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The interplay between diet and the enteric nervous system in the pathophysiology of colorectal cancer

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Abstract: Colorectal cancer (CRC) represents the third most diagnosed cancer worldwide, with 1.9 million new cases reported annually. Notwithstanding the progress made in the field of therapeutic modalities and the advent of early diagnosis, CRC continues to represent the second most common cause of cancer-related mortality. The interactions between cancer cells and enteric nervous system (ENS) neurons are of great importance for the prevention and/or progression of CRC. Dietary factors play an important role in regulating both processes. The consumption of foods rich in polyphenols, omega-3 fatty acids, and the use of probiotics has been shown to promote proper ENS function, which in turn has been demonstrated to indirectly inhibit the development or progression of CRC. Conversely, a diet comprising a high proportion of saturated fats and refined sugars can induce oxidative stress and inflammation, which exacerbates the disease. Nutritional education and dietary modifications can reduce the incidence of new cases of CRC and improve prognosis. Further research into the potential anti- or pro-cancer effects of food substances is recommended.

Keywords: carcinogenesis, colorectal cancer, diet, enteric nervous system, neuromodulation, perivascular invasion.

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Introduction

Colorectal cancer (CRC) is the third most diagnosed malignancy, with approximately 1.9 million new cases detected annually, which is the equivalent to 10% of all newly diagnosed cancers worldwide [1]. It is projected that by the year 2030, this percentage will have increased to as much as 60 [1]. The most recent data on cancer incidence and mortality in the United States, collected between 2015 and 2019, revealed that the average annual incidence rate of CRC was 33% higher in men than in women, and the overall mortality rate was 43% greater in men than in women.

Furthermore, women exhibit a slightly higher five-year relative survival rate than men [2]. It is evident that the survival rate of patients with CRC has increased because of therapeutic advances and the development of early detection methods. Nevertheless, CRC remains the second most common cause of cancer-related deaths [3]. In 2020, there were 935,173 deaths from CRC worldwide, representing 9% of all cancer deaths [1]. It is estimated that 75–80% of CRC cases are spontaneous cancers caused by mutations in genes responsible for the growth, differentiation, and proliferation of epithelial cells. These mutations are associated with the adenoma-carcinoma sequence. Of the lesions, 72% are seen in the colon and 28% in the rectum [1]. Surgical treatment is the preferred intervention for early detected CRC, while neoadjuvant therapy is utilized in advanced cases with metastasis [4]. Extensive research has led to a better understanding of cancer progression, with the focus shifting from genetic and epigenetic abnormalities to understanding the importance and role of the tumor microenvironment [5–7]. Notwithstanding the growing interest in the role of nerve fibers in cancer research in the field of oncology [8], glial cells and intestinal neurons have received relatively little attention. Furthermore, the extant evidence suggests that elevated levels of neuronal markers are associated with a less favorable prognosis in CRC [9].

The enteric nervous system (ENS) is comprised of over 500 million neurons, the majority of which are classified as afferent neurons, motor neurons, and interneurons [10]. Additionally, the system contains approximately 1,000 to 1,500 million glial cells, which serve a range of nutritional and regulatory functions [11]. Neurons form plexuses and nerve fibers. Two plexuses can be distinguished: the submucosal plexus, located in the submucosa of the intestine, and the myenteric plexus, situated between the circular and longitudinal layers of smooth muscle [10]. Neurons interact with one another *via* a variety of neurotransmitters. The neurotransmitters in the ENS are e.g. acetylcholine (ACh), vasoactive intestinal peptide (VIP), serotonin (5-hydroxytryptamine, 5-HT), nitric oxide (NO). The two most important neurotransmitters are ACh and VIP, which have opposing effects. ACh stimulates the contraction and secretory activity of the intestine, whereas VIP is responsible for the relaxation of smooth muscle, particularly those in blood vessels [10]. ENS plays a pivotal role in regulating intestinal function. It affects a multitude of processes, including secretion, peristaltic movements, the intestinal barrier, and microvascular circulation [12].

A recent discovery has revealed a correlation between several types of cancer (including pancreatic cancer and stomach cancer) and active paracrine communication between neurons and tumor cells [8]. This paper aims to summarize the current state of knowledge on the interactions between the ENS, CRC, and patients' diet.

