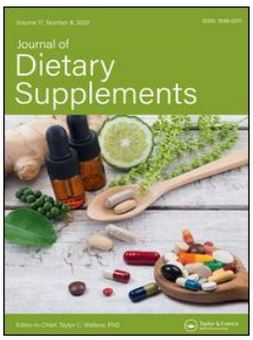

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Anthocran® Phytosome®: Prevention of Recurring Urinary Infections and Symptoms after Catheterization

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ABSTRACT

In this preliminary pilot registry study, we investigated the effects of the oral supplementation of a standardized cranberry extract (Anthocran® Phytosome®, Indena) delivered by a lecithin-based system, for the prophylactic management of recurrent-urinary tract infections (R-UTIs). We included 64 otherwise healthy subjects who underwent a surgical procedure and required post-surgical urinary catheterization for high-risk UTIs or a previous history of R-UTIs. Patients were given supplementation with the standardized cranberry extract at the dose of either 120 mg/day ($n = 12$) or 240 mg/day ($n = 12$) or assigned to a control group consisting of standard management (SM; $n = 18$) or nitrofurantoin administration ($n = 22$) for 4 weeks. After 4 weeks, patients receiving the standardized cranberry supplementation reported to have a more effective reduction in UTI symptoms, as assessed on the visual analogue scale, compared with patients in the SM or nitrofurantoin groups. The occurrence of hematuria and urine bacterial contamination were decreased among patients treated with the supplement compared with controls ($p < 0.05$). The cranberry extract was also superior to the control management in terms of recurrence of signs/symptoms, with none of the patients in this group suffering from a R-UTI in the 3 months following the study end ($p < 0.05$). The supplementation showed an optimal safety profile, with no significant adverse events and no drop-outs in the supplement group. This registry shows that this cranberry extract is effective as a supplementary, preventive management in preventing post-operative, post-catheter UTIs; the product has a good tolerability profile.

KEYWORDS

recurrent urinary tract infection; Anthocran® Phytosome®; cranberry extract; proanthocyanidins; urinary catheterization; hematuria

Introduction

Recurrent lower urinary tract infections (R-UTIs) are common after urinary catheterization in surgical patients even after procedures without significant complications (1). The correct placement of the urinary catheter and its management is essential to reduce the occurrence of post-operative urinary complications that may be of bacterial

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(associated to persisting infections) or post-traumatic origin (when the catheter causes minimal trauma to the urothelium) (2, 3). Great attention and care are required to handle these complications, which may be distressing and may complicate the post-operative recovery. The use of antibiotics during/after surgery may further complicate the infection by selecting bacterial strains that are resistant to antibiotic treatments (4). R-UTIs may persist for months after surgery if the treatment is not adequate (4).

UTIs can occur also in non-surgical patients, particularly in women (4). UTIs are also common in men and tend to recur in subjects with lower urinary tract anomalies, anatomical variations, in patients suffering from partial or temporary obstruction of the urinary tract, after catheterization or surgery, and in subjects with benign prostatic hypertrophy (5, 6).

R-UTIs are defined as the occurrence of at least three episodes of UTI in the previous year, or two episodes in the last 6 months (4). They generally occur in susceptible subjects (including surgical patients) and are a significant source of morbidity and healthcare costs (3, 7, 8). R-UTIs are classified to be of mild/moderate intensity when signs/symptoms last less than 3 days, no hospitalization is needed, and subjects present minor signs/symptoms, such as fever, fatigue and mild pain (4).

Prophylaxis may be defined on the basis of patient's characteristics – i.e. in case the syndrome has a considerable impact on people's lives, as in immunocompromised subjects, in younger, active, working subjects; or conversely, if it may be less important – i.e. in older subjects spending most of their time at home (4, 9, 10).

The Infectious Disease Society of America recommends a 5-day course of nitrofurantoin as first-line treatment of acute, uncomplicated UTIs or cystitis with documented infection (1). Often (in more than 35% of subjects), other antibiotics, (i.e. fosfomycin tromethamine used daily as a single or double dose) may be used according to local practice, which may vary in different countries and settings (1, 2, 6, 7, 11–19).

