Review of the use of gentian violet in dermatology practice

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Abstract

Objective: To review the use of gentian violet in dermatology.

Design: A comprehensive literature search on gentian violet in dermatology practice was performed through PubMed.

Results: Gentian violet is effective in treating methicillin-resistant Staphylococcus aureus-colonized skin lesions; mean number of days for complete eradication was 9.1 days. Gentian violet is almost as effective as ketoconazole and more effective than nystatin in the treatment of oral thrush in AIDS patients. In an in vitro study on cutaneous T cell lymphoma cell lines, there was no difference between nitrogen mustard and gentian violet in stimulating apoptosis. When comparing gentian violet to silver sulfadiazine dressings in healing burn wounds, the gentian violet treatment group reported less pain, fewer febrile episodes, and decreased bacterial growth compared to control. In atopic dermatitis subjects, gentian violet decreased Staphylococcus aureus colonization and improved disease severity in lesional skin compared to non-lesional skin.

Conclusion: Studies have investigated gentian violet's antibacterial, antifungal, antiviral, antiparasitic, anti-angiogenic, antitumor, and wound healing properties. Gentian violet is a low cost and well-tolerated topical agent with the potential for widespread applications in dermatology.

Keywords: gentian violet, antibacterial, cancer, wound healing, antiparasitic, dermatitis, community dermatology

Introduction

Historically known for its use in gram staining, gentian violet has since become recognized for its therapeutic potential [1]. Gentian violet is a triphenylmethane dye made of hexamethyl-rosaniline and is available as an over-the-counter aqueous solution (**Figure 1**), [2]. Although gentian violet is primarily used as a solution, studies have used gentian violet in different forms including ointments and suspension; the dye may also be incorporated into wound dressings [3-5].

The popularity of gentian violet has grown owing to its antimicrobial properties and low cost. Since then, gentian violet has been used in multiple conditions including impetigo, atopic dermatitis, pressure sores, and burns [6-8]. Gentian violet's antibacterial mechanism of action is not well characterized.

Figure 1. *An example of a gentian violet 1% solution bottle.*

However, possible mechanisms include inhibition of protein synthesis, bacterial cell wall interference, photodynamic action, metabolic interference, and redox reactions [9]. To explore gentian violet's role in dermatology practice, we conducted a literature review of gentian violet's use in the field of dermatology. We first describe gentian violet's anti-angiogenic, antibacterial, antifungal, antiviral, and antiparasitic properties. We then report gentian violet's efficacy in the treatment of different dermatologic conditions, including dermatologic malignancies, wound healing, and inflammatory dermatoses, followed by gentian violet's reported adverse effects.

Methods

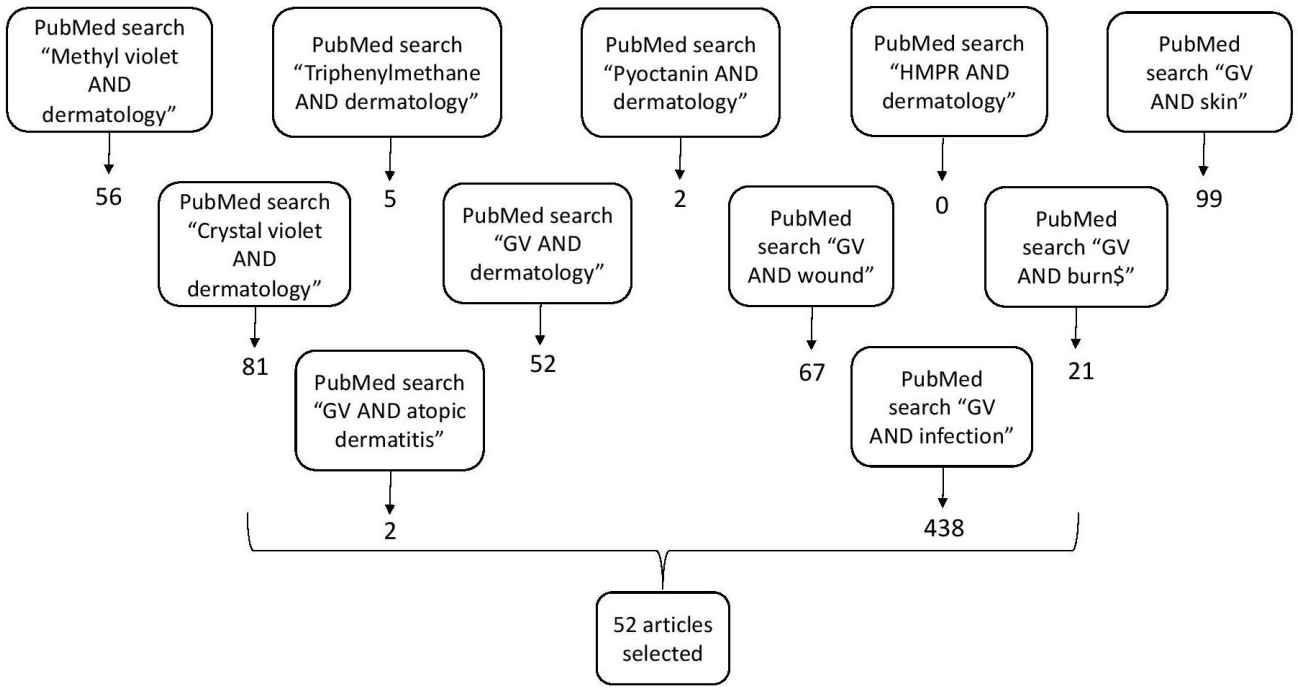
A PubMed search was conducted on March 18, 2019, using the keywords "gentian violet AND dermatology," "crystal violet AND dermatology," "methyl violet AND dermatology," "triphenylmethane AND dermatology," "pyoctanin AND dermatology," "gentian violet AND skin," "gentian violet AND burn$," "gentian violet AND atopic dermatitis," and "hexamethylpararosaniline AND dermatology." Search terms limited to English and human subjects included "gentian violet AND infection," "gentian violet AND skin," and gentian violet AND wound" (**Figure 2**). Studies met the inclusion criteria if gentian violet was studied for a dermatologic condition and described its physiologic properties or adverse effects.

