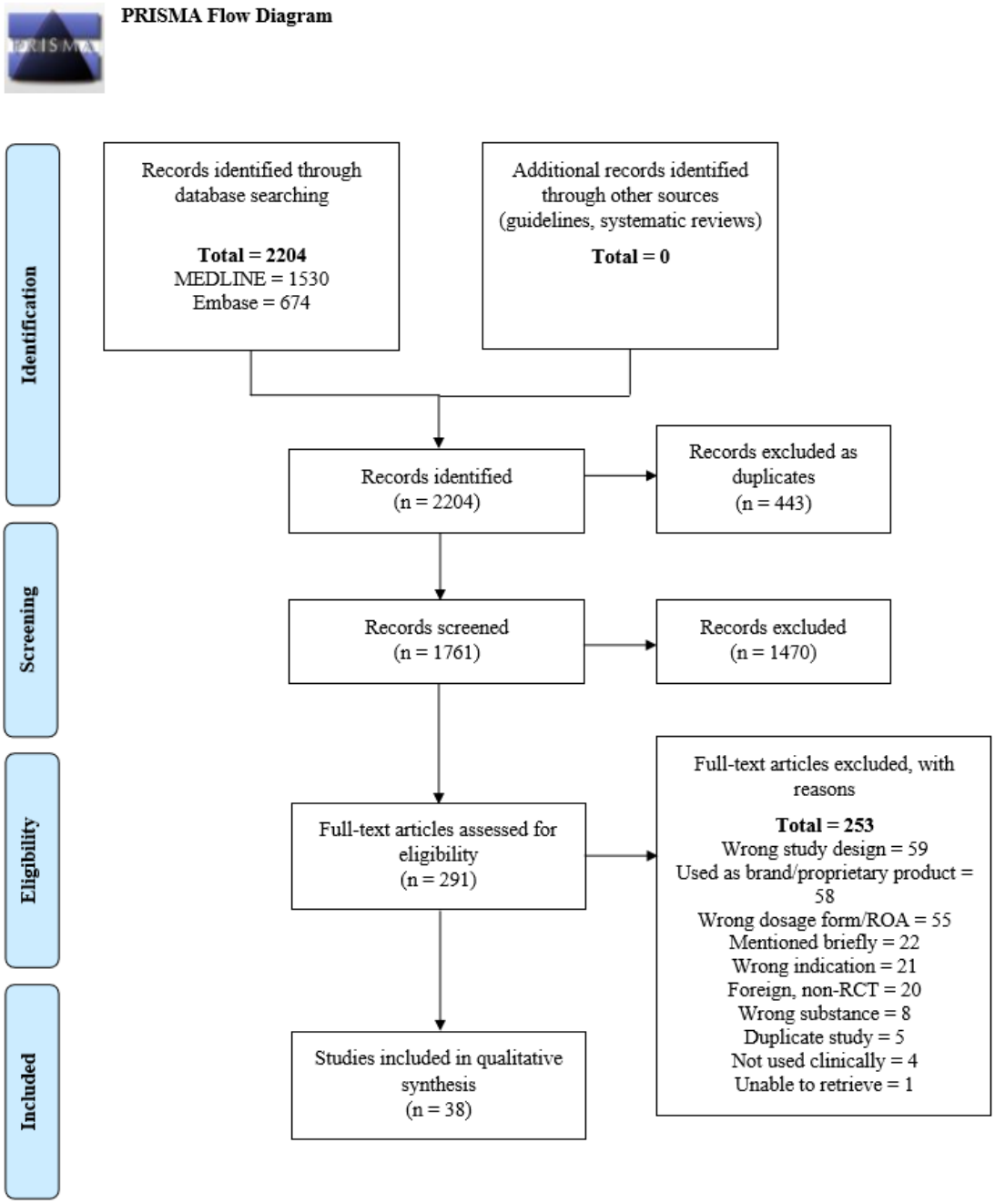
Salicylic acid is also used in the management of psoriasis. Psoriasis is a multisystem chronic immune-mediated inflammatory disease with skin manifestations.[19] Topical medications, such as vitamin D analogs, corticosteroids, tar-based products, dithranol, and salicylic acid, are first-line therapies for the cutaneous manifestations of mild to moderate psoriasis.[17,42] Salicylic acid and other keratolytics are used in the topical treatment of psoriasis to promote: softening and hydration of the stratum corneum; desquamation of hyperkeratotic skin; pruritus relief; barrier repair; and the penetration of other topical anti-psoriasis medications.[19,42,43] Salicylic acid is most beneficial in the presence of thick or scaly psoriatic plaques, where it is used to break down these thick, scaly crusts prior to the application of another topical medication.[43] In a 2013 systematic review of "classical" topical therapies for chronic plaque psoriasis, the authors noted that "The use of salicylic acid, as an adjunct treatment, is adored by some dermatologists and refuted by others."[43] These authors concluded that amongst the combinations reviewed, "the combination regimen of topical corticosteroids and salicylic acid is recommended above monotherapy with either component."[43] In a 2015 systematic review of the role of keratolytics and emollients in the treatment of psoriasis, 3 of the included studies utilized salicylic acid 6% as a monotherapy and 5 of the included studies used salicylic acid 2-5% in combination with betamethasone dipropionate or mometasone furoate.[19] The results of the included studies supported the use of salicylic acid as a monotherapy for treatment of scalp psoriasis and as an adjuvant therapy for treatment of other areas of the skin affected by psoriasis. Evidence from randomized controlled trials showed that the use of salicylic acid in combination with betamethasone propionate or mometasone furoate resulted in a more rapid onset of action and overall reduction in psoriasis, erythema, induration, and desquamation as well as a more favorable patient evaluation compared to use of the corticosteroid alone. A 2016 Cochrane review of topical treatments for scalp psoriasis found insufficient evidence to assess the efficacy and safety of salicylic acid for the management of this condition.[44]

In 2020, the AAD and National Psoriasis Foundation released their guideline on the management of psoriasis with topical therapy.[17] Salicylic acid was recommended for treatment of mild to moderate psoriasis either alone or in combination with another topical therapy for 8-16 weeks (strength of recommendation: B; level of evidence: I-II). Salicylic acid was also recommended for treatment of moderate to severe psoriasis and/or palmar-plantar psoriasis in combination with corticosteroids (strength of recommendation: B; level of evidence: I). The off-label combination of tacrolimus and salicylic acid 6% was recommended for treatment of plaque psoriasis (strength of recommendation: B; level of evidence: II). The authors of the guideline noted that the improved efficacy observed when corticosteroids are used with salicylic acid is likely due to the keratolytic action of salicylic acid and subsequent enhanced skin penetration of the corticosteroids. When used in combination with salicylic acid, only small quantities of high-potency topical corticosteroids should be administered to

reduce the risk of systemic corticosteroid absorption. Systemic absorption of salicylic acid and the risk of salicylate toxicity are concerns when treating a large body surface area (>20%) or patients with renal or hepatic disease.

In 2019, Börjesson et al described two cases in which compounded topical preparations were unsuccessful in managing diffuse plaque psoriasis.[45] In one patient, a compounded topical preparation of minoxidil, clobetasol propionate, and hydroxy-progesterone in an alcohol-based vehicle was applied daily for 16 weeks with no improvement in lesions. In another patient, a compounded topical preparation, formulated by a pharmacist from a dermatologist's prescription, of resorcinol 1 g, salicylic acid 3 g, tretinoin 30 g, and betamethasone dipropionate 90 g was used for 16 weeks. When the patients presented to the authors' clinic in France, the compounded topical preparations were discontinued and systemic therapy (methotrexate, cyclosporine) was initiated; both patients achieved complete remission with systemic therapy. The authors used these cases to demonstrate the potential ineffectiveness and harm of compounded topical preparations in the management of psoriasis. The authors noted that in the 1970s, dermatology textbooks recommended the use of compounded topical preparations with tar and salicylic acid for the treatment of severe psoriasis.[45] They observed that the use compounded topical preparations for treatment of psoriasis remained common until the end of last century, at which time the availability and use of topical steroids and vitamin D analogs for mild to moderate psoriasis and systemic therapy and phototherapy for severe psoriasis became more common and considered best practice. The authors stated that compounded topical preparations for psoriasis "are considered outdated because of the increasingly important therapeutic armamentarium."[45] Chemical stability, compatibility between ingredients, risk of bacterial contamination, and lack of evidence-based literature demonstrating efficacy are some of the problems encountered with the use of compounded topical preparations. The authors concluded that "the use of compounded topical preparations should be strictly regulated and standardized" and that physicians should be aware of the criteria for use of systemic therapy in patients with severe psoriasis.[45]

Figure 1. PRISMA flow diagram showing literature screening and selection.



