Immunonutrition hope? Oncoxin as cancer treatment supplement

Scoping review

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Keywords: Immune response; nutritional supplement; cancer; oncoxin

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Abstract:

Purpose: This study aimed to determine the efficacy and safety of Oncoxin as an antitumoral supplement, and to describe its mechanism of action.

Methods: We performed this scoping review according to the recommendations of the Joanna Briggs Institute and included patients older than 18 years-old who have any kind of tumor and receive Oncoxin as a supplement. We focused on the efficacy in terms of antitumoral properties, quality of life and survival, safety in terms of adverse events, and the mechanism of action. We did not limit for language or setting. We searched MEDLINE (Pubmed), EMBASE (Scopus), LILACS, and the Cochrane Central Register of Controlled Trials (CENTRAL) from inception to nowadays.

Results: We found a promising increment of survival when taking Oncoxin as a supplementary treatment. Additionally, the quality of life increased in terms of Karnofsky and EORTC scales. Regarding the mechanism of action, studies suggest it modifies inflammatory mediators' expression, as evidenced by the reduction of COX-2, IL-1β, IL-6, TNF-α, IL-1β, IL-12, and IFN-γ. Besides, it promotes an arrest in

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the progression of cells from G1 into S, along with an increase in p27 and a decrease in cyclin D1 and pRb.

Conclusions: We found promising complementary effects of Oncoxin to the standard treatment of cancer patients in diverse scenarios, with putative robust mechanisms of action. In addition to clinically relevant impacts verified in clinical trials, as well as it decreases the levels of pro-inflammatory cytokines, it can also decrease cytokines with antitumor activity such as IFN-γ, which should be further explored in larger trials and the long term.

Keywords: immune response; nutritional supplement; cancer; oncoxin

Introduction

Cancer's natural history and the clinical outcome depend upon complex interactions among tumor cells, the immune system, and host bodily homeostasis. Oncoimmunology is a new pillar of cancer therapy adding to surgery, chemo- and radiotherapy, and it is just the tip of an iceberg of new opportunities to improve patient recovery, recently demonstrated by the strategies that have motivated the 2018 Nobel Prize in Medicine (1–3).

A hyperinflammatory state depletes antioxidant defenses and suppresses lymphocyte function. In cancer patients, immunosuppression installs by diverse mechanisms, including increased inflammatory and oxidant stress. However, ROS or nitric oxide (NO, RNS) may play a double-faced role in cancer, entailing protumorigenic and tumor-suppressing effects in early and later stages, respectively. In that sense, antioxidants could be deleterious in the escape phase (3rd phase) during which ROS or nitric oxide would have an anti-tumor effect, depending on their concentrations (4). The potential to modulate the activity of the immune system by interventions with specific nutrients is termed immunonutrition that may be applied to any situation in which an altered supply of nutrients is used to modify inflammatory or immune responses (5). The nutrients most often studied were arginine, glutamine, branched-chain amino acids, n-3 fatty acids, and nucleotides.

The immunonutrition has the potential to counteract cancer patients' usual adverse situations (malnutrition and impaired immune function) positively influencing their recovery. In this scenario, Oncoxin Oral Solution (OOS) is an oral nutritional supplement that includes recognized anti-cancer antioxidants (green tea's polyphenols, epigallocatechin 3-gallate, vitamin B6, and vitamin C), anti-inflammatories, immunomodulators (cinnamic and glycyrrhizin acids), L-arginine and L-cysteine (6,7). It has been described that arginine increases the number of T cells and enhances T cell function; epigallocatechin 3-gallate has shown a reduction of tumor growth in prostate cancer. In the same way, other mechanisms have been found, such as the induction of pro-apoptotic pathways, the reduction of inflammation through NF-kB, and antioxidant properties (5, 7, 8).

This study aimed to determine the efficacy and safety of Oncoxin as an antitumoral supplement and to describe its mechanisms of action.

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Methods

We performed this scoping review according to the recommendations of the Joanna Briggs Institute (9).

- **Eligibility criteria**

Participants: Patients older than 18 years-old who have any kind of tumor and receive Oncoxin as a supplement.