Results

Properties of gentian violet

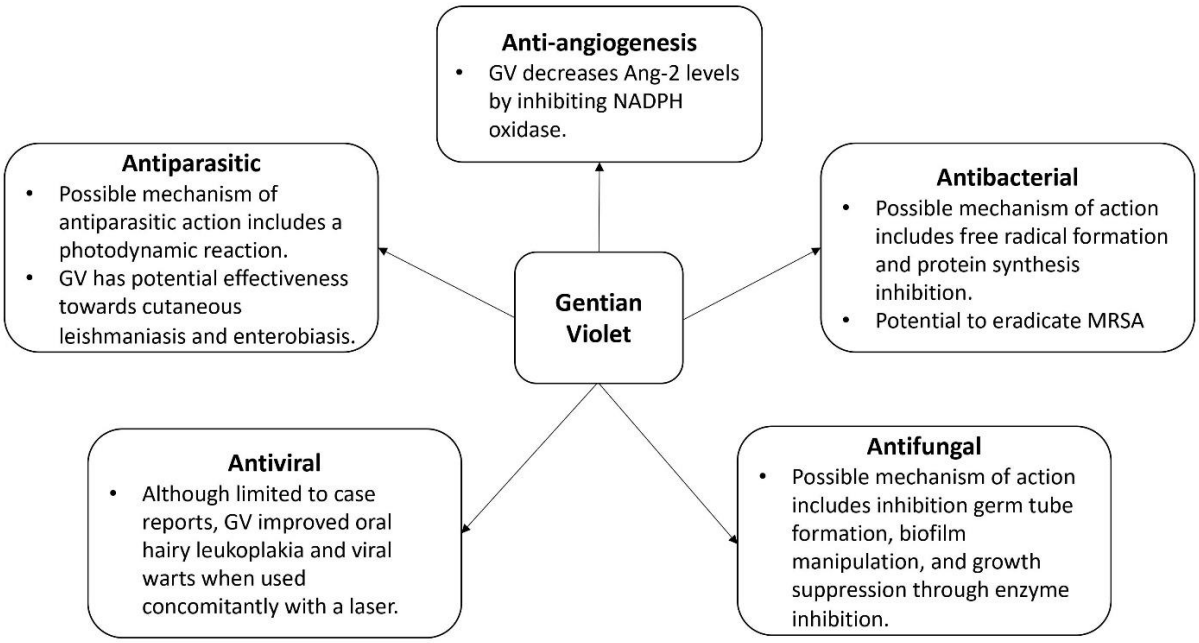
Anti-angiogenic properties

Angiogenesis is a key factor in the pathogenesis of multiple skin conditions including hemangiomas and inflammatory dermatoses. Angiogenesis is influenced by two angiopoietins, angiopoietin 1 and 2. Although angiopoietin 1 stabilizes the vasculature, angiopoietin 2 influences vessel permeability and is a key culprit in tumor angiogenesis [10]. Suppressing nicotinamide adenine dinucleotide phosphate oxidase can suppress angiopoietin 2 levels; gentian violet's ability to suppress nicotinamide adenine dinucleotide phosphate oxidase was recognized as a potential therapeutic mechanism in targeting angiopoietin 2-influenced pathologies (**Figure 3**), [11]. Two studies confirmed that gentian violet decreased angiopoietin 2 levels [11, 12]. Of those two



T- Clinical Trial; CR- Case Report; CS- Case Series; GV- Gentian Violet; HMPR- Hexamethylpararosaniline;

Figure 2. *Flow chart of the gentian violet PubMed search.*



GV- Gentian Violet; MRSA- Methicillin Resistant *Staphylococcus Aureus*; Ang- Angiopoietin;

Figure 3. *Properties of gentian violet.*

studies, one mouse study reported that intralesional injection of gentian violet diminished the size of a hemangioma by 92.6% compared to control (No P value reported), [12].

Antibacterial properties

Gentian violet has antibacterial properties [13-15]. Possible mechanisms of action include photodynamic action mediated by free radical formation and protein synthesis suppression [6, 9]. Since methicillin-resistant *Staphylococcus aureus* (MRSA) colonizes chronic ulcers, a study investigated gentian violet's efficacy on MRSA [16]. Eighteen subjects diagnosed with MRSA-colonized decubitus ulcers were scrubbed with 0.1% aqueous gentian violet solution followed by a daily application of 0.1% gentian violet ointment. Subjects with superficial decubitus ulcers reported MRSA eradication in 5 days of treatment, whereas deeper decubitus ulcers reported MRSA eradication in 14.6 days (P<0.025). The average length of time to achieve complete MRSA clearance was 10.9 days [3]. Another study followed the results of application of 0.5% gentian violet solution once a day on 28 cutaneous skin lesions colonized with MRSA. Skin pathologies included erosions, impetigo, umbilical infection, ulcers, angular cheilitis, and paronychia. Mean number of days for complete eradication of MRSA was 9.1 days [17]. Other studies report similar efficacy against MRSA [17-20]. *Streptococcus*, *Proteus*, and *Pseudomonas aeruginosa* are also susceptible to gentian violet [21, 22].

