

## Focus on Ulcerative Colitis: Stable Gastric Pentadecapeptide BPC 157

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**Abstract:** Stable gastric pentadecapeptide BPC 157 (GEPPPGKPADDAGLV, M.W. 1419) may be the new drug stable in human gastric juice, effective both in the upper and lower GI tract, and free of side effects. BPC 157, in addition to an antiulcer effect efficient in therapy of inflammatory bowel disease (IBD) (PL 14736) so far only tested in clinical phase II, has a very safe profile, and exhibited a particular wound healing effect. It also has shown to interact with the NO-system, providing endothelium protection and angiogenic effect, even in severely impaired conditions (i.e., it stimulated expression of early growth response 1 gene responsible for cytokine and growth factor generation and early extracellular matrix (collagen) formation (but also its repressor nerve growth factor 1- A binding protein-2)), important to counteract severe complications of advanced and poorly controlled IBD. Hopefully, the lessons from animal studies, particularly advanced intestinal anastomosis healing, reversed short bowel syndrome and fistula healing indicate BPC 157's high significance in further IBD therapy. Also, this supportive evidence (i.e., no toxic effect, limit test negative, LD1 not achieved, no side effect in trials) may counteract the problems commonly exercised in the use of peptidergic agents, particularly those used on a long-term basis.

**Keywords:** BPC 157, intestinal anastomosis, short bowel, colcutaneous fistulas, inflammatory bowel disease.

### INTRODUCTION

Very recently, we reviewed stable gastric pentadecapeptide BPC 157 as a possible novel therapy in gastrointestinal tract [1].

Here, to explain the background that may be important to finally introduce this peptide in current therapy we focused on ulcerative colitis respecting several important points: the cause of inflammatory bowel disease (IBD) remains unknown; the number of drugs is currently used as specific anti-inflammatory agents in IBD; plethora of side effects of drugs currently used in IBD; and the room left for novel therapy candidates that may be free of such side effects.

In general, with an undefined essential cause of IBD [2-4], the success of the therapy should be the major determinant (and also, with increasing epidemiological and laboratory data suggesting that it is genetically determined, causing inappropriately severe and/or prolonged mucosal inflammatory response to as yet undefined environmental factor(s)). Contrary, the side effects may be a problem to interpret that the IBD essential cause had been therapeutically approached more than before or even reached and likely counteracted. In principle, such an iatrogenic approach solves the essential IBD cause through the suggested mechanisms of action of the used drugs, i.e., corticosteroids, aminosallylates, azathioprine, 6-mercaptopurine, cyclosporine, methotrexate, metronidazole and infliximab providing that the suggested mechanisms may be obviously different (i.e., antibody that binds TNF (tumour necrosis factor) on activating T-cells inducing apoptosis and down-regulation of cytokine cascade (infliximab); inhibition of interleukin (IL)-2 gene transcription to reduce helper and cytotoxic function and proliferation of T-cells (cyclosporine); inhibition of DNA synthesis (azathioprine)). Consequently, all these agents have in common a certain level of effectiveness. However, they also have in common a wide range of side effects [2-4].

Therefore, providing that proof of efficacy may be the confirmation of etiology as well, some of the side effects that may be life threatening (i.e., malignancy) [2-4], prove to be uncontrolled circumstances even if the therapy has impressive results, including sparingly healed mucosal lesions like in the case of infliximab. Thus, from the iatrogenic point of view, the therapy of IBD should not be connected with the increasing degree of side effects that may

be severe. Thereby, the commonly present high range of side effects with all currently used agents [2-4] indeed may indicate that a novel candidate should be introduced in the therapy to improve IBD therapy and therapeutically approach the essential IBD cause. In contrast to the present high range of the side effects in IBD therapy [1-3], the major determinant should be high safety.

This was the first reason why we focused on ulcerative colitis and possible application of stable gastric pentadecapeptide BPC 157 (for review see, i.e. [1,5]).

