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Skin Microbiota Transplantation by Nivea Refining Clear-Up Strips Could Reverse Erythema Scores in Dogs with Atopic Dermatitis: Novel Strategy for Skin Microbiome Manuplation: Cohort Study

Atopik Dermatitli Köpeklerde Nivea Gözenek Arındırıcı Temizleme Bantları ile Yapılan Deri Mikrobiyota Transplantasyonu Eritem Skorlarını Tersine Çevirebilir: Deri Mikrobiyom Manüpilasyonu İçin Yeni Strateji: Kohort Araştırması

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ABSTRACT Objective: Skin microbiota transplantation (SMT) has aroused our interest for several years, with clinical trials. In the present study the purposes were i) to examine the practicability of SMT by Nivea Refining Clear-Up Strips able to transfer unenriched skin microbiota communities and, ii) to analyze the efficacy of SMT on erythema scores comparatively. **Material and Methods:** Briefly SMT was repeated on days 5 and 12, and the results were compared to initial values. In a total of 4 different healthy anatomical locations of the same case were selected, the strips were placed on moistened skin and allowed them to dry for 10-12 minutes. Then were carefully peeled off, all 4 strips were transferred to the erythema involved skin tissue were also moistured and allowed to attach for at least 12-15 minutes. The skin erythema severity was estimated with visual analogue scale erythema severity score (VAS-ESS) and Atopic Dermatitis Area and Severity Index (ADASI). **Results:** The Pearson correlations between the factor scores were all above 0.22 and statistically significant ($p<0.001$) between day 5 ADASI and VAS-ESS scores ($r=0.033$) and between day 5 ADASI and day 12 VAS-ESS scores ($r=0.048$, $p<0.001$). **Conclusion:** In conclusion by use of SMT ADASI and VAS-ESS scores were decreased. Transfer of skin microbiota between 2 dissimilar autologous microenvironments for each case (at the same host) enrolled would have helped hastening clinical recovery in dogs with atopic dermatitis.

Keywords: Atopy; dog; erythema; microbiome transplant; skin

ÖZET Amaç: Deri mikrobiyota transplantasyonu (DMT), klinik deneyimlerimizle oldukça fazla yıldır dikkatimizi çekmektedir. Bu çalışmanın amaçları i) zenginleştirilmemiş deri mikrobiyotasını transfer edebilen Nivea Gözenek Arındırıcı Temizleme Bantları ile DMT'nin uygulanabilirliğini incelemek ve, ii) DMT'nin eritem skorlaması üzerindeki etkinliğini karşılaştırmalı olarak analiz etmekti. **Gereç ve Yöntemler:** Kısacası DMT 5 ve 12. günlerde tekrar edildi ve sonuçlar başlangıç verileri ile karşılaştırıldı. Aynı vakada toplamda anatomik olarak sağlıklı 4 farklı bölge seçilerek temizleme bantları nemlendirilen seçilmiş bölgelere yerleştirildi ve 10-12 dakika beklendi. Ardından dikkatli bir şekilde temizleme bantları çıkarıldıktan sonra ayrıca nemlendirilmiş olan eritemli bölgelere yerleştirilerek en az 12-15 dk beklendi. Deri eritem şiddeti vizüel analog skalası (VAS-ESS) ve Atopik Dermatit Bölge ve Şiddet İndeksi (ADASI) ile tahminlendi. **Bulgular:** Faktör puanları arasındaki Pearson korelasyonlarının tamamı 0,22'nin üzerindeydi ve 5. gün ADASI ve VAS-ESS puanları ($r=0,033$) ve 5. gün ADASI ve 12. gün VAS-ESS puanları ($r=0,048$) ($p<0,001$) arasında istatistiksel olarak anlamlı ($p<0,001$) farklılıklar mevcuttu. **Sonuç:** Sonuç olarak, DMT ile ADASI ve VAS-ESS azaldı. Her bir vakada (aynı konakçıda) ki benzer olmayan otolog mikroçevre arasında deri mikrobiyota transferi, atopik dermatitli köpeklerde klinik iyileşmenin hızlanmasına yardımcı olmuştur.

