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Anti-inflammatory effects exerted by Killox®, an innovative formulation of food supplement with curcumin, in urology

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Abstract. – OBJECTIVE: In this Open Controlled Trial we administered an innovative formulation of food supplement with curcumin (Killox®) to test its efficacy, safety and compatibility with other drugs, in the therapy of post-surgery complications of transurethral resection of prostate (TURP) and transurethral resection of bladder (TURB), and in the prevention of late complications. Furthermore, Killox® effects were verified in subjects with benign prostatic hyperplasia (BPH).

PATIENTS AND METHODS: Killox® was administered to 40 TURP patients for 20 days, to 10 TURB patients for 10 days and to 30 BPH patients for 60 days. The study was an open controlled trial, approved by the internal Review Board, with a completely independent set of retrospective observations.

RESULTS: In the subjects who underwent surgery the treatment warded off postoperative and late complications, whereas among controls, without anti-inflammatory therapy after surgery until one week later, 21 (52.5%) out of 40 TURP subjects and 4 (40%) out of 10 TURB subjects were still found with symptoms of inflammation and urinary burning, and they had to be treated with nonsteroidal anti-inflammatory drugs (NSAIDs) for seven days. Moreover among controls 2 in TURP group presented an urethral stricture, and no one in TURB group. Killox® patients did not report any adverse effect and the therapy was well tolerated, instead among 21 control subjects, who were treated with NSAIDs, 7 reported nausea and epigastric pain. Also in BPH patients the product was effective in a satisfying manner, shortening the duration of irritation symptoms. Noteworthy, Killox® administration did not modify the efficacy of the other treatments. The effect of Killox® was found statistically significant vs controls.

CONCLUSIONS: The therapeutic activity and safety of Killox® in urology allow physicians to administer a new efficient product in substitution of NSAIDs.

Key Words:
BPH, Curcumin, N-acetylcysteine, NSAIDs, Resveratrol, TURB, TURP, Zinc.

Introduction

Benign prostatic hyperplasia (BPH) is a highly frequent diagnosis among the elderly[1], related to the presence of prostatic enlargement connected with an inflammatory state. BPH is a major cause of lower urinary tract symptoms (LUTS)[2]. BPH can be treated only pharmacologically or also surgically, using the transurethral resection of the prostate (TURP). This procedure still represents the best choice to reduce surgically BPH. TURP consists in the elimination of a part of the gland, by means of an instrument (the resectoscope) inserted through the urethra. In this way it is possible to excise only the excess of prostate tissue, while the outer capsule is left whole[3,4]. Many other techniques are described and in use for BPH treatment, like laser and plasma vaporization or laser and plasma enucleation, but, compared with them, TURP actually represents the gold standard for benign prostatic hyperplasia treatment. Evidences indicate that prostatic inflammation may contribute to prostate growth, in terms of hyperplastic changes[5]. Thus, any pharmacological treatment of BPH, even without surgery, has always involved the administration of NSAIDs. On the other hand, transurethral resection of bladder (TURB) is a surgical procedure with a lighted tube inserted through the urethra into the bladder. TURB is the first form of treatment in bladder cancers to eradicate and examine bladder tissue and/or tumor, and also to remove lesions. It provides diagnostic, therapeutic and prognostic

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possibilities[6]. As result of surgery, there are bladder spasms and burning urination[4], sometimes disabling, symptoms that can be treated with NSAIDs, if they last more than a few days.

However, adverse effects can often be associated to the administration of NSAIDs, such as nonspecific colitis, and, eventually, large intestinal ulcers, bleeding, and perforation. Moreover, NSAIDs may induce relapse of classic inflammatory bowel disease and contribute to the appearance of severe diverticular diseases (fistula and perforation). These drugs may sporadically cause small intestinal perforations, ulcers, and strictures requiring then surgery. NSAIDs, however, can often lead to inflammation of small intestine, with blood loss and protein loss complications (like heartburn, vomiting, diarrhea, nausea) which are painful and difficult to manage. Furthermore, NSAIDs have shown adverse effects also at renal, cardiovascular, hepatic, pulmonary, hematologic, nervous (CNS) and skin level[7,8].

