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SYSTEMATIC REVIEW

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Immunonutrition hope? Oral nutritional supplement on cancer treatment

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Abstract

Objectives: To determine the efficacy and safety of antitumoral nutritional supplement (Oncoxin®), and to describe its mechanism of action.

Methods: Scoping review according to the recommendations of the Joanna Briggs Institute included patients older than 18 years who have any kind of tumour and receive Oncoxin® as a supplement regarding the efficacy in terms of antitumoral properties, quality of life and survival, safety in terms of adverse events, and the mechanism of action. With no limit for language or setting, MEDLINE (Pubmed), EMBASE (Scopus), LILACS and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched from database inception to May 2021.

Findings: A promising increment of survival and quality of life in terms of Karnofsky and EORTC scales. Regarding the mechanism of action, studies suggest that 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 the progression of cells from G1 into S, along with an increase in p27 and a decrease in cyclin D1 and pRb. 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.

Interpretations and implications: Current literature shows promising complementary effects of oral supplements to the standard treatment of cancer patients in diverse scenarios. It might help patients to deal with toxicities and adverse effects related to cancer treatment and improve their nutritional or clinical profiles.

1 | INTRODUCTION

Cancer's natural history and clinical outcome depend upon complex interactions among tumour cells, the immune system and host body 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 defences and suppresses lymphocyte function. In cancer patients, immunosuppression installs by diverse mechanisms, including increased inflammatory and oxidant stress. However, reactive oxygen species (ROS) or nitric oxide, reactive nitrogen species may play a double-faced role in cancer, entailing protumorigenic and tumour-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 a pro-tumour 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, tryptophan and nucleotides like thymine.[6]

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 recognised 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.[7,8] 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 tumour 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.[5,8,9]

While dietary supplements and medicines are widely marketed over the internet, many uncertainties and conflicts underlie the supplements market, mainly limited evidence from toxicological in vivo and human clinical studies. The evidence of studies is central in decision-making for healthy individuals and patients.

This study's clinical question is to determine the efficacy and safety of Oncoxin® (Catalysis S.L., Madrid, Spain), as an antitumoral supplement and to describe its mechanisms of action.

Review criteria

- According to the recommendations of the Joanna Briggs Institute, we searched MEDLINE (Pubmed), EMBASE (Scopus), LILACS and the Cochrane Central Register of Controlled Trials (CENTRAL) from inception to nowadays.

Message for the clinic

- Current literature shows promising complementary effects of oral supplements to the standard treatment of cancer patients in diverse scenarios.
- It might help patients to deal with toxicities and adverse effects related to cancer treatment and improve their nutritional or clinical profiles.

2 | METHODS

We performed this scoping review according to the recommendations of the Joanna Briggs Institute.[10]

2.1 | Eligibility criteria

- *Participants*: Patients older than 18 years who have any kind of tumour 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 language or setting and included in vitro, in vivo or molecular studies to explore the mechanism of action.

2.2 | 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 the database inception to May 2021. Appendix 1 brings the search strategy in detail.
- We 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.

2.3 | 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 standardised form independently extracted the following information from each article: author, publication year, study design, geographical location (origin), authors names, title, objectives, inclusion and exclusion criteria, number of patients included, loss to follow-up, timing, methods, intervention type, comparator, duration of the intervention, definitions of outcomes, outcomes, funding source and other key findings.

2.4 | 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.

3 | RESULTS

3.1 | Study selection

We found a total of 38 studies with search strategies and three with other sources. After exclusions, we finally included 16 studies in the qualitative analysis[7,11-25] (Figure 1).

3.2 | Characteristics of included studies

Six human studies with reported outcomes were found, including two non-randomised clinical trials, two randomised controlled clinical trials and one phase II randomised 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.[11,16-20] The number of subjects included varied from 15 to 133 balanced between treatment and placebo arms, and the follow-up was up to 12 months.