Interactions between the enteric nervous system, colorectal cancer and diet

The interactions between the ENS and CRC can be divided into two categories: mechanical (e.g., neoneurogenesis, perineural invasion) and neuroregulatory.

The process of neoneurogenesis is defined as the formation of new nerve fibers within a tumor [13]. CRC has the capacity to establish a pro-neurogenic microenvironment through the secretion of neurotrophins (e.g. nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), glial cell line-derived neurotrophic factor (GDNF)), which facilitate neurite growth and neuronal differentiation [14]. Moreover, circulating neural progenitor cells can infiltrate tumor tissues, thereby accelerating the process of neurogenesis. The findings indicate that neurogenesis is associated with a more aggressive disease course and worsen clinical outcomes [15].

Perineural invasion (PNI) is a process by which tumor cells spread along nerve fibers, including those formed by neoneurogenesis. PNI is a common occurrence in malignant neoplasms, including CRC and is linked to tumor invasion, metastasis, and pain [16]. The presence of PNI is associated with a higher risk of poor prognosis [16].

Neuroregulation is the process by which the nervous system controls and coordinates the functions of organs and systems in the body, ensuring that they function properly and can respond to changes in the internal and external environment. This process includes mechanisms based on nerve impulses, as well as the secretion of neurotransmitters and hormones.

The ENS neurons serve as a source of neurotrophins, neurotransmitters, netrines, signaling proteins and cytokines that play a key role in carcinogenesis and regulation of inflammation. These molecules exhibit indirect effects through the production of signaling substances (e.g., interleukin (IL)-1β, IL-6, IL-10 and others), as well as through direct effects on the intestinal barrier [17].

The current research findings suggest that the course of the described mechanisms may be influenced by dietary factors. The aforementioned data are presented in Table 1.

Neurotrophins

Neurotrophins are a family of proteins that, in conjunction with specific receptors, are responsible for the survival, growth, and function of nerve cells [13]. The expression of these proteins occurs in neurons (also belonging to ENS), astrocytes, and in cancer cells [13]. Neurotrophins encompass a diverse array of proteins, including NGF, BDNF, GDNF and others [13]. Neurotrophins facilitate the process of PNI using ENS neurons and neoneurogenesis in CRC [13].

NGF induces phosphorylation of tropomyosin-related kinase A (TrkA), thereby activating the mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK) signaling pathway, which in turn promotes tumor metastasis [13]. Elevated NGF levels in tissues are associated with increased expression of matrix metalloproteinases (MMP) (e.g., MMP2 and MMP9), which are responsible for tissue degradation [13]. Furthermore, NGF stimulates the innervation of perivascular nerves, which in turn regulates blood flow in tumors [13].

In the case of CRC, particularly in its advanced stage, BDNF and TrkB are overexpressed in comparison to healthy tissue [13]. This is correlated with an increased incidence of lymphatic metastasis and increased proliferation of cancer cells [13]. In addition to its role in regulating blood flow, BDNF has been shown to enhance the migration of CRC cells by regulating the activation of vascular endothelial growth factor (VEGF)/Heme Oxygenase-1 (HO-1) *via* the ERK, p38, and Phosphoinositide 3-Kinase/Protein kinase B (PI3K/Akt) signaling pathway [13].

The consumption of foods rich in polyphenols, omega-3 fatty acids, and the use of probiotics help maintain normal concentrations of NGF and BDNF [18]. Conversely, a diet rich in saturated fats may disrupt their levels by inducing oxidative stress and inducing inflammation, which will be described in the further part of the paper [18].

Another neuropathic factor, GDNF plays a significant role in the pathogenesis of CRC [19]. By interacting with VEGF and the VEGFR1 receptor, it increases the migration and invasion of tumor cells. This mechanism is linked to the p38 and PI3K/Akt signaling pathways, as well as the accumulation and activity of hypoxia-inducible factor 1α in the cell nucleus [19].

Leptin, a hormone primarily produced in white adipose tissue, has been demonstrated to increase GDNF production in the ENS [20]. Consumption of foods rich in refined sugars and

Table 1. Factors modulating the development, progression and course of colorectal cancer via the enteric nervous system and their potential relationship between their concentration and the consumed diet.