For this reason, physicians need and seek for new treatments which can effectively substitute NSAIDs therapies in urology. Different natural sources can represent a valuable source of bioactive agents for treating several inflammatory diseases, avoiding side effects at therapeutic doses. In this work we have highlighted the effect of the combination of curcumin, resveratrol, N-acetylcysteine (NAC) and zinc delivered by a single product. The aim of this study was to test the efficacy of Killox®, an innovative formulation of food supplement with curcumin, resveratrol, NAC and zinc, as alternative to NSAIDs, for the treatment of the postoperative complications (bladder spasms and burning urination) of TURP and TURB, the prevention of late complications (urethral stricture and bladder neck sclerosis), related to these surgical operations, and the reduction of irritation symptoms in subjects with benign prostatic hyperplasia (BPH) not suitable for surgery.

Patients and Methods

Patients were assessed for eligibility from November 2014 to June 2015 at Urology Unit, Private Hospital "Regina Pacis", San Cataldo (CL). The following inclusion criteria were applied: the subjects had to be between 50 and 85 years old and they had to undergo to TURP or TURB; the exclusion criteria were as following: subjects under antithrombotic therapy, HCV patients with thrombocytopenia and serious enzymatic alterations. For BPH patients not eligible for surgery, the subjects had to be between 59 and 64 years old and they were BPH patients with International Prostate Symptom Score (Urological Sciences Research Foundation) score (IPSS) <19; no exclusion criteria for them were employed.

At the same time a literature review was conducted, searching for similar reports and results using Pubmed.org and Google Scholar. The following keywords were used: BPH, LUTS, TURP, complications after TURP, management of symptoms, curcumin, NSAIDs safety. Articles not in English were excluded. The protocol was approved by the internal Review Board. Data recorded by the reviewer during this revision were:

In subjects who underwent TURP and TURB: patients' age, burning urination and presence of LUTS after surgery (evaluated through the IPSS, a written screening tool used to screen for, rapidly diagnose, track the symptoms, and suggest the management of BPH symptoms), presence of side effects (vomit, nausea, diarrhea, heartburn, headache).

In BPH subjects: patients' age, digital rectal examination (DRE), PSA total and free, urinary-tract echography, basic evaluation of LUTS (evaluated through the IPSS), presence of side effects (vomit, nausea, diarrhea, heartburn, headache).

All the patients gave an oral informed consent before entering the study. The study was an Open Controlled Trial with a completely independent set of retrospective observations.

Treatment schedules:

Killox® tablets were administered (twice a day) to the patients of the case study group since discharge from hospital (treatment duration: 20 days for TURP and 10 days for TURB).

Killox® tablets were administered once a day to BPH patients of the case study group for 60 days, in association with dietary supplement.

Killox® (curcuminoids 190 mg, resveratrol 20 mg, NAC 100 mg, zinc 6 mg) is made with the innovative formulation of the enterosoma technology to obtain an improved gut absorption and systemic bioavailability. This technology is based on the combination of specific natural polysaccharides, amino-acid derivatives and polyphenols from plant extracts that work in synergy to reduce the intestinal and hepatic degradation of active ingredients, thus improving their effectiveness. The mentioned technology (En-

terosoma™, Labomar Research Patent Pending) consists of a gastro-resistant tablet containing, in the inner core, besides BC, a CH polymer and an organic acid that once dispersed into the enteric fluids produce CH cationization. CH is a polyamino sugar not soluble in water except for acidic water solution (pH<5). Acidic groups, indeed, protonate amino groups of glucosamine units present in the CH structure, taking place to a poly-cationic ammonic molecule. Particularly, the acidic molecule selected to project this technology is N-Acetylcysteine (NAC) that is a sulphureted N-Acetylated amino acid very notorious as mucolytic agent (Figure 1).