Finally, we found 10 in vitro (human or murine cell lines) and/or in vivo (murine models) studies assessing mechanisms of action of Oncoxin®. Breast cancer, acute myeloid leukaemia (AML), colorectal cancer (CRC) metastasis to the liver, HCC, small-cell lung cancer (SCLC), pancreatic adenocarcinoma, glioblastoma (GBM) and melanoma were the types of cancers described. All of them were performed in Spain.[7,12-15,21-25]

Table S1 describes in detail the characteristics of basic and human included studies.

3.3 | 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 well-being), survival, tumour 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.[16] There were no other adverse effects.

3.4 | Survival

Uddin et al reported an overall survival of 87.65% in experimental groups vs 74.68% in controls of patients with head and throat, breast, and uterine cervix cancer after 12 months.[11] Al-Mahtab et al reported survival of 21% in 19 patients with end-stage hepatocellular carcinoma treated with Oncoxin® vs 0% in 10 patients of the control group at 6 months. There was also a significantly increased rate of survival two months after study commencement (47% in the Oncoxin® group vs 0% in the control, $P < .0001$).[17] Rivas et al 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 ($P = .599$).[18]

3.5 | Quality of life and well-being

Two studies evaluated patients with Karnofsky's Performance Status (KPS). Uddin et al showed a 59.26% increase in Karnofsky Index in the experimental group vs 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.[11] Patients with breast cancer who took Oncoxin® and underwent radiotherapy showed a significant improvement in KPS by almost 50% (87 ± 8 in patients receiving Oncoxin vs 45 ± 7 after 3-4 weeks in the control group). 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% vs 92% in the control group).[19]

Rivas et al 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 ($P = .0017$) and symptoms (asthenia $P = .0009$, nausea/vomiting $P = .0107$ and pain $P = .0112$). They only compared the Oncoxin® group vs control at the beginning without finding significant differences.[18]

In patients with end-stage HCC, Al-Matab et al 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.[17]

Finally, Kaidarova et al[16] 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 2 and 3 weeks, and found a clinically meaningful improvement in QoL after 3 weeks compared with those in the control group ($P < .001$). There were no significant differences in the emotional score, and significant differences in the physical score were present after week 3 ($P < .001$). They also found significant differences for well-being at visits 2 and 3 ($P < .05$), and for tiredness after 3 weeks ($P < .001$).

3.6 | Toxicities and adverse effects related to oncologic treatment

Uddin et al described that patients who received Oncoxin® during a year showed a decreased incidence of leukopenia, increased

