MINERVA
GASTROENTEROLOGY

VOLUME 68 · 2022

PERFORMANCE OF A MULTICOMPOUNDS NUTRACEUTICAL FORMULATION IN PATIENTS WITH SYMPTOMATIC UNCOMPLICATED DIVERTICULAR DISEASE

Giovanni BRANDIMARTE, Giovanni V. FRAJESE, Stefano BARGIGGIA, Danilo CASTELLANI, Andrea COCCO, Raffaele COLUCCI, Enrica EVANGELISTA, Antonietta G. GRAVINA, Domenico NAPOLETANO, Elisabetta NARDI, Tammaro MAISTO, Antonino MORABITO, Giuseppe PIANESE, Antonio ROMANO, Rodolfo SACCO, Luca SEDIARI, Nicola SINNONA, Lorenza TIFI, Alessandro D'AVINO, Walter ELISEI, Antonio TURSI

EDIZIONI · MINERVA · MEDICA

PUBBLICAZIONE PERIODICA TRIMESTRALE - POSTE ITALIANE S.P.A. - SPED. IN A.P. D.L. 353/2003 (CONV. IN L. 27/02/2004 N° 46) ART. 1, COMMA 1, DCB/CN - ISSN 2724-5985 TAXE PERÇUE

Online version at http://www.minervamedica.it

Minerva Gastroenterology 2022;68
DOI: 10.23736/S2724-5985.22.03132-1

ORIGINAL ARTICLE

Performance of a multicompounds nutraceutical formulation in patients with symptomatic uncomplicated diverticular disease

Giovanni BRANDIMARTE [1], Giovanni V. FRAJESE [2], Stefano BARGIGGIA [3], Danilo CASTELLANI [4], Andrea COCCO [5], Raffaele COLUCCI [6], Enrica EVANGELISTA [7], Antonietta G. GRAVINA [8], Domenico NAPOLETANO [9], Elisabetta NARDI [4], Tammaro MAISTO [10], Antonino MORABITO [11], Giuseppe PIANESE [12], Antonio ROMANO [13], Rodolfo SACCO [14], Luca SEDIARI [4], Nicola SINNONA [15], Lorenza TIFI [16], Alessandro D'AVINO [1], Walter ELISEI [17], Antonio TURSI [18, 19] *

[1]Division of Internal Medicine and Gastroenterology, Cristo Re Hospital, Rome, Italy; [2]Section of Human Health, Department of Human Health and Exercise Sciences, Foro Italico University, Rome, Italy; [3]Division of Gastroenterology and Digestive Endoscopy, San Carlo Nursing Home, Paderno Dugnano, Milan, Italy; [4]Unit of Gastroenterology and Hepatology, Department of Medicine and Surgery, Santa Maria della Misericordia University Hospital, University of Perugia, Perugia, Italy; [5]Division of Gastroenterology, S. Pertini Hospital, Rome, Italy; [6]Unit of Digestive Endoscopy, San Matteo degli Infermi Hospital, Spoleto, Perugia, Italy; [7]Private Practitioner, Sora, Latina, Italy; [8]Department of Precision Medicine, Luigi Vanvitelli University, Naples, Italy; [9]Service of Digestive Endoscopy, Pineta Grande Hospital, Castel Volturno, Caserta, Italy; [10]Unit of Gastroenterology and Digestive Endoscopy, San Giovanni di Dio Hospital, Frattamaggiore, Naples, Italy; [11]Service of Digestive Endoscopy, Villa dei Gerani Nursing Home, Vibo Valentia, Italy; [12]Unit of Digestive Endoscopy, Santa Maria Goretti Hospital, Latina, Italy; [13]Private Practitioner, Pisa, Italy; [14]Division of Gastroenterology, Ospedali Riuniti Hospital, Foggia, Italy; [15]Service of Digestive Endoscopy, San Marco Nursing Home, Latina, Italy; [16]Division of Gastroenterology and Digestive Endoscopy, Città di Castello Hospital, Città di Castello, Perugia, Italy; [17]Division of Gastroenterology, S. Camillo Hospital, Rome, Italy; [18]Territorial Gastroenterology Service, ASL BAT, Andria, Barletta-Andria-Trani, Italy; [19]Department of Medical and Surgical Sciences, Sacred Heart Catholic University, Rome, Italy

*Corresponding author: Antonio Tursi, via Torino 49, 76123 Andria, Barletta-Andria-Trani, Italy. E-mail: antotursi@tiscali.it

ABSTRACT

BACKGROUND: Symptomatic uncomplicated diverticular disease (SUDD) is a recognized clinical condition characterized by abdominal pain and changes in bowel habits, attributed to diverticula but without macroscopic signs of diverticulitis. There is no consensus about the management of these patients. Enteroflegin®, an association of natural active ingredients, could be effective in the treatment of those patients.