Newborn umbilical cords are generally managed with dry cord care. However, since the umbilical cord is a high risk location for bacterial colonization, the use of an antibacterial agent to prevent omphalitis may prevent future complications [23-25]. A study randomized 766 newborns to either receive dry cord care or triple dye therapy. The triple dye consisted of gentian violet, brilliant green, and proflavine hemisulphate. At the two to 5-day follow-up, 309 subjects in the dry cord care group revealed more exudate (7.4% versus 0.3%; P<0.001) and bad odor (2.9% versus 0.7%; P=0.04) compared to the 309 subjects in the triple dye therapy group; however, there were no differences in redness (1.6% versus 0.7%; P=0.45) and warmth (0.7% versus 0.3%; P=1.00). At the 3-week follow-up, there were no differences in reported exudate (27.2% versus 23.9%;

P=0.43), bad odor (15.7% versus 13.2%; P=0.45), redness (7.3% versus 6.2%; P=0.63), and warmth (2.8% versus 1.3%; P=0.33) between the dry cord care and triple dye group. When bacteriologic cultures were obtained from both groups, the dry cord care group were more colonized with *Escherichia coli* (34.2% versus 22.1%; P=0.001), *S. aureus* (31.3% versus 2.8%; P<0.001), and group B *Streptococcus* (11.7% versus 6.0%; P=0.02) than the triple dye group. Furthermore, one subject receiving dry cord care was diagnosed with omphalitis [24]. Another study comparing triple dye therapy to alcohol swab therapy in umbilical cord care (N=599) reported the alcohol group required shorter time for cord separation than the triple dye group (10 days versus 13 days; P<0.0001). Furthermore, one subject in the triple dye group was diagnosed with omphalitis [26]. Although triple dye therapy was reported to diminish bacterial colonization, another study failed to provide evidence that triple dye effectively maintained eradication of MRSA 11 days postpartum [27].

Gentian violet's antibacterial properties were further explored by investigating its potential for prophylaxis of percutaneous site infections [28, 29]. Nine subjects with percutaneous implantation of a ventricular assist device were prophylactically managed with a daily application of 0.01% gentian violet ointment on the percutaneous site and one subject was treated with gentian violet for an active percutaneous infection. Of the 10 subjects who received a ventricular assist device, 8 subjects received an extracorporeal ventricular assist device and two subjects received an implantable ventricular assist device. Mean infection-free period was 144.2 days. All 8 subjects with extracorporeal ventricular assist devices died, related to heart failure, stroke, or multisystem failure. However, all subjects receiving gentian violet prophylaxis had negative cultures. Both subjects who received implantable ventricular assist devices survived and had no evidence of infection at two and 20 months after implantation [29].

Antifungal properties

Gentian violet also has antifungal properties [13]. Possible mechanisms of action include biofilm and thioredoxin reductase two suppression with subsequent fungal death [6, 30]. The antifungal effect of gentian violet was tested on *Candida albicans* phospholipase, proteinase, and germ tube formation. Two µg/mL gentian violet lowered phospholipase, proteinase, and germ tube formation (P<0.05). The MIC_{50} and MIC_{90} of gentian violet for *C. albicans* were 0.25 and 0.5µg/mL compared to 8 and 16µg/mL for fluconazole, respectively (No P value reported), [31]. A study exploring gentian violet's MIC_{50} and MIC_{90} on *C. albicans* reported similar results between gentian violet and fluconazole, although no P value was reported (MIC_{50}: 0.06 versus 0.25µg/mL; MIC_{90}: 0.12 versus 8µg/mL, respectively), [30]. Other studies have also shown similar results in the treatment of *C. albicans* [32]. Gentian violet decreased biofilm mass and thickness of *C. albicans* better than control (1.06mg versus 2.39 mg, P=0.0004; 22µm versus 98µm, P=0.008, respectively), [30]. When used in oral thrush, gentian violet was almost as effective as ketoconazole and more effective than nystatin (42%; 43%; 9%; P<0.05, respectively) [33]. Furthermore, gentian violet was effective in the treatment of oral thrush in three other studies when applied even up to four times a day [34-36].

Antiviral properties

Studies have explored gentian violet's antiviral properties against the Epstein-Barr virus and human papillomavirus. Possible mechanisms of action include viral envelope destruction and viral membrane destruction through cationic binding [37, 38]. Oral hairy leukoplakia is caused by infection of the epithelial cells by the Epstein-Barr virus. A 33-year-old male with oral hairy leukoplakia reported complete resolution and remission for 6 months when 2% gentian violet was applied three times in one month [39]. Another study reported the successful treatment of multiple warts in an immunocompromised patient after initial application of 0.5% gentian violet on the warts, followed by a 585 nm pulse dye laser. Gentian violet was applied before laser treatment every 1-to-3 months for six years [40].

Antiparasitic properties

Although gentian violet has antiparasitic properties, the mechanism of action is not well characterized. A

possible mechanism includes gentian violet's ability to generate photodynamic action through free radical formation. When visible light strikes the dye, gentian violet creates a free radical through photoreduction. The free radical increases toxicity with subsequent cell death [9]. When exploring the efficacy of oral gentian violet tablets in enterobiasis, gentian violet taken two to three times a day for 7 days cured 80% of cases in 33 children [41]. Another study reported an 81% cure rate in 26 children with enterobiasis managed with gentian violet suspension [5].

