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Antiviral Research 67 (2005) 155–162
Antiviral Research
www.elsevier.com/locate/antiviral

Effect of resveratrol on herpes simplex virus vaginal infection in the mouse

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Received 11 May 2004; accepted 22 June 2005

Abstract

Resveratrol (3,5,4′-trihydroxystilbene) is a natural component of certain foods, such as grapes, that, when topically applied, has been shown to limit HSV-1 lesion formation in the skin of mice [Antiviral Res. 61:19–26, 2004]. To determine if it is active on genital HSV infection, the vagina of mice were infected with HSV-2 or HSV-1 and treated with a cream formulation of resveratrol. Mice were evaluated daily for extravaginal disease and vaginal swabs were taken regularly and assayed for infectious virus. Initial studies demonstrated that 19% resveratrol cream administered intravaginally five times a day for 5 days beginning 1 h after infection significantly reduced HSV-2 replication beginning on day 1 of infection and prevented extravaginal disease when compared to animals treated with placebo. When resveratrol was tested at a concentration of 6.25% and 12.5% administered five times a day, 6.25% limited virus replication only on day 1 and delayed development of extravaginal disease by 1 day. However, 12.5% resveratrol inhibited HSV-2 replication beginning on day 1 and abolished extravaginal disease. If the number of applications per day was reduced to three for 5 days, 12.5% resveratrol inhibited HSV-2 replication only on day 1, while 19% resveratrol inhibited it throughout the 9-day assay period. When the animals with three treatments per day were examined for extravaginal disease, it was found that 12.5% resveratrol was ineffective when compared to placebo, while animals treated with 19% resveratrol did not exhibit extravaginal disease. When treatment was delayed 6 h, 12.5% resveratrol did not inhibit HSV-2 replication or extravaginal lesion formation, but 19% resveratrol did. When resveratrol was used to treat vaginal HSV-1 infection, it was found that 12.5% resveratrol did not limit replication or prevent extravaginal lesion formation. In contrast, 19% resveratrol did significantly limit vaginal HSV-1 replication and reduced extravaginal lesion formation, but the latter was not significant. Mortality rates in placebo-treated animals was 37%, 6.25% resveratrol-treated animals was 40%, 12.5% resveratrol-treated animals was 24%, and 19% resveratrol-treated animals was 3%. Collectively, these results demonstrate that resveratrol cream inhibits or reduces HSV replication in the vagina of mice and limits extravaginal disease.

Keywords: Resveratrol; Herpes simplex virus; Mouse

1. Introduction

Genital herpes simplex virus (HSV) infection afflicts a significant proportion of individuals (Whitley and Gnann, 1993). Once infected, the virus remains in the sacral ganglia where it can serve as a source of recurring infection in the afflicted individual. These recurring infections in turn serve as a source of infection for an unwitting contact or a newborn passing through the birth canal (Whitley et al., 1980).

The first line of treatment for genital HSV infection has been acyclovir (Elion et al., 1977), or its derivatives, such as valaciclovir (Spruance et al., 1996). In spite of the success of these drugs, the number of individuals with genital HSV infections has steadily increased and is estimated to be approximately 86 million worldwide (Halioua and Malkin, 1999). But studies have shown that the estimate of HSV-2 infection may be low because type-specific serological studies have revealed that the seroprevalence of HSV-2 infection among individuals is considerably higher than the reported history of genital HSV-2 (Janier et al., 1999; Leone et al., 2004). In addition, the number of HSV-1 genital

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doi:10.1016/j.antiviral.2005.06.008

infections has increased relative to HSV-2 genital infections (Roberts et al., 2003; Tran et al., 2004) and is now equal to, or in excess of, the number of HSV-2 genital infections in some geographical areas (Samra et al., 2003).

Because of the high number of genital HSV infections and because they are life-long and recurrences serve as a source of infection for others, the development of novel anti-HSV products to treat such infections is ongoing. One approach has been to examine natural products isolated from plants for anti-HSV activity. Efforts in this area are extensive and positive results have been obtained using extracts from plants (Nakano et al., 1998; Chiang et al., 2003; Lipipun et al., 2003), root tubers (Nawawi et al., 1999), bark (Cheng et al., 2003), flowers (Suksamrarn et al., 2003), leaves (Janwitayanuchit et al., 2003), and fruit (Docherty et al., 1999, 2004).