Concept: We focused on the efficacy in terms of antitumoral properties, quality of life, survival, and safety in terms of adverse events.

Context: We did not limit for language or setting and included *in vitro*, *in vivo*, or molecular studies to explore the mechanism of action.

- **Information sources**

We conducted the literature search following the use of medical subject headings (MeSh), Emtree language, Decs, and text words related. We searched MEDLINE (PubMed), EMBASE (Scopus), LILACS, and the Cochrane Central Register of Controlled Trials (CENTRAL) from inception to nowadays. **Appendix 1** brings the search strategy in detail.

Were included any kind of studies (human primary studies, systematic reviews, and reviews) to respond to the first objective and (animal) to understand the mechanism of action.

To ensure literature saturation, we scanned references from relevant articles identified through the search, conferences, thesis databases, Open Grey, Google scholar, and clinicaltrials.gov, among others. We contacted the authors by e-mail in case of missing information.

- **Data collection**

Two researchers reviewed each reference by title and abstract. Then they scanned full-texts of relevant studies, applied pre-specified inclusion and exclusion criteria, and extracted the data. Disagreements were resolved by consensus. Two trained reviewers using a standardized form independently extracted the following information from each article: author, publication year, study design, geographic location (origin), authors names, title, objectives, inclusion and exclusion criteria, number of patients included, losses to follow up, timing, methods, intervention type, comparator, duration of the intervention, definitions of outcomes, outcomes, funding source and other key findings.

- **Synthesis of results**

We descriptively showed the results, trying to respond to the two objectives. Results can also be classified under main conceptual categories to facilitate the reader´s comprehension.

Results

- **Study selection**

We found a total of 37 studies with the search strategies and three with other sources. After exclusions, we finally included 15 studies in the qualitative analysis (6,10–23) (**Figure 1**).

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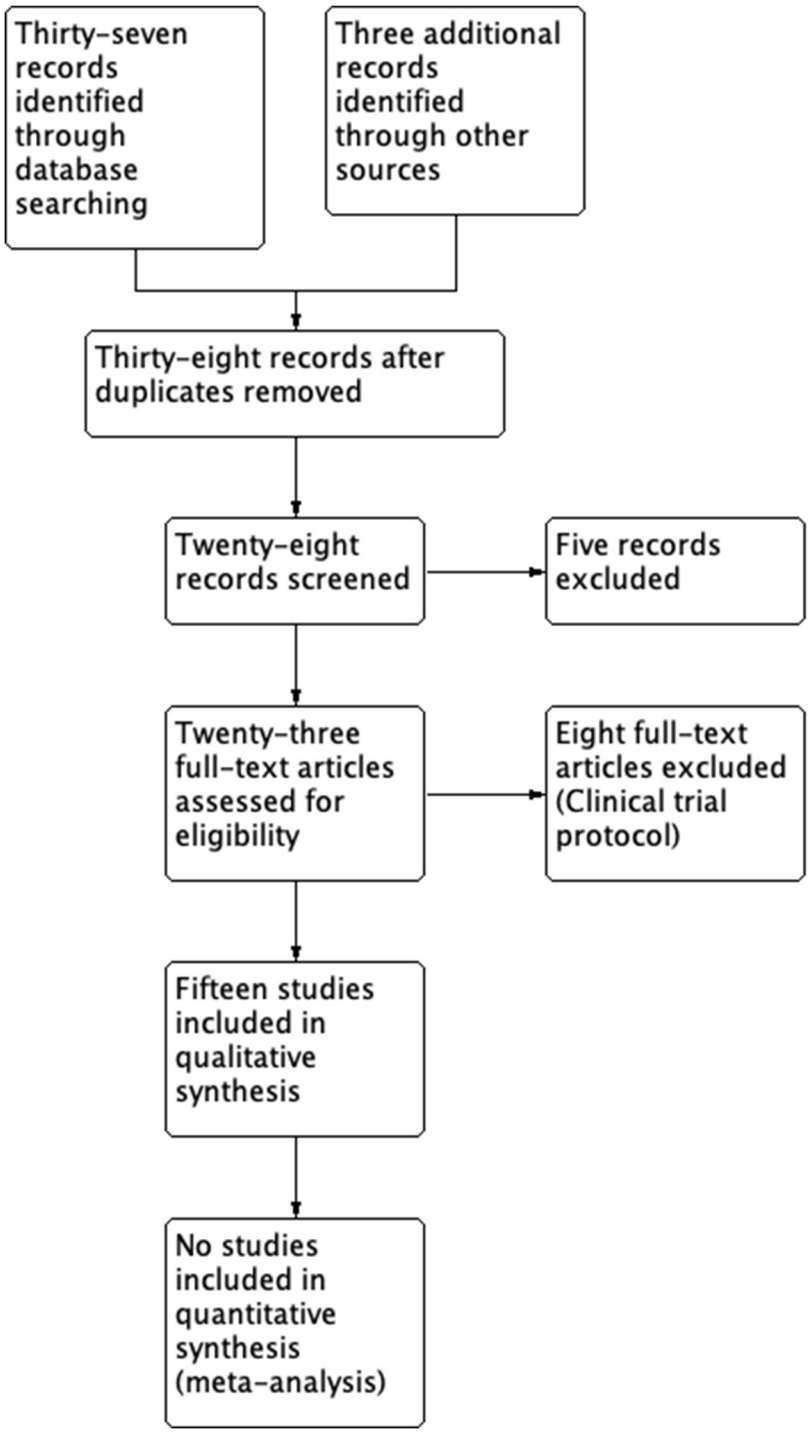