Anahtar Kelimeler: Atopi; köpek; eritem; mikrobiyom transplantı; deri

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Atopic dermatitis (AD) among dogs has generally been presented as an inherited inflammatory and pruritic allergic skin disease.[1] Cutaneous microbiome may be the provenance of secondary infections dominating the severity of canine AD.[2] Regarding bacterial cultures *Staphylococcus pseudintermedius* and/or *Malassezia pachydermatis* are the vast majority prominent bacterium/fungal representative.[3] Furthermore, canine skin microbiome belonging to the skin of AD dogs presented relative abundance of the *Staphylococcus* genus in contrast to to healthy dogs, along with lower bacterial diversity detected on dermatological locations affected by AD flares among dogs.[4-6] Among dogs, peculiar locations of the skin are prone to be influenced by AD.[7] The degree of erythema reflects disease severity among dogs with AD.

In the present study we aimed i) to examine the practicability of skin microbiota transplantation (SMT) by Nivea Refining Clear-Up Strips (Nivea Beiersdorf, Germany) able to transfer unenriched skin microbiota communities among 4 different anatomical sites of the same host and, ii) to analyze the efficacy of SMT on erythema scores comperatively.

MATERIAL AND METHODS

DEMOGRAPHIC DATA

We selected, a total of 7, pure-bred (n=5) and cross-bred (n=2) client-owned dogs, at the age of 3 to 7.5 years old, of both sexes and various sizes with a diagnosis of AD on referral to Aydın Adnan Menderes University Faculty of Veterinary, Department of Internal Medicine Clinics (to those of solely involved researchers). Diagnosis of AD was mainly based on i) excluding other relevant skin conditions, ii) detailed lab work compassing historical/clinical features of the condition, iii) interpretation of clinical criteria denoted as "Favrot's criteria" and, iv) determination of immunoglobulin (Ig)E by in vivo allergen-specific IgE testing (Polycheck®, German).[1,7] The erythema severity was estimated in the abdominal/inguinal regions on the skin in 2 ways: i) adapted from Cugmas and Olivry,[8] erythema severity score was detected by use of visual analogue scale (VAS) (0 to 4; no erythema to severe erythema, respectively) and denoted as visual analogue scale erytheme severity score (VAS-ESS) and ii) adapted from Psoriasis Area and Severity Index (PASI) score indicating (partially) erythema severity score was detected by use of dermatoscopy (DermLite DL4 basic, 3Gen Inc.; San Juan Capistrano, CA, USA) and a smart phone (iPhone 6 plus with attachment device) in comparison with VAS (0 to 4; absent to very severe erythema, respectively) (Figure 1, Figure 2).[8] Nomenclature was adopted from PASI and altered as Atopic Dermatitis Area and Severity Index (ADASI). The reason for comparative evaluation was not to detect which one is superior to other, whereas detecting the rationale for finding the practical solutions that is applicable

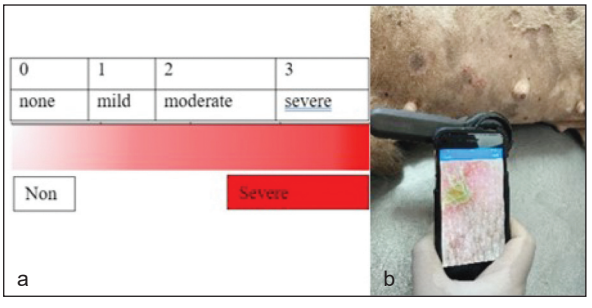

FIGURE 1: a) Adapted from Cugmas and Olivry,[8] erythema severity score was denoted as visual analogue scale erytheme severity score (VAS-ESS). **b)** In the present case with multiple coalescent lesion, namely epidermal collarette with erythema scores of VAS-ESS 2. Visually this newly created visual analogue scale with a continuous palette of red shades were adopted from Cugmas and Olivry.[8] The researcher in issue, labeled a dot cross matching the sensed severity of skin erythema based on DermLite dermatoscopic examination results. Furthermore, the available score value was transfered to its relevant point, as explained above (0%, no erythema; 100%, the most severe erythema).

