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REVIEW ARTICLE

Alternatives for the Prevention of Cancer Recurrences: Immunonutrition, Cat's Claw and Rhopalurus Junceus Venom

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ABSTRACT

Over the years, cancer treatment has focused on its eradication once it has been detected, however, it's common to find that a large number of neoplasms redevelop in patients, which reduces their quality and life expectancy when going through surgical treatments, chemotherapy and radiotherapy schemes once again. Several studies have been developed on some alternatives for the treatment of cancer that can be used as preventive methods for relapses, such as immunonutrition that is based on the administration of amino acids that contain sulfides, fatty acids, omega 3, vitamin and some minerals; the *Uncaria tomentosa* which is a plant that grows like a vine under tropical trees and whose extracts can induce oxidative stress; and the poison of *Rhopalurus junceus* (blue scorpion) which has been shown to induce necrosis or apoptosis in different malignant cell lines. This review summarizes points in favor of the use of Immunonutrition, *Uncaria tomentosa* and *Rhopalurus junceus* venom to limit a cancer recurrence.

Keywords: Neoplasms, Epidemiology, Incidence, Mortality, Recurrence, Therapy, Prevention, Cat's Claw, Immunonutrition, Scorpion Venom, Rhopalurus Junceus.

INTRODUCTION

Neoplasms can be defined as an alteration of cell growth triggered by a series of acquired genetic alterations, leading to clonal progeny.[1] Over the years, cancer treatment has focused on eradication once detected. However, it is common to find that many neoplasias re-develop in patients who had been considered cured. This reduces their life quality and expectancy when going through surgical treatments, along with chemotherapy and radiotherapy regimens again. Therefore there are various methods to diagnose cancer, as in the case of imaging tests such as computed tomography, magnetic resonance imaging, nuclear tomography or scintigraphy, positron emission tomography, x-ray and ultrasound.[2] Being an example of the last, endoscopic ultrasonography, allows the different layers of the digestive tract wall to be visualized and a peri-digestive area about 6 cm around the organ to be explored.[3] Likewise, other diagnostic tests are of significant help, like laboratory tests, which manage to identify tumor markers and biopsy, in which case methods are used to extract samples, like the use of a thin needle to perform bone marrow aspiration, lumbar punctures and some biopsies of the breast, prostate and liver. The use of endoscopy, taking colonoscopy and bronchoscopy as an example, exfoliative cytology, to analyze the cellular desquamation of cells and is commonly used for the diagnosis of cervical cancer, and finally surgery in which the area with abnormal cells is removed, which may be incision or excision.[2]

However, more innovative methods are currently being developed and used, such as the use of micro RNA (miRNA), as a tool for the forecasting and diagnosis in different cancers, observing that the miRNA expression profiles are correlated with the origin of the tissue development, for that reason they can be used to detect tumors.[4] Similarly, it's necessary to define recurrence and regression to delve more into the subject, defining the first as the illness reappearance sometime after the first onset.[5] and regression according to the Royal Spanish Academy as the retrocession or action of going back.[6]

Due to the increasing rate of cancer globally, research has begun to investigate ways to prevent this disease, detect it early and subsequently prevent its recurrence in treated individuals. This review mentions the relevant aspects of three methods that have the potential to become an effective therapy for cancer recurrence prevention, as well as list some advantages and disadvantages of each option to serve as a possible

prophylactic option for cancer recurrence.

METHODS

This was a review of published articles that was performed regarding the recent epidemiology of cancer and its recurrence, and a preventive therapy against regression of neoplasms with an emphasis on the use of immunonutrition, *Uncaria tomentosa*, and *Rhopalurus junceus* venom. The selected keywords used in PubMed, ScienceDirect and Mendeley were "neoplasm," "relapse," "prevention," "immunonutrition and cancer," "cat's claw and therapeutic use," "scorpion venoms and therapeutic use" and "Rhoapalurus."

The figures of the estimated number of cancer cases during 2020 were obtained from the page of the International Agency for Research on Cancer from the World Health Organization (WHO). The mortality rates and the frequency of its recurrence were obtained through the available values on the incidence, mortality and prevalence page corresponding to the year 2020; later, the mortality percentage was obtained using the formula Mortality (%) = (mortality in 2020/ incidence in 2020) X (100).