Adapted from:
Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol.* 2009;62(10):1006-1012. Available from: http://www.prisma-statement.org/.

Table 3. Types of studies

Types of Studies	**Number of Studies**
Descriptive[46]	1
Experimental[47-84]	37
Observational	0

Table 4. Number of studies by country

Country	Number of Studies
Australia[81]	1
Canada[58]	1
Egypt[50,73]	2
Germany[77]	1
India[62-64,78,81]	5
Iran[69]	1
Israel[83]	1
Italy[57,70,88]	3
The Netherlands[55,56,90]	2
Pakistan[49,71]	2
Russia[73]	1
Spain[76]	1
Sweden[64]	1
Turkey[49]	1
UK[59,83,84]	3
US[46-48,52-54,58,60,65,66,68,69,74,79]	10
Multiple Countries • Austria, Germany[80] • Belgium, US[71] • Iran, Lebanon[75]	3
	Total US[a]: 11 Total Non-US Countries[a]: 29

[a]Study 71 counted in both US and non-US total

Table 5. Summary of included studies

Refer to Appendix 2

Table 6. Dosage by indication – US

Indication	Dose	Concentration	Dosage Form	Route of Administration	Duration of Treatment
Acne[52,54,58,60,68,69,74,79]	–	1-2%	–	Topical	8 weeks
		1-2%	Cleanser		6-12 weeks
		1%	Gel		6 weeks
		2%	Lotion		12 weeks
		–	Peel		12 weeks
Dandruff[66,75]	–	2%	Shampoo		28-35 days
Photodamaged facial skin[51]	–	–	Peel		4 sessions
Psoriasis[48,65,66]	–	6%	Gel		–
		2-6%	Shampoo		28-35 days
Seborrheic dermatitis[46,63]	–	2%	Shampoo		35 days

Abbreviations: "–", not mentioned.

Table 7. Dosage by indication – non-US countries

Indication	Dose	Concentration	Dosage Form	Route of Administration	Duration of Treatment
Acne[49-51,62,72,73,78,81,88,89]	–	5%	Cream	Topical	6 days - 12 weeks
		2%	Gel		8 weeks
		2-3%	Lotion		12 weeks
		20-30%	Peel		8-20 weeks
Dandruff[67,75,83]	–	2-3%	Shampoo		4 weeks
Actinic keratosis[80]	–	10%	–		12 weeks
Psoriasis[55,61,63,64,76,77,87,90]	–	2-3%	–		8 weeks; 21-33 sessions
	100 g/week	2-5%	Cream		18 weeks
	–	2-3%	Lotion		3 weeks – 18 months
		2%	Paste		2 weeks
		2%	Shampoo		8 weeks
Scalp dermatoses[56]	–	2%	Lotion		3 weeks
Seborrheic dermatitis[70,83]	–	3%	Shampoo		4 weeks
Warts[56,57,71,80,82,84,85]	–	15%	–		6 weeks - 4 months
		10-16.7%	Solution		4-12 weeks

Abbreviations: "–", not mentioned.

Table 8. Number of studies by combination

	Combination Formula	Number of Studies
	Salicylic acid 2% / Sodium sulfacetamide 8%	0
	Salicylic acid 2% / Ciclopirox 0.77% / Zinc pyrithione 1%	0
	Salicylic acid 2% / Ketoconazole 2% / Zinc pyrithione 1%	0
	Salicylic acid 3% / Ciclopirox 0.77% / Clobetasol propionate 0.05% / Tea tree oil 1%	0
	Salicylic acid 3% / Ciclopirox 0.77% / Clobetasol propionate 0.05% / Zinc pyrithione 1%	0
	Salicylic acid 4% / Clobetasol propionate 0.05% / Urea 40%	0
	Salicylic acid 5% / Sodium sulfacetamide 10%	0
	Salicylic acid 6% / Clobetasol propionate 0.05% / Coal tar solution 8%	0
	Salicylic acid 17% / Cimetidine 5% / Ibuprofen 2%	0
	Salicylic acid 30% / Lactic acid 30%	0
	Salicylic acid 30% / Cantharidin 1% / Podophyllum resin 5%	0
	Salicylic acid 30% / Imiquimod 5% / Tretinoin 0.1%	0
	Salicylic acid 40% / Cimetidine 10% / Lidocaine 5%	0
Others found in literature	Salicylic acid / Capryloyl salicylic acid / *N*-2-hydroxyethylpiperazine-*N*'-2-ethanesulfonic acid (HEPES) / Glycolic acid / Citric acid / Dioic acid[50]	1
	Salicylic acid / Gluconolactone / Verbascoside / *Ocimum gratissimum* – cream[82]	1
	Salicylic acid / Glycolic acid / Ichthyol pale / urea / Polidocanol – shampoo[72]	1
	Salicylic acid / Glycolic acid / Trimethylglycine / Zinc / Potassium alum / Allantoin – lotion[67]	1

	Salicylic acid 1 part / Lactic acid 1 par t– paint[79]	1
	Salicylic acid / Lactic acid / Phenylethyl resorcinol – chemical peel[51]	1
	Salicylic acid 1% / Glycolic acid 10% / Botanical ingredients – gel[52]	1
	Salicylic acid 2% / Alpha-hydroxy acid retinoid conjugate 0.1% / Lactic acid 10.4% – serum[57]	1
	Salicylic acid 2-3% / Anthralin 0.1-3% – in petrolatum or zinc oxide paste[53,58]	2
	Salicylic acid 2% / Betamethasone dipropionate – cream, lotion[56,60,73]	3
	Salicylic acid 2-3% / Clindamycin phosphate 1% – lotion[49,69]	2
	Salicylic acid 2% / Unspecified “antioxidants and anti-inflammatory ingredients” – lotion[55,65,66]	3
	Salicylic acid 2% / Piroctone olamine 0.75% – shampoo[64,71]	2
	Salicylic acid 2% / Sulfur 2% – shampoo[63]	1
	Salicylic acid 2% / Sulfur 2% / Hexachlorophene 1% / Kerohydric – shampoo[46]	1
	Salicylic acid 3% / Ciclopirox 1.5% – shampoo[78]	1
	Salicylic acid 3% / Clobetasol propionate 0.05% – lotion[61]	1
	Salicylic acid 3% / Kunzea oil 20% / Liquor carbonis detergens 5% – lotion, ointment[81]	1
	Salicylic acid 5% / Triamcinolone acetonide 0.1% – cream[84]	1
	Salicylic acid 10% / 5-Fluorouracil – solution[77,80]	2
	Salicylic acid 15% / Lactic acid 15% – form not specified[54,68]	2
	Salicylic acid 16.7% / Lactic acid 16.7% – solution[75]	1
	Salicylic acid 17% / Lactic acid 17% / Citric acid 8% – chemical peel[70]	1

	Salicylic acid 20% / Azelaic acid 20% – chemical peel[48]	1
	Salicylic acid 20% / Mandelic acid 10% – peel[59,74,76]	3

Table 9. Compounded products – US

No compounded products from reported studies

Table 10. Compounded products – non-US countries

No compounded products from reported studies

Results of interviews

Two hundred eighty-five SMEs were contacted for interviews; 96 agreed to be interviewed, and 189 declined or failed to respond to the interview request. One SME discussed salicylic acid. The SME was a medical doctor who was board-certified in dermatology, working as a consultant, formerly in an academic medical center. The SME had been in practice for 40 years.