One of these botanical agents is resveratrol (3,5,4′-trihydroxystilbene) which has been shown to have anti-HSV properties in vitro (Docherty et al., 1999) and in vivo (Docherty et al., 2004). Resveratrol is a non-flavonoid phenol compound produced by some spermatophytes, such as grapes. It is present in grape skins, but not flesh, and therefore is found in red wine where it has been identified as the major active compound of stilbene phytoalexins. It has been reported that resveratrol has anti-cancer properties (Jang et al., 1997), anti-inflammatory properties (Chan et al., 2000; Donnelly et al., 2004), anti-mycotic properties (Jeandet et al., 1995), anti-bacterial properties (Mahady and Pendland, 2000; Docherty et al., 2001; Chan, 2002), and beneficial cardiac effects (Goldberg et al., 1995).

When resveratrol was used to treat epidermal HSV infections in a mouse model, it was shown to be effective against HSV-1 (Docherty et al., 2004). The studies presented here were designed to examine the effectiveness of the drug against HSV vaginal infection in the mouse. The results demonstrate that it was effective against HSV-2 and HSV-1 vaginal infection in the mouse, but was dependent on resveratrol concentration, time of administration after infection, number of treatments per day and virus type.

2. Materials and methods

2.1. Virus

Two different HSV types were used in this study. HSV-2, isolated from a genital lesion, and HSV-1, isolated from an oral lesion, were previously characterized (Zimmerman et al., 1985). Virus pools were prepared in Vero cells in complete media (Media 199 supplemented with 5% fetal calf serum, 0.075% $NaHCO_3$, and 50 μg/ml gentamycin sulfate). Virus was quantified by the plaque assay in Vero cells.

2.2. Drug

Resveratrol was prepared in a polyethylene glycol base. The qualitative composition of the placebo was identical to the resveratrol cream with the exception of the absence of resveratrol. The pH of the placebo was 5.6, while resveratrol preparations were 6.0. Viscosity for the placebo was 10,500 cP while the resveratrol preparations were 8500 cP.

2.3. In vivo studies

All animal studies were reviewed and approved by the IACUC. Five-week-old SKH1 mice (Charles River, MA) which are hairless, euthymic, and immunocompetent were used in all studies. Each group of animals contained 9–11 mice.

Three days prior to infection, mice were injected subcutaneously with 1.0–1.25 mg progesterone in phosphate-buffered saline (pH 7.4). On the day of infection, the mice were anesthetized with nembutal, the vagina swabbed with a Tris-buffered saline (pH 7.4)-soaked calcium alginate swab, dried with a calcium alginate swab and inoculated with 10 μl of HSV-2 or HSV-1 containing 10^5 plaque-forming units (pfu) of virus. The average infection rate using this amount of virus and progesterone was 70% (low, 60%; high, 80%).

Animals were treated starting 1, 6, or 12 h after infection with placebo, 6.25%, 12.5%, or 19% resveratrol. In one study, 5% acyclovir in 0.5% methylcellulose and 0.2% Tween 80 was included. If animals were treated three times a day, the treatment intervals were 4 h apart beginning at 8:00 a.m. and ending at 4:00 p.m. If animals were treated five times a day, the treatment intervals were 3 h apart beginning at 8:00 a.m. and ending at 8:00 p.m. Regardless of drug concentration or number of treatments each day, all animals were treated in all studies for 5 days.

Drugs were administered through polyvinyl chloride tubing 1 mm in diameter attached to a 1 ml syringe. Thirty microliters of drug were injected into the vaginal vault at the designated times using new tubing for each animal.

Vaginal samples for infectious virus were taken every other day for 9 days beginning on day 1 post-infection. After the sample was taken by insertion and rotation of a sterile calcium alginate swab in the vagina, the swab was immersed in cold complete media and frozen at −80 °C until quantitated by the plaque assay on Vero cells. Samples were not taken after day 9 because virus was not recovered from the vagina beyond that point.

Extravaginal signs of disease were recorded daily for 11 days for each animal and scored on a five-point scale as follows: 0, no infection; 1, few isolated papules and slight redness of extravaginal tissue; 2, few isolated papules, ulcers, and/or eschar and/or swelling and redness of extravaginal tissue; 3, multiple fused ulcers/eschars, moderate swelling and redness of extravaginal tissue with extension to surrounding tissue; 4, ulceration with severe redness and swelling of extravaginal tissue with extension to surrounding tissue, rear leg paralysis; 5, severe ulceration of extravaginal tissue with extension to surrounding tissue, weight loss, rear leg paralysis, and death. Data were not collected beyond 11 days

because it was noted that, by day 11, animals recovered with no further progression of extravaginal disease or died.