The percentage of recurrence of the different mentioned neoplasms was obtained by calculating an average of the recurrence percentages reported in the various articles consulted. The frequency of recurrence of each cancer was multiplied by its corresponding prevalence to get an estimate of cases in which the neoplasm recurred. This value was used for the calculation in other formulas, the product between the previously obtained value and the percentage of mortality for each neoplasm. The results were a second value necessary for the calculation of the following formulas and corresponds to the number of deaths in cases of recurrence for 2020. This value was used in a rule of three along with the total deaths due to neoplasia during 2020 as 100%; by this method, the percentage of deaths corresponding to cases of recurrence during 2020 was calculated.

The percentage of mortality in recurrence during 2020 was calculated with the formula: Mortality in recurrence (%) = (number of deaths in cases of recurrence in 2020/cases in which there was a recurrence from the prevalence at one year of 2020) X (100); the lethality in recurrence was calculated with the formula: Recurrence fatality (%) = (number of deaths in cases of recurrence in 2020/prevalence at one year of 2020) X (100).

The epidemiological analysis of some neoplasms in Mexico during 2020 was done by converting the values of age-standardized incidence rates (ASR) from map mode, available on the previously mentioned page, to the whole number using a rule of three between the total of cancer cases in Mexico in 2020, their respective ASR and the ASR of the main neoplasms according to the graph shown in the toolbar of the page.

RESULTS

This review included 50 papers, two of them from Mexico and one book. Table 1 shows the world figures about the 12 most common cancers in the world, as well as their mortality rates and the frequency of their recurrence.[7-38] Figure 1 illustrates the information regarding the percentage of mortality in recurrence during 2020. Finally, table 2 shows the epidemiological analysis of some neoplasms in Mexico during 2020.

DISCUSSION

Immunonutrition

Clinical nutrition is based on the perfect metabolic restitution and the recovery of the immune response.[39] It has been found that during the postoperative period in patients with head and neck cancer, the enteral nutrition administration with arginine reduces the percentage of fistulas development and hospital stay.[40]

Immunonutrition is based on the aminoacids administration containing sulfides, fatty acids, omega 3, vitamin and some minerals. One of its main objectives is to supply essential substrates to cancer patients close to surgery due to its influence on cellular immune function and the inflammatory response. On the other hand, it has been observed that in the patients with poor nutrition, it decreases humoral and cell-mediated response, so it seriously affects the cicatrization and increases the risk of infection, conditioning an increase in morbidity and perioperative mortality.[39] From what was noted above, it has been proposed that the immunonutrition improves the antibody-dependent cellular cytotoxicity by natural killer (NK) cells, overexpress KNG2D and CD16, increases the level of NK-CD56, T helper type 17 cells (Th17), as well as modulates T and NK cell-mediated immunity.[39]

It is used much more frequently in patients who are going to have a surgical operation for some gastrointestinal neoplasia such as cancer of the esophagus, gastric, colon and rectum,[39] because malnourished patients have higher postoperative morbidity and mortality, which leads to an increase in hospital stay and a worse quality of life with respect to

nourished patients. For this reason, in a prospective and randomized 11-months study, carried out at the General University Hospital of Ciudad Real, it was concluded that patients treated with oral supplementation using immunonutrients have fewer infectious complications, especially in surgical wound infection, intraabdominal abscess or pneumonia, due to arginine, ω-3 fatty acids and nucleotides, regulate the host's immune response, keep the mucosal barrier functionality, and help to modulate the local or systemic inflammatory reaction, the nitrogen balance and protein synthesis, becoming very beneficial for postoperative cancer patients.[41]

It has also been shown that patients undergoing surgery for colorectal cancer have better postoperative results if nutritional therapy is administered in the preoperative and continued in the postoperative period because it's associated with a lower incidence of complications such as paralytic ileus, infections, bleeding, among others. In turn, it's more convenient to administer nutrition by the enteral route whenever is possible since its observed preservation of intestinal mucosa integrity and also there are fewer complications.[42]

On the other hand, the immunonutrition administered to patients who will submit to hepatectomy has been shown to help reduce infectious complications and hospital stay, especially if it's administered postoperatively and there is even a decrease in mortality when formulas with ω-3 FA are included.[43]

