

Gastric pentadecapeptide BPC 157 in cytoprotection to resolve major vessel occlusion disturbances, ischemia-reperfusion injury following Pringle maneuver, and Budd-Chiari syndrome

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Cytoprotective gastric pentadecapeptide BPC 157 resolves major vessel occlusion disturbances, ischemia-reperfusion injury following Pringle maneuver, and Budd-Chiari syndrome

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Abstract

The stable gastric pentadecapeptide BPC 157 counteracts various venous occlusion-induced syndromes. Summarized are all these arguments, in the Robert's cytoprotection concept, to substantiate the resolution of different major vessel occlusion disturbances, in particular ischemia-reperfusion injury following the Pringle maneuver and Budd-Chiari syndrome, which was obtained by BPC 157 therapy. Conceptually, there is a new point, namely, endothelium maintenance to epithelium maintenance (the recruitment of collateral blood vessels to compensate for vessel occlusion and reestablish blood flow or bypass the occluded or ruptured vessel). In this paper, we summarize the evidence of the native cytoprotective gastric pentadecapeptide BPC 157, which is stable in the human gastric juice, is a membrane stabilizer and counteracts gut-leaky syndrome. As a particular target, it is distinctive from the standard peptide growth factors, involving particular molecular pathways and controlling VEGF and NO pathways. In the early 1990s, BPC 157 appeared as a late outbreak of the Robert's and Szabo's cytoprotection-organoprotection concept, like the previous theoretical/practical breakthrough in the 1980s and the brain-gut axis and gut-brain axis. As the time went on, with its reported effects, it is likely most useful theory practical implementation and justification. Meantime, several reviews suggest that BPC 157, which does not have a lethal dose, has profound cytoprotective activity, used to be demonstrated in ulcerative colitis and multiple sclerosis trials. Likely, it may bring the theory to practical application, starting with the

and experimental

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initial argument, no degradation in human gastric juice for more than 24 h, and thereby, the therapeutic effectiveness (including *via* a therapeutic per-oral regimen) and pleiotropic beneficial effects.

Key Words: Gastric pentadecapeptide BPC 157; Cytoprotection; Major vessel occlusion disturbances; Pringle maneuver; Budd-Chiari syndrome; Therapy

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Core Tip: Summarizing the essential epithelium and endothelium protection interplay described in Robert's and Szabo's cytoprotection concept, and the role of the stable pentadecapeptide BPC 157 as a likely mediator, we suggest that BPC 157 may be a useful cytoprotective therapy. The hope is that it could finally bring into practice the huge theoretical importance of all aspects of the cytoprotection concept. Conceptually, there is a new point to discuss, namely, endothelium maintenance to epithelium maintenance (recruitment of collateral blood vessels to compensate for vessel occlusion and reestablish blood flow or bypass the occluded or ruptured vessel). BPC 157 counteracts various venous occlusion-induced syndromes, as well as inferior caval vein syndrome, ischemia-reperfusion injury following Pringle maneuver, and Budd-Chiari syndrome in rats. Activation of the alternative collateral pathways to bypass occlusion and reestablish alternative blood flow, results in the counteraction of the consequent syndromes. The severe venous occlusion-induced disturbances, the high portal and caval hypertension, aortal hypotension, arterial and venous thrombosis, both peripherally and centrally, and various organ lesions (*i.e.*, gastrointestinal, liver, kidney, heart, and brain) were all attenuated and/or eliminated. Furthermore, this particular beneficial effect may be competing with the Virchow's triad that can be a common presentation [*i.e.*, duodenal venous congestion lesions, perforated cecum, ischemic/reperfusion colitis, bile duct ligation-induced liver cirrhosis and portal hypertension, temporary portal triad occlusion (ischemia-reperfusion injury following the Pringle maneuver), and suprahepatic occlusion of the inferior caval vein (Budd-Chiari syndrome)]. The resolution of these various venous occlusion-induced syndromes emphasizes the evidence that as the native cytoprotective gastric peptide and a stable gastric pentadecapeptide membrane stabilizer, BPC 157, which is stable in the human gastric juice and counteracts gut-leaky syndrome, is a particular target and easily distinguished from standard peptide growth factors, involving particular molecular pathways, and specifically controlling the VEGF and NO pathways, in particular the prostaglandin pathway.

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INTRODUCTION

The current review aims to evaluate whether the stable gastric pentadecapeptide BPC 157, which has consistent efficacy in the co-, pre-, and post-treatment regimens, with a rapid onset of the therapeutic effect, as well as the parenteral and per-oral effectiveness, may bring the Robert's cytoprotection theory into practical application[1].

As previously stated[1], all of the studies to date that have tested the stable gastric pentadecapeptide BPC 157 as a treatment have demonstrated extremely positive healing effects for various injury types in numerous organ systems. Its practical significance as a prototypic cytoprotective agent and an important mediator of Robert's cytoprotection[1], and its contribution to resolving Selye's stress response[1], and brain-gut and gut-brain axis activity have been reported[2]. Additional particular points are its wide interactions with the nitric oxide (NO) system[1] and prostaglandin

system and counteraction of the toxicity of non-steroidal-anti-inflammatory drugs[1]. Its therapeutic effects on fistula healing[1] and damaged skin, muscles, tendons, ligaments, and bone comparable to those in the gastrointestinal tract[3,4] and wound healing, in particular[3], are also reviewed. The counteraction of tumor-induced muscle cachexia and the signaling process implicated in cancer cachexia[5] and leaky gut, and its membrane stabilizer and free radical scavenger activity[6] are highlighted. The final focus is on the particular effect of BPC 157 on blood vessels and vessel recruitment[1,7]. In addition, BPC 157, due to its profound cytoprotective activity, which has been demonstrated in ulcerative colitis and applied to multiple sclerosis trials, may be used, since it does not have a lethal dose (LD1)[1,6]. In one of the most recent studies[3], BPC 157 was found to be distributed in the gastrointestinal mucosa, lung, bronchial epithelium, epidermal layer of the skin, and kidney glomeruli by *in situ* hybridization and immunostaining. These data suggest that BPC 157 may have additional regulatory roles in the function of the lungs, kidneys, and skin in humans, in addition to being isolated from gastric juice and primarily acting in the gastrointestinal system[3]. BPC 157 has also been reviewed in several other articles[8].

In the present review, we discuss the cytoprotective activity of the gastric pentadecapeptide BPC 157[1] to resolve major vessel occlusion disturbances, ischemia-reperfusion injury following the Pringle maneuver, and Budd-Chiari syndrome[9-11], providing evidence that it may bring the cytoprotection theory to practical application. On the other hand, as mentioned above, the stable gastric pentadecapeptide BPC 157 perfectly matched with the original Robert's cytoprotective requirements for the stomach, or even extended it[1]. These requirements are the protection of the epithelium ("epithelial pathway") and endothelium ("endothelial pathway"), and the maintenance of gastrointestinal mucosal integrity to obtain a large beneficial effect inside and outside the gastrointestinal tract. Typically, human gastric juice rapidly destroyed standard growth factors within 15 min[12,13]. In contrast, BPC 157, with its essential gastric juice origin and stability in human gastric juice for more than 24 h [12], was matched in the local level (stomach, the permanent maintenance of the mucosal integrity, and thereby the entire gastrointestinal tract)[1]. Therefore, BPC 157 has particular therapeutic effectiveness, including *via* a therapeutic per-oral regimen, and pleiotropic beneficial effects. This local stomach and gastrointestinal tract protection was further extended to the general level (protection of other organs) (cytoprotection to organoprotection)[1]. As previously mentioned, BPC 157 could follow both the "epithelial" and "endothelial" pathways in Robert's cytoprotection[1,7, 12,14].

According to Andre Robert[14] in 1975, the first indication for cytoprotection was the evidence that certain prostaglandins (PGF2 and PGFB, which could not affect gastric acid secretion) protected the gastric mucosa against indomethacin, in a gastric acid-independent manner, *via* a mechanism other than the inhibition of gastric acid secretion[14-16]. Therefore, the term *cytoprotection* pioneered by Robert[14-16] was introduced in 1979 against the noxious effect of both intragastric alcohol application and the use of nonsteroidal anti-inflammatory drugs (NSAIDs). According to Robert's concept, the rapid onset of gastric cytoprotection would be the most remarkable aspect [14-16]. Prostaglandins reduce the development of gastric necrotic lesions when given orally at an appropriate dose as late as 1 min before the administration of absolute ethanol. Knowing this "before but not after effectiveness" as a limitation, Robert appreciated the curing of the already existing lesions as the further possibility[14-16]. The full explanation was provided in a few subsequent reviews[14-16] and the full argument was later substantiated[14-16]. In our view of the new cytoprotection principle, the essential evidence of Robert (epithelial protection) is the remarkable ability of endogenous and exogenous cytoprotective agents (*i.e.*, prostaglandins) to prevent rapidly acute gastric hemorrhagic lesions induced by diverse noxious stimuli such as ethanol, bile acids, hyperosmolar solutions, and NSAIDs such as aspirin or indomethacin. According to the claims of Robert [*i.e.*, cytoprotection preventing mucosal necrosis caused by noxious agents due to the direct damage of cells or a local deficiency of cytoprotective mediators (*i.e.*, prostaglandins)], the cytoprotection concept also goes beyond peptic ulcer therapy[14-16]. Moreover, in Robert's view[14], the demonstration of adaptive cytoprotection suggests that cytoprotection by prostaglandins may be a physiological phenomenon[14]. One milliliter of 20% ethanol (as small irritant) given orally (note, in Robert's publication, "orally" implies administration *via* a tube into the stomach, or rather intragastric application, see Chapter 2.1.3. *Epithelial pathway to adaptive cytoprotection*) to fasted rats 15 min prior to giving absolute ethanol (regarded as a strong irritant) prevented the gastric mucosal necrosis caused by the latter[17]. For the effectiveness of cytoprotective agents, the concept holds the protection of stomach cells (cytoprotection) and other epithelia (organoprotection)

against direct injury to cells induced by various noxious agents[14-16]. In addition, see the notation for the cytoprotection-organoprotection for other agents[18,19].

