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Research Article

Reformulation and Scientific Evaluation of CUSOCO: A Traditional Toothpaste Formula from Classical Tamil Literature towards treatment of Halitosis

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Abstract

In order to achieve the multi-claim products required for dental-health-care and hygiene, it is indispensable for the formulator to use a wide range of ingredients however, with the advent of technology the chemically synthesised products are not of demand in the market as they have side effects and are considered to unsafe for human use. This places quite a number of demands on the use of PBNPs in the development process. Use of PBNPs innovations in the areas of pharmaceutical technology have contributed significantly to the formulation of dental-health-care products with superior efficacy as well as other attributes that may contribute to clinical response and patient acceptability. Improved clinical efficacy and tolerability, along with conditioning signals, should encourage patient compliance with oral hygiene. *Cuminum cyminum* seeds are being habitually used in traditional cuisines of different cultures. In India, it is used in both whole and ground form as a traditional ingredient to make dishes without perceptive medicinal knowledge/ properties behind. In Kerala, decoction of cumin seeds is used for drinking (Jeera water). In Tamilnadu, cumin seeds are the key ingredient of Rasam. Fruit of *Solanum lycopersicum* is one of the important savoury vegetable used in traditional Indian cuisines. The oil of *Cocos nucifera* fruits are used in cooking in Kerala and TamilNadu. In the present study, composition (paste) prepared by mixing of 2 drops of *S. lycopersicum* fruit juice, 2 drops of *C. nucifera* and 1g of *C. cyminum* seed powder were tested on 100 subjects with felt bad breath. Results of the present study was found to be effective in controlling bad breath (odour) in 74 subjects after the treatment (period of clinical trial) except 09 of 83 subjects who were diabetic.

Keywords: Oral hygiene; bad breath; halitosis; *Cuminum cyminum; Solanum lycopersicum; Cocos nucifera;* CUSOCO; dental-health-care

INTRODUCTION

Over the years, advances in oral care have significantly improved the oral health of millions of people across the world. However, incidences of dental caries and oral diseases remain on the rise due to the increase in availability of sugars in the food and increase in the consumption of soft drinks[1]. The change in our diets has led to an increase in dental erosion that allows oral microbial flora to flourish[2]. Halitosis is an unpleasant or cantankerous odour of unhygienic oral health condition and it is common among majority of human population across all age groups[3]. It has been pointed out that, throughout the world, nearly 30 - 50% of the population has experience the problem of halitosis[4-6]. Halitosis, oral malodour, or bad mouth breath is a universal medico social problem across all communities and refers to the unpleasant odour that originates from the mouth or elsewhere in the oral cavity[7]. Almost all the people have unpleasant oral odour at some time[8]. When halitosis is severe or longstanding; it may psychologically decrease the self-confidence and social interactions of affected person[7]. Reports have suggested that gastrointestinal diseases may cause halitosis. *H. pylori* infection, which causes gastric ulcers, is considered as a possible cause for halitosis[9]. Halitosis may be due lack of proper oral cleansing and xerostomia (dryness of mouth) oral cavity contains volatile sulphur compounds (VSCs) such as

hydrogen sulphide, methyl mercaptan, dimethyl-sulphide, and organic acids[10-13], and volatile sulphur compound producing bacteria associated with gingivitis and periodontitis such as *Porphyromonas gingivalis, Prevotella intermedias*, *Actinobacillus actinomycetemcomitans*, *Campylobacter rectus*, *Fusobacterium nucleatum, Pepto streptococcus micros, Bacteroides forsythus*, *Eubacterium* species[14] and spirochetes[15], medical problems such as renal failure, cirrhosis of liver, and diabetes mellitus[16-18], or it could be due to microbial degradation of proteins[19], or presence of decay or retention of food between the teeth. Till date no tooth paste or oral mouth wash has been so effective in solving the long term oral problems associated with halitosis.