2.4. Statistical analysis

Each experimental group contained 9–11 animals. Vaginal titer data were log transformed and treatment groups compared day to day by independent samples *t*-test. The equality of variances was not assumed for non-homogenous variance according to the Levene test. All reported *p*-values are two sided and all significant confidence intervals are at a 0.05 level.

3. Results

3.1. Effect of resveratrol on HSV-2 vaginal infection

Initial studies were designed to determine if resveratrol could adversely affect HSV-2 replication in the mouse vagina. For this purpose, the maximum concentration of resveratrol (i.e. 19%) and applications (i.e. five applications per day for 5 days) was used beginning 1 h after infection. The results presented in Fig. 1a demonstrate that 19% resveratrol administered intravaginally five times a day significantly inhibited HSV-2 replication on days 1 ($p = 0.042$), 3 ($p = 0.002$), and 5 ($p = 0.003$) when compared to animals treated with placebo. There was no significant difference on day 7 between placebo-treated animals and 19% resveratrol or acyclovir-treated animals because the number of placebo-treated animals from which virus was recovered had diminished considerably as did the amount of virus recovered from them. Acyclovir was included as a positive control and significantly inhibited vaginal HSV-2 production on days 3 ($p = 0.002$) and 5 ($p = 0.003$) (Fig. 1a). Acyclovir was inhibitory on days 1 and 7, but did not reach significance; while on day 9, acyclovir, like resveratrol, was not significant because placebo animals had recovered from the infection or died. HSV-2 was recovered from one acyclovir-treated animal on day 1 and a different acyclovir-treated animal on day 9. Animals in the three groups were examined daily for signs of extravaginal disease. The earliest sign of extravaginal infection occurred in the placebo group on day 5. The difference between the placebo group and the 19% resveratrol or acyclovir-treated group was apparent on days 5–8 (Fig. 1b). However, by day 9, one acyclovir-treated mouse exhibited characteristic signs of HSV-induced extravaginal disease abolishing any significant difference between the acyclovir and placebo group. In this study, none of the 19% resveratrol-treated mice showed signs of extravaginal HSV disease (Fig. 1b) but a significant difference between placebo and 19% resveratrol-treated animals was not reached until days 10 and 11.

Two placebo-treated mice and one acyclovir-treated mouse died, but none of the resveratrol animals expired (Table 1). These results suggest that resveratrol is capable

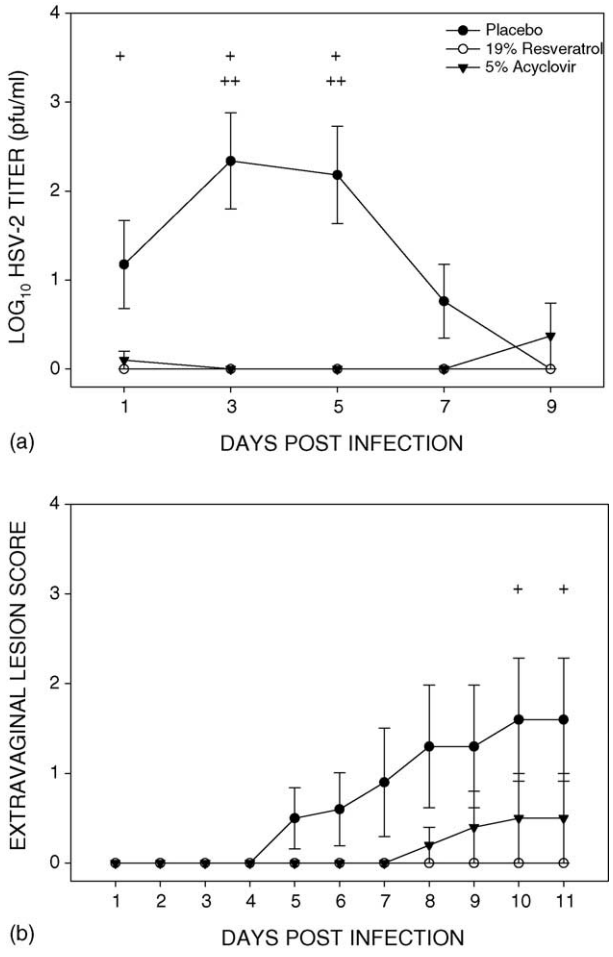

Fig. 1. Resveratrol or acyclovir treatment of HSV-2 vaginal infection. Beginning 1 h after infection, the vagina of SKH1 mice were treated every 3 h five times a day for 5 days with placebo, 19% resveratrol or 5% acyclovir. (a) Vaginal titers are log transformed and reported as the mean, ±S.E.M. and (b) extravaginal lesion score is reported as the mean, ±S.E.M. $^{+}p < 0.05$ comparing vaginal titers or lesion score of placebo vs. 19% resveratrol as determined by independent samples *t*-test; $^{++}p < 0.05$ comparing vaginal titers or lesion score of placebo vs. acyclovir as determined by independent samples *t*-test.

of adversely affecting HSV-2 replication in the mouse vagina as well as limiting extravaginal disease.