Longer-term antibiotic prophylaxis may also be used in subjects with more complex R-UTIs, particularly after surgery and urinary catheterization. Longer periods of management (i.e. 6–12 months) with antimicrobial prophylaxis have been shown to effectively reduce the occurrence of R-UTIs. However, frequent or long-term use of antibiotics increase costs and side effects and may lead to the selection of adaptive, multi-drug-resistant organisms, decreasing the efficacy of antimicrobial treatments (3, 8).

The long-term use of nitrofurantoin has been associated with anemia, pulmonary toxicity, hepatic disease and neuropathy in some patients (15, 20).

At the moment, there is no well-defined recommendation for a 'standard' prophylactic antibiotic management to prevent R-UTIs, particularly in post-surgical, post-catheter conditions.

Several studies have observed the beneficial role of cranberry products in reducing the frequency of R-UTIs (21, 22). The complex mixture of proanthocyanidins (PACs), flavonols and hydroxycinnamic acids contained in cranberry extract seems to decrease biofilm formation and reduce inflammation. This activity is mainly exerted by preventing bacterial adhesion and co-aggregation rather than through a direct bactericidal activity (22–26, 28). Thanks to its beneficial properties, cranberry use is also used as

a supplementary management model for UTIs in the Merck Manual (1) and can safely be suggested as a complementary therapy (21, 26).

Despite the large number of interventional studies on the effects of cranberry extracts in R-UTIs, a standard regimen has not been clearly defined and each dose depends on the specific product. This is mainly due to a lack of standardization of cranberry products used in different trials.

A recent study by our group suggests that the daily intake of 36 mg of PACs contributes to decreasing UTIs and inflammation to the walls of the urinary tract (24).

This may be relevant in the evolution of UTIs in which the inflammatory components may be more important than the actual bacterial contamination. PAC concentration in this study was measured by the 4-dimethylaminocinnamaldehyd (DMAC) method, which gives a global measurement of A- and B-type PACS.

The Indena cranberry product used in this trial, namely Anthocran® Phytosome®, is a food-grade delivery system based on lecithin, developed to enhance the distribution of the cranberry active principles in the target organs. It is standardized to contain PACs in the range of 6–9% bearing antioxidant and anti-inflammatory properties, which seem to be effective on UTIs, as shown in recent studies (22–25, 27, 28).

This registry evaluated the prophylactic effects of the oral supplementation with Anthocran® Phytosome® (for 4 weeks) in otherwise healthy subjects, after surgery requiring urinary catheterization, focusing on the signs/symptoms of UTIs, recurrence rates and urine evaluation.

Subjects and methods

Supplement studies are aimed to define the field of activity of pharmaceutical standard (PS) supplements and possible preventive, preferably non-severe conditions (9,10, 23). These studies are designed and organized with the full attention and participation of the evaluated subjects. The best fields of application for supplements are borderline applications or the supplementary management of some risk conditions. Supplements, unless there are specific claims, are not generally used for the treatment of signs/symptoms or to address by themselves clinical conditions. The aim of these studies is to produce supplementary data to be compared with "background" historical data (i.e. based on the best available standard management for comparable subjects) or to other management plans.

In this type of study, supplements are used according to the following rules:

1. The product is not formally prescribed but suggested to the subjects under evaluation. In this particular study, the use of Anthocran® Phytosome® was suggested as an option as it is possibly capable of improving the management of the risk condition leading to R-UTI.
2. The product is only used on top of what is considered at the time as the "standard" or "best management/care," if available, for that condition, according to relevant international guidelines.
3. The use of the product should not interfere with any other treatment or preventive measure.

4. Time: the period of follow-up is considered variable according to the needs and availability of the patients or registry subjects. The observation period could therefore be variable and not prefixed. Ideally, the product administration should continue as long as needed to see results or changes.
5. The type of evaluation for these studies is always a registry.
6. The evaluation of the compliance concerning the use of the product is of significant value, indicating how many subjects are actually willing to use it.
7. There is no defined group allocation and no randomization. Subjects decide – on the basis of the initial briefing – which management group they want to join, including the control (non-supplement) group. Control groups, if present, are not necessarily parallel.
8. Open label: subjects are always informed about the supplement or any treatment and management measure. No placebo is used, but a possible placebo effect is also carefully explained and considered.
9. Data and results are analyzed only after the observation period, ideally, when sufficient evidence is collected. The time needed to detect differences among group is also considered an effectiveness target.