In the traditional Tamil Literature text ***Jeeragam*** means curing from within. **Jeera** - Cumin (*Cuminum cyminum* L.) is an annual and herbaceous plant (Family: Apiaceae). It is a multipurpose plant species cultivated in the Middle East, India, China, and several Mediterranean countries, including Tunisia. Its fruit, known as cumin seed, is most widely used for culinary and medicinal purposes[20]. It is generally used as a food additive, popular spice, and flavouring agent in many cuisines. Cumin has also been widely used in traditional medicine to treat a variety of diseases[21-27]. Pharmacological studies have proven that *C. cyminum* exerts antimicrobial, insecticidal, anti-inflammatory, analgesic, antioxidant, anticancer, antidiabetic, antiplatelet aggregation, hypotensive, bronchodilatory, immunological, contraceptive, anti-amyloidogenic, anti-osteoporotic, aldose reductase, α-glucosidase and tyrosinase inhibitory effects[28,29]. The medicinal parts were Cumin oil extracted from the ripe fruit and the ripe, dried fruit[25]. Phytochemical analysis of *C. cyminum* revealed that it contains alkaloid, coumarin, anthraquinone, flavonoid, glycoside, protein, resin, saponin, tannin and steroid[28,29]. Hence, in the present investigation "CUSOCO" was prepared in the form of paste from cumin (*Cuminum cyminum*) seeds as base (primary source), fruits of tomato (*Solanum lycopersicum)* and oil of coconut (*Cocos nucifera*) as supplementary products. The formulation was clinically tested among the peoples who had halitosis condition to validate this formulation.

MATERIALS AND METHOD

Study sample selection

In the present study, samples 100 people with in the age group of 18 and 45 y were randomly selected as a study subjects from Katpadi Town, Vellore District, TN, India. A simple questionnaire was given to each subject to record the data about the oral hygiene and halitosis. Based on the answers, 100 subjects who strongly believe existence of halitosis were randomly selected for halitosis detection test to ensure halitosis condition. Halitosis detection test was conducted in all study subjects by using organoleptic method. Among the study subjects, 22 were females and 78 were males.

Halitosis detection

The organoleptic method a simple, easy and frequently used method to detect halitosis[30]. In this method, a simple plastic tube is placed in the mouth of the person being examined, to prevent the dilution of the breath by the surrounding air and other end of the tube is very near to the nose of the assessor. While the study subjects slowly exhales, the "judges" assesses the odour at the other end of the tube. In this test the embarrassing situation between both study subjects and the assessor were avoided by keeping an opaque privacy screen between them to ensure no visual contact. All the study subjects were tested for the halitosis by this organoleptic method. The individuals with halitosis were identified and experimented with the trial formulation to validate their potentiality in prevention of halitosis and maintenance of oral hygiene.

Experiment with halitosis affected human

The persons with halitosis were subjected to validation experiment with the trial formulation. For all patients, the paste containing herbal formulation and the procedure to prepare the tooth paste were clearly explained (1gm *Cuminum cyminum* + 2 drops of *Solanum lycopersicum* fruit extract + 2 drops of pure *Cocos nucifera* oil) and it was recommended that they may use this formulation instead of chemical paste already in the usage for everyday practice. The paste obtained by mixing of three food ingredients are named as CUSOCO for our convenience based on the joining of first two letters of all three food ingredients. All the patients were assessed for their halitosis level in the 0 day (just before the first day of brushing) 5th day, 10th day, 15 and 30th day after the experiment (used after the herbal CUSOCO paste). The halitosis level of all patients of from 0 to 30th days results were compared to know if any improvement exists in halitosis reduction. All the patients are requested to brush their teeth at least twice a day to achieve a healing effect and use the dental floss after eating because normal brushing cannot eliminate bacterial plaque in between teeth. In addition the study subjects were asked to practice tongue cleaning because many people have a habit of brushing their teeth but they do not know that the tongue is also a part of the practice.