The SME noted that salicylic acid is used topically at high concentrations for wart removal because it softens the nail plate. The SME felt that high concentration (40-60%) products should be reserved for office-applied procedures and only used once or for a limited time. Podiatrists and dermatologists may want to have higher concentrations of salicylic acid available to treat patients with severe onychomycosis or other conditions. There is a 40% salicylic acid plaster available under the name Mediplast®, and since it is a plaster, can be cut based on how much is needed delivering the medication where they want it without having to worry about patients applying it to the wrong area or diverting the medicine. For plantar warts, the SME debrides the wart as best they can, then applies the salicylic acid plaster and sees the patient again in a week. Once the wart gets very soft, they debride it again, reapply the plaster, and repeat until the wart is completely removed. The SME said, "you can't get [the higher concentrations] unless you make them." The only other keratolytic with similar potency as salicylic acid at high concentrations is urea, which is also used to treat warts.

Currently there are various OTC salicylic acid products available in lower concentrations (2-5%), which are usually used for acne, rosacea, psoriasis, or seborrheic dermatitis. These lower concentration products are safe for patients to apply at home. The SME said, "Neutrogena's got like 12 different anti-acne products."

Salicylic acid was nominated for use in combination with several APIs. The SME explained that lidocaine is used to lessen pain; ciclopirox and ketoconazole are used for fungal infections; coal tar and zinc pyrithione are used for dandruff, seborrheic dermatitis, and psoriasis; and sodium sulfacetamide and tretinoin are for treatment of acne. Tretinoin also has keratolytic properties, as does cimetidine, imiquimod, lactic acid, and urea, so these can also be used to soften warts. Cantharidin, podophyllum, and tea tree oil are also used for warts. Lactic acid can be used for ichthyosis vulgaris (fish-like scales on the anterior shins) which is common, particularly in Irish Celtic populations in winter. Tea tree oil is also used for rosacea, dandruff, and inflammatory conditions such as atopic dermatitis and psoriasis. The SME said there is older literature about the oral use of cimetidine to treat warts, but not topical use. The SME was unsure why ibuprofen would be needed with salicylic acid.

The SME stated that patients can find some of these combinations with salicylic acid in OTC products, but there is value in being able to tweak them to desired specifications, such as wanting a gel instead of a cream or excluding ingredients or preservatives that a patient cannot tolerate. Compounded products containing salicylic acid in higher concentrations are for in-office use by clinicians, while products containing salicylic acid in lower concentrations are available OTC.

Results of survey

Twelve people responded to the survey distributed via professional medical associations and available on the project website; refer to Table 11 for respondent characteristics.

Among respondents, 12 (100%) used salicylic acid. Respondents used salicylic acid for acne (9, 22% of 41 responses, where respondents were allowed to select multiple indications), warts (7, 17%), keratosis (6, 15%), psoriasis (5, 12%), seborrheic dermatitis (5, 12%), dandruff (3, 7%), eczema (3, 7%), and fungal infections (2, 4.88%) (refer to Table 12). One respondent (2%) reported using salicylic acid in a "Modified Jessner's Solution. 2.5 or 5% combination of Lactic Acid, Resorcinol, and Salicylic Acid. Used for comedonal acne and keratosis pilaris".

The 12 respondents who reported using salicylic acid utilized the substance as an FDA-approved product (25% of 24 responses, where respondents were allowed to select multiple options), compounded drug product (46%) and OTC drug product (29%). The 12 respondents used compounded salicylic acid due to lack of commercial products in an appropriate dosage form, strength or combination (42% of 19 responses, where respondents were allowed to select multiple reasons), patient allergies (16%), other patient conditions preventing use of commercial products (26%), or no commercially available products with salicylic acid (16%). Explanations for using compounded salicylic acid due to lack of commercial products in an appropriate dosage form, strength or combination included: "Jessner's Solution is 14% strength…way too strong;" "Compounded with FU topical for warts;" and "To boost a keratolytic effect." Explanations for using compounded salicylic acid due to patient conditions preventing use of commercial products included: "Thick plaque Psoriasis can respond well to the addition of 3-5% Sa. Ac and 5-8% LCD (tar) to a class 1 topical steroid ointment like Clobetasol" and "Sensitive to inactive contained in the commercially available [products]."

The majority of respondents (7, 64%) did not stock non-patient-specific compounded salicylic acid at their practice. The 4 respondents who did stock non-patient-specific salicylic acid purchased, or had the patient purchase, the product from an outsourcing facility (100%). Refer to Table 14 for how respondents obtained compounded salicylic acid.

Table 11. Characteristics of survey respondents

Terminal Clinical Degree	Responses, n (N=12)
Doctor of Medicine (MD)	9
Doctor of Osteopathic Medicine (DO)	2
Doctor of Medicine in Dentistry (DMD/DDS)	0
Doctor of Pharmacy (PharmD) or Bachelor of Science in Pharmacy (BS Pharm)	0
Naturopathic Doctor (ND)	0
Nurse Practitioner (NP)	1
Physician Assistant (PA)	0
No Response	0
Practice Setting	**Responses, n (N=12)**
Physician office or private practice	12
Outpatient clinic	0
Hospital or health system	0
Academic medical center	0
Emergency room	0
Operating room	0
No response	0

Table 12. Conditions for which salicylic acid was prescribed or administered

Condition	Responses, n (N=41)[a,b]
Acne	9
Dandruff	3
Eczema	3
Fungal infections	2
Keratosis	6
Psoriasis	5
Seborrheic dermatitis	5
Warts	7
Other[c]	1
No Response	0

[a]Out of 12 respondents, 12 reported prescribing or using salicylic acid.
[b]Survey respondents allowed to select multiple conditions.
[c]"Modified Jessner's Solution. 2.5 or 5% combination of Lactic Acid, Resorcinol, and Salicylic Acid. Used for comedonal acne and keratosis pilaris".

Table 13. Reasons for using compounded salicylic acid

Reason	Responses, n (N=19)[a,b]
Commercial product not available in desired dosage form, strength or combination	8
Patient allergies prevent use of commercial products	3
Patient conditions prevent use of commercial products	5
No commercial products	3

[a]Out of 12 respondents, 12 reported prescribing or using salicylic acid.
[b]Survey respondents allowed to select multiple reasons.

Table 14. Use of non-patient-specific compounded salicylic acid

Do you stock non-patient-specific compounded salicylic acid at your practice?	**Responses, n (N=12)**
Yes	4
No	7
No response	1
How do you obtain your stock of non-patient-specific compounded salicylic acid?	
Compound yourself at practice	0
Product compounded by in-house pharmacy	0
Purchase from compounding pharmacy	0
Purchase from outsourcing facility	4
No response	8

CONCLUSION

Salicylic acid was nominated for inclusion on the 503B Bulks List as a topical cream, gel, lotion, body wash, shampoo, and solution for use in combination with other APIs to treat various skin conditions. Salicylic acid is available in the nominated dosage form and ROA in Abu Dhabi, Australia, Canada, Ireland, Saudi Arabia, and UK.

From the literature review and interviews conducted, salicylic acid is a keratolytic agent used in a variety of topical forms and combinations for management of acne, warts, actinic keratosis, photodamaged facial skin, psoriasis, and seborrheic dermatoses. The SME stated that lower concentrations can be applied at home, but high concentration products should be reserved for office use and should only be used for a limited time.

