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Sinecatechins

Treatment of Genital Warts

USAN

Kunecatechins
Polyphenon® E
Veregen™

A defined, low-caffeine green tea (*Camellia sinensis*) polyphenol extract containing 85-95% of catechins including epigallocatechin gallate (55%), epicatechin, epigallocatechin, epicatechin gallate, gallocatechin gallate, gallocatechin, catechin gallate and catechin, and approximately 2.5% of other components (gallic acid, caffeine and theobromine)

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Abstract

Sinecatechins (kunecatechins, Polyphenon® E) is an extract from green tea (*Camellia sinensis*) formulated in a 15% ointment. Sinecatechins contain catechins, in particular epigallocatechin gallate, which has shown potent activity against cancer and virally infected cells. Based on international phase III trials, the FDA approved sinecatechins (Veregen™) as the first botanical for the topical treatment of external genital and perianal warts (condylomata acuminata) in immunocompetent patients aged 18 years and over, and it was just recently launched in the U.S. While < 5% of study patients dropped out due to side effects, about 67% experienced some type of adverse event, the most common of which were erythema, erosion, edema, itching, burning, pain, induration and vesicular eruption.

Background

Green tea (*Camellia sinensis*) is a plant that has generated much interest in its health-enhancing and disease-fighting potential because it contains catechins. The most active of these catechins (detailed below) are referred to as sinecatechins (kunecatechins, Polyphenon® E, Veregen™) (1). Evidence has shown that these compounds are effective at clearing genital warts, and they may also be useful against cancer. Sinecatechins were shown to be effective orally and topically against infection of cervical cells by human papillomavirus (HPV) (2), to inhibit hamster buccal pouch carcinogenesis (3) and to inhibit pulmonary adenoma formation and growth in A/J mice (4). Lu *et al*. have identified patterns of gene expression that both offered clues for green tea's potential mechanisms of action and provided a molecular signature specific for green tea exposure (5).

(–)-Epigallocatechin gallate and sinecatechins inhibit the activation of the human epidermal growth factor receptor (EGFR, ErbB1) and human epidermal growth factor receptor-2 (HER2, c-erbB-2) signaling pathways in human colon cancer cells, as well as the growth of these cells (6). Hirose *et al*. found that sinecatechins may exert a weak inhibitory effect on the early promotion stage of mammary gland carcinogenesis in female Sprague-Dawley rats pretreated with 7,12-dimethylbenz[*a*]anthracene (7), and other studies in rats showed a significant and dose-dependent preventive effect against chemically induced urinary bladder tumors, but not mammary tumors, which appeared to be attributable to differences in the bioavailability of polyphenols at different organ sites (8). Epigallocatechin gallate, the most abundant catechin in green tea, and to a greater extent catechin gallate and epicatechin gallate, have antiproliferative effects against human oral cavity tumor cells (9).

Sinecatechins (1) is a botanical drug product which is a partially purified fraction of the water extract of green tea leaves from *C. sinensis* (L.), a mixture of catechins and other green tea components. Catechins constitute 85-95% (by weight) of the total drug substance, which includes epigallocatechin gallate (55%) (EGCg) (Fig. 1), other catechin derivatives such as epicatechin (EC), epigallocatechin (EGC), epicatechin gallate (ECg) and additional

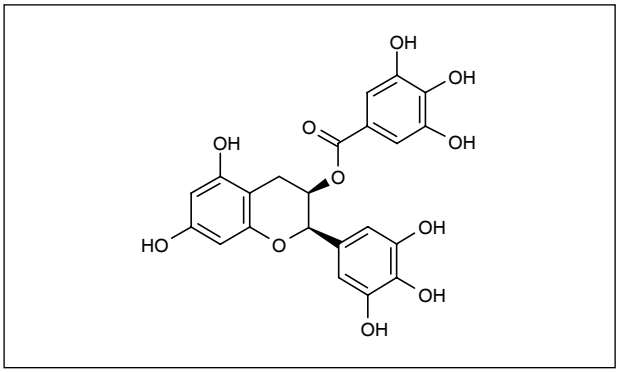

Fig. 1. Structure of epigallocatechin gallate.