Figure 1. Flowchart of selected studies

- **Characteristics of included studies**

Six human studies with reported outcomes were found, including two non-randomized clinical trials, two randomized controlled clinical trials, and one phase II randomized controlled clinical trial. The types of cancer included were end-stage hepatocellular carcinoma (HCC), head and neck cancer, breast cancer, gastric cancer, non-small cell lung cancer (NSCLC), and one study included any type of

malignant neoplasm. Two of them were from Bangladesh, one from Cuba, one from Russia, and the other one from Russia and Kazakhstan (10,15–19). The number of subjects included varied from 15 to 133 balanced between treatment and placebo arms, and the follow-up varied from 0 to 12 months.

Finally, we found nine in vitro (human or murine cell lines) and/or in vivo (murine models) studies assessing mechanisms of action of Oncoxin. Breast cancer, acute myeloid leukemia (AML), colorectal cancer (CRC) metastasis to the liver, HCC, small cell lung cancer (SCLC), pancreatic adenocarcinoma, and glioblastoma (GBM) were the types of cancers described. All of them were performed in Spain (6,11–14,20–23).

Appendix 2 describes in detail the characteristics of basic and human included studies.

- **Efficacy and Safety of Oncoxin**

Clinical trials in humans assessed the efficacy and the safety in terms of several variables including quality of life (evaluating symptoms, Karnofsky index, psycho-emotional state or wellbeing), survival, tumor progression, nutritional condition (which included body mass, appetite, days with regular food intake), and tolerance to oncologic treatment (chemo- and/or radiotherapy). Oncoxin was well tolerated except for nausea, which was reported in seven patients in the study performed by Kaidarova et al. 2019 (15). There were no other adverse effects.

- **Survival**

Uddin et al. 2009 reported an overall survival of 87.65% in experimental groups versus 74.68% in controls of patients with head and throat, breast, and uterine cervix cancer after 12 months (10). Al-Mahtab et al. 2015 reported survival of 21% in 19 patients with end-stage hepatocellular carcinoma treated with Oncoxin versus 0% in 10 patients of the control group at six months. They found a significant difference ($p<0.0001$) 2 months after the study, beginning with a 47% survival in the Oncoxin group versus 0% in the control (16). Rivas et al. 2018 found survival of 67% in patients with head and neck carcinoma who received Oncoxin compared to placebo with a 63% survival during a year without significant difference ($p=0.599$) (17).

