Topical lipophilic epigallocatechin-3-gallate on herpes labialis: a phase II clinical trial of AverTeaX formula

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Objective. Previous in vitro and in vivo studies indicated that catechins from the tea plant (*Camellia sinensis*) have a therapeutic effect on herpes simplex virus infections. The aim of this study was to clinically evaluate a topical proprietary formulation containing lipophilic catechins (AverTeaX, Camellix, LLC, Evans, GA, USA) on recurrent herpes labialis.
Study Design. A double-blind, placebo-controlled, randomized trial with 40 participants, initially in two groups.
Results. Compared with the vehicle (100% glycerin USP, CVS Pharmacies, Inc., Woonsocket, RI, USA) group, AverTeaX applied topically six to eight times daily resulted in a significant reduction in clinical episode duration (median 4.5 days vs. 9 days; $P = .003$) and shortened blistering and ulceration stages within an episode from a median of 3 days to 1 day ($P = .0003$). Median quality-of-life scores, based on a multiquestion survey, showed significant differences between the groups with respect to duration of itching, from a median of 4 days to 1 day ($P = .0021$), and duration until symptom free, from a median of 8 days to 4 days ($P = .0016$). Significant differences were not found for median scores for itching, pain, burning, swelling, bleeding, and stress. Adverse effects were not reported.
Conclusion. AverTeaX formulation containing lipophilic catechins effectively inhibited herpes simplex labialis infection with clinical significance. (Oral Surg Oral Med Oral Pathol Oral Radiol 2015;120:717-724)

Most cases of recurrent herpes labialis (RHL), commonly referred to as cold sores or fever blisters, are caused by reactivation of latent herpes simplex virus type 1 (HSV-1). A minority of cases is caused by herpes simplex virus type 2 (HSV-2), which causes the majority of genital herpes).[1] An estimated 500,000 primary infections (primary herpetic gingivostomatitis) occur annually in the United States, mainly during childhood through nonsexual contact with a body fluid of infected individuals.[2] In contrast, HSV-2 infection is primarily through sexual contact, with 300,000 infections annually.[3] The prevalence of HSV-1 increases with age, from 40% to 50% in adolescence to more than 60% in later adulthood.[2] Primary herpetic gingivostomatitis mainly affects the lips, the gingiva, the buccal mucosa, the hard and soft palates, and the tongue, whereas RHL mainly targets the lips. Symptoms of RHL can be characterized by distinctive stages—prodromal, blistering, ulceration, scabbing, and healing. The prodromal stage often lasts less than 24 hours and is associated with localized mild burning, itching, and erythema. The blistering stage is characterized by fluid-filled vesicles in the epithelium and is followed by the ulceration stage, in which the vesicles break down to become painful ulcers. The duration of the combined blistering stage and the ulceration stage (blistering/ulceration stages) within an episode lasts for 3 to 4 days in total, and these stages are associated with mild to moderate pain, itching, burning, bleeding, and erythema. The duration of the next two stages (scabbing stage and healing stage) varies between 3 and 7 days, depending on the severity of the lesions created by the previous stages. In total, a typical episode of RHL in an otherwise healthy individual lasts 7 to 14 days from the initiation of the prodromal stage to complete healing, indicated by loss of the crust/scab.[2,4]

Despite the significant effort and resources that have been put into developing effective vaccines against

Statement of Clinical Relevance

Topical application of lipophilic tea catechins resulted in a significant reduction in the duration of episodes and blister or ulceration of herpes labialis. It has the potential to provide effective topical treatment of recurrent herpes labialis.

