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Gentian Violet: A 19th Century Drug Re-Emerges in the 21st Century

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Abstract

Gentian violet (GV) has a long and varied history as a medicinal agent. Historically used as an anti-bacterial and anti-fungal, recent reports have shown its utility as an anti-trypanosomal, anti-viral and anti-angiogenic agent. The objective of this paper is to summarize evidence regarding the efficacy, and safety of GV use in dermatology. Recent discoveries have found novel targets of GV, namely NADPH oxidase in mammalian cells and thioredoxin reductase 2 in bacterial, fungal, and parasitic cells. These discoveries have expanded the use of GV in the 21st century. Given that GV is well tolerated, effective and inexpensive, its use in dermatology is predicted to increase.

Keywords

Gentian Violet; crystal violet; triphenylmethane dye; triphenylmethane dye

Introduction

Gentian violet ((GV) hexamethyl pararosaniline, also known as crystal violet, methyl violet) is a triphenylmethane dye with anti-bacterial, anti-fungal, anti-helminthic, anti-trypanosomal, anti-angiogenic and anti-tumor properties. GV has a lengthy history and has been used successfully as monotherapy and an adjunct to treatment in a variety of diseases.

Synthesis of GV was attributed French chemist Charles Lauth in 1861 under the name of ‘Violet de Paris’¹ and was popularized by George Grubler, a German pharmacist in 1880.² Grubler marketed his dye only to biologists and it was not used in textiles.³ In 1884 Hans Gram noted the irreversible fixation of GV by Gram positive bacteria, which became the basis of the Gram stain for categorizing bacteria.⁴ GV was first introduced as an antiseptic by Stilling in 1891, which he marketed as pyoctanin. Stilling made boisterous claims about pyoctanin’s therapeutic use and advocated it for wounds, ulcers and infections of the eye. One physician from Vienna reported injections of pyoctanin successfully treating two cases of sarcoma⁶, predating GV’s use in the treatment of malignant melanoma and as an inhibitor of angiogenesis by over 120 years. However, pyoctanin did not come into favor and its

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Conflicts of Interest

Drs. Maley and Arbiser have no conflicts of interest to report.

curative allegations were disputed.⁷ For the next two decades, further experimentation with GV in human subjects was abandoned.

In 1912, Churchman noted the bacteriostatic action of GV against Gram-positive microorganisms both in vitro and in animal studies.⁸ Based upon results from Churchman, in 1925 Hinton used GV intravenously in 12 patients with severe sepsis from Gram positive organisms, of which seven patients improved.⁹ In 1928, a case of staphylococcal meningitis was also cured by intrathecal injections of GV.¹⁰ Throughout the first half of the 20th century, GV was widely adopted for use in a variety of diseases including trench mouth¹¹, thrush¹², impetigo¹³, burns¹⁴, pinworm¹⁵, cutaneous¹⁶ and systemic fungal infections¹⁷. Claims of GV's efficacy during this time period are difficult to ascertain, given that the composition of GV dyes varied and the authors did not always describe the solutions used in their publications. Following discovery and mass production of sulfa drugs and penicillin in the 1940's, GV fell out of favor with physicians and scientific research became focused on the discovery of novel classes of antibiotics.

With the emergence of antibiotic resistance there has been a recent resurgence into the GV therapy for anti-sepsis, as well as for a variety of other uses. Recent studies of its mechanisms of activity have expanded its potential uses in dermatology. GV is readily available, inexpensive (\$0.16 USD/mL for a 2% solution)¹⁸, easy to use and has minimal side effects. The purpose of this article is to review uses of GV in dermatology as well as to discuss potential applications and areas of future research.