NAC has been chosen because of its double chemical behavior both acidic and mucolytic. Mentioning this well documented mucolytic activity, some published papers refer about the enteric absorption enhancing properties of NAC strictly connected to its own capability to reduce enteric mucous viscosity[9,10]. NAC reduces mucous viscosity cleaving the S-S bounds of mucoproteins and according to this mechanism, it works efficiently in reducing viscosity of the enteric covering mucous layer though to prevent active compounds to be absorbed. This polycationic structure is thought to be the keystone to achieve both Pg-P activity modulation and TJ cohesion lowering as described (Figure 2). The powder core of the tablet comprising BC, CH and NAC is further moistened with Polysorbate 80 (PS 80), a notorious high HLB surfacting agent with ascertained activity of enteric and mucosal absorption enhancer, synergistic with NAC[9-11]. The mechanism involved seems regard the deterging action of PS 80 onto the cell membrane lipids. For last, the described tablet nucleus is coated with a gastro-resistant film to avoid premature cationization of CH occurring in the stomach by the side of gastric chloride acid that would compromise the enteric absorption enhancing effect. In summary, according to the aforementioned considerations, a synergy between interaction with Pg-P and TJ exerted by cationized CH and mucolytic activity on enteric mucous layer exerted by NAC are the main deliverables of this new technology.

The protocol envisaged a retrospective cohort of TURP and TURB patients without anti-inflammatory treatment as control group, and

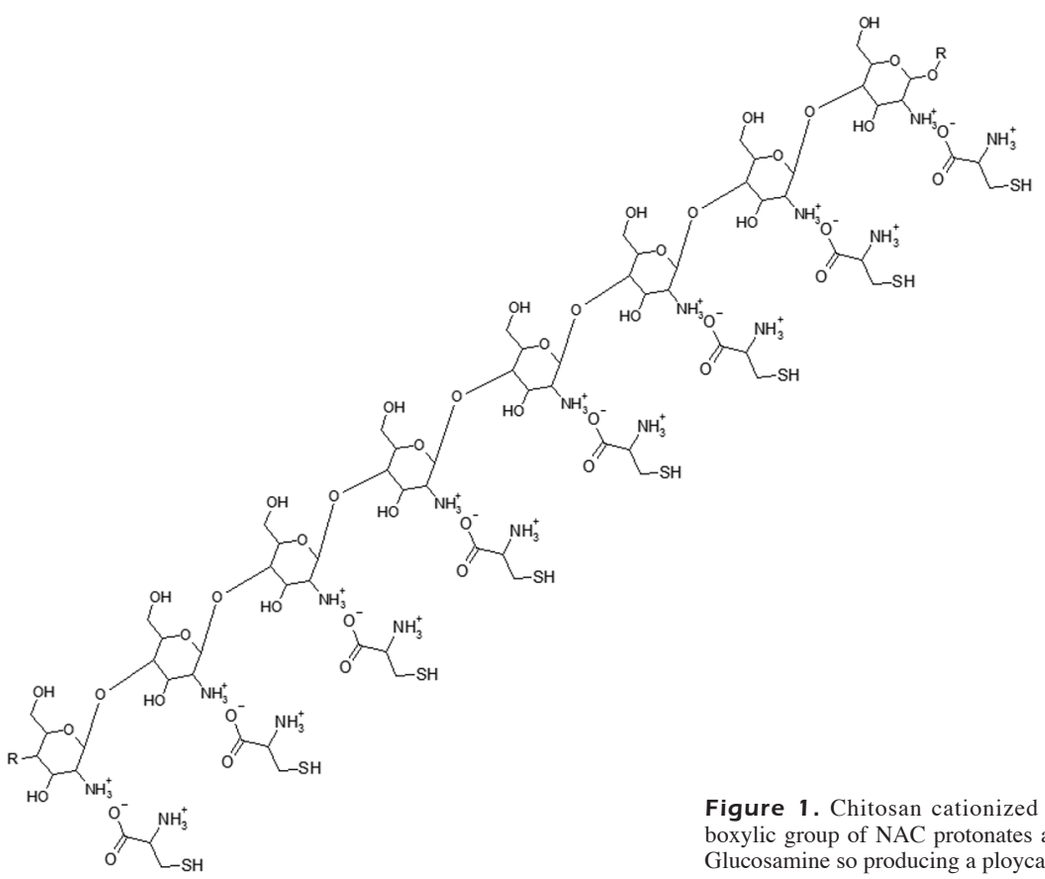

Figure 1. Chitosan cationized by NAC. Carboxylic group of NAC protonates aminic group of Glucosamine so producing a ploycation.

