RESEARCH ARTICLE

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Intestinal Permeability Targeted Rectal Enema Nutraceutical Intervention in Dogs with Cutaneous Adverse Food Reactions: Gut-Brain-Skin Axis Directed Pro-active Treatment

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Abstract

Inflammatory cutaneous disorders have frequently been subjected to treatment trials with very limited success by pharmaceutical intervention, such as corticosteroids and non-steroidal anti-inflammatory drugs. Nevertheless, the latter drugs might be usual suspects for undesirable side effects. In an attempt to overcome those side effects, natural nutraceuticals are being investigated by the present researchers group. In this scenario, 5 different set of nutraceutical interventions [were numbered by their relevant usage order as Nutr-i1 to Nutr-i5] via rectal enema was deemed available at the present study as a novel protocol for pro-active treatment of cutaneous adverse food reactions (caFr) among dogs involved. In a total of 10 dogs with caFr, at the age of 2 to 7 years old, of both sexes, from various breeds diagnosis was based on i) in vitro serum testing for selected/specific IgE ii) intradermal testing different antigens, iii) elimination diet trial and iv) treatment based respond evaluation. Pruritus, as a vast majority presented clinical sign, scoring deemed available visual analog scale (pVaS). Mean ($\bar{X}$ ± Sd) pVaS scores showed significant decreases after treatment in contrast to prior values [1.4 ± 1.27 vs.7.7 ± 1.62, respectively ($p<0.005$)]. As discussed herein in the whole manuscript, all Nutr-i1 to Nutr-i5 protocols showed pro-active treatment efficacy, which could contribute to novel protocol establishment.

Keywords: Inflammatoric cutaneous disorders, nutraceutical, phytotherapy, polyphenol, probiotic.

INTRODUCTION

Cutaneous adverse food reactions (caFr) is one of the foremost diagnoses frequently detected in dogs/cats with allergic diseases (Olivry and Mueller, 2017). The latter caFr might mimic either noncutaneous (Mueller and Olivry, 2017) or cutaneous clinical signs. Given itching is generally regarded as the vast majority of clinical finding affecting pets with a caFr (Shimakura and Kawano, 2021), consensus/accepted guidelines on caFr in dogs and cats are lacking.

Pathogenesis of caFr is generally based on hypersensitivity and food antigen that stimulate to the immune system considering related studies (Picco et al., 2008; Nemser et al., 2014; Mueller and Unterer, 2018). Unlike humans, there is an indistinguishable anamnesis and clinical background between caFr and atopic dermatitis that usually confusing (Hillier and Griffin, 2001; Olivry et al., 2007). Some studies showed that the pathophysiology of caFr and atopic dermatitis were shown similarities due to increased food-specific immunoglobulin in dogs with atopic dermatitis and gastrointestinal disease (Foster et al., 2003; Pucheu-Haston et al., 2020).

Increased mucosal permeability in dogs with gastrointestinal tract disease is caused by increased antigenic stimulation. Indeed, it is known that food-specific IgG levels are increased in those dogs (Foster et al., 2020). Most of the studies demonstrate a close relation of gut–skin axis in dogs (Craig, 2016; De Pessemier et al., 2021; Rostaher et al., 2022; Ural, 2022). The gut microbiome as breeding of the immune system has the ability to tolerate and avoiding from allergies (Salzman, 2014; Aitoro et al., 2017; Wang et al., 2021; Augustine et al., 2022). Hence the probiotic could be capable of regulating the immune system [via changing gut microbiota and leading to the mucosal/systemic immune defense by modification of cytokine releasing and intestinal IgA responses]. They concurrently modulate to Th1/Th2 balance by suppressing the Th2 response and stimulating the Th1 response for preventing allergies. Thereby, probiotics diminish allergic inflammation by contributing to provide the balance of increased butyrate, cytokine response, and decreased eosinophil production (Eslami et al., 2020; Lunjani et al., 2020; Royal and Gray, 2020).

Furthermore to the present authors' knowledge novel/natural treatment protocols are necessary, which prompted us to perform the present study. Therefore, our purpose was to establish a natural rectal enema protocol by use of phyto agents and probiotic combination. This protocol was directed to intestinal permeability restorative compounds, which were preferred.