3.2. Drug concentration

Studies were performed to establish the lowest concentration of resveratrol that could be used to control HSV-2 replication in the mouse vagina. For this purpose, animals were inoculated and treatment begun 1 h after infection with placebo, 6.25% or 12.5% resveratrol administered five times a day for 5 days. The results in Fig. 2a demonstrate that other than day 1, all other time points (i.e. days 3, 5, 7, and 9) were not significantly different from placebo when animals were treated with 6.25% resveratrol. This contrasts with the results that were obtained with 12.5% resveratrol treatment which revealed that this concentration of drug significantly reduced HSV-2 replication in the vagina on days

Table 1
Mortality rates of mice treated with placebo or drug

Treatments per day[a]	Placebo	6.25% Resveratrol	12.5% Resveratrol	19% Resveratrol	5% Acyclovir
a	2/10[b]	–	–	0/10	1/10
b	6/10	4/10	0/11	–	–
c	4/10	–	3/10	0/10	–
d	5/11	–	3/11	1/10	–
e	2/10	–	4/10	0/10	–

[a] a: HSV-2 infection, animals treated five times a day beginning 1 h after infection; b: HSV-2 infection, animals treated five times a day beginning 1 h after infection; c: HSV-2 infection, animals treated three times a day beginning 1 h after infection; d: HSV-2 infection, animals treated five times a day beginning 6 h after infection; e: HSV-1 infection, animals treated five times a day beginning 1 h after infection.
[b] Number of dead animals/number of total animals in the group.

1 ($p = 0.006$), 3 ($p = 0.001$), 5 ($p = 0.001$), and 7 ($p = 0.013$) when compared to placebo. There was no significant difference between placebo and 12.5% resveratrol on day 9 because placebo-treated animals had either recovered or died from infection.

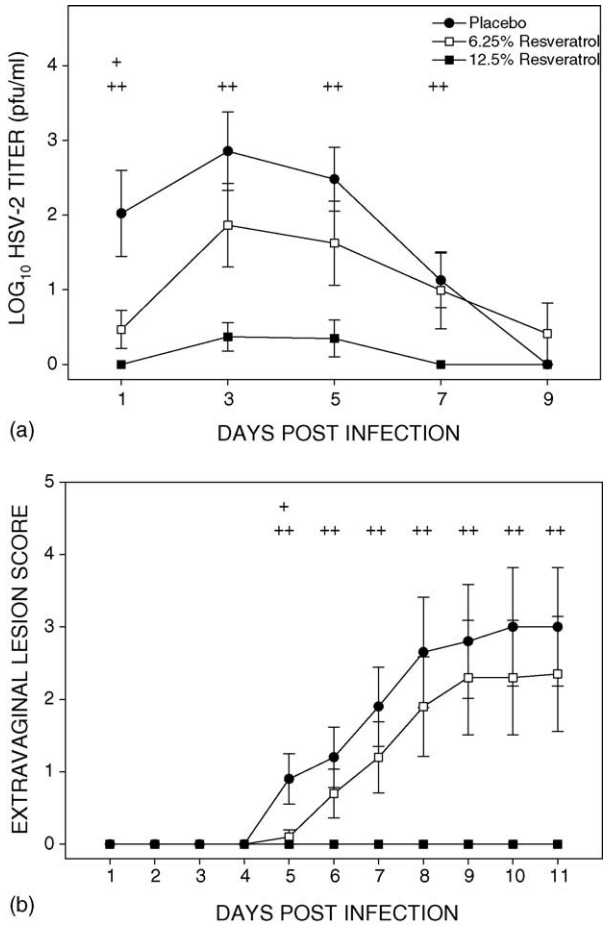

Fig. 2. Treatment of HSV-2 vaginal infection with reduced concentrations of resveratrol. Beginning 1 h after infection, the vagina of SKH1 mice were treated every 3 h five times a day for 5 days with placebo, 6.25% or 12.5% resveratrol. (a) Vaginal titers are log transformed and reported as the mean, ±S.E.M. and (b) extravaginal lesion score is reported as the mean, ±S.E.M. $^{+}p < 0.05$ comparing vaginal titers or lesion score of placebo vs. 6.25% resveratrol as determined by independent samples *t*-test; $^{++}p < 0.05$ comparing vaginal titers or lesion score of placebo vs. 12.5% resveratrol as determined by independent samples *t*-test.