- **Quality of life and well being**

Two studies evaluated patients with Karnofsky's Performance Status (KPS). Uddin et al. 2009 showed a 59.26% increase in Karnofsky Index in the experimental group versus 30.38% in the control. They also reported a significant improvement of general state and substantial psycho-emotional improvement in terms of fewer episodes of depression and increased optimism (10). Patients with breast cancer undergoing radiotherapy showed a significant decrease of KPS by almost 50%, 45±7.2 after 3-4 weeks in the control group versus 87±8.53 in patients receiving Oncoxin. Also, the authors assessed the quality of life (QoL) in this study using Beck's Depression Inventory-II (BDI-II) and found a lower incidence of post-radiotherapy events in patients treated with Oncoxin (44% versus 92% in the control group) (18).

Rivas et al. 2018 evaluated QoL using the general questionnaire from the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30. They compared results within the Oncoxin group at the beginning and the end of the study. They found significant differences in scales of physical functioning ($p=0.0017$)

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and symptoms (asthenia p=0.0009, nausea/vomiting p=0.0107, and pain p=0.0112). They only compared the Oncoxin group versus control at the beginning without finding significant differences (17).

In patients with end-stage HCC, Al-Matab et al. 2015 described that most of the patients taking Oncoxin reported a feeling of well-being, and three patients reported that they were feeling well after its intake (16).

Finally, Kaidarova et al. 2019 (15) evaluated the differences in QoL when giving Oncoxin to a group of patients with gastric cancer or NSCLC receiving paclitaxel/carboplatin using the Symptom Distress Score of the Edmonton Symptom Assessment System (SDS ESAS) questionnaire. They compared results at the baseline, at two weeks and three weeks, and found a clinically meaningful improvement in QoL after three weeks compared with those in the control group ($p<0.001$). There were no significant differences in the emotional score, and significant differences in the physical score were present after week 3 ($p<0.001$). They also found significant differences for well-being at visits 2 and 3 ($p<0.05$), and for tiredness after three weeks ($p<0.001$).

- **Toxicities and adverse effects related to oncologic treatment**

Uddin et al. 2009 described that patients who received Oncoxin during a year showed a decreased incidence of leukopenia, increased resistance to aggressive oncological treatment, and a decrease of acute effects of radiation. As they reported, the group receiving Oncoxin without chemotherapy tolerated radiotherapy much better (10).

In patients with head and neck carcinoma, there were no differences among radio-chemotherapy adverse events in the intervention group versus the conservative management group. However, in the group receiving Oncoxin no severe toxicities were recorded, in contrast with the placebo group, which had 12% of Grade-III toxicities (due to dysphagia and dyspnea) assessed by the Common Terminology Criteria for Adverse Events, showing a significant difference ($p=0.01$) (17).

Shumsky et al. 2019 evaluated the efficacy of Oncoxin in patients treated with radio and/or chemotherapy with oral mucositis, assessed by the Mean WHO Oral Toxicity Scale grade. They found significantly lower grades of mucositis in patients receiving Oncoxin versus patients in control at 6-8 days after the first visit ($p=0.02$) and 19-21 days ($p<0.001$). Furthermore, they evaluated individual toxicity grades according to the grading criteria of the National Cancer Institute Common Toxicity Criteria, finding significant differences in the four toxicity related domains (leukocytes $p=0.04$, infections $p<0.005$, alanine aminotransferase $p=0.04$, aspartate aminotransferase $p=0.012$) after 19-21 days (19). Kaidarova et al. 2019, also found significant differences (alanine aminotransferase $p=0.005$, aspartate aminotransferase $p<0.001$) after 20 days, and hemoglobin just after two weeks ($p<0.001$). They did not find differences in bilirubin, alkaline phosphatase, leukocytes, lymphocytes, or platelets (15).

- **Clinical and laboratory outcomes**

Uddin et al. 2009 reported an increase of 1-4 kg in patients receiving Oncoxin (10). Shumsky et al. 2019 did not found a significant difference in body mass index between both groups. However, patients treated with Oncoxin gained 2.5 kg (-1.86

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to 6-86) while patients in control lost 2.8 kg (-4.96 to -0.55) with significant difference (p=0.03) (19).