METHODS: We conducted a retrospective observational study to evaluate the performances of Enteroflegin® in patients with SUDD. Patients were treated with Enteroflegin® 2 cp/day for 10 days per month for 6 months. Primary endpoint was the clinical remission rate, defined as the absence of any symptoms; secondary endpoints were the impact of the treatment on reduction of symptoms, on fecal calprotectin (FC) expression, and the prevention of acute diverticulitis.

RESULTS: Three hundred and fifty patients were retrospectively enrolled (183 males, median age 64 years, IQR 54-70). Enteroflegin® was effective in inducing remission in 9.34% and 17.64% of patients at 3 and 6 months respectively ($P<0.001$). Reduction of symptoms occurred in 92.3% and in 85.3% of patients at 3 and 6 months respectively ($P<0.001$), and symptoms' recurrence or worsening was recorded in only 1.71% of patients during the follow-up. FC expression dropped from 181.3 μg/g at baseline to 100.2 μg/g ($P<0.001$) and to 67.9 μg/g ($P<0.001$) at 3 and 6 months of follow-up respectively. No adverse event was recorded during the follow-up. Finally, acute diverticulitis occurred in just 2% of patients during the follow-up.

CONCLUSIONS: Enteroflegin® seems to be an effective nutraceutical compound in obtaining remission and symptom relief in SUDD patients. Further randomized, placebo-controlled clinical trials are needed to confirm these preliminary data.

(*Cite this article as:* Brandimarte G, Frajese GV, Bargiggia S, Castellani D, Cocco A, Colucci R, *et al.* Performance of a multicompounds nutraceutical formulation in patients with symptomatic uncomplicated diverticular disease. Minerva Gastroenterol 2022;68. DOI: 10.23736/S2724-5985.22.03132-1)

KEY WORDS: Diverticular diseases; Disease management; Dietary supplements.

Diverticulosis of the colon is main finding on colonoscopies.[1] Approximately one forth of patients with diverticula develop symptoms, which can range from symptomatic uncomplicated diverticular disease (SUDD) to acute diverticulitis and its complications (perforation, peritonitis, fistulas, abscesses).[2]

SUDD is a clinical syndrome characterized by left lower abdominal pain, bloating and altered bowel habits, including constipation or diarrhea, attributed to diverticula in the absence of macroscopic signs of diverticular inflammation.[2] The pathogenesis of SUDD is still not well understood, although genetic susceptibility, diet, neuromuscular dysfunction, altered gut microbiome and chronic mucosal inflammation play a key role, thus representing an attractive therapeutic target.[2, 3] The most frequent drugs used in treating patients with SUDD are represented by rifaximin, mesalazine and probiotics.[4] Systematic reviews and meta-analyses found rifaximin, mesalazine and probiotics effective in the treatment of symptoms in SUDD patients.[5-7] However, despite the different therapeutic possibilities, there is no consensus yet about the management of SUDD patients.

Recently, clinical studies showed that the use of nutraceutical compounds may reduce the intestinal inflammatory response and intestinal permeability.[8, 9] As consequence, some studies assessing the efficacy of some nutraceutical formulations in treating SUDD patients are becoming now available.[10] Enteroflegin® is an association of natural active ingredients: *Hericium erinaceus*, Quercitin, Niacin and Biotin). This formulation has been on the Italian market since October 2019, and it is advised in patients with bowel habits alteration (mainly diarrhea), impaired intestinal permeability and microbiota imbalance.[11]

The aim of this study was to evaluate the efficacy of Enteroflegin® in the treatment of patients complaint with SUDD.

Materials and methods

We evaluated retrospectively the efficacy of Enteroflegin® in inducing and maintaining remission of symptoms in adult patients affected by SUDD. We assessed patients who were enrolled and followed-up between 1st January 2020 and 30th June 2021, and having a 6-months follow-up. Since this was a retrospective study, Ethical Commitee approval was not required by the Italian law.