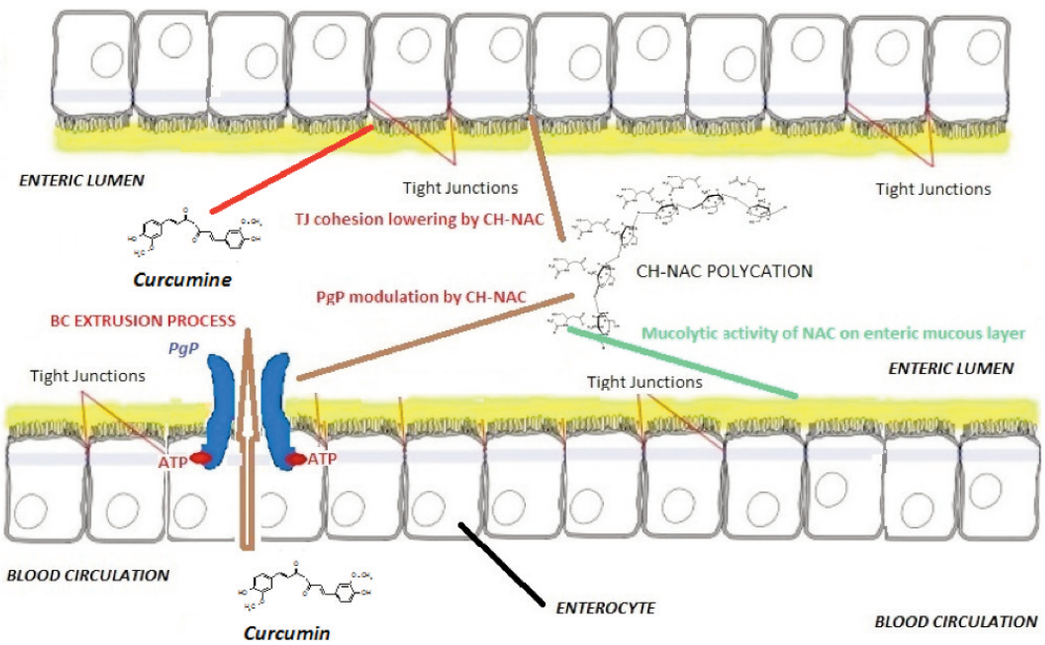

Figure 2. Postulated mechanism of action of Enterosoma™ in modulating PgP activity and TJ cohesion lowering.

with homogeneous features with the subjects in Killox® group. After surgery, both groups were administered chinolonics once a day orally for a time range from 5 to 10 days on the basis of the patient's needs, and subcutaneously heparin at low MW from 15 to 20 days on the basis of the patient's needs. The protocol had established two medical examinations: 14 days and 120 days after surgery. Control subjects reporting burning sensation after two weeks, were administered NSAID 200 mg per day, for one week. The primary outcome was the decrease in regression time of the irritation and painful symptoms. The improvement was evaluated after 14 days.

Furthermore, the protocol envisaged a retrospective cohort of BPH patients as control group, and with homogeneous features with the subjects in Killox® group, with IPSS score <19; both groups were administered dietary supplements for BPH during 60 days. The protocol had established a medical examination after 60 days. The outcome was the decrease of IPSS score.

Statistical Analysis

A sheet was given to all patients after surgery, when discharged from hospital, to record day by day the presence or absence of pain, dysuria, urgency, burning urination, frequency, and nocturia. After the first medical examination, these records were analyzed. Statistical analysis was done using Chi square test. The cut-off for statistical significance was set at $p \leq 0.05$.

BPH patients answered the questions to assess the IPSS scores, which have been recorded in the personal sheet and compared with answers provided 60 days later. These records were statistically analyzed using Mann-Whitney U test, with SPSS software (SPSS Inc., Chicago, IL, USA). The cut-off for statistical significance was set at $p \leq 0.05$.