Namely, the pentadecapeptide BPC 157 may be the new drug stable in human gastric juice, effective both in the upper and lower GI tract (for review see, i.e. [1,5]). BPC 157, in addition to an antiulcer effect efficient in therapy of inflammatory bowel disease (PL 14736) so far only tested in clinical phase II, has a very safe profile and LD1 could be not achieved (for review see, i.e., [1,5]). It also has exhibited a particular wound healing effect [6-9] and interaction with the NO-system [10-15] providing endothelium protection [16-22] and an angiogenic effect [23-30], even in severely impaired conditions (for review see, i.e. [1,5]) (i.e., it stimulated expression of early growth response 1 (egr-1) gene responsible for cytokine and growth factor generation and early extracellular matrix (collagen) formation (but also its repressor nerve growth factor 1- A binding protein-2 (nab2) [6])). Therefore, this may be seen also when confronted with severe complications of advanced and poorly controlled IBD, including failure of intestinal anastomosis healing [31], short bowel syndrome [32] and fistulas [11]. Finally it exhibits effectiveness when given parenterally, perorally, or locally, and without the need for a carrier (for review see, i.e. [1,5]).

Thereby, providing that the more or less efficacy in non-complicated IBD may be common for all standard agents [2-4], our next focus will be on the BPC 157 effect on IBD-intestinal complications (anastomosis healing, short bowel syndrome and fistulas, where standard agents may be less effective) [2-4], and then, we will focus on BPC 157 effect on extra-intestinal association and complications of IBD (i.e., joint/bones, liver, eye) (where standard agents were commonly not considered) [2-4]. Importantly, pentadecapeptide BPC 157's beneficial effect on both the wound and mucosa healing (for review see, i.e. [1,5]) reduces the number of inflammatory cells [6-9] and levels of leukotriene B4 (LTB4), thromboxane B2 (TXB2), and myeloperoxidase (MPO) in the serum and inflamed tissues [28,33,34] and increases macrophages activity [35]. Thus, providing the already demonstrated effectiveness of BPC 157 in IBD (for review see, i.e., [1,5]), the demonstration that it may be effective also in recidive

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counteraction [36,37], the lessons from animal studies [11,31,32] should indicate its importance in further IBD therapy.

Finally, non-steroidal anti-inflammatory drugs have all been reported to be potential triggers of IBD [38] and since BPC 157 may have a particular beneficial effect on different lesions that may be induced by various NSAIDs, and thereby acts like an "antagonist" of NSAIDs [39-43], this issue will be also particularly focused.

### BPC 157 vs. Standard Peptides

We applied pentadecapeptide BPC 157 (manufactured by Diagen, Ljubljana, Slovenia, GEPPPGKPADAGLV, M.W. 1419, a partial sequence of human gastric juice protein BPC, peptide with 99% (HPLC) purity, freely soluble in water at pH 7.0 and in saline), always given alone, without any carrier, µg-ng dose ranges and ways of application, intraperitoneal, intragastrical, in drinking water or topically, at the site of injury. In addition, BPC 157 was found to be stable at least 24h in human gastric juice and consequently, because of its anti-ulcerogenic potential in different, but relevant ulcer models, suggested to be novel mediator of Robert's cytoprotection and adaptive cytoprotection (for review see, i.e. [1,5]). Thereby, such kind of unlimited applications of BPC 157 regimens contrasts with the evidence for standard peptides providing that at least in many occasions they need a carrier (one or more) to become effective and furthermore, that their application prefers to be local, at the site of injury, given into the injury defect (for review see, i.e., [44]). With BPC 157 given alone, without a carrier, BPC 157 application strategy (for review see, i.e. [1,5]) considerably overrides the standard peptides and their use with different carriers (i.e., peptide+carrier(s) complex) to establish the therapeutic effect (thereby erroneously) ascribed to the given peptide. Therefore, the activity – methodology dilemma whereby it is difficult to identify the real active part in peptide+carrier complex (peptide, carrier, peptide+carrier complex or neither of them) or specify their particular contribution is not applicable to BPC 157 (for review see, i.e., [44]). Finally, in BPC 157 – standard peptides relation, apart from the evidence that this anti-ulcer peptide may be effective in both upper and lower GI tract injuries (for review see, i.e., [1,5]), involving also a particular sphincter function control [45,46], the key difference appears in the healing outside the GI tract, with marked improvement of healing of tissue injuries (i.e., hypovascular, hypocellular, hyponeurial) such as transected or detached Achilles tendon [26,28-30], transected ligament [23], transected or crushed muscle [24,25,27] or even bone pseudoarthrosis or peridontitis and alveolar bone [47,48] that otherwise would hardly heal.

Thereby, in general terms, providing commonality in healing processes, these healing effects may indicate that it may be likely more effective than the standard agents in the therapy of IBD (Fig. 1).