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HSV-1 and HSV-2, attempts at vaccine development based on immune recognition of particular viral glycoproteins have failed.[3] Currently, treatment of RHL is aimed at symptomatic relief and reducing episode duration. Medications for RHL rely mainly on antiviral nucleotide analogues applied topically or taken systemically. An exception is 10% docosanol topical cream (Abreva), which is a fatty acyl alcohol.[4,5] Thus far, there is no evidence showing an impact of medications on the epidemiology of HSV-1 or HSV-2.[3] However, strains resistant to antiviral drugs, due to mutations in the viral DNA polymerase gene, are being increasingly found.[5-7] The working mechanisms of nucleotide analogue medications, resulting in interruption of viral DNA replication, rely on reactivation or infection of HSV involving viral particles that have already entered host cells before the drug effect. These mechanisms ignore two important processes of the HSV infectious cycle: (1) anterograde-directed spread from the axons of the peripheral nervous system to epithelial cells and (2) virion attachment and entry.[8] None of the currently available medications prevents virion entry into epithelial cells. In principle, among all the processes in the HSV infectious cycle, the most vulnerable process is anterograde-directed spread, in which often just a single virion exits the peripheral nervous system to initiate an entire episode of RHL.[9] This limitation of HSV transmission creates a bottleneck in the HSV infectious cycle.[9] All currently available medications fail to take advantage of this bottleneck.

Taken together, the current approaches to treat RHL are relatively ineffective, are associated with side effects, and have the potential to induce drug-resistant viral strains. An ideal antiherpetic agent would be a lipophilic compound that can be integrated into the lipid membrane and binds to viral particles through high-affinity but nonspecific binding, leading to inactivation of the virus. Such a compound could be a novel and more effective approach without side effects and have the potential to provide significant impact to HSV epidemiology globally.

Previous studies suggest that epigallocatechin-3-gallate (EGCG), a major component of extracts from the leaves of the *Camellia sinensis* (tea) plant, could be a strong candidate for the next generation of HSV medications. This is due to its ability to bind nonspecifically and inactivate multiple types of viruses.[10-14] EGCG is an important ingredient in green tea, with known benefits for the human epidermis, such as antioxidant, UV-protective, antimicrobial, and anticancer properties, and without known side effects when these beverages are consumed regularly.[15,16] Importantly, increased efficacy, lipid solubility, and stability of EGCG were achieved when the lipophilic fatty esters of EGCG were tested against HSV and influenza viruses.[11,16,17] Recently, tea polyphenol palmitate (palmitoyl esters of tea polyphenols, mainly EGCG-palmitate) have been classified as nontoxic food additives by the Chinese Food and Drug Administration, with a maximum dose of .6 g/kg (National Health and Family Planning Commission of the People's Republic of China Announcement 11, June 12, 2014).

Based on these observations, we completed a case series using lipophilic EGCG for the treatment of RHL. The results indicated that this agent has the potential to cause substantial reductions in the duration of symptoms at different stages of the infection.[18] The phase II trial tested the efficacy of a topical formulation containing lipophilic EGCG in participants with RHL. The proprietary topical preparation (AverTeaX, Camellix, LLC, Evans, GA, USA) contains EGCG stearates, in a vehicle (placebo) of 100% glycerin United States Pharmacopeia (USP) (manufactured by Nomax, Inc., St. Louis, MI, USA, a U.S. Food and Drug Administration [FDA]—registered pharmaceutical manufacturer).

STUDY DESIGN AND METHODS

This clinical trial used a randomized, double-blind, placebo-controlled design involving 40 participants with RHL (20 in the vehicle [100% glycerin USP, CVS Pharmacies, Inc., Woonsocket, RI, USA] group and 20 in the AverTeaX group). This number was based on a power analysis using estimates of the coefficient of variation for vehicle group total episode duration (8.26 days) and AverTeaX group total episode duration (5.45 days). The duration of an episode was defined as the period between the first sign of recurrence perceived by the participant and the loss of the crust/scab. A sample size of 20 participants per group would yield 80% power for detecting an improvement of at least 65% in total episode duration when comparing active treatment versus placebo using a significance level of $P = .05$. The research proposal was approved by the Medical Ethics Committee of Stomatology Hospital, Zhejiang University School of Medicine, China. Clinical research participants read the Helsinki Declaration and followed the guidelines in this investigation.