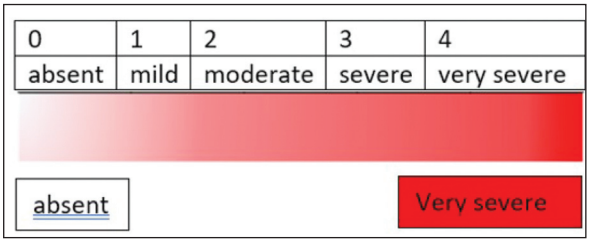

FIGURE 2: a) Adapted from PASI score indicating (partially) erythema severity score was detected by use of visual analogue scale (0 to 4; absent to very severe erythema, respectively). Nomenclature was adopted from PASI and altered as ADASI 1, b) In the present case with multiple coalescent lesion, namely epidermal collarette with erythema scores of ADASI 2.

to field veterinary surgeons. Twenty five years of experienced gastroentero-dermatologist (first author K.U.) gave his first opinion doble blinded to case enrollment, which was then relevant researchers participated in erythema grading, yet only the dedicated veterinary surgeon (H.E. or S.E.) who was the clinician performing the assessment, similar to previous study.[8]

SKIN MICROBIOTA TRANSPLANTATION BY USE OF NIVEA REFINING CLEAR-UP STRIPS

Each box of Nivea Refining Clear-Up Strips was unboxed, and every single strip was separated. In a total of 4 different anatomical locations were selected [to those of apparently healthy skin tissue with hair growth and no evidence of primary or secondary skin lesion (i.e. erythema and others)], we placed the strips on moistened skin (Bepanthol Sensiderm Cream, Bayer, Türkiye) and allowed them to dry for 10-12 minutes. Then were carefully peeled off, all 4 strips were transferred to the erythema involved skin tissue (inguinal or abdominal area) which were also moistured and allowed to attach for at least 2-15 minutes. Finally at the end of trial all strips were removed. None of the cases were allowed to have a bath during trial. No evidence of any side effects was noticed. There were no unsatisfactory or unpleasant owner reports.

ETHICAL APPROVAL

All animals were subjected to humane treatment in accordance with the "Guide for the Care and Use of Laboratory Animals" (www.nap.edu/catalog/5140.html). Human principles were applied to animal care and use in all procedure. Moreover, the study was approved by the local ethic committee of Aydın Adnan Menderes University-HADYEK on October 27, 2021 with no: 64583101/2019/022. Written owner consent was deemed available for all participant dogs.

RESULTS

We assessed the erythema severity in 7 dogs. We excluded several other dogs from further analysis because of comorbidities. There were no side effects, nor complication during trial. No unpleasant nor unsatisfactory owner report were existed. In all 7 dogs SMT was well accepted as shown in Figure 3, Figure 4, Figure 5. Dermatoscopic evaluation were deemed available supporting both diagnosis and ADASI-VAS-ESS (Figure 6).

FIGURE 3: This figure depicts one of the cases enrolled at this study comparatively presenting both VAS-ESS and ADASI scores on days 0 to 12, respectively, throughout the trial.
VAS-ESS: Visual analogue scale erythema severity score; ADASI: Atopic Dermatitis Area and Severity Index.