Definition of Gentian Violet

Today, GV USP is defined as hexamethylrosaniline, a completely symmetric molecule in which every amino group contains 2 methyl groups.¹⁹ Given that GV is a trimer of dimethylaniline, which is resonance stabilized to yield a highly colored compound, there are six methyl groups. However, in the past, there was considerable variability of the composition of GV, with compounds containing less than the maximum 6 methyl groups possible. Early preparations of GV were called methyl violet, and had mixtures of hexamethylrosaniline (GV, Methyl violet 10B, crystal violet) and pentamethylrosaniline (Methyl violet 2B).

Antibacterial activity

GV was revisited as an anti-microbial for dermatological disease by Bakker et al in 1992.²⁰ The authors were investigating writing a formulary for dermatological preparations to be used in developing countries. Thus they required a drug that was inexpensive, simple to prepare, chemically stable, active in low concentrations, with a broad spectrum and minimal resistance as well as minimal toxicity. The authors applied gentian violet and a related triphenylmethane dye, brilliant green, to 5 bacterial species (*Streptococcus A & B*, *Proteus*, *Pseudomonas aeruginosa* and *Staphylococcus aureus*) as well as *Candida albicans* in vitro. The study showed that GV was very effective, with a low critical concentration, against *Candida* and *Streptococcus* and *Staphylococcus* species, and moderately effective against the Gram negative bacteria. GV was found to be more potent and effective against a greater

number of bacteria than its related compound, brilliant green. The investigators also found that increasing the pH lead to greater activity of GV against *S. aureus*.

The exact mechanism of action of GV is unknown.²¹ Multiple hypothesis exist for an explanation of its anti-microbial effects^{4,22}: an alteration in redox potential by the dye²³, inhibition of reduced nicotinamide adenine dinucleotides phosphate (NADPH) oxidases²⁴, free radical formation^{25,26}, formation of an un-ionized complex of bacteria with the dye²⁷, inhibition of protein synthesis^{28,29}, inhibition of glutamine synthesis²⁹, uncoupling of oxidative phosphorylation³¹ or inhibition of formation of the bacterial cell wall³². Recently, our group discovered that the closely related dye brilliant green formed covalent adducts with thioredoxin reductase 2, a protein conserved from bacteria to humans, with an essential function for cellular activity (Figure 1).³³ Notably, gentian violet is highly effective against Gram positive bacteria, which also form adducts with gentian violet, due to its ability to penetrate the bacterial cell wall and covalently bond to proteins. GV is far less effective against Gram negative bacteria and *Mycobacterium*, presumably due to its inability to penetrate the lipids surrounding the cell wall. This is the basis of the Gram stain, which is still in clinical use for over a century.

Clinical studies of the efficacy of GV in skin infections are mostly limited to case reports and case series with a small number of patients. Brockrow et al. investigated the use of GV in impetiginized eczema both in vitro and in vivo.³⁴ The researchers divided 38 consecutive patients with acute eczema colonized with *S. aureus* into three treatment groups: 0.3% GV, topical diflucortolone, and a 10% tar solution. Of the three treatments, GV was the only treatment to show anti-staphylococcus activity in vitro. Additionally, GV was found to significantly reduce *S. aureus* density in lesional and unaffected skin and also significantly reduced the clinical severity of eczema after 4 days. No adverse events were reported by the authors. In a 2010 study, the senior author (JA) also reported a case of severe eczema superinfected with group A *Streptococcus*, unresponsive to conventional therapy, successfully treated with oral doxycycline and daily applications of a 1% solution of GV.³⁵ The results of these studies are concordant with the recent evidence that treatment of impetiginized eczema reduces eczema severity.³⁶

GV has also been used for many years in preventing bacterial colonization of the umbilical stump following childbirth.^{37,38}

Treatment of Methicillin Resistant *Staphylococcus aureus*

Multiple studies have proven GV's efficacy against methicillin resistant *Staphylococcus aureus* (MRSA).³⁹ Taguchi et al. first documented GV's effectiveness against MRSA in vivo.⁴⁰ Similar to the observations by Bakker et al. with methicillin sensitive staphylococcus aureas²⁰, GV was found to have a very low minimum inhibitory concentration against MRSA. Clinically, multiple studies have shown GV's use against MRSA in the setting of ulcers. A randomized controlled trial performed by Toba et al. showed that GV, when compared to standard treatment of MRSA infected ulcers with iodine, was more effective in killing MRSA.⁴¹ After 14 weeks of treatment with GV, the pressure ulcers decreased to 45% of the area at the start of treatment and no adverse events occurred during the study period.