Results

For TURP and TURB among fifty-six assessed subjects a total number of fifty subjects were included in the study group. The age ranged between 50 and 85 years, with a mean value of 68.3 ± 3.9 years. The mean age in control group was 69.7 ± 2.6 years. Characteristics in both treated and control groups were homogeneous. The patients compliance was satisfying for all treatments and no drop-out was reported. All individuals treated with Killox®, except one in TURP group, completely recovered in 14 days after surgery, whereas among controls 21 (52.5%) out of 40 TURP subjects and 4 (40%) out of 10 TURB subjects were found still with symptoms of inflammation and urinary burning (Figure 3A and 3B).

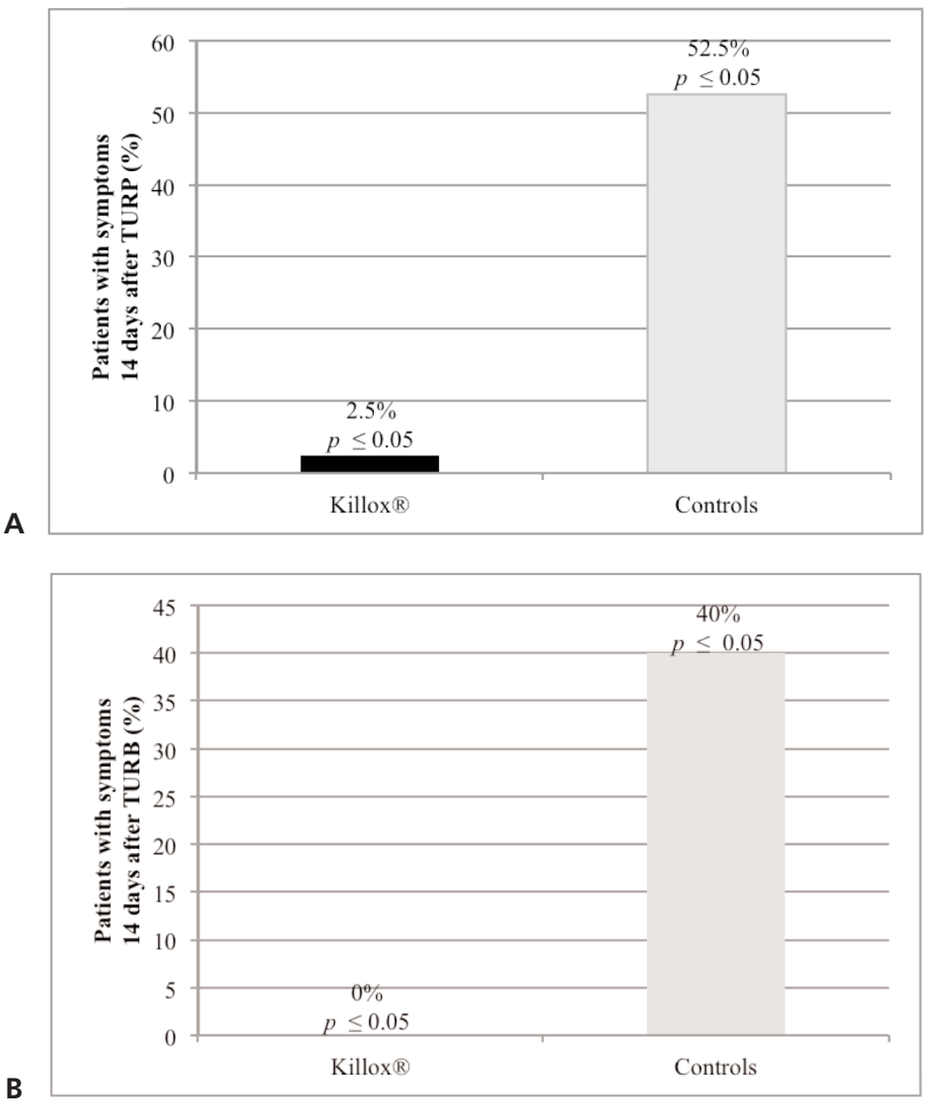

Figure 3. A, First medical examination: in TURP group, all patients treated with Killox®, except one, completely recovered 14 days later the surgery, whereas, among controls, 21 out of 40 subjects were found still with symptoms of inflammation and urinary burning. The result is significant at $p \leq 0.05$. ***B,*** First medical examination: in TURB group, all patients treated with Killox® completely recovered 14 days later the surgery, whereas, among controls, 4 out of 10 subjects were found still with symptoms of inflammation and urinary burning. The result is significant at $p \leq 0.05$.