Factors	Potential effect of abnormal amounts of factors on ENS-mediated CRC development or progression	Food products and supplements that can modulate the concentration of the factor in the system	Ref.
NGF and BDNF	Facilitate the process of PNI using ENS neurons and neo-neurogenesis in CRC.	Food products and supplements that normalize factors levels: 1. foods rich in polyphenols: berries, dark chocolate, green tea, olive oil, 2. foods rich in omega-3 fatty acids: fatty fish, walnuts, chia seeds, eggs, soybeans, 3. probiotics. Food products that disrupt factors levels: 1. foods rich in saturated fats: palm oil, coconut oil, butter, cheese, beef, pork, lamb, processed meats like sausages, fast foods.	[13, 18]
GDNF	Facilitate the process of PNI using ENS neurons and neo-neurogenesis in CRC.	Diet that normalizes factor levels: 1. low-calorie diet, 2. diet rich in protein, 3. low-carbohydrate diet. Food products that disrupt factor levels: 1. foods rich in saturated fats: palm oil, coconut oil, butter, cheese, beef, pork, lamb, processed meats like sausages, fast foods, 2. foods rich in refined sugars: sweets and snacks, baked goods, sweetened carbonated beverages, energetics, sweetened breakfast cereals.	[13, 42]
Netrin-1	Facilitate the process of tumor induction and the migration of tumor cancer cells.	Diet that normalizes factor levels: 1. balanced diet to maintain a healthy body weight. Diet and food products that disrupt factor levels: 1. foods rich in saturated fats: palm oil, coconut oil, butter, cheese, beef, pork, lamb, processed meats like sausages, fast foods, 2. foods rich in refined sugars: sweets and snacks, baked goods, sweetened carbonated beverages, energetics, sweetened breakfast cereals, 3. calorically unbalanced diet, leading to obesity.	[27, 28]
Inflammatory mediators (e.g.: serotonin, SP, Il-6, TNF-α, NO)	Endogenous inflammatory factors lead to DNA damage, increased cell proliferation, angiogenesis and immunosuppression.	Food products and supplements that have been demonstrated to reduce inflammation: 1. foods rich in fiber: fruits and vegetables, whole grain products, 2. foods rich in omega-3 fatty acids: fatty fish. Walnuts, chia seeds, eggs, soybeans, 3. probiotics and prebiotics, 4. spices and herbs, e.g. turmeric, ginger, 5. quercetin, 6. flaxseed.	

Factors	Potential effect of abnormal amounts of factors on ENS-mediated CRC development or progression	Food products and supplements that can modulate the concentration of the factor in the system	Ref.
		Food products that induce inflammation: 1. alcohol, 2. foods rich in saturated fats: palm oil, coconut oil, butter, cheese, beef, pork, lamb, processed meats like sausages, fast foods, 3. foods rich in refined sugars: sweets and snacks, baked goods, sweetened breakfast cereals, sweetened carbonated beverages, energetics.	[30, 34, 36]
Proteins S100	Promote carcinogenesis, including proliferation, invasion and migration of cancer cells, as well as angiogenesis.	Food products and supplements that have been demonstrated to reduce inflammation: 1. foods rich in resveratrol: berries, dark chocolate, grapes, 2. foods rich in omega-3 fatty acids: fatty fish. Walnuts, chia seeds, eggs, soybeans, 3. green tea, 4. spices and herbs, e.g. curcumin 5. quercetin Diet and food products that disrupt factor levels: 1. foods rich in saturated fats: palm oil, coconut oil, butter, cheese, beef, pork, lamb, processed meats like sausages, fast foods, 2. products with a high glycemic index: sweets and snacks, baked goods, Sweetened carbonated beverages, energetics, sweetened breakfast cereals, 3. ketogenic diet, 4. foods that cause oxidative stress: processed foods, red meat, alcohol, sweets, carbonated drinks.	[39, 43]
Tissue hormones (Leptin, Cholecystokinin)	Cause a decrease in GI peristalsis and contributes to the development of constipation.	Diet that normalizes factors levels: 1. low calorie diet, 2. diet rich in protein, 3. low-carbohydrate diet. Food products that disrupt factors levels: 1. foods rich in saturated fats: palm oil, coconut oil, butter, cheese, beef, pork, lamb, processed meats like sausages, fast foods.	[20, 42]

BDNF — Brain-derived neurotrophic factor, CCK — Cholecystokinin, CRC — Colorectal cancer, ENS — Enteric nervous system, GDNF — Glial cell line-derived neurotrophic factor, GI — Gastrointestinal, HFD — High-fat diet, IL — Interleukin, NGF — Nerve growth factor, PNI — Perineural invasion, ROS — Reactive oxygen species, SP — Substance P, TNF-α — Tumor necrosis factor α

saturated fats (commonly referred to as the Western diet) and eating meals at irregular intervals can increase leptin levels, which in turn increases GDNF production [20]. The enhanced production of GDNF additionally activates the described pathways, ultimately resulting in a more unfavorable prognosis for the CRC patient.