Saji et al. showed that by using an ointment containing 0.1% gentian violet to 12 cases of patients with MRSA infected decubitus ulcers, MRSA was eliminated completely from the infected areas of the skin within 4 weeks.⁴² A subsequent report by the same group showed that among 18 patients with MRSA infected ulcers, the average time to eradication of MRSA was 10.8 days (+/- 2.7).⁴³ In both studies, there were not any appreciable side effects among the patients treated with GV. Recently, among 28 cases of MRSA pyoderma treated with GV, Okano et al. found that the mean time for eradication was 9.1 +/- 6.0 days.⁴⁴ Concurrent with findings from previously mentioned studies, GV had a low minimum inhibitory concentration for MRSA and no appreciable side effects were reported.

Outside the field of dermatology, GV has been successfully to treat MRSA in otitis media⁴⁵, mediastinitis⁴⁶, prosthetic vascular bypass graft infection⁴⁷, as well as nasal carriage of MRSA⁴⁴. In the face of increasing incidence and emerging resistance to standard therapies, GV has emerged as a potential treatment option for MRSA infections.

Treatment of Gram negative organisms

While early studies of GV found it to be less effective against Gram negative organisms⁸, separate studies by Bakker²⁰ and Fung⁴⁸ have found that GV inhibited growth of *Pseudomonas*, an extremely virulent Gram negative rod, in vitro. Recently a report by Wang et al.⁴⁹ showed that GV disrupts *Pseudomonas* biofilms in vitro. Biofilms are an organized community of microorganisms encased in an extracellular matrix that is adherent to a surface and are a significant source of resistance to host defense as well as resistance to antibiotics.⁵⁰ Additionally, invasive devices such as endotracheal tubes, central venous catheters, and urinary catheters coated with gentian, a mixture of gentian violet and chlorhexidine, have been shown to reduce bacterial adherence and prolong antimicrobial durability against the Gram negative organisms *Pseudomonas*, *E. Coli* and *Klebsiella* both in vitro and in vivo.^{51,52} These findings build upon previous research by Bhatnagar, who showed that GV's antibacterial effects on silastic implants.⁵³

Antimycotic activity

Churchman first showed the antimycotic effects of GV against multiple species of *Candida* in his initial 1912 experiments.⁸ In 1927, intravenous GV was reported to have treated a systemic *Blastomyces* infection.¹⁷ Currently, multiple studies have proven the efficacy of GV against *Candida* in the setting of catheter infections.^{51,52,54} GV was shown to not only have direct fungicidal action, but also disrupt the adherence of *Candida* to catheters. Silver alloy coated urinary catheters are currently the most common catheter used in the United States, but only reduce the relative risk of UTI by 32%.⁵⁵ GV coated catheters were found to be significantly superior to silver alloy urinary catheters in reducing colony counts of seven different microorganisms as well as reducing *E. Coli* burden in the bladder and urine in an in vivo rabbit model.⁵¹

GV has also been used extensively for oral candidiasis (thrush). Painting the mouth of an infant with oral thrush with GV has for more than 90 years been a safe and effective treatment.^{12,56,57} More recently, GV has been used to treat oral candidiasis in human immunodeficiency virus (HIV) infected individuals, especially in developing countries^{58,59}

where treatment with fluconazole is impractical due to availability, cost of treatment and the development of resistance.^{60,61} In a randomized trial comparing GV to nystatin and ketoconazole amongst patients with HIV and oral candidiasis, after 14 days, 11/26 (42%) patients treated with GV had complete resolution of their disease, compared with 10/23 (43%) patients treated with ketoconazole and only (2/23 (9%) patients treated with nystatin.⁵⁸