Study population and recruitment

The clinical protocol, with full informed consent from study participants, was approved by the Medical Ethics Committee of Zhejiang University School of Medicine, Stomatology Hospital, China. Potential candidates were identified from a pool of participants responding to a local public announcement and initially screened in the General Dentistry Clinic. Candidates were given a simple explanation of the study and questioned as to

Table I. Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
1. Previously diagnosed with recurrent herpes labialis	1. Pregnant or breast feeding
2. Able to visit the clinic within 24 hours of symptom development (within 12 hours preferred)	2. Taking antiviral medication or hydrocortisone or other medications altering immune activity within the past 7 days
3. Have had at least three episode of herpes labialis during the past 12 months, each episode lasting more than 6 days	3. Under other therapy for recurrent herpes labialis
4. A minimum of 30 days after the last episode	4. Immunodeficiency diseases, such as acquired immunodeficiency syndrome
5. Over the age of 18 years	5. Concurrent with other oral mucosa diseases
6. Not taking antiviral medication before and during the trial	6. Blood disease, such as lymphatic disease or leukemia
7. Willing to return for all study-associated visits	7. Cancer or cancer therapy within last 6 months
8. Able to read, understand, and sign the informed consent document	8. Syphilis
	9. Psychological disorders
	10. Allergic to tea components
	11. Fever higher than 38°C
	12. Unable to understand the consent form
	13. Unwilling to return for all clinic visits

their willingness to participate. Those participants expressing a desire to volunteer were formally screened for eligibility. No monetary incentive was offered. However, participants were reimbursed with RMB300 (approximately $50) at the completion of treatment for transportation costs after each participant completed the required daily clinic visits. Appropriate measures were taken to protect the privacy of study volunteers per established Zhejiang University policies. Eligibility was assessed on the basis of inclusion and exclusion criteria, which are listed in Table I. After determination of eligibility, an initial questionnaire (not a quality-of-life [QOL] questionnaire) was administered that asked the participant to provide demographic details, such as name, gender, age, and race, as well as typical recurrence frequency, location, size, episode duration, potential trigger, and scores of symptoms based on previous episodes. Participants eligible for the clinical trial were randomly assigned, after a new recurrence of episode, to two groups by the lead dentist (Dr. Man Zhao), who used block randomization with block size 6. The randomization scheme was obtained from www.randomization.com.

Participants received the test formula (A for AverTeaX or B for vehicle) at the first clinic visit, within 24 hours after symptoms appeared; they immediately applied the formula on the affected area(s) and subsequently six to eight times each day during the day. Each participant was requested to complete a questionnaire during each daily visit for QOL assessment, which included scores (range 1-5) on itching, pain, burning, swelling, tightness, bleeding, and stress. One vial of the test formula, along with instructions for topical application, was provided to each participant to take home for self-application. The amount of drug or vehicle applied to the infected area was sufficient to completely cover the lesion. Each vial contained either 1.5 mL of AverTeaX formula dissolved in 100% glycerin USP (Camellix) or 1.5 mL of vehicle only. Participants were instructed to return each day at the same time of day to the General Dentistry Clinic for examination and photographing of the infected area. Following the initial application, participants were instructed to topically apply the AverTeaX formula or the placebo six to eight times daily. During each subsequent daily visit at the clinic, participants were asked to complete a QOL questionnaire and undergo a thorough oral examination. The daily visits continued until the lesion was healed (indicated by loss of crust/scab), and a written release was issued by the lead dentist. Each participant was requested to comply with all the instructions and complete the entire study period, although they were free to drop out of the study at any time.

Blinding

The AverTeaX formula and the vehicle were identical in appearance, texture, and taste and were packaged identically, with the intervention coded as A and the vehicle as B. Only one person (SH, who was not involved in patient care) controlled the code, and all clinical staff and participants were blinded to the treatment, which was revealed after all participants completed the trial and all statistical data were collected from the statistician.

