

Treatment of Atrophic Rhinitis with Manuka Honey— a non-randomized control trial, and a new theory of etiopathogenesis for the disease.

Saurav Sarkar

All India Institute of Medical Sciences, BBSR

Suvendu Purkait

All India Institute of Medical Sciences, BBSR

Rituparna Maiti

All India Institute of Medical Sciences, BBSR

Prity Sharma

All India Institute of Medical Sciences, BBSR

Giriprasad Venugopal

All India Institute of Medical Sciences, BBSR

Naresh Mutha

All India Institute of Medical Sciences, BBSR

Balamurugan Ramadass (✉ balaramadass1@gmail.com)

All India Institute of Medical Sciences, BBSR <https://orcid.org/0000-0002-8158-230X>

Article

Keywords: Atrophic rhinitis, nasal microbiome, Honey, Prebiotics, SCFA

Posted Date: January 8th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-137101/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

Exact etiology of Atrophic rhinitis (AtR) is yet unknown. Polygenic and polybacterial causes have been implicated in the onset and progression of this disease. AtR doesn't respond to any particular modality of treatment that targets specific etiology, this describes its multifactorial nature. In this study, we report on a non-randomized control trial on the use of a nasal spray of 10% Manuka honey in patients with AtR attending the out-patient unit of the Department of Otorhinolaryngology and Head Neck Surgery. In this study, we show significant observations: 1. Decreased fetid smell, 2. Thickening of the mucosa, 3. Decreased inflammation with healed mucosal ulcers, 4. Increased concentration of the mucosal glands, 5. Alteration in Nasal microbiome, and 6. Increased expression of SCFA receptors. These changes occurred in response to honey therapy, and are consequent to the resetting of the Nasal microbiome.

Introduction

Atrophic Rhinitis (AtR) is a chronic inflammatory condition of the nose with unknown etiology. The incidence of Primary AtR is uncommon in developed countries. It has declined markedly in North America, Britain, and some parts of Europe, with no such decline in Asia and Africa. Primary AtR is high in developing countries, especially in countries with a warm climate; with the highest prevalence seen in the arid areas bordering the great deserts^{1,2}. Primary AtR affects about 1% of the Indian population and is more frequent in young and middle-aged individuals, with a female preponderance. It affects people with low-socioeconomic status residing in conditions of poor hygiene. The disease has a colossal impact on the social life of the patient. Social ostracization is common in patients due to the obnoxious smell, emitted from the nose of these patients³⁻⁴.

Over the years, many factors have been thought to contribute to the development of this disease. The factors include nutritional deficiency (iron, fat-soluble vitamins, and proteins, phospholipid), autonomic dysfunction leading to excessive vasoconstriction, reflex sympathetic dystrophic syndrome, endocrinal deficiency with imbalances due to estrogen deficiency, immune dysfunction, and biofilm formation⁵⁻⁹, but none has been proven to be the direct cause. AtR is essentially diagnosed clinically, based on the triad of fetor, greenish crusts, and roomy nasal cavities, typically seen in full-blown cases in later stages. In the early stages, the patient may only complain of altered smell with the presence of thick crusts. Early in the disease, the turbinates may look normal, but in the later stages, the turbinates are atrophied. None of the studies done so far has been able to establish an ideal management protocol for the disease⁹⁻¹⁰. However, they have suggested methods to control nasal dryness by using lubricants or methods to decrease evaporation from the mucosal surface. Some studies have tried antibiotics with limited success¹¹. The variable responses to different treatment regimes are due to the multifactorial nature of this disease^{12,13}. It does not respond to any particular modality of treatment targeting a specific etiology.

Throughout the history of the human race, honey has been used as a medicine, the most persistent use being dressing of wounds. Manuka honey is a monofloral honey produced by certain *Leptospermum* species native to New Zealand and Australia. This has been registered by appropriate medical regulatory

bodies as a wound care product^{14,15}. In this study, we proposed to treat AtR by using honey locally to heal the ulcers and to regenerate the mucosa by replenishing the commensal microflora of the nose. Honey is a product that has been used by the Asian Indian population for time immemorial in various forms it is well accepted culturally and ethnically. The acceptance and adherence to the honey treatment strategy were thereby not doubted by the AtR patient population under treatment.

Materials And Methods

We conducted this study in Odisha a state in the eastern region of India, which typically has hot and humid conditions throughout the year. Twenty five patients were screened for the study and six participants were rejected of whom two were diabetic, four had a history of some nasal surgery. Investigations were done to rule out secondary causes for the condition. Following the inclusion and exclusion criteria for the study, 19-candidates were enrolled for the study (Fig 1 - CONSORT).

Procedure: Nasal endoscopy was done crusts were removed and a score was assigned depending on clinical feature which could be noted by doing nasal endoscopy. The score was assigned as per the following clinical features: Crusting: Gross – 2; Minimal – 1; Nil – 0; Discharge: Thick – 2; Thin – 1; Absent – 0; Nasal mucosa: Congested – 2; Not congested – 1; Atrophic turbinate: Present – 1; Not Present – 0; Size of Nasal cavity: Roomy – 2; Not roomy – 1. A nasal mucosal biopsy was taken from both sides on day-1 of the study. The right side of the nasal cavity of each patient was considered as the test (as the rule for all tests) and the left side was considered as control. After taking the biopsy the right nasal cavity (test) was sprayed with freshly prepared manuka honey solution in normal saline (10%) and the left nasal cavity (control) was sprayed with normal saline only, using separate applicators. The spraying of honey preparation was done twice a week for 8 weeks. During this period, they were instructed not to apply anything else in their nose or take any other medications without information from the Principal Investigator. At the end of the study duration following the intervention (at the end of 8 weeks), a repeat endoscopic score was assigned to the nasal cavities (both test and control sides), and the nasal mucosa was again biopsied, from nasal cavities (both test and control sides) from all the patients.