Characteristics of this registry

This study was a pilot, registry study. It was an observational study (registry) supervised by the IAPSS (International Agency for Pharma Standard Supplements). We included otherwise healthy subjects (BMI <26) who underwent a non-complicated surgical procedure (i.e. intestinal resection for localized tumors with no metastasis, no occlusion and no complication) and, unfortunately, required urinary catheterization during the perioperative period because of a history of R-UTIs or risk for UTIs. Subjects were defined at risk if they had reported at least two symptomatic UTIs in the previous year or an episode of UTI in the previous month. During the peri-surgical period, patients also received appropriate antibiotic coverage (cephalosporin as individually appropriate for each subject) (14).

Exclusion criteria for these subjects included diabetes, any other chronic clinical condition or risk conditions, immune-compromising diseases, co-morbidities, corticosteroids treatment for any reason, mycosis or chemotherapy treatment within 6 months before inclusion, chronic inflammatory bowel disease, and any possible or suspected intolerance or allergy to PS supplements and specifically cranberry.

At the end of the catheterization, the removed indwelling part of the urinary catheter was tested for the presence of bacteria. If the cultures revealed a significant bacterial load, the subjects were excluded from the registry and were treated with an appropriate antibiotic management according to the culture and antibiograms. In addition, in case blood was visible in the urine, subjects were not included in the registry.

In case the catheter was clean and there was no accumulation of bacteria or blood in the urine (according to the upper limits in Table 1), the subjects were included in the registry and were assigned either to the Anthocran® Phytosome® prophylaxis group,

Table 1. Upper limits for defining "normal" urines (29).

Parameter	Upper limit
Red blood cells/erythrocytes	2–3/HPF
RBC	Negative
White blood cells/leukocytes	Negative <10/µl or mm^3
Blood/(actually hemoglobin) (dipstick scale 0–4+)	Negative
Bacterial cultures	<100,000 CFU/mL

HPF: high-powered field; RBC: red blood cells; CFU: colony-forming unit.

in which they received the supplement ingredient at the dose of 120 mg/day or 240 mg/day, or to a control group consisting of standard management (SM) or administration of nitrofurantoin (50 mg three-times/daily) for 4 weeks.

SM included accurate hygiene (without using local disinfectants), improved bladder care (drinking and voiding at appropriate time, according to need – i.e. without waiting for hours), avoiding use of too much caffeine, spices and alcohol and a careful hydration. In addition, a program of mild exercise (20–30 min walking daily, avoiding sitting in the same position for hours) was also recommended.

Patients included did not use any other supplement.

Study measures and target parameters

The registry evaluated the occurrence of urinary symptoms in the 4 weeks of follow-up. An episode of UTI was indicated by the occurrence of specific signs/symptoms (e.g. frequency, dysuria, nocturia, urgency, pain), presence of increased bacterial charge in the urines, visible presence of blood in the urine and need for consultation and specialist's evaluation.

Clinical efficacy of the supplement ingredient was determined by evaluating main target parameters: signs/symptoms (on a visual analogue scale ranging from 0 to 4), the presence of blood cells in the urine and bacterial contamination (as in Table 1) (30, 31) and recurrence of a UTI. Safety and tolerability were also assessed by weekly contacts and laboratory measurements. Adverse events were evaluated throughout the registry. All clinical adverse experiences were evaluated in terms of intensity: mild, moderate or severe, also considering duration, seriousness, outcome and relationship to the study product.

All results and data were evaluated by an external panel, not in contact with the registry subjects.

Statistical analysis

Statistical analysis was used to evaluate clinical efficacy. On the basis of the model study of Burleigh et al. (28) at least two groups of more than 10 subjects would be needed to evaluate differences in the target parameters after 4 weeks of supplementation. Non-parametric statistics (ANOVA, with Bonferroni correction) was used to evaluate the differences between signs/symptoms. Furthermore, the difference in the occurrence of episodes of infections in the management groups was analyzed using the ANOVA (with Bonferroni correction). A sigma plot software was used.

Results

The registry included 64 subjects; 24 were treated with Anthocran® Phytosome®, at the dose of 120 mg/day (12 received 1 capsule/day and 12 received 2 capsules/day), 18 subjects followed the SM program and 22 were treated with nitrofurantoin 150 mg/day. The percentage of women within each group was as follows: Anthocran® Phytosome® (1 cap/day) 42%; Anthocran® Phytosome® (2 cap/day) 50%; SM only 44%; nitrofurantoin 150 mg/day 45%.

