Clinical Interventions in Aging

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ORIGINAL RESEARCH

# Efficacy of a Neuroimmune Therapy Including Pineal Methoxyindoles, Angiotensin 1-7, and Endocannabinoids in Cancer, Autoimmune, and Neurodegenerative Diseases

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**Purpose:** Recent advancements in psycho-neuro-endocrine-immunology indicate that numerous noncommunicable diseases (NCDs) originate from disruptions in the cytokine immune network, resulting in chronic inflammatory responses. This persistent low-degree inflammation is attributed to deficiencies in crucial endogenous anti-inflammatory neuroendocrine systems, including the pineal gland, the endocannabinoid system, and the angiotensin-converting enzyme 2 / angiotensin 1–7 axis. The administration of pineal methoxyindoles (melatonin, 5-methoxytryptamine), cannabinoids, and angiotensin 1–7 may entail potential therapeutic benefits for NCDs, particularly for patients who do not respond to conventional treatments.

**Patients and Methods:** This study evaluates the safety and efficacy of a neuroimmune regimen comprising melatonin (100 mg/day at night), 5-methoxytryptamine (30 mg in the early afternoon), angiotensin 1–7 (0.5 mg twice daily), and cannabidiol (20 mg twice daily) in 306 patients with NCDs, including advanced cancer, autoimmune diseases, neurodegenerative disorders, depression, and cardiovascular disease.

**Results:** The neuroimmune regimen successfully halted cancer progression in 68% of cancer patients, who also reported improvements in mood, sleep, and relief from anxiety, pain, and fatigue. In patients with autoimmune diseases, the treatment effectively controlled the disease process, remarkable in cases of multiple sclerosis. Additionally, positive outcomes were observed in patients with Parkinson's disease, Alzheimer's disease, and depression.

**Conclusion:** Randomized controlled trials are required to assess this therapeutic approach for NCDs that includes endogenous neuroendocrine molecules regulating immune responses in an anti-inflammatory manner.

**Keywords:** melatonin, 5-methoxytryptamine, metainflammation, noncommunicable diseases, oxytocin, pinoline

## Introduction

The subtle imbalance of inflammatory and anti-inflammatory signals observed in noncommunicable diseases (NCDs), especially as people age, is called "metainflammation" (or "inflammaging").[1] Metainflammation involves increased inflammatory markers such as tumor necrosis factor-α, interferon-β, interleukin (IL)-1, IL-6, IL-8, IL-12, IL-17, IL-22, chemokines, C-reactive protein, and monocyte chemoattractant protein-1.[2] These inflammatory signals contribute to the development of NCDs, a name given to chronic, non transmisibles diseases like cancer,[3,4] cardiovascular disorders,[5] metabolic syndrome,[6,7] diabetes,[8,9] neurodegenerative disorders,[10,11] and renal[12] and lung[13] diseases. Globally NCDs are



Received: 14 January 2025
Accepted: 19 April 2025
Published: 29 April 2025

responsible for 74% of all deaths,[14] with 17 million occurring before 70 years of age; 86% of these deaths occur in low developed countries.

NCDs involve alterations in pro- and anti-inflammatory pathways. Major proinflammatory pathways include nuclear factor-κB[15] and cyclooxygenase,[16] while anti-inflammatory pathways involve specialized pro-resolving mediators[17,18] and the melatonin / endocannabinoid / angiotensin 1,7 axis pathways.[19,20] The body's ability to cope with inflammation decreases with age, thus favoring proinflammatory processes.[1] As the global population ages, health challenges increase, including the prevalence of NCDs.[21–23]

Despite numerous studies in the psycho-neuro-endocrine-immunology field demonstrating that the nervous, immune and endocrine systems are not physiologically segregated and cannot be considered as isolated entities,[24–26] the diagnosis and therapies of NCDs continue to be separately carried out in the clinical practice.[27] This separation between experimental and clinical medicine has become questioned by the discovery of human endogenous molecules providing anti-inflammatory and antitumor activity in NCDs. Showing very few or no toxicity, three fundamental classes constitute the core of a possible therapeutic approach to treat NCDs, ie, the endogenous anti-inflammatory and antitumor network given by pineal methoxyindoles,[28] endocannabinoids,[29] and angiotensin 1–7.[30]

We hereby report a retrospective cross-sectional study of 306 adult patients with NCDs to assess the therapeutic efficacy and safety of a neuroimmune regimen containing the above mentioned antiinflammatory compounds. This neuroimmune regimen (melatonin, 5-methoxytryptamine, endocannabinoids, and angiotensin 1–7) was tested in patients with advanced, untreatable cancers, autoimmune diseases, neurodegenerative pathologies, neuropsychiatric disorders, and cardiopulmonary pathologies.