### BPC 157 in the Ulcerative Colitis

First demonstration was with a single intracolonic administration of trinitrobenzene sulfonic acid (TNBS) and severe colonic damage, characterized by areas of necrosis surrounded by areas of acute inflammation and associated with high myeloperoxidase (MPO) activity, mainly as a reflection of neutrophilic infiltration into the damaged tissue [34]. The administration of BPC 157 significantly reduced the extent of TNBS-induced colonic damage in a dose-dependent manner. Of note, this was associated with a statistically significant and dose-dependent reduction in colonic tissue MPO activity [34]. Subsequently, as an advantage of considering cysteamine as a directly acting cytotoxic agent, intrarectal administration of the cysteamine (200 or 400 mg/kg b.w.) produced severe colon lesions (i.e. transmural inflammation with serosal involvement) in rats

[36,37]. Pentadecapeptide BPC 157 (10 µg or 10 ng/kg b.w., intraperitoneally, intragastrically or intrarectally), given in either regimen, inhibited the severe cysteamine colon lesions, assessed after 30 min, 60 min, 180 min, 24 h, 48 h, 72 h following cysteamine dose [36]. Moreover, BPC 157 also reversed the protracted cysteamine colon injury: the 1 week-regimen (once daily application) started after 1 month post-cysteamine, as well as the 2 weeks-regimen (once daily application), which started after 3 months. The effect on recidive lesion was also tested. These cysteamine lesions may reappear after stopping therapy (after stopping therapy for 3 weeks at the end of 2-weeks regimen started in 3 months-cysteamine female rats) in sulphasalazine group, while this reappearance is markedly antagonized in pentadecapeptide BPC 157 rats (cysteamine-colon lesion still substantially low) [37].

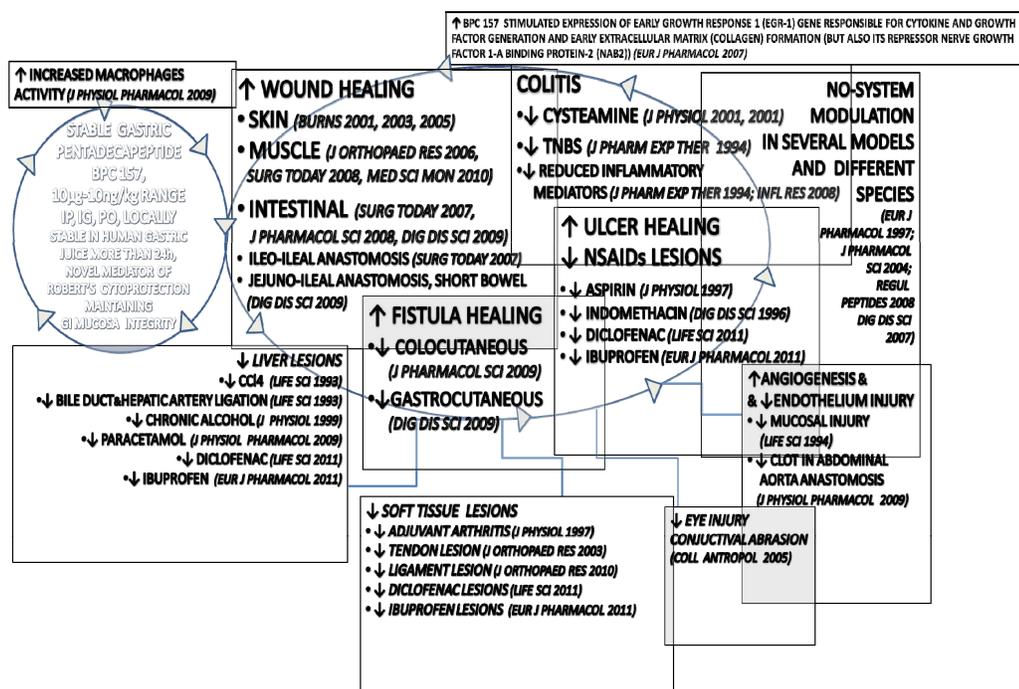
Of note, in these colitis models [34,36,37], the BPC 157's effectiveness is at least partly shared with standard agents. However, being more effective, BPC 157 may be interesting providing the extended cysteamine specific ulcerogenic effect, cysteamine colon/duodenum lesion-link and an extenuation of agents protection from upper to lower part of gastrointestinal tract and vice versa, thus, potentially more important for both further experimental and clinical research [34,36,37]. Therefore, after providing the compelling evidence from ulcerative colitis experimental studies [34,36,37], we will focus on the BPC 157 effect on IBD-intestinal complications (anastomosis healing, short bowel syndrome and fistulas) (where standard agents may be less effective [2-4]) and extra-intestinal association and complications of IBD (i.e., joint/bones, liver, eye) (where standard agents were commonly not considered) [2-4].