In the study performed by Kaidarova et al. 2019, a higher proportion of patients receiving Oncoxin maintained or increased their body mass and albumin levels compared to controls (p<0.05), with odds ratios (OR) of unchanged or increased body mass of 2.74 (95%CI 1.32-5.67) and 3.07 (95%CI 1.45-6.52) at 2 and 3 weeks respectively, and OR for serum albumin of 4.20 (95%CI 1.96-8.98) and 11.46 (95%CI 4.41-29.8) at 2 and 3 weeks respectively (15).

Rivas et al. 2018 evaluated weight loss as part of toxicities, and they found no significant difference between both groups (p=0.372). They also evaluated the antitumor response and tumor progression. They did not find a significant difference between both groups when evaluated according to Response Evaluation Criteria In Solid Tumors (RECIST) 4-6 weeks after the culmination of radiotherapy and chemotherapy treatment (p=0.284), and one year after patient inclusion (p=0.603). 79% of patients treated with Oncoxin had a complete response, while 60% of patients in the placebo group achieved it (17).

Al-Mahtab et al. 2015 found a higher number of patients presenting ascites, diffuse HCC, multiple HCC, solitary HCC, and hepatic encephalopathy in patients receiving Oncoxin. Besides, they found higher levels of alpha-fetoprotein (AFP) in patients treated with Oncoxin (6113±12327 versus 7062.1±14464.8 ng/ml in controls). Furthermore, a higher number of patients in the control group presented bilirubin levels > 5 mg/dL (16).

Finally, Shumsky et al. 2019 evaluated food intake and appetite. They found that patients treated with Oncoxin had more days with regular food intake compared to controls after 19-21 days (p=0.04). However, there were no differences in days with normal appetite (p=0.13), but in the control group, there were no days with a normal appetite, while in the Oncoxin group, there were 4.80 (0.59-9.01) days with normal appetite (19).

Kaidarova et al. 2019 evaluated appetite as part of the SDS ESAS with significant differences at visits 2 and 3 (p<0.05) (15). Rivas et al. evaluated loss of appetite included in QLQ-C30 without a difference in the Oncoxin group at the end of the study (p=0.14) (17). Also, 32% of patients with end-stage HCC receiving Oncoxin reported an improvement of appetite (16).

- **Mechanisms of action**

For assessing the mechanism of action, studies *in vitro* and *in vivo* using murine models tried to describe the effect of Oncoxin on immune mechanisms, cell cycle progression, proliferation, apoptosis, and transcriptional effects based on gene expression. They also studied the effect on tumor development and progression, and the effect in combination with conventional antitumoral treatments.

Oncoxin modifies inflammatory mediators expression (7), as evidenced by elevation of IL-6 in AML indicating stimulation of immune system (20); reduction of RNA levels of COX-2, IFN-γ, IL-1β, IL-6, and TNF-α in CRC metastasis to the liver (22); reduction of IL-1β, IL-12, and IFN-γ, and elevation of IL-10 in pancreatic tumor-bearing mice, as well as, reverted the expression of genes already reported as being altered in pancreatic cancer (13).

Hernández-SanMiguel et al. 2019 did not find any effect of Oncoxin on glioblastoma (GBM) cell viability, however, they found that Oncoxin inhibited the self-

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renewal capacity of cancer stem cells in some GBM cells. Moreover, Oncoxin could exert its antitumorigenic action in this type of cancer through the inhibition of M2 macrophages (immunosuppressive) differentiation and reduction in the levels of reactive oxygen species in the macrophages (14).

Hernandez-García et al. 2015 in HER2-overexpressing breast cancer cell lines, found an increase in the proportion of cells treated with Oncoxin in the G0/G1 phases of the cell cycle, suggesting an arrest in the progression of cells from G1 into S. Also, treatment with Oncoxin caused an increase in p27, together with decreases in cyclin D1 and pRb (20). These results were similar to those described by Diaz-Rodriguez et al., 2017, who found that Oncoxin delayed not only G1 to S phase progression but also M to G1 phase progression in cells of HCC, suggesting a delay in cell cycle progression rather than cell cycle arrest (23).

Diaz-Rodriguez et al. 2018 also found that Oncoxin induced cell death and cell cycle delay. Biochemical and genomic analyses performed showed that Oncoxin augmented p27 in cell lines of SCLC treated with Oncoxin. This effect was observed *in vivo* when the p27 pathway was found to be upregulated in the Oncoxin-treated tumors (12). In CRC metastasis to the liver, there was an increase in the number of cells in phase G2/M and a slight reduction in the number of cells in phase S (22).