Gentian violet also exhibits antiparasitic activity against cutaneous leishmaniasis *in vitro* and *in vivo*. A promastigote assay containing *Leishmania amazonensis* was used to investigate the lowest concentration of a medication needed to achieve 50% inhibition of promastigote growth (IC_{50}). Compared to ten different triphenylmethane derivatives, gentian violet had the lowest IC_{50} in the promastigote assay (0.025μM; no P-value reported) and the second lowest IC_{50} in the intracellular amastigote assay (0.17 μM; no P-value reported). In vivo, 1% gentian violet applied twice a day for 20 days completely cleared all parasites from mice infected with *L. amazonensis* compared to control (P<0.005). Gentian violet was also considered safe owing to its low level of cytotoxicity towards normal macrophages [42].

Gentian violet and the treatment of dermatologic conditions

Dermatologic malignancies

A key contributor to the pathogenesis of cutaneous T cell lymphoma is its ability to avoid apoptosis. Therefore, research has explored potential therapies to induce apoptosis in malignant cells. An in vitro study explored the ability of gentian violet to stimulate extrinsic apoptosis and inhibit cutaneous T cell lymphoma cell proliferation. In this study, cutaneous T cell lymphoma included both Sezary syndrome and mycosis fungoides. Investigators measured the level of cleaved caspase-8 as a marker of extrinsic apoptotic activation — gentian violet stimulated high levels of cleaved caspase-8 in cutaneous T cell lymphoma cell lines. Furthermore, gentian violet induced 40% to 70% apoptosis in five different cutaneous T cell lymphoma cell lines in vitro, and 75% to 90% in Sezary syndrome cell lines ex vivo compared to dimethylsulfoxide as control (P<0.01). When compared to nitrogen mustard, an effective apoptotic stimulator, gentian violet was superior in stimulating apoptosis in one cutaneous T cell lymphoma cell line whereas nitrogen mustard was superior in another (P<0.01). There were no significant differences in all other cutaneous T cell lymphoma cell lines exposed to either nitrogen mustard or gentian violet. Nitrogen mustard stimulated more apoptosis in normal keratinocytes than gentian violet, although no statistically significant difference was reported [43].

Since nuclear factor-κB (NF-κB) is upregulated in cutaneous T cell lymphoma, investigators measured the level of NF-κB as a biomarker for cutaneous T cell lymphoma proliferation. Gentian violet decreased the level of NF-κB in cutaneous T cell lymphoma cell lines with simultaneous elevation of inhibitory κB, an inhibitor of NF-κB [43]. These findings suggest gentian violet may be able to suppress cutaneous T cell lymphoma proliferation by decreasing NF-κB.

A case reported an 84-year-old woman with recurrent biopsy-proven cutaneous diffuse B cell lymphoma. Since the patient did not qualify for the recommended chemotherapy, she was initiated on radiation therapy. Despite clearance of the lesions with radiotherapy, she had biopsy-proven recurrence of cutaneous diffuse B cell lymphoma on her leg. Gentian violet was poured into the biopsy site and left to heal. After a 4-month loss to follow-up, the nodule resolved and maintained remission for one year [44].

The management of cutaneous metastatic melanoma may include radiation, surgery, or chemotherapy. However, when such options fail, novel methods may be needed for palliative purposes. A 92 year-old man with three recurrent metastatic melanoma lesions on the scalp previously failed surgical excision and radiation therapy. After debulking all lesions, cryotherapy was applied to the lesions for 30 seconds. Once thawed, 1% gentian violet and imiquimod were applied to the lesions daily. At a 2-year follow-up, there were no signs of recurrence [45, 46].

Gentian violet may influence melanoma through its effects on Sox2. Sox2 is a transcription factor involved in the tumorigenicity of human melanoma-initiating cells. Gentian violet suppresses the survival of melanoma cells by phosphorylating signal transducer and activator of transcription (STAT)-3 and impairs the binding and activation of STAT3 onto the *Sox2* gene promoter [47].

Wound healing

Successful wound healing is a treatment hurdle for even the most experienced healthcare providers. Depending on the clinical presentation, treatment options for wound healing include debridement or protective treatment [48, 49]. When wound ulcers need a protective and stabilizing treatment option, gentian violet has been recommended for its ability to create an impermeable protective coating on wound eschars.

Gentian violet has also been shown to facilitate wound healing in a variety of dermatologic conditions, including pyoderma gangrenosum, epidermolysis bullosa, calciphylaxis, and foreign body granulomas. It has been used prophylactically in the prevention of percutaneous site infections (**Table 1**), [28, 50-56]. A third of patients who receive radiation therapy may suffer from moist desquamation, an adverse effect from radiation therapy [4, 57-60]. Moist desquamation occurs from radiation-induced destruction of cells in the basal layer and increases the risk of infection while decreasing patient quality of life [61]. Gentian violet may also be a useful treatment for moist desquamation because of its ability to create a protective crust, low cost, and antimicrobial properties [13, 62-64].