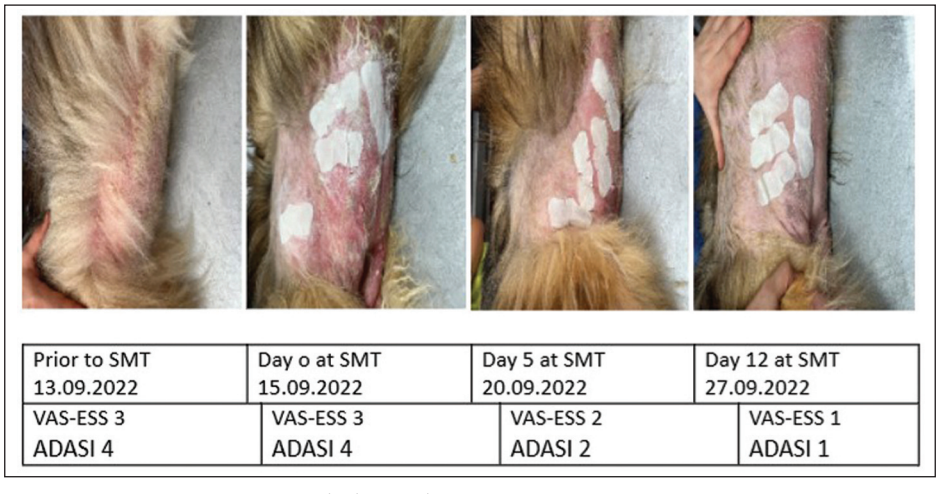

FIGURE 4: Clearly depicting prior to and thereafter on days 0th, 5th, and 12th days during SMT. Nivea Refining Clear-Up Strips were attached to the erythematous skin as seen. On days 5 and 12, both VAS-ESS and ADASI scores were decreased significantly ($p<0.001$).
SMT: Skin microbiota transplantation; VAS-ESS: Visual analogue scale erythema severity score; ADASI: Atopic Dermatitis Area and Severity Index.

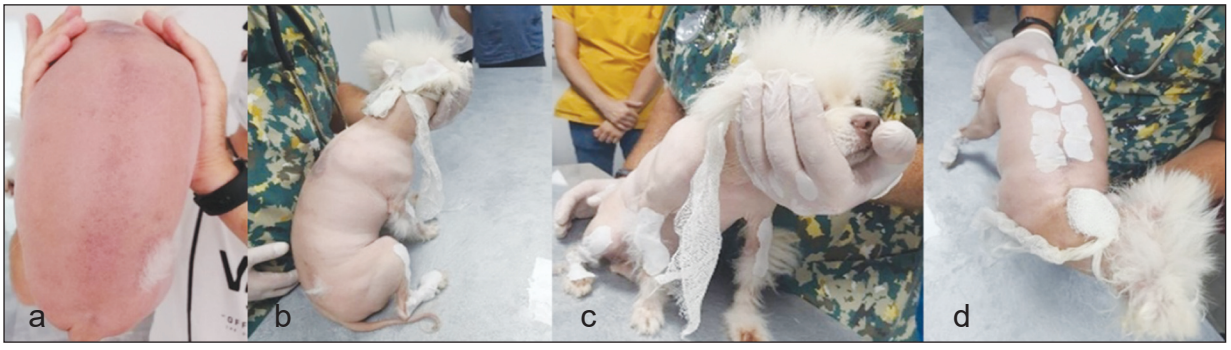

FIGURE 5: One of the cases enrolled at this study with **a)** severe erythema (VAS-ESS 3, ADASI 4) on day 0 before SMT, **b)** and **c)** Nivea Refining Clear-Up Strips were firstly attached to the apparently healthy skin and **d)** then were transferred to the targeted area, in this case dorso-lumber region and abdomen recorded on day 12 when erythema scores were diminished (VAS-ESS 1, ADASI 1).
VAS-ESS: Visual analogue scale erythema severity score; ADASI: Atopic Dermatitis Area and Severity Index; SMT: Skin microbiota transplantation.