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minor catechin derivatives, *i.e.*, gallocatechin gallate (GCg), gallocatechin (GC), catechin gallate (Cg) and catechin (C) (Fig. 2). In addition to the known catechin components, sinecatechins also contain gallic acid, caffeine and theobromine, which together constitute about 2.5%. The remaining amount of sinecatechins contains undefined botanical constituents derived from green tea leaves.

Polyphenon® E is a standardized green tea polyphenol mixture prepared by Mitsui Norin that contains 64.3% EGCg, 3.1% (–)-epigallocatechin (EGC), 9.1% (–)-epicatechin (EC), 8.1% (–)-epicatechin-3-gallate and other polyphenols.

Clinical studies have focused on using sinecatechins for the treatment of genital warts. Positive phase III results were obtained using sinecatechins for the treatment of genital warts in international trials (1, 10, 11). On October 31, 2006, the FDA approved sinecatechins in an ointment formulation as the first botanical for the topical treatment of external genital and perianal warts (condylomata acuminata) in immunocompetent patients aged 18 years and above, and the product was recently launched in the U.S. (12, 13).

Preclinical Pharmacology

The mode of action of sinecatechins in the clearance of genital and perianal warts is unknown. *In vitro*, sinecatechins exerted antioxidant activity, but the clinical significance of this finding is unknown. It also has antiproliferative effects, the significance of which is also unclear. MediGene has suggested that it penetrates the skin and exerts immunomodulatory effects and also directly acts on infected cells via effects on cytokines and interferons (1).

Pharmacokinetics

The pharmacokinetics of topically applied sinecatechins have not been sufficiently characterized at this time, although data suggest that systemic exposure to catechins after repeated topical application as a 15% ointment is likely to be less than that observed after a single oral intake of 400 ml green tea (1).

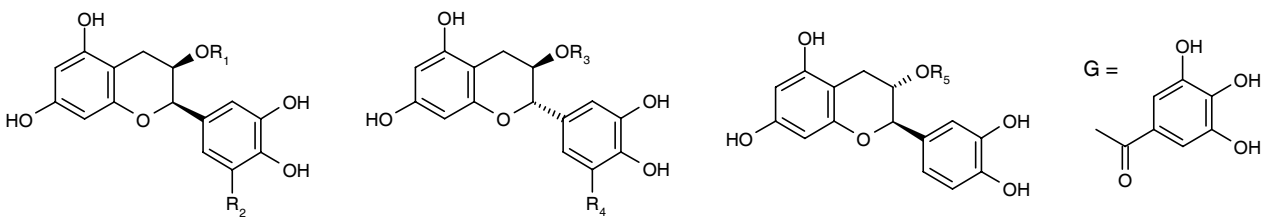
Safety

A variety of tests have been performed to investigate the carcinogenic and mutagenic effects of sinecatechins. In an oral (gavage) carcinogenicity study, sinecatechins were administered daily for 26 weeks to p53 transgenic mice at doses up to 500 mg/kg/day (22-fold the maximum recommended human dose, or MRHD). Treatment with sinecatechins was not associated with an increased incidence of either neoplastic or non-neoplastic lesions in the organs and tissues examined. Sinecatechins demonstrated no carcinogenic effect in the Ames test, *in vivo* rat micronucleus assay, the UDS test or the transgenic mouse mutation assay. Some mutagenic potential, however, was seen in the mouse lymphoma mutation assay (1).

Daily vaginal administration of sinecatechins 15% ointment to rats from day 4 before mating and throughout mating until day 17 of gestation did not cause adverse effects on mating performance and fertility at doses up to 0.15 ml/rat/day. This dose corresponds to approximately 150 mg/rat/day (8-fold the MRHD) (1).

Based on the aforementioned tests, the MRHD of sinecatechins ointment 15% was estimated to be 250 mg 3 times daily, containing 112.5 mg sinecatechins. Specifically, the dosing was based on animal models extrapolated using defined animal multiples to define human exposure levels. That is, dose multiples were calculated based on the human equivalent dose (HED) (1).