Of the 19-participants with primary AtR who were enrolled for the study, 9-participants were males and 10 were females. The average age of the study group was 33.8 ± 10.7 years. The participants were predominantly rural and semi-urban dwellers with an average hemoglobin percentage of 11.8 ± 1.7 mg%, average ESR 18.6 ± 16.2 mm at the end of 1st hour, and an average leucocyte count of $9,439 \pm 1680$ per Cumm.

AtR patients presented with a wide range of symptoms, nasal obstruction was the commonest presenting symptom (100%) to epiphora which was the least common presenting symptom (5.26%) (**Table 1**). Epiphora as a presenting symptom has not been reported before in other studies on AtR.

Effects Of Intervention

Clinical endoscopic findings improved: We found improvement of clinical endoscopic parameters, almost in all cases on the test side following the intervention. Using the Fischer exact test, we found that the improvement in nasal crusting, nasal discharge, and nasal mucosal condition in the test side to be statistically significant. However, the improvement in the size of the nasal cavity and atrophic turbinates was not statistically significant. This is evident from the endoscopic scores assigned to the test and control sides before and after the intervention (Table 2). The pre-intervention scores between the two sides of the nasal cavity were not found to be statistically significant, reflecting the fact that the pre-treatment condition of the test side and the control side of the participants were similar. However, the post-intervention scores on 3 features of crusting, mucosal congestion, and discharge were found to be statistically significant improvement on the test side. However, the features of atrophic turbinates and nasal cavity roominess though different was not statistically significant (***Table 2***).

Nasal obstruction, crust formation, and nasal discharge improved: There was an improvement in the patient symptom as well, following the intervention. Patients presented with the symptoms a wide range of symptoms which were: nasal obstruction, foul smell, impaired smell sensation, crusting, nasal discharge, epistaxis, headache, epiphora, and myiasis in the nasal cavity. Following the intervention, the patients were enquired about the improvement of their symptoms in the sides of the nose. The symptom of epiphora and myiasis were excluded as only one patient presented with those. A 2X2 contingency table was made and Fischer exact test was applied for each symptom whether improved or not improved in the test side and the control side. It was found that except for headache there was an improvement of symptoms in all the cases. However, the improvement was statistically significant in the test side for nasal obstruction, crust formation, and nasal discharge (Table 3).

Each symptom was given a score of 1 and the cumulative score was noted in each patient before and after the intervention and compared between the test and the control side. A maximum possible score was 9 for a patient who would be having all the 9 symptoms, and a minimum of 0 who would not have any of the symptoms. There was no difference in symptom scores between the test and control side pre-intervention. But a statistically significant difference in the cumulative symptom score was found between the test and control side following the intervention. This clearly was indicative of the improvement in the test side following the intervention (Table 4).

Restoration of mucosal glands: Specimen from the nasal cavity was examined histopathologically for the following features; basement membrane thickening, presence of granulation tissue, fibrosis, mucus gland concentration, bacterial colonies, and glandular hypertrophy. All the features in the post-treatment specimens had improved. However, only three features were statistically significant. The pre-treatment features were similar in both test and control specimens, indicating the improvement was due to the specific intervention made during the study (Table 5).

Emphasis was given on the presence of mucus-secreting glands, as the dryness (due to thinning) of the mucosa and glandular atrophy are the hallmark of this disease. Median and interquartile range was used to compare the histological feature of glandular hypertrophy. The pre-treatment values showed no

statistically significant difference between the test and the control side. The post-treatment values showed improvement on the test side, which was statistically significant (Table 6). Figure 2 shows the decrease in inflammation in the test side with the restoration of mucus glands following treatment compared to the pre-treatment slide.

Alteration in Nasal microbiome: We propose that the marked clinical and histological improvement in the test side be due to the change in the microbiome of the nasal cavity on the test side. The nasal microbiome was analyzed to understand the differences in detail. Microbiome analysis was performed on Twenty samples, ten each from the test (right) side and control (left) side, of which five samples each were from before treatment and after treatment. The genus composition of the nasal microbiome pre-and post-treatment in the case and control group is in Figure 3. Actinobacteria and Proteobacteria are the most abundant microbes, with a marginally higher amount in the test side, followed by Bacteroides. The least abundant in either sample before or after treatment is the Vibrionaceae. The alpha diversity is found to be increased post-treatment on the test (right) side compared to the control side. The real observed diversity of species between the test (right) and control side, more evident with the Shannon index, as shown in figure 4.

The beta diversity of the samples collected before and after treatment in the control (Left) side cluster closely. In contrast, the groups cluster distinctly before and after on the test (right) side, suggesting an effect on the microbial composition following the intervention in the test side, Figure 5a. The Venn diagram plotted, filtering OTUs that are 80% abundant at the species level for each of the study group, About 78 OTUS were identified to be common among all four groups, while 0, 2, 1, and 15 OTUs were found specific to the Left (untreated), Left (Treated), Right (untreated) and Right (treated) groups respectively, Figure 5b.

Two types of analysis for the bacterial groups at all bacterial levels were done, and a statistical difference was observed. The Kruskal Wallis test was used to test all four groups together, Figure 6b. However, for this strategy, first, it is crucial to have the same microbiota composition before the treatment in the right and the left sides. The risk is not to detect some taxa that are influenced by the treatment, and, some taxa might be present that are not stable over time. For these reasons, a second strategy was adopted. Where, the difference between 'before' and 'after' intervention was calculated (additionally, convert the difference by log2). And, the difference between the test (right) and the control (left) side was compared using (Wilcoxon test). In the data, some taxa increased on the test (right) side and decreased on the control (left) side, Figure 6a.

Certain bacteria have increased and others were decreased in proportion in the test side compared to the control side following the intervention. These are *Rhodobacter spheroides*, *Plancomycete sp.*, *Sphingomonas asaccharolytica*, Bacteroides caccae, Methylothermobacter mobilis, Staphylococcus aureus, Comamonas terrigena, Flexithrix dorotheae and Roseicyclus mahoneyensis, Figure 6b.