Given its low cost and ease of use, gentian violet has the potential for widespread applications in wound healing and the treatment of bacterial infections in developing countries. One epidemiologic study explored the most prevalent skin diseases in 5780 children attending school in Africa and then re-evaluated the children after educating them and their families on the management of their skin disease. Before initiating an educational program on the management of their skin conditions, bacterial infections (including impetigo, tropical ulcers, infected wounds, and folliculitis) were the most prevalent dermatoses in all children examined (12.7%). After educating the children and their families on recognizing and managing bacterial infections with 1% gentian violet solution, the children were re-examined one and 5 years later. After one year, the prevalence of bacterial infections dropped from 12.7% to 10.8% ($P<0.05$), whereas the 5-year difference dropped from 12.7% to 11.3% (no P value reported), [65, 66].

Inflammatory dermatoses

Erythema multiforme has characteristic keratinocyte necrosis and elevated angiopoietin two [67-69]. Keratinocyte necrosis in erythema multiforme involves nitric oxide and superoxide [70]. Because gentian violet decreases angiopoietin 2 and superoxide levels by suppressing nicotinamide adenine dinucleotide phosphate oxidase, gentian violet may be an alternative treatment option for erythema multiforme in patients who fail or have contraindications to first-line treatment [12]. Topical gentian violet successfully treated a 42-year-old man with extensive erythema multiforme. Since his end-stage renal disease and type 1 diabetes were contraindications for systemic corticosteroids, gentian violet served as a successful treatment alternative. The study did not report how frequently gentian violet was applied [69].

Gentian violet's efficacy for irritant contact dermatitis was investigated in 18 subjects instructed to apply sodium lauryl sulfate daily to produce an irritant contact dermatitis on their bilateral arms. The subjects were then instructed to apply 0.5% gentian violet solution to the affected area on one arm and a placebo solution on the other. Efficacy was measured using corneometry (measured water content in the stratum corneum), subpapillary blood flow, and transepidermal water loss. Elevated subpapillary blood flow represented increased severity. After 14 days, gentian violet was superior to placebo in effects on corneometry ($P<0.05$), transepidermal water loss ($P<0.001$), and subpapillary blood flow ($P<0.001$), [71]. Another case reported the successful resolution of digital dermatitis using topical gentian violet and a tetracycline spray [72].

When exploring the efficacy of gentian violet in atopic dermatitis, 38 atopic dermatitis subjects colonized with *S. aureus* were divided into three treatment groups — 0.3% gentian violet solution, 10% tar solution, and diflucortolone-21-valerate. All groups were instructed to apply the assigned medication to an eczematous and non-eczematous patch on the arm twice a day for four days. The bactericidal efficacy of all groups was measured by culturing the treated locations and the atopic dermatitis efficacy was measured by the SCORAD index looking at erythema, edema, oozing, excoriation, lichenification, and pruritus. Severity of each SCORAD item was graded from 0 (absent) to 3 (severe). The gentian violet group reported a difference in *S. aureus* colonization between lesional and non-lesional skin at day four (P<0.001) and the SCORAD index improved from baseline to day four (7.6 to 3.9; P=0.001). Both tar and diflucortolone groups did not achieve a significant difference in *S. aureus* colonization between lesional and non-lesional skin at day four (no P value reported). Furthermore, there were no significant improvements in the SCORAD index seen in the tar and difluocortolone groups (8 to 3.4, P=0.06; 7.8 to 5.8, no P-value reported, respectively), [8]. Another case of impetiginized atopic dermatitis managed with twice daily topical application of 1% gentian violet solution and 100mg of oral doxycycline taken twice a day showed similar positive results with marked improvement by two weeks [73].

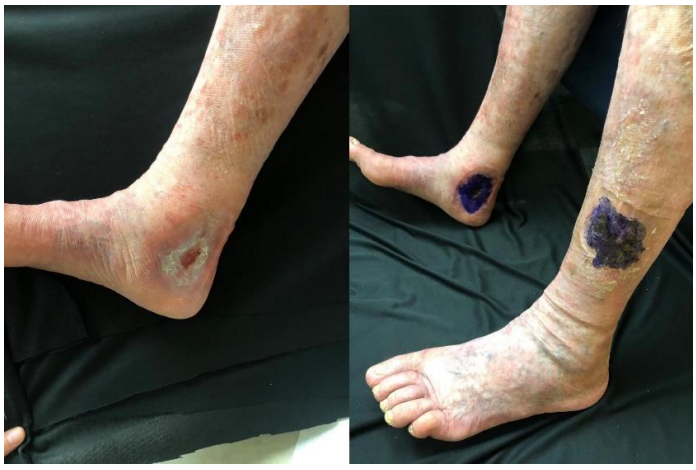


Figure 4. *The image on the left depicts an ulcer posterior to the medial malleolus of the right lower extremity whereas the image on the right depicts the same ulcer and another ulcer on the left lower extremity after application of gentian violet 1% solution.*

Pachyonychia congenita is a genetic keratin disorder with a cutaneous presentation of nail dystrophy and plantar keratoderma [74]. Transgrediens pachyonychia congenita is the cutaneous spread of keratoderma beyond the sole of the foot [75]. In a case series of 7 subjects diagnosed with transgrediens pachyonychia congenita, two subjects were managed with gentian violet. Although both subjects reported improvements, both applied other treatments including oral and topical antibiotics simultaneously [75].