MATERIALS AND METHODS

Study population

A total of 10 dogs with caFr, at the age of 2 to 7 years old, of both sexes, from various breeds.

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Diagnosis-The most challenging part

In the present study in an attempt to take steps for a tentative diagnosis of caFr: i) in vitro serum testing for selected/specific IgE (Polycheck in vitro IgE testing, Biocheck, distributed by RDA Grup, Turkey) ii) intradermal testing of different antigens (Artuvetrin® Skin Test, Nextmune, The Netherlands), iii) elimination diet trial (Bethlehem et al., 2012; Ricci et al., 2013; Mueller and Olivry, 2017) and iv) treatment based respond evaluation. Clinical signs were challenging (alopecia, crusting, scaling etc.). Pruritus scoring deemed available visual analog scale (pVaS).

Food challenge test

The food challenge testing is denoted as improvement within the clinical signs (whether if) based on pVaS ≤ 2, similar to what has been described elsewhere (Shimakura, 2021). This procedure was attended as the first part of this trial and denoted as an active therapeutical intervention, which was followed by the second part of our study 6 weeks after the food challenge test. Even if the challenge was initiated on the first day through animal the owners keep eye on the dogs at natural sources for 3 days. The complete procedure [challenging, consumption of original food, recording the timeline of prior clinical signs detected along with the body locations affected] was very similar to the previous description (Shimakura, 2021).

Ural Breakthrough Nutracuetical Component: pro-active treatment

This treatment second line, however baseline pro-active, protocol involving natural compounds were given in rectal route similar to what has been described elsewhere (Ural et al., 2021a,b). Briefly on 5 different nutraceutical sessions, with 15 minutes apart from each other relevant ones, the necessary combination was prepared (as formula was shown in Figure 1. involving palliative submarine), which was then rectally administered as an enema model (Ural et al., 2021a,b). The treatment trial involved 10 days for rectal enema. Each nutraceutical intervention (shortly abbreviated as Nutr-i1 to Nutr-i5) was performed by the researchers involved at this study with deep experience. Oral consumption of altered calendar probiotic therapy (Ural et al., 2020) lasted at month 3, weekly changed.

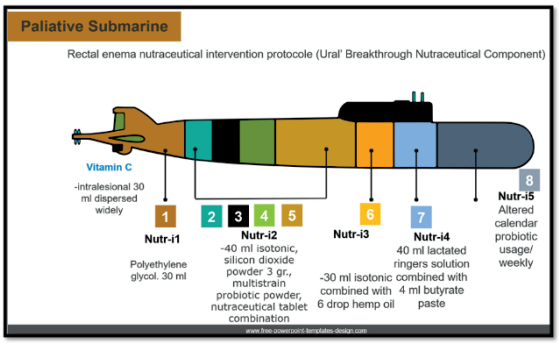

Figure 1. Nutraceutical interventions (Nutr-i) were numbered by their relevant usage order as a rectal enema.

Nutr-i1: Golytely oral sol. powder [polyethylene glycol (pEg 3350)], **Nutr-i2:** Zoosorb Powder (silicon dioxide), Assos Gutfeel Powder (multistrain probiotic), Theravet Skin Tablet [multi polyphenol ingredient nutraceutical formulized by the first author of this research, K.U.], **Nutr-i3:** Theravet Hemp Oil (pure hemp oil formulized by the first author of this research, K.U), **Nutr-i4:** Nucron Paste (Butyrate along with other nutraceuticals), **Nutr-i5:** oral usage of Triogermila I Vial [*Bacillus subtilis*, *Bacillus caogulans*, *Bacillus clausii*] 2x1 p.o. and Twippy Drop 2x10 p.o. [*Lactobacillus rhamnosus* (GG), *Lactobacillus acidophilus*, (LA-5®), *Streptococcus thermophilus* (STY-31™), *Bifidobacterium animalis subsp.Lactis* (BB-12®), *Lactobacillus delbrueckii subsp. Bulgaricus* (LBY-27™)]

Descriptive statistical interpretation

Descriptive statistics for enrolled values were tabulated in an attempt to indicate the mean and standard deviations. Wilcoxon test was used to determine the statistical differences of pruritus Vas scores prior to and thereafter treatment. A p value of < 0.05 was considered significant by using the SPSS 26.0 program (IBM, USA) in all analyzes.