### BPC 157 in the Intestinal Anastomosis Healing

In inflammatory bowel disease with compromised healing, the dehiscence of intestinal anastomosis the of healing after a small bowel resection and ileoileal anastomosis still remains a challenging problem which requires a suitable solution [2-4], especially in peptide therapy. The major arguments for the BPC 157 application to rescue poor ileoileal anastomosis healing [31] were various models of ulcer and wound healing, presenting that this peptide is more effective than the standard treatments (for review see, i.e. [1,5]).

In principle, the post-anastomosis course goes with commonly known presentation (i.e., adhesion formation with many neighboring small intestine loops, with the stomach and liver "packed", strong edema, necrosis, increase in the number of granulocytes, but a poor formation of granulation tissue, reticulin, and collagen, and inadequate epithelization) resulting in poor healing with significant delay (i.e., biomechanically weak anastomosis could initially sustain only a small volume and small pressure, without any increase during the first 5 days) and definitive functional incapacity (anastomotic values consistently remain far below healthy values). A particular point considered intestinal passage obstruction and the deterioration of the filling of vessels with blood and therefore leading to empty vessels, absent epithelial regeneration and muscularis (both mucosae and propriae) ending abruptly.

Generally, like in other wound healing studies [6-9], pentadecapeptide BPC 157's significant improvement was both macroscopical and microscopical, and most importantly also biomechanical (i.e., BPC 157-anastomosis without leakage demonstrated markedly higher volume and pressure values, a continuous increase reaching the healthy values already by the end of the first week) providing the tensile strength of anastomosis to be a direct reflection of the successful repair process [49]. In particular for ameliorated anastomosis course, BPC 157 significantly improved all of the parameters of anastomotic wound healing, and it was immediately effective [31]. Generally, these effects appear to



**Fig. (1).** Summary of BPC 157 activities in experimental models that may be essential to achieve a correspondingly higher degree of healing in IBD patients that would antagonize flares in IBD (i.e., NSAIDs-toxicity), induce healing of the imminent complications (i.e., fistulas, anastomosis failure, short bowel syndrome after massive resection) and extra-intestinal association and complications of IBD (i.e., joint/bones, liver, eye). Note, in addition to the very safe profile of BPC 157 (LD1 could be not achieved), it expresses a particular combination of wound healing effect and beneficial effect on colitis (i.e., absent recidive in cysteamine enema induced colitis) with BPC 157 therapy. Likewise, note that BPC 157 healing involves a special wound healing effect, an effect on collagen (increased expression of egr-1 gene responsible for cytokine and growth factor generation and early extracellular matrix (collagen) formation, but also its repressor nab2), NO-system-modulation (in particular, in colocutaneous fistulas healing), angiogenesis, increased macrophages activity, and reduced level of inflammatory mediators. Thus, BPC 157 (regularly effective in the same µg-ng range, applied parenterally, intragastrically, perorally (in drinking water) or locally (topically)) may be an endogenous “fly-wheel” (BPC 157 was suggested to be novel mediator of Robert’s cytoprotection maintaining GI tract mucosal integrity) that may consistently trigger the circle of healing processes to overwhelm healing failure in IBD. ↑ increase; ↓ decrease.

be dose-dependent, present with both microgram and nanogram regimens, and are thereby not random and in congruence with the effectiveness of regimens in other wound healing, with a microgram-beneficial effect having a prior presentation. It seems that these effects (i.e., edema markedly attenuated, the number of granulocytes decreased, subsequent (from day 4 or 5) necrosis attenuated, while granulation tissue, reticulin, and collagen formation substantially increased result with the adhesion formation attenuated, blood vessels filled with blood, and intestinal passage preserved (mild obstruction only temporarily)) present increased and progressed epithelization with strands of newly formed muscle in all BPC 157-rats [31].

