

REVIEW

GENTIAN VIOLET: WHAT WE KNOW AND WHAT IS AHEAD OF US

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Abstract: At present, the only active substance of Gentian Violet (GV) is methylrosaniline – a triphenyl-methane dye of which amino group contains 2 methyl groups. GV can be used to treat uncomplicated bacterial and/or yeast infections, support antibiotic therapy of more severe infections, but also to protect medical equipment against colonization by microorganisms. In the light of recent studies, there are many new possibilities for GV application. It has been shown to be effective in the treatment of viral infections, some chronic skin diseases and oncology. GV can induce apoptosis of tumor cells among others by elevating caspase 8, inhibiting NADPH oxidases, decreasing mitochondrial thioredoxin 2 or inhibiting STAT3/SOX2 axis. Preclinical and in vitro studies have also demonstrated GV efficacy in the treatment of breast cancer, melanoma tumors and cutaneous T-cell lymphoma. There is no unambiguous evidence indicating the toxicity of GV, whereas its safety has been proven by its long history of use, its inclusion in numerous guidelines and its legal trade and distribution with no specific approval requested in many countries around the world. The article gathers the available knowledge about GV and its potential use in the future.

Keywords: p53, crystal violet, gentian violet, fungal infection, bacterial infection

Gentian Violet (GV), also known as gentian or crystal violet, has a long, more than a 100-year old history of use. At present, methylrosaniline chloride is considered to be the only active GV substance (Fig. 1) (1, 2). In the past, GV was as a mixture of dyes with different numbers of methyl substituents (3). During that period it had appeared under many names some of which, although mistakenly, are still

used as synonyms. Currently, gentian, crystal violet and methylrosaniline are considered to be the correct synonyms for gentian violet (2). Names such as pyocyaninum, aniline violet and brilliant violet, although obsolete, are still often used also in scientific publications. GV is often confused with methyl violet which is a completely different compound (a mixture of three, four, five and six methyl dyes) (4). Charles Lauth is the discoverer of GV, which was a mixture of many dyes at the time. He synthesized it in 1861 and called it Paris Violet (5). It was launched on the market and disseminated about twenty years later by George Grubler. Originally, it was used as a biological agent and only later as an industrial dye. Of particular importance to GV is Georg Hans Gram, who used it for dyeing histological preparations, which provided the basis for the most widespread division of bacteria into Gram positive and Gram negative (6). GV was often used because of its low price, high stability and tolerance, and it was very commonly used until the beginning of the 20th century (7). It was then used to treat wounds (8), oral candidiasis (9), impetigo (10), burns (11), pinworms (12) and even generalized mycoses and sepsis (13). Due to the variable composition of formulations, the lack of established

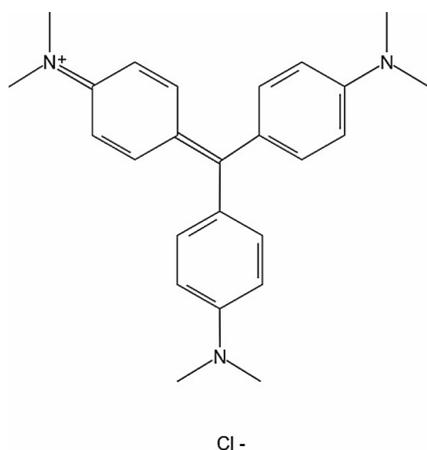


Figure 1. Gentian Violet (methylrosaniline) chloride structure (1)

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active substance, bitter taste and discoloration of the skin and mucous membranes it was then replaced by sulfonamides, later on by penicillin and other antibiotics which then showed much greater effectiveness (7). In highly developed countries, this has been maintained until today. Things are different in the third world countries where the low price of GV (about ≤ 0.22 for 1 mL of a 1% solution in the United Kingdom) (14) makes it easily available and often used. Externally it is mainly used for the treatment of fungal infections of the skin and mucous membranes and because of its bactericidal properties, it is employed for wound disinfection and treatment of infections (15). It is also administered with transfused blood to prevent the transfer of trypanosomiasis (16). Early 20th century studies indicate the possibility of intravenous injection without the occurrence of serious complications (13).