AML tumors treated with Oncoxin showed a decrease in cell proliferation. This effect was consistent with analyses of gene expression identifying some involved in cell cycle regulation and progression such as CDK15 or RGCC, and a decrease in the amount of Leukemia Inhibitory Factor (LIF) was also found (21). Finally, Pérez-Peña et al. 2019 studied cells of SCLC and AML treated with Oncoxin. They identified a group of genes deregulated corresponding to cell cycle checkpoints and found the E2F–TFDP pathway to be the significant deregulated route (6).

Among mechanisms of apoptosis and cell death induction described, HER2-overexpressing breast cancer cells treated with Oncoxin increased annexin V, staining of DNA in the Sub-G0 region, cleavage of PARP (an indicative of caspase activation), activation of caspase 8 and 3, and increased γ-H2AX (as an indication of a DNA damage response secondary to apoptotic DNA laddering) (20).

Marquez et al. 2016 found an increase in cell number in sub-G1 in vitro and intratumoral increase of caspase-3 in vivo in CRC metastasis to the liver (22). Diaz-Rodriguez et al. 2018 also reported that Oncoxin caused cell death by activation of caspases as determined by western blotting assessing levels of PARP or caspases. They also found that several intracellular pathways involved in cell proliferation or apoptosis were deregulated, including the DNA damage response pathways, cell cycle regulation, or the PI3K/AKT/mTOR, Wnt, or insulin signaling (12).

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Discussion

The medical literature has several studies describing a promissory potential supplementary effect of Oncoxin to standard cancer treatment scenarios of diverse origins, types, and stages, especially concentrating in more advanced settings, with laboratory and clinical evidence of benefits such as increments in survival and quality of life and minimal adverse effects described so far (7,20,23).

Up to now the explored possible mechanisms of action go from immune modulation to interferences in germane mechanisms such as cell cycle, proliferation, and apoptosis regulation (7).

Notably, as well as it decreased the levels of pro-inflammatory cytokines, it can also decrease antitumor cytokines, such as IFN-γ; moreover, the change in this cytokine level was opposed to IL-10 that have increased in pancreatic tumor-bearing mice (20). In contrast, it has been reported that systemic IL-10 administration can lead to increased release of antitumor cytokine IFN-γ through enhancing the activity of CD8+ tumor-infiltrating T cells (TILs), and to the downregulation of the protumoral cytokine transforming growth factor-beta (TGF-β) levels in patients with solid tumors (24).

The decreased levels of IFN-γ induced by Oncoxin supplementation would be a consequence of a negative feedback loop created by IL-10, as a potent immunoregulatory cytokine, to control the production of IFN-γ. Additionally, Oncoxin may also blur the 'danger signal'; such a condition can result in downregulation of IFN-γ (25). Nevertheless, such a premise should be experimentally validated, knowing that IL-10 has been demonstrated to induce several essential mechanisms for effective antitumor immune surveillance, including expression of IFN-γ (26).

Also, human studies were conducted independently by different groups and countries including Bangladesh, Cuba, and Russia, allowing a wide ethnic diversity exploration. Moreover, clinical trials included studies in diverse types of cancer such as prostate, gastric, cervical/endometrial, breast, and metastatic/advanced ovarian epithelial cancers, melanoma, HCC, and metastatic colorectal adenocarcinoma.

Besides, the literature supporting the Oncoxin supplemental interference in diverse cancer scenarios is realistic and with robust methodologies including prospective randomized placebo-controlled studies. Despite that, multiple limitations exist among the included studies, such as open-labeled trials, lack of control groups, small sample size, which could introduce bias in the results.

Future studies should confirm and further explore Oncoxin incremental mechanisms to different standard cancer treatments and offer more detailed mechanistic studies in addition to larger cohorts with longer follow-up to corroborate previous results.