When the animals were examined for extravaginal disease, it was noted that 6.25% resveratrol differed from placebo-treated animals only on day 5 of the infection when lesions first appeared in the placebo-treated group. Animals that were treated with 12.5% resveratrol did not exhibit extravaginal pathology at any time during the 11 days the animals were monitored (Fig. 2b) and were significantly different ($p < 0.05$) from placebo-treated mice from the development of the first lesions on day 5 in the placebo group until the conclusion of the study on day 11 (Fig. 2b).

Six placebo-treated animals and four of the 6.25% resveratrol-treated animals died. None of the animals treated with 12.5% resveratrol expired (Table 1). These results suggest that a concentration of at least 12.5% resveratrol was required to adversely affect HSV-2 replication in the mouse vagina.

3.3. Reduced number of treatments per day

Studies were carried out in which vaginally infected animals were treated with resveratrol three times a day rather than five as in previous studies. Animals were infected with HSV-2 and drug administration was begun 1 h after infection as before. Results presented in Fig. 3a demonstrate that 12.5% resveratrol was only effective ($p = 0.03$) on day 1 of the infection when compared to placebo. However, 19% resveratrol was effective on days 1 ($p = 0.02$), 3 ($p = 0.03$), 5 ($p = 0.01$), and 7 ($p = 0.05$) when compared to placebo-treated animals (Fig. 3a). There was no difference on day 9 because placebo-treated animals had either recovered or died from the infection.

When the animals were evaluated for extravaginal disease, it was noted that 12.5% resveratrol delayed the appearance of clinical disease by approximately 2 days when compared to placebo. However, there was not a significant difference at any point between the two groups (Fig. 3b). In contrast, animals treated with 19% resveratrol did not exhibit detectable extravaginal lesions throughout the study and differed significantly from the placebo group from the initial appearance of lesions on day 5 until the conclusion of the study on day 11 (Fig. 3b).

Four placebo-treated animals and three of the 12.5% resveratrol-treated animals died. None of the animals treated with 19% resveratrol expired (Table 1). These results

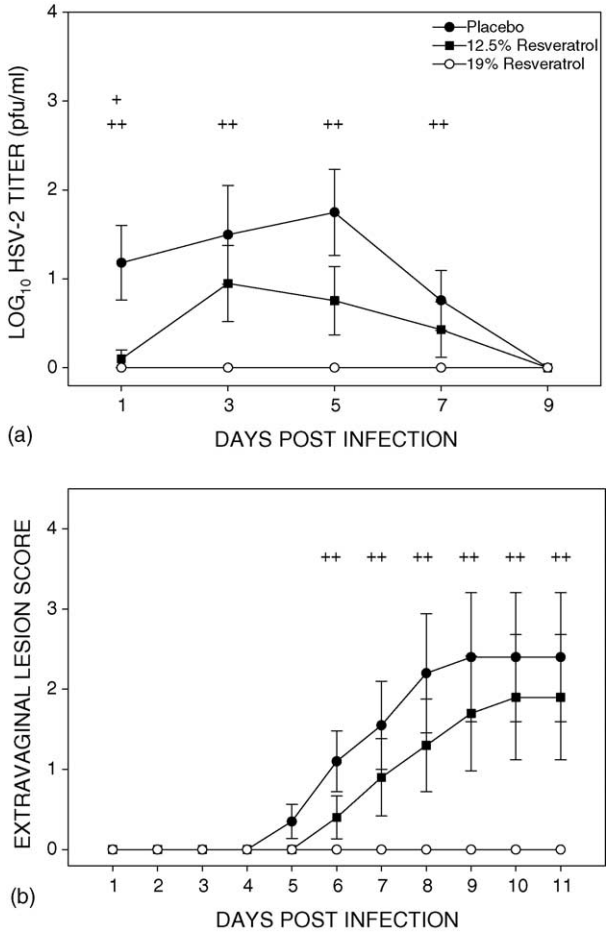

Fig. 3. Treatment of HSV-2 vaginal infection with fewer applications of resveratrol per day. Beginning 1 h after infection, the vagina of SKH1 mice were treated every 4 h three times a day for 5 days with placebo, 12.5% or 19% resveratrol. (a) Vaginal titers are log transformed and reported as the mean, ±S.E.M. and (b) extravaginal lesion score is reported as the mean, ±S.E.M. $^{+}p < 0.05$ comparing vaginal titers or lesion score of placebo vs. 12.5% resveratrol as determined by independent samples *t*-test; $^{++}p < 0.05$ comparing vaginal titers or lesion score of placebo vs. 19% resveratrol as determined by independent samples *t*-test.