Also, another systematic review states that immunonutrition is based on the implementation of certain nutritional formulas which in general include polyunsaturated fatty acids (FA) ω-3, arginine, glutamine and nucleotides, which can be administered parenterally or enterally, being of great help during any surgical intervention for cancer, since omega-3 fatty acids modify inflammation and immune reactions in tissues, likewise glutamine is important in incorporating the intestinal barrier function. Also, RNA tends to improve hypoimmunity and strengthens the defenses of cancer patients; on the other hand, arginine elevates immune function and there is improvement in the nitrogen balance.[43] At the same time, some studies talk about their job as an aminoacid that is usually incorporated into parenteral and enteral immunonutrition during the preoperative period of cancer surgery, which is considered to help reduce hospital stays and decreasing the risk of infectious complications.[44]

The immunomodulatory work provided by immunonutrition supports the enhanced activity of the immune system. This phenomenon may improve the response to potentially malignant cellular remnants present in patients previously treated for some types of cancer.

***Uncaria tomentosa:* Cat's claw**

The *Uncaria tomentosa (U. tomentosa)* is a plant that grows like a climbing plant under tropical trees. Due to the arrangement of its curved spines that resemble cat's claws at the base of their leaves, it is known in some South American countries as "uña de gato."[45] The compounds extracted from its root, leaves and bark have been investigated for their antiviral, antitumor, antimutagenic and anti-inflammatory effects. In general, its alkaloid components and its isomeric derivatives generate its´ important effects against cancer cells.[46,47]

The different doses used in *in-vitro* cell crop has a significant impact on the efficiency of extracts from cat's claw to induce apoptosis in malignant cells.[48,49]

Ciani et al. studied the antiproliferative activity and proapoptotic effect of the aqueous extract of the bark of *Uncaria tomentosa* (UT-ex) in the HaCat cells (spontaneously immortalized adult skin keratinocytes), A431 cells (carcinoma human epidermoid cells) and head and neck cell lines SCC011, SCC013 y SCC022 (originally derived from patients with carcinoma of squamous cells of the upper aerodigestive tract). They observed that cell viability of the different cell lines studied progressively was declined at UT-ex concentrations greater than 1.5 mg/ml, being the most sensitive cell type A431 and the most resistant the SCC022; reaching concentrations of 10 mg/ml all cell lines experienced a reduction in the ability to repair damage to its ADN and enter to the process of cell death.[48] They determined that UT-ex is capable of inducing oxidative stress in the different cell types studied; in addition, at high concentrations of the extract it reduces the YB-1 protein concentration that is responsible for protecting the cell against oxidative stress and repairing damage to the cellular genetic code when it interacts with other complexes, so the cell death caused by this compound derived from cat's claw is dependent on reactive oxygen species (ROS) and inhibition of antioxidant mechanisms.[48]

The difference in the preparation of cat's claw extracts is also related to different results and mechanisms of action in its antitumor activity.[47,49] Aljehani in 2015 conducted a study with human MCF7 cells (positive for ER gene of human breast cancer), MDA-MB-231 (triple-negative breast cancer cell), HBL 100 (breast cell without malignancy), HEK293T (embryonic kidney cell) and HSG (salivary gland cell); incubating each cell line in ethanol extracts prepared with 1 gram of cat's claw in 10% of ethanol to the 70% and phosphate-buffered saline or PBS which were prepared with 1 gram of *Uncaria*

Table 1: Epidemiological analysis of some neoplasms in the world.[7–38]

Cancer	Incidence during 2020	Mortality during 2020	Mortality (%) 2020	Prevalence at one year 2020	Recurrence rate (%)	% of total deaths corresponding to recurrence	Mortality in recurrence 2020 (%)	Lethality of recurrence
Breast	2 261 419	684 996	30.29	1 835 833	30%	24.35	30.29	9.09
Lung	2 206 771	1 796 144	81.39	1 170 519	25%	13.26	81.39	20.35
Colorectal	1 931 590	935 173	48.41	1 451 431	28.5%	21.42	48.42	13.80
Prostate	1 414 259	375 304	26.54	1 193 715	26.5%	22.37	26.54	7.03
Stomach	1 089 103	768 793	70.59	640 850	23%	13.53	70.59	16.24
Liver	905 677	830 180	91.66	449 222	50.5%	25.05	91.66	46.29
Cervical	604 127	341 831	56.58	410 809	30%	20.4	56.58	16.97
Esophagus	604 100	544 076	90.06	320 916	43.25%	22.97	90.06	38.95
Thyroid	586 202	43 646	7.45	469 802	15%	12.03	7.45	1.12
Bladder	573 278	212 536	37.07	454 015	34.16%	27.05	37.07	12.66
Pancreas	495 773	466 003	94	214 471	50.51%	21.85	94	47.48
Leukemia	474 519	311 594	65.67	336 669	30.86%	21.9	65.67	20.27