Increased expression of SCFA receptors: There was a significant difference in microbiome pattern in the test and control side post-intervention. There was clinical improvement in between the test and control

side following the intervention. Gut microbiome studies have found that Short-chain fatty acids (SCFAs), are generated by the healthy microbiome¹⁶. The SCFAs play an anti-inflammatory role through activation of the GPR43 receptors. These GPR43 receptors are detected by immunohistochemistry.

GPR43 receptors was found to be increased in the post-intervention test specimen (Fig 7). In view of the improvement with honey therapy, the subjects were prescribed to use honey on both sides following the study. They are being followed up clinically following the study for a period of 8 months and above, and 18 patients were found to be doing well with relief from symptoms. One patient did not follow up after completion of the study.

Discussion

AtR is a chronic, progressive degenerative condition of the nasal cavity characterized by a foul odour (ozena), nasal obstruction, dryness, and crusting. Endoscopic inspection reveals a large, wide nasal cavity with dried mucosa. Classically, the management of patients with primary AtR aims to alleviate symptoms using nasal irrigation douche or ointment application. Attempts of treating this nasal condition started as early as 1971, closure of the nostril (Young's operation¹⁷) and endonasal microplasty (intranasal implant insertion), were the surgical management of primary AtR¹⁸, these options had its demerit on the possibility of decreased quality of life of the patient. Studies using rifampicin, cotrimoxazole and ciprofloxacin for the disease^{11,19,20} and found rifampicin to be the most effective treatment. In addition the use of lubricants like sesame oil in controlling the signs and symptoms of AtR was also attempted²¹. None, however, could establish an ideal or definitive management protocol for the disease. Even though rifampicin shows promise in the treatment of AtR, but in our opinion, its use should be reserved for Tuberculosis, especially in developing countries like India.

Honey formulations have been tried for the treatment of various sinus and nasal inflammations. It was found that thyme honey spray reduces inflammation and polyp formation in chronic rhinosinusitis patients, their research also revealed accelerated mucosal healing in those patients¹³. We designed a study with monofloral Manuka honey as it has a specific carbohydrate concentration containing compound (data Provided in SI). Manuka honey disrupts cellular aggregates, it prevents the formation of biofilms by a wide range of problematic pathogens²², including Streptococcus and Staphylococcus species, Pseudomonas aeruginosa, Escherichia coli, Proteus mirabilis, Enterobacter cloacae, Acinetobacter baumannii, and Klebsiella pneumonia^{23,24}. This has clear clinical implications for using honey on wounds containing biofilms. In this study, following the intervention, we found significant improvement in the symptom score of the patients suffering from AtR. We observed a decrease in fetid smell and the histopathological study showed thickening of the mucosa, decreased inflammation with healed mucosal ulcers, and increased concentration of the mucosal glands. The mucosal sparing effect occurred due to honey therapy. In a similar study honey was used in the treatment of AtR showed significant improvement compared to the group in which 25% anhydrous glucose in glycerin was used²⁵.

However, in their study, the type of honey used was not specified and the cause for improvement was not evaluated.

We hypothesized that the Manuka honey would have a therapeutic effect on AtR and propose, Evidences from this study indicate a **new theory of aetiology of causation of the AtR** : In AtR, nasal obstruction, fetid smell, impaired smell sensation, crusting, nasal discharge are caused due to 'dysbiosis'. The bacteria which harbour the nose in this disease, feed on the mucosal layer causing erosion and produces fetid smell due to the release of sulfur-containing metabolic end products. This progressive damage may momentarily respond to antibiotics or other therapy that alter microbes or provide lubrication locally. Manuka honey as opposed to antibiotics, is a concoction of complex carbohydrate, these carbohydrates promote microbial diversity. The complex carbohydrates of Honey provide the microbes (source of energy), altering the microenvironment and alters the pH of the nasal cavity. The altered microenvironment and pH, along with ambient nutrition, changes the unhealthy ambient microbiome. The healthy microbiome is allowed to flourish in the nose. Correction of 'dysbiosis' has mucosal sparing effect in these patients is due to the 'colonization resistance' which is offered by the stabilizing bacteria. Improved mucosa provides required lubrication and the healing of the ulcers is enhanced by the Short chain fatty acids produced by the renewed nasal microbiome.

To support our theory, we showed an improvement in all the clinical symptoms in all our patients. Mucosal thickening, Altered nasal microbiome, increased GPR43 expression are proofs for healthier resetting nasal micro-environment.

Microbiome, is the entire population of microorganisms that are present in an ecologic niche, irrespective of their cultivability. In human body, these ecological niches are sites like the gut, skin or nasal cavity²⁶. Studies suggest that each body habitat has its own characteristic bacterial community which changes throughout the life of the person depending on the age^{22,27,28}. The commensal bacteria which is present in the human nasal cavity suppress opportunistic pathogen colonization. The competition they offer to the pathogens for the limited space, nutrients and may also be due to metabolites they produce that may not be favourable to the competitors²⁹. Studies suggest that environmental factors have a role in the modulation of the nasal microbiome composition^{30,31}. Some organisms, like the *Staphylococcus aureus*, can be both commensal as well as an opportunistic pathogen^{32,33}.

An imbalance in the ambient microbial community or the microbiome dysbiosis can impact human health significantly and has been implicated for various diseases of the gut as per studies³⁴. Nasal microbiome dysbiosis has been associated with chronic rhinosinusitis; neurological diseases like to Parkinson's disease, allergic rhinitis, asthma and otitis media.