Visit schedule

Participants with a history of RHL were asked to complete an initial questionnaire. If they met the screening criteria (see Table I), the research coordinator was notified and met with the participant either immediately or at a scheduled appointment. The research coordinator reviewed the information on the screening form and verified that the participant was

eligible for the study. The research coordinator then explained the details of the study to the patient and obtained written informed consent. Once the patient signed the informed consent document, the research coordinator obtained demographic data, medical history, and contact information from the participant. Any information missing was noted for follow-up by the research coordinator. Finally, the participants enrolled in the trial were provided instructions with regard to future visits.

Clinical examination and data collection

The research coordinator met participants daily at each stage of data collection to ensure that everything had been processed properly. Participants showing the initial sign of recurrence (day 0) were admitted without appointment. An oral examination was performed each day (at approximately the same time of day for each patient) and documented, photographs were taken, and a QOL questionnaire was completed to record the time of the current episode and the scores of the symptoms—itchiness, pain, burning, swelling, tightness, bleeding, and stress. This daily oral examination at the clinic included lesion size measurement, location and number of lesions, current stage of episode (prodromal, blistering, ulceration, scabbing, or healing stage), and potential adverse effects. The above information was recorded in combination with the daily QOL questionnaire to generate a one-page document per day for each participant, along with a file of daily photographs. Based on these data and records, QOL scores, the duration of an episode, and the duration of each stage within an episode from each participant were established for statistical analysis to be conducted after the entire trial was completed. The duration of an episode was measured by days, from day 0 to the last visit when the crust/scab had been lost. The durations of the blister and ulceration stages were measured on the basis of the time (in days) from the beginning of the blistering stage (i.e., the first appearance of a fluid-filled blister) to the end of the ulceration stage (i.e., the end of active bleeding, and fluid discharge, but not including the subsequent crust/scab formation and healing). The viral species (i.e., HSV-1 or HSV-2) was not identified by laboratory test due to the specifications of the approved noninvasive protocol.

Data management

Data collection was via paper forms that were later recorded into the participants' secure patient chart files along with the electronic health records stored in a data management system. Appropriate measures were taken to protect the privacy of the study volunteers and maintain confidentiality of study data, according to Zhejiang University policy. Hardcopy records were maintained and secured in the clinical files of the General Dentistry Department.

QOL scales. The QOL questionnaire was designed for the participants to provide scores of symptoms (clinical scores) during the current episode at each daily visit until the lesion was healed, as has been described previously.[19] The research coordinator met with each participant during the daily visit and administered the QOL questionnaire. The coordinator presented the questionnaire and instructions in the same way to all participants. Participants scores were based on a scale of 0 to 5 on itching, pain, burning, swelling, tightness, bleeding, and psychological stress (0 = none, 1 = mild, 2 = moderate, 3 = serious, 4 = severe, and 5 = very severe).

Statistics

All collected data were analyzed by SPSS Version 17.0 (SPSS Statistics for Windows, Version 17.0, released 2008; SPSS Inc., Chicago, IL, USA). The last observation was carried forward in the event of a missing value. The mean values with standard deviations (SDs) and the median values with ranges of the scores of the symptoms and the duration of the symptoms were calculated for both the AverTeaX and vehicle groups. Mann-Whitney U tests were carried out for comparison between the two groups. Two-tailed P values were calculated. $P < .05$ was considered statistically significant for single comparison. For multiple comparisons of QOL questionnaires, a Bonferroni correction to α was applied ($n = 7$, $\alpha = .007$; $n = 8$, $\alpha = .0063$).

RESULTS

Baseline data and patient flow

Detailed patient demographic data are listed in Table II. Thirty-nine participants completed the treatment out of the 40 recruited and randomized. Significant differences in demographic characteristics were not found between groups. One patient in Group B (vehicle group) did not complete the trial due to a conflict in scheduling (a meeting out of study site). During the entire trial period, no adverse effect was reported or observed.