Urinary symptoms associated to inflammation were evaluated at inclusion and weekly during follow-up.

At inclusion, all registry subjects presented with clear urine according to the limit reported in Table 1. The resulting four groups of subjects were comparable for age and sex distribution (Table 2), and signs/symptoms at inclusion (determined at the time of the placement of the catheter) were similar and of minor–moderate intensity in all four groups.

After 4 weeks, Anthocran® Phytosome® was more effective compared with SM and treatment with nitrofurantoin. It demonstrated a decrease in the occurrence of UTI/symptoms on the visual analogue scale ($p < 0.05$), the presence of blood cells in urine (hematuria; $p < 0.05$) and the presence of bacterial contamination in the urine ($p < 0.05$) as described in Table 3. Moreover, Anthocran® Phytosome® management was superior to the two control groups in terms of recurrence of signs/symptoms within the 3 months following the 4-week supplementation period. In fact, subjects who were treated with Anthocran® Phytosome® did not have a R-UTI in the following 3 months, while R-UTIs were reported in three out of 18 subjects who underwent SM and in four out of 22 subjects treated with nitrofurantoin ($p < 0.05$).

There were no significant adverse events associated with Anthocran® Phytosome® as no side effects were reported by the subjects to the clinicians. In addition, the biochemical and clinical parameters were the same at baseline and at the end of the supplementation and none of the subjects enrolled in the registry dropped out during the study.

Discussion

Post-catheter surgical infective and inflammatory complications are common and make complex the recovery after surgery in many patients (5). This post-surgical registry indicates that Anthocran® Phytosome® prophylaxis helps to control new possible post-operative and post-catheter urinary symptomatic infections/inflammations in uncomplicated subjects with previous history of UTIs.

Symptoms may be clearly associated to a new infection developing after urinary catheterization. Furthermore, anatomical abnormalities may contribute to the development of new infections after catheterization, particularly in women. However, UTI symptoms can be present even with clear urine and without any evidence of bacterial contamination (4).

Often, bacterial remnants remaining after the destruction of the bacterial cells by the antibiotic management may be present at the level of the transitional urothelium or within the urothelial cells. These remnants or minor bacterial fragments may start

Table 2. Subjects baseline characteristics.

	Total subjects (n)	Male/female (n)	Age (years); mean (SD)	Days of catheterization mean (SD)
Anthocran® Phytosome® (1 cap/day)	12	7/5	52.1 (2.2)	3.1 (0.3)
Anthocran® Phytosome® (2 caps/day)	12	6/6	53.2 (2)	3 (0.2)
SM only	18	10/8	52.3 (2.3)	3.02 (0.1)
Nitrofurantoin 150 mg/day	22	12/10	53.2 (2)	3 (0.1)

Cap: capsule; SM: standard management.

Table 3. Clinical efficacy and safety of Anthocran® Phytosome® vs SM or nitrofurantoin.

	UTI sign/symptoms (score 0–4)		Hematuria (n/total subjects)		Bacterial contamination (n/total subjects)		AEs, (n)		Recurrence rate at 3 months (n/ total subjects)
	Baseline	*4 weeks*	*Baseline*	*4 weeks*	*Baseline*	*4 weeks*	*Baseline*	*4 weeks*	
Anthocran® Phytosome® (1 cap/day)	3.4 (0.2)	0.8 (0.3)*	3/12	0/12*	2/12	0/12*	0	3 (0.2)	0
Anthocran® Phytosome® (2 caps/day)	3.4 (0.1)	0.2*	3/12	0/12*	2/12	0/12*	0	3 (0.3)	0
SM only	3.32 (0.5)	1.45 (0.4)	4/18	3/18	3/18	2/18	0	2.2 (0.8)	3/18
nitrofurantoin 150 mg/day	3.29 (0.3)	1.33 (0.2)	3/22	2/22	2/22	2/22	0	2.2 (0.3)	4/22

*Statistically significant ($p < 0.05$).
SM: standard management; AE: adverse events.

a clear inflammatory process, characterized by humoral response in association with significant symptoms apparently caused by an infection. The inflammation – which is not an infection caused by active replicating bacteria – clinically mimics an actual bacterial presence (5). This mechanism of molecular mimicry is often present in symptomatic R-UTI episodes even in non-surgical subjects. In these subjects, the inflammatory component at the level of the transitional cells is more important (and often the only component) than the infective component, which may be absent or very difficult to detect. Nevertheless, the precise characterization of the underlying inflammation process was beyond the aim of the present study. The PS supplements are not intended to treat a pathological condition alone. The identification of the symptoms, that could be ascribed to the inflammation, were instead of major interest, since they allow the recognition of patients in need of the prevention treatment that can be promptly provided as soon as the symptoms appear.