Table 2: Epidemiological analysis of some neoplasms in Mexico during 2020 [7]

Cancer	Incidence	1-year prevalence	Mortality
Prostate	58 761	21 093	15 132
Breast	56 394	23 682	15 132
Cervical	17 545	6 959	8 137
Colorectal	14 760	10 636	7 709
Thyroid	11 279	8 774	957
Uterus	10 583	4 246	2 284
Ovary	9 469	3 630	5 853
Stomach	8 633	4 876	6 710
Non melanoma skin	8 076	6 971	914
Leukemia	7 519	5 057	5 139
Liver	7 380	3 529	7 138
Lung	7 380	3 706	6 995
Pancreas	4 874	2 201	4 711

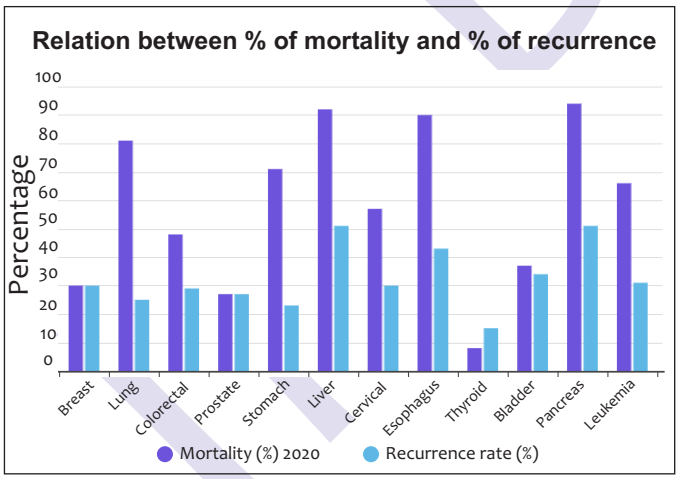

Figure 1: Relation between the mortality rate and recurrence rate of the 12 main malignancies in the world during 2020

tomentosa in 9 ml of water and 1 ml of broth of 10X PBS, giving treatment at different concentrations.[49] Treatment with a high dose to 1% of ethanol extract inhibited the growth of MCF7 cells by 65% and 35% to MDA-MB-231 cells. Meanwhile, the growth of non-malignant cells was reduced after treatment; on the other side the PBS extract at a dose of 1% inhibited the growth of 30% of the MCF7 cells treated in its solution, there wasn't significant effect in the other cell lines.[49] They analyzed the morphology of the MCF7 line, and at high concentrations observed a significant change in its form, which was coincident with the reduction of its viability; this same phenomenon was identified in HEK293T crops.[49] The MCF7 cells migration was reduced after treatment with high-dose ethanolic extract; although this effect also arose with the use of PBS extract, it didn't occur to the same extent.[49] The 1% ethanolic extract induced nuclear fragmentation and formation of apoptotic bodies in MCF7, the PBS extract led to the condensation and nuclear fragmentation in the same cell line after 72 hours of treatment. After using the TUNEL test to detect cell apoptosis, it was established that ethanolic extract is more effective in driving MCF7 cells to apoptosis, particularly after 72 hours of treatment.[49] The MCF7 cells treated with ethanolic extract showed a significant increase in caspases 8 and 9. These results suggest that apoptosis induced by the ethanolic extract of cat's claw occurs by the action of caspases.[49]

The proapoptotic capacity shown by *Uncaria tomentosa* extracts used *in vitro* cell models suggests a good coadjuvant option to continue oncology patients the treatment who have undergone chemotherapy or radiotherapy sessions, eradicating remaining malignant cells and even those resistant to common schemes. However, clinical trials in animals and humans are needed to know their pharmacokinetic and pharmacodynamic qualities, as well as the side and possibly toxic effects of their use.