An interesting and supportive point for markedly improved ileoileal anastomosis healing [31] may be that BPC 157 in addition to gastrointestinal anastomoses [31,32,50,51], may improve the anastomosis healing of other tissues as well (i.e., nerve [52], vessels [16]).

### BPC 157 in Short Bowel Syndrome

Besides generally compromised healing in inflammatory bowel disease, the malnutrition may be a particular problem, particularly after intestine resection [2-4], thus the research of the short bowel syndrome may be very important. Of note, after massive intestinal resection leading to short bowel, the malnutrition problem is certainly further complicated with poor healing of the intestinal anastomosis and functional incapability of the post-anastomotic remained intestine. Thereby, the major argument and advantage for the BPC 157 application was its strong effectiveness in intestinal anastomosis healing and ability to completely reverse otherwise

poor detrimental anastomosis healing course [11]. Providing that the success of BPC 157 application in rat intestinal anastomosis healing [11] was based on the better effectiveness with peroral application relative to the standard treatments in various models of ulcer and wound (for review see, i.e., [1,5]), in rescuing rats with short bowel (constant weight gain above preoperative values eventually reached the level of healthy rats) we demonstrated the effectiveness of BPC 157 given in intraperitoneal and peroral regimens [31].

On the other hand, the improved anastomosis healing required for the successful rescue of short bowel syndrome was largely neglected and some of the growth factors supposed to alleviate short bowel syndrome, i.e., EGF, have not even been tested for healing of intestinal anastomosis. Unlike common adaptive theory (i.e., [52]) adaptation in whole wall, in reality, adaptive intestine increase, produced by standard peptide growth factors, was limited to only one layer, and not presented in others (for review see [32]). Along with this, in rats with short bowel standard growth factors do not induce weight gain, and therefore, they might only decrease (but not eliminate) weight loss (for review see [32]). Besides, standard peptide growth factors exhibited an imperfect activity requiring a special application route (e.g., subcutaneous pump) [53,54].

Thereby, when pentadecapeptide BPC 157 regimens were given, the downhill post massive resection course (that has not previously been reversed [32,53,54]) was completely counteracted [32] and a consistent weight in rats with short bowel till the level of healthy (0-7-14-21-28 day period) may provide a particular relevance for the adaptive increase of BPC 157 evidenced in all

three intestinal layers (villus height, crypt depth and muscle thickness) where its effect on inner (circular) muscular layer may be particularly specific and important [32]. Namely, whilst after massive intestine resection the constant increase should be common for all of the wall layers of the remaining intestine, the inner circular muscular layer is the only layer that after initial increase would constantly decrease, and therefore, likely relevant for detrimental outcome despite the two (villus height, crypt depth) or four (inner circular and outer longitudinal muscle layer) times increase over preoperative healthy values [32]. Of note, during the remaining intestine adaptation and repair, the effect of BPC 157 on inner smooth muscle accords well with the with strands of newly formed muscle in all BPC 157-rats during ileo-ileal anastomosis healing [31]. Accordingly, BPC 157 treated rats with short bowel exhibited increased breaking strength of anastomosis, and they could sustain a considerably higher volume until leak induction [32].

### BPC 157 in Colocutaneous Fistulas

Colocutaneous fistula as a regular consequence of healing failure is present in diseases such as diverticular disease, Crohn's disease, and colon malignancies, or also in recovery from surgery [55]. Of note, in relation to the success of the standard therapy (in particular infliximab), the rehabilitation i.e., fistula closure, tolerates even remarkable side effects [2-4].

On the other hand, colocutaneous fistula is an anomalous connection between the skin and colon that provides the direct contact of these different, normally separated tissues. Thereby, it presents special new, unusual circumstances and particular healing difficulties [11]. Basically, fistula closure should correlate with the agents' potency to (simultaneously) induce the healing of the skin and colonic wounds [10]. Surprisingly, these were not investigated in experimental studies. Thereby, the colocutaneous fistula closure, skin and colon defect healing with the stable gastric pentadecapeptide BPC 157 (for review see, i.e. [1,5]) therapy (10 µg/kg, 10 ng/kg applied in drinking water or once daily intraperitoneally for 28 days) could have a particular relevance in colocutaneous fistula healing. Given in the same dose range, it ameliorated the skin [6-10] and visceral (i.e., anastomosis) [31,32,50,51] wound healing. Its strong anti-ulcer activity in the whole gastrointestinal tract (for review see, i.e., [1,5]) led to its application in inflammatory bowel disease therapy with no toxic effect, negative limit test, lethal dose (LD1) not achieved, and no side effects in trials (for review see, i.e., [1,5]), thus a very safe peptide profile may be advantageous for colocutaneous fistula therapy.