However, these subjects may be treated with a new antibiotic course, which may be ineffective against the inflammation (5). The prolongation of the antibiotic treatment may also expose subjects to significant side effects, such as those reported with long-term use of nitrofurantoin (32).

New PS supplements may offer an interesting alternative solution for preventing R-UTIs after surgical procedures, without using antibiotics (33, 34). Anthocran® has shown very promising results in the prevention of UTIs both in young healthy subjects an in older men suffering from benign prostatic hyperplasia (8, 26).

The results of this registry study confirm the efficacy of Anthocran® Phytosome®, the food-grade delivery system of the cranberry extract, which is a more cost–effectiveness ingredient, for the prophylaxis of R-UTIs in subjects who underwent catheterization during surgical procedures.

In the study, a specific control group supplemented with lecithin alone was not included. Nevertheless, the use of lecithin as emulsifier, stabilizer, dispersing aid, and release agent is acknowledged as the molecule is recognized as a safe and inactive compound (35). Lecithin has been used as excipient in a study evaluating the antibiotic resistance to urinary infections in mice, with no specific reports of involvement in any mechanism but the generation of an oral dispersion to favor administration (36). In addition, in human patients, lecithin has been tested as a coating agent for catheter and its presence has not reported to be associated to any specific effect (37). The cranberry PS supplement showed significantly superior results in the reduction of UTI symptoms, hematuria and bacterial contamination compared with SM or treatment with nitrofurantoin and prevented the re-occurrence of UTIs in the 3 months following treatment.

No significant adverse events were reported during the study. Indeed, despite the natural origin of the cranberry extract, it may happen that some individuals could develop side effects in response to its administration. An excessive chronic intake of cranberry extract has been related to an increased risk of development of kidney stones (38). The complete lack of adverse events confirm the safety and tolerability profile of this product.

Despite the very promising results, we are aware that this study presents some limitations. First of all, the small number of patients enrolled and the narrow age window of the participants. Further studies designed for increased sample size, including patients spanning a wider age interval will give important information about the efficacy of the product in the prevention of UTI for the general population.

Other limitations are implicit as any other observational study. These include the absence of a placebo group; the fact that the supplemental product was not prescribed but only suggested as an option to the patients; the time of follow-up, that was variable and not standardized, according to the needs and availability of the patients or registry subjects; the absence of clearly defined group allocation and of randomization, as the patients could independently decide which management group they want to join; and the fact that control groups were not necessarily parallel.

Conclusion

Anthocran® Phytosome® supplementary management is effective in preventing post-operative, post-catheter UTIs with good tolerability and without exposing subjects the need of antibiotic therapy. Avoiding these distressing post-catheter complications can speed up the recovery of surgical patients.

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Disclosure statement

Antonella Riva, Pietro Allegrini, Giovanna Petrangolini and Stefano Togni are employees of Indena. All the other authors confirm that they have no conflicts of interest with respect to the work described in this manuscript.

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Andrea Ledda, after graduating in Medicine and Surgery in 1979 at the "Gabriele D'Annunzio" University of Chieti, enriched his training by specializing in Andrology in 1982 at the University of Pisa. From 1981 to 1999, Dr. Ledda was head of the Andrology Unit of the Urological Clinic of the University of Chieti. From 1984 to 1994 he held the position of Head of the Andrology Center of the Pierangeli Clinic in Pescara. Since 1991 he has been Research Fellow of the Academic Surgical Unit of S. Mary Hospital (London) and since 1992 he has been a Fellow at the Royal Society of Medicine (R.S.M.) in London. From 1987 to 1991, the Doctor was a professor of Andrology at the Specialization School of Gynecology and Obstetrics of the University of Chieti and at the Specialization School of Endocrinology of the same University. In the same years, Dr. Ledda also taught Andrology at the Postgraduate School of General Surgery of the University of Chieti.