GV has shown excellent anti-candidal efficacy in vitro, with significantly greater antimycotic activity against 91 candidal strains than other topical alternatives to fluconazole such as chlorhexidine and povidone iodine in one study⁶², and a markedly lower minimal inhibitory concentration when compared to povidone iodine against 102 yeast isolates in a second study.⁶³ GV has also been found to inhibit biofilms of *Candida* isolates taken from HIV infected patients in vitro.⁶⁴

Currently we also use gentian violet for onychomycosis, with application of 1–2% GV to pared nails 3× weekly for one month, and have noted significant improvement (unpublished data). Further studies are needed to establish mycological clearance.

In the previously mentioned studies, topical application of GV for oral candidiasis was well tolerated by all of the patients, with staining of the teeth and infrequent local irritation being the only reported concerns.^{58,59} There have been reports toxicity of gentian violet in the treatment of oral candidiasis, including oral mucosal irritation^{65,66} and necrosis⁶⁷, difficulty with breast feeding⁶⁸ and obstructive laryngotracheitis⁶⁹.

Recently our group demonstrated that tinea versicolor retains topical GV and that GV can be applied as a bedside test to determine the presence of fungal colonization since other hypopigmentary disorders do not accentuate with GV. We have named this phenomenon *in vivo Gram staining*.⁷⁰

Additional antimicrobial effects

In addition to having antibacterial and antimycotic properties, GV is also effective against a broad spectrum of infectious agents. GV has been used since the 1950's as a blood additive for prevention of the transmission of Chagas' disease (caused by protozoan parasite *T. cruzi*) in Latin America where the disease is endemic.^{71–73} GV has been postulated to form a radical by abstracting an electron from NADPH or NADH that is cytotoxic to the Chagas trypanosome.⁷⁴

Hundreds of thousands of patients have received blood transfusions containing GV, without side effects and without any reported cases of transmissible Chagas disease.^{73,75} A recent study found that GV was effective against the protozoa *Leishmania*, the causative agent of cutaneous leishmaniasis, both in vitro and in vivo in a mouse model.⁷⁶ Gentian violet has also been used historically to treat the parasitic nematodes *Strongyloides*^{77,78} and *Enterobium* (pinworm)^{15,79,80}.

Two studies have shown GV to have antiviral activity. A case report published by the author (JA) reported complete resolution of biopsy proven oral hairy leukoplakia (caused by the

Epstein-Barr virus) in an HIV infected patient following 3 treatments with GV.⁸¹ A 2009 study demonstrated the anti-viral properties of GV in vitro against the Nipah and Hendra viruses.⁸²

Anti-angiogenesis and anti-tumor activity

Recent investigational use of GV has shown that it is efficacious as both an anti-angiogenic and anti-tumor agent. Angiogenesis is the generation of new microvessels sprouting from the preexisting vasculature, and has been implicated in the development of a number of dermatological conditions, including hemangiomas, psoriasis, atopic dermatitis, lupus, tumor growth and metastasis.⁸³ As such, angiogenesis is a pivotal target for development of pharmacological treatments for a variety of conditions. Angiopoietins are Tie2 receptor ligands that play key roles in angiogenesis. Angiopoietin-2 (ang-2) in particular is a mediator of pathologic vascular permeability, while angiopoietin-1 mediates vascular stability. Ang-2 is stored in endothelial cells and expressed in growing blood vessels. It promotes angiogenesis and tumor growth by destabilizing blood vessels⁸⁴ and is also involved in promotion of vascular leak in the inflammatory response, allowing cellular elements to translocate across the vascular wall.⁸⁵ Because of its role in mediating inflammatory and tumor angiogenesis, ang-2 is a particular target of antiangiogenic strategies, because blockade of ang-2 results in a decrease of both vascular permeability and angiogenesis. This process has been termed vascular normalization.⁸⁶⁻⁹⁰ Inhibition of Ang2 may promote vessel stability and reduce angiogenesis as well as promote antibiotic delivery to sites of infection by reducing third spacing.³⁹ Finally, NADPH oxidase blockade may impinge on additional inflammatory pathways. Ultraviolet radiation induces NADPH oxidase activates the NLRP3 inflammasome. The NLRP3 inflammasome then leads to the production of caspase-1, which increases mature IL-1b, and thus stimulates inflammation.⁹¹