We observed a significant difference in nasal microbial profile post-intervention, in the test side compared to the control side. There is an altered abundance of bacterial species *Rhodobacter spheroides*, *Plancomycete sp.*, *Sphingomonas asaccharolytica*, *Bacteroides caccae*, *Methylotenera mobilis*, *Stapia indica*, *Comamonas terrigena*, *Flexithrix dorotheae* and *Roseicyclus mahoneyensis*. There was an

improvement, in clinical and histological parameters in all patients following intervention in the test side. We deduce that these changes are due to the resetting of the microbiome.

During health and in the absence of antibiotic exposure the microbiome can effectively inhibit colonization and overgrowth by invading microbes such as pathogens. This phenomenon is called 'colonization resistance' and is associated with a stable and diverse microbiome in tandem with a controlled lack of inflammation and involves specific interactions between the mucosal immune system and the microbiome. It is the mechanism whereby the intestinal microbiota protects itself against incursion by new and often harmful microorganisms. In our opinion a similar mechanism is occurring in the nasal cavity as well.

The change in microbiome changes the inflammatory process by acting on the G protein-coupled receptor 43 (GPR43 receptors¹⁶). The new, healthy microbiome in nose produces short-chain fatty acids (SCFAs) following metabolism of complex carbohydrates in honey. The SCFAs targets several receptors G protein-coupled receptors on the cell surface of which the most notable is the GPR43. Role of GPR43 in regulating the role of intestinal inflammatory responses have been studied. It has been found that mice which are GPR43-deficient have exacerbated disease symptoms. The results suggest that GPR43 mediates the protective effects of SCFA in intestinal inflammation. Studies have shown that dietary fibers with long-chain carbohydrates with high solubility act as a source of energy for selected groups of bacteria, possessing the ability to promote the growth of beneficial microorganisms. These prebiotics have been identified as potential Nasal spray in modifying Nasal microbiome for health.

Limitations of the study: The limitation of the study lies in the fact that it is not a randomized control study and is conducted in a single institution. Post-surgical secondary AtR could have been included to increase the ambit of treatment. A randomized control study which would be multi-institutional would have yielded a much diverse and more valid data. Having said that the present study does have its advantage. The case and control being the same person eliminates selection bias and matching bias. The study does conclude with the improvement following the intervention. It tried to search for the reasons for the improvement. By doing so, the study has come up with a new theory of etiology for the disease.

Conclusion

Manuka honey having a concoction of complex carbohydrates acts as a prebiotic promoting beneficial microbiome of the nasal cavity. The healthy microbiome provides colonization resistance and produces SCFAs, which play an anti-inflammatory role decreasing the existing inflammation. The disease process halts, mucosa heals, and normalcy returns. The cure for the disease provided by Manuka honey helps us establish the microbiome theory, for the Primary AtR, which can be extrapolated for secondary AtR too, especially those caused after extensive nasal surgery.

Declarations

Contributions :The author's responsibilities were as follows—**SS** and **BR**: were responsible for conception, analysis of data, and writing the manuscript; **SS, SP, PS** and **RM**: were responsible for sample, Histopathology, and clinical data collection; **FM, GV, NM** and **BR**: were responsible for the Sequencing and data analyses. None of the authors had a personal or financial conflict of interest.

Sequence data are available in the NCBI Nucleotide Archive under BioProject ID PRJNA682099.

References

1. Chaturvedi VN. ENT Disorders in a Tropical Environment. in (ed. Kameswaran S, K. M.) 119–28. (MERF Publications, 1999).
2. Ly, T. H. *et al.* Diagnostic Criteria for Atrophic Rhinosinusitis. *Am. J. Med.* **122**, 747–753 (2009).
3. Amreliwala MS, Jain SKT, Raizada RM, Sinha V, C. V. Atrophic rhinitis: an inherited condition. *Indian J. Clin. Pract.* **4**, 43–6 (1993).
4. Medina, L. *et al.* Clinical, genetic and immunologic analysis of a family affected by ozena. *Eur. Arch. Oto-Rhino-Laryngology* **260**, 390–394 (2003).
5. Barkve, H. & Djupesland, G. Ozaena and Iron Deficiency. *Br. Med. J.* **2**, 336–337 (1968).
6. Sayed, R. H., Abou-Elhamd, K. E., Abdel-Kader, M. & Saleem, T. H. Study of surfactant level in cases of primary atrophic rhinitis. *J. Laryngol. Otol.* **114**, 254–9 (2000).
7. Artilles F, Bordes A, Conde A, Dominguez S, Ramos JL, S. S. Chronic atrophic rhinitis and Klebsiella ozaenae infection. *Enferm. Infecc. Microbiol. Clin.* **18**, 299-300 (2000).
8. Bunnag C, Jareoncharsri P, Tansuriyawong P, Bhothisuwan W & Chantarakul N. *Characteristics of atrophic rhinitis in Thai patients at the Siriraj Hospital. Rhinology* vol. 37 (1999).
9. Medina L, Benazzo M, Bertino G, Montecuccio CM, Danesino C, Martinetti M, et al. Clinical, genetic and immunological analysis of a family affected by ozaena. *Eur. Arch. Oto-Rhino-Laryngology* 390-4. (2003).
10. Altaş, B. *et al.* Is Ozone (O₃) Treatment Effective in Atrophic Rhinitis? Experimental Animal Study. *Otolaryngol. Pol.* **72**, 37–44 (2018).
11. Johannes Borgstein, Eduardo Sada, R. C. rifampicin/co-trimoxazole. *Lancet* 122 (1993).
12. Johnsen, J., Bratt, B. M., Michel-Barron, O., Glennow, C. & Petruson, B. Pure sesame oil vs isotonic sodium chloride solution as treatment for dry nasal mucosa. *Arch. Otolaryngol. - Head Neck Surg.* **127**, 1353–1356 (2001).
13. Hashemian, F. *et al.* The effect of thyme honey nasal spray on chronic rhinosinusitis: A double-blind randomized controlled clinical trial. *Eur. Arch. Oto-Rhino-Laryngology* **272**, 1429–1435 (2015).
14. Sojka, M., Valachova, I., Bucekova, M. & Majtan, J. Antibiofilm efficacy of honey and bee-derived defensin-1 on multispecies wound biofilm. *J. Med. Microbiol.* **65**, 337–344 (2016).
15. Sarah Elizabeth Maddocks, Rowena Eleri Jenkins, Richard Samuel Rowlands, Kevin John Purdy, R. A. C. Manuka honey inhibits adhesion and invasion of medically important wound bacteria in vitro.