Numbers of participants analyzed

In Group A (intervention using the AverTeaX formula), all 20 participants completed the study. In Group B (vehicle), 19 of 20 participants completed the study. In both groups, each participant reported applying the test formula six to eight times daily. Among the participants in Group A, two initiated use of the test article within 1 hour of recurrence, five started after 12 hours, and one initiated use after 23 hours. In Group B, two participants

Table II. Initial questionnaire responses and patient demographic characteristics

Group	*A (AverTeaX)*	*B (Vehicle)*
Total number participants		
Recruited/enrolled	20	20
Race: Han Chinese	20 (100%)	20 (100%)
Completed study (female)	17	17
Completed study (male)	3	2
Age range	24-58	24-58
Average age	33 ± 8.9	32 ± 9.8
Length of typical episode (days)	10.7 ± 2.25	9.1 ± 2.25
Total QOL score of a typical episode	7.45 ± 4.06	7.53 ± 4.43
Recurrence per year	3.1 ± 1.59	2.6 ± 1.86

QOL, Quality of life.

started using the test article within 1 hour, six after 12 hours, and one after 23 hours of recurrence. There was no significant difference in the mean initiation time of treatment between the two groups ($P = .52$, two-tailed t test).

Episode duration

We found no significant difference between the groups in the mean length of time between the participant sensing a recurrence and initiation of test material application (two tailed t test, $P > .05$), which was less than 10 hours in both groups. There was a significant difference ($P = .003$) in episode duration (the lasting time of the entire episode from recurrence to loss of crust/scab) between the two groups. Participants in the AverTeaX group experienced a 4.5-day episode duration (median, ranging from 1 to 11 days, n = 20). In the vehicle group, the median episode duration was 9 days (median, ranging from 2 to 11 days, n = 19) (Table III).

Duration of blister and ulceration stages

The time (days) from the beginning of the blistering stage (i.e., the first appearance of a fluid-filled blister) to the end of the ulceration stage (i.e., the end of active bleeding, and fluid discharge, but not including the subsequent crust/scab formation and resolution) was measured for the two groups. There was a significant difference ($P = .0003$) in the combined duration of the blister and ulceration stages between the two groups. Participants in the AverTeaX group experienced a 1-day duration of the combined stages (median, ranging from 0 to 3 days, n = 20). In the vehicle group, the median duration was 3 days (median, ranging from 0 to 6 days, n = 19) (see Table III).

QOL and statistical analyses

Summary statistics and analysis of the QOL questionnaires are presented in Table IV. As a measure of QOL, the sums of daily scores from each participant for each symptom assessed were used, as well as the durations of each symptom (measured from day 0 until the last clinic visit). Median scores for itching, pain, burning, swelling, bleeding, and stress did not show a significant difference between the groups after Bonferroni correction for multiple comparisons ($\alpha = .007$, n = 7). For duration of symptoms, the AverTeaX group showed a statistically significant shortening of both the duration of itching and the time until symptom free, after Bonferroni correction for multiple comparisons ($\alpha = .0063$, n = 8). Other measures did not show a significant change after Bonferroni correction.

DISCUSSION

Treatment of RHL with currently available over-the-counter and prescription antiviral topical medications provides moderate relief of symptoms and shortened episode duration. A multicenter, double-blinded, placebo-controlled, randomized clinical trial reported in 2001, using 10% docosanol cream (Abreva, a 22-carbon-long saturated fatty alcohol), resulted in an 18-hour reduction in episode duration.[20] This agent was well tolerated at the 10% concentration, and no reports of resistant viral strains have been reported. However, the effectiveness of this medication has been questioned, with the claim that the 10% docosanol cream is barely effective or no more

Table III. Duration of episode and duration of blister/ulceration stages (days) in participants

Participant	*Group A Episode (days)*	*(AverTeaX) Blister/Ulcer (days)*	*Group B Episode (days)*	*(Vehicle) Blister/Ulcer (days)*
1	4	1	11	3
2	1	0	4	2
3	4	2	10	3
4	4	0	5	1
5	7	1	11	4
6	5	2	3	0
7	9	3	6	4
8	9	3	9	4
9	11	3	4	2
10	5	1	10	6
11	4	0	8	2
12	8	1	11	2
13	11	3	8	2
14	1	1	11	4
15	8	2	9	4
16	3	1	7	3
17	6	1	10	2
18	4	0	6	2
19	1	1	9	4
20	4	1		
Median	4.5	1	9	3
Range	1-11	0-3	2-11	0-6
P^*	.003	.0003		

*Between groups.