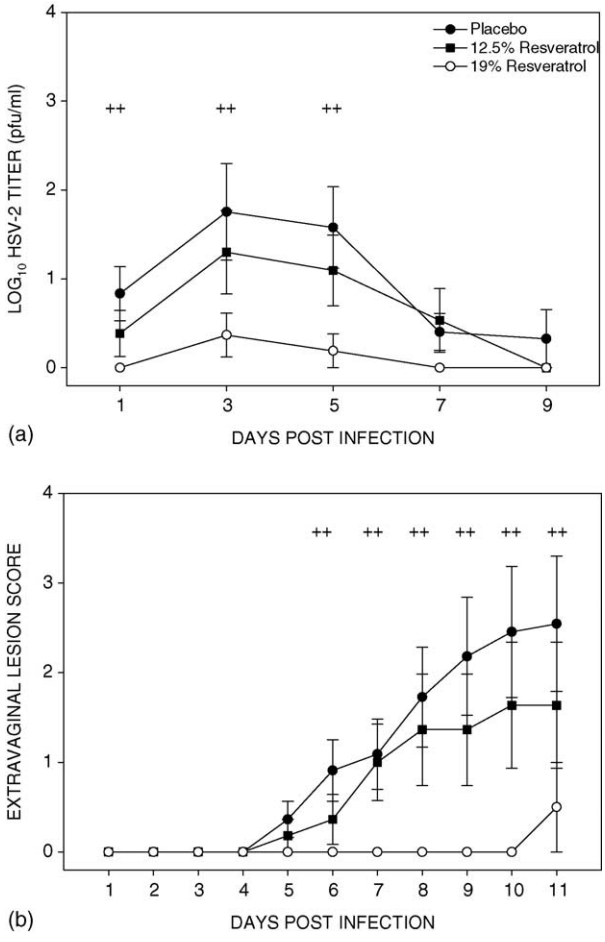

Fig. 4. Delayed treatment of HSV-2 vaginal infection with resveratrol. Beginning 6 h after infection, the vagina of SKH1 mice were treated every 3 h five times a day for 5 days with placebo, 12.5% or 19% resveratrol. (a) Vaginal titers are log transformed and reported as the mean, ±S.E.M. and (b) extravaginal lesion score is reported as the mean, ±S.E.M. $^{+}p < 0.05$ comparing vaginal titers or lesion score of placebo vs. 12.5% resveratrol as determined by independent samples *t*-test; $^{++}p < 0.05$ comparing vaginal titers or lesion score of placebo vs. 19% resveratrol as determined by independent samples *t*-test.

indicate that when animals were treated three times a day, 19% resveratrol was effective, but not 12.5% resveratrol.

3.4. Delayed resveratrol treatment of HSV-2 vaginal infection

All previous studies began drug treatment 1 h after vaginal infection. To determine how soon treatment needed to be started to be effective, drug administration was delayed for 6 and 12 h after infection. Once started, the drug was administered five times a day for 5 days. The results presented in Fig. 4a reveal that if treatment was begun 6 h after infection, 12.5% resveratrol did not inhibit HSV-2 replication at any of the time points tested when compared to placebo-treated animals. In contrast, 19% resveratrol was effective on days 1 ($p = 0.021$), 3 ($p = 0.036$), and 5 ($p = 0.015$) when compared to placebo-treated animals. By days 7 and 9, the number of placebo-treated animals positive for virus and the amount of virus recovered from them decreased or they had died, negating any significant difference between them and animals treated with 19% resveratrol.

When the animals were examined for extravaginal disease, it was noted that observable symptoms appeared on day 5 in the placebo and 12.5% resveratrol-treated mice, but not mice treated with 19% resveratrol. From days 6 to 11, placebo-treated and 12.5% resveratrol-treated mice showed no significant difference in extravaginal lesion score (Fig. 4b). But, if the animals were treated with 19% resveratrol, there was a significant difference between them and the placebo group on days 6 through the completion of the study on day 11 (Fig. 4b).

Five placebo-treated animals, three of the 12.5% resveratrol-treated animals and one 19% resveratrol-treated animal died (Table 1).