From the survey responses, 12 out of 12 respondents used salicylic acid. The most common indication respondents used compounded salicylic acid for was acne. Lack of commercial products in an appropriate dosage form, strength or combination and patient conditions preventing use of commercial salicylic acid were some of the reasons for using the compounded salicylic acid product over an FDA-approved product. Four respondents reported stocking compounded salicylic acid at their practice.

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APPENDICES

Appendix 1. Search strategies for bibliographic databases

MEDLINE search strategy

- Platform: Ovid
- Years searched: Ovid MEDLINE and epub ahead of print, in-process and other non-indexed citations and daily 1946 to December 3, 2019
- Date last searched: December 4, 2019
- Limits: Humans (search hedge); English language; Publication type (search hedge)
- Number of results: 674

1	salicylic acid/	6337
2	salicylates/	12947
3	salicylic acid$.tw.	12034
4	carboxyphenol.tw.	6
5	hydroxybenzoic acid$.tw.	2503
6	or/1-5	26476
7	administration, topical/	37746
8	administration, cutaneous/	21496
9	topical$.tw.	101315
10	cutaneous$.tw.	146736
11	emulsions/	17359
12	gels/	28349
13	liniments/	122
14	ointments/	12683
15	skin cream/	913
16	emulsion?.tw.	31388
17	peel?.tw.	7622
18	liniment?.tw.	141
19	ointment?.tw.	11563
20	salve?.tw.	336

21	paste?.tw.	11878
22	unguent?.tw.	47
23	lotion?.tw.	2225
24	cream?.tw.	18251
25	cleanser?.tw.	1006
26	body wash$.tw.	245
27	shampoo$.tw.	1462
28	face wash$.tw.	188
29	facial wash$.tw.	10
30	or/7-29	370406
31	drug therapy/	30247
32	drug therapy.fs.	2161115
33	tu.fs.	2173179
34	therap$.tw.	2655948
35	treat$.tw.	5268909
36	or/31-35	7616253
37	and/6,30,36	1182
38	exp animals/ not humans/	4648305
39	37 not 38	1066
40	limit 39 to english language	828
41	(review or systematic review or meta analysis).pt.	2648619
42	40 not 41	674

Embase search strategy

- Platform: Elsevier
- Years searched: 1947 to present
- Date last searched: December 4, 2019
- Limits: Humans (search hedge); English language; Publication type: article, article in press, conference abstract, conference paper, data papers, erratum, letter, note
- Number of results: 1530

1	salicylic acid'/de	25612
2	salicylic acid*':ti,ab,tn	14563
3	carboxyphenol':ti,ab,tn	7
4	hydroxybenzoic acid*':ti,ab,tn	3161
5	#1 OR #2 OR #3 OR #4	34004
6	topical drug administration'/de	81095
7	cutaneous drug administration'/de	582
8	topical*':ti,ab	144253
9	cutaneous*':ti,ab	211053
10	cream'/de	9000
11	gel'/de	32461
12	liniment'/de	247
13	lotion'/de	2768
14	ointment'/exp	18217
15	paste'/de	2462
16	pomade'/de	79
17	shampoo'/de	2235
18	emulsion'/exp	42610
19	emulsion$':ti,ab	42753
20	liniment$':ti,ab	230
21	ointment$':ti,ab	21100
22	salve$':ti,ab	468

23	paste$':ti,ab	14327
24	unguent$':ti,ab	92
25	lotion$':ti,ab	3895
26	cream$':ti,ab	28635
27	peel$':ti,ab	10054
28	cleanser$':ti,ab	1491
29	body wash*':ti,ab	368
30	shampoo*':ti,ab	2294
31	face wash*':ti,ab	252
32	facial wash*':ti,ab	19
33	#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32	537700
34	drug therapy'/de	694126
35	anti-infective therapy'/exp	218345
36	antimicrobial therapy'/exp	216101
37	antifungal therapy'/de	3688
38	drug therapy':lnk	3798078
39	therap*':ti,ab	4004917
40	treat*':ti,ab	7645279
41	#34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40	11216737
42	#5 AND #33 AND #41	3142
43	[animals]/lim NOT [humans]/lim	5959620
44	#42 NOT #43	2996
45	#42 NOT #43 AND [english]/lim	2356
46	#42 NOT #43 AND [english]/lim AND ([article]/lim OR [article in press]/lim OR [conference abstract]/lim OR [conference paper]/lim OR [data papers]/lim OR [erratum]/lim OR [letter]/lim OR [note]/lim)	1530