Embryofetal development studies were conducted in rats and rabbits using intravaginal and systemic routes of administration. Oral administration of sinecatechins during the period of organogenesis (gestational days 6-15 in rats and 6-18 in rabbits) did not cause treatment-related



Component	Abbrev.	R_1	R_2	R_3	R_4	R_5
(–)-Epigallocatechin Gallate	(–)-EGCg	G	OH	–	–	–
(–)-Epicatechin Gallate	(–)-ECg	G	H	–	–	–
(–)-Epigallocatechin	(–)-EGC	H	OH	–	–	–
(–)-Epicatechin	(–)-EC	H	H	–	–	–
(–)-Gallocatechin Gallate	(–)-GCg	–	–	G	OH	–
(–)-Gallocatechin	(–)-GC	–	–	H	OH	–
(–)-Catechin Gallate	(–)-Cg	–	–	G	H	–
(+)-Catechin	(+)-C	–	–	–	–	H

Fig. 2. Structures of various catechins in sinecatechins.

effects on embryofetal development or teratogenicity at doses of up to 1000 mg/kg/day (86-fold the MRHD in rats; 173-fold the MRHD in rabbits). In the presence of maternal toxicity (characterized by marked local irritation at the administration sites and decreased body weight and food consumption) in pregnant female rabbits, s.c. doses of 12 and 36 mg/kg/day of sinecatechins during the period of organogenesis (gestational days 6-19) resulted in reduced fetal body weights and delays in skeletal ossification. No treatment-related effects on embryofetal development were noted at 4 mg/kg/day (0.7-fold the MRHD) and there was no evidence of teratogenic effects at any of the doses evaluated in this study (1).

A combined fertility/embryofetal development study using daily vaginal administration of sinecatechins ointment 15% to rats from day 4 before mating and throughout mating until day 17 of gestation did not show treatment-related effects on embryofetal development or teratogenicity at doses up to 0.15 ml/rat/day (8-fold the MRHD) (1).

A pre- and postnatal development study was conducted in rats using vaginal administration of sinecatechins ointment 15% at doses of 0.05, 0.10 and 0.15 ml/rat/day from day 6 of gestation through parturition and lactation. The high and intermediate dose levels resulted in increased mortality in the F0 dams, associated with indications of parturition complications. The highest dose also resulted in an increased incidence of stillbirths. There were no other treatment-related effects on pre- and postnatal development, growth, reproduction and fertility at any dose tested (1).

In clinical trials in the United States, the incidence of local adverse events leading to discontinuation or dose interruption (reduction) was 5% (19 of 397) (Table I). Adverse events included application-site reactions (local pain, erythema, vesicles, skin erosion/ulceration), phimosis, inguinal lymphadenitis, urethral meatal stenosis, dysuria, genital herpes simplex, vulvitis, hypersensitivity, pruritus, pyodermitis, skin ulcer, erosions in the urethral meatus and superinfection of warts and ulcers. Phimosis occurred in 3% of uncircumcised male subjects (5 of 174) treated with sinecatechins and in 1% (1 of 99) of those treated with vehicle. Other less common adverse events included cervical dysplasia, pelvic pain, cutaneous facial rash and staphylococcemia. In a dermal sensitization study of sinecatechins ointment in healthy volunteers, hypersensitivity (type IV) was observed in 5 of 209 subjects (2.4%) under occlusive conditions (1).

Table I: Local and regional adverse reactions during treatment with sinecatechins (% subjects).

	Veregen™ (n=397)	Vehicle (n=207)
Erythema	70	32
Pruritus	69	45
Burning	67	31
Pain/discomfort	56	14
Erosion/ulceration	49	10
Edema	45	11
Induration	35	11
Rash vesicular	20	6
Regional lymphadenitis	3	1
Desquamation	5	<1
Discharge	3	<1
Bleeding	2	<1
Reaction	2	0
Scar	1	0
Irritation	1	0
Rash	1	0

Table II: Efficacy of sinecatechins by region.