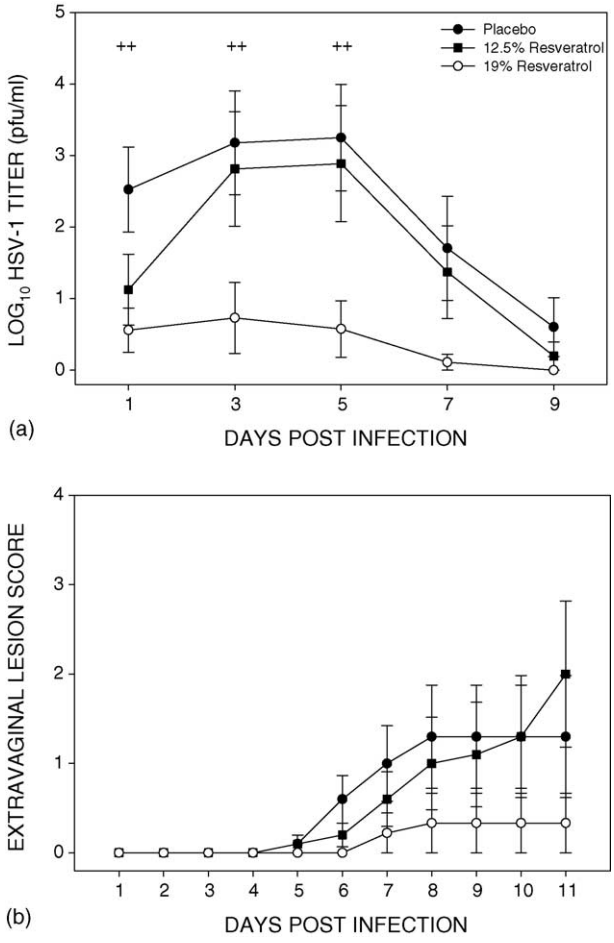

Fig. 5. Treatment of HSV-1 vaginal infection with resveratrol. Beginning 1 h after infection, the vagina of SKH1 mice were treated every 3 h five times a day for 5 days with placebo, 12.5% or 19% resveratrol. (a) Vaginal titers are log transformed and reported as the mean, ±S.E.M. and (b) extravaginal lesion score is reported as the mean, ±S.E.M. $^{+}p < 0.05$ comparing vaginal titers or lesion score of placebo vs. 12.5% resveratrol as determined by independent samples *t*-test; $^{++}p < 0.05$ comparing vaginal titers or lesion score of placebo vs. 19% resveratrol as determined by independent samples *t*-test.

If treatment was delayed for 12 h, neither 12.5% resveratrol or 19% resveratrol were effective in reducing vaginal virus replication or extravaginal lesion formation. Collectively, these results suggest that treatment with higher concentrations of resveratrol should begin within 6 h after infection.

3.5. *Effect of resveratrol on vaginal HSV-1 infection*

Studies were carried out to determine the ability of resveratrol to limit HSV-1 infection in the mouse vagina. Infected mice were treated five times a day for 5 days with placebo, 12.5% or 19% resveratrol beginning 1 h after infection. The results presented in Fig. 5a reveal that 12.5% resveratrol was not effective in limiting HSV-1 replication in the vagina at any time point tested. However, 19% resveratrol was effective at 1 ($p = 0.011$), 3 ($p = 0.014$), and 5 ($p = 0.007$) days post-treatment. By days 7 and 9, there was no significant difference between the three groups (Fig. 5a).

When scoring extravaginal disease, there was no difference between the three groups even though the mean lesion score of 19% resveratrol was noticeably less than the placebo or 12.5% resveratrol-treated group (Fig. 5b).

Two placebo-treated animals and four 12.5% resveratrol-treated animals died. None of the animals treated with 19% resveratrol expired (Table 1).

4. Discussion

The results of this study demonstrate that the topical application of resveratrol is able to significantly reduce morbidity, mortality, and HSV replication in the vagina of SKH1 mice. The in vivo effectiveness of resveratrol was influenced by drug concentration, number of applications per day, the amount of time between initial infection and the start of treatment and the virus type. In one study, acyclovir was used for comparative purposes and both it and resveratrol yielded similar degrees of effectiveness.