Inclusion criteria were considered: males and females aged >30 years; diagnosis of diverticular disease diagnosed for the first time or established by previous colonoscopy (performed no more than one year before enrolment); symptomatic episode of SUDD no more than 4 weeks prior to study entry; increased expression of fecal calprotectin (FC). Exclusion criteria were considered: presence of acute diverticulitis and/or its complications (fistulas, abscesses, and/or stenoses); use of probiotic preparations either prescribed or over-the counter within two weeks prior to study entry; use of mesalazine either prescribed or over-the counter within two weeks prior to study entry; antibiotic therapy (included non-absorbable antibiotics) or NSAIDs (except for acetyl-salicylic ≤100 mg/day) within 4 weeks prior to study entry; diverticular colitis; active or recent peptic ulcer; chronic renal insufficiency; lactulose-lactitol use in the two weeks before the enrolment and during the study; recent history or suspicion of alcohol abuse or drug addiction.

The study includes only patients who underwent colonoscopy with detection of diverticu-

losis through the colon, when possible scored according to the Diverticular Inflammation and Complications Assessment (DICA) Classification.[12]

Patients were assessed at baseline and at 3 and 6 months after the beginning of the treatment regarding their general conditions, symptoms and adverse events.

The primary endpoint of the study was the clinical remission rate, defined as the disappearance of any symptom, assessed by using a Visual Analogue Scale (VAS scale, a 10 point visual scale, assigning numerical values of 0 for absence of symptom until 10 for the most severe symptom). Secondary end-points were considered improvement of symptoms, assessed by a VAS scale, prevention of acute diverticulitis, reduction of FC expression, the rate of adverse events.

Treatment and product

Patients were recommended to use as a unique treatment Enteroflegin® tablets two times daily for the first 10 days of each month, for a total of 6 months. The average contents for 1 tablet is: *Hericium erinaceus* dust 700 mg, *Hericium erinaceus* dry extract 300 mg, Quercetin 98% 50 mg, Biotin 225 µg, Niacin 27 mg.

Enteroflegin® is manufactured by Gruppo Farmaimpresa s.r.l. (Serravalle Scrivia, Alessandria, Italy) and traded by Fenix Pharma Soc. Coop.p.A. (Rome, Italy). The product was notified to the Italian Health Authorities in October, 2019.

Statistical analysis

Descriptive features were expressed in median and interquartile ranges for continuous variables and in terms of frequencies for categorical variables. Data were analyzed with IBM-SPSS Statistics version 23.0 (IBMCorp., Armonk, NY, USA). Categorical variables were compared using a Chi-square test or a Fisher's Exact test, as appropriate, and the two-tailed t test for continuous variables.

Factors associated with improvement of symptoms at 6 months were investigated by logistic regression analysis. P values <0.05 were considered good evidence against the null hypothesis. Predictors of decrease in FC mean values were detected by linear regression considering P values <0.05 as statistically significant.

Results

Three-hundred and fifty patients were enrolled according to the inclusion/exclusion criteria. Baseline characteristics were available for all patients, and are shown in the Table I. One hundred eighty-three patients (52.3%) were male with a median age of 64 years (IQR. 54-70); 30.9% of patients were smokers with a median BMI of 25 kg/m^2 (IQR 23-28); median FC was 181.3 µg/g (IQR 88.5-220), and 10% of them (35 patients) had a past history of appendectomy. All principal variables were normally distributed.

At baseline, all patients referred at least one symptom, with median VAS Score of 5,4, and abdominal pain was present in 96.7% of them (the VAS score for abdominal pain was 6 at baseline, IQR 5-7). At 3 months, 182 (52%) patients had available data, whilst at 6 months data were available from 102 (29.9%) of them.

DICA Endoscopic Score was available in 274 patients at baseline: 105 (38.3%) of them were scored as DICA 1, 126 (46%) as DICA 2, and 43 (15.7%) as DICA 3.

Regarding the primary endpoint, we found that the remission, namely the complete disappearance of any symptom, was reached in 17/182 (9.34%) and in 18/102 (17.64%) patients at 3 and 6 months respectively (P<0.001) (Figure 1A).