Futur. Microbiol **8**, 1523–36 (2013).

16. Sivaprakasam, S., Prasad, P. D. & Singh, N. Benefits of short-chain fatty acids and their receptors in inflammation and carcinogenesis. *Pharmacology and Therapeutics* vol. 164 144–151 (2016).
17. Young, A. Closure of the nostrils in atrophic rhinitis. *J. Laryngol. Otol.* **85**, 715–718 (1971).
18. Saunders WH. Atrophic rhinitis; results of surgical treatment. *AMA Arch Otolaryngol* 342–5 (1958).
19. Nielsen BC, Olinder-Nielsen AM, M. A. Successful treatment of ozena with ciprofloxacin. *Rhinology* **33**, 57–60 (1995).
20. Jaswal, A. *et al.* Novel treatment of atrophic rhinitis: Early results. *Eur. Arch. Oto-Rhino-Laryngology* **265**, 1211–1217 (2008).
21. Johnsen, J., Bratt, B. M., Michel-Barron, O., Glennow, C. & Petruson, B. Pure Sesame Oil vs Isotonic Sodium Chloride Solution as Treatment for Dry Nasal Mucosa. *Arch. Otolaryngol. - Head Neck Surg.* **127**, 1353–6 (2001).
22. Kilty, S. J., Duval, M., Chan, F. T., Ferris, W. & Slinger, R. Methylglyoxal: (Active agent of manuka honey) in vitro activity against bacterial biofilms. *Int. Forum Allergy Rhinol.* **1**, 348–350 (2011).
23. Roberts, A. E., Maddocks, S. E., and Cooper, R. A. Manuka honey is bactericidal against *Pseudomonas aeruginosa* and results in differential expression of *oprF* and *algD*. *Microbiology* **158**, 3005–3013 (2012).
24. Halstead, F. D., Webber, M. A., Rauf, M., Burt, R., Dryden, M., and O. & A., B. In vitro activity of an engineered honey, medical-grade honeys, and antimicrobial wound dressings against biofilm-producing clinical bacterial isolates. *J. Wound Care* **25**, 93–102 (2016).
25. Kilty, S. J., Duval, M., Chan, F. T., Ferris, W., and Slinger, R. Methylglyoxal: (active agent of manuka honey) in vitro activity against bacterial biofilms. *Int. Forum Allergy Rhinol.* **1**, 348–350 (2011).
26. Dimitri-Pinheiro, S., Soares, R. & Barata, P. The Microbiome of the Nose—Friend or Foe? *Allergy Rhinol.* **11**, 215265672091160 (2020).
27. Wilson, M. T. & Hamilos, D. L. The Nasal and Sinus Microbiome in Health and Disease. *Curr. Allergy Asthma Rep.* **14**, 1–10 (2014).
28. Thomas S, IZard J, Walsh E, et al. The host microbiome regulates and maintains human health: a primer and perspective for non-microbiologists. *Cancer Res.* **77**, 1783–1812 (2017).
29. Hardy BL, Dickey SW, Plaut RD, et al. *Corynebacterium pseudodiphtheriticum* exploits *Staphylococcus aureus* virulence components in a novel polymicrobial defense strategy. *MBio* **10**, e02491–18. (2019).
30. Rawls M, E. A. The microbiome of the nose. *Ann Allergy Asthma Immunol* **122**, 17–24 (2019).
31. Arrieta MC, Stiemsma LT, Amenyogbe N, B. E. & B., F. The intestinal microbiome in early life: health and disease. *Front Immunol.* **5**, 427 (2014).
32. Otto M. Basis of virulence in community-associated methicillin-resistant *Staphylococcus aureus*. *Ann Rev Microbiol.* **64**, 143–162 (2010).

33. Kluytmans JA, W. H. Nasal carriage of *Staphylococcus aureus* and prevention of nosocomial infections. *Infection*. **33**, 3–8 (2005).
34. Costello EK, Lauber CL, Hamady M, Fierer N, G. & JI, K. R. Bacterial community variation in human body habitats across space and time. *Sci. (New York, NY)* **326**, 1694–1697 (2009).