RESULTS AND DISCUSSION

The most effective way of preventing the development of dental disease is in controlling the production of dental plaque. Plaque is a soft thin layer which deposits on teeth gums and all appliances fitted in the mouth. It is formed by microbial action[31]. Halitosis is a common no-risk health problem among humans and can be caused by oral or non-oral factors. The term Halitosis[32] derived from halitus (breathed air) and the osis (pathologic alteration). It means disagreeable bad or unpleasant odour emanating from mouth-breath. More than 50% of general population have halitosis[33]. Most of the bad breath comes mainly due to inadequate hygiene or due to hygiene deficient in contact points, the formation of periodontal pockets due to the presence of supra-gingival or sub-gingival plaque or calculus and the surface of the tongue, whose anatomy favours the accumulation of bacteria[34-37]. Such a condition has no health-risk. However, social anxiety among halitosis patients is high; it tends to precede depression and alcoholic dependence. Worldwide, one-third of social anxiety disorder patients have concomitant psychological disorders such as depression or alcohol dependence. Mood disorders, particularly major depression, was the most common other lifetime diagnosis (70.2%). A large majority (70.2%) suffered from, at least, one other anxiety disorder in their lifetime and, in particular, panic disorder with or without agoraphobia (49.1%). Alcohol (28.1%) and substance (15.8%) abuse or dependence were also common lifetime diagnoses[38]. Sometimes, social anxiety disorder amalgamated with other psychological diseases leads to increase the risk of suicide[39]. Excessive anxiety in social situations causes a considerable distress and impairs in functional ability in daily lives[40]. Most of the halitosis patients turn to "soft" medicine that offers a wide range of disciplines to treat bad breath; homeopathy, herbal medicine and aromatherapy as an alternative treatments, or complementary to conventional medicine. In India, particularly in Tamilnadu, majority of the people used the traditional mode of treatment to treat the halitosis[41]. Hence, in the present investigation, the herbal treatments which were used generation by generation to treat halitosis were experimented on halitosis affected persons to validate and evaluate their potential in curing halitosis.

For this study, totally 100 individuals who felt the bad mouth smell was randomly selected and they were re-checked and confirmed by organoleptic method. According to the obtained results of the present study, five individual out of 100 has pseudo-halitosis effect. Even though, these five individuals are not having any bad smell in their mouth they are psychologically worried about the halitosis. Sometimes people who do not have symptoms of halitosis yet feel like having it are referred to as pseudo-halitosis or halitophobia[42]. Five (5) individuals with pseudo halitosis, identified using organoleptic test were counselled on 1st day and were excluded from the study. Likewise, 12 individuals self-reported for halitosis but not having halitosis were identified and excluded from the study. The final set comprising of 83 study subjects excluding 12+5 individuals were tested with the CUSOCO formulation.

Results of the organoleptic test showed 30 individuals with discontinuous halitosis, 29 individuals with slight halitosis and remaining 24 individuals with worst halitosis condition. The herbal formulation CUSOCO was recommended to all (88) subjects out of 100 except the sampling individuals (12) who are not having any halitosis. The halitosis conditions of all 88 individuals were checked by organoleptic method 0, 7, 15 and 30th days after the use of this herbal tooth paste to brush the tooth. The obtained results showed 67 individuals are not having any bad smell in their mouth have some concordance with the findings that *in-vivo* study of chlor-hexidine mouth rinse, containing pericarp extracts of *Garcinia mangostana* L. showed a significant reduction of VSCs level in gingivitis patients[43].

However, 14 individuals had a moderate level of smell and remaining 7 are not having any improvement out of 88 individuals (Table 1). The results of 15th day observation showed 75 individuals without any halitosis, 6 individuals with moderate halitosis and 7 individuals without any improvement. On the 30th observation exhibited 81 individuals are not having any halitosis showed a similarity with that report of toothpaste mixed with Chinese herb extract showed better in vitro inhibition effect on VSCs genesis anaerobic bacteria than most other toothpaste on market. Even after 30 days treatment, 7 individuals are not having any improvement in their halitosis condition were reanalysed to find weather it may be due to oral and dental problems or some other problems.