GV downregulates the production of ang-2 by blocking NADPH oxidase, which is a master regulator of angiogenesis, and regulates both ang-2 and vascular endothelial growth factor.⁹² In a previous study, we found GV to be effective in reducing intratumor levels of ang-2 expression in a murine model of hemangioma as well as reducing tumor size by 95.7% compared to controls.²⁴ A recent study was performed with topical eosin solution, a triphenylmethamine dye structurally similar to GV, in treatment of 18 cases of ulcerated infantile hemangioma. Complete ulcer healing occurred in 16 patients after 4 weeks of therapy and decreased ang-2 expression was found in hemangioma cells in vitro following treatment with eosin.⁹³ Topical administration of angiogenesis inhibitors allows targeted therapy and avoids systemic drug absorption and adverse effects such as vessel regression in healthy tissues and rebound angiogenesis following discontinuation of therapy.^{86,88,94} Further studies are needed to explore the potential benefits of GV as an inhibitor of angiogenesis in dermatological disease. Recently, topical rapamycin has been shown to be effective in inhibiting reperfusion of regeneration and revascularization of photocoagulated blood vessels in humans and animal models of port wine stain birthmarks.^{95,96}

Finally, our group has created triphenylmethane analogs of GV for systemic anticancer therapies. One of our derivatives, imipramine blue, was synthesized from the tricyclic antidepressant imipramine and is considerably more lipophilic than GV. Imipramine blue

crosses the blood brain barrier, especially when administered in a liposomal vehicle. Remarkably, imipramine blue prevents the invasive behavior of glioblastoma in rats, and when combined with liposomal doxorubicin, results in long term remission from glioblastoma.^{97,98} We anticipate that imipramine blue will be useful in the treatment of tumors that use superoxide for signaling, a phenotype known as the reactive oxygen driven tumor.⁹⁹ Of interest, GV is effective in murine models of mesothelioma.¹⁰⁰

Recently, there has been an extensive investigation into angiogenesis inhibitors for the treatment of advanced melanoma, most notably in the clinical trials of Axitinib¹⁰¹ and Bevacizumab¹⁰². Further investigations into the clinical benefit of angiogenesis inhibitors in melanoma are needed. We have reported a case of cutaneous melanoma metastasis successfully treated with no recurrence at 6 months with combination of imiquimod and GV.¹⁰³ It is hypothesized that GV, in addition to directly inhibiting angiogenesis, may potentiate an immune response broader than that of imiquimod alone. A potential mechanism is that melanoma may express immunosuppressive molecules such as B7H1, CD200, indoleamine 2,3-dioxygenase and interleukin-10 which kill cytotoxic T cells and promote the development of regulatory T-cells and myeloid dendritic cells.^{104–108} We have preliminary data that brilliant green downregulates B7-H1 in a variety of tumor cells (Arbiser and Parsa, unpublished data). Addition of NADPH blockade by gentian violet may enhance the response to interferons by blocking the development of regulatory T-cells and myeloid dendritic cells. Based on these findings, we also routinely use the combination of GV and imiquimod on plantar warts. In the case of plantar warts, we pare the lesions, apply 2% GV, and then instruct the patient to apply GV prior to imiquimod to the warts daily.