Neurotransmitters

Ach, which is produced by nerve cells is a key neurotransmitter in the ENS [10]. In CRC, the synthesis of ACh by tumor cells is also seen [10]. Through autocrine and paracrine signaling, ACh may interact with muscarinic receptors on the surface of the same or neighboring tumor cells [10]. Of particular importance is the activation of muscarinic M3 receptors, which initiates intracellular signaling pathways (Wingless-Related Integration Site (Wnt)/β-catenin, MAPK/ERK, PI3K/Akt pathways) that promote tumor cell proliferation, invasion, and survival [10]. Furthermore, the action of ACh has been linked to maintaining the integrity of the intestinal barrier by modulating tight junctions (TJs) between epithelial cells [21]. Disruption of the structure of TJs can lead to chronic inflammation, dysbiosis, increased intestinal permeability, and oxidative stress, which are factors that promote carcinogenesis [21]. ACh secreted by neurons interacts also with nicotinic receptors of immune cells [17]. The stimulation of α7nAChR receptors on macrophages has been demonstrated to reduce the production of pro-inflammatory cytokines, including tumor necrosis factor α (TNF-α), IL-1β, and IL-6, thereby leading to a reduction in inflammation [17]. Furthermore, ACh stimulates the production of mucus by goblet cells, which serves to protect the intestinal epithelium from microorganisms and toxins [17].

One of the factors that enables ENS-mediated modulation of ACh levels is the choline content of the diet. The most optimal sources of choline are egg yolk, meat products, offal, particularly poultry liver and beef liver, legumes, fish, and dairy products [22].

Another neurotransmitter that plays a significant role in the development of CRC is VIP [10]. By interacting with specific receptors on the cell surface, VIP induces signaling pathways (cAMP-Rap1/RAS-BRAF-MAPK-ERK) that promote proliferation or induce antimetastatic effects [10]. Furthermore, VIP interacts with immune cells, thereby influencing the tumor microenvironment, which may affect inflammation and angiogenesis [10].

A diet high in fat (HFD), carbohydrates, alcohol, and products with a high salt content have been shown to disrupt VIP production in ENS [23, 24], while the consumption of fiber, probiotics, and prebiotics has been demonstrated to maintain normal VIP production [25]. Disturbed VIP production promotes the procarcinogenic effects of VIP.

The role of neurotransmitters such as NO and serotonin during inflammatory reactions is significant. A detailed discussion of these molecules can be found in subsection 2.4.

Netrin-1

Intestinal neurons are known to produce a secretory protein related to laminin like netrin-1 during gastrointestinal (GI) organogenesis [26]. Netrin-1 has been demonstrated to possess anti-apoptotic properties because of its interaction with the dependency receptors, the colorectal cancer suppressor (DCC) and the uncoordinated-5 homolog (UNC5H) [27]. It should be noted that dependency receptors induce apoptosis, whereas the netrin-1 molecule has the opposite effect when it attaches to them [27]. An increase in the synthesis of netrin-1 in gastrointestinal

tissues has been demonstrated to result in impaired removal of damaged cells, which can lead to tumor induction and facilitate metastasis [27, 28].

The findings of study conducted by Kalani *et al.* suggest that dietary alterations may influence netrin-1 concentrations within the body [29]. A diet high in protein, low in folate and vitamins B6 and B12 can result in the reduction of netrin-1 levels through the epigenetic silencing of the *NTN1* gene promoter [29]. On the other hand, the consumption of an unbalanced diet, which can lead to obesity, has been linked to an increase in *NTN-1* gene expression [28]. This, in turn, has been shown to enhance anti-apoptotic effects and increase the risk of developing cancer [28].