About the secondary endpoints, we found a

TABLE I.—*Baseline characteristics in the studied population (350 patients).*

	N. (%)	Median IQR
Sex male	183 (52.3%)	
Age (median)	64	54-70
BMI (median kg/m^2)	25	23-28
Smoking habit	108 (30.9%)	
DICA Score 1	105 (38.1%)	
DICA Score 2	126 (46%)	
DICA Score 3	43 (15.7%)	
Appendectomy	35 (10%)	
Baseline fecal calprotectin (median µg/g)	181.3	88.5-220
Abdominal pain	342 (96.7%)	
VAS Scale (median)	6	5-7

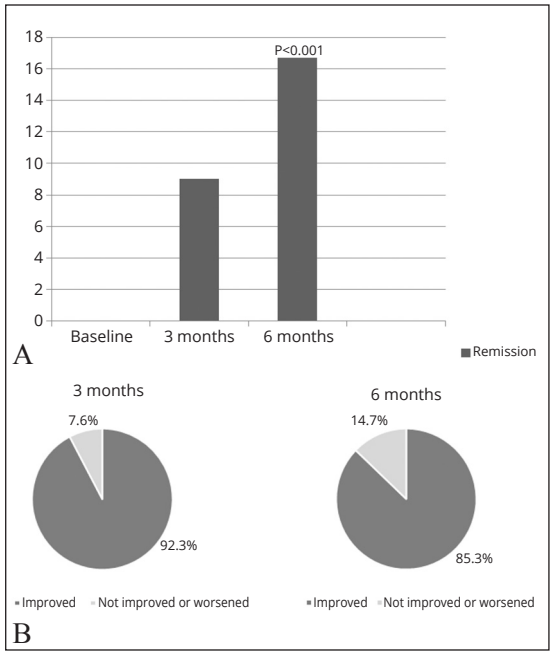

Figure 1.—A) Remission reached during the follow-up (in percentage); B) patients' symptoms during the follow-up (in percentage).

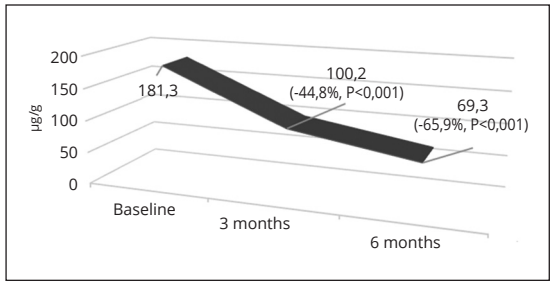

Figure 2.—Mean fecal calprotectin values during the follow-up.

reduction of symptoms in 168/182 (92.3%) and in 87/102 (85.3%) patients at 3 and 6 months respectively (P<0.001, Figure 1B). At logistic regression, we did not find any factor independentely associated to the improvement of symptoms at 3 and 6 month of follow-up.

FC collection was available in all patients at baseline, while it was available in 250 patients and in 194 patients at 3 and 6 months respectively. FC values decreased of 44.78% (-81.1 µg/g, t=10.5, P<0.001) and of 65.9% (-133.4 µg/g, t=12.02, P<0.001) at 3 and 6 months of follow-up respectively (Figure 2). Comparing the FC values and VAS score for abdominal pain in the patients in whom the VAS Score was available during the follow-up, we observed a significant reduction of mean VAS Score in parallel to the falling of the FC values: in fact the VAS score for abdominal pain was -2.6 points (-47.3%, t=14.2, P<0.001) at 3 and -4.6 points (-71.9%, t=17.4, P<0.001) at 6 months respectively. A linear regression has been perfomed to find predictors of decrease in FC values and we found that patients with a higher number of symptoms (P<0.001) and a higher FC value at baseline (P<0.001) were more likely to improve their outcome at 6 months of follow-up.

About the safety, any adverse event was not recorded during a 6-month follow-up. Significantly, symptoms' recurrence or worsening was recorded in only 6 patients (1.71%) during the 6-month follow-up. Finally, just seven cases (2%) of acute diverticulitis were recorded during the follow-up, 4 cases in patients having DICA 2 and 3 cases in patients having DICA 3 Score at baseline.

Discussion

Although it has been recently hypothesized that the real prevalence of SUDD is lower than previously though,[13] it remains a clinical entity that significantly impair the patients' quality of life.[14, 15] The main goal of treatment is therefore to reduce symptoms and, if possible, prevent the onset of acute diverticulitis.