Rhopalurus Junceus

Scorpion venoms have been studied for their antimicrobial, anesthetic, and antitumor capabilities. The investigations are mainly focused on the species belonging to North America, China and India; however, in recent years, the Habana scorpion has begun to have relevance. The poison of the species *Rhopalurus junceus* (*R. junceus*), also known as blue scorpion, has been used for various therapeutic purposes in Cuban medicine, that is the reason why several preparations are marketed in this country freely.[50,51] The venom of this species turns out to be harmless to mammals, causing only numbness, inflammation and paresthesia in the areas infiltrated by it. It has also been demonstrated in animal experiments that oral and intravenous administration allows a good bioavailability of the active components of the venom, which preserves good stability and a particular specificity by being

Table 3: Mechanisms of action by which immunonutrition, Uncaria tomentosa extracts and Rhopalurus junceus venom have potential as therapies in the treatment of malignant tumors

Therapy	Mechanism of action
Immunonutrition	● Through the administration of immunostimulant components such as omega 3 and arginine, it increases the immune function of patients, improves the inflammatory response and promotes the activation of Natural Killer cells by antibodies and T helper lymphocyte activity.
Extracts of Uncaria Tomentosa	● Induce oxidative stress in malignant cells, decreasing their ability to repair damage in the genetic material, altering their migration capacity and increasing caspase synthesis, which finally induces an apoptotic state.
Rhopalurus Junceus Venom	● Depending on the type of malignant cell and its sensitivity to the venom of this scorpion, there may be apoptosis induced by an increase in the expression of the p53 and bax genes, necrosis due to caspase expression from intrinsic and extrinsic pathways. ● It also alters ion channels of malignant cells, which delays tumor growth, proliferation, migration and signaling.

Table 4: Advantages and disadvantages of immunonutrition, *Uncaria tomentosa* extracts and *Rhopalurus junceus* venom, to be considered as therapies against the recurrence of a neoplasm

Therapy	Advantages	Disadvantages
Immunonutrition	● Has been implemented in hospitalized patients with good results in the postoperative of some tumors. ● It reduces the time of hospitalization in the postoperative period.	● There aren't studies with a strong relationship in the treatment or prevention of cancer.
Extracts of *Uncaria Tomentosa*	● It has a wide variety of components with antitumor activity. ● There are many ways to prepare extracts from its roots.	● It affects non-malignant cells, altering their growth. ● The plant grows exclusively in the Amazonian climate so its commercialization is difficult. ● It has not been implemented in animal or human models for therapeutic purposes against cancer. ● Its pharmacokinetics and pharmacodynamics aren't known.
***Rhopalurus Junceus* Venom**	● The venom is harmless to healthy cells. ● Its bioavailability and stability in animal models is known. ● Its effectiveness has been proven in various cell lines. ● Increases the cytotoxic activity of other drugs used in chemotherapy. ● It's already marketed for therapeutic purposes against cancer in Cuba.	● So far its research and formal medical use is limited to the Habana. ● Research on scorpion venoms as antineoplastic therapy has focused on other species.

stored for a longer time in cancerous tissues.[50,52]

In recent years and due to the increased resistance to chemotherapy of some tumors, an attempt has been made to find therapeutic alternatives, being venoms a territory to explore with many possibilities. In a study conducted to verify the effectiveness of the scorpion venom *R. junceus* in mice, it was found that it caused a cytotoxic effect in the murine breast cancer cell line F3II during the 72 hours, as well as the apoptosis of these cancer cells after 48 hours by causing the activation of the P53 protein. On the other hand, it was also found that when 0.8 and 3.2 mg/kg were administered, there was a delay in tumor growth, which in turn caused necrosis in the tumor.[53]

The R. junceus venom has been shown to be effective in decreasing the malignant cell lines viability and inducing apoptosis and necrosis in epithelial cell neoplasms in vitro.[51,52] Garcia et al. using blue scorpion venom prepared in distilled water, incubated human cancer cell lines at increasing doses from 0.1 to 1 mg/ml of the preparation, recording changes in cells after 8, 24 and 48 hours, the cell line most susceptible to changes was that from lung carcinoma. The most resistant was adenocarcinoma of the cervix; no evidence was found that the venom affects cells of hematopoietic origin. Therefore, the authors suggest a particular activity according to the histology of the tumor. [51] In this same study, evidence was found of decreased viability of malignant cells, increased expression of genes such as *p53* and *bax* especially in cells with greater resistance to the preparation with venom. These genes are involved in apoptotic processes; morphological studies of adenocarcinoma cells of the cervix suggested that the treated cell lines suffered from apoptosis.[51] Necrotic effects were observed in the most sensitive cell lines; in lung carcinoma, a decrease was found in the *BCL2* gene expression, and after being cropped for 48 hours, they underwent morphological changes typical of a cell with a high degree of necrosis.[51] Necrosis or apoptosis of a malignant cell line treated with *R. junceus* venom depends on its histological type and sensitivity.[51]