Inflammatory mediators

Interactions between the ENS and the immune system are key to elucidating the mechanisms by which inflammation can cause tumorigenesis in the colon [17]. Chronic intestinal inflammation has been shown to promote colon cancer development through the production of reactive oxygen species (ROS) and reactive nitrogen species (RNS), the release of pro-inflammatory cytokines (e.g., TNF-α, IL-6), the secretion of neurotransmitters, and changes in the tissue microenvironment, leading to DNA damage, increased cell proliferation, angiogenesis and immunosuppression [30]. ROS and RNS produced by macrophages and neutrophils in response to inflammation, can induce DNA damage in intestinal epithelial cells and ENS neurons. Mutations arising in genes responsible for cell cycle regulation and apoptosis are particularly dangerous. Among the most well-known mutations of this type is a mutation in the *TP53* gene, leading to increased activity of the kappa-light-chain-enhancer of activated B cells (NF-κB) and Signal Transducer and Activator of Transcription 3 (STAT3) signaling pathways.

NF-κB a key transcription factor in ENS neurons and intestinal cells [30], coordinates the immune response by regulating the production of inflammatory cytokines (such as TNF-α, IL-1 and IL-6) [31]. Increased NF-κB exhibits carcinogenic effects through stimulation of gene expression, including cyclin D1, cyclin E, cyclin-dependent kinases 2 and c-Myc, as well as granulocyte and macrophage colony-stimulating factor and IL-6 [30]. In addition, it exerts anti-apoptotic effects by affecting Bcl-2 family genes, apoptosis inhibitors and FLICE-like cellular inhibitory protein [31]. Overactivation of NF-κB has been shown to promote epithelial-mesenchymal transition and metastasis through increased expression of MMP2/9 genes [32]. In addition, NF-κB has been shown to stimulate the expression of VEGF, a key regulator of angiogenesis, which in turn leads to increased tumor vascularization [31]. Current findings indicate that NF-κB plays a role in the development of resistance to chemotherapy [33].

Consumption of a high-fat diet rich in saturated fatty acids raises blood NF-κB levels while, following a low-fat diet that includes flaxseed consumption may reduce its levels [34].

STAT3 is a key transcription factor involved in CRC carcinogenesis [35]. STAT3 activation occurs in neurons and ENS glial cells via cytokines, among others. IL-6 activates Janus kinase (JAK), which phosphorylates STAT3 [35]. The next step is the dimerization of STAT3 and its penetration into the cell nucleus, where it regulates the expression of genes such as cyclin D1, Bcl-2, VEGF, MMP9, SNAIL [35]. Activation of these genes induces cell proliferation, impaired apoptosis, angiogenesis, invasion and migration of tumor cells. The STAT3 pathway is also implicated in inducing resistance to chemotherapy by enhancing lactate metabolism under conditions of reduced tissue oxygen concentration [35]. It has been shown that a high-fat diet can enhance activation of the STAT3 pathway, while quercetin supplementation can inhibit it [36].

Additionally, inflammatory processes in the gastrointestinal tract have been shown to increase neurogenesis, which is regulated by serotonin and its receptors, including the 5-HT4 receptor [17]. The increase in neurogenesis can result in altered intestinal motility and can affect the tumor microenvironment [17]. In addition, there is a decrease in serotonin transporter activity, resulting in increased availability of 5-HT, which can modulate the inflammatory response and promote angiogenesis and tumor cell proliferation [17]. Elevated serotonin levels may be associated with tryptophan consumption.

Enteric glial cells (EGCs) play an important role in the inflammatory response. EGCs can modulate the function of immune cells, such as mast cells and macrophages, by releasing signaling molecules (e.g., IL-6 and TNF-α) [37]. In addition, EGCs regulate the expression of TJs and mucins, which are essential for maintaining barrier integrity, which plays a key role in protection against pathogens and toxins [37]. P2X purinoceptor 7 receptors on neurons, which are activated during inflammation, lead to the release of purines, which in turn activate glial cells to produce NO, thereby exacerbating inflammation [17].

Dietary foods that reduce inflammation have been shown to include vegetables, fruits, foods rich in fiber, omega-3 fatty acids, probiotics, prebiotics, turmeric, ginger and whole grain products [38]. In contrast, foods that cause inflammation include alcohol, red meat, foods containing preservatives and artificial colors, simple sugars and sweets [38].