The treatment of SUDD such as rifaximin and mesalazine make diverticular disease an attractive challenge for gastroenterologists, mainly due to contrasting data about the drugs mainy used in the treatment. In particular the main doubts on the use of rifaximin are related to the risk of adverse events and allergic reactions and to the possible antibiotic resistance.[16] For mesalazine, on the other hand, there are no definite data to confirm its effectiveness in preventing acute diverticulitis in SUDD patients.[4] From these conflicting data arises the unmet need for new therapeutic targets, which by acting with different and combined mechanisms can allow the control of the symptoms.

Nutraceuticals are becoming an attractive

therapeutic choice also in treating diverticular disease. Recently, an association of natural active ingredients containing *Boswellia serrata*, inulin, niacin, cranberry, vitamin B1, B2, B6, B12, zinc and folic acid, was found effective in reducing symptoms in SUDD patients.[17] Moreover, Burdock, a plant which is widely used in Asian medicine thanks to its anti-inflammatory properties,[18] was found effective in preventing acute diverticulitis recurrence in Japanese population.[19]

Our study shows that Enteroflegin®, a new nutraceutical formulation, could be an interesting option in managing SUDD patients. First, this nutraceutical formulation has been found very effective in reducing symptoms in these patients; second, it was able to obtain remission, namely the complete disappearance of any symptom, in almost 20% of patients. This is a significant endpoint, because any other nutraceutical formulation was able to obtain this result, and also because this means that the quality of life of those patients may improve under treatment with this nutraceutical formulation. We do not know the mechanism that determines these results. A first hypothesis could be that Enteroflegin® may modulate the activity of the gut microbiota thanks to the combination of the various ingredients that compose it. We know that microbial imbalance may have a role in the symptom's occurrence in SUDD patients.[2] *Hericium erinaceus* is a medicinal mushroom used since ancient times and rich in beta-glucans, insoluble and indigestible polysaccharides that are fermented and processed by the bacteria (in particular *Bifidobacteria*),[20, 21] and transformed into molecules with a prebiotic action.[22] This mechanisms may therefore counteract the microbial imbalance that characterize SUDD patients. Another hypothesis, more intriguing, is that Enteroflegin® could also inhibit the low-grade inflammation in SUDD patients and therefore could determine a significant benefit that lasts over time. *Hericium erinaceus* modulates inflammatory processes by contributing to normal intestinal function.[23] Quercetin, a naturally occurring polyphenol flavonoid,[24] is used as a nutritional supplement for the treatment of several diseases, and systemic or local infammation. Quercetin directly targets cellular substrates regulating the cell cycle, and inflammation.[24-26] Finally, it seems to be able to regulate tight junctions function.[27] Biotin is a water-soluble vitamin and an essential micronutrient that must be obtained from exogenous sources such as dairy, liver, egg yolk, and vegetables, or from commensal bacteria.[28] Its classic role is as a covalently bound coenzyme for cytoplasmic carboxylases used in fatty acid homeostasis, gluconeogenesis, and other metabolic pathways[28] but emerging data also have identified a role in cellular stress response,[29] gene regulation,[30] and immune responses.[31] Niacin has proven anti-inflammatory effects, suppressing pro-inflammatory gene expression on M1 macrophages and improving vascular permeability.[32] This hypothesis is supported by the effect of Enteroflegin® on the FC expression. We found that this formulation was able to reduce significantly FC levels during the follow-up, and that abdominal pain significantly improved parallel to the FC falling.

Strengths and limitations of the study

Of course, this study has strength and weaknesses. The main strength was that it is multicenter study enrolling a large population, which reflects the real clinical practice in using this nutraceutical formulation in Italy. Another strength of this study is that FC was assessed for the first time in order to have an objective tool to confirm the clinical response. Finally, a strength of the study is that Enteroflegin® seemed to be very safe, since no patients developed adverse events. Moreover, a small percentage of patients underwent to acute diverticulitis, mainly when scored as DICA 2 and 3. This last finding is in line with the recent literature data, which found DICA 2 and DICA 3 patients at higher risk of acute diverticulitis.[33] The main limit of this study is the retrospective design, which does not allow to have the same follow-up for the enrolled patients. Furthermore, the absence of a placebo-arm lead to consider this study as an interesting study that has to be confirmed by further controlled trials.

Conclusions

Despite these limitations, we believe that this study is another piece of the puzzle in choosing the right treatment for SUDD patients. Monthly

treatment Enteroflegin® seems to be an effective and safe chance to control symptoms in SUDD patients. Further randomized and placebo-controlled clinical trials are needed to confirm the efficacy and safety data of this nutraceutical formulation and to rule out a possible placebo effect related to its intake.