Adverse Effects

Adverse effects associated with gentian violet include stinging, contact dermatitis, staining, irritation, mucous membrane lesions, epistaxis, keratoconjunctivitis, and stains (**Table 2**), [9, 33, 34, 76-80]. Application of gentian violet 2% to oral lesions in an infant and gentian violet 1% to oral lesions in a neonate led to difficulty breastfeeding and obstructive laryngotracheitis, respectively [81, 82]. Serious adverse effects include a case reporting necrosis of the oral mucosa and skin when applied orally and topically [83, 84]. Murine studies feeding gentian violet to mice increased the risk of hepatocellular carcinoma, sarcoma, and thyroid cancer [85, 86]. Owing to gentian violet's influence on thyroid peroxidase, gentian violet may cause hypothyroidism [87]. Contaminated gentian violet also led to infection after surgery [88].

Discussion

Gentian violet's multiple mechanisms of action may explain its therapeutic potential in a variety of cutaneous diseases. Gentian violet may be useful in managing some inflammatory skin conditions because of its ability to inhibit nicotinamide adenine dinucleotide phosphate oxidase and downregulate superoxide production and angiopoietin two levels [11, 89]. Its antimicrobial properties and ability to create a protective barrier over wounds helps to promote wound healing (**Figures 4, 5**), [90]. Gentian violet may also palliatively manage certain cancers; it has been shown to activate the extrinsic apoptosis

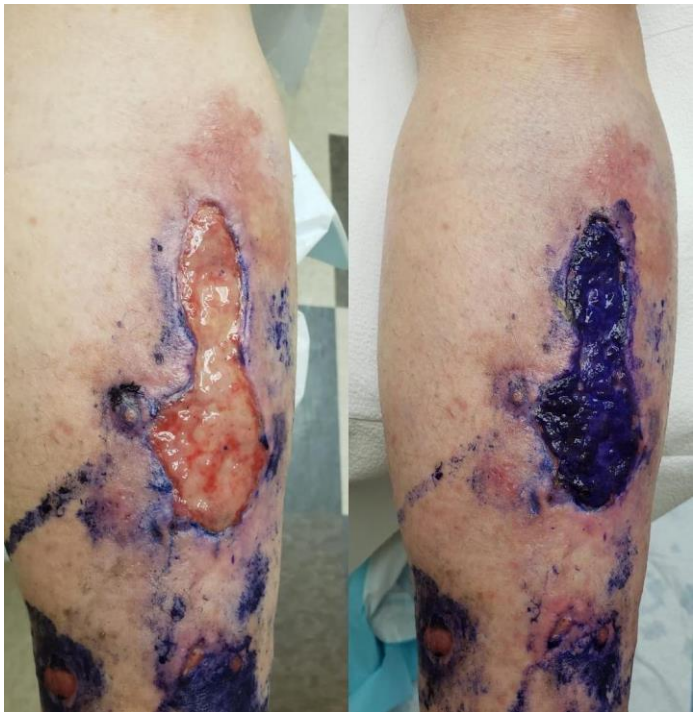


Figure 5. *The image on the left depicts an ulcerative variant of necrobiosis lipoidica before painting gentian violet onto the ulcer whereas the image on the right depicts the necrobiosis lipoidica ulcer painted with gentian violet 1% solution.*

pathway in cutaneous T cell lymphoma tumor cells and impair binding and activation of STAT3 onto the *Sox2* gene promoter, a transcription factor involved in the pathogenesis of melanoma [43, 47].

There are insufficient high quality, randomized, double-blinded, placebo-controlled clinical trials using gentian violet. Furthermore, many studies also tested the efficacy of gentian violet alongside concomitant medications (e.g. gentian violet and imiquimod in the treatment of cutaneous melanoma metastases, gentian violet and methylene blue foam dressings in wound healing, and gentian violet and oral doxycycline in treatment of impetiginized atopic dermatitis), confounding the results.

Gentian violet is a safe, well-tolerated therapeutic option for a variety of dermatologic conditions. Most adverse effects were described in case reports, in which different formulations and strengths of gentian violet were used. The composition of gentian violet dyes through time and the exact formulations used in each case report are not well known. Different formulations of gentian violet, such as those based in alcohol, may also cause more dryness and irritation. Animal studies showed increased rates of hepatocellular carcinoma and follicular cell adenocarcinoma of the thyroid gland with oral administration of gentian violet. However, large doses (100, 300, and 600 parts per million) were used continuously over two years [85, 86]. Despite human use of gentian violet for over a century, gentian violet has not been associated with cancer in human studies [87].

Other dyes used in dermatology include brilliant green, malachite green, fuchsin in Castellani paint, and tolonium chloride. Although Castellani paint originally contained gentian violet, the modified form contains fuchsin, boric acid, phenol, resorcinol, acetone, alcohol, and water. Castellani paint is applied topically in dermatitis, burns, and cutaneous fungal and bacterial infections. Castellani paint may be used in erosio interdigitalis blastomycetica twice a day until complete resolution. However, providers should educate their patients about burning on initial application [2].

Gentian violet is readily available over-the-counter and can be purchased online at websites such as Amazon and Walmart; 1% gentian violet solution can be purchased for $0.14 per milliliter at the time of publication. Other formulations include 0.1%, 0.5%, and 2% solution, 0.1% and 0.01% ointments, suspensions, and wound dressings coated in gentian violet. Oral gentian violet tablets are no longer available. Oral gentian violet troches are not available but could be developed for oral candidiasis. We recommend topical application of 1% gentian violet solution once or twice daily to the affected areas on the skin. For the treatment of mucosal lesions (e.g. oral candidiasis) in infants and children, 1% gentian violet solution is generally applied sparingly to the affected areas once or twice daily for no more than three days given reports of ulceration and necrosis of the oral mucosa occurring within as little as four days of application of gentian violet. Gentian violet should not be used in patients with known hypersensitivity to the dye and should not be used in or near the eyes. Patients should discontinue gentian violet if they develop severe irritation to the dye. Patients should also be warned that use of gentian violet could result in temporary purple

staining of skin, clothing, and anything else gentian violet contacts. Therefore, advise patients to use disposable trays to apply gentian violet and protect surrounding areas from stains. Gentian violet should be stored in a tightly closed container, protected from light [91].