Tables

Tables 1-6 are available in the Supplemental Files section

Figures

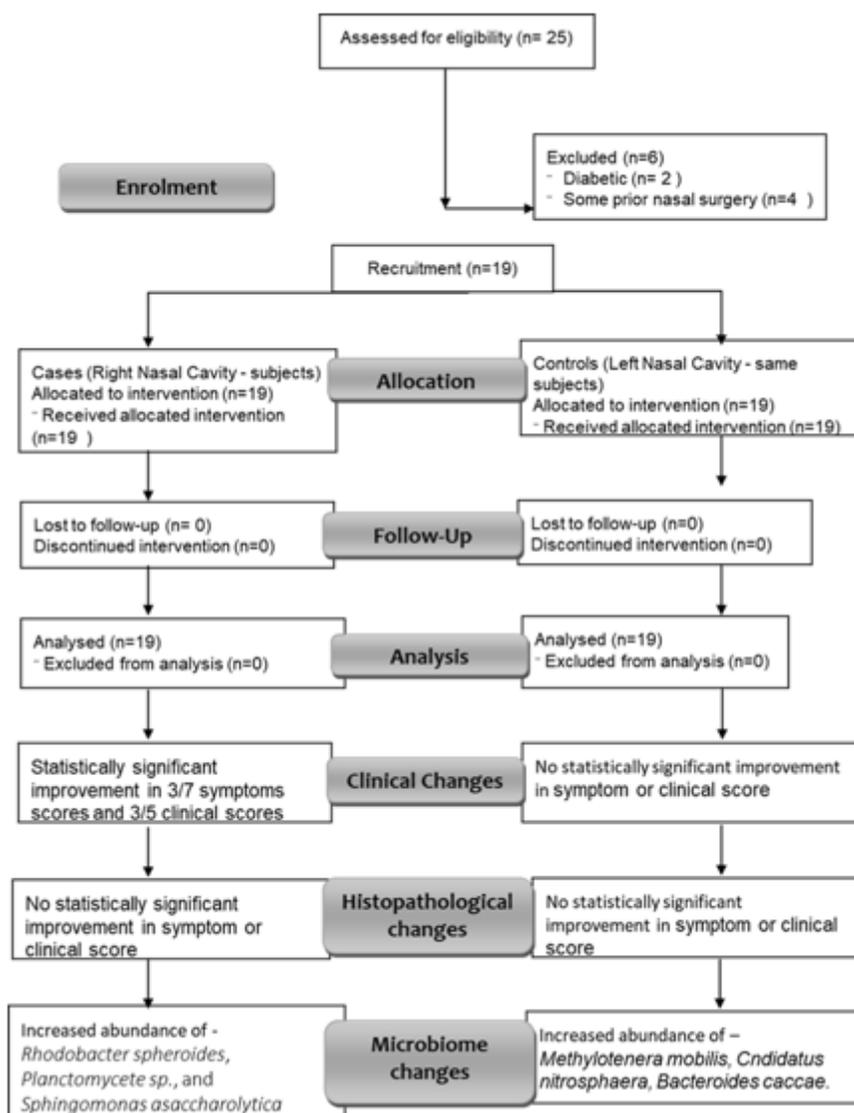


Figure 1

CONSORT, Screening and enrolment of study Participants.

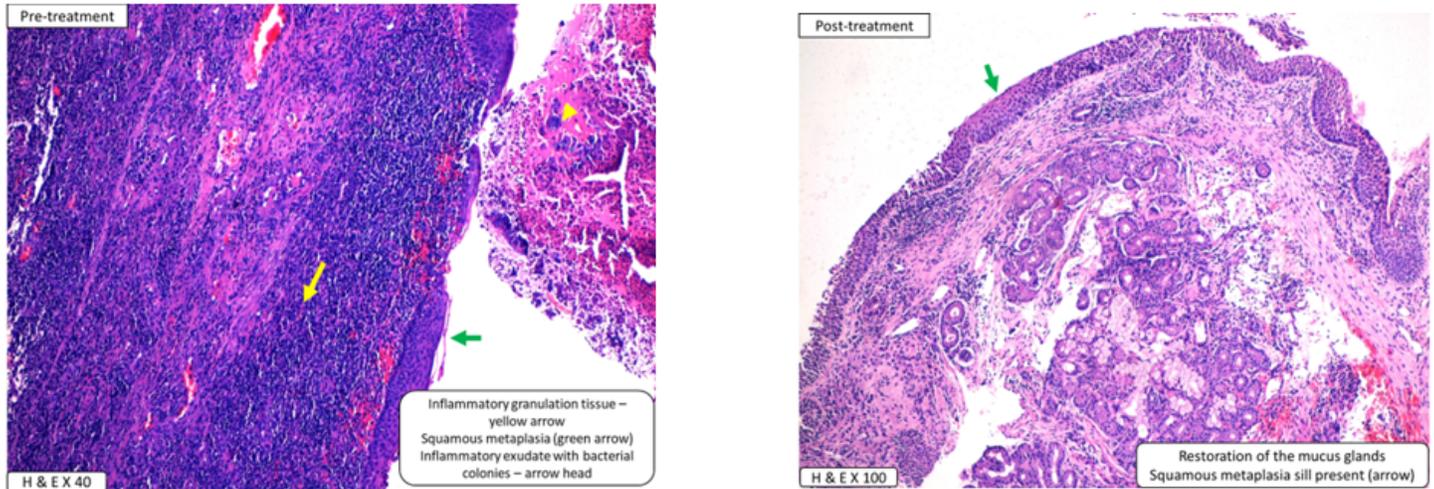


Figure 2

Restoration of mucosal thickening, The pre and post treatment histopathological slides showing decrease in inflammation with restoration of mucus glands in the right side.