The results of the present study observed at 0 days and 7th day, 15th day and 30 day of experiment interprets that both worst halitosis (24) and moderate halitosis (59) of 0 days drastically reduced to 07 and 14 at 7th day observation. The halitosis reduction in worst and moderate patients gives clear cut evidence for the ability of present herbal composition in curing halitosis. The worst halitosis observed at 7th day was not observed further change upto 30th day. But moderate conditions of 14 individuals were further reduced the numbers to 06 and level to 0 at 15th and 30th day observation Table 2, Fig. 1.

Many plants such as *Elettaria cardamomum, Salvadora persica, Illicium verum,* and *Origanum vulgare* were widely used by 76% traditional healers to treat halitosis and 64.9% patients themselves used to treat halitosis without any scientific validation. *Salvadora persica*, (Miswak) was widely used to treat halitosis because of anti-inflammatory effect[44] and contains vitamin C that helps in healing gingival edema and bleeding[45]. The alcoholic extract of *Curcuma zedoaria* was used auxiliary component in the mouthwash to treat dental plaque and gingivitis[46]. Hence, in the present investigation, the traditional preparation CUSOCO was evaluated for its efficacy on the management of halitosis.

CONCLUSION

In the present study, composition (paste) prepared by mixing of 2 drops of *S. lycopersicum* fruit juice, 2 drops of *C. nucifera* and 1g of *C. cyminum* seed powder were tested on 100 subjects with felt bad breath. Results of the present study was found to be effective in controlling bad breath (odour) in 74 subjects after the treatment (period of clinical trial) except 09 of 83 subjects who were diabetic. However, phytocompounds present in CUSOCO formulation must be scientifically analysed and validated before put to regular practice.

REFERENCES

1. Aspinall SR, Parker JK, Khutoryanskiy VV. Oral care product formulations, properties and challenges. Colloids and Surfaces B: Biointerfaces. 2021 Apr 1; 200:111567 https://doi.org/10.1016/j.colsurfb.2021.111567

2. Naidoo S. Oral health and nutrition. Oral Health Care-Prosthodontics, periodontology, Biology, Research and Systemic Conditions. 2012 Feb 29 https://doi.org/10.5772/33921

3. Buunk-Werkhoven YA, Dijkstra-le Clercq M, Verheggen-Udding EL, De Jong N, Spreen M. Halitosis and oral health-related quality of life: a case report. International journal of dental hygiene. 2012 Feb; 10(1):3-8. https://doi.org/10.1111/j.1601-5037.2011.00512.x

4. Cortelli JR, Barbosa MD, Westphal MA. Halitosis: a review of associated factors and therapeutic approach. Brazilian oral research. 2008; 22:44-54 https://doi.org/10.1590/S1806-83242008000500007

5. Ueno M, Yanagisawa T, Shinada K, Ohara S, Kawaguchi Y. Prevalence of oral malodor and related factors among adults in Akita Prefecture. Journal of medical and dental sciences. 2007; 54(3):159-65

6. Liu XN, Shinada K, Chen XC, Zhang BX, Yaegaki K, Kawaguchi Y. Oral malodor-related parameters in the Chinese general population. Journal of clinical periodontology. 2006 Jan; 33(1):31-6 https://doi.org/10.1111/j.1600-051X.2005.00862.x

7. Morita M, Wang HL. Association between oral malodor and adult periodontitis: a review. Journal of clinical periodontology. 2001 Sep; 28(9):813-9 https://doi.org/10.1034/j.1600-051x.2001.028009813.x

8. Scully C, Felix DH. Oral medicine-update for the dental practitioner: dry mouth and disorders of salivation. British dental journal. 2005 Oct; 199(7):423-7 https://doi.org/10.1038/sj.bdj.4812740

9. Hoshi K, Yamano Y, Mitsunaga A, Shimizu S, Kagawa J, Ogiuchi H. Gastrointestinal diseases and halitosis: association of gastric Helicobacter pyloriinfection. International dental journal. 2002 Jun; 52 (S5P1):207-11 https://doi.org/10.1002/j.1875-595X.2002.tb00926.x

10. Tonzetich J. Oral malodour. An indicator of health status and oral cleanliness. Int Dent J.. 1978; 28:309-19

11. Yaegaki K, Coil JM. Examination, classification, and treatment of halitosis; clinical perspectives. Journal-canadian dental association. 2000 May 1; 66(5):257-61