Gentian violet is an inexpensive, safe, and versatile agent with anti-angiogenic, antibacterial, antifungal, antiviral, antiparasitic, antitumor, and wound healing properties. It has been used in low-income countries given its low cost and long shelf life. In the face of growing antibiotic resistance, there is renewed interest in the use of gentian violet as an antimicrobial agent given its efficacy against MRSA, *Streptococcus,* and *Pseudomonas*. The therapeutic potential of gentian violet against cancer should be further explored to fully capitalize its anti-angiogenic and tumor suppressing properties.

Conclusion

Gentian violet is a cheap, safe, and well-tolerated topical agent that possesses anti-angiogenic, antimicrobial, antitumor, and wound healing properties. Gentian violet may be used as an alternative treatment option for patients with certain inflammatory dermatoses who previously failed conventional therapy.

Potential conflicts of interest

Dr. Steven Feldman has received research, speaking and/or consulting support from a variety of companies including Galderma, GSK/Stiefel, Almirall, Leo Pharma, Boehringer Ingelheim, Mylan, Celgene, Pfizer, Valeant, Abbvie, Samsung, Janssen, Lilly, Menlo, Merck, Novartis, Regeneron, Sanofi, Novan, Qurient, National Biological Corporation, Caremark, Advance Medical, Sun Pharma, Suncare Research, Informa, UpToDate and National Psoriasis Foundation. He is founder and majority owner of www.DrScore.com and founder and part owner of Causa Research, a company dedicated to enhancing patients' adherence to treatment. Dr. Adrian Pona, Eugenie Quan, and Dr. Abigail Cline declare no conflict of interest to disclose.

Acknowledgements

The authors would like to thank Rebecca Hunt DO, Steve Jurko DO, and Rima Ghamrawi for acquiring excellent photos for the readers of this review article.

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Table 1. *Clinical efficacy of gentian violet on wound healing.*

Authorship	Disease	Study Design	Sample Size	Duration	Intervention	Results
Farid et al. [90]	Open wounds/ eschars (e.g. pressure ulcers, traumatic wounds)	Retro	70	1 year	Daily application of topical 1% GV	103 out of 111 wounds healed completely Average time to achieve complete wound healing was 24.6 days No wounds complicated by infection
Lullove et al. [56]	Lower extremity wounds (e.g. diabetic ulcers, venous ulcers, pressure ulcers)	Retro	53	24 weeks	Debridement with use of GV and MB polyurethane antibacterial foam dressings, twice a week for 4 weeks followed by once a week	Mean reduction of wound surface area by 38.5% (Week 4), 73.3% (Week 8), and 91.3% (Week 12) Mean time to achieve complete wound closure was 10.6 weeks
Coutts et al. [55]	Lower extremity chronic wounds	CS	15	4 weeks	Foam dressing consisting of polyvinyl alcohol foam bound with GV and MB	Decreasing wound size observed by 4 weeks of treatment in 8 of 14 subjects, whereas 1 subject reported no improvement and 5 subjects reported an increase in wound size
Woo et al. [54]	Chronic wounds with local infection	P	29	4 weeks	GV and MB foam dressing, changed 3 times per week	Improvement of mean wound surface area by 42.5% (21.4 to 12.3 cm^2; P<0.005) at week 4 Wound infection scores improved after 4 weeks of treatment (75%, *P*<0.001)
Toba et al. [19]	Pressure sores infected with MRSA	P, R	19	14 weeks	GV plus dibutyryl cAMP vs povidone-iodine plus sugar	93% of cultures taken from pressure sores showed no MRSA in the GV arm compared to 74% in the povidone-iodine arm (P<0.01) Iodine sugar improved pressure ulcer size by 55.7% from baseline compared to GV improving pressure ulcer size by 44.6% from baseline at Week 14
Choudhary et al. [53]	Burn wounds (TBSA 15% to 50%)	P, R	400	Unknown	Topical 1% GV lotion vs silver sulfadiazene	GV group reported less pain (no *P*-value reported) and fewer febrile episodes compared to control, respectively (20% vs 70%; no P-value reported) 68% of subjects in the GV grew bacteria compared to 100% of control subjects (no P-value reported). Most frequent organism grown in the GV group were Staphylococcal species compared to Pseudomonal species in the control group
Thompson [52]	1st or 2nd degree burns	CS	4	Unknown	GV and penicillin solution	All subjects reported complete healing of their burns