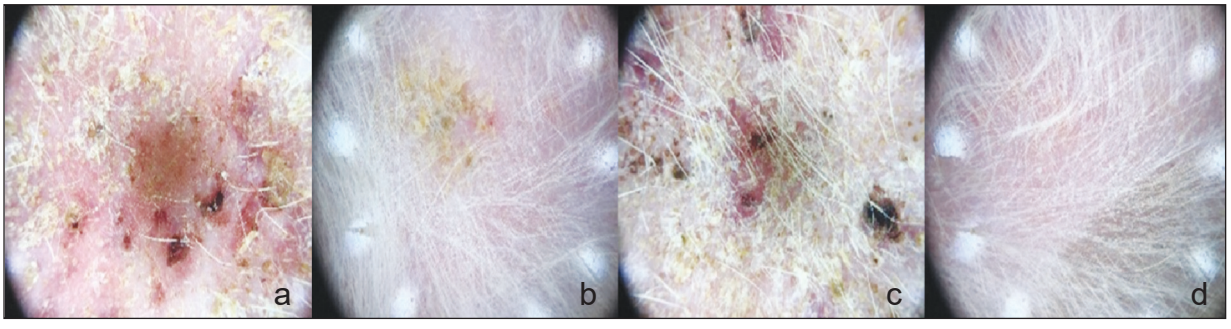

FIGURE 6: Dermatoscopic interpretation of erythema in different dogs with AD reflecting ADASI vs. VAS-ESS comparatively and respectively, as **a)** 3 vs 2, **b)** 1 vs 1, **c)** 3 vs 2 and **d)** 1 vs 1.
AD: Atopic dermatitis; ADASI: Atopic Dermatitis Area and Severity Index; VAS-ESS: Visual analogue scale erythema severity score.

CORRELATION AMONG TWO SCORING SYSTEMS

The correlations between our 2 selected indicators were then assessed based on our assigned factor analysis (erythema scores). The Pearson correlations between the factor scores were all above 0.22 and statistically significant ($p<0.001$) between day 5 ADASI and VAS-ESS scores ($r=0.033$) and between day 5 ADASI and day 12 VAS-ESS ($r=0.048$). Other relevant factors showed positive but insignificant correlations as shown in Table 1 and Figure 7.

TABLE 1: As days progress correlation was weakened, whereas strong correlation was evident among between day 5 ADASI and VAS-ESS scores (r=0.033) and between day 5 ADASI and day 12 VAS-ESS (r=0.048) (p<0.001). Positive correlation was evident throughout trial between ADASI and VAS-ESS.

	VAS-ESS Day 0	VAS-ESS Day 5	VAS-ESS Day 12
ADASI	R=0.39	R=0.81	R=0.81
Day 0	P=0.338	P=0.062	P=0.095
ADASI	R=0.22	R=0.87	R=0.84
Day 5	P=0.686	P=0. 033	P=0.048
ADASI	R=0.25	R=0.67	R=0.30
Day 12	P=0.667	P=0.190	P=1.000

ADASI: Atopic Dermatitis Area and Severity Index; VAS-ESS: Visual analogue scale erythema severity score.

DISCUSSION

To the best of our knowledge until recently SMT researches were fascinated on moving single, augmented strains of bacteria for targeting sites preferably than an entire community. In a prospective pilot research, the practicability of transferring unimproved skin microbiota communities between 2 anatomical locations belonging to the same host.[9] In the present study, to our knowledge for the first time, at least in our country, SMT were deemed available