Conclusions

Current literature shows promising complementary effects of Oncoxin to the standard treatment of cancer patients in diverse scenarios. This is a well-tolerated and safe supplement that seems to improve survival, well-being, and quality of life in cancer patients, nonetheless multiple methodological issues are limiting the supporting evidence and room for future studies. It might help patients to deal with

toxicities and adverse effects related to cancer treatment and improve their nutritional or clinical profiles. As well as it decreases the levels of pro-inflammatory cytokines, it can also decrease cytokines with antitumor activity. Besides, it could exert an arrest in the progression of the cell cycle, inducing cell death, and cell cycle delay, which involves several intracellular pathways.

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Author Contributions:
HAGP: data collection, data analysis, manuscript writing
JCGO: data collection, data analysis, manuscript writing
LOR: project development, data analysis, manuscript writing

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Appendix 1: Search strategy
Appendix 2: Characteristics of included studies

Appendix1. Search Strategy

MedLine (PubMed):
(Oncoxin.mp or ocoxin.mp or (Ocoxin Oral solution).mp or exp ocoxin or (ascorbic acid).mp or (plant extracts).mp or (vitamin b12).mp or (vitamin b 6).mp) AND (exp neoplasms or cancer*.mp or neoplasm*.mp or neoplasia*.mp or tumor*.mp or malignac*.mp)

Embase (Scopus):
TITLE-ABS-KEY(Oncoxin or ocoxin or "Ocoxin Oral solution" or "ascorbic acid" or "plant extracts" or "vitamin b12" or "vitamin b 6") AND TITLE-ABS-KEY("cancer*" or "neoplasm*" or "neoplasia*" or "tumor*" or "malignac*")

Central (Ovid)
(Oncoxin.mp or ocoxin.mp or (Ocoxin Oral solution).mp or exp ocoxin or (ascorbic acid).mp or (plant extracts).mp or (vitamin b12).mp or (vitamin b 6).mp) AND (exp neoplasms or cancer*.mp or neoplasm*.mp or neoplasia*.mp or tumor*.mp or malignac*.mp)

References

1. Leach DR, Krummel MF, Allison JP. Enhancement of antitumor immunity by CTLA-4 blockade. Science (80-). 1996;271(5256):1734–1736.
2. Iwai Y, Terawaki S, Honjo T. PD-1 blockade inhibits hematogenous spread of poorly immunogenic tumor cells by enhanced recruitment of effector T cells. Int Immunol. 2005;17(2):133–44.
3. Sharma P, Allison JP. Dissecting the mechanisms of immune checkpoint therapy. Nat Rev Immunol. 2020 Feb;20(2):75–6.
4. Mijatović S, Savić-Radojević A, Plješa-Ercegovac M, Simić T, Nicoletti F, Maksimović-Ivanić D. The double-faced role of nitric oxide and reactive oxygen species in solid tumors. Vol. 9, Antioxidants. MDPI AG; 2020.
5. Calder PC. Immunonutrition. Vol. 327, British Medical Journal. BMJ Publishing Group; 2003. p. 117–8.
6. Pérez-Peña J, Díaz-Rodríguez E, Sanz E, Pandiella A. Central role of cell cycle regulation in the antitumoral action of ocoxin. Nutrients. 2019;11(5):1–12.
7. Pandiella-Alonso A, Díaz-Rodríguez E, Sanz E. Antitumoral Properties of the Nutritional Supplement Ocoxin Oral Solution: A Comprehensive Review. Nutrients. 2020;12(9):2661.
8. Masko E, Allott E, Freedland S. The Relationship Between Nutrition and Prostate Cancer: Is More Always Better? Eur Urol. 2013;63(5):810–020.
9. Peters M, Godfrey C, McInerney P, Baldini Soares C, Khalil H, Parker D. Scoping Reviews. In: Aromataris E, Munn Z (Editors)., editors. Joanna Briggs Institute Reviewer's Manual. First. Australia: The Joanna Briggs Institute; 2017.
10. Uddin D, Islam MA, Mahmood I, Ghosh AK, Khatun RA, Kundu S. Findings of the 3-Month Supportive Treatment with Oncoxin Solution Beside the Standard Modalities of Patients with Different Neoplastic Diseases. J Teach Assoc. 2009;22(2):172–5.
11. Hernandez-Unzueta I, Benedicto A, Olaso E, Sanz E, Viera C, Arteta B, et al. Ocoxin oral solution® as a complement to irinotecan chemotherapy in the metastatic progression of colorectal cancer to the liver. Oncol Lett. 2017;13(6):4002–12.
12. Díaz-Rodríguez E, Sanz E, Pandiella A. Antitumoral effect of Ocoxin, a natural compound-containing nutritional supplement, in small cell lung cancer. Int J Oncol. 2018;53(1):113–23.
13. Hernandez-Unzueta I, Benedicto A, Romayor I, Herrero A, Sanz E, Arteta B, et al. Ocoxin Oral Solution Exerts an Antitumoral Effect in Pancreatic Cancer and Reduces the Stromal-Mediated Chemoresistance. Pancreas. 2019;48(4):555–67.
14. Hernández-SanMiguel E, Gargini R, Cejalvo T, Segura-Collar B, Núñez-Hervada P, Hortigüela R, et al. Ocoxin Modulates Cancer Stem Cells and M2 Macrophage Polarization in Glioblastoma. Oxid Med Cell Longev. 2019;2019:1–12.
15. Kaidarova DR, Kopp MV, Pokrovsky VS, Dzhugashvili M, Akimzhanova ZM, Abdrakhmanov RZ, et al. Multicomponent nutritional supplement Oncoxin