In the early 1980s, the concept obtained an additional key, the concomitant protection of the stomach endothelium[20,21] or Szabo's vascular injury, as an early pathogenic factor in the development of ethanol-induced gastric hemorrhagic erosions. Demonstration of the vascular injury was seen within 1 min, as was the estimated effect of the agents[20,21]. This vascular point in ethanol-induced gastric lesions was fully elaborated in a series of subsequent reports[22]. Since then, the rapid recovery of damaged endothelium may be considered a shared effect of the cytoprotective agents [23].

Thus, the cytoprotection theory holds that cytoprotective agents should exert direct epithelial and endothelial cell protection inside and outside of the gastrointestinal tract [14-16], *via* the "epithelial pathway" and "endothelial pathway". There is an essential involvement in the stomach protection: Endothelium protection to epithelium protection[14-16]. Each of these pathways originates as a result of the increase in cytoprotective activity, together manifested as an increased therapeutic effect in both the prophylactic process (important for maintaining undisturbed organ function) and the therapeutic process (important for the possible reversal of the damaged tissue to a normal structure, and the interruption of damaging events). Unfortunately, such practical realization of the highly conceptualized theory is lacking. The anticipated huge range of organ lesions that should be counteracted and protection against non-specific lesions[1], as well as the rapid onset of action implemented in the agents' efficacy, as a resolving outcome, remains obscure.

On the other hand, in addition to the proposed role of BPC 157[1,7], within Robert's concept of cytoprotection, different points of view and different highlights can be clearly seen. Certainly, such a multitude illustrates the essential value of the potential application of the concept. The emphasis was on NO, carbon monoxide and hydrogen sulfide[24-26], sulfhydryls (SH)[20,27,28] in parallel with prostaglandins, as well as histamine[23], prostaglandins[17], EP1 and IP receptors[29,30], the healing action of antacid[31], sucralfate[31,32], heat shock protein 70 (HSP70)[33], and the renin-angiotensin system and active angiotensin metabolites[34]. Further illustrative emphases include opioids[35], alpha-2 adrenoreceptors[36], glucocorticoids[20,37-39], thyrotropin-releasing hormone (TRH)[40-43], capsaicin[44-46], dopamine[19,47-51], somatostatin[18,52,53], epidermal growth factor (EGF)[53-55], bombesin[56], ghrelin [17,34,57], cholecystokinin (CCK) and leptin[58,59], melatonin[60], neurotensin[61], fibroblast growth factor (FGF)[62,63], agmatine[64], amino acids[65], second-generation histamine H(2)-receptor antagonists[66], hemeoxygenase-1[67,68], and the molecular basis of alcohol-related gastric and colon cancer (acetaldehyde)[69].

Finally, a historical cytoprotection review, along with many original details, is given by Mozsik[70].

The term cytoprotection was commonly coined in other organ studies, *i.e.*, the heart and brain[71,72], kidney[73], liver[74], eye[75], skin and wounds[76], bone[77], and skeletal muscle[78].

Unfortunately, the multitude of agents supposed to be involved did not resolve the conceptual problems that were initially shown with the prime agents, providing the limited therapeutic potential of prostaglandins in stomach lesions (*i.e.*, prostaglandins might only prevent rather than cure any already established stomach lesions)[14-16]. Likewise, there was an even more limited therapeutic potential in the healing of other organs (prostaglandins were only effective in a few organ lesions)[79-81]. The switching to other cytoprotective agents (*i.e.*, sulfhydryls[19,21], somatostatin[18], EGF [53], TRH[41,67,82], opioids[83], dopamine[50,51,61], and CCK) led to similar incomplete results in both stomach and other organ lesions (for review see[1,7]). Consequently, considering the application and efficacy of standard agents, a considerable gap remains between the theoretical potential and practical realization[1,7]. Considering the supplemental endothelium protection, after initial demonstration in the stomach, no endothelial protection outside the stomach was investigated at the time[22]. Of note, BPC 157 appears to resolve both of these issues, *i.e.*, the "epithelium pathway" and "endothelium pathway" in cytoprotection[1,7], and may both prevent lesion development and cure any established lesions.

Likewise, to illustrate the failed realization of the concept with standard antiulcer agents, in addition to only prophylactic effectiveness in stomach lesions and a few other organs in which effectiveness was shown, the theoretical/practical problem is that standard cytoprotective agents also demonstrated the opposite outcome[42,84]. The intriguing point is the sulfhydryl prototype, cysteamine, and sulfhydryl conceptual involvement[19,21]. Cysteamine is highly protective in alcohol-induced stomach lesions[19,21], but, in contrast, cysteamine application provided the most

valuable standard model for the induction of duodenal[85,86] and colon[87] lesions. Also, we emphasized[1] that Robert's concept[14-17] largely applied the antecedent Selye's stress concept[88,89] which essentially contributed[90] to the introduction of corticosteroid therapy[91]. Of note, both concepts act against various noxious non-specific agents that would induce non-specific lesions[1]. Both concepts also hold organoprotection (Selye's concept of homeostasis that should be reestablished by the stress response[88] *vs* Robert's direct stomach cell protection that should be generalized by the application of cytoprotective agents[14-16]), and adaptation [Selye's small stress that protects against severe stress[89] *vs* Robert's small irritants that protect against strong irritants (adaptive cytoprotection[17])]. However, the essential first mediator of Selye's stress concept[88,89], which would integrate the adaptive bodily stress response and reestablish organoprotective bodily homeostasis, remained undiscovered, and appeared to be a major weakness of the concept that would preclude its practical realization[92,93].

For the classic concepts of Robert and Selye[14-16,88], the adverse effects of the prototype agents (*i.e.*, mediators) appeared to be an additional pitfall. Obviously, protection against direct injury to the cell in Robert's cytoprotection concept[14-16] certainly precludes any adverse effects, which are quite common with the application of prostaglandin analogues[65]. Likewise, the reestablishing of homeostasis (Selye's stress response defined "as such") [88] does not include the adverse effects that have been commonly known for the application of corticosteroids since early times[94]. As BPC 157 appears to be very safe and LD1 was not achieved, with no side effects reported in clinical trials, the possible switching of beneficial effects to negative ones (over-shutting phenomenon) appears to be highly unlikely[1].

However, whatever the pitfalls may be, these two concepts[14-16,88] provided a firm theoretical frame for the development of novel agents and therapies. It should be practically realized and demonstrated, in addition to the local (stomach) beneficial effect, by the agents' pleiotropic beneficial effects[1,7]. If properly followed, it may fulfill the first conceptual beneficial point (starting with Robert's cytoprotection[14-16], local protection and therapy of the stomach and gastrointestinal tract achieved) by the next extended beneficial point (the protection of other organs [epithelia] and the achievement of therapy), and bring them together to a reality that can no longer be disputed.

Thus, in the early 1990s, pentadecapeptide BPC 157[1,7] appeared as a late outbreak of the cytoprotection-organoprotection concept of Robert and Szabo[14-16,18,19], for epithelial and endothelial protection, like the previous theoretical/practical breakthrough in the 1980s[14-16,18,19] and the brain-gut axis and gut-brain axis[3]. As time went on, with its reported effects, BPC 157 could be most useful in the practical implementation and justification of the theory[1]. All arguments were given to bring the long-standing theory into practice, starting with the initial argument of the lack of degradation in human gastric juice for more than 24 h[12], and thereby the therapeutic effectiveness (including *via* a therapeutic per-oral regimen) and pleiotropic beneficial effect[1,7].

BPC 157 IN CYTOPROTECTION

Overall, and in particular for the role and cytoprotective effectiveness of BPC 157, it is safe to speculate that the efficacy and activity limitation of this agent, and thereby its practical application, would be determined by the foundation of the standing concepts, and *vice versa*. Briefly, the agent "runs" within the concept frame, and *vice versa*. Ideally, agent and concept can match completely (as may be seen with the achieved extent of the obtained beneficial effects; cytoprotection can be manifested as a huge range of beneficial effects, both inside and outside the gastrointestinal tract). General pitfalls may be the number of mentioned cytoprotective agents that have previously failed to match the required cytoprotection concept. In general, this means more problems with the use of new agents, and more problems for the concept to maintain its validity and less possibility (enthusiasm and belief) to be once applied. Alternatively, if there were no known agents which fulfilled the requirements of the standing concepts, the agent's efficacy and activity would determine the opposition to the "law" of the standing concepts and form a new relevant concept.