12. Oho T, Yoshida Y, Shimazaki Y, Yamashita Y, Koga T. Characteristics of patients complaining of halitosis and the usefulness of gas chromatography for diagnosing halitosis. Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology. 2001 May 1; 91(5):531-4 https://doi.org/10.1067/moe.2001.112543

13. Söder B, Johansson B, Söder PO. The relation between foetor ex ore, oral hygiene and periodontal disease. Swedish dental journal. 2000 Jan 1; 24(3):73-82.

14. Chattopadhyay I, Lu W, Manikam R, Malarvili MB, Ambati RR, Gundamaraju R. Can metagenomics unravel the impact of oral bacteriome in human diseases?. Biotechnology and Genetic Engineering Reviews. 2022 Jul 23:1-33 https://doi.org/10.1080/02648725.2022.2102877

15. Tonzetich J. Production and origin of oral malodor: a review of mechanisms and methods of analysis. Journal of periodontology. 1977 Jan 1; 48(1):13-20. https://doi.org/10.1902/jop.1977.48.1.13

16. Cortelli JR, Barbosa MD, Westphal MA. Halitosis: a review of associated factors and therapeutic approach. Brazilian oral research. 2008; 22:44-54 https://doi.org/10.1590/S1806-83242008000500007

17. Asokan S, Kumar RS, Emmadi P, Raghuraman R, Sivakumar N. Effect of oil pulling on halitosis and microorganisms causing halitosis: A randomized controlled pilot trial. Journal of Indian Society of Pedodontics and Preventive Dentistry. 2011 Apr 1; 29(2):90 https://doi.org/10.4103/0970-4388.84678

18. Bosy A. Oral malodor: philosophical and practical aspects. Journal (Canadian Dental Association). 1997 Mar 1; 63(3):196-201

19. Tonzetich J. Production and origin of oral malodor: a review of mechanisms and methods of analysis. Journal of periodontology. 1977 Jan 1; 48(1):13-20 https://doi.org/10.1902/jop.1977.48.1.13

20. Yuan H, Ma Q, Ye L, Piao G. The traditional medicine and modern medicine from natural products. Molecules. 2016; 21(5):559. https://doi.org/10.3390/molecules21050559

21. Thomford NE, Senthebane DA, Rowe A, Munro D, Seele P, Maroyi A, Dzobo K. Natural products for drug discovery in the 21st century: innovations for novel drug discovery. International journal of molecular sciences 2018; 19(6):1578. https://doi.org/10.3390/ijms19061578

22. Atanasov AG, Zotchev SB, Dirsch VM, Supuran CT. Natural products in drug discovery: advances and opportunities. Nature Reviews Drug Discovery 2021; 20(3):200-16. https://doi.org/10.1038/s41573-020-00114-z

23. Atanasov AG, Waltenberger B, Pferschy-Wenzig EM, Linder T, Wawrosch C, Uhrin P, Temml V, Wang L, Schwaiger S, Heiss EH, Rollinger JM. Discovery and resupply of pharmacologically active plant-derived natural products: A review. Biotechnology advances 2015; 33(8):1582-614. https://doi.org/10.1016/j.biotechadv.2015.08.001

24. Newman DJ, Cragg GM. Natural products as sources of new drugs over the nearly four decades from 01/1981 to 09/2019. Journal of Natural Products. 2020; 83(3):770-803. https://doi.org/10.1021/acs.jnatprod.9b01285

25. Al-Snafi AE. The pharmacological activities of Cuminum cyminum-A review. IOSR Journal of Pharmacy. 2016; 6(6):46-65.

26. Mnif S, Aifa S. Cumin (Cuminum cyminum L.) from traditional uses to potential biomedical applications. Chem Biodivers. 2015; 12(5):733-42. https://doi.org/10.1002/cbdv.201400305

27. Nadeem M, Riaz A. Cumin (Cuminum cyminum) as a potential source of antioxidants. Pakistan Journal of Food Sciences. 2012; 22(2):101-7.