Several studies have reported varying degrees of success using topical applications of different preparations to treat HSV infections. These include buffer gel, a spermicide, that claims to offer significant protection against vaginal and rectal transmission of HSV-2 in the mouse (Zeitlin et al., 2001), Pro 2000, which is a 4% gel, protected against HSV-2 vaginal infection in the mouse if applied before virus infection (Bourne et al., 1999), and an herbal preparation using a sage-rhubarb extract (Saller et al., 2001). Interestingly, while effective orally, topically applied acyclovir was relatively ineffective when used to treat human genital infections (Mertz, 1996) and ineffective in treating labial HSV infections (Spruance et al., 1984).

In the studies presented here, when resveratrol was tested topically in the HSV-infected vagina of mice, it effectively limited viral replication. However, the results suggest that this effectiveness is dependent upon multiple variables. Generally, the higher the concentration of the drug and the earlier the application after infection, the more favorable the outcome. For example, 19% resveratrol was the highest and most effective concentration used. In some studies, however, virus was recovered from a few animals treated with 19% resveratrol (Figs. 4a and 5a). But the amount of virus recovered was always significantly lower than animals treated with lower concentrations of resveratrol or placebo-treated animals. Similarly, the amount of virus recovered from animals treated with 12.5% resveratrol was always lower than that recovered from animals treated with 6.25% resveratrol or placebo (Fig. 2a). This was not true, however, when comparing 6.25% resveratrol-treated animals with placebo-treated, from which similar amounts of virus were recovered (Fig. 2a).

Like all anti-HSV drugs, the earlier that treatment with either 12.5% or 19% resveratrol was started, the better the outcome. In most studies presented here, treatment was begun

1 h after infection. When treatment was delayed until 6 h after infection, 19% resveratrol remained effective but 12.5% resveratrol was not. When treatment was delayed until 12 h after infection, neither concentration of resveratrol was effective. These results are reminiscent of an early study with topical acyclovir treatment of HSV labialis (Spruance et al., 1982). In that study, patients that were treated 0–8 h after onset of lesions observed an antiviral effect that was not observed in patients that were treated beginning 9–25 h after onset. Results, such as this as well as our results with resveratrol, suggest that topical application may be effective against HSV in those patients with recurrent disease that are familiar with the prodrome and begin treatment early.

When collectively examining mortality patterns in this study (Table 1), it was noted that 37% of the placebo-treated animals died, 40% of the 6.25% resveratrol-treated animals died, 23% of the 12.5% resveratrol-treated animals died, 3% of the 19% resveratrol-treated animals died, and 10% of the acyclovir-treated animals died. These data suggest that 19% resveratrol treatment limited viral replication and ultimately host invasion which would have resulted in animal death.

Curiously, when resveratrol was used to treat HSV-1 vaginal infections, it was found that the 12.5% concentration was not effective, but the 19% concentration limited vaginal replication of virus when compared to placebo (Fig. 5a). It is unknown why the lower resveratrol concentration was not particularly effective in limiting HSV-1 replication since it showed efficacy against HSV-2 in some studies presented here. However, it was noted that HSV-1 infection resulted in higher vaginal virus titers than HSV-2. For example, placebo-treated animals in Fig. 5, positive for virus on days 3 and 5, averaged HSV-1 titers of 3.5×10^4 and 4.4×10^4 pfu/ml, respectively. In contrast, the HSV-2 vaginal titers in Fig. 1a for placebo-treated animals on days 3 and 5 were 2.2×10^3 and 1.3×10^3 pfu/ml which is a 94% and 97% difference, respectively, in virus amount. Whether or not the ability of HSV-1 to replicate to higher titers in the vagina resulted in 12.5% resveratrol ineffectiveness is unknown, particularly since 12.5% resveratrol was shown to inhibit HSV-1 in vivo (Docherty et al., 2004) in the mouse epidermis when applied five times a day for 5 days.

The mechanism by which resveratrol inhibits HSV production is currently unknown. Numerous properties have been ascribed to this drug including cell cycle arrest (Ragione et al., 1998), cell DNA polymerase inhibition (Sun et al., 1998), and anti-inflammatory properties (Culpitt et al., 2003; Donnelly et al., 2004; Leiro et al., 2004) to name but a few. Because HSV immunopathology is the result of both viral cell destruction and the responding inflammatory response, the anti-inflammatory properties of resveratrol are an intriguing bonus to the use of this drug to treat HSV infections.

The effectiveness of resveratrol on vaginal HSV replication presented here extends the in vivo studies in which resveratrol was shown to limit HSV epidermal infection (Docherty et al., 2004). Its low toxicity, ready availability, anti-HSV properties, anti-inflammatory properties, and ease of use make it a viable candidate for a new and novel anti-HSV agent.

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