As of today, GV is a forgotten drug. In the era of the growing resistance of bacteria and fungi, the re-discovery of drugs can be an effective alternative in the treatment of many infections. Recent reports indicate that GV has numerous properties that have not been known until now. This review was carried out in order to collect and organize knowledge about GV, to indicate its applications in specific diseases and to present the latest reports on its characteristics unknown so far. According to the authors, numerous undiscovered features of GV reveals that this drug has large research potential.

Characteristics

GV is methylosaniline chloride – a dye with triphenylmethane and six methyl substituents. It dissolves well in the water in which it has a violet color and bitter taste. Its activity depends on the pH, but it works better in an alkaline environment (1, 2, 3, 17). GV uptake in the gastrointestinal tract is very efficient. The half-life is approximately 1.5 h (17). Due to frequent veterinary, use GV has been well studied on animals as a mixture with a certain amount of 5-methyl dye. Clinical trials on humans have not been conducted. In some animals, GV accumulation in adipose tissue has been shown (18).

The properties of GV which have been confirmed include antifungal, antibacterial, antiprotozoal and anthelmintic properties (19). Further potential – and currently investigated properties also include anti-mitotic (20), anti-neoplastic (21) and anti-angiogenic (22, 23) effects. The antifungal activity is strongest against *Candida albicans* (24–27), although the spectrum is most likely to be much higher as evidenced by the overall efficacy in the treatment of cutaneous fungal infections. GV defi-

nately works more effectively against Gram-positive bacteria (*Streptococcus A & B*, *Staphylococcus aureus*) (15). Gram-negative bacteria are more resistant due to the external lipid membrane, however, GV-susceptible strains have been identified (*Proteus*, *Pseudomonas aeruginosa*) (15). GV is also used to treat Chagas disease (*Trypanosoma cruzi*) (16) and pinworms (*Enterobius vermicularis*) (12).

The mechanism of action

The exact chemical mechanism of GV has not been clearly explained. It is assumed that GV works in various ways. Antimicrobial properties are believed to be connected with the GV ability to alter the redox potential (16, 28). The consequence of this is damage to DNA or mitochondrial dysfunction and the death of microorganisms. Another hypothesis assumes that bactericidal or bacteriostatic activity is associated with the formation of complexes with the cell wall of bacteria or disorders of glutamic acid metabolism (29). It was also noted that GV is able to combine with proteins. The ability to block nicotinamide adenine dinucleotide phosphate (NADPH) oxidase explains the positive effect on inflammatory pathways (21, 22). Binding to caspases and inhibition of SOX 2 proteins is expected to exacerbate apoptosis and produce an antitumor effect (23). It is also assumed (in vitro studies) that GV may stimulate the p53 antitumor gene in a direct or indirect way by inhibiting NOX gene expression which is responsible for blocking p53 (21). GV, similarly to other cationic triphenylmethanes, can also induce tumor cell death by impairment of mitochondrial function. It is considered that cationic triphenylmethanes decrease mitochondrial thioredoxin 2 (Trx2), which plays an important role in cellular regulation and apoptosis (30). Disruption of the mitochondrial and cytoplasmic redox system might account for the most important antitumor and antimicrobial mechanisms of gentian violet.

To determine which mechanisms and to what extent such mechanisms underlie the properties of GV additional research is needed to help determine the possibilities of GV application in various diseases and to indicate the directions of further clinical trials.

Applications

Gentian Violet can be used to treat bacterial, fungal, mucous and skin infections, as well as treating wounds and burns. It is possible to apply the medicine precisely by brushing it onto the affected areas. The application accuracy is facilitated by the violet color.

Fungal infections

GV has demonstrated outstanding performance in the treatment of oral candidiasis in patients with HIV. In studies comparing treatment efficacy (mouth washing and oral drug administration) GV oral candidiasis in a non-discoloration concentration had similar efficacy to nystatin (31). In another study, the effectiveness of GV applied at a higher concentration of 0.5% was higher than that of nystatin and the same as ketoconazole (32). In the treatment of throat infections, the effectiveness of nystatin and GV were similar but significantly lower than ketoconazole. This proves that GV can be used successfully in adjuvant therapy (33). The combined use of nystatin and GV is yet to be studied. In the case of mucous membrane infections or open wounds, it is recommended to use aqueous solutions of GV to avoid irritation. In addition, it is possible to use GV to protect against infection. It has been shown that in addition to fungicidal and fungicidal properties, GV impedes microbial colonization of surfaces (34). Studies carried out in the United States have shown great effectiveness of GV-coated catheters (35).