S100 family proteins

Glial cells belonging to the ENS play a pivotal role in the CRC microenvironment by producing S100 family proteins (S100A8/A9; S100A4; S100A6; S100A11; S100B) [39]. These proteins are involved in processes related to carcinogenesis, including proliferation, invasion, and migration of tumor cells, as well as angiogenesis [39]. In addition, they activate the NF-κB signaling pathway [39].

Consumption of foods rich in saturated fatty acids, foods that cause oxidative stress, and those with a high glycemic index can lead to increased levels of S100 proteins, as demonstrated by studies on the ketogenic diet [40]. The ingestion of foods rich in resveratrol, curcumin, omega-3 fatty acids, and quercetin, as well as the consumption of green tea, has been demonstrated to reduce the levels of these compounds in animal studies [41].

Tissue hormones

Leptin is a hormone produced by adipocytes; it has been demonstrated to reduce appetite and increase energy metabolism [20]. Cholecystokinin (CCK) is a hormone secreted by intestinal cells in response to the presence of fats and proteins in the small intestine; CCK performs several functions, including inhibiting gastric emptying, stimulating the secretion of pancreatic enzymes, and regulating the sensation of satiety [20]. It has been demonstrated that HFD leads to an increase in serum leptin levels and the induction of alterations in intracellular signaling pathways, including STAT3 [20]. This results in a reduction in the neuronal response to leptin [20]. A persistent elevation of leptin levels can result in the downregulation of leptin receptors on ENS neurons, thereby reducing their number [20]. A reduction in leptin sensitivity affects CCK signaling, thereby reducing the efficacy of this hormone in regulating GI motility [20]. Consequently, HFD may result in a reduction in the number of CCK receptors on ENS neurons, thereby diminishing their

sensitivity to the hormone [20]. As a result, a decrease in GI peristalsis was noted, which subsequently contributed to the development of constipation, a known risk factor for CRC [20].

Summary

The intricate relationship between diet, the ENS, and the pathophysiology of CRC is a subject of growing scientific inquiry. A comprehensive understanding of these interactions is vital for the development of effective strategies for the prevention and treatment of CRC, including the implementation of personalized dietary interventions. The data presented in this article can serve as a valuable reference for the development of dietary plans for this group of patients. The current state of knowledge indicates that the Western diet has the most pronounced effect on ENS levels. Therefore, it is of particular importance to limit the intake of foods belonging to this dietary group in favor of a diet containing a significant proportion of unprocessed foods of plant origin. Similarly, it is of great importance to ensure an adequate intake of other nutrients, including dietary fiber, omega-3 fatty acids, and probiotics.

In the future, it is advisable to conduct studies to identify the key factor among those described, using in vivo models. The next step should be to determine which substances or products most effectively inhibit this factor.

Authors' contributions

A.T.Z. and J.F. provided the overall concept and framework of the review; W.M.J. and A.T.Z. researched and identified appropriate articles, and wrote the manuscript; W.M.J., J.F. and A.T.Z. revised the manuscript. All authors read and approved the final version of the manuscript.

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Abbreviations

Ach — Acetylcholine
Akt — Protein kinase B
BDNF — Brain-derived neurotrophic factor
CCK — Cholecystokinin
CRC — Colorectal cancer
EGCs — Enteric glial cells
ENS — Enteric nervous system
ERK — Extracellular signal-regulated kinase
GDNF — Glial cell line-derived neurotrophic factor
GI — Gastrointestinal
HFD — High-fat diet
HO-1 — Heme Oxygenase-1
5-HT — 5-hydroxytryptamin, serotonin
IL — Interleukin
JAK — Janus kinase
MAPK — Mitogen-activated protein kinase
MMP — Matrix metalloproteinases
NGF — Nerve growth factor
NF-κB — Nuclear factor kappa-light-chain-enhancer of activated B cells
NO — Nitric oxide
PI3K — Phosphoinositide 3-Kinase

PNI — Perineural invasion
ROS — Reactive oxygen species
RNS — Reactive nitrogen species
SP — Substance P
TJs — Tight junctions
TNF-α — Tumor necrosis factor α
TrkA — Tropomyosin-related kinase A
VEGF — Vascular endothelial growth factor
VIP — Vasoactive intestinal peptide
WNT — Wingless-Related Integration Site

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