## Patients and Methods

From March 2020 to April 2023, 306 patients with systemic diseases were evaluated (M/F: 141/165; median age: 64 years; range: 16–92 years). This is a single arm interventional study (before-and-after study) to evaluate the effectiveness of the neuroimmune regimen by comparing outcomes measured before and after the intervention is applied.

Eligibility criteria for cancer patients were: 1) histologically proven neoplasms and measurable lesions assessed by The WHO clinical classification of tumors[31] and by performing CT scan, NMR, or PET every 3-months; 2) lack of response to the standard medical oncological therapies, including the most widely used chemotherapy, endocrine treatment, anti-angiogenic therapy, targeted and immunotherapies, or progression under treatment; 3) a life expectancy less than 1 year (mostly less than 6 months); 4) no other concomitant complementary cancer therapies.

As far as patients with other systemic diseases, the eligible criteria were the existence of clinically evaluable parameters, consisting of autoantibody titer for patients with autoimmune disease, cognitive tests and neuropsychiatric clinical investigation for neuropsychiatric patients, and the common clinical evaluations of the cardio-pulmonary functions in patients with cardio-pulmonary pathologies.

The exclusion criteria were chronic therapy with pregabalin because of its inhibitory action on angiotensin 1–7 activity[32] or with fentanyl or other major opiates, because of their important immunosuppressive action on anticancer immunity.[33]

The WHO clinical classification of tumors comprises several response categories to evaluate the effectiveness of treatments in oncology.[31] They include: Complete Response (CR) indicating the disappearance of all signs of cancer. Partial Response (PR) indicating a significant reduction in tumor size or extent of metastasis, but not a complete disappearance. Typically, this means a decrease of at least 30% in the size of the measurable tumor lesions. Stable Disease (SD): This classification is used when the cancer has neither decreased significantly in size nor increased. Essentially, the disease remains unchanged, indicating that the treatment has halted the progression of the disease but has not reduced the tumor size. Disease Control (DC): This term encompasses both complete and partial responses, as well as stable disease. It indicates that the treatment has been effective in controlling the disease, preventing further progression. Progressive Disease (PD): This indicates that the cancer has increased in size or spread to new areas despite treatment.

After the approval of the local Ethical Committee of the Institute of Biological Medicine (acta no. 01/10, dated February 1, 2020), the clinical protocol was explained to each patient, particularly emphasizing the novelty of using

natural molecules drawn from human body itself, and a written consent was obtained in each case. All procedures were conducted in accordance with the Declaration of Helsinki.

The neuroimmune regimen included the oral administration of angiotensin 1–7 0.5 mg twice/day (8.00 A.M. and 8.00 P.M) in association with two major oncostatic pineal hormones (melatonin 100 mg/day at bedtime, 5-methoxytryptamine 30 mg/day in the early afternoon), and with cannabidiol at a dose of 20 mg twice/day. For patients affected by primary or relapsed glioblastoma, a third pineal oncostatic hormone was administered (beta-carboline 6-methoxy-1,2,3,4-tetra-hydro -beta-carboline, pinoline) at a dose of 1 mg at 8.00 P.M.[34] In the group of hypertensive patients, six of them were already under treatment with anti-hypertensive agents, while the remaining eight patients started with the neuroimmune regimen for personal decision. In patients suffering from depression, the protocol included the oral administration of oxytocin at a dose of 1–2 mg twice/day because of its documented efficacy in improving mood and in the relief of anxiety.[35] The neuroimmune regimen was continued without interruption until disease progression. Patients were also investigated for their changes in the immunobiological response in relation to the clinical course of their pathology, and the immune status was assessed by determining the values of lymphocyte-to-monocyte ratio (LMR), whose progressive decline predicts a poor prognosis either in cancer[36] or in cardiovascular and pulmonary diseases.[37] LMR has been shown to be a significant prognostic marker in several types of cancer, including glioma, breast cancer, and small cell lung cancer. LMR reflects the balance between lymphocytes, which are crucial for adaptive immune responses, and monocytes, which are involved in inflammation and tissue repair. A low LMR indicates a higher inflammatory state and a potentially compromised immune response. Normal values of LMR observed in our laboratory were higher than 2.1 (95% confidence limits) and were established on the basis of the values found in a control group of 300 age-and sex-matched healthy subjects. LMR was evaluated before the onset of treatment, and at monthly intervals.

Data were reported as frequency (%) or mean ± SEM, as appropriate. After verifying for normality for distribution, paired *t*-test were used for LMR evaluation. In addition, as far as oncological patients, the 1-year percent of survival was evaluated using the Kaplan-Meier method and Log rank test in a group of 188 advanced cancer patients who received the neuroimmune regimen as compared to a historical control group of 200 age-, sex-, and histotype-matched untreatable cancer patients, who were treated with only palliative therapy.