Appendix 2. Summary of included studies

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Indication 1: Acne					
Abbasi et al, 2010, Pakistan[47]	Random study	60 Patients with acne (50%, 20-28 y)	Study used 6 unique multi-ingredient anti-acne creams Non-inflammatory acne • Sample 3 (8) • Sample 4 (7) Inflammatory acne (papules, pustules) • Sample 1 (9) • Sample 5: product with salicylic acid (6) Inflammatory acne (nodules, cysts) • Sample 2 (15) • Sample 6 (15)	Number of comedones	"This study depicted that these prepared new formulations are very good therapeutic compositions for acne. Especially, the sample 1 and 2 exhibited much higher potential with negligible side effects so they seem most suitable to be used commercially."
Abdel Hay et al, 2019, Egypt[48]	Single-blinded RCT	34 Patients with mild to moderate acne (9%, 18-35 y)	• Salicylic acid 20% + azelaic acid 20% peel (SA+AA) (34) • Trichloroacetic acid peel 25% (TCA) (34)	Physician-reported clinical improvement by counting the number of comedones	"Chemical peeling is effective in controlling mild–moderate acne…Combined SA+AA are recommended at early stage of treatment if patients have more inflammatory lesions, while TCA is recommended if patients have more non-inflammatory lesions."
Babayeva et al, 2011, Turkey[49]	Single-blind, randomized, 1: 1 parallel group and comparative investigation	46 Patients with mild-moderate facial acne vulgaris (21.7%, 18-31 y)	• Salicylic acid + clindamycin phosphate (SA+CDP) (23) • Tretinoin and clindamycin phosphate (all-TRA+CDP) (23)	Total lesion, inflammatory lesion and noninflammatory lesion counts	"Combination of SA+CDP and all-TRA+CDP was effective in decreasing lesion counts and well tolerated with minimal local cutaneous reactions in patients with mild to moderate acne vulgaris."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Baumann *et al*, 2013, US[50]	Single blind split face study	28 Patients with mild to moderate acne vulgaris (sex not mentioned, 18-40 y)	• Treatment A: Salicylic acid + capryloyl salicylic acid + HEPES + glycolic acid + citric acid + dioic acid (28) • Treatment B: Benzoyl peroxide 5% + clindamycin 1% (28)	Lesion counts and questionnaires	"Statistically significant improvement across all categories for treatment A and treatment B. There was also no significant difference between the products, leading to the conclusion that treatment A is as effective as treatment B across all categories. It should be noted that treatment A showed a higher incidence of stinging during the week 1 evaluation."
Bhatia *et al*, 2014, US[52]	Single center open label clinical study	25 Patients volunteers (sex, age not mentioned)	• Salicylic acid 1% + glycolic acid 10% + botanicals (25)	Acne grade	"Results of the present study suggest that the tested skin care regimen offers rapid acne clearance and excellent tolerability that together may help to improve patient adherence as well as treatment outcome."
Colvan *et al*, 2015, US[55]	Open-label, single-center pilot study	8 Patients with moderate facial acne and Fitzpatrick Skin Types II-IV (sex not mentioned, 23-37 y)	• Salicylic acid, lactic acid, resorcinol, retinol (8)	Investigator's global assessment of acne severity (IGA), acne lesion counts, post-inflammatory hyperpigmentation or erythema and tolerability assessments	"This pilot study suggests that the combination of new acne lotion with a series of chemical peels may provide a well-tolerated solution for adult patients seeking an effective treatment for moderate facial acne as well as post inflammatory hyperpigmentation and/or erythema."
Draelos *et al*, 2016, US[57]	Open label study	27 Patients with mild-moderate acne (0%, 20-58 y)	• Salicylic acid 2%, alpha-hydroxy acid retinoid conjugate (AHA-RC) 0.1%, lactic acid 10.4% (27)	Comprehensive lesion count: total inflammatory and noninflammatory lesions, stinging	"The topical combination of lactic acid, SA, and AHA-RC produced acne improvement after 4 weeks with continuing cumulative improvement at 8 weeks."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Garg et al, 2009, India[59]	Randomized comparative study	44 Patients with Fitzpatrick skin types IV to VI with acne vulgaris, post-acne scarring, and hyperpigmentation (25%, 16-27 y)	• Glycolic acid 35% peel (GA) (22) • Salicylic 20% + mandelic acid 10% combination peel (SMPs) (22)	Clinical features of facial acne, scarring, and hyperpigmentation	"Both the agents were effective and safe in Indian patients, with SMPs being better for active acne and post-acne hyperpigmentation."
Makino *et al*, 2015, US[65]	Randomized, investigator-blind comparator study	73 Patients with moderate facial acne (sex not mentioned, 16-45 y)	• R1: Salicylic acid (SA) 2%, retinol 0.5%* • R2: SA 2%* • R3: adapalene 0.1% + benzoyl peroxide 2.5% gel* *Number of patients in each group not provided	Investigator's global assessment of acne severity (IGA), acne lesion counts, global post inflammatory hyperpigmentation/erythema, tolerability assessments, target inflammatory lesion (TIL)	"All 3 regimens provided significant reductions in mean scores for IGA, acne counts (noninflammatory and inflammatory lesions) and global PIH/PIE [acne lesion counts, global post inflammatory hyperpigmentation/erythema] at weeks 4, 8, and 12. There were no significant differences in efficacy between the 3 regimens. Notably, R1 was the only regimen that provided early significant reductions in the erythema and size of TIL at 24 and 48 hours…All three regimens were well-tolerated. Results suggest that this SA/retinol-based regimen may provide a rapid reduction in erythema and size of TIL."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Makino *et al*, 2014, US[69]	Open-label, single-center clinical study	23 Patients with mild-moderate facial acne and Fitzpatrick skin types I-V (0%, 25 years and older)	• Salicylic acid (2%) + 4-ethoxybenzaldehyde + antioxidant and anti-inflammatory ingredients (23)	Target inflammatory lesion (TIL), target post inflammatory lesion (TPIL), investigator's global assessment of acne severity (IGA), acne lesion counts	"Significant reductions in mean scores for IGA and inflammatory lesion counts were observed at 48 h and weeks 4, 8 and 12. Significant reductions in the TIL and TPIL occurred at all visits. The acne lotion was very well-tolerated with mean tolerability scores remaining below mild. The study suggests that our new acne lotion may provide a comprehensive solution for patients seeking an effective, nondrying treatment for mild to moderate acne as well as post inflammatory lesions."
Nilfroushzadeh et al, 2009, Iran[69]	Single-blinded clinical trial	42 Patients with mild-moderate acne vulgaris (0%, 15-25 y)	• Group A: Clindamycin 1% (C lotion) (14) • Group B: Clindamycin 1% + Tretinoin 0.025% (CT lotion) (14) • Group C: Clindamycin 1% + Salicylic acid 2% (CS lotion) (14)	Total lesion counting, acne severity index, closed comedones number, open comedones number, papule numbers, pustules number, side effects	"Our data suggested that the efficacy of CS lotion was significantly more than C lotion with respect to the TLC [total lesion counting] and ASI [acne severity index], although there was no significant difference between CS and CT lotion."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Nofal et al, 2018, Egypt[70]	Randomized controlled trial	45 Patients with mild-moderate acne with no treatment 2 months before the study • Group A (6.7%, Mean 19.6 y, SD 3.48) • Group B (13.3%, Mean 17.8 y, SD 1.78) • Group C (6.7%, Mean 18.7 y, SD 2.79)	• Group A: Right side of face given modified Jessner's solution (MJ) followed by trichloroacetic acid (TCA) 20%; left side given TCA 30% alone (15) • Group B: Right side given salicylic acid 20% + mandelic acid 10% (SM); left side given salicylic acid 30% alone (15) • Group C: Right side given MJ followed by TCA 20%; left side given SM (15)	Michalson acne score, quartile grading scale, and patient satisfaction	"In conclusion, combination peels achieved a higher and earlier therapeutic response with a reasonable cost that is maintained for a relatively long periods than single peel. Combination sequential peels gave the best results."
Sarkar et al, 2019, India[74]	Randomized controlled trial	45 Patients with active acne (Grade 1 and 2) and post acne pigmentation (33%, 16-38 y)	• Group A: Glycolic acid 35% (15) • Group B: Salicylic acid 20% + mandelic acid 10% (15) • Group C: Phytic acid (15)	Percent reduction in acne score, percentage of post acne hyperpigmentation index and reduction in inflammatory and noninflammatory lesion count	"All three chemical peels are effective in the treatment of mild to moderate acne in Asian population. No significant adverse effects were noted."
Sidiq et al, 2019, India[76]	Prospective, comparative study	50 Patients with mild-moderate acne vulgaris Grade 1 or Grade 2 • Group A: 35%, mean 20.4 y Group B: 33%, mean 20.5y	• Group A: salicylic acid 30% (25) • Group B: salicylic acid 20% + mandelic acid 10% (25)	Clinical improvement & physician's global assessment scale	"This study infers that reduction in active acne lesions was much more with 30% salicylic acid peel, whereas post acne melanosis reduced much with the combination peel (SMP). We conclude that both salicylic acid (SA) and salicylic + mandelic acid peel are efficient, well tolerated and reasonably safe procedure that can be used as treatment modality in acne vulgaris."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Sidiq et al, 2019, India[76]	Prospective, comparative study	50 Patients with mild-moderate acne vulgaris Grade 1 or Grade 2 • Group A: 35%, mean 20.4 y • Group B: 33%, mean 20.5y	• Group A: salicylic acid 30% (25) • Group B: salicylic acid 20% + mandelic acid 10% (25)	Clinical improvement & physician's global assessment scale	"This study infers that reduction in active acne lesions was much more with 30% salicylic acid peel, whereas post acne melanosis reduced much with the combination peel (SMP). We conclude that both salicylic acid (SA) and salicylic + mandelic acid peel are efficient, well tolerated and reasonably safe procedure that can be used as treatment modality in acne vulgaris."
Tolino et al, 2018, Italy[82]	Single center, randomized, double-blind comparative clinical trial	240 Patients with mild to moderate acne (50%, 12-35 y) • Group A and B: Females • Group C and D: Males	• Group A: Topical + oral (60) • Group B: Topical + placebo (60) • Group C: Topical + oral (60) • Group D: Topical + placebo (60):	Improvement in Global Acne Grading System score	"Successful treatment of acne implicates that the therapy should be personalized to patients features. Our study demonstrated that the new compound can be considered a possible valid option in the treatment of mild and moderate acne and a tool to diversify the treatment in men and women in order to improve compliance and therapeutic adherence."
Touitou, 2008, Israel[83]	Randomized, double-blind, parallel-group, placebo-controlled clinical trial	40 Patients with mild to moderate acne vulgaris (sex not mentioned, 18-41 y)	• Clindamycin phosphate + salicylic acid (CLSA) (21) • Placebo (19)	Partial and complete resolution of comedones, pustules and total number of lesions	"The treatment efficiency accompanied by a very good tolerability by the patients shows that the CLSA combination could be beneficial in treatment of acne vulgaris."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Indication 2: Dandruff					
Leyden *et al*, 1987, US[63]	Randomized, double-blind study	48 Patients with moderate to severe dandruff (60%, 18-49y)	• Sulfur 2% + salicylic acid 2% (12) • Sulfur 2% (12) • Salicylic acid 2% (12) • Shampoo vehicle (12)	Corneocyte counts, changes in clinical grading scale	"Significantly greater and earlier reductions in both degree of scaling and corneocyte counts were seen in subjects treated with the formula containing both sulfur 2% and salicylic acid 2% in the shampoo base than in those who received either active ingredient alone or the shampoo vehicle"
Loden et al, 2000, Sweden[64]	Randomized, double blind study	19 Patients with dandruff on both side of head (57.9%, mean 26 y)	• Piroctone olamine 0.75% + salicylic acid 2% (19) • Zinc pyrithione 1% (19) • *Patients acted as their own controls	Severity score of dandruff	"Both shampoos were highly effective in reducing the dandruff. The combination of piroctone olamine and salicylic acid appeared to be slightly more effective than zinc pyrithione in reducing the severity and area affected by the scaling."
Pierard *et al*, 2000, Belgium, US[71]	Randomized, double-blind clinical study	60 Men with a diagnosed moderate or marked dandruff condition (21-44 y)	• Tar shampoo (30) • Non-tar shampoo: Salicylic acid 2% + piroctone olamine 0.75% + elubiol 0.5% (30)	Severity of dandruff (clinical scoring), scaliness of scalp and Malassezia spp. count	"It is concluded that a formulation associating salicylic acid, piroctone olamine and elubiol exhibited increased beneficial effects compared to the coal tar shampoo."
Squire et al, 2002, UK[78]	Single-blind, single-center, parallel group clinical trial	161 Healthy subjects with mild, moderate or severe dandruff and/or seborrheic dermatitis (34%, 12-70 y)	• Ciclopirox olamine 1.5% + salicylic acid 3% (CPO/SA) (105) • Ketoconazole 2% (56)	Mean change in the clinical assessment of the dandruff score in each scalp quadrant	"The study demonstrated that both CPO/SA and Nizoral® were safe and effective in the treatment of dandruff and seborrheic dermatitis."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Indication 3: Actinic keratosis					
Stockfleth et al, 2011, Austria, Germany[80]	Randomized, placebo-controlled, double-blind, three-armed, parallel-group, multi-center trial	470 Patients with 4-10 actinic keratosis (AK) lesions in the face/forehead or bald scalp (sex and age not mentioned)	• 5-fluorouracil 0.5% + salicylic acid 10% (5-FU/SA) • Vehicle of 5-FU/SA • Diclofenac 3% + hyaluronic acid	Sustained clinical clearance of actinic keratoses lesions	"Low dose 5-fluorouracil combined with 10% salicylic acid once daily was a highly effective lesion directed treatment of mild to moderate hyperkeratotic AK..."
Simon et al, 2015, Germany[77]	Exploratory, open, randomized, prospective study	66 With moderate-severe hyperkeratotic actinic keratosis (AK) (88%, 18-85 y)	• Topical 0.5% 5-fluorouracil + 10% salicylic acid (5-FU/SA) (33) • Cryotherapy (33)	Lesion clearance and recurrence	Topical once-daily 6-week treatment of grade II/III hyperkeratotic AK with 0.5% 5-FU/SA was associated with greater histological clearance than cryosurgery and a lower incidence of lesion recurrence.
Indication 4: Photodamaged facial skin					
Berson *et al*, 2016, US[51]	Single center clinical study	37 Female patients with mild to moderate photodamaged skin (0%, 35-55 y)	Salicylic acid + lactic acid + phenylethyl resorcinol peel (Jessner's peel) (37)	Expert clinical grading of facial skin attributes using a 10-point scale	"Statistically significant improvements were observed in fine lines and wrinkles, firmness, elasticity, skin radiance, skin tone evenness and clarity, skin roughness, appearance of dark/sunspots, hyperpigmentation, PIH, pore appearance, neck crepiness and the overall skin appearance at all time points."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Indication 5: Psoriasis					
Boer et al, 1986, the Netherlands[53]	Single center open label bilateral comparison	15 Patients with chronic plaque-type psoriasis (47%, 16-68 y, mean 41.7 y)	Group 1 (5) • Salicylic acid 2% + anthralin 0.3% • Salicylic acid 2% Group 2 (5) • Salicylic acid 2% + anthralin, strength increasing from 0.3% to 1% to 3% • Salicylic acid 2% Group 3 (5): same as Group 2 but failed UVB light treatment	Scaling and induration grading	"In summary, our results show that the addition of short-contact anthralin to ultraviolet B phototherapy in outpatients yielded only moderate improvement in a minority of patients with psoriasis."
Dutz et al, 1998, Canada[58]	Open, controlled, bilateral half-body comparison study	18 Patients with symmetric plaque-type psoriasis (sex not mentioned, 16-72 y, mean age 40)	All patients received coal tar oil 50% + salicylic acid 5% in hydrophilic petrolatum + UVB on both sides of the body. On one side of the body: Calcipotriol 0.05mcg/ml On the other side of the body: • Day 1,2: Anthralin 0.1% + salicylic acid 3% in zinc oxide paste • Day 3-5: Anthralin 0.2% + salicylic acid 3% in zinc oxide paste • Day 8-10: anthralin 1% + salicylic acid 3% in hydrophilic petrolatum • Day 11: anthralin 2% + salicylic acid 3% in hydrophilic petrolatum	Psoriasis Activity and Severity Index (PASI) score	"Based on our experience, we believe calcipotriol to be a safe and effective adjunct to intensive UVB light treatment in a day care treatment setting. Overall, patients preferred calcipotriol to anthralin when used in combination with UVB and tars, although the objective efficacy was similar."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Kar et al, 1999, India[63]	Randomized	120 Patients with moderate to severe scalp psoriasis (more than 20% of body surface area) (82%, 21-50 y)	All patients received photochemotherapy with psoralen using natural sunlight (PUVASOL) • Group I: No topical medication except coconut oil (60) • Group II: Betamethasone dipropionate 0.05% + salicylic acid 2% lotion (60)	Erythema, induration, scale, and pruritus	"Combined therapy with PUVASOL and topical betamethasone dipropionate 0.05% with salicylic acid 2% application appears to be safe and an effective treatment for scalp psoriasis."
Karamata et al, 2017, India[61]	Prospective, observational study	126 Patients with newly diagnosed moderate severity psoriasis. • Group A: 65%, 41.01 ± 1.87 y • Group B: 67%, 41.31 ± 1.76 y • Group C: 70%, 40.93 ± 1.47 y	• Group A: Clobetasol propionate (0.05%) + salicylic acid (3%) lotion for scalp and betamethasone valerate (0.05%) cream for body • Group B: Tablet methotrexate along with topical treatment that group A received • Group C: Capsule cyclosporine (100 mg 2 times a day) along with topical treatment that group A received	Psoriasis Area Severity Index	"Combination therapy (topical + systemic) is more efficacious than topical therapy alone. Patients treated with combined topical and systemic therapy (methotrexate and cyclosporine) demonstrate a better improvement in quality of life as compared to those receiving topical therapy alone. Methotrexate and cyclosporine are equally efficacious in treating and improving quality of life in patients of psoriasis."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Regana et al, 2009, Spain[76]	Open, randomized, comparative study	37 Patients with scalp psoriasis (sex and age not mentioned)	• Shampoo A: Urea, salicylic acid, glycolic acid, ichthyol pale, and polidocanol (27) • Shampoo B: Coal tar (10)	Symptoms were evaluated (erythema, desquamation, infiltration, pruritus, and stinging sensation) using visual analogue scales; overall efficacy, tolerability, and cosmetic properties of the products were scored on 4-point scales	Shampoo A for scalp psoriasis was more effective in controlling pruritus and stinging sensation than the coal tar shampoo, and its cosmetic properties were also significantly better.
Rudych et al, 2010, Russia[73]	Randomized controlled trial	55 Patients with psoriasis (sex not mentioned, 19-55 y)	• 5% salicylic acid ointment (15) • 2% salicylic acid betamethasone (15) • Psoriane: 2% salicylic acid, glycolic and citric hydroxyacids (25)	Reduction of PASI score	The creme containing 2% salicylic acid and betamethasone and the Psoriane shampoo were the most efficacious in the treatment of scalp psoriasis.
Thomas et al, 2015, Australia[81]	Randomized, comparative, active-controlled, double-blind trial	30 Patients with mild to moderate psoriasis affecting at least 10% of one or more body regions (40%, 25-74 y)	• Test formulation: 3% salicylic acid + liquid carbonis detergens + cod liver oil + vanillin + 20% kunzea oil (15) • Control formulation: same as test formulation, but without kunzea oil (15)	Reduction in PASI score; degree of pruritus on a visual analogue scale	Both trialed medications containing the 3% salicylic agent showed significant improvement in psoriasis signs (redness, thickness and scaliness) as evident by the 51% decrease in the PASI score, but the control group also demonstrated a significant 60% decrease in the PASI score.