These patients had to follow a NSAIDs therapy (200 mg, once a day) for seven days. The effect of Killox® was found statistically significant in both trials (for TURP and TURB) in comparison with controls. For TURP, the Chi-square statistic is 25.0784. The *p*-value is <0.00001. The result is significant at $p \leq 0.05$. For TURB, the Chi-square statistic is 5 and the *p*-value 0.025347. The result is again significant at $p \leq 0.05$.

At the second medical examination, late complications, related to TURP and TURB (urethral stricture and bladder neck sclerosis), were not detected in Killox® subjects, whereas among controls 2 in TURP group presented an urethral stricture (result not statistically significant), and no one in TURB group (Figure 4).

Whereas Killox® patients did not report any adverse effect and the therapy was well tolerated, among the 21 control subjects, who were treated with NSAIDs, 7 had nausea and epigastric pain. Noteworthy, Killox® administration did not modify the efficacy of the other treatments (chinolonics and heparin).

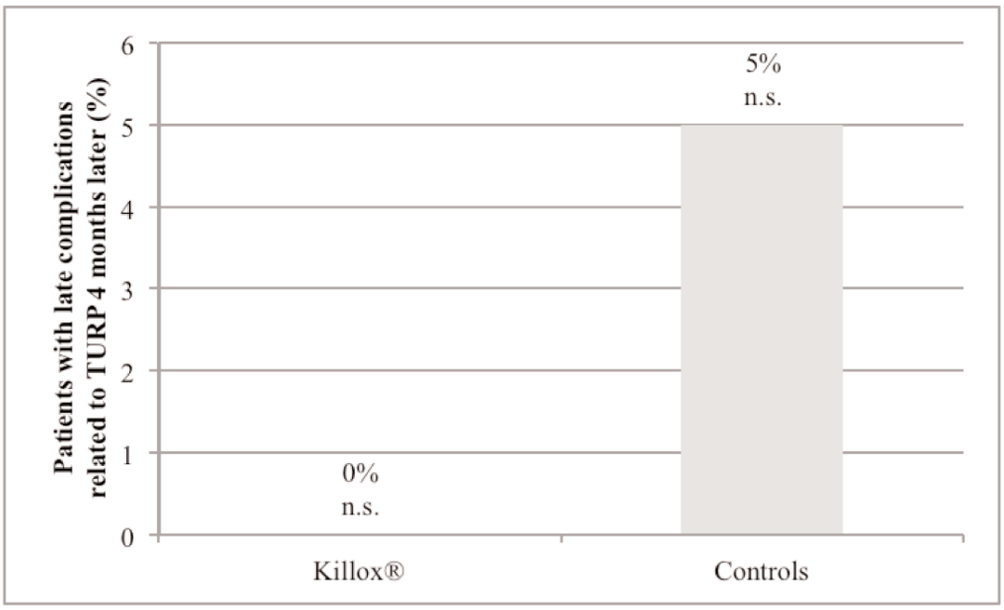

Figure 4. At the second medical examination (4 months after the surgical operation), late complications, related to TURP and TURB (urethral stricture and bladder neck sclerosis), were not detected in Killox® subjects, whereas among controls 2 in TURP group presented an urethral stricture. The result is not statistically significant.

The product demonstrated also encouraging effects in the 30 BPH patients, enrolled in the study. The mean age in study group was 64 ± 6 years and in control group was 65.5 ± 6.5 years. The two sets of subjects showed homogeneous features. The patients' compliance was satisfying for the treatments and no drop-out was reported. At the medical examination all individuals treated with Killox® reported decreasing inflammatory ailments with reduction of IPSS score between 20% and 25% within sixty days since the beginning of its administration, without relapses, whereas in control group IPSS score reduced between 10% and 15%. These results showed a statistically significant difference in comparison with controls, using Mann-Whitney U test. The Z-Score is 6.6456. The *p*-value is 0. The result is significant at $p \leq 0.05$ (Figure 5). As found in TURP and TURB group, the administration of Killox® did not cause side effects or interferences with patients' therapy.