Illustratively, regarding the sympathetic system function, Alhquist's receptor concept[95] (*i.e.*, six catecholamines, and their different order of potency depending on the tissue involved, to anticipate the presentation of the particular alpha and beta receptors) discharged the long-standing "law" of physiology, Cannon's concept of two

mediator substances (sympathin E and sympathin I)[96]. Although there was an overlap of several years, Alhquist's receptor concept accuracy[95] envisaged the development of specific blocking agents in the subsequent years[97], and the consequent regular use of beta blockers in a large range of indications[98]. However, similar general acceptance and applicability did not arrive for the cytoprotection concept, nor was there any proof[99,100], when years later, as alternative gastric acid-nondependent, Robert's cytoprotection theory challenged the peptic ulcer therapy[14-16]. The lack of a practical solution and the absence of any commonly applicable cytoprotective therapy[99,100] mean that the "law" "no acid-no ulcer" and the superiority of H2-blockers were not discharged until the present time[101].

In the early 1990s, BPC 157 was introduced as a pentadecapeptide with cytoprotective effects[1,18,19], many years after the breakthrough of the original concepts of Robert[14-16] and Selye[88]. The surveillance of these two major concepts[14-16,88] and their development and achievements lacking full realization and adequate practical application[92,93,99,100] considered the introduction of BPC 157 to be too late a challenge. Seeing from the achieved perspective of all agents tested as standard cytoprotective agents, it was safe to speculate that a novel agent would hardly achieve a wider range of pleiotropic beneficial effects and drug characteristics that remained elusive for years.

However, conceptually, there is a new point, namely, endothelium maintenance to epithelium maintenance is upgraded to endothelium maintenance to epithelium maintenance (collateral blood vessels to compensate for vessel occlusion and reestablish blood flow or bypass the occluded or ruptured vessel)^[1,7]. The recruitment of collateral blood vessels would compensate for vessel occlusion and reestablish blood flow[1,7,9-11]. BPC 157 counteracted various venous occlusion-induced syndromes[9-11], inferior caval vein syndrome[9], ischemia-reperfusion injury following Pringle maneuver[10], and Budd-Chiari syndrome[11] in rats. This beneficial effect was also shown for other syndromes, *i.e.*, duodenal venous congestion lesions, perforated cecum, ischemic/reperfusion colitis, and bile duct ligation induced liver cirrhosis and portal hypertension[1,7]. The resolution of these various venous occlusion-induced syndromes[1,7,9-11] emphasized the practical evidence. The stable gastric pentadecapeptide BPC 157, as a membrane stabilizer[5], likely acts as the native cytoprotective gastric peptide[1,3,7], which is resistant and stable in human gastric juice[12], and counteracts gut-leaky syndrome[6]. As a particular target, it is distinct from the standard peptide growth factors[3], involving particular molecular pathways [102-105], particularly controlling VEGF and NO pathways[1,106,107], and the prostaglandin pathway[1].

Epithelial pathway in stomach and gastrointestinal tract healing for cytoprotection against direct cell injury produced by direct contact with noxious agents

BPC 157 consistently counteracted the gastric lesions induced by 96% alcohol[1]. Of note, epithelial protection, as direct cytoprotection against direct cell injury produced by direct contact with noxious agents (*i.e.*, alcohol)[14-16], appears to be essential to resolve the follow-up of Robert's stomach cytoprotection ("epithelial pathway") [14-16]. As with Robert's alcohol intragastric application, this was a more advantageous therapeutic effect, overriding previous common limitations shared by standard cytoprotective agents (*i.e.*, prophylactic effect that may only counteract lesion development, but is unable to cure already existing lesions upgraded to the equal therapeutic ability[1]). BPC 157 demonstrated very consistent efficacy in alcohol-induced gastric lesions for co-, pre-, and post-treatment regimens, with a rapid onset of therapeutic effect, thereby providing consistent evidence for undistributed pertinent and specific effects, such as protection and healing, and the likely positive effects of an unusually high range[1]. This essential stomach point is confirmed and appreciated by others[108]. The BPC 157 equipotent (co-, pre-, and post-treatment regimens, per-oral and parenteral) beneficial effect is particular. There are constant interactions with the NO system and capsaicin-sensitive somatosensory neurons, since it consistently appears in naive rats as well as in those challenged with NOS blockade (NOS blocker L-NAME), NOS substrate L-arginine (NOS over-activity), NO system immobilization (concomitant application of L-NAME and L-arginine), capsaicin (as newborn or adult), or small exogenous or endogenous irritants[1,7]. A comparable beneficial effect was also achieved *in vitro* (denervated (isolated) gastric mucosal cells)[109,110].

Further supporting evidence included a strong reduction of the Monastral blue staining in ethanol-treated rats and, thereby, endothelium maintenance[1,7] and comparable beneficial effect in the stress gastric ulcer model[1] and cysteamine-duodenal ulcer model[1]. The same high efficacy was observed for both intragastric

and intraperitoneal regimens[1,7]. The evidence that BPC 157 fully counteracted NSAID-induced gastric and intestinal lesions is consistent with the prostaglandin requirement of Robert's model, and the beneficial effect of BPC 157 in the entire gastrointestinal tract[1]. Also, in addition to cysteamine- or ischemia/reperfusion-induced colitis[1,7], BPC 157 counteracted trinitrobenzene sulfonic acid (TNBS)[111] or iodoacetamide[112,113]-induced ulcerative colitis. Of note, the beneficial effect of BPC 157 is long-lasting, and may also counteract ulcer recidivation (*i.e.*, cysteamine ulcerative colitis)[1,7]. Also important for the issue of cytoprotection is the evidence that BPC 157 may counteract stomach ulcer and induce ulcer regression (*i.e.*, clopidogrel-induced)[114], as recently demonstrated in another prototype model of direct injury, Okabe's direct acetic acid application into stomach-induced gastric lesions[115,116], which is also commonly used in cytoprotection studies[1].

Provided that the essential point for lesions in Robert's cytoprotection model would be the injury made by direct contact (damage) to the cells[14-16], the perforation lesion instantly made by surgery is thereby a prototype[1]. The healing of perforated injury by the application of BPC 157 is an important conceptual point[1]. Further consequent evidence includes the healing of skin wounds and other wounds[1,3]. Importantly, proper wound healing includes the achievement of all four major events (vascular constriction, loose platelet plug, fibrin mesh to ensure stability of platelet plug, and dissolution of the clot) that occur in a set order following the loss of vascular integrity [3]. As a result, an agent applied in wound healing, such as stable gastric pentadecapeptide BPC 157, which is shown to be effective in wound healing, should also be effective in bleeding disorders[3].

Together, these consistent beneficial effects clearly indicated a full potential, in addition to the achievement of local protection and therapy of the stomach and gastrointestinal tract[1], toward Robert's point (other organ (epithelia) protection and therapy achieved)[14-16]. Of note, as pointed out, these studies indicated the use of the stress gastric ulcer models as a "cytoprotective" model (*i.e.*, not related to gastric acid secretion)[39]. The significance of the stress gastric ulcer models is fairly described in several reviews[117-121]. Likewise, the connection with the prostaglandin system (and thereby, Robert's cytoprotection) is fully substantiated[31]. For BPC 157, the use of the prolonged restraint stress procedure[1] was important, provided that the use of the restraint stress methodology by gradually modulating/increasing the level of the stress[39,120] (*e.g.*, usual cold + 3 h[39,120] *vs* 48 h restraint stress[1]) fully highlighted its efficacy[1]. Thereby, we could consistently suggest the effectiveness of BPC 157 over the application of standard H2-blockers or dopamine agonists[1].

Likewise, providing protection against the possible negative influence of gastric acid (hyper)secretion, in addition to the counteraction of Shay stomach ulcers induced by pylorus ligation[122] (but no influence on gastric acid secretion[123]) by BPC 157, there is some antagonism of the cysteamine-induced duodenal ulcer[1]. Since the Szabo's study[86], cysteamine-duodenal ulcers are commonly related to gastric acid hypersecretion[124-127]. However, we should consider stress lesions[85] as cytoprotection before Robert's cytoprotection[14-16], and thereby, Selye's "stress view"[85]. The introduction of cysteamine duodenal ulcers in rats will overcome the problems arising from multiple gastric erosions as the most characteristic rat gastrointestinal manifestations of exposure to stress, and would closely mimic human "stress ulcers", which are frequently localized in the duodenum[85]. Selye and Szabo considered the duodenal ulcer potency of various agents, and also emphasized "some relation to nonspecific stress" since cysteamine was the most potent agent of the other agents assessed (acetanilide, allylchloride, acetaminophen, 4,4-diaminodiphenylmethane, propionitrile, and 3,4-toluendiamine) which were capable of inducing such lesions [85]. Yet, at that time, no mention was made on any influence of dopamine or gastric acid secretion[85]. With such particular "stress" notation to the duodenal lesions[85], initiation goes along with the emergence of the histamine, and the H2 receptor blocker-mediated resolution of peptic ulcers[128]. The subsequent cysteamine report by Szabo in the *Lancet* revealed the dopamine and gastric acid hypersecretion background, meaning that it became a seminal dopamine paper[86].