Table IV. Summary statistics for quality of life (QOL) questionnaires

	AverTeaX (n = 20)		*Vehicle (n = 19)*		
	Median (Range)	*Mean ± SD*	*Median (Range)*	*Mean ± SD*	*P value*
Sum of scores of symptoms (1-5 scale each questionnaire)					
Itching	2 (0-10)	2.80 ± 2.93	5 (0-19)	5.58 ± 4.81	.026
Pain	2.5 (0-16)	3.60 ± 3.73	5 (0-17)	6.26 ± 5.23	.1615
Burning	3 (0-12)	3.30 ± 2.87	4 (0-16)	5.05 ± 4.21	.1868
Swelling	2 (0-13)	3.90 ± 3.46	5 (0-17)	5.26 ± 4.08	.1645
Tightness	5 (1-19)	6.35 ± 6.43	8 (0-21)	7.63 ± 5.43	.242
Bleeding	0 (0-13)	1.05 ± 2.87	0 (0-7)	1.58 ± 2.39	.4413
Stress	1.5 (0-10)	2.30 ± 3.06	1 (0-14)	2.00 ± 3.70	.6527
Duration of symptoms (days)					
Itching	1 (0-5)	1.35 ± 1.53	4 (0-7)	3.84 ± 2.83	.0021*
Pain	1 (0-7)	1.80 ± 2.07	4 (0-11)	4.32 ± 3.50	.011
Burning	1 (0-4)	1.45 ± 1.23	2 (0-8)	2.79 ± 2.46	.0427
Swelling	1.5 (0-7)	1.95 ± 1.76	3 (0-8)	2.68 ± 2.11	.247
Tightness	4 (1-10)	4.50 ± 2.59	7 (0-11)	5.84 ± 3.69	.1994
Bleeding	0 (0-10)	1.75 ± 3.16	0 (0-8)	2.21 ± 3.29	.6588
Stress	0 (0-8)	1.65 ± 2.68	0 (0-9)	1.16 ± 2.52	.558
Until symptom free	4 (1-10)	4.7 ± 2.52	8 (3-11)	7.47 ± 2.59	.0016*

*Statistically significant between groups; multiple comparisons, a Bonferroni correction to α was applied (n = 7 for scores of symptoms, $\alpha = .007$; n = 8 for duration of symptoms, $\alpha = .0063$).

effective than polyethylene glycol (an inactive ingredient).[21]

In 2002, a report of a multicenter clinical trial with 248 participants found that 1% penciclovir cream, an antiviral prescription drug, led to a trend toward a shorter time of healing.[19] It was later found in two large clinical trials of 1% penciclovir that a 24-hour reduction in classic oral lesions was obtained (from 5.6 days to 4.6 days in comparison with placebo), if the medication was applied within 1 hour of first signs of RHL symptoms.[22]

During the same year, two clinical trials using 5% acyclovir cream showed a .5-day and a .6-day reduction in episode duration, respectively, with statistical significance.[23] Another clinical trial using 5% acyclovir and 1% hydrocortisone (Xerese) yielded a 1.1-day reduction in episode duration (9.0 days vs. 10.1 days of placebo).[24]

Since these medications became available, attempts to develop vaccines or medications with a different mechanism of action and higher potency have not been successful. However, HSV strains resistant to antiviral drugs have been increasingly reported, especially in immunocompromised patients.[25] A 10-year survey in France demonstrated that while the prevalence of acyclovir resistance HSV in an immunocompetent population remains stable (.5%), HSV resistant to acyclovir increased significantly from 3.8% to 15.7% from 2002 to 2011 in immunocompromised patients.[26] Therefore, novel therapy with better efficacy, low potential for resistance, and a completely different mode of action is urgently needed.[27,28]