Furthermore, BPC 157 parenterally or perorally accelerated the healing of colonic and skin defect, and the suitable closure of the fistula, macro/microscopically, biomechanically, and functionally (larger water volume sustained without fistula leaking). This may be related to BPC 157's ability to rescue the NO-system (NOS-blocker, L-NAME aggravated the healing failure of colocutaneous fistulas, skin, and colon wounds) through nullifying the L-NAME effect and thereby the effect of blunted NO generation, which was more effective than applications of L-arginine, the NO-precursor [11].

### BPC 157 Antagonizes NSAIDs-Toxicity

Besides counteraction of bleeding aspirin-gastric ulcers [39], BPC 157 also counteracts other NSAIDs-toxicity, using the same dose range [39-43]. These include gastric and small intestine ulcers (i.e., induced by indomethacin, diclofenac, ibuprofen [39,40,42,43]), hepatotoxicity (paracetamol, diclofenac, ibuprofen) [41-43] and encephalopathy (paracetamol, diclofenac, ibuprofen) [41-43]. Thus, it is likely that BPC 157 may accordingly antagonize also the NSAIDs flares in IBD.

Therefore, after reviewing BPC 157/NSAIDs relation, summarizing the topic of BPC 157 and IBD-intestinal complications may have particular emphasize. With summarizing advanced anastomosis healing, reversed short bowel syndrome and fistula healing [11,31,32] in relation to BPC 157 and likely BPC 157 advantageous effectiveness in further IBD therapy, particularly providing BPC 157 on NSAIDs-toxicity [39-43], we should emphasize the increased tensile strength of anastomosis. This should be considered as a direct reflection of the successful repair process [31,49], the counteraction of an escalating short bowel syndrome by BPC 157 (constant weight gain, grossly, microscopically, biomechanically) as a direct reflection of the successful both the adaptive and repair process [31], fistulas as general indication of an underlying active disease (for review see, i.e., [11,55]), and thereby BPC 157 induced fistula closure could be perceived a solution of underlying active disease using both parenteral and peroral application BPC 157 regimens. This should be obviously supported by consistent antagonization of the toxicity induced by various NSAIDs [39-43].

In support, BPC 157 may also accelerate the healing of gastrocutaneous fistulas, leading to rapid healing of the skin as well as the stomach defect. Therefore, this will result in successful fistula closure, and no fistula leaking upon maximal stomach fulfilling and distension, thereby indicating that this healing ability may be common in both upper and lower gastrointestinal tract [56].

Finally, pursuing the view that the proof of efficacy should be the proof of etiology, particularly when obtained without toxicity (LD1 could be not achieved in BPC 157 toxicity study) [1,5], we should conclude that BPC 157 may be a suitable candidate to markedly improve IBD therapy.

On the other hand, if proving efficacy can prove the etiology, then aiming BPC 157 therapy to improve IBD therapy should consider also the extra-intestinal association and complications of IBD (i.e., joint/bones, liver, eye).

### Extra-Intestinal Association and Complications of IBD (i.e., Joint/Bones, Liver, Eye) and BPC 157

Providing that the therapy of extra-intestinal complications of IBD (i.e., joint/bones, liver, eye) remains outside of the focus of the current therapy [2-4], we should instead elaborate the suggested BPC 157 – egr-1-naB2-collagen-wound healing-endothelium-NO-system relation to healing (for review see, i.e., [1,5]) (i.e., BPC 157 interaction with NO-system was established in several models and several species [10-15] while NO-system is commonly proposed to have an important role in wound healing and IBD [11]), that may be responsible for the supposed higher BPC 157 efficacy in further IBD therapy and furthermore, briefly review further experimental arguments suggested from extra-intestinal association and complications of IBD (i.e., joint/bones, liver, eye) [2-4].