Also, this beneficial effect in cysteamine-induced duodenal ulcers[1] combined BPC 157 application with the dopamine system. Szabo provided cysteamine as a dopamine antagonist and its close similarity with the parkinsonogenic neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) (that also induced duodenal ulcers)[129, 130] in support of the theory holding schizophrenia, Parkinson's disease, and ulcer disease as dopamine system failures, and dopamine antagonists (ulcerogenic potential)/dopamine agonists (therapy) in peptic ulcer therapy[131]. Lately, the interaction of BPC 157 with the dopamine system was reviewed[2]; BPC 157 counteracted the effect of neuroleptics (haloperidol), MPTP, and reserpine (*i.e.*,

akinesia, catalepsy, hypothermia, and gastric lesions). Also, BPC 157 counteracted the models resembling positive-like symptoms of schizophrenia[55], and haloperidol-induced catalepsy and gastric ulcers[2]. This effect, as a close interaction with dopamine system functioning, was able to determine an active gut-brain axis or brain-gut axis functioning[2]. It should be noted that BPC 157 also counteracted various encephalopathies and behavioral disturbances, and may therefore represent essential brain-gut and gut-brain axis activities[2]. As an extension of the therapeutic effect, BPC 157 also counteracted the typical and atypical neuroleptic-induced arrhythmias, QTc-interval prolongation[1]. The counteraction of the prolonged QT interval appeared as part of the large therapeutic effect of BPC 157 on the heart disturbances noted in the prevention and reversal of doxorubicin-induced chronic heart failure[1], and the counteraction of various arrhythmias[1], including those induced by venous occlusion [9-11].

Subsequently, again with the 96% alcohol-induced gastric lesion[1], the cytoprotective effect of BPC 157 was closely related to the NO system that should have an essential role in the maintenance of gastrointestinal mucosa integrity, and, more importantly, in endothelial functioning[1,8]. BPC 157 induced NO release from homogenate supernatants of the gastric mucosa from the rat stomach, which is particularly resistant to the NOS blocker N(G)-nitro-L-arginine methylester (L-NAME), and may counteract the NOS substrate L-arginine-induced NO over-release[1]. This particular interaction may be seen in various models and species with the ability of BPC 157 to counteract the adverse effects of L-NAME and L-arginine application[1].

Also, an essential point to remember in the cytoprotective effect of agents is capsaicin-sensitive afferent neurons[45,46], which regulate vascular function in many somatic and visceral tissues, including the regulation of local blood flow in the gastrointestinal tract. Thereby, the important point is that the beneficial effect of BPC 157 in gastric lesions induced by ethanol, restraint stress, or indomethacin was combined with the maintained as well as restored capsaicin-sensitive afferent neurons [1]. Quite recently, this cytoprotective notation was confirmed with the evidence that BPC 157 acts *via* inhibition of the release of enteric serotonin, an increase in the rat and human survival rate of cultured enteric neurons, and the proliferation of cultured enteric glial cells (EGCs)[132]. It was suggested that the inhibition of the release of enteric serotonin may be related to the release of serotonin noted in several brain areas (*i.e.*, nigrostriatum) after the administration of BPC 157[2,132].

Together, these findings clearly indicate a complex involvement of BPC 157 in the practical realization of cytoprotection as a non-gastric acid dependent phenomenon and “direct cell injury to cell – direct cell protection” principle. Furthermore, unlike its ulcerogenic effect ascribed to gastric acid hypersecretion[86], we showed that the application of cysteamine after gastrectomy induced duodenal ulcers in gastrectomized rats, and BPC 157, as well as all standard anti-ulcer agents, may clearly antagonize these cysteamine-induced ulcers in gastrectomized rats[1]. Interestingly, sialoadenectomy abolished the beneficial effect of standard antiulcer agents on cysteamine-induced duodenal ulcers, while BPC 157 was also effective in sialec-tomized rats[1]. As mentioned above, further evidence showed cysteamine enema-induced ulcerative colitis[1]. Thus, these findings may be used as a full argument that cysteamine-induced ulcer appears as originally suggested (stress ulcer, non-gastric acid-dependent)[5,8] while cytoprotection, as the non-gastric acid-dependent phenomenon and “direct cell injury to cell – direct cell protection” principle, is continuously operating[1].

Epithelial pathway for innate cytoprotection both inside and outside the gastrointestinal tract

The wider range of BPC 157 therapy[1,7] follows the definition of the innate cytoprotective potential in additional circumstances (*i.e.*, other epithelial healing), which has to combine the healing of different tissues, and is thus a pleiotropic beneficial effect[14-16]. Provided that cytoprotection represents a huge range of beneficial effects as the prototype model[1], there was a consistent demonstration of the strong therapeutic effect of BPC 157[1]. As emphasized, it not only occurred in the entire gastrointestinal tract[1,2], but also in various liver lesions, acute pancreatitis, and heart, lung, and kidney disturbances[1]. The consistent beneficial effects that include a considerable number of models may clearly verify the large range of therapeutic effects[1]. For instance, there are therapeutic effects in the liver lesion network against prolonged restraint stress, bile duct and hepatic artery ligation, CCl₄ application, chronic alcohol drinking, NSAID over-dose application, insulin over-dose, and bile duct ligation-induced cirrhosis[1]. In particular, the beneficial effects occur against ischemia-reperfusion injury following Pringle maneuver[10], and Budd-Chiari syndrome[11] in

rats. Acute pancreatitis models were represented by bile duct ligation or lower esophageal and pyloric sphincter dysfunction[1]. As already mentioned, heart disturbance counteraction[1] was based on doxorubicin-induced chronic heart failure [57], and the counteraction of various, quite distinctive arrhythmias. This may be clearly seen providing the wide range of noxious events tested (*i.e.*, digitalis, hyperkalemia, bupivacaine, and lidocaine)[1] and venous occlusion procedures applied[9-11]. Likewise, the lung lesion counteraction is based on edema of the interstitium, and substantial dilatation and congestion of the capillaries in the alveolar septum in the lung of rats with venous occlusion syndromes[10,11]. If not corrected, the lung congestion appears as a common outcome (*i.e.*, time-dependent and time-independent features that can be acute respiratory distress syndrome exudative phase features); acute lung injury is a primary component of multiple organ dysfunction syndromes triggered by intestinal ischemia-reperfusion, which results in high mortality and acute lung injury[133,134].

Likewise, as a general follow-up of Robert's cytoprotection, the BPC 157 wound healing studies appear to be well founded[1,3]. As well as gastrointestinal ulcers, consistent evidence includes various skin wounds. In addition to the incisional wound and deep burns and fistula wounds[1,3], there were also diabetic ulcers[102,135] and alkali wounds[105]. These beneficial effects also include the healing of muscle (*i.e.*, the healing of the transected, crushed and denervated muscle), tendons (transected Achilles' tendon and Achilles' tendon detached from the calcaneus), ligaments (transected medial collateral ligament), and bone (alveolar bone loss and radial pseudoarthrosis)[3]. The delivery of BPC 157 was through local (*i.e.*, cream application) and systemic (*i.e.*, intraperitoneally, or intragastrically, or per-orally in drinking water) methods[1,3]. The therapeutic effects of BPC 157 on tendon and muscle healing was also investigated[3,103,104,107]. Moreover, there is a strong practical distinction from the standard angiogenic factors[3]. As pointed out, bFGF, EGF, and VEGF gastrointestinal tract studies demonstrated improved healing[3]. However, most of their corresponding studies on tendon, muscle, and bone injuries provide evidence of their increased presentation along with various procedures used to produce beneficial effects, compared to fewer studies *in vitro*[3]. *In vivo* healing evidence of these standard angiogenic growth factors was limited, commonly to local application. Evidently, providing the use of different carriers with corresponding peptides, there is an obvious attribution problem due to different combinations of peptide + carrier complex. Thereby, for the standard growth factors and use of different carriers, there is inadequate evidence due to diverse healing evidence with diverse carriers and delivery systems[3]. Contrary to this, BPC 157, using the same regimens as gastrointestinal healing studies (always given alone, without carrier), improves tendon, ligament and bone healing, accurately implementing its own angiogenic effect in healing[3]. Important for the particular effect on angiogenesis (particular in consideration of the corneal avascularity as "angiogenic privilege", no formation of corneal neovascularization which is essential for corneal wound healing)[136], later studies also included corneal wound healing and maintained corneal transparency (rescued total debridement of the corneal epithelium and perforating corneal incisions)[3]. The evidence that BPC 157 eye drops successfully close perforating corneal incisions in live rats is consistent with the cytoprotection/endothelial/mucosal protection model[3]. Regardless of its complex function in the corneal endothelium, endothelial maintenance by BPC 157 is also implicated in the healing of corneal ulcers in live rats [3]. Since this model is sensible, we suggest that BPC 157 should have tissue-specific healing effects[3]. Thus, we can envisage a particular healing potential in cytoprotection terms. From the method viewpoint[1,3], all of these lesions are within the scope of Robert's direct cell injury produced by direct contact[14-16].

In addition, there is quite indicative evidence about the simultaneous healing of different tissues. There is healing of various anastomoses (vessel, nerve, and gastrointestinal tract) and of various fistulas (surgically induced by defects and anastomosis creation), both external and internal[1]. Together, these findings showed that this additional extent (*i.e.*, the healing of other epithelia) may be combined in the simultaneous healing of different tissues, such as the simultaneous healing of fistula defects and the closing of fistulas[1]. A particular point is that these rat fistulas are severe, considering the significant size of the defect relative to the small size of the corresponding rat tissue[1]. Illustratively, rectovaginal fistulas in rats, with a 5 mm defect *vs* a 2.4 cm vaginal length, result in long-lasting defects and spontaneous patency of the fistula, leading to fecal matter leaking through the vagina; this actually mimics severe fistulas that may not spontaneously heal, thereby clearly emphasizing the beneficial effect of BPC 157[1].

Further, for BPC 157, in an additional cytoprotective extent (*i.e.*, other epithelia healing), epithelium protection is based on the extended relevance of the intragastric alcohol or NSAIDs on the stomach lesions commonly used in Robert's cytoprotection studies[1,14-16]. Namely, Robert's first epithelium protection, or the direct cell protection against cell injury produced by direct contact with the noxious agents, used intragastric alcohol or NSAIDs to induce stomach lesions[14-16]. Consequently, further evidence toward an additional extent (*i.e.*, other epithelia healing) follows other adverse effects of alcohol and NSAIDs and their consistent counteraction[1,7].