## Results

Table 1 summarizes the results of the neuroimmune regimen used in 306 patients with noncommunicable diseases (NCDs) refractory to standard therapies. Among patients with advanced, untreatable solid tumors, a complete response (CR) was observed in 8/188 (4%) of treated cancer patients. A partial response (PR) was achieved in 31/188 (12%)

**Table 1** Melatonin + 5-Methoxytryptamine + Angiotensin 1–7 + Cannabidiol Treatment in 306 Patients With Noncommunicable Diseases (NCDs) Refractory to Standard Therapies

| NCDs | N | Clinical Response (WHO)* | | | | | |
|---|---|---|---|---|---|---|---|
| | | CR | PR | CR + PR | SD | DC | PD |
| Solid Tumors | 188 | 8 (4%) | 23 (12%) | 31 (16%) | 97 (52%) | 128 (68%) | 60 (32%) |
| - Common breast cancer | 9 | 1 (11%) | 2 (22%) | 3 (33%) | 4 (44%) | 7 (78%) | 2 (22%) |
| - Triple negative breast cancer | 19 | 1 (1%) | 3 (16%) | 4 (21%) | 9 (47%) | 13 (68%) | 6 (32%) |
| - Lung adenocarcinoma | 9 | 0 | 2 (22%) | 2 (22%) | 4 (44%) | 6 (67%) | 3 (33%) |
| - Colorectal cancer | 14 | 0 | 2 (14%) | 2 (14%) | 7 (50%) | 9 (64%) | 5 (36%) |
| - Pancreatic adenocarcinoma | 19 | 0 | 2 (11%) | 2 (11%) | 8 (42%) | 10 (53%) | 9 (47%) |

(*Continued*)


https://doi.org/10.2147/CIA.S513910

**Table 1** (Continued).

| **NCDs** | **N** | | | | | | |
|---|---|---|---|---|---|---|---|
| - Biliary tract carcinoma | 6 | 0 | 1 (17%) | 1 (17%) | 3 (50%) | 4 (67%) | 2 (33%) |
| - Gastric cancer | 4 | 1 (25%) | 0 | 1 (25%) | 1 (25%) | 2 (50%) | 2 (50%) |
| - Bladder cancer | 4 | 0 | 0 | 0 | 3 (75%) | 3 (75%) | 1 (25%) |
| - Renal cell carcinoma | 3 | 0 | 0 | 0 | 2 (67%) | 2 (67%) | 1 (33%) |
| - Gynecologic tumors | 4 | 0 | 0 | 0 | 3 (75%) | 3 (75%) | 1 (25%) |
| - Prostate cancer | 4 | 0 | 1 (25%) | 1 (25%) | 1 (25%) | 2 (50%) | 2 (50%) |
| - Glioblastoma | 48 | 5 (10%) | 5 (10%) | 10 (21%) | 25 (52%) | 35 (73%) | 13 (27%) |
| - Malignant astrocytoma | 6 | 0 | 1 (17%) | 1 (17%) | 3 (50%) | 4 (67%) | 2 (33%) |
| - Neuroendocrine tumors | 29 | 0 | 3 (10%) | 3 (10%) | 19 (66%) | 22 (76%) | 7 (24%) |
| - Sarcomas | 7 | 0 | 0 | 0 | 4 (57%) | 4 (57%) | 3 (43%) |
| - Malignant melanoma | 3 | 0 | 1 (33%) | 1 (33%) | 1 (33%) | 2 (67%) | 1 (33%) |
| Hematologic Tumors | 11 | 0 | 1 (9%) | 1 (9%) | 6 (55%) | 7 (64%) | 4 (36%) |
| - Multiple Myeloma | 5 | 0 | 0 | 0 | 3 (60%) | 3 (60%) | 2 (40%) |
| - Chronic lymphatic leukemia | 4 | 0 | 1 (25%) | 1 (25%) | 2 (50%) | 3 (75%) | 1 (25%) |
| - Myeloid leukemia | 2 | 0 | 0 | 0 | 1 (50%) | 1 (50%) | 1 (50%) |
| | | **Clinical Benefits** | | | | | |
| Multiple Sclerosis | 17 | No progression for at least 2 years in 13/17 (76%) patients | | | | | |
| Hashimoto Thyroiditis | 7 | Decline in anti-thyroglobulin antibody levels in 6/7 (86%) cases | | | | | |
| Other Autoimmune Diseases | 12 | Decline in antinuclear antibody concentration in 9/12 (75%) patients | | | | | |
| Idiopathic Hypertension | 14 | Normalization of blood pressure in 10/14 (71%) cases | | | | | |
| Heart Failure | 9 | Decline in brain natriuretic peptide in 6/9 (67%) cases | | | | | |
| Pulmonary Diseases | 7 | No worsening in 5/7 (71%) patients with chronic bronchitis | | | | | |
| Neurodegenerative Diseases | 19 | Benefits in 12/19 (63%) patients | | | | | |
| - Parkinson's disease | 12 | Neurological benefits in 7/12 (58%) cases | | | | | |
| - Alzheimer's disease | 6 