Bacterial infections

Gentian violet can be successfully used in the treatment of diseases caused by the invasion of Gram-positive bacteria (especially *Streptococcus A & B*, *Staphylococcus aureus*) and some Gram-negative strains (*Proteus*, *Pseudomonas aeruginosa*) (15). The use of GV for the eradication of methicillin-resistant *Staphylococcus aureus* (MRSA) is extremely promising (36-40). Studies on a group of 38 patients with acute eczema colonized by *S. aureus* showed an improvement in the clinical condition within 4 days. The improvement was better than in the concurrent study with glucocorticosteroids and 10% tar solution. The authors did not report any adverse events (40, 41). Subsequent reports showed the efficacy in the eradication of MRSA from ulcers in about 10.5 days (37). GV can also be applied in the external ear MRSA infection and nasal infection. In terms of intravenous GV application, it was successfully used in the treatment of mediastinitis (42) and vascular graft infection (43). In the face of increasing incidence of MRSA infection and emerging resistance to standard therapies, GV emerged as a potential treatment option for many bacterial infections, especially MRSA. Infrequent use of GV may result in reduced GV-resistance in bacteria.

Wounds

Studies suggest that GV is an effective local remedy for healing small, superficial wounds. When

applied in geriatric patients GV successfully promoted wound healing (44). The observation shows that scar tissue formation after GV application is comparable with other means or is only insignificantly higher. However, while using GV careful attention must always be paid to avoid covering the entire wound, which can make it impossible to assess the wound condition (8).

Burns

Gentian violet can produce positive results in the management of 1st and 2nd degree burns. A study at the Chhattisgarh Institute of Medical Sciences in Bilaspur showed that GV is an effective treatment for burns. Studies have shown comparable efficacy in non-conservative treatment with a slight increase in scarring (45). In the treatment of post-irradiation burns, GV effectiveness is comparable but patients' satisfaction is decreased. (46, 47). Therefore, it seems reasonable to use GV as the first aid in burns whenever other medicines are not available, or as a complementary therapy when mono-therapy does not produce the expected results (11, 45).

Anti-parasitic effect

Blood transfusion is an important mechanism for transmitting Chagas disease. The addition of GV to the collected blood prevents transmission of the disease after blood transfusion (16). GV presence in blood decreases its quality slightly yet it is not significant enough to cause any clinical symptoms (48). This efficiency together with the low price of GV makes it an extremely economical prophylactic element (48, 49). In studies by R.C. Jung, about 81-92% efficacy in the treatment of pinworm infections (*Enterobius vermicularis*) with GV suspensions and good treatment tolerability were demonstrated (50). However, taking into account the efficacy of other anti-parasitic drugs, it is recommended to use GV only in the absence of an alternative.

Potential new applications of GV

GV can be a potential drug in the treatment of cancer, viral and chronic infections as well as in congenital skin diseases.

Anti-cancer therapy

In current studies, it has been shown that GV can cause a strong anti-proliferative effect on malignant melanoma cells. In the treatment of melanoma metastases to the skin, neoplastic regression was observed when the therapy with imiquimod was applied (23). GV led to an increase in the inflammatory response. In vitro studies have shown that GV

impairs melanoma stem cell survival and self-renewal by inhibiting STAT3/SOX2 axis. GV has a negative effect on the signal transducer by blocking the transcription factor which prevents activation. GV promotes mitochondrial apoptosis and G2-cycle arrest too. This leads to the destruction of tumor stem cells in the apoptosis mechanism (51). The use of GV, alone or with other anti-tumor drugs, in malignant melanoma treatment, increases the chances of recovery.

In other *in vitro* studies performed on breast cancer cells (MDA-MB-231 triple negative line), GV was shown to inhibit tumor cell proliferation and stimulate their apoptosis (52). The effect depended on the applied dose. Studies on mice with bone metastases of breast cancer induced and treated with GV showed a reduction in bone tissue damage due to tumor growth. The mechanism by which GV leads to apoptosis is unknown, however, it is most likely to be related to its ability to bind to proteins, in this case with caspases. Studies have revealed that in the presence of a caspase-3 inhibitor, MDA-MB-231 cells were completely protected against the inhibitory effects of gentian violet. This may indicate GV activity by the regulation of the caspase function (52).