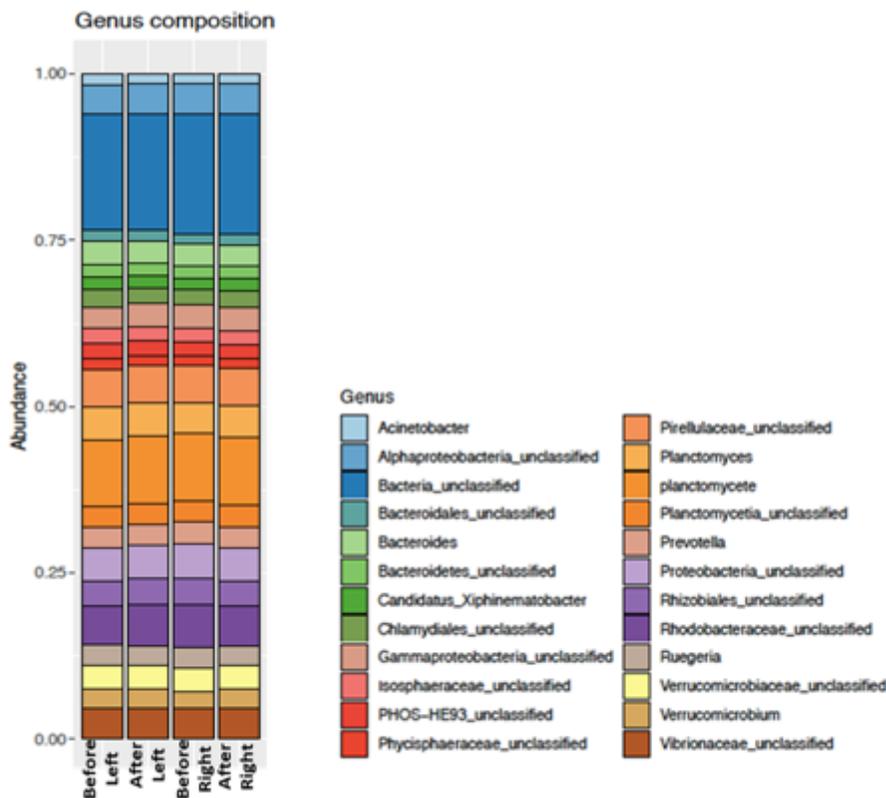


Figure 3

Nasal Microbiome Composition in Atrophic rhinitis, the genus composition in the pre and post treatment specimens in the test(right) and control(left) side.

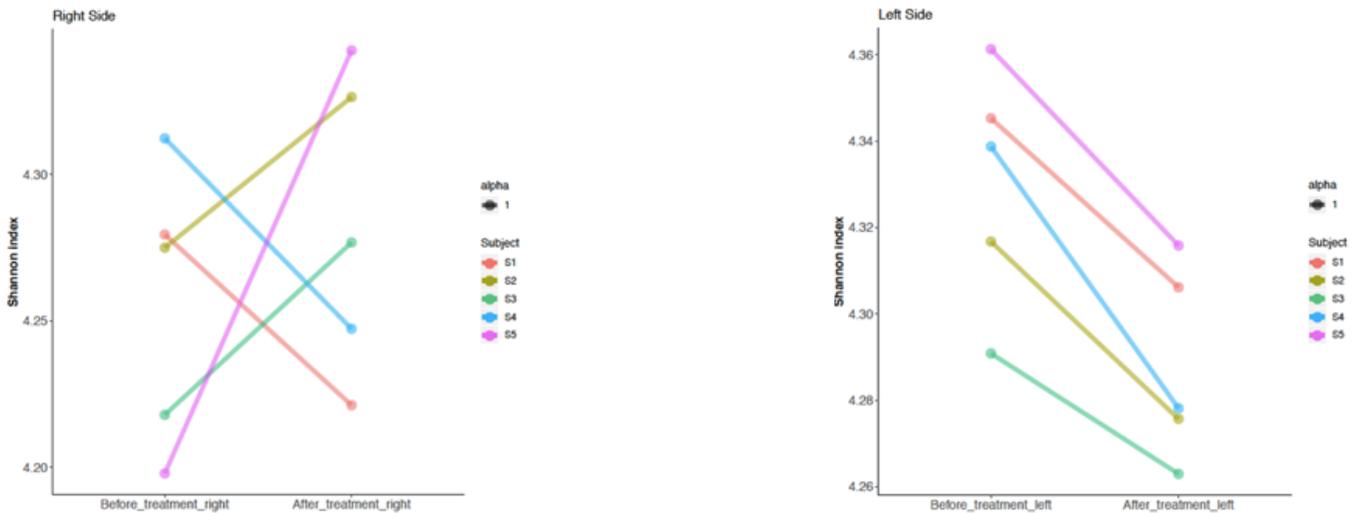


Figure 4

Increase in Nasal Microbiome diversity with honey treatment in Atrophic rhinitis patients; Alpha-diversity using the Shannon index based on Bray-Curtis distances. There is decreased diversity in the post treatment in the control(Left) side when compared to the test(Right).

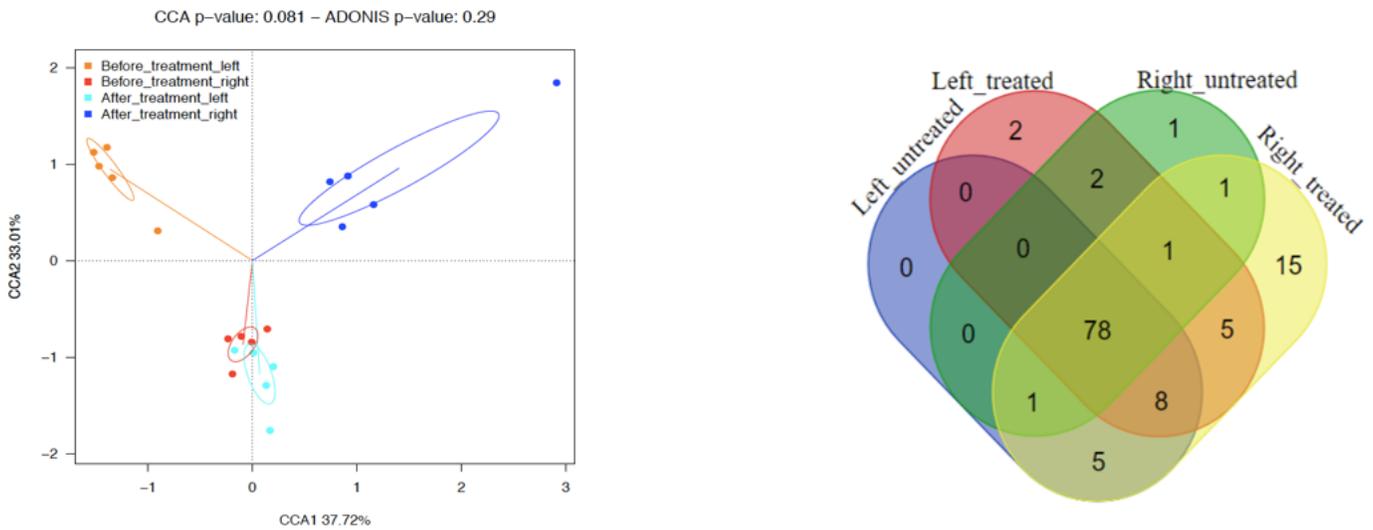


Figure 5

Figure 5a: canonical correspondence analysis (CCA) was performed to study the beta Diversity between nasal microbiome in Left Before treatment, Left After Treatment, Right Before treatment and Right After treatment in Atrophic rhinitis patients. Figure 5b: Venn diagram with filtered OTUs with 80% abundance at species level for each group. we observed that all 4 groups shared 78 OTUs, whereas 0, 2, 1 and 15 OTUs were specific to the Left (untreated), Left (Treated), Right (untreated) and Right (treated) groups.