References

1. Tursi A. Diverticulosis today: unfashionable and still under-researched. Therap Adv Gastroenterol 2016;9:213–28.

2. Tursi A, Scarpignato C, Strate LL, Lanas A, Kruis W, Lahat A, *et al.* Colonic diverticular disease. Nat Rev Dis Primers 2020;6:20.

3. Abenavoli L, Scarpellini E, Luzza F. The role of gut microbiota in gastrointestinal diseases: the heart of the matter. Minerva Gastroenterol 2021;67:312–3.

4. Tursi A, Brandimarte G, Di Mario F, Lanas A, Scarpignato C, Bafutto M, *et al.* International Consensus on Diverticulosis and Diverticular Disease. Statements from the 3rd International Symposium on Diverticular Disease. J Gastrointestin Liver Dis 2019;28(suppl. 4):57–66.

5. Bianchi M, Festa V, Moretti A, Ciaco A, Mangone M, Tornatore V, *et al.* Meta-analysis: long-term therapy with rifaximin in the management of uncomplicated diverticular disease. Aliment Pharmacol Ther 2011;33:902–10.

6. Picchio M, Elisei W, Tursi A. Mesalazine to treat symptomatic uncomplicated diverticular disease and to prevent acute diverticulitis occurrence. A systematic review with meta-analysis of randomized, placebo-controlled trials. J Gastrointestin Liver Dis 2018;27:291–7.

7. Lahner E, Bellisario C, Hassan C, Zullo A, Esposito G, Annibale B. Probiotics in the Treatment of Diverticular Disease. A Systematic Review. J Gastrointestin Liver Dis 2016;25:79–86.

8. Larussa T, Imeneo M, Luzza F. Potential role of nutraceutical compounds in inflammatory bowel disease. World J Gastroenterol 2017;23:2483–92.

9. Bischoff SC, Barbara G, Buurman W, Ockhuizen T, Schulzke JD, Serino M, *et al.* Intestinal permeability—a new target for disease prevention and therapy. BMC Gastroenterol 2014;14:189.

10. Mizuki A, Bafutto Ferreira AA, Bafutto Ferreira EH. Other treatments. In: Tursi A, Editor. Bafutto M, Brandimarte G, Chaves de Oliveira E. Colonic Diverticular Disease. Cham: Springer Nature AG; 2022.

11. Enteroflegin equilibrio intestinale [Internet]. Avaliable from: https://fenixlife.it/product/enteroflegin-equilibrio-intestinale/ [cited 2022, Mar 8].

12. Tursi A, Brandimarte G, Di Mario F, Andreoli A, Annunziata ML, Astegiano M, *et al.* Development and validation of an endoscopic classification of diverticular disease of the colon: the DICA classification. Dig Dis 2015;33:68–76.

13. Tursi A, Elisei W, Franceschi M, Picchio M, Di Mario F, Brandimarte G. The prevalence of symptomatic uncomplicated diverticular disease could be lower than expected: a single-center colonoscopy-based cohort study. Eur J Gastroenterol Hepatol 2021;33(Suppl 1):e478–83.

14. Comparato G, Fanigliulo L, Aragona G, Cavestro GM, Cavallaro LG, Leandro G, *et al.* Quality of life in uncomplicated symptomatic diverticular disease: is it another good reason for treatment? Dig Dis 2007;25:252–9.

15. Tursi A, Franceschi M, Elisei W, Picchio M, Mario FD, Brandimarte G. The natural history of symptomatic uncomplicated diverticular disease: a long-term follow-up study. Ann Gastroenterol 2021;34:208–13.

16. Lacy BE. Review article: an analysis of safety profiles of treatments for diarrhoea-predominant irritable bowel syndrome. Aliment Pharmacol Ther 2018;48:817–30.

17. D'Amico F, Fiorini G, Tursi A, Saracino IM, Pavoni M, Danese S, *et al.* Efficacy of a new nutraceutial formulation in patients with Symptomatic Uncomplicated Diverticular Disease (SUDD): a prospective, observational study. J Gastrointestin Liver Dis 2019;28(suppl. 4):49–52.

18. Gao Q, Yang M, Zuo Z. Overview of the anti-inflammatory effects, pharmacokinetic properties and clinical efficacies of arctigenin and arctiin from Arctium lappa L. Acta Pharmacol Sin 2018;39:787–801.