28. Ramya S, Loganathan T, Chandran M, Priyanka R, Kavipriya K, Pushpalatha GG, Aruna D, Ramanathan L, Jayakumararaj R, Saluja V. Phytochemical Screening, GCMS, FTIR profile of Bioactive Natural Products in the methanolic extracts of Cuminum cyminum seeds and oil. Journal of Drug Delivery and Therapeutics. 2022 Apr 15; 12(2-S):110-8. https://doi.org/10.22270/jddt.v12i2-S.5280

29. Ramya S, Loganathan T, Chandran M, Priyanka R, Kavipriya K, Pushpalatha GL, Aruna D, Abraham GC, Jayakumararaj R. ADME-Tox profile of Cuminaldehyde (4-Isopropylbenzaldehyde) from Cuminum cyminum seeds for potential biomedical applications. Journal of Drug Delivery and Therapeutics. 2022 Apr 15; 12(2-S):127-41. https://doi.org/10.22270/jddt.v12i2-S.5286

30. World Health Organization. Oral health surveys: basic methods. World Health Organization; 2013

31. Vranic E, Lacevic A, Mehmedagic A, Uzunovic A. Formulation ingredients for toothpastes and mouthwashes. Bosnian journal of basic medical sciences. 2004 Nov; 4(4):51 https://doi.org/10.17305/bjbms.2004.3362

32. Hine MK. Halitosis. The Journal of the American Dental Association. 1957 Jul 1; 55(1):37-46 https://doi.org/10.14219/jada.archive.1957.0147

33. Seemann R, Conceicao MD, Filippi A, Greenman J, Lenton P, Nachnani S, Quirynen M, Roldán S, Schulze H, Sterer N, Tangerman A. Halitosis management by the general dental practitioner-results of an international consensus workshop. Journal of breath research. 2014 Feb 24; 8(1):017101 https://doi.org/10.1088/1752-7155/8/1/017101

34. Yaegaki K, Sanada K. Effects of a two-phase oil-water mouthwash on halitosis. Clinical preventive dentistry. 1992 Jan 1; 14(1):5-9

35. Yaegaki K, Coil JM. Examination, classification, and treatment of halitosis; clinical perspectives. Journal-canadian dental association. 2000 May 1; 66(5):257-61

36. Touyz LZ. Oral malodor-a review. Journal (Canadian Dental Association). 1993 Jul 1; 59(7):607-10

37. Touyz LZ. Oral malodor: A clinical appraisal: Mechanism, diagnosis & therapy. IOSR-JDMS. 2013; 11:85-9 https://doi.org/10.9790/0853-1168589

38. Van Ameringen M, Mancini C, Styan G, Donison D. Relationship of social phobia with other psychiatric illness. Journal of affective disorders. 1991 Feb 1; 21(2):93-9 https://doi.org/10.1016/0165-0327(91)90055-W

39. Schneier FR, Johnson J, Hornig CD, Liebowitz MR, Weissman MM. Social phobia: Comorbidity and morbidity in an epidemiologic sample. Archives of general psychiatry. 1992 Apr 1; 49(4):282-8 https://doi.org/10.1001/archpsyc.1992.01820040034004

40. Wittchen HU, Fuetsch M, Sonntag H, Müller N, Liebowitz M. Disability and quality of life in pure and comorbid social phobia. Findings from a controlled study. European Psychiatry. 2000; 15(1):46-58 https://doi.org/10.1016/S0924-9338(00)00211-X

41. Rajmohan M, Madankumar PD, Shivakumar M, Uma KS. Awareness on Oral Health among Ayurvedha and Siddha Practitioners in Chennai, Tamil Nadu-A Questionairre Study. Medical Journal of Islamic World Academy of Sciences. 2012 Apr; 20(2):43-8