Dermatitis and other uses in dermatology

GV has been used successfully for treatment of dermatitis, especially in the setting of radiation. However in a recent survey of 45 external beam radiotherapy institutions in the United Kingdom, GV was only used in 2/45 departments (4%) for moist desquamation, while 33/45 institutions were treating with hydrogels (73%).¹⁰⁹ The institutional preference to use hydrogel over GV may stem from the results of two studies, which showed patients prefer hydrogel to GV due to the skin discoloration and drying effect of GV and that GV was less effective than hydrogel in wound healing.^{110,111} However, these studies are limited by their extremely small sample studies, and further research in this area is needed, especially given the anti-microbial properties of GV compared to hydrogel and the high risk of infection in patients with radiation dermatitis.

There have also been published case reports of GV treating the skin lesions of transgrediens pachyonychia congenita¹¹² and hypereosinophilic syndrome.¹¹³ A recent study showing that topical administration of GV may be effective in treating purigo nodularis and atopic dermatitis, and further study is needed.¹¹⁴ We have found that atopic dermatitis expresses high levels of ang-2, accounting for the vascular permeability and erythema observed in atopic dermatitis.³⁵ In addition, since atopic dermatitis is usually colonized with Gram positive organisms, especially MRSA, treatment with GV has the dual benefit of decreasing bacterial colonization as well as reducing proinflammatory ang-2. Finally, it has been demonstrated that crystal violet selectively photo-oxidizes cysteine to cysteic acid over the

complete pH range. While this quality has not been fully utilized, it could potentially be used in the future to determine the oxidation state of free sulhydryls in cells and tissue specimens¹¹⁵. The published dermatologic clinical studies of gentian violet are summarized in Table 1.

Toxicity

Since it has been shown that GV can interact with the DNA of cells¹¹⁶, some controversy exists on its safety and oncogenic potential. In vivo studies have shown that GV acts as a mitotic poison as well as a clastogen.^{117,118} Studies in mice that have been fed extremely large doses of GV showed an increased in hepatocellular carcinoma^{119,120} and in a large trial conducted by the food and drug administration of the United States (FDA), GV fed to rats were shown to have an increase in thyroid cancer after two years.¹²¹ This latter finding is likely due to GV's inhibition of thyroid peroxidase, given the recent finding that GV is a NADPH oxidase inhibitor²⁴, GV likely also inhibits thyroid peroxidase, a structurally similar molecule causing hypothyroidism and feedback stimulation of thyroid-stimulating hormone from the pituitary gland, causing the replication of thyroid cells.¹²²

We believe that GV is extremely safe and without major contraindications for use. Despite more than a century of use, no cases of cancer have been definitively linked to GV. Toxicity of GV in humans is limited to case reports,^{65–69,123–126} trials involving the use of GV have shown no or very mild adverse effects^{33,39,40,57,58} and the FDA allows the sale of gentian violet over the counter.

Summary

Gentian violet is an inexpensive drug with a long history of topical use, as well as systemic use, especially in the prevention of Chagas disease through sterilization of blood transfusions in endemic areas of South America. Given that it is stable at room temperature for years, it has become a staple of dermatologic treatment in underdeveloped countries. However, several factors, including the development of antibiotic resistance, use of catheters and indwelling devices, suggest that GV should be used more extensively in the developed world as well. The clinical usefulness of GV appears to be linked to two distinct mechanisms of action (Figure 1). In mammalian cells, GV inhibits the NADPH oxidase complex, including Nox1,2, and 4, leading to downregulation of superoxide production (Fig 1a). In bacteria, fungi and parasites, gentian violet may form a covalent adduct with thioredoxin 2 (Trx2) (Fig 1B). The discovery that GV inhibits NADPH oxidase demonstrates that GV has an effect on the host as well as infectious organisms, and this can be used to augment anti-angiogenesis and tumor immunity in the 21st century.