19. Mizuki A, Tatemichi M, Nakazawa A, Tsukada N, Nagata H, Kinoshita Y. Effects of Burdock tea on recurrence of colonic diverticulitis and diverticular bleeding: an open-labelled randomized clinical trial. Sci Rep 2019;9:6793.

20. Khan MA, Tania M, Liu R, Rahman MM. Hericium erinaceus: an edible mushroom with medicinal values. J Complement Integr Med 2013;10:/j/jcim.2013.10.issue-1/jcim-2013-0001/jcim-2013-0001.xml.

21. Yang Y, Ye H, Zhao C, Ren L, Wang C, Georgiev MI, *et al.* Value added immunoregulatory polysaccharides of Hericium erinaceus and their effect on the gut microbiota. Carbohydr Polym 2021;262:117668.

22. Yang Y, Zhao C, Diao M, Zhong S, Sun M, Sun B, *et al.* The Prebiotic Activity of Simulated Gastric and Intestinal Digesta of Polysaccharides from the Hericium erinaceus. Molecules 2018;23:3158.

23. Ren Y, Geng Y, Du Y, Li W, Lu ZM, Xu HY, *et al.* Polysaccharide of Hericium erinaceus attenuates colitis in C57BL/6 mice via regulation of oxidative stress, inflammation-related signaling pathways and modulating the composition of the gut microbiota. J Nutr Biochem 2018;57:67–76.

24. D'Andrea G. Quercetin: A flavonol with multifaceted therapeutic applications? Fitoterapia 2015;106:256–71.

25. Russo M, Spagnuolo C, Tedesco I, Bilotto S, Russo GL. The flavonoid quercetin in disease prevention and therapy: facts and fancies. Biochem Pharmacol 2012;83:6–15.

26. Boots AW, Haenen GR, Bast A. Health effects of quercetin: from antioxidant to nutraceutical. Eur J Pharmacol 2008;585:325–37.

27. Suzuki T, Hara H. Role of flavonoids in intestinal tight junction regulation. J Nutr Biochem 2011;22:401–8.

28. Said HM. Biotin: biochemical, physiological and clinical aspects. Subcell Biochem 2012;56:1–19.

29. Madsen CT, Sylvestersen KB, Young C, Larsen SC, Poulsen JW, Andersen MA, *et al.* Biotin starvation causes mitochondrial protein hyperacetylation and partial rescue by the SIRT3-like deacetylase Hst4p. Nat Commun 2015;6:7726.

30. Rodriguez-Melendez R, Zempleni J. Regulation of gene expression by biotin (review) [review]. J Nutr Biochem 2003;14:680–90.

31. Kuroishi T. Regulation of immunological and inflammatory functions by biotin. Can J Physiol Pharmacol 2015;93:1091–6.

32. Wise A, Foord SM, Fraser NJ, Barnes AA, Elshourbagy N, Eilert M, *et al.* Molecular identification of high and low affinity receptors for nicotinic acid. J Biol Chem 2003;278:9869–74.

33. Tursi A, Brandimarte G, Di Mario F, Elisei W, Picchio M, Allegretta L, *et al.*; DICA International Group. Prognostic performance of the 'DICA' endoscopic classification and the 'CODA' score in predicting clinical outcomes of diverticular disease: an international, multicentre, prospective cohort study. Gut 2021;gutjnl-2021-325574.

Conflicts of interest.—The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Authors' contributions.—Giovanni Brandimarte and Antonio Tursi have given substantial contributions to the conception or the design of the manuscript; Giovanni Brandimarte, Giovanni V. Frajese, Stefano Bargiggia, Danilo Castellani, Andrea Cocco, Raffaele Colucci, Enrica Evangelista, Antonietta G. Gravina, Domenico Napoletano, Elisabetta Nardi, Tammaro Maisto, Antonino Morabito, Giuseppe Pianese, Antonio Romano, Rodolfo Sacco, Luca Sediari, Nicola Sinnona, Lorenza Tifi, Alessandro Davino, Walter Elisei, Antonio Tursi; have given substantial contributions to acquisition, analysis and interpretation of the data; Antonio Tursi revised it critically. All authors have participated to drafting the manuscript. All authors read and approved the final version of the manuscript.

History.—Article first published online: _____. – Manuscript accepted: February 23, 2022. - Manuscript revised: Febraury 14, 2022. - Manuscript received: January 7, 2022.