Giovanni Belcaro, He is the founder of the Irvine Vascular Lab of the University of Chieti-Pescara, Italy, and the head of the San Valentino Vascular Screening Project. Graduated in Medicine and Surgery, he specialized in General Surgery and later in Thoracic Surgery. He holds a PhD from University College (St Mary's Hospital Campus), London, working with HHG Eastcott and Prof AN Nicolaides. He obtained the Diploma (Imperial College Certificate) in Vascular Surgery and Microcirculation (UCL London). He is a fellow of the Royal Society of Medicine in London, and was a British Council Scholar. He worked at the Bispebjerg in Copenhagen. He is the author of more than 30 books and over 500 scientific articles and original publications.

Maria R. Cesarone, after the Degree in Medicine and Surgery, got Specialization in Pediatrics. Her research work in Neonatology with the first ultrasound studies on cerebral flow in newborns and on neonatal microcirculation was then followed by a Master in Angiology/ Circulation Sciences in an International Union of Angiology program. She has more tha 200 publications, mainly on vascular and microcirculatory topics.

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Beatrice Feragalli, is a medical doctor of the Department of Medical, Oral and Biotechnological Sciences, University of Gabriele d'Annunzio Chieti and Pescara. She developed important skill

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Antonella Riva, is a Senior Research Scientist deeply involved in the biological and clinical characterizations of botanicals and in the identification of new health-food ingredients in immunology, sports nutrition, gastrointestinal health, cardiovascular risk management and chronic degenerative disorders. She is the Product Research Manager at Indena S.p. A, Milano, Italy. She is the author of more than 100 research articles on medical and biological topics with particular attention to health food published on the major international journals. She has also attended international symposia and she is member of several international scientific associations.

Pietro Allegrini, is Research and Development Director at Indena SpA, an Italian company involved in process research, manufacturing and commercialization of active pharmaceutical and nutraceutical ingredients. He received his BS/MS degree from the University of Milan in 1987 and completed the Specialization Course in Chemical Synthesis at the University of Milan in 1991. He was awarded with the prize "Federchimica: per un futuro intelligente" for his master thesis and in 2018 with the prize of the Italian Chemical Society – Organic Chemistry division for Industrial research. His industrial career has been devoted to process chemistry applied to the industrial synthesis of fine chemicals and, since 1994, active pharmaceutical ingredients. Before joining Indena he was in charge of the development and pilot plant team at Zambon Chemical Division and R&D Director at Dipharma. He has authored about 50 research papers and reviews and he is co-author of over 150 international patent applications in the areas of photochromic compounds, novel polymorphs, process chemistry, namely involving hazardous reactions, transition-metal and enzymatic catalysis and natural products. His main current research interests are the extraction and purification of pharmaceutical intermediates and active ingredients as well as food supplement ingredients from botanical sources and the development of industrial processes for the synthesis of pharmaceutical products. He is co-founder of ISPROCHEM, an international school of process chemistry. He is also cofounder and part of the organizing and teaching committee of the Master School in Process Development Applied to Active Pharmaceutical Ingredients of the University of Milan.

Giovanna Petrangolini, M.B.Sc., after spending two fellowship periods in London at the School of Pharmacy (1998, 2000), worked as Researcher at the Fondazione I.R.C.C.S. Istituto Neurologico C. Besta (Milan, 2001) and as Senior Researcher in Fondazione IRCCS Istituto Nazionale dei Tumori (Milan) in preclinical oncology (2002-2010). Since 2010 she is Senior Research Scientist in R&D at Indena S.p.A dedicated to preclinical and clinical research with particular expertise in pharmaceutical and botanical products in the fields of Oncology and CNS, Cardiovascular and Gastrointestinal disorders. She is member of different scientific societies (SIC, EACR, MASCC, AFI, SIMEF) and co-author of more than 60 international peer-review publications.

Stefano Togni, is currently acting as Business Development Director at Indena, with a strong collaboration with external and internal R&D teams; areas of research are currently focused on the clinical validation of nutraceutical ingredients for prominent health conditions, followed by their market rollout and their ongoing scientific support. He has a scientific background (University Degree as DVM) coupled with a post-degree training in Scientific Communication and in Intellectual Property. Areas of scientific interest are immunology, sports nutrition, gastrointestinal health, cardiovascular risk management and chronic degenerative disorders. He is the author of more than 80 research articles on medical and biological topics with particular attention to nutraceuticals, published on the major international journals. He is member of DCAT.

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