	Complete clearance
All countries (includes the United States)	
Veregen™ 15% (n=397)	213 (53.6%)
Vehicle (n=207)	73 (35.3%)
United States	
Veregen™ 15% (n=21)	5 (23.8%)
Vehicle (n=9)	0 (0.0%)

Table III: Efficacy of sinecatechins by gender.

	Complete clearance
Males	
Veregen™ 15% (n=205)	97 (47.3%)
Vehicle (n=118)	34 (28.8%)
Females	
Veregen™ 15% (n = 192)	116 (60.4%)
Vehicle (n=89)	39 (43.8%)

Clinical Studies

The efficacy and safety of sinecatechins (10% and 15% ointments) in the treatment of external genital and perianal warts were assessed in two randomized, double-blind, vehicle-controlled studies in immunocompetent patients 18 years of age and older (Tables II and III) (1, 10, 11). Subjects in these studies applied the ointment 3 times daily for up to 16 weeks or until complete clearance of all warts (baseline and new warts occurring during treatment). In both studies, the median baseline wart area was 51 mm^2 (range: 12-585 mm^2), and the median baseline number of warts was 6 (range: 2-30). The primary efficacy outcome measure was the response rate defined as the proportion of patients with complete clinical (visual) clearance of all external genital and perianal warts (baseline and new) by week 16. Among patients from all countries, including the United States, treated with 15% ointment, 213 (53.6%) patients treated with sinecatechins experienced complete clearance *versus* 73 (35.3%) patients treated with vehicle. Among patients from the United States (n=30), 5 (23.8%) sinecatechin-treated patients experienced complete clearance *versus* 0 patients treated with vehicle. Men treated with sinecatechins (n=205) experienced lower clearance rates than women (n=192; 47.3% *vs.* 60.4%), a trend also observed among patients treated with vehicle. The median time to complete wart clearance for patients treated with sinecat-

echins was 16 weeks in the first trial and 10 weeks in the second trial.

The results from a multicenter, randomized, double-blind, placebo-controlled phase II/III trial in 242 patients with external genital warts treated with sinecatechins 10% cream or 15% ointment or placebo for 12 weeks, followed by a 12-week follow-up period, were recently reported. The intent-to-treat population consisted of 238 patients and a total of 221 patients completed the study. The primary endpoint was complete clearance of baseline warts, which was achieved by 59.0%, 46.8% and 37.3% of the intent-to-treat population on 15% ointment, 10% cream and placebo, respectively; the respective values for male patients were 61.0%, 53.8% and 40.5% and the respective values for females were 56.8%, 39.5% and 34.1%. Complete clearance of all warts (both baseline and new warts) occurred in 56.4% and 45.5% of patients on the 15% ointment and 10% cream, respectively, after 12 weeks compared to 37.2-37.5% of those on placebo. As a secondary endpoint, 75-100% clearance was achieved in 80.8% of those on 15% ointment *versus* 54.5% and 51.8% of those on 10% cream and placebo, respectively, and similar significant differences were seen in males and females. Recurrence of baseline warts at 12 weeks after the end of treatment was observed in 3 male patients in each treatment group, with overall recurrence rates of 10.6%, 11.8% and 10.3%, respectively, for the 15% ointment, 10% cream and placebo groups. Local skin signs/symptoms occurred in all three treatment groups and were mostly mild to moderate in intensity, the most frequent being erythema, burning and itching, and resolved with continued treatment; no serious adverse events were reported (14).

Conclusions

Many treatments exist for genital warts, including cryotherapy, imiquimod (Aldara®), intralesional interferon, podophyllotoxin, podophyllin resin, surgical excision, laser/electrosurgery and trichloroacetic acid (15). As no head-to-head studies have been done comparing topical agents, it is impossible to determine which agent is optimal in terms of efficacy and safety. Sinecatechins are certainly a promising novel therapy for the treatment of genital warts and may find further applications in the treatment of actinic keratoses and superficial basal cell carcinoma, like imiquimod. Sinecatechins' place among therapies for genital warts, its first and only approved use, is not yet known and will likely become evident following its clinical use. As a botanical, it may appeal to patients who prefer natural treatments and may increase compliance and, by extension, efficacy.