Gentian Violet anticancer activity may partly depend on p-53 activation. Tumor cell growth inhibition and apoptosis are controlled by targeted genes set to action by the p-53 transcription factor. It is suggested that GV may inhibit NADPH oxidases (NOX). Overexpression of NADPH oxidases plays a role in cancer progression, e.g., NOX1 inhibit onco-suppressor p53 (21). Studies on colon cancer and glioblastoma cells confirmed that GV was able to increase the transcriptional activity of P53 through NOX1 inhibition (21). Considering that tumors contain mutations in the P53 gene, this creates a large therapeutic potential for GV.

In the preclinical study, GV appeared to be the potential drug in the treatment of cutaneous T-cell lymphoma (CTCL). GV induced apoptosis tumor cells via elevating caspase 8, via Tumor Necrosis Factor (TNF) and FAS-related inducing ligand pathways (53).

There is a known case of a GV efficiency in the treatment of primary diffuse cutaneous lymphoma (PCLBCL) in an 84-year-old woman. The patient was initially treated with radiotherapy, which caused temporary regression. Treatment of the recurrence was not possible due to comorbidities. Since the patient could not be qualified for chemotherapy, radiotherapy or surgery local treatment was applied. GV was used 3 times which resulted in complete remission of changes (54).

Research on GV also includes its use as a model for the synthesis of new compounds with anticancer properties. Analogs with structures and properties of triphenylmethanes were used in the treatment of B-cell lymphoid malignancies. These analogs induced caspase-dependent apoptosis in tumor cells by disrupting the work of apoptosis-regulating protein. This confirmed a large GV value both as a medicinal intervention and as a research area (55).

Antiviral activity

Two studies have shown GV antiviral activity. After 3 series of GV applied via biopsy a complete resolution of the hairy leukoplakia (caused by the Epstein-Barr virus) was observed in a patient infected with HIV (56). Moreover, in 2009, the antiviral properties of GV were demonstrated in an *in vitro* study with the Nipah and Hendra viruses (57).

Others

GV positive use in the treatment of congenital nail thickening (Latin: *transgrediens pachyonychia congenita*) (58) and locally in the hypereosinophilic syndrome has also been reported (59). To date, no studies have been carried out on the effectiveness of GV in the fight against acne. However, indirect evidence suggests its potential use. GV penetrates well into the hair follicles (60) and as Gram-positive *Propionibacterium acnes* is responsible for the cause of more than 80% of acne (61), GV is likely to be an effective anti-acne agent.

Toxicity

GV, even when contaminated by other dyes, is considered a safe drug with a limited number of side effects (20, 61, 62, 63). The potential side effects of short-term oral application include nausea and irritation of mucous membranes (32). There are no complications when GV is administered to the skin. The exact frequency of complications has not been determined. Reports on severe side effects of GV are mainly limited to descriptions of individual cases, which included tracheitis (64), transient leukopenia and necrosis of the oral mucosa (65). Studies on the long-term effects of GV have shown an increased risk of hepatocellular carcinoma in mice and follicular thyroid adenoma in rats (66). It should be remembered, however, that the exposure time and the dose were extremely high in these studies. It is doubtful, however, that such doses over such long intervals could be required in humans during therapy or that there is a need to use similar doses at such long intervals. The safety of GV, in turn, is evi-

denced by the lack of complications despite its frequent use in blood transfusion, its free trade approval by FDA (62) and its inclusion in many national and WHO recommendations (67). Intravenous administration may be associated with discoloration of the vessels and muscles, nausea and blood clots at the injection sites.

Gentian preparations

Most often GV is used as 0.5%, 1% or 2% aqueous solutions or spirits (68). The higher the concentration, the greater the discoloration and potential irritation of the skin or mucous membranes. Preparations based on the spirit are recommended for external infections without skin disruption and absolutely not recommended to be used on

mucous membranes (19). Aqueous solutions do not cause irritation, therefore it is recommended to use them on open wounds and mucous membranes. It is possible to dilute the solutions, with 0.000165% being considered a non-discoloration concentration (24). Studies show that such a concentration of GV already has fungicidal properties. In addition, GV occurs in the form of antibacterial foam, spray and dressings (69). However, these forms are less accessible or popular. In addition to external administration and application on mucous membranes, intravenous injection is possible, although there are no preparations for such an administration available, neither are there precise descriptions of its side effects.