Discussion

As shown by our study, Killox® was able to significantly reduce the inflammatory symptoms in subjects who underwent TURP and TURB, and in those ones affected by BPH, not suitable for surgery. Killox® patients reported neither postoperative complications, nor late complications. The therapy was well tolerated, unlike NSAIDs treatments. Furthermore, Killox® administration did not modify the efficacy of the other drugs.

The explanation of these very promising effects are consistent with the activities exerted by the four components of Killox®: curcumin, in combination with resveratrol, NAC and zinc. Curcumin (Figure 6) is the main biologically active component of the Indian spice Turmeric.

It is extracted from the ground rhizomes of the plant *Curcuma longa* Linn and, as concentrated, it is effective in preventing or fighting inflammation. Turmeric use has a long history in food as a spice, mainly as a constituent of several varieties of curry powders and sauces, where curcumin is a main coloring substance. It was already used as a drug in writings dating back to over 2,000 years ago, extensively used in the Indian Ayurveda and the traditional Chinese medicine. Already in the 13th century, Marco Polo, writing about his travels in China, describes this spice. Curcumin (chemically diferuloylmethane) has many and very interesting therapeutic properties studied widely by researchers all over the world[12-14]. In the curcuminoid extracts, it represents approximately the 80%, whereas the remaining is composed by other derivatives, demethoxycurcumin (17 %) and bisdemethoxycurcumin (3%)[15].

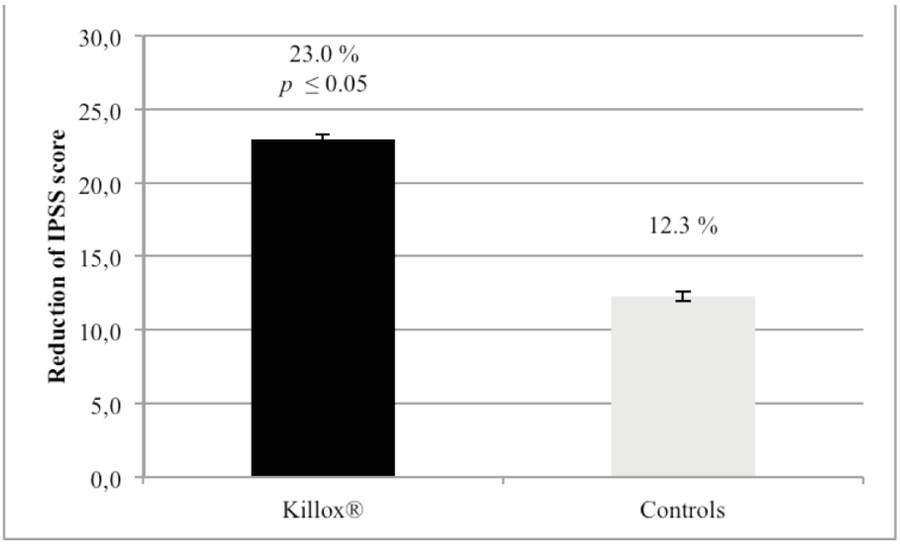

Figure 5. Reduction of IPSS score: all patients treated with Killox® reported decreasing inflammatory ailments within sixty days since the beginning of its administration, whereas a lesser reduction was found in controls. The difference was statistically different, using Mann-Whitney U test. The Z-Score is 6.6456. The *p*-value is 0. The result is significant at $p \leq 0.05$.

It has been reported that curcumin is a promising bioactive agent, having a key role in numerous key molecular signaling pathways related to inflammation and allergy through the modulation of nuclear factor kappa B, NF-κB and nuclear factor E2-related factor 2, Nrf2[16-19]. Curcumin suppresses the activation of NF-kB and it induces Nrf2 and its related antioxidant response. Having a highly electron-conjugated system, curcumin may act as a natural free radical scavenger. From the standpoint of therapeutic efficacy, curcumin has shown to be a promising antibacterial, antiviral, and antifungal agent. Clinical studies have also shown that co-administration of curcumin with conventional drugs is effective, well-tolerated as a safe drug.