RESULTS

Demographic and evidenced based clinical photographs were deemed available between Figure 2-5 showing 5 out of 10 cases. A mini atlas was shown above in an attempt to attract the interest of readers. Another purpose was to perform a small-scale lesion mapping which will guide readers for their future and similar cases. pVas scores were shown in Table 1 above.

This lesion mapping should have helped audiences for better understanding the mechanism of action and therapeutical outcomes. Furthermore, all cases were experienced at the clinic with special reference to its gut-brain-skin axis. Regarding this axis, clinical findings should be directed to neurotransmitters, neuroendocrine network, and messenger molecules.

Figure 2. Dorsolomber lesions (crusting, total alopecia, hyperpigmentation and comedone formation) were evident, excluding Favrot Criteria and atopic dermatitis. One of the hardest cases, existed at this study, which was very well respond to the Nutr-i1 and -i5 treatment protocol.

Figure 3. Two different cases with caFr. As seen above lesion demography was not very unfamiliar, however some similarities (alopecia, dorso-lomber lesions etc.). Both dogs were responsive to the Nutr-i1 and -i5 treatment protocol used in this study.

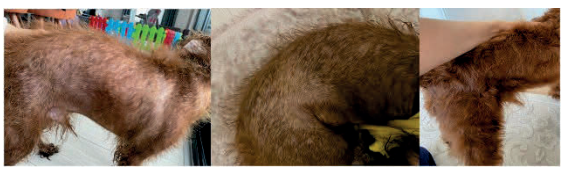

Figure 4. Latero-lateral lesions in a dog with caFr, previously nourished with a high carbonhydrate diet, which was then altered by the present researchers and siwtched to 17% carbonhydrate involving commercial dog food along with rectal enema nutraceuticals.

Figure 5. Resolution and withdrawal of hyperpigmentation and pruritus ani in a dog with caFr which was very good responder to the treatment protocol used in this study.

DISCUSSION AND CONCLUSION

In this part of this manuscript, the researchers will in-depth and separately discuss nutraceutical interventions, for a better understanding of the mechanism of action. Finally will mix relevant data for a conclusion. All 5 and different set of rectal enema would be briefly focused on the mechanism of action within the scope of the present study.

Hemp oil

At inflammatory conditions various cellular pathways might be active within the intestinal environment, directing to a probable pathological condition (Wood et al., 1999; Massa et al., 2004). Human ileum and colon tissues expressed functional CB1 receptors along with elevated populations of CB1-expressing cells following inflammation (Pertwee, 2001; Massa et al., 2004). Considering the small intestine, CB1 receptors involvement for the management of intestinal motility at croton oil-induced inflammation was well recognized. Cannabinoid usage was capable of delaying gastrointestinal transit to those of croton oil-treated mice (Izzo et al., 2001). Furthermore, it was claimed that elevated CB1 receptor expression in jejunum inflammation might bestow within this preservative efficacy. CB1 receptors tempered gastrointestinal motility in the course of croton oil-induced inflammation among mice (Izzo et al., 2001; Nagarkatti et al., 2009). The potential anti-inflammatory efficacy of cannabinoids was discussed in a well-designed review (Nagarkatti et al., 2009), which could attribute to the nutraceutical efficacy obtained at this study herein. The endogenous cannabinoid system is capable of prevention as opposed to inflammatory alterations. All aforementioned facts proposed that activated CB1 and the endogenous cannabinoid system is an untimely and significant physiological pace in colon defense against inflammation (Nagarkatti et al., 2009). All data support that cannabinoids, hemp oil was the choice in this study, adjusting the tissue response as oppose to overwhelming inflammation in the colon (Nagarkatti et al., 2009). Furthermore, given hemp seed oil might mitigate against several dermatitis types [i.e. eczema, seborrheic dermatitis, psoriasis, lichen planus, and acne roseacea] (Tabassum and Hamdani, 2014) and be supportive against bacterial, viral, fungal infections and for the control of scabies (Olsen et al., 2001), available efficacy in the present study should be related to secondary dermatological supportive effects of hemp oil.