In 2012, we reported in a case series that lipophilic EGCG could prevent the breakout of an episode if applied at the prodromal stage and significantly reduce episode duration when applied during the blistering stage.[18] The present study, using a double-blinded, placebo-controlled, randomized study design, demonstrated that the AverTeaX formula led to a statistically significant reduction in episode duration in comparison with the vehicle, from 9 days to 4.5 days (see Table III). These data represent a 50% reduction in episode duration. Importantly, in the AverTeaX group, the duration of the blistering/ulceration stages was only 1 day in comparison with 3 days in the vehicle group, representing a 66% reduction. To the best of our knowledge, there has been no report, from any clinical trial, of a treatment for RHL demonstrating these levels of effectiveness in reduction of episode duration or blistering/ulceration. We reported previously that at a 50-μM level (approximately .004% weight per volume [w/v] in cell culture medium), lipophilic EGCG is able to completely block infectious HSV-1 particles from cell entry in vitro.[29] Thus, the rapid cessation of blistering/ulceration and 50% reduction of episode duration by the AverTeaX formula could be due to the high affinity and high potency of lipophilic EGCG in inactivating HSV-1.

In the present study, among the changes in clinical symptoms affecting QOL, as represented by the sum of self-scores of symptoms and duration of symptoms, duration until symptom free was reduced significantly from 8 days in the vehicle group to 4 days in the AverTeaX group (median, $P = .0016$), and duration of itching (median 1 day vs. 4 days, $P = .0021$) also showed a significant decrease, after Bonferroni correction for multiple comparisons (see Table IV). These

results indicate that an improvement in QOL, with respect to duration of itching and duration until symptom free, are associated with the use of the AverTeaX formula.

Importantly, the AverTeaX formula was not associated with any reported or observed adverse effect. This could be due to the nature of EGCG, a naturally occurring compound from tea leaves, and the low concentration of lipophilic EGCG in the formula.

EGCG is a known antioxidant, and fruits containing antioxidants have been shown to be virucidal against HSV-1.[30] However, the antimicrobial properties of EGCG result from its direct binding to lipid membranes, especially to membrane proteins, rather than antioxidant activity.[31] A recent study has suggested that EGCG at micromolar levels inhibits the infectivity of a diverse group of enveloped and non-enveloped viruses through nonspecific but direct binding to viral surface proteins, thereby inhibiting the attachment of viruses to human cells.[32] EGCG inhibits HSV-1, HSV-2, hepatitis C virus (HCV), influenza A virus (IAV), vaccinia virus (VACV), adenovirus (AdV), vesicular stomatitis virus (VSV), reovirus (RV), mouse cytomegalovirus (mCMV), and Sindbis virus (SIN).[31] These results are consistent with our observation that inactivation of HSV-1 was through nonspecific binding of lipophilic EGCG to viral coat proteins.[29] Similarly, a report from the U.S. Army Medical Research Institute of Infectious Diseases demonstrated that at micromolar levels, EGCG inhibits Ebola virus infection of human cells in a dose-dependent manner.[33] In summary, EGCG, especially lipophilic EGCG, is a candidate for the next generation of nontoxic molecules active against a broad range of viral infections, with high efficacy but without the potential to induce resistance. Thus, this class of compounds has the potential to be developed into novel inhibitory and preventive strategies against many human viruses.

CONCLUSIONS

The AverTeaX formula provided an effective reduction of episodes and combined duration of blistering/ulceration. The AverTeaX formula has the potential to provide an effective therapeutic approach to treat herpes labialis with a different mechanism of action from that of currently approved products. Therefore, clinical trials with a large patient population are warranted, and the detailed mechanisms of action need to be further understood.

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