42. Dudzik A, Chomyszyn-Gajewska M. Pseudohalitosis and halitophobia. Przeglad lekarski. 2014 Jan 1; 71(5):274-6

43. Rassameemasmaung S, Sirikulsathean A, Amornchat C, Hirunrat K, Rojanapanthu P, Gritsanapan W. Effects of herbal mouthwash containing the pericarp extract of Garcinia mangostana L on halitosis, plaque and papillary bleeding index. Journal of the International Academy of Periodontology. 2007 Jan 1; 9(1):19-25

44. KC HY, Rao V. Evaluation of topical anti-inflammatory effect of Azadirachta indica leaf extract. International Research Journal of Pharmaceutical and Applied Sciences. 2012 Oct 30; 2(5):60-4

45. El-Hilaly J, Hmammouchi M, Lyoussi B. Ethnobotanical studies and economic evaluation of medicinal plants in Taounate province (Northern Morocco). Journal of Ethnopharmacology. 2003 Jun 1; 86(2-3):149-58 https://doi.org/10.1016/S0378-8741(03)00012-6

46. do Egito Vasconcelos BC, Novaes M, Sandrini FA, de Albuquerque Maranhão Filho AW, Coimbra LS. Prevalence of oral mucosa lesions in diabetic patients: a preliminary study. Brazilian journal of otorhinolaryngology. 2008 May 1; 74(3):423-8 https://doi.org/10.1016/S1808-8694(15)30578-4

Table 1 Validation of herbal composition CUSOCO on halitosis patients

Halitosis condition	Number of Individuals			
	0 day	7th day	15th day	30th day
Worst	24	07	07	07
Moderate	59	14	06	0
Pseudo halitosis	0	0	0	0
Without halitosis	0	67	75	81
Total	83	84	88	88

Table 2 Statistical analysis to validate herbal composition CUSOCO

	0_day	7th_day	15th_day	30th_day
N	5	5	5	5
Min	0	0	0	0
Max	83	84	88	88
Sum	166	172	176	176
Mean	33.2	34.4	35.2	35.2
Std. error	16.48454	17.13651	19.05098	20.19752
Variance	1358.7	1468.3	1814.7	2039.7
Stand. dev	36.86055	38.3184	42.5993	45.16304
Median	24	14	7	7
25 prcntil	0	3.5	3	0
75 prcntil	71	75.5	81.5	84.5
Skewness	0.555019	0.64357	0.643047	0.604361
Kurtosis	-1.88517	-2.59681	-2.99874	-3.2303
Geom. mean	0	0	0	0
Coeff. var	111.0257	111.3907	121.0207	128.3041

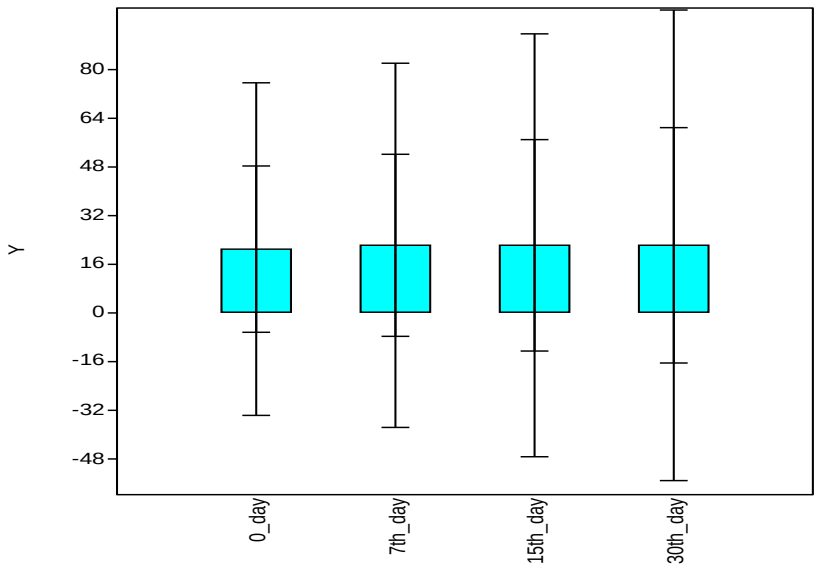

Table 2 Box plot analysis of data on validation of herbal formulation