Table 1. Evaluation of the level of evidence according to the Center for Evidence-Based Medicine (70).

Disorder	Level of evidence	Results	Type of study	References
Fungal infection	1A	High efficacy in the treatment of candidiasis of the skin and mucous membranes and simple fungal infections. In local treatment, efficacy comparable to nystatin.	Randomized controlled	(31-33)
Bacterial infection	1A	The Gram-positive and some Gram-negative bacteria show sensitivity. The exact mechanism is unknown. Effectiveness depends on the pH environment.	Randomized controlled	(15, 34-40)
Antiparasitic infections	2B	Preventing the transmission of Chagas disease in blood transfusion. Effectiveness in the treatment of pinworms (eradication in about 80%)	Open clinical trials	(16, 49-50)
Virus infection	4	Effectiveness in the treatment of hairy leukoplakia and inhibition of Nipah and Hendra viruses has been demonstrated	Case report	(56, 57)
Treatment of wounds	1A	Scarring unnoticeable or not much greater than with regular therapy. High efficacy against resistant strains - MRSA	Open clinical trials	(8, 45)
Treatment of burns	1A	Effectiveness in 1st and 2nd degree burns	Randomized controlled, clinical trials	(11, 45-47)
Surface protection	5	Gentian-coated Foley catheters were more effective in preventing colonization and prevention of urinary tract infections than silver and uncoated catheters	Laboratory studies	(34, 35)
Tumor therapy	4/5	Effective use in the metastasis of malignant melanoma, breast cancer and primary diffuse lymphoma from B lymphocytes. Potential efficacy in p53-dependent tumors	Case report and laboratory studies	(21, 23, 51-55)
Treatment of atopic dermatitis	2A	Efficacy in the treatment of eczema with <i>Staphylococcus aureus</i> invasion. Cured within 4 days up to 2 weeks. GV works more effectively without co-administration of glucocorticoids	Open clinical trials	(40)
Treatment of transgrediens pachyonychia congenita	4	Reduction of symptoms of excessive keratocytosis	Case report	(58)

Level of evidence

The studies on GV carried out so far have different levels of evidence according to the Center for Evidence-Based Medicine (Table 1) (70). Antifungal and antibacterial activity has been confirmed most strongly. The level of evidence seems lower when GV is used in the prevention of colonization and atopic dermatitis. Its use in other cases is confirmed by the descriptions of individual cases or indirectly by the results of laboratory tests.

Review restrictions

This review has a significant limitation which results from the complicated history of GV, i.e., the variability in its composition over the last hundred years. In the past, GV consisted of 4-6 methyl dyes, currently, it is only available as a 6 methyl dyes formula. This undermines the accuracy of the studies carried out so far. It is not certain what the level of the concentration of methylrosaniline was in the preparations used by researchers and how many other dyes there were. The uncertainty also refers to recent studies because the purity of GV preparations is not legally stipulated. The regulations allow for up to 10% of impurities, most often with methyl violet 6B. It is possible, therefore, that the results obtained so far may be confounded by the presence of other compounds to a confusing degree. This indicates the need to verify existing research.

Summary

GV is a poorly investigated substance despite its over 100-year history of use. It is a relatively safe but long-forgotten drug. It is well absorbed by the gastrointestinal tract, and in some species it accumulates in adipose tissue. Its strength depends on the pH value: the greater the pH the better GV works. In clinical practice, it is most often used on the skin and mucous membranes. It is popular in poorly developed countries, where, due to its low price, it is the only available therapeutic option. Due to the development of drug resistance of bacteria and fungi in developed countries, GV is recommended for consideration as a potential therapeutic solution. It can be used as a monotherapy as well as an adjuvant therapy. GV shows great effectiveness in simple, uncomplicated fungal infections (especially *Candida albicans*) and bacterial infections (especially Gram-positive bacteria) where it works well as a first-line drug. In other situations, it should be considered only after exhausting other therapeutic options or as part of adjuvant therapy. Due to the small number of tests, not all of its properties have been recognized. Its potential anticancer properties make it an increasing-

ly frequent research object. The precise designation of the action spectrum of GV may render it a “new”, useful tool in the treatment of infections and many other diseases, including cancer.

Conflicts of interests

The authors declare that they have no conflict of interest in relation to the work described.

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