Polyethylene glycol

As one of the most multi-faceted molecules, pEg are concomittantly destinate various pathological conditions [immune activation, tight junction function, cell membrane dysfunction, tissue edema and the integrity of the mucosal barrier]. Beacuse of their large molecular volume and hydrophilic chattels, pEg give rise to an oncotic plunge to confiscate water molecules and diminish tissue edema. Mechanism of action for pEG include i) free-radical scavengers, ii) patching damaged cell membranes by formation of reversible complexes with membrane lipids, in an attempt to maintain cell integrity, iii) substitute mucins for preserving and restoring the epithelial mucin layer (Valuckaite et al., 2013), iv) protection of intestinal epithelial cells against various stressors (Valuckaite et al., 2009; Edelstein et al., 2011). In the present study as used in Nutr-i1 formula, pEg could have helped to dampen inflammatory conditions (along with other protocol steps used) and might be responsible for the restoration of the integrity of the mucosal barrier (Ural et al., 2021c).

Silicon dioxide: an enterosorbent

The siliceous enterosorbent silicon dioxide was frequently investigated for its effective heavy metal removal (Li et al., 2011). On the other side it was proposed oral consumption of siliceous small nanoparticles exhibited a risk for worsening intestinal inflammation through activation of the ASC inflammasome (Yazdi et al., 2010; Ogawa et al., 2021). In the present study it was suggested that rectal enema protocol (not oral usage) Nutr-i2 involving silicon dioxide might have helped recovery by toxin/heavy metal binding efficacy (Agaba et al., 2018).

Butyrate

Given major short-chain fatty acids [acetate, propionate, and butyrate], take part in significant roles in the conservation, boosting, and safeguarding of the intestinal tight junction barrier. Among short-chain fatty acids, various mechanisms of action for butyrate on the tight junction barrier has been proposed: i) stimulation of the epithelial metabolism along with depletion of intracellular oxygen, consequently enhancing barrier integrity (Kelly et al., 2015), ii) induction of claudin-3 expression via the Akt pathway in the colon (Yan and Ajuwon, 2017; Feng et al., 2018), iii) elevation of lipoxygenase expression and tight junction barrier integrity through cellular production of hydroxyeicosatetraenoic acid in Caco-2 cells (Ohata et al., 2005). As has been used as Nutr-i4 protocol in this study lactated ringer solution was used as a substrate for commercially available (ready-to-use) butyrate. Utilization of lactate specifically attributed to solely selected bacterial species within clostridial cluster XIVa, though not belonging to all butyrate-producing bacteria (Duncan et al., 2004). In a prior well-written review *Clostridium butyricum* and other relevant microbial communities as dark fermentation bioreactors were denoted as cell factories converting lactate and acetate to butyrate (Detman et al., 2019). Lactate along with butyrate usage should have helped recovery observed at this study. Researcher group of this study with the discovery and guidance of the first author has been elucidating.

Polyphenol combination

Commercially available Nutr-i2 involved a well-designed and formulated (by the first author K.U.) polyphenol combination involving licorice root, pumpkin seed, broccoli sprout, black cumin (*Nigella sativa*), vitamins A-D3-E, zinc-oxide, garlic extract, biotin, collagen and evening primrose which could all contribute to anti-oxidant, anti-inflammatory and anti-histaminic, anti-infectious features of this compound (Theravet Skin Tablet, Naturmed, Antalya, Turkey) used. Dedicated to the first (founder) authors' surname, Ural Breakthrough Nutraceutical Component (Figure 1), this pro-active treatment protocol involved natural compounds given in rectal route similar to what have been described previously (Ural et al., 2021a,b). Briefly on 5 different Nutr-i sessions (as a palliative submarine model), with 15 minutes apart from each other relevant ones (shown in Figure 1), which was then rectally administered as an enema model (Ural et al., 2021a,b). Treatment trial involved 10 days for rectal enema. Each session (from Nutr-i1 to Nutr-i5) was performed by the researchers involved at this study with deep experience. As mentioned above mechanism of action for active ingredients (Table 2) might have helped recovery available at this study.