For instance, BPC 157 may both prevent and reverse adjuvant arthritis in rats [39] (noteworthy, attenuation of NSIDs-gastrointestinal ulcers in the same dose range may certainly contribute to the generalization of beneficial effect of BPC 157 (for review see, i.e., [1,5])). There is a marked improvement of soft tissue injuries (i.e., hypovascular, hypocellular, hyponural) such as transected tendon, transected ligament, transected muscle [24-30]. Likewise, BPC 157 may heal pseudoarthrosis in rabbits [47], and very recently, in rat periodontitis, BPC 157 treatment significantly reduced both plasma extravasation, histological alterations and alveolar bone resorption [48].

BPC 157 may protect liver against different noxious events, mild (fatty liver) till severe (necrosis), providing a wide range of protection against ischemia, bile duct ligation, formation of free radicals (CCl<sub>4</sub>, paracetamol, diclofenac), severe intestinal lesions and increased toxins formation (diclofenac), and severe hepatic

encephalopathy (paracetamol, diclofenac, ibuprofen). Effects are also observed in continuous alcohol drinking, portal hypertension, insulin over-dose-hypoglycemia and glycogen deprivation [17,39,40,42,43,57-60]. Generally, BPC 157,  $\mu\text{g-ng}$ -regimens given alone intraperitoneally, intragastrically, or per-orally in drinking water, dose-regimens and application methods which have been successfully used before in other experiments, in the healing process convert rapidly from a failure to a success permitting liver function in either condition (for review see, [i.e., 1]).

BPC 157 may be strongly effective in corneal healing and eye healing [61].

Finally, the angiogenic effect may be also responsible for the beneficial effect of BPC 157 obtained in anastomosis healing, short bowel syndrome and fistula healing [1,5], and thereby worthy to IBD therapy.

In this, we should emphasize that most of BPC 157's beneficial effects on wound healing were noted in wounds that would otherwise not heal [6-9,16-30]. Thereby, the healing obtained in the worst conditions (i.e., severe burns, significantly damaged blood vessels supply and/or hypocellular, hypovascular and hyponeural tissue and/or severely compromised healing condition (systemic corticosteroid, diabetes mellitus)) always exhibit a shift toward the left in blood vessel presentation that may be accordingly considered to be a potent angiogenic response essential in BPC 157 healing effect and relevant for the improvement of IBD therapy (for review see, i.e., [1,5]).

The final proof for endothelium protection [16-22], maintenance of blood flow and thereby prevention of severe ischemia (i.e., filling of vessels in anastomosis healing) may be the evidence obtained after 24 h following abdominal aorta termino-terminal anastomosis, showing that BPC 157 (10  $\mu\text{g/kg}$ ) may also decrease clot formation after aortic anastomosis and preserve walking ability and muscle strength when given as a bath immediately after aortic anastomosis creation or given in rats with a formed clot obstructing more than a third of the aortic lumen. These animals also expressed severely impaired walking ability, painful screaming and weak muscle strength. Within a 3 minute post-application interval, pentadecapeptide BPC 157 rapidly recovered the function of lower limbs and muscle strength while no clot could be seen in rats at the anastomosis site [16].

Thus, it seems that the noted beneficial effects on extra-intestinal association and complications of IBD (i.e., joint/bones, liver, eye) along with other mentioned effects (i.e., endothelium protection, blood vessels integrity, angiogenesis) could be convincingly considered as hallmarks of the higher efficacy of BPC 157 in further IBD therapy.

## CONCLUSION

Therefore, we suggest that the lessons from initial clinical trials and quite extensive animal studies (BPC 157 vs. standard peptides; BPC 157 in the ulcerative colitis; BPC 157 in the intestinal anastomosis healing; BPC 157 in short bowel syndrome; BPC 157 in colocolic fistulas; BPC 157 antagonizes NSAIDs-toxicity; Extra-intestinal association and complications of IBD (i.e., joint/bones, liver, eye) and BPC 157) should indicate BPC 157's high significance in further IBD therapy. Also, this supportive evidence (i.e., no toxic effect, limit test negative, lethal dose not achieved, no side effect in trials (for review see, i.e., [1,5])) may counteract the caution commonly exercised with the use of some of the peptidergic agents, particularly those used on a long-term basis [52]. For instance, the epidermal growth factor has been shown to promote growth of several tumor cell lines [62], and the development of hyperplastic lesions in the colons of subjects treated with GLP-2 for prolonged periods of time needs careful surveillance [63], while BPC 157 inhibits growth of several tumor

cell lines and counteracts the effect of vascular endothelial growth factor (VEGF) [64].

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