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Abbreviations

GV	Gentian Violet
MRSA	Methicillin-resistant <i>Staphylococcus aureus</i>
HIV	Human Immunodeficiency Virus
ang-2	Angiopoietin-2
NADPH	nicotinamide adenine dinucleotide phosphate
FDA	Food and Drug Administration

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- Gentian Violet has an extensive history as an anti-bacterial and anti-fungal agent
- New discoveries have expanded upon its historical uses use, as well as new anti-parasitic, anti-angiogenic and anti-tumor therapies. GV is well tolerated, and inexpensive with a wide spectrum of applications

Figure 1. Dual mechanisms of action of Gentian violet

In mammalian cells (A), GV blocks the activity of NADPH oxidases 1,2, and 4 to inhibit the conversion of molecular oxygen to superoxide. Decreased superoxide results in decreased oxidation of I κ B, leading to NF κ B inhibition and anti-inflammatory activity. In bacterial, fungal, and parasitic cells (B), GV forms a covalent adduct with thioredoxin reductase 2 (TRX2), leading to malfunction of TRX2 and subsequent cell death.

Table 1

Clinical studies of cutaneous disorders treated with gentian violet (GV)

Reference (author, year)	Disorder	Type of study, intervention, number of patients	Results
Brockrow et al. ³³ , 1999	Staphylococcus Aureus colonized atopic eczema	Open label trial, comparison between topical 0.3% aqueous gentian violet to diflucortolone-21-valerate and tar solution, n=31	significant reduction in eczema severity and reduction of S. aureus density after four days
Stoff et al. ³⁴ , 2010	Group A Streptococcus colonized atopic eczema	Case report, GV 1% solution applied to affected areas twice daily and doxycycline 100 mg bid, n=1	Complete resolution at two week follow up
Toba et al. ⁴⁰ , 1997	Pressure sores infected with MRSA	Randomized controlled trial, GV plus dibutyl cAMP vs. povidone-iodine plus sugar, n=19	At 14 weeks mean area of pressure sores decreased by 45%, 93% of culture dishes showed no S. aureus
Saij et al. ⁴² , 1993	MRSA infected decubitus ulcers	Open label trial, 0.1% GV applied to ulcers following 2–24 weeks of failed eradication with antibiotic therapy, n=18	Complete eradication of MRSA in average of 10.5 +/- 2.5 days
Okano et al. ⁴³ , 2000	MRSA infected pyodermas	Open label trial, 0.5% GV applied qd, n=28	Complete eradication of MRSA in average of 9.1 +/- 6 days
Nyst et al. ⁵⁷ , 1992	oropharyngeal and esophageal candidiasis in AIDS	Randomized unblinded, 0.5% GV aqueous solution vs. ketoconazole vs. nystatin, n=141	Resolution of oropharyngeal lesions in 42%, improvement in 39%. Resolution of esophageal lesions in 9%, improvement in 32%
Wright et al. ⁵⁸ , 2009	Oropharyngeal candidiasis in AIDS	Randomized controlled trial, 0.5% GV aqueous solution vs. lemon grass vs. lemon juice, n=90	Resolution of oropharyngeal lesions in 52%
Bhandarkar et al. ⁷⁹ , 2008	Oral hairy leukoplakia in AIDS	Case report, 2% GV, n=1	Complete clinical resolution after three treatments
Lapidoth et al. ⁸⁵ , 2009	Ulcerated infantile hemangiomas	Open label trial, Eosin 2% solution tid qd under dressing, n=18	Complete ulcer healing in 88% after four weeks
Arbiser et al. ⁸⁸ , 2012	Cutaneous melanoma metastasis	Case report, 1% GV plus imiquimod follow cryotherapy, n=1	No recurrence at 6 months follow up
Harris et al. ⁹⁷ , 2012	Transgrediens pachyonychia congenita	Case report, 2% GV, n=2	Substantial clinical improvement