and its influence on quality of life and therapy toxicity in patients receiving adjuvant chemotherapy. Oncol Lett. 2019;18(5):5644–52.
16. Al-Mahtab M, Akbar SMF, Khan MSI, Rahman S. Increased survival of patients with end-stage hepatocellular carcinoma due to intake of ONCOXIN®, a dietary supplement. Indian J Cancer. 2015;52(3):443–6.
17. Rivas IC, Silva JA, Alfonso G, Candanedo H, Cuervo Y, Mestre B, et al. Oncoxin-Viusid with Radiotherapy and Chemotherapy in Patients with Head and Neck Cancer: Results from a Phase II, Randomised, Double-Blind Study. J Cancer Sci Ther. 2018;10(10):317–27.
18. Sengupta AK. Supportive benefits of a nutritional supplement in breast cancer patients receiving radiation therapy. Support Care Cancer. 2018;26(Suppl 2):S272.
19. Shumsky A, Bilan E, Sanz E, Petrovskiy F. Oncoxin nutritional supplement in the management of chemotherapy- and/or radiotherapy-associated oral mucositis. Mol Clin Oncol. 2019;463–8.
20. Hernández-García S, González V, Sanz E, Pandiella A. Effect of Oncoxin Oral Solution in HER2-Overexpressing Breast Cancer. Nutr Cancer. 2015;67(7):1159–69.
21. Díaz-Rodríguez E, Hernández-García S, Sanz E, Pandiella A. Antitumoral effect of Ocoxin on acute myeloid leukemia. Oncotarget. 2016;7(5):6231–42.
22. Márquez J, Mena J, Hernandez-Un Zueta I, Benedicto A, Sanz E, Arteta B, et al. Ocoxin® oral solution slows down tumor growth in an experimental model of colorectal cancer metastasis to the liver in Balb/c mice. Oncol Rep. 2016;35(3):1265–72.
23. Díaz-Rodríguez E, El-Mallah AM, Sanz E, Pandiella A. Antitumoral effect of ocoxin in hepatocellular carcinoma. Oncol Lett. 2017;14(2):1950–8.
24. Zhang H, Wang Y, Hwang ES, He YW. Interleukin-10: An immune-activating cytokine in cancer immunotherapy. J Clin Oncol. 2016 Oct;34(29):3576–8.
25. Hadjidj Z, Messali R, Aribi M. Lack of cell movement impairs survival of peripheral blood IL-2-stimulated natural killer cells originating from solid cancer and promotes red blood cells to induce their switch toward a regulatory phenotype. Immunol Lett. 2020;221:6–17.
26. Mumm J, Emmerich J, Zhang X, Chan I, Wu L, Mauze S, et al. IL-10 elicits IFNγ-dependent tumor immune surveillance. Cancer Cell. 2011;20:781–96.