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Van der Rhee et al, 1980, the Netherlands[84]	Multicenter, double-blind trial	87 Ambulatory outpatients with psoriasis vulgaris involving at least 15% of the skin surface, who had been unsuccessfully treated with 1+ generally accepted therapies for psoriasis • Regimen 1: 62%, 43.7 y • Regimen 2: 52%, 44.7 y • Regimen 3: 52%, 43.7 y	• Regimen 1: Oral aromatic retinoid + topical placebo cream (29) • Regimen 2: Oral aromatic retinoid + topical 0.1% triamcinolone acetonide and 5% salicylic acid cream (29) • Regimen 3: Oral placebo + topical 0.1% triamcinolone acetonide and 5% salicylic acid cream (29)	Intensity score of the lesions of 6 body areas: scalp, arms, hands, trunk, legs, and feet; desquamation score from 0 (no desquamation) to 8 (very marked desquamation); scale for erythema and infiltration from 0 (no erythema) to 8 (very marked infiltration)	"Regimen I had virtually no effect and regimen 2 gave better results than regimen 3 for almost all parameters, although statistical significance was reached for only some of them. Combination of the aromatic retinoid given in low dosage orally with corticosteroids topically is as effective as therapy with the retinoid in high dosage alone, but with markedly less side-effects. "
Indication 6: Scalp dermatoses					
Curley et al, 1990, UK[56]	Double-blind randomized study	56 Patients with moderate to severe dermatoses (39%, 14-81 y)	• Betamethasone dipropionate 0.5% + salicylic acid 2% (28) • Betamethasone valerate 1% (28)	Symptoms graded on 5-point scale	"There was a trend towards the symptoms of psoriasis patients improving more quickly on betamethasone dipropionate than on betamethasone valerate, with a statistically significant difference between treatments. For the symptom of excoriation, the betamethasone dipropionate patients tended to respond better, whereas betamethasone valerate relieved inflammation more swiftly. The salicylic acid in the former could be expected to relieve scaling and excoriation more effectively while the higher concentration of betamethasone in the valerate preparation could be expected to have more anti-inflammatory effect.