Table 1. pVaS scores prior to and thereafter Nutr-i1 and -i5 for all cases were deemed available and completely finished study without any side effects.

Score	*Before Treatment* ($\overline{X}$ ± Sd)	*After Treatment* ($\overline{X}$ ± Sd)	*P value*
Vas	7.7 ± 1.62	1.4 ± 1.27	0.005

Vas: Visual analog scale

Probiotic

Two different version of probiotic selection were deemed available: namely soil based one (Triogermila-I Vial, Algae Pharma, İstanbul, Turkey) and Twippy Drop (Valens, İstanbul, Turkey). This previously described altered calendar probiotic therapy (Ural et al., 2020) was lasted at month 3, in which probiotic selections were weekly changed.

Streptococcus thermophilus, which was one of the involved probiotics at Twippy Drop, presented effective support in dermatological disorders both *in-vitro* and *in-vivo* studies; i) elevating the production of beneficial lipids in the stratum corneum [i.e. ceramides, employing moisture in the skin (Di Marzio et al., 1999) and phytosphingosine, combatting *C. acnes* (Pavicic et al., 2007). In this study this probiotic species could have helped restoration of beneficial lipids in the stratum corneum, as reported above.

In the present study 3 different Bacillus strains were composed of soil based probiotic choice for therapeutical armamentarium. Bacillus probiotics possess their benefits by digestive enzyme production (Danilova and Sharipova, 2020). Bioactive probiotic molecules exhibited inflammation combatting efficacy through a) exopolysaccharides, b) molecules of cell envelope c) secretion of proteins. Given prior description of cell envelope-associated probiotic molecules, accompanied by secreted protein and carbohydrate probiotics, exopolysaccharide (ePs) exhibited by *B. subtilis* might have helped combatting against inflammation (Zamora-Pineda et al., 2022). The latter anti-inflammatory action of *B. subtilis* prevented different T cell-mediated diseases and alleviated allergic eosinophilia (Swartzendruber et al., 2019).

In conclusion at the present study altered calendar probiotic therapy all contributed to recovery obtained in all cases, as brief explanation was given herein. All Nutr-i1 to Nutr-i5 protocol showed pro-active treatment efficacy, which could contribute to novel protocol establishment.

Table 2. Selected active ingredients of Nutr-i2 and mechanism of action by references.

Active Ingredients	Mechanism of action
Licorice root (root extract)	-Skin protection for combatting oxidative stress (Castangia et al., 2015; Mostafa et al., 2014) -Acceleration of wound epithelization Kotian et al., 2018) - Efficacous for diminshing atopic dermatitis (Yu et al., 2017) -Acive component, glabridin, acts as antioxidant, estrogenic, anti-inflammatory, and skin-whitening agent (Simmler et al., 2013), exhibits skin depigmentation activity (Pastorino et al., 2018).
Pumpkin seed	-Anti-inflammatory against facial acne (Al-Noor, 2017) -Block the action of 5-alpha reductase, antiandrogenic effects (Esfandiari and Kelly, 2005; Kwon et al., 2007)
Broccoli sprout (Brassica oleracea L. var. italica Plenck)	-Antioxidant (Fahey and Talalay, 1999). -Antiinflammatoric (Talalay, 2007) and -Antimutagenic agents (Kern et al., 2007)
Black cumin (*Nigella sativa*)	-Anti-viral (Ma et al., 1994; Salem and Hossain, 2000) -Anti-fungal (Kader et al., 1995; Aljabre et al., 2005) -Effective agaisnt vitiligo (Ali and Meitei, 2011)

Conflict of Interest

The authors declare that they have no competing interests.

Authorship contributions

Concept: K.U., Design: K.U., Data Collection or Processing: K.U., H.E., S.E., T.A., C.B., G.G., Analysis or Interpretation: K.U., H.E., Literature Search: K.U., Writing: K.U., H.E.

Financial Support

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Ethical Approval

This study was obtained from routinely ill dogs admitted to the Internal Medicine Clinic of the Faculty of Veterinary Medicine, Adnan Menderes University, and no procedures were performed in dogs for study purposes, and the diagnosis and treatment intervention were obtained within the scope of routine clinical evaluation. This study was performed according to The Declaration of Helsinki, Ethical Principles.

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