In addition to the 96% alcohol intragastric application-induced gastric lesions, BPC 157 largely counteracted chronic alcohol drinking-induced stomach lesions, liver failure, and portal hypertension, providing evidence that it may act as an alcohol antagonist[1]. Likewise, BPC 157 promptly counteracted acute alcohol (4 g/kg intraperitoneally) intoxication (*i.e.*, quickly produced and sustained anesthesia, hypothermia, increased ethanol blood values, 25% fatality, 90-min assessment period) given before or after ethanol[1]. In addition, BPC 157 counteracted chronic (withdrawal) alcohol intoxication, and was suggested as an alcohol antagonist[1], peripherally and centrally (of note, BPC 157 may attenuate the effect of thiopental anesthesia)[2].

Confronted with the over-dose application of various NSAIDs[1], similar beneficial effects occurred against various gastrointestinal lesions, and liver and encephalopathies; the worst damaged areas showed the most evident therapeutic effect[1]. Prolonged bleeding, consequent thrombocytopenia, and thrombocyte malfunctioning were also attenuated and/or counteracted[1,3,7]. Therefore, it seems that BPC 157 may particularly affect the functioning of the prostaglandins system[1,3,7] (interestingly, unlike NSAIDs and corticosteroids, BPC 157 strongly prevented adjuvant arthritis development and reversed the already formed adjuvant arthritis in rats[1]). The final clue may be that BPC 157 counteracted indomethacin-induced leaky gut syndrome[6]. It acts *via* increasing tight junction protein ZO-1 expression, and transepithelial resistance, inhibiting the mRNA of inflammatory mediators (*iNOS*, *IL-6*, *IFN γ* , and *TNF- α*), and increasing the expression of HSP 70 and 90, and antioxidant proteins, such as HO-1, NQO-1, glutathione reductase, glutathione peroxidase 2, and GST-pi[6]. Considering the importance of the leaky gut as an essential mechanism responsible for various severe systemic diseases, this may fully substantiate the significance of BPC 157 in the realization of that additional cytoprotective extent (*i.e.*, other epithelia healing)[6]. Also, BPC 157 counteracted other encephalopathies induced by various noxious events (insulin over-dose, cuprizone, multiple sclerosis mimicking neurotoxin, magnesium over-dose, brain trauma, spinal cord compression, and stroke)[1,2].

Epithelial pathway for adaptive cytoprotection

We also demonstrated that BPC 157 may regulate cytoprotection adaptation processes (adaptive cytoprotection)[1], functioning of the endogenous adaptive processes essential for permanent mucosal maintenance, and afford defensive reactions that start after any injurious event[1]. This follows Robert's connotation about the cytoprotection as a physiologic process[14-16] based on the adaptive cytoprotection evidence of Robert's small irritant to the stomach that precedes and protects against any subsequent major injurious event (*i.e.*, Robert's strong irritant to the stomach)[17]. Evidently, cytoprotective agents should have a more extensive action, participate in Robert's first epithelium protection, exhibit direct cell protection against cell injury produced by direct contact with noxious agents, and also participate in adaptive cytoprotection, in the next defensive reaction, and afford its final beneficial effects (*i.e.*, permanently attenuated lesion consequences)[1]. Thus, whatever the small irritant may be, whether exogenous (mild alcohol) or endogenous (*i.e.*, accumulated gastric juice, gastric acid, *i.e.*, made by gastrojejunal anastomosis), BPC 157 administration strongly contributed to the final attenuation of stomach lesions[1]. Thus, BPC 157 strongly contributes to and improves the presentation of adaptive cytoprotection processes[1]. Specifically, BPC 157 would improve adaptation processes in the damaged intestine, through a prostaglandin-related process, as it may be strongly aggravated by the application of NSAIDs[1]. In rats with short bowel surgery, the BPC 157 therapy, per-oral (in drinking water) and parenteral, causes constant weight gain (even more than preoperative values), with all three wall layers accordingly increased (*i.e.*, villus height, crypt depth, and muscle thickness [inner (circular) muscular layer] also increased), but no difference in jejunal and ileal diameters, and increased anastomosis strength. These beneficial effects of BPC 157 (*i.e.*, the weight gain in the BPC 157 rats with short bowel, all three wall layers accordingly increased) appear to be particular[1]. Namely, standard growth factors [even using a special application route (*e.g.*, subcutaneous pump)][137,138] at best may induce a decrease in weight loss[139-

142], with an increase in one layer, but not in the other. There is also some caution about the use of peptidergic agents, and adaptation processes, particularly on a long-term basis[140]. There is some growth of several tumor cell lines (EGF)[143,144], and hyperplastic lesions in the colon (subjects treated with GLP-2[145]). In contrast to adequately controlled adaptive processes, supportive evidence for BPC 157 (*i.e.*, BPC 157 administration showed no toxic effect and was limit test negative, with LD1 not achieved, and no side-effects in trials[1,3]) shows that it inhibits the growth of several tumor cell lines and counteracts the tumor-promoting effect of vascular endothelial growth factor (VEGF)[1,4]. In mice with C26 colon adenocarcinoma, BPC 157 counteracted tumor-cachexia and markedly prolonged survival[5]. BPC 157 afforded significant mitigating action against cancer cachexia-induced muscle degeneration, inflammation, and catabolism. BPC 157 significantly corrected deranged muscle proliferation as well as myogenesis, counteracted an increase in proinflammatory cytokines such as IL-6 and TNF- α looking at muscle metabolism relevant to cancer cachexia, as well as any changes in the expression of FoxO3a, p-AKT, p-mTOR, and P-GSK-3 β [5]. Also important for its likely control of the adaptation processes, and prostaglandin-system function, in the short bowel rats, BPC 157 may counteract gastrointestinal lesions and the concomitant liver and brain lesions, and the additional aggravation that would otherwise appear with the application of diclofenac[1].

Also, it is possible that BPC 157 would afford an adaptive cytoprotective reaction regardless of the site of its initiation in the gastrointestinal tract[1]. Supporting evidence was also provided showing that adaptation cytoprotection accordingly occurs in the complete gastrointestinal tract, lasting for a considerable time, depending on the part that is initially targeted by the small irritant, stomach, duodenum, or colon, enabling the other parts to be more resistant to any subsequent strong irritant challenge[1]. Considering the eating and drinking habits, the adaptive cytoprotection in the gastrointestinal tract starts in the upper parts, in the stomach and duodenum, and may beneficially affect other parts (and thereby, adaptive cytoprotection occurs between stomach \rightarrow stomach; stomach \rightarrow duodenum, stomach \rightarrow colon; duodenum \rightarrow duodenum; duodenum \rightarrow stomach, duodenum \rightarrow colon)[1]. The colon seems to be distinctive and passive, as it could not initiate an adaptive cytoprotection response[1]. We used combinations of specific agents for initial small lesion and final more severe lesion [1 mL/rat of 25% or 96% ethanol intragastrically (stomach); cysteamine 40 mg/kg or 400 mg/kg subcutaneously (duodenum); cysteamine 40 mg/kg or 400 mg/kg intrarectally (colon)][1]. All of these ulcerogens were known to be inhibited by BPC 157[1].

Finally, with normal eating and drinking, Robert's adaptive cytoprotection (*i.e.*, Robert's small irritant to the stomach and Robert's strong irritant to the stomach) showed another essential point. We used the tongue as the initial target[1]. Within the very short time needed to swallow, the stomach is immediately affected, and the lesions are considerably less than those obtained with the direct instillation of alcohol into the stomach[1]. The application of BPC 157 considerably afforded this spontaneous healing effect, and additionally mitigated tongue, esophageal, gastric, and duodenal lesions, and reversed lower esophageal and pyloric sphincter impairment, through an action which seems to be NO system dependent[1]. Actually, it means that Robert's cytoprotection and adaptive cytoprotection following the direct application of noxious agents into the stomach completely avoid the regular defensive response that would occur with the tongue (and not the stomach) as the initial target.

On the other hand, this emphasizes the original significance of Robert's application of alcohol directly into the stomach, and thereby cytoprotection, as the direct cell protection against direct cell injury produced by direct contact with the noxious agents. Robert's regimen (alcohol applied in the stomach directly, by tube) regularly skips the existing defensive system (*i.e.*, starting with the tongue). Consequently, spontaneous rapid healing mechanisms remain skipped and not activated. Thereby, the essential ability of the cytoprotective agents would depend more on their own healing capacity, and their ability to act rapidly to induce healing.

Thus, such a huge range of healing effects, as noted with the applications of BPC 157, should be a prerequisite for realizing the endothelium pathway (blood vessel recruitment and activation towards defect or bypassing vessel occlusion)[1,7].

Endothelium pathway (endothelium maintenance to epithelium maintenance)

We already emphasized[1,7] the original cytoprotection studies[14-16,20,21] from the 1980s, which demonstrated significant stomach endothelium lesions, and verified the consequent change in stomach injuries *via* the endothelium pathway (endothelium maintenance \rightarrow epithelium maintenance)[14-16,20,21]. Since that time, the cytoprotective endothelium pathway remained to be fully elaborated for therapeutic

purposes, both as a stomach therapy and as a more general therapy. With this high therapy requirement, we summarize the additional evidence. These highlights include the Virchow triad situation, endothelium injury, thrombus, and stasis, preceding the current demonstration that the administration of BPC 157 may finally induce the rapid recruitment of existing blood vessels and activate particular collateral pathways when confronted with vessel occlusion[1,7,9-11]. That pathway activation would accordingly compensate for the occlusion of vessels, and mitigate the consequent noxious chain of events[1,7,9-11]. We would analyze the possible cause in the indicated cytoprotection terms leading to an extension of the endothelium pathway to blood vessel recruitment and activation towards defect or bypassing vessel occlusion[1,7,9-11].