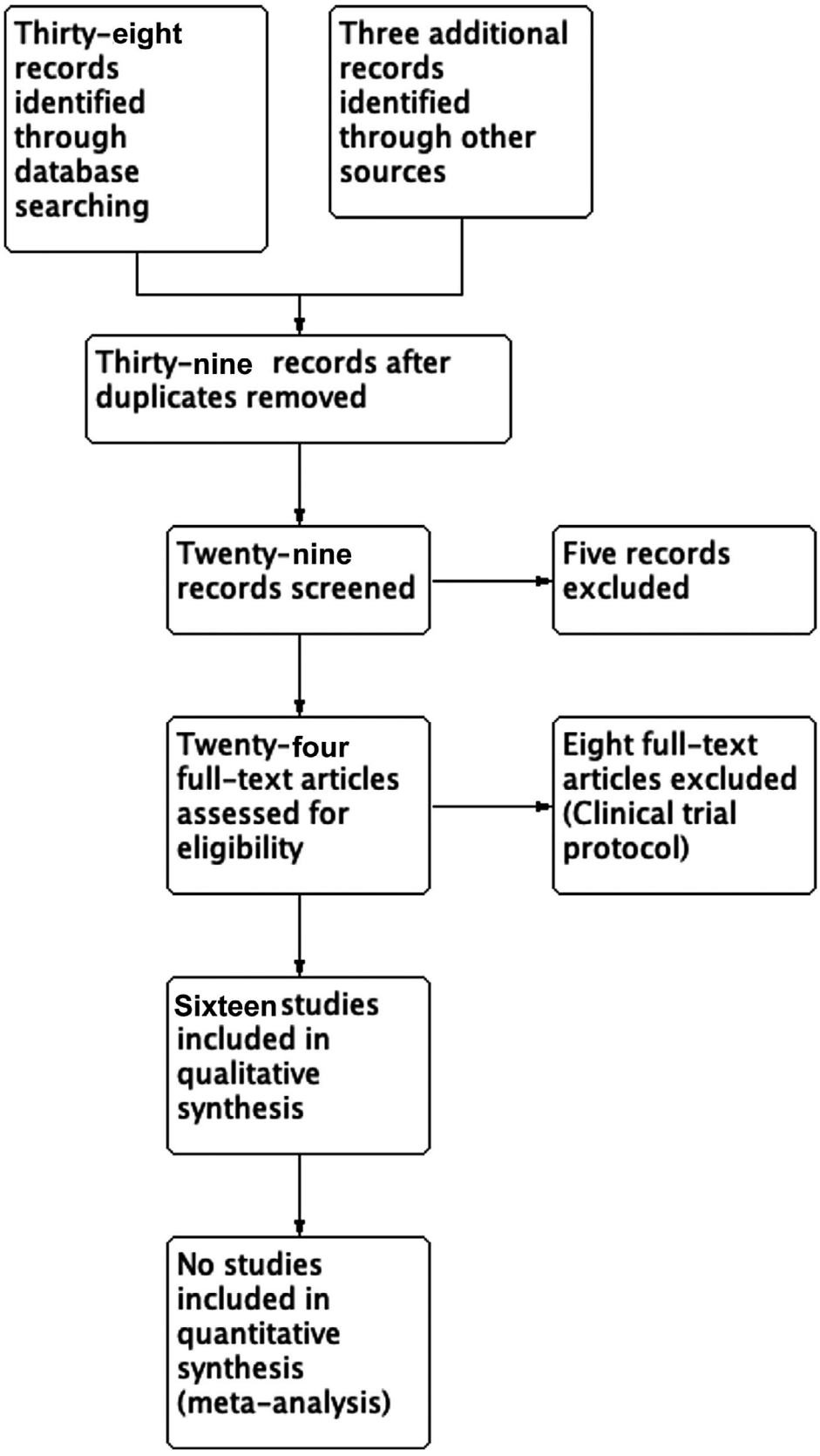

FIGURE 1 Flowchart of selected studies

resistance to aggressive oncological treatment and a decrease in acute effects of radiation. As they reported, the group receiving Oncoxin® without chemotherapy-tolerated radiotherapy much better.[11]

In patients with head and neck carcinoma, there were no differences among radio-chemotherapy adverse events in the intervention group vs 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 dyspnoea) assessed by the Common Terminology Criteria for Adverse Events, showing a significant difference ($P = .01$).[18]

Shumsky et al 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® vs patients in control at 6-8 days after the first visit ($P = .02$) and 19-21 days ($P < .001$). 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 $P = .04$, infections $P < .005$, alanine aminotransferase $P = .04$, aspartate aminotransferase $P = .012$) after 19-21 days.[20] Kaidarova et al also found significant differences, with lower levels of alanine aminotransferase $P = .005$, and aspartate aminotransferase $P < .001$ in Oncoxin® group after 20 days, and reduced drops in haemoglobin after 2 weeks ($P < .001$). On the contrary, they did not find differences in bilirubin, alkaline phosphatase, leukocytes, lymphocytes or platelet levels among groups.[16]

3.7 | Clinical and laboratory outcomes

Uddin et al reported an increase of 1-4 kg in patients with neck and throat, breast and uterine cervix cancer receiving Oncoxin®.[11] Shumsky et al did not find a significant difference in body mass index between both groups of patients with malignant neoplasms. However, patients treated with Oncoxin® gained 2.5 kg (−1.86 to 6.86) while patients in control lost 2.8 kg (−4.96 to −0.55) with significant difference ($P = .03$).[20]