Sources

MediGene AG (DE); distributed in the U.S. by Bradley Pharmaceuticals, Inc. The catechin extract (Polyphenon® E) is manufactured by Mitsui Norin Co., Ltd. (JP).

References

1. Veregen™ Package Insert. http://www.veregenrx.com

2. Ahn, W.S., Yoo, J., Huh, S.W. et al. *Protective effects of green tea extracts (polyphenon E and EGCG) on human cervical lesions*. Eur J Cancer Prev 2003, 12(5): 383-90.

3. Chandra Mohan, K.V., Subapriya, R., Hara, Y., Nagini, S. *Enhancement of erythrocyte antioxidants by green and black tea polyphenols during 7,12-dimethylbenz[a]anthracene-induced hamster buccal pouch carcinogenesis*. J Med Food 2006, 9(3): 373-7.

4. Yan, Y., Wang, Y., Tan, Q., Hara, Y., Yun, T.K., Lubet, R.A., You, M. *Efficacy of polyphenon E, red ginseng, and rapamycin on benzo(a)pyrene-induced lung tumorigenesis in A/J mice*. Neoplasia 2006, 8(1): 52-8.

5. Lu, Y., Yao, R., Yan, Y., Wang, Y., Hara, Y., Lubet, R.A., You, M. *A gene expression signature that can predict green tea exposure and chemopreventive efficacy of lung cancer in mice*. Cancer Res 2006, 66(4): 1956-63.

6. Shimizu, M., Deguchi, A., Lim, J.T., Moriwaki, H., Kopelovich, L., Weinstein, I.B. *(–)-Epigallocatechin gallate and polyphenon E inhibit growth and activation of the epidermal growth factor receptor and human epidermal growth factor receptor-2 signaling pathways in human colon cancer cells*. Clin Cancer Res 2005, 11(7): 2735-46.

7. Hirose, M., Mizoguchi, Y., Yaono, M., Tanaka, H., Yamaguchi, T., Shirai, T. *Effects of green tea catechins on the progression or late promotion stage of mammary gland carcinogenesis in female Sprague-Dawley rats pretreated with 7,12-dimethylbenz(a)anthracene*. Cancer Lett 1997, 112(2): 141-7.

8. Lubet, R.A., Yang, C.S., Lee, M.J. et al. *Preventive effects of polyphenon E on urinary bladder and mammary cancers in rats and correlations with serum and urine levels of tea polyphenols*. Mol Cancer Ther 2007, 6(7): 2022-8.

9. Babich, H., Zuckerbraun, H.L., Weinerman, S.M. *In vitro cytotoxicity of (–)-catechin gallate, a minor polyphenol in green tea*. Toxicol Lett 2007, 171(3): 171-80.

10. *MediGene successfully completes pivotal clinical phase III trials of Polyphenon® E ointment for the treatment of genital warts*. MediGene Press Release, December 7, 2004.

11. *Efficacy and safety study of Polyphenon E to treat external genital warts (NCT00449982)*. ClinicalTrials.gov Web site, December 19, 2007.

12. *Bradley Pharmaceuticals launches Veregen™ (sinecatechins) ointment, 15%*. Bradley Pharmaceuticals, Inc. Press Release, December 14, 2007.

13. *MediGene's second drug, Veregen™ (Polyphenon® E ointment) launched*. MediGene AG Press Release, December 14, 2007.

14. Gross, G., Meyer, K.-G., Pres, H., Thielert, C., Tawfik, H., Mescheder, A. *A randomized, double-blind, four-arm parallel-group, placebo-controlled phase II/III study to investigate the clinical efficacy of two galenic formulations of Polyphenon® E in the treatment of external genital warts*. J Eur Acad Dermatol Venereol 2007, 21(10): 1404-12.

15. Scheinfeld, N., Lehman, D.S. *An evidence-based review of medical and surgical treatments of genital warts*. Dermatol Online J 2006, 12(3): 5.