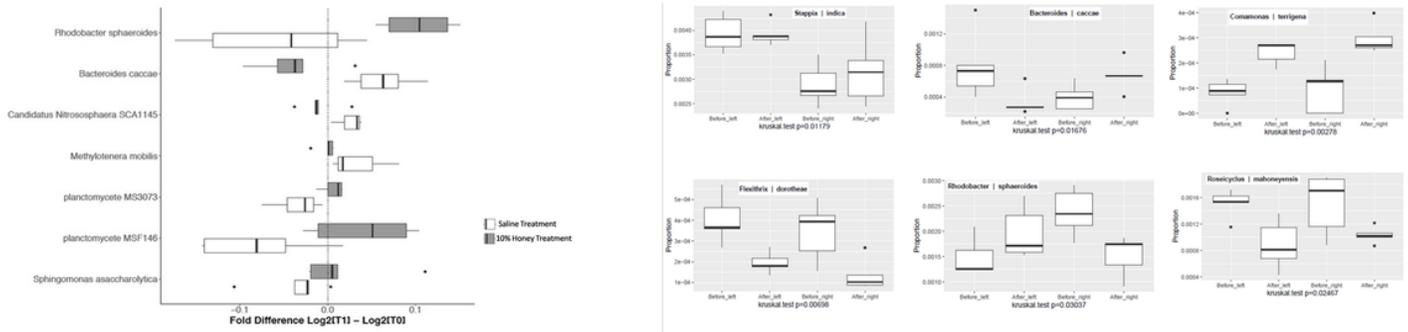


Figure 6

Figure 6a: The fold differences in species before and after treatment in test (right) and control (left) side in Atrophic rhinitis patients. Figure 6b: proportions of specific species before and after treatment in test (right) and control (left) side in Atrophic rhinitis patients.

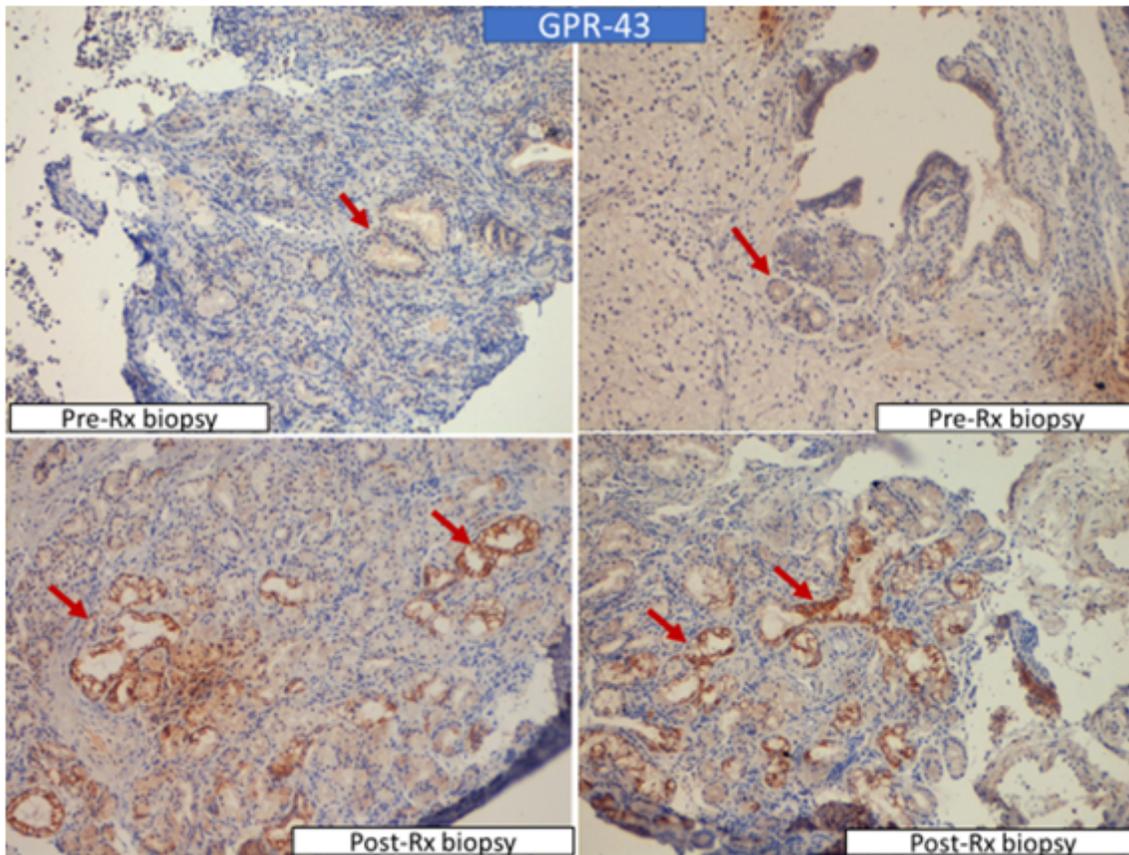


Figure 7

The Immunohistochemistry pictures showing increased GPR43 receptors in the post treatment biopsy specimens

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Tables.docx](#)
- [SupplementaryInformation.docx](#)