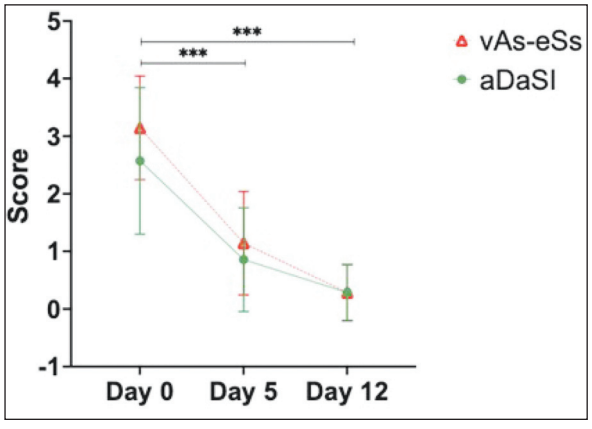

FIGURE 7: Mean±standard deviation alterations among 2 scoring systems in relationship with study duration, timeline. There were statistically significant differences on erythema scores (ADASI vs. VAS-ESS) among day 0 and day 5, and between day 0 and day 12 (p<0.001***, each).
ADASI: Atopic Dermatitis Area and Severity Index; VAS-ESS: Visual analogue scale erythema severity score.

(after 7 years of preparation along with unwritten observations and relevant data) with an unenriched skin microbiota obtained by Nivea Refining Clear-Up Strips and then were transferred between 4 different anatomical locations at the same case in a total of 7 diseased dogs with AD. Briefly this technique (as explained at material and methods section) was composed of the latter test strips attached to the apparently healthy locations were at least touched and enriched for 10-12 minutes and then were gently collected, attached to the diseased skin tissue with erythema.

Regarding skin microbiome manipulation strategies, various methodologies should be attempted. Skin microbiome transplantation should deemed available as one of the strategies. Given well recognized fecal microbiota transplantation against *Clostridium difficile* infections and there afterwards for combatting AD in dogs, SMT should be promising alternative for at least dermatology field.[10-13] For a SMT, the cutaneous microbiome of a healthy one is conveyed to the cleansed skin location of another individual through a purpose of ameliorating the cutaneous disorder of the latter. As a superiority, the microbiome is conveyed in its natural territory. Although uncomplicated, the latter methodology possesses various pitfalls. Solely stubby units of bacteria could be culling from the integumentary system. For overwhelming this disadvantage a culturing step is customarily required to acquire adequate amounts of bacteria, in which the latter methodology is not ascendible or industry pertinent. On the other hand, it is unclear which microorganism are conveyed to the integumentary system, to those of probably pathogenic taxa might also be transmitted.[14] In the present study, with the owner permission Nivea Refining Clear-Up Strips were used noninvasively with the aim of skin microbiota transplantation at the same host. Although it was unfortunately impossible to involve culturing step (due to the absence of and microbiologist work on this field), the present researcher group took the responsibility even if pathogenic taxa might also be transmitted as reported previously.[14] Written owner consent was also deemed available, in which all cases were in close monitorization. Incidentally there were no undesired side effects were noted. This may be related to experienced skills and placement of strips on moistened skin, which was composed of a cream involving pre-biotic.

Cutaneous microbiome is proportionally stable over time. Matching microbiome arise back through after washing/cosmetic applications, even if the latter involves antimicrobial agents.[14,15] In a prior study evaluating microbiota dynamics after epidermal barrier disruption, tape stripping revealed that the cutaneous microbiota has already been derived from the skin. Following skin removal of 2 weeks, the newly existed skin microbiota was more identical to that of the deeper stratum corneum layers in comparison to initial surface microbiome.[16] It was determined that elevated concentrations of bacterial DNA were evident on hair follicle in contrast to epidermal layer.[17] Bacterial DNA was existed both in dermis and relevant adipose tissue whereas it was unknown even if those bacteria were alive.[17] Taking into account the latter data, it was hypothesized that deeper layer of integumentary system is the core skin microbiome.[14] This data was cautiously and interestingly taken into consideration as because Nivea Refining Clear-Up Strips could have helped recovery of core skin microbiome by this route in the present study.