Resveratrol (3,5,4'-Trihydroxystilbene) is a natural polyphenol. Though its chemical structure was characterized in 1940, which has been used in traditional medicinal preparations, such as darakchasava or manakka, for more than 2000 years. Resveratrol is classified as phytoalexin, a self-protective substance produced by plants, under attack by pathogens, to fight them. The accumulation of these substances, in more than 70 species of plants, is produced by a natural mechanism of resistance to infection, UV radiation, chemical substances and, in general, stressful situations for the plant[20]. Resveratrol is also classified as a bioactive molecule with antioxidant and anti-inflammatory activity in humans, useful for preventing and fighting cancer and other pathologies[21], thanks to its capability to inhibit the activation of NF-kB and to stimulate the Nrf2 pathway[22-24]. Resveratrol has also been reported as preventive agent for coronary heart disease in people eating elevate quantities of saturated fat, but also drinking regularly red wine, such as in the north of France (it is the so called "French paradox")[25].

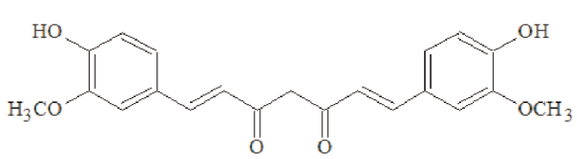

Figure 6. Structural formula of curcumin.

As mentioned before, N-acetylcysteine (NAC) is an essential element of the enterosoma technology, used for Killox®, but it also provides an additional therapeutic role to the product. Like curcumin and resveratrol, N-acetylcysteine (NAC) is another natural molecule, a thiol-containing compound, used for over 30 years in clinics with well documented benefits in a wide range of therapeutic applications[26-28]. Of note, NAC is an intermediary in the conversion of Cys to glutathione (GSH)[29], a powerful antioxidant. NAC is produced endogenously and found in foods. Also this molecule exerts a potent anti-inflammatory and antioxidant activi-

ty, acting by blocking the activation of NF-KB pathway and inducing the Nrf2 translocation to the nucleus[29,30].

Zinc is a well-known essential element for human health, endowed with an antioxidant and anti-inflammatory action, by its pivotal role in inducing the transcription function of Nrf2, and in hindering that one of NF-kB[31-33].

Curcumin, resveratrol, N-acetylcysteine (NAC) and zinc as here described modulate NF-κB and Nrf2, signaling pathways. This modulation leads to reduce many inflammatory processes.

All these natural molecules (curcumin, resveratrol, NAC) or elements (zinc) inhibit the downstream inflammatory burst, which means the inhibition of pro-inflammatory cytokines, myeloperoxidase, COX-1, COX-2, iNOS by blocking the NF-kB pathway and stimulating the Nrf2 pathway. Among these natural molecules, curcumin is surely the most powerful and promising anti-inflammatory agent. Features of Killox® are its clinical efficacy, tolerability (proper to a food supplement) and possibility to be associated with drugs (antibiotics, heparin), without reciprocal disturbances or interferences.

Conclusions

Killox®, as a combination of 4 natural active principles and an innovative formulation that improves gut absorption and systemic bioavailability, is able to exert very promising analgesic and anti-inflammatory effects. In our study, the use of Killox® after TURP and TURB has shown to obtain an improved progressive reduction of the burning sensation, in this way speeding up the time healing without adverse effects, and permitting the simultaneous treatment with other drugs (antibiotics, heparin). Furthermore, it also prevents late complications, related to TURP and TURB, such as urethral stricture and bladder neck sclerosis. A significant improvement of LUTS (irritation symptoms) was found in subjects affected by BPH, and this is a further support to the anti-inflammatory profile of the product. No side effects or reduced efficacy of the treatment for prostate were reported to be associated with the use of Killox®. In summary, the therapeutic activity and safety of Killox® allow physicians to administer patients a new efficient product in substitution of NSAIDs.

Conflict of Interest

Andrea Fratter is manager at Research and Innovation Technology, LABOMAR Research, Istrana, Italy. Vincenzo Cosentino and Marco Cosentino declare that they do not have any conflict of interest regarding the publication of this paper.

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