In the study performed by Kaidarova et al, which included patients with gastric cancer or NSCLC, a higher proportion of patients receiving Oncoxin® maintained or increased their body mass and albumin levels compared to controls ($P < .05$), with odds ratios (ORs) 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.[16]

Rivas et al evaluated weight loss in patients with head and neck cancers as part of toxicities, and they found no significant difference between groups ($P = .372$). They also evaluated the antitumor response and tumour 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 ($P = .284$), and 1 year after patient inclusion ($P = .603$). 79% of patients treated with Oncoxin® had a complete response while 60% of patients in the placebo group achieved it.[18]

Finally, Shumsky et al evaluated food intake and appetite. They found that patients treated with Oncoxin® had more days with a regular food intake compared to controls after 19-21 days ($P = .04$), and patients in the control group had no days with a normal appetite.[20]

Kaidarova et al evaluated appetite as part of the SDS ESAS with significant differences after 2 and 3 weeks ($P < .05$).[16] Also, 32% of patients with end-stage HCC receiving Oncoxin® reported an improvement of appetite.[17] Rivas et al evaluated loss of appetite included in QLQ-C30 without a difference in the Oncoxin® group at the end of the study ($P = .14$).[18]

3.8 | 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 tumour development and progression, and the effect in combination with conventional antitumoral treatments.

Oncoxin® modifies inflammatory mediators expression,[8] as evidenced by elevation of IL-6 in AML indicating stimulation of immune system[21]; reduction of RNA levels of COX-2, IFN-γ, IL-1β, IL-6 and TNF-α in CRC metastasis to the liver[23]; reduction of IL-1β, IL-12 and IFN-γ, and elevation of IL-10 in pancreatic tumour-bearing mice, as well as, reverted the expression of genes already reported as being altered in pancreatic cancer.[14]

Hernández-SanMiguel et al did not find any effect of Oncoxin® on glioblastoma (GBM) cell viability; however, they found that Oncoxin® inhibited the self-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.[15]

Hernandez-García et al, 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.[21] These results were similar to those described by Diaz-Rodriguez et al, 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.[24]

Diaz-Rodriguez et al 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 tumours.[13] 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.[23]

AML tumours 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 Leukaemia Inhibitory Factor (LIF) was also found.[22] Finally, Pérez-Peña et al 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.[7]

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).[21]

Marquez et al 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.[23] Diaz-Rodriguez et al 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 signalling.[13]

Also, Oncoxin® has recently been shown to interfere in the tumour microenvironment by reducing the fibroblast-mediated tumour progression, overcoming resistance against targeted therapy with the BRAF inhibitor and impairing fibroblast-mediated tumour cell migration in melanoma cell lines in vitro and in vivo.[25] Such potentials need to be confirmed in clinical trials.

4 | 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.[8,21,24]

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.[8]

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 tumour-bearing mice.[22] 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+ tumour-infiltrating T cells (TILs), and to the downregulation of the protumoral cytokine transforming growth factor-beta (TGF-β) levels in patients with solid tumours.[26]

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.[27] 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.[28]

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 randomised placebo-controlled studies.[29] Despite that, multiple limitations exist among the included studies, such as open-labelled trials, lack of control groups, small sample size, which could introduce bias in the results. Also, there was a significant clinical heterogeneity related to various methods of dietary factors, centre settings, populations enrolled, among others.

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.

5 | 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 and those 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. Although results look promising, further studies are required to explore opportunities to improve cancer patients' outcomes.

DISCLOSURES

The authors declare that they have no relevant financial interests.

AUTHOR CONTRIBUTIONS

HAGP: data collection, data analysis and manuscript writing. JCGO: data collection, data analysis and manuscript writing. LOR: project development, data analysis and manuscript writing.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available in the public domain. MEDLINE (Pubmed), EMBASE (Scopus), LILACS, and the Cochrane Central Register of Controlled Trials (CENTRAL) from inception to nowadays.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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APPENDIX 1
SEARCH STRATEGY

Medline (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)

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 "tumour*" 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)