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Indication 7: Seborrheic dermatitis					
Leyden *et al*, 1987, US[63]	Randomized, double-blind study	48 Patients, moderate to severe dandruff, rating scale between 4 and 7 (60%, 18-49 y)	• Sulfur 2% + salicylic acid 2% shampoo (12) • Sulfur 2% shampoo (12) • Salicylic acid 2% shampoo (12) • Shampoo vehicle (12)	Corneocyte counts, changes in clinical grading scale	Combination and salicylic acid alone showed significant improvement.
Morganti et al, 2014, Italy[67]	Double-blind placebo	60 Patients with scalp seborrheic dermatitis (sex, age not mentioned)	• Salicylic acid 2% lotion with glycolic acid, zinc, trimethylglycine, potassium alum, allantoin	Control of dandruff scales and reduction of surface lipids and free fatty acids/triglycerides ratio	Salicylic acid water solution seems to be an innovative and effective option for scalp seborrheic dermatitis.
Perlstein *et al*, 1960, US[46]	Cases	214 Patients with seborrheic dermatitis (35%, 14-65 y)	• 2% sulfur + 2% salicylic acid + 1% hexachlorophene + kerohydric + anionic surface cleansers and wetting agents (214)	Improvement in seborrheic dermatitis	"Of 208 successive cases of seborrheic dermatitis, 96% were successfully treated with the new anti-seborrheic shampoo. No cases of primary irritancy or acute contact dermatitis observed."
Squire et al, 2002, UK[78]	Single-blind, single-center, parallel group clinical trial	161 Subjects with mild, moderate, or severe dandruff and/or seborrheic dermatitis (34%, 12-70 y)	• 1.5% ciclopirox olamine + 3% salicylic acid shampoo (105) • Nizoral (2% ketoconazole) (56)	Mean change in the clinical assessment of the dandruff score in each scalp quadrant	"This study demonstrated that ciclopirox olamine 1.5% + salicylic acid 3% shampoo was effective in the treatment of dandruff and seborrheic dermatitis and that its effect was sustained beyond the end of a 4-week treatment period. Of particular note, was its rapid effectiveness at reducing the itching of seborrheic dermatitis. The shampoo was well tolerated and well accepted by the study subjects. It was shown to be comparable with Nizoral®."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Indication 8: Warts					
Cassano et al, 2011, Italy[54]	Open label study	172 Patients with cutaneous viral warts (52%, 14-77y)	• Conventional standard therapy (CST*) alone (83) • CST + nutraceutical** (89) *CST consisted of liquid nitrogen cryotherapy, or topical salicylic acid 15% + lactic acid 15% **Nutraceutical consisted of methionine, inulin, *Echinacea angustifolia*, *Echinacea purpurea*, probiotics, taurine, vitamin C, coenzyme Q10, vitamin B3, zinc gluconate, vitamin A.	Total wart count, response rate, number of new warts	"Our pilot experience seems to suggest that nutraceutical is safe and beneficial in patients with cutaneous warts, and capable of enhancing the response to CST. Double-blind randomized placebo-controlled trials with large number of patients and long-term follow-up period are however required to obtain definite information."
Niazi et al, 2018, Pakistan[68]	Randomized controlled trial	210 Patients with common viral warts for more than 3 months (11.9%, 10-50 y)	• Group A: 20% zinc oxide paste (105) • Group B: 15% salicylic acid + 15% lactic acid (105)	More than 50% decrease in size of common warts after 3 months of therapy	"Topically applied 15% salicylic acid-15% lactic acid combination is superior in efficacy to 20% zinc oxide paste in treatment of common viral warts."
Shahmoradi et al, 2015, Iran, Lebanon[75]	Randomized controlled trial	60 Patients with at least 2 warts (37%, 15-60 y)	• Pyruvic acid 70% (30) • Salicylic acid 16.7% + lactic acid 16.7% + collodion 100% (30)	Size (mean size of all warts) and number of warts	"Topical pyruvic acid and compound salicylic acid had the same efficacy and complications in treating plantar warts."

Author, Year, Country	Study Type[a]	Patient Population (% male, age)	Intervention/Comparator (# of patients)	Primary Outcome Measure	Authors' Conclusions
Steele et al, 1988, UK[79]	Randomized controlled trial	Hand wart trial: 129 patients (sex, age not mentioned) Plantar wart trial: 78 patients (sex, age not mentioned)	Hand wart trial: • Liquid nitrogen (40) • Wart paint: lactic acid + salicylic acid + collodion (38) • Liquid nitrogen + wart paint (38) Plantar wart trial: • Liquid nitrogen (26) • Wart paint (22) • Liquid nitrogen + wart paint (25)	Complete, incomplete or no cure of warts	Combination therapy of liquid nitrogen applied weekly plus a daily application of wart paint was significantly more effective than either method used separately.