After presenting the initial cytoprotection concept (*i.e.*, epithelial pathway)[14-16], the endothelial pathway appeared as a further clarification of the development of stomach lesions in the concept of cytoprotection[14-16,20,21]. As a common point[47] appeared the evidence that with alcohol intragastric instillation, these vascular changes are early events, even before the appearance of gross hemorrhagic lesions, occurring within seconds or minutes during the development of moderate or severe gastric mucosal injury with interstitial hemorrhage and the necrosis of glandular epithelial cells[14-16,20,21]. Additionally, there is early stasis of mucosal blood flow and thrombi formation (within 30 s), often in regions without deep necrotic lesions. Even more, there was the rapid and complete cessation of blood flow to areas of mucosal damage consequent to ethanol administration[146]. Thus, although this was not initially claimed for the beneficial effect of prostaglandin and cysteamine application[14-16], we can envisage the particular Virchow triad presentation[1,7]. Unlike the initial claim for generalization of the epithelial stomach protection to other epithelial protection (cytoprotection → organoprotection)[14-16,19], at that time, these studies[14-16,20,21] made no attempt to generalize the findings seen for endothelium recovery in the stomach.

A strong reduction of Monastral blue staining and maintenance of the endothelium integrity after alcohol intragastric application was considered to be essential for the healing effect of BPC 157[1]. An interesting insight appeared after absolute alcohol instillation in the fully distended rat stomach, and gastric, esophageal, and duodenal lesions. Throughout the next 3 min, left gastric artery blood vessels clearly disappeared at the serosal site, indicative of the loss of vessel integrity and function. In contrast, constant vessel presentation could predict the beneficial effect of the applied agent. After pentadecapeptide BPC 157 instillation into the stomach, the vessel presentation remained constant, and lesions of the stomach, esophagus, and duodenum were inhibited[1]. Standards (atropine, ranitidine, and omeprazole) could only slightly improve the vessel presentation compared to control values, and only had a partial effect on the lesions[1]. Furthermore, for BPC 157, this maintenance of the endothelium integrity initially revealed a strong inhering angiogenic effect, which was more potent than those noted for standard antiulcer agents[1,7]. This appeared as a follow-up of “direct” cellular pharmacological treatment for ulcer with growth factors, notably bFGF and PDGF, that should result in the superior quality of ulcer healing by optimal angiogenesis, and thereby dense granulation tissue, as well as the complete re-epithelization and restoration with minimal inflammation[32]. Moreover, with BPC 157, it appears that angiogenesis was closely related to its wound healing and promotion, as well as healing in other tissues (*i.e.*, muscle, tendon, and ligament, known to be hypovascular tissues)[3]. In particular, in both muscle (transected or crushed) and transected tendon healing, we noted an increase in early angiogenesis (and the increased expression of VEGF, Factor VIII, and CD34), while late angiogenesis decreased (and the expression of VEGF, Factor VIII, and CD34 was decreased)[3]. The therapeutic potential (*i.e.*, acceleration of the blood flow recovery and vessel number in rats with hind limb ischemia) of pro-angiogenic BPC 157 is associated with VEGFR2 activation and up-regulation[107]. It also immediately triggered the internalization of VEGFR2 and subsequently activated the phosphorylation of VEGFR2 and Akt, and the eNOS signaling pathway without the need for other known ligands or shear stress [107].

On the other hand, as the reduction of Monastral blue staining and maintenance of the endothelium integrity after alcohol intragastric application is an immediate effect of BPC 157, we should consider the pleiotropic beneficial effects of BPC 157 in the entire gastrointestinal tract[1,7]. This should provide evidence that it effectively combines its particular mediator role (as an original anti-ulcer peptide which is stable in human gastric juice for longer than 24 h[12]) and thereby, in Robert’s stomach cytoprotection, protection against direct cell injury made by direct contact of various noxious agents and required endothelium protection and maintenance of the endothelium function[1,7]. This has to be an immediate and rapid effect[1,7]. Thereby,

BPC 157, as a cytoprotective agent in the entire gastrointestinal tract, may both prevent and reverse the Virchow triad situation, and have an additional modulatory role[1,7].

As the first evidence of the implementation of the endothelium maintenance originally noted in stomach cytoprotection studies[1], BPC 157 prevents and reverses thrombosis formation after abdominal aorta anastomosis, or major vein occlusion[1,7,9-11]. Furthermore, BPC 157 may attenuate the prolonged bleeding that appeared after different injuries (*i.e.*, tail or leg amputation, organ perforation, and prolonged occlusion of the inferior caval vein) or anticoagulants, such as heparin or warfarin, and aspirin and the NOS substrate L-arginine application[1,7,9]. Also, it was shown that BPC 157 maintains thrombocyte function, without interfering with coagulation pathways[1,7]. Furthermore, there is evidence that BPC 157 counteracted stroke, given in reperfusion, after clamping of the common carotid arteries [*i.e.*, both early and delayed neural hippocampal damage, achieving full functional recovery (Morris water maze test, inclined beam-walking test, and lateral push test)][147]. Together, this may be a particular modulatory effect or NO-system-related effect[1]. BPC 157 may counteract both the NOS blocker L-NAME's pro-thrombotic effect and the NOS substrate L-arginine's anti-thrombotic effect in the same way that it counteracted both L-NAME-induced hypertension and L-arginine-induced hypotension, and could induce the NO release on its own, which is quite resistant to L-NAME application[1]. Finally, in addition to the VEGFR2-Akt-eNOS signaling pathway being activated without the need for other known ligands or shear stress[107], there is a direct effect on vasomotor tone (*i.e.*, specific activation of Src-Caveolin-1-endothelial nitric oxide synthase (eNOS) pathway)[106]. Also, it should be recalled that four major events (vascular constriction, loose platelet plug, fibrin mesh to insure stability of platelet plug, and dissolution of the clot) are implicated in the wound healing process and occur in a set order following the loss of vascular integrity[3]. Consequently, it may be not surprising that an agent implemented in wound healing, such as stable gastric pentadecapeptide BPC 157, should be effective in this particular way also in bleeding disorders[1,3], due to its innate cytoprotective effect, and the fact that it has been shown to be an effective therapy in wound healing[3].

Finally, in consideration of the previous original findings in cytoprotection endothelium studies (complete cessation of blood flow to areas of mucosal damage and rapid cloth formation consequent to ethanol administration[146]), and resolving of the presented Virchow triad circumstances, we suggested that the beneficial effect of cytoprotective agents should be related to the resolution of this noxious chain of events[1,7]. Thus, conclusive evidence involves confrontation with permanent major vessel occlusion, and therapeutic evidence that BPC 157 administration quickly recruits vessels to rapidly activate the collateral pathway which would adequately compensate for vessel occlusion and reestablish blood flow[1,7,9-11]. There, the alleviated peripheral vascular occlusion disturbances rapidly activated alternative bypassing pathways[1,7,9-11], appears to be an additional follow-up of its essential endothelium protection[1], which was long ago implemented as an essential class activity of cytoprotective agents[13]; however, in this way, this has so far only been implemented by the application and beneficial effects of the stable gastric pentadecapeptide BPC 157[1,7,9-11].

Rapid activation of a bypassing loop from the existing vessels

With BPC 157 therapy, when confronted with the occluded vessel in rats with distinctive vascular occlusion disturbances, we first reported the rapid activation of a bypassing loop recruited from the existing vessels (*i.e.*, intestinal arcade vessel network, or the left ovarian vein)[1,7,9-11]. The evidence [1,7,9-11] included the infrarenal occlusion of the inferior caval vein, left colic artery and vein occlusion ischemic/reperfusion ulcerative colitis, superior anterior pancreaticoduodenal vein-induced duodenal venous congestion lesions, bile duct ligation-induced liver cirrhosis and portal hypertension, temporary occlusion of the portal triad (Pringle maneuver)-induced ischemia-reperfusion injury[10], and suprahepatic occlusion of the inferior caval vein-induced Budd-Chiari syndrome[11]. This occurred in rats with a ligated part of the left colic artery and vein, ischemic/reperfusion colitis, or an infrarenal ligation of the inferior vena cava[1,7,9-11]. Evidently, the BPC 157 application-induced activation of the collateral pathways (the left ovarian vein and other veins in rats with infrarenal occlusion of the inferior caval vein) may rapidly resolve any systemic disturbances (*i.e.*, caval hypertension, aortal hypotension, heart dysfunction, thrombosis, and consequent thrombocytopenia, and induced bleeding prolongation in rats with infrarenal occlusion of the inferior caval vein)[1,7,9-11]. Likewise, there is also the local injury counteraction (attenuated/counteracted ischemia/reperfusion injury) in a rat study of the ischemic/reperfusion colitis[1,7]. As emphasized[1], with

part of the left colic vein and artery excluded by two ligations, along with BPC 157 application, blood vessels propagated toward the injury obstruction, bypassing it, interconnecting collaterals between arcades, and reestablishing the inside-outside point. In reperfusion, the application of BPC 157 after the initiation of full reperfusion with both ligations removed resulted in increased vessel presentation and arcade interconnections. With application of BPC 157 in ischemia as well as in reperfusion, the mucosal folds were recovered, and the pale areas were small and markedly reduced in size[1]. In the ischemia and even more so in the reperfusion, oxidative stress was counteracted, and the otherwise increased MDA (as a result of the lysis of endothelial cells^[148,149]) and NO levels in colon tissue were found to be normal in rats that received BPC 157 bath treatment[1]. This occurs as before in both ischemic and reperfusion conditions in the various tissues (*i.e.*, the colon, duodenum, cecum, liver, and veins) and plasma[1,7,9-11]. Thus, the action of BPC 157 as a free radical scavenger (noted also in the other tissues, *i.e.*, gastrointestinal sphincters, stomach, duodenum, bowel adhesions, bladder, and brain[1,7,9-11]) may considerably contribute to its pleiotropic beneficial effects and maintain endothelial function. Notably, BPC 157 contains four carboxylic groups that could be active in scavenger process, and if they are reactivated (by, *e.g.*, glutathione or enzymes), the overall antioxidant activity could be very high [1].