Nivea Refining Clear-Up Strips manufactured for removal of blackheads on the T-Zone, has been

preferred at this study. This product that could be able to efficiently remove unwanted substances even after first application, even if in contact with water, arresting impurities and unblocking the pores. The latter also involves citric acid, an exfoliating ingredient with regenerating benefits. It might be questionable that usage of citric acid might be of beneficial. In a prior trial with AD model, citric acid inhibited pseudomonas ceramidase and resulted in suppressing the inflammation. In that study it was suggested that citric acid alleviated AD induced by the infection of bacteria in the skin.[18] Given this data, it should not be unwise to draw conclusion that citric acid involved in Nivea Refining Clear-Up Strips used at this study, should have helped regression of erythema with the latter mechanism. Furthermore taking into account mean±standard deviation alterations among 2 scoring systems recorded at the present study, statistically significant differences (ADASI vs. VAS-ESS) among day 0 and day 5, and between day 0 and day 12 ($p<0.001^{***}$, each) were evident. This could be briefly explained within the next paragraph.

Someone might speculate that how SMT could reverse erythema? In prior research, it was detected that distinct skin microbiome signatures could be in relationship with different clinical signs. For instance, thicker integumentary tissue and elevated pain levels markedly correlated with diminished relative abundance of *Propionibacterium* on to the lesional skin.[19] Which was also detected within AD.[5] It is still questionable even if *Propionibacterium* participates a preventive role in diminishing clinical signs and inflammation or merely denoting dysbiosis that needs to be addressed.[19] *Staphylococcus* species was in relationship with severe erythema intensity among patients with mycosis fungoides. *Staphylococcus aureus* colonization in mouse linked to powerful T helper 17 cell polarization and influence inflammation.[20] Hence *S. aureus* skin colonization was related to severity of clinical signs in AD.[21] Taking into account this relevant data aforementioned above it should not be unwise to draw preliminary conclusion that SMT between 2 dissimilar autologous microenvironments at the same host, as was validated in the present study, should have helped decreasing *S. aureus* skin colonization (we could better say probably, as because skin microbiota analysis were not deemed available, which could be our subsequent purpose for next research) in all 7 dogs enrolled herein.

In a prior study it was hypothesized whether if movement of superficial skin microbial communities was reasonable/practicable. In that trial based on the topographical variability of cutaneous microbiota within a single host, researchers pick out locations (the antecubital fossa and the upper back) with a distinctive configuration of microbes.[9,22] In the present study we similarly used selected anatomical locations (with a healthy tissue without alopecia, crust, hyperpigmentation) with a contrasting composition of microbes. On the other hand in the present study, we were unable to assess the efficacy of our technique (evidence of cultured microorganisms and sequenced taxa) at microbiological level.[9]

CONCLUSION

Herein, as an evidenced based veterinary medicine, we aimed to follow the reflection of SMT by Nivea Refining Clear-Up Strip transferred species (with the disadvantage of unknown skin microbiota alterations before and after, however this would be the purpose of our subsequent study) and demonstrated that this easy, reasonably priced (in reality very cheap) and simple (but deep experienced skills and facilities are necessary) method for moving superficial skin microbiota could hasten recovery along with other relevant supportive measures (pre- and pro-biotics and nutraceuticals etc.). This methodology composed of transfer of skin microbiota between 2 dissimilar autologous microenvironments (at the same host) would have helped hastening clinical recovery (at least dogs involved herein). Our arousing interest would competitively be grown. Thus, subsequent study would be targeted.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that

provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Kerem Ural;* ***Design:*** *Kerem Ural;* ***Control/Supervision:*** *Kerem Ural;* ***Data Collection and/or Processing:*** *Kerem Ural, Hasan Erdoğan, Songül Erdoğan;* ***Analysis and/or Interpretation:*** *Kerem Ural;* ***Literature Review:*** *Kerem Ural;* ***Writing the Article:*** *Kerem Ural;* ***Critical Review:*** *Kerem Ural, Hasan Erdoğan, Songül Erdoğan;* ***References and Fundings:*** *Kerem Ural, Hasan Erdoğan, Songül Erdoğan;* ***Materials:*** *Kerem Ural, Hasan Erdoğan, Songül Erdoğan.*

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