In the same way, it's claimed that the *R. junceus* venom is effective in cancer treatment by confirming its anticancer effect for inhibiting the progress of the murine breast tumor effect achieved through the CD31 protein expression reduction, this protein that acts as a prognostic marker for cancers such as endometrium, in addition to being found in arterioles, venules and capillaries of most cancers.[53] The caspases action induction by intrinsic and extrinsic route is another effect to be highlighted of the *R. junceus* venom on malignant cells. It's, therefore, a very complete alternative that should be studied for its wide range of antitumor effects.[51]

It is also considered that scorpion venom has great importance by acting on channels for ions such as Na, K, Cl and Ca_2, since these channels represent a crucial part for cell proliferation, migration and signaling. In addition to being positively regulated, they are related to carcinogenic characteristics. Therefore, scorpion venom toxins have the function of blocking these channels that are overexpressed in some types of cancer such as breast, colon, lung, liver, glioblastoma and prostate cancer, another reason why these toxins are said to have anticarcinogenic properties.[53]

Another study conducted to evaluate the *R. junceus* venom effectiveness with cytostatics in cervical cancer HeLa cell lines showed that it promotes synergistic effects at low cytostatic concentrations, in addition to increasing cytotoxic effects in the HeLa cell line, in cervical cancer cells in combination with low doses of drugs such as 5-FU, CDDP and DOX. Scorpion venom has been shown to cause apoptosis of cancerous HeLa cells via proapoptotic genes such as *p53* and *bax*.[54]

The mechanisms by which *R. junceus* venom acts vary among different malignant cells; its stability, selectivity for cancerous lines and availability for use in humans places it as one of the best therapeutic alternatives that can be used as an adjuvant to oncological therapies and even as an option to prevent recurrence of neoplasms.

CONCLUSION

It is expected that the recurrence cases will increase in conjunction with the number of cancer incidence per year. Faced with this situation, new methods of preventing and treating malignancy are being explored. The mechanisms by which these new proposals act are very diverse, so there is still a long way to go in the search for a solution. Table 3 and 4 summarize the mechanisms of action of the therapies explored in this article, as well as a brief analysis of their advantages and disadvantages.

Some of the proposed alternatives, such as immunonutrition, have been shown to be effective during surgery for some types of cancer, with fewer infectious complications observed, a better quality of life, shorter hospital stays and lower postoperative morbidity and mortality due to the immune response regulation and inflammation modification, especially if it is administered enterally. However, the little focus of this therapy in the field of oncology is the most significant limitation for its application as a preventive treatment for relapses.

Uncaria tomentosa extracts, for their part, show good effectiveness against different malignant cell lines; the diversity of its preparations and active components allows them to trigger apoptotic effects at high doses in cell crops. In addition, it decreases the migration of malignant cells, and these processes are mediated by the induction of oxidative stress and the increase of caspases. Despite this, there is still great difficulty in reaching experimentation in animal models. Many factors that alter the response to treatment with cat's claw are unknown. Also, the difficulty of growing this plant in high altitude and cold areas of the planet is an obstacle to its commercialization.

Scorpion venoms have also been extensively studied for their antitumor, antimicrobial and anesthetic effects, demonstrating in several studies that the *Rhopalurus junceus* venom is effective in cancer treatment because its anticancer effect acts by selectively causing cell death in malignant lines, inhibiting tumor progression, blocking cellular channels for some specific ions, increasing the cytotoxic effects of some chemotherapeutic drugs and increasing the expression of the apoptotic genes. It is a highly complete alternative in terms of mechanisms of action, adding its good bioavailability and stability after being administered orally and intravenously. It becomes one of the possible therapies to be developed in the coming years in the fight against cancer.

In conclusion, to prevent malignant tumors recurrence, the most promising prospect as a new therapy is the use of blue scorpion venom or *Rhopalurus junceus*. At the moment, it is only marketed as naturopathic therapy. However, the growing amount of research on its use will lead to the formal implementation of this poison in controlled studies in animal models and later in humans. With the results obtained in vitro so far, it can be suspected that it will be one of the new treatments against cancer and its recurrence in the future.

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