Thus, relieving Virchow's triad situation is the particular activation of collateral pathways corresponding to the damaging occlusion [*i.e.*, mentioned passing through arcade vessels (occlusion of the left colic artery and vein) or the left ovarian vein (infrarenal occlusion of the inferior caval vein)][1,7,9-11]. As pointed out[1,7,9-11], the superior anterior pancreaticoduodenal vein-inferior anterior pancreaticoduodenal vein-superior mesenteric vein appears to counteract duodenal congestion lesions[1,7,9-11]. A porto-caval shunt appears with the portal vein-superior mesenteric vein-inferior mesenteric vein-rectal vein-left iliac vein-inferior caval vein pathway to counteract portal hypertension in rats with bile duct occlusion or ischemia-reperfusion injury following Pringle maneuver[1,7,9-11]. The inferior caval vein - azygos vein - left superior caval vein pathway appears to counteract Budd-Chiari syndrome in rats[1,7,9-11].

Of note, an adequate compensation regularly occurred. As pointed out in our venous occlusion studies[10,11], there is consistent evidence in rats with bile duct ligation. Preventing the development of portal hypertension, and the rapid reversal of the already established portal hypertension, are both among its additional beneficial effects[150]. We noted that BPC 157 therapy markedly abated jaundice, ascites, and nodular, steatotic livers with large dilatation of the main bile duct, increased liver and/or cyst weight, and decreased body weight[150]. Furthermore, the piecemeal necrosis, focal lytic necrosis, apoptosis, and focal inflammation, disturbed cell proliferation (Ki-67-staining), cytoskeletal structure in the hepatic stellate cell (α -SMA staining), and collagen presentation (Mallory staining) were all counteracted, providing evidence that BPC 157 may affect both liver fibrosis and portal hypertension [150]. Thus, this may be the principle seen in venous occlusion studies[10,11].

As previously reviewed[1], in rats with a perforated cecum, BPC 157 application rapidly reversed the regular noxious course, with the rapid disappearance of blood vessels at the cecum serosa (emptied/disappeared), thereby producing a large immediate defect, with bleeding, the leakage of fluid, increased oxidative stress, and disturbed NO-levels in cecal tissue. With BPC 157, there is immediate blood vessel recruitment and activation ("running") towards the site of injury[150], as was described in the "bypassing" of vessel occlusion *via* alternative pathways[9-11], which can likely cure rats and reestablish blood flow. Also, a small-vessel network appeared around the perforated defect with BPC 157 bath administration; cecal defect enlargement reversed to defect contraction (*i.e.*, each defect breaks blood flow) may be a result of the reestablishment of blood flow as well as the shortened bleeding time from the perforated cecum[1]. Less bleeding corresponds to the beneficial effects in rats with amputation, anticoagulant or aspirin application, or vein obstruction; direct defect closing corresponds to the closing of various fistula defects, which were also surgically created in corresponding tissues[1,7,9] (*i.e.*, all by Robert's direct injury to the cell by direct contact).

Along with these findings[1,7,9-11] is the beneficial effect of BPC 157 in rats with a damaged peritoneum. Endothelium maintenance → epithelium maintenance = blood vessel recruitment and activation ("running") towards the site of injury, also described as "bypassing" the occlusion *via* alternative ways[1,7,9-11], was seen with BPC 157 administration after parietal peritoneum excision with an underlying superficial layer of muscle tissue in rats to counteract failed vasculature, and finally to counteract the increased formation of adhesions. Rapid abundant vascular vessels in and close to the

defect mean that BPC 157 could interfere with the motion of the coagulation cascade once the peritoneum is damaged[1,7,9-11]. When two damaged peritoneal surfaces come into contact with each other, BPC 157 is likely to interfere the temporary role of fibrin in healing without adhesions that must be degraded by the fibrinolytic system for the restoration of normal tissue structure and function, as it reversed the healing that would result in fusion to form a connection, *e.g.*, an adhesion[151,152].

Finally, with the BPC 157 therapy in the Pringle maneuver in rats[10], severe preportal hypertension, temporary portal triad obstruction, ischemia, and short and prolonged reperfusion, we resolved the regular lack of adequate portocaval shunting as the most detrimental feature that should be counteracted[10]. With the stable gastric pentadecapeptide BPC 157, we noted the resolution of damage, either following occlusion or following the re-opening of the hepatic artery, portal vein, and bile duct. Therefore, in the portal triad obstruction syndrome in rats, in the rapidly activated manner, portal vein-superior mesenteric vein-inferior mesenteric vein-rectal vein-left iliac vein-inferior caval vein pathway would appear as specific activation of the collateral circulation, as the bypassing loop that can rapidly circumvent occlusions and decompress portal triad obstruction in rats upon BPC 157 administration[10]. That solution in rats with ischemia and reperfusion following the Pringle maneuver goes along with the resolution of oxidative stress, hemodynamic disturbances, severe portal and caval hypertension, aortic hypotension, rapid clot formation in the portal vein, superior mesenteric vein, lienal vein, inferior caval vein, and hepatic artery, ascites, peaked P waves, tachycardia, increased serum values, and gross intestine, liver, lung, spleen, and heart lesions[19]. In particular, it goes along with the application of agents during reperfusion. Furthermore, the pentadecapeptide BPC 157 resolved the suprahepatic occlusion of the inferior caval vein in a Budd-Chiari syndrome model in rats[11]. Budd-Chiari syndrome was perceived as originally suggested[153,154], a hepatic venous outflow obstruction and its manifestation, regardless of cause, but this was mostly attributed to thrombosis, which can be located anywhere from the small hepatic veins to the entrance of the inferior vena cava into the right atrium[153,154]. Thereby, bypassing the occlusion in the rat Budd-Chiari syndrome along with pharmacotherapy treatment should be essential. BPC 157 therapy results in the rapidly activated azygos/hemiazygos vein bypassing pathway, upgrading an inadequate rescuing inferior-superior vena cava shunt to an adequate one, as well as a portocaval shunt[11]. Consequently, the caval and portal hypertension and aortal hypotension presented by Budd-Chiari syndrome rats were largely eliminated by BPC 157 therapy [11]. Largely attenuated consequent disturbances (rapid clot formation in the portal vein, superior mesenteric vein, splenic vein, inferior vena cava, hepatic artery, and coronary artery, as well as peaked P waves, significant ST elevation, tachycardia, gross organ lesions, and liver and spleen weight increases) together support this contention [11].

Thus, BPC 157 application may counteract a life-threatening syndrome[9-11]. Characterized by the multiple mutual cause-consequence relationships in vascular occlusion-induced syndrome presentation in rats, the generalized thrombosis and stasis, vascular failure, and heart dysfunction, lung congestion appears to be a common outcome (*i.e.*, time-dependent and time-independent features that the exudative phase features of acute respiratory distress syndrome)[9-11]. Acute lung injury is a primary component of multiple organ dysfunction syndrome triggered by intestinal ischemia-reperfusion. The results may be high mortality and acute lung injury[155,156], followed by liver failure (substantial congestion of central vein as well as branches of portal veins in portal triads), kidney congestion, prominent portal and caval hypertension, aortal hypotension, and consequential gastrointestinal hemorrhagic lesions[9-11]. Therefore, the previously mentioned beneficial effects, in elaborating the cytoprotective “epithelial pathway” (*i.e.*, counteracted various heart or liver lesions), including the combined and simultaneous healing of different tissues[1], may also be essential. In particular, the compensatory efficacy of new functional equilibrium (“endothelium pathway”) with the activated specific functioning collateral pathways[13-15] is also ascertained with an important notification for the general pathology of the portal hypertension[1,7]. Namely, BPC 157 counteracted all portal hypertension presentations whatever the cause, post-hepatic, hepatic, and pre-hepatic [1,9-11].

In addition, as in venous-occlusion syndromes[9-11], BPC 157 also counteracted various lung lesions[1,7].