Conwell et al. [51]	Pyoderma gangernosum	CS	16	20 weeks	GV and MB foam dressing	16 of 20 subjects completely cleared
Venugopal et al. [76]	Non-Herlitz epidermolysis bullosa	CR	1	4 weeks	Topical 0.1% GV	GV reduced ulcer size on the left leg by 57% compared to 21% on the right leg (control) at Week 4 No improvement in Dermatology Life Quality Index and Quality of Life in epidermolysis bullosa scores from baseline to Week 4. Visual analogue scale for oozing improved in 4 weeks, but pain and odor did not improve.
Famorca et al. [50]	Calciphylaxis	CR	1	Unknown	GV and MB foam dressings along with other wound care techniques	Successful resolution of peristomal calciphylaxis in a 33 year-old male
Moyses-Neto et al. [28]	Foreign body granulomas	CS	42	26 months	Peritoneal dialysis patients were instructed to wash the peritoneal site with topical 1% GV solution 3 times a day. Those with diagnosed infection were also treated with prescribed antibiotics	50.9% of the patients were infected with either *Staphylococcus epidermidis*, *Staphylococcus aureus*, or other gram-negative bacteria Although all foreign body granulomas healed, 54.5% of granulomas healed in 30 days whereas 9% of granulomas healed later than 90 days
Gollins et al. [64]	Moist desquamation	RCT	30	Until wound healed	Topical 0.5% aqueous GV applied 4 times daily vs hydrogel dressing (96% water, 4% polyethylene oxide) applied twice daily	Median healing time was 12 days in the hydrogel group and over 30 days in the GV group. Subjects in the hydrogel group were more likely to completely heal compared to the GV group (hazard ratio of healing: 7.95; 95% CI: 2.20-28.68; P=0.002). Ten of the 16 subjects in the GV group withdrew due to stinging and failure to heal, whereas 2 of 14 subjects in the hydrogel group withdrew (P=0.021)
Mak et al. [62]	Moist desquamation	P, R	39	Until wound healed	Hydrocolloid dressing vs topical GV	No differences in healing time (11.7 vs 11.42 days, P=0.83) GV group demonstrated decreased wound size and reduced wound pain, but decreased dressing comfort and aesthetic acceptance
Mak et al. [63]	Moist desquamation	RCT	146	Until wound healed	Nonadherent absorbent dressing vs GV	No difference between median wound time healing (14 days vs 14 days; P=0.09), wound pain (P=0.07), sleep disturbance (P=0.17), appearance (P=0.33), and social isolation (P=0.21) during dressing treatment. A multivariate analysis showed difference between GV or

						nonadherent absorbent dressing in prolonging the wound healing time (Hazard ratio: 1.16; 95% CI: 0.8-1.6; P=0.39)

GV- Gentian violet; MB- Methylene blue; RCT- Randomized controlled trial; CS- Case series; CR- Case report; R- Randomized; P- Prospective.

Table 2. *Reported adverse events of gentian violet.*

Authorship	Study Design	Sample Size	Intervention	Adverse Event
Bielicky et al. [77]	CS	11	Patch test with GV placed for 20-24 hours in patients already sensitized to brilliant green	Allergic contact dermatitis
Lawrence et al. [80]	CR	1	Patch test with 0.25% gentian violet solution	Allergic contact dermatitis
Torres et al. [79]	CR	1	3% GV ointment left on for 14 hours in 28-year-old woman with negative patch testing	Irritant contact dermatitis that appeared clinically similar to 2nd degree burn (erythematous, edematous, bullous lesions)
Bjornberg et al. [84]	CR	3	1% GV solution applied to open areas of skin	Skin necrosis
Safranek et al. [88]	CS	8	Contaminated GV skin-marking solution used in patients undergoing facelift or augmentation mammoplasty	Postoperative surgical wound infections due to rapidly growing Mycobacterium chelonae
Slotkowski [78]	CR	1	GV applied 2-3 times daily for 5 weeks for oral candidiasis in a 6-week-old infant	Ulceration, "gelatinous-like lesions" involving mostly the buccal mucosa and undersurface of tongue Mouth tenderness, gagging, choking while feeding
Baca et al. [81]	CR	1	1% GV solution twice daily for 1 day then 4 times daily for 2 days for oral candidiasis in a 4-week-old infant	Obstructive laryngotracheitis requiring intubation Choking and gagging during feedings
Utter [82]	CR	1	2% GV solution twice daily for 6 days for oral candidiasis in 1-month-old infant	Ulcerations underneath the tongue, swelling of oral cavity and tongue
John [83]	CR	2	GV solution applied for 2 weeks for oral candidiasis in a 1-month-old infant 0.5% GV solution applied 5 times daily for 3 days for oral candidiasis in 2-week-old infant	Ulceration and necrosis of oral mucosa Partial upper airway obstruction
Littlefield et al. [85]	RCT	1440	720 male and 720 female mice fed GV at 0, 100 (~100mg/kg), 300 (~250mg/kg), or 600 (~475mg/kg) ppm for 12, 18, or 24 months	Higher mortality rates 15% at 24 months for control 28, 27, 64% in 100, 300, 600ppm dose groups, respectively for females 14, 20, 23% in 100, 300, 600ppm dose groups, respectively for males Positive dose response for hepatocellular carcinoma in males at 24 months and females at 18 and 24 months at 300 to 600ppm doses Positive dose response in females for erythropoiesis in spleen, atrophy of ovaries, adenoma of Harderian gland, presence of type A reticulum cell sarcomas in the bladder, uterus, ovaries, vagina

Littlefield et al. [86]	RCT	1140	570 male and 570 female rats fed GV at 0, 100, 300, or 600ppm for 12, 18, or 24 months	Higher mortality rates 33% at 24 months for control 66% in 600ppm dose group for females 48, 39% in 300, 600ppm dose groups, respectively for males Higher incidence of follicular cell adenocarcinoma of thyroid gland for males at 600ppm and females at 300 and 600ppm Higher incidence of hepatocellular adenomas in males at 300, 600ppm and females at 300ppm Dose-time-related incidence of mononuclear cell leukemia in females

GV- Gentian violet; RCT- Randomized controlled trial; CS- Case series; CR- Case report.