Abbreviations: AK, actinic keratosis; all-TRA, all-trans retinoic acid (tretinoin); AHA-RC, alpha-hydroxy acid retinoid conjugate; AA, azelaic acid; CDP, clindamycin phosphate; 5-FU, 5-fluorouracil; HEPES, N-2-hydroxyethylpiperazine-N'-2-ethanesulfonic acid; IGA, investigator's global assessment of acne severity; PASI, Psoriasis Activity and Severity Index; SA, salicylic acid; TIL, target inflammatory lesion; TPIL, target post-inflammatory lesion; TCA, trichloroacetic acid.

[a]As defined by authors.

Appendix 3. Survey instrument for professional medical associations

Welcome. We want to understand your clinical use of compounded salicylic acid. Your feedback will help the Food and Drug Administration (FDA) develop a list of drugs that can be used in compounding by 503B outsourcing facilities. Your anonymous responses will be shared with the FDA. The time required to complete this survey is approximately 10-15 minutes.

If you have additional questions or concerns about this study, please email: compounding@rx.umaryland.edu.

If you have questions about your rights as a research subject, please contact HRPO at 410-760-5037 or hrpo@umaryland.edu.

Thank you,

Dr. Ashlee Mattingly,
Principal Investigator
The University of Maryland School of Pharmacy

An agency may not conduct or sponsor, and a person is not required to respond to a collection of information unless it displays a currently valid OMB control number.

OMB Control No. 0910-0871
Expiration date: June 30, 2022

1. How familiar are you with the following terms?

	Very familiar	Somewhat familiar	Not familiar
Compounded drugs (medications prepared to meet a patient-specific need)	o	o	o
503A Compounding pharmacy (a pharmacy that prepares compounded medications prescribed by practitioners to meet a patient-specific need)	o	o	o
503B Outsourcing facility (a facility that compounds larger quantities without the receipt of a patient-specific prescription)	o	o	o

2. Do you prescribe or administer salicylic acid to your patients?

   - o Yes
   - o No

3. I prescribe or administer salicylic acid for the following conditions or diseases: (check all that apply)

   - o Acne
   - o Dandruff
   - o Eczema
   - o Fungal infections
   - o Keratosis
   - o Psoriasis
   - o Seborrheic dermatitis
   - o Warts
   - o Other (please describe) _____

4. I use salicylic acid with my patients as the following: (check all that apply)

   - o FDA-approved drug product
   - o Compounded drug product
   - o Over-the-counter drug product
   - o Dietary supplement (e.g. vitamin or herbal supplement sold in retail)
   - o Other (please describe) _____

5. I use compounded salicylic acid because: (check all that apply)

    - o Commercial products are not available in the dosage form, strength, or combination I need. (please explain) _____
    - o Patient allergies prevent me from using commercially available products. (please explain) _____
    - o Patient conditions prevent me from using commercially available products. (please explain) _____
    - o There are no commercially available products containing salicylic acid.
    - o Other (please explain) _____

6. Do you stock non-patient-specific compounded salicylic acid at your practice?

    - o Yes
    - o No
    - o I'm not sure

7. I obtain compounded salicylic acid from the following: (check all that apply)

    - o Compound myself at my practice
    - o Have the product compounded by an in-house pharmacy
    - o Purchase, or have a patient purchase, from a compounding pharmacy
    - o Purchase, or have a patient purchase, from an outsourcing facility
    - o Other (please explain) _____

8. What is your practice setting? (check all that apply)

    - o Physician office/private practice
    - o Outpatient clinic
    - o Hospital/health system
    - o Academic medical center
    - o Emergency room
    - o Operating room
    - o Other (please describe) _____

9. What degree do you hold? (check all that apply)

    - o Doctor of Medicine (MD)
    - o Doctor of Osteopathic Medicine (DO)
    - o Doctor of Medicine in Dentistry (DMD/DDS)
    - o Doctor of Pharmacy (PharmD) or Bachelor of Science in Pharmacy (BS Pharm)
    - o Naturopathic Doctor (ND)
    - o Nurse Practitioner (NP)
    - o Physician Assistant (PA)
    - o Other (please describe) _____

Appendix 4. Survey distribution to professional associations

Specialty	Association[a]	Agreed/Declined, Reason for Declining
Allergy/Immunology	American Academy of Allergy, Asthma, and Immunology (AAAI)	Declined – survey not approved
Anesthesia	American Society of Regional Anesthesia and Pain Medicine (ASRA)	Declined – failed to respond
	Society for Ambulatory Anesthesia (SAMBA)	Declined – failed to respond
	Society for Neuroscience in Anesthesiology and Critical Care	Declined – failed to respond
Critical Care	Critical Care Societies Collaborative	Declined – failed to respond
Dentistry & Oral Medicine	Academy of General Dentistry (AGD)	Declined – provided interview referrals
	American Dental Association (ADA)	Declined – failed to respond
Dermatology	American Academy of Dermatology (AAD)	Agreed
	American Osteopathic College of Dermatology (AOCD)	Declined – not interested
Endocrinology	The Endocrine Society (ENDO)	Agreed
	Pediatric Endocrine Society	Agreed
Gastroenterology	American Gastroenterological Association (AGA)	Declined – failed to respond
	Obesity Medicine Association (OMA)	Declined – did not have anyone to contribute to research
Hematology	American Society of Hematology (ASH)	Declined – does not distribute surveys
Infectious Disease	American Academy of HIV Medicine (AAHIVM)	Declined – failed to respond
Medicine	American Medical Association (AMA)	Declined – failed to respond

Naturopathy	American Association of Naturopathic Physicians (AANP)	Agreed
	The Oncology Association of Naturopathic Physicians (OncANP)	Agreed
Nephrology	American College of Clinical Pharmacists: Nephrology Practice Network	Agreed
	American Society of Nephrology	Declined – provided interview referrals
Nutrition	American Society for Parenteral and Enteral Nutrition (ASPEN)	Declined – provided interview referrals
Obstetrics and Gynecology	American Gynecological and Obstetrical Society (AGOS)	Declined – failed to respond
	Nurse Practitioners in Women's Health	Agreed
Ophthalmology	American Academy of Ophthalmology (AAO)	Agreed
Otolaryngology	American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS)	Declined – survey not approved
Pain Management	American Academy of Pain Medicine (AAPM)	Declined – survey not approved
	American Academy of Physical Medicine and Rehabilitation	Declined – failed to respond
Pediatrics and Neonatology	American Academy of Pediatrics (AAP)	Agreed
Primary Care	American College of Physicians (ACP)	Declined – failed to respond
Psychiatry	American Academy of Clinical Psychiatrists	Declined – failed to respond
	American Association for Geriatric Psychiatry	Declined – failed to respond
Rheumatology	American College of Rheumatology (ACR)	Agreed

Surgery	Ambulatory Surgery Center Association (ASCA)	Agreed
	American Academy of Orthopaedic Surgeons (AAOS)	Declined – no interest in participation from members
	American Association of Hip and Knee Surgeons (AAHKS)	Declined – only send surveys from members
	American College of Surgeons (ACS)	Agreed
	American Society for Metabolic and Bariatric Surgery (AMBS)	Declined – only send surveys from members
	The Association of Bone and Joint Surgeons	Declined – failed to respond
	Physician Assistants in Orthopaedic Surgery	Declined – failed to respond
	Society of American Gastrointestinal and Endoscopic Surgeons (SAGES)	Declined – failed to respond
	Society of Gynecologic Surgeons (SGS)	Declined – policy limits number of surveys per year and do not have a method to identify if any of the SGS members are using ipamorelin
Toxicology	American Academy of Environmental Medicine (AAEM)	Declined – failed to respond
Urology	Sexual Medicine Society of North America (SMSNA)	Agreed

[a]Associations that declined in Year 1 were not contacted in Year 2.