Finally, with holistic concepts, any criticisms about the cytoprotection concept, such as “cytoprotection”, “as everything and nothing”, and “cytoprotection which is not mechanism”, and thereby, criticisms about peptides and cytoprotection, could not be avoided. The general point that animal studies *per se* may be cautious regarding their

results and the relative paucity of BPC 157 clinical data was also reported[1]. On the other hand, it should be noted that BPC 157 was proven to be efficacious in ulcerative colitis, both in clinical settings[157,158] and in experimental ischemic/reperfusion ulcerative colitis studies in rats and other ulcerative colitis models[1]. A particular point is the very safe profile (LD1 could be not achieved)[1,3,7], a point that was recently confirmed in a large study by Xu *et al*[159]. In this context, the role of the animal model is indispensable, and the practical evidence is even more important. Besides the majority of studies with BPC 157 conducted on rodents that were given an injection of the supplement, there have also been a considerable number of studies, particularly in gastrointestinal research, with intragastric application or peroral application in drinking water (regularly used in fistulas studies[1,3]), that are correspondingly effective. There are also studies in other species, *i.e.*, birds and insects (given in the food), which favor a more general effect of BPC 157 application[1,7]. Lastly, the suitability of the models used for the topic of cytoprotection, in particular, since Robert's original description of the cytoprotection in rats[14-16], evidently resolves the practical/theoretical consideration of the cause-consequence issue. Thus, the suited models and lesion counteraction clearly indicate the beneficial effects. The deciding result exemplified the resolved endothelium pathway (blood vessel recruitment and activation towards defect or bypassing vessel occlusion)[1], but the particular background still needs to be further elaborated. Note, the consistently used range of BPC 157 application (μ g-ng) may also suggest a physiological role, in accordance with *in situ* hybridization and immunostaining for BPC 157 in the gastrointestinal mucosa, lung bronchial epithelium, epidermal layer of the skin, and kidney glomeruli[3]. Thereby, illustrative examples for further research may be the evidence that BPC 157 exhibited a specific effect on the *Egr*, *Nos*, *Srf*, *Vegfr*, *Akt1*, *Plcy*, and *Kras* pathways in infrarenal occlusion-induced inferior caval vein syndrome in rats. This appears in a timely manner, to be increased, decreased, or unchanged, depending on whether the vessel was blinded (the right ovarian vein and inferior caval vein) or open and served as an alternative operating pathway (the left ovarian vein)[9]. Also, to support the beneficial effect of BPC 157 on brain lesions, given in reperfusion in stroke rats[147], BPC 157 therapy counteracted both early and delayed neural hippocampal damage, showing that achieving full functional recovery can restore recognition memory deficits along with a therapeutic effect[147]. mRNA expression studies at 1 h and 24 h, provided strongly elevated (*Egr1*, *Akt1*, *Kras*, *Src*, *Foxo*, *Srf*, *Vegfr2*, *Nos3*, and *Nos1*) and decreased (*Nos2* and *Nfkb*) gene expression (*Mapk1* not changed). This may be how BPC 157 acts[147].

In conclusion, Robert's cytoprotection concept[14-16] was initially of intense interest, but lately received the claim that the concept's foundation ("gastric cytoprotection") is still relevant[23]. Anyway, the essential rebuilding was lacking. Now, the concept has been reexamined for many major reasons (Figure 1): (1) The gastric pentadecapeptide BPC 157, thought to be an essential cytoprotective mediator that is native to and stable in human gastric juice, was noted to have a pleiotropic beneficial effect[1,3]; (2) With the administration of BPC 157, in prophylactic as well as in therapeutic regimens, there is evidence of the innate Robert's cell protection in the stomach epithelium against direct injury (which may be induced by various noxious agents) using either method of application, which provides the ability to realize the protection of other epithelia as well[1-3]; (3) BPC 157 effectively combines its particular mediator role (as an original anti-ulcer peptide that is stable in human gastric juice for longer than 24 h); therefore, in Robert's stomach cytoprotection, it has a protective effect against direct cell injury made by the direct contact of various noxious agents, requiring endothelial protection and the maintenance of endothelial function. This has to be an immediate and rapid effect[1]; (4) As first evidence of the implementation of the endothelial maintenance originally noted in stomach cytoprotection studies, BPC 157 prevents and reverses thrombosis after abdominal aorta anastomosis, or major vein occlusion[1,7,9-11]. Furthermore, BPC 157 may attenuate the prolonged bleeding that appeared after different injuries or anticoagulant, heparin or warfarin, and aspirin application[1,7,9-11]. Also, BPC 157 maintains thrombocyte function, without interfering with coagulation pathways[1,7,9-11]; and (5) The vessel recruitment activated collateral pathways to bypass vessel occlusion as a new conceptual point in the cytoprotection concept, and cytoprotective agent activity[1,7,9-11]. BPC 157 counteracted various venous occlusion-induced syndromes, inferior caval vein syndrome[9], ischemia/reperfusion injury following Pringle maneuver[10], and Budd-Chiari syndrome[11] in rats. Activation of the alternative collateral pathways to bypass occlusion, and reestablishing alternative blood flow result in counteraction of the consequent syndromes[1,7,9-11]. Due to the severe venous occlusion-induced disturbances, the high portal and caval hypertension and aortal hypotension, arterial

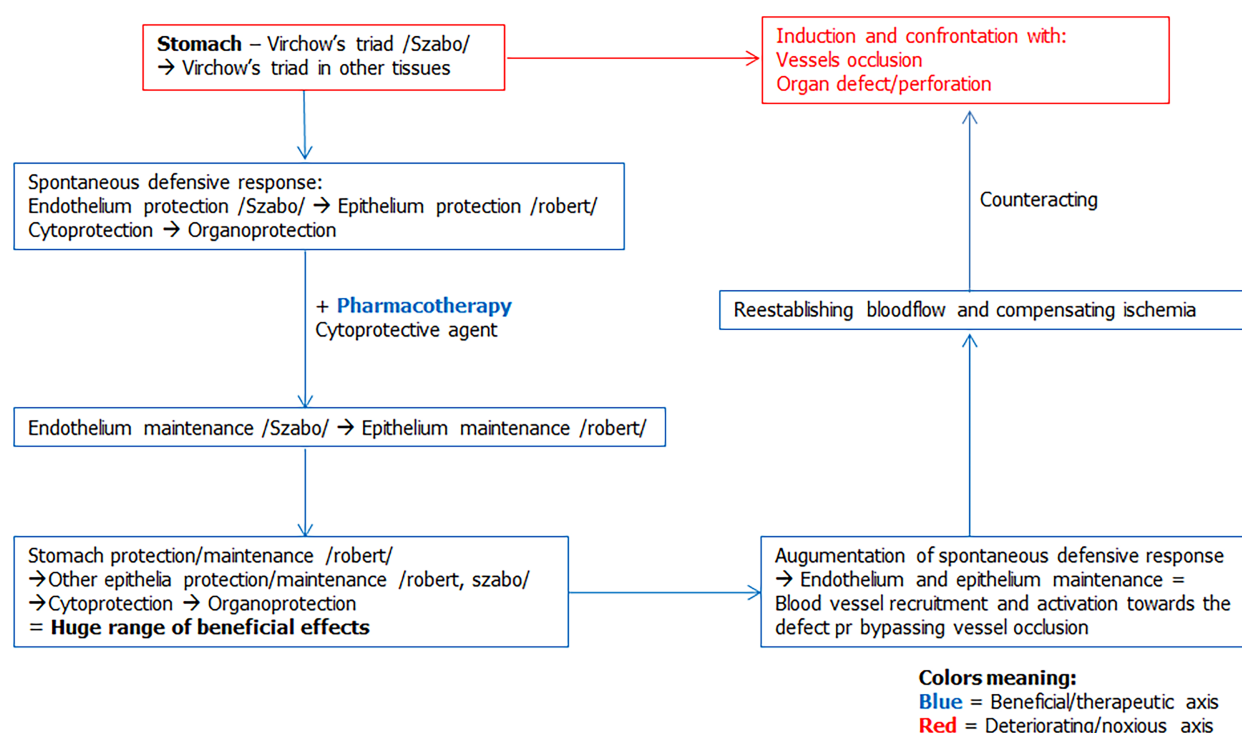


Figure 1 Summarizing the essential epithelium and endothelium protection interplay known in Robert's and Szabo's cytoprotection concept, and the role of the stable pentadecapeptide BPC 157 as a likely mediator, we suggest that BPC 157 may be a useful cytoprotective therapy. Hopefully, it may finally realize in the practice the huge theoretical importance of all aspects of the cytoprotection concept. Conceptually, there is a new point, namely, endothelium maintenance to epithelium maintenance (the recruitment of collateral blood vessels to compensate for vessel occlusion and reestablish blood flow or bypass the occluded or ruptured vessel). BPC 157 counteracts various venous occlusion-induced syndromes, inferior caval vein syndrome, ischemia-reperfusion injury following the Pringle maneuver, and Budd-Chiari syndrome in rats. Activation of the alternative collateral pathways to bypass occlusion, and reestablishing alternative blood flow, result in the counteraction of the full consequent perilous syndromes.

and venous thrombosis, both peripherally and centrally, and various organs lesions (*i.e.*, gastrointestinal, liver, kidney, heart, and brain) were all attenuated and/or eliminated[1,7,9-11]. Furthermore, this particular beneficial effect may be competing with the Virchow's triad situation that is commonly presented [*i.e.*, duodenal venous congestion lesions, perforated cecum, ischemic/reperfusion colitis, bile duct ligation-induced liver cirrhosis and portal hypertension, portal triad temporary occlusion (ischemia-reperfusion injury following the Pringle maneuver), and suprahepatic occlusion of the inferior caval vein (Budd-Chiari-syndrome)][1,7,9-11,150].

CONCLUSION

BPC 157 may be a useful cytoprotective therapy, which may finally result in the huge theoretical to practical importance of all aspects of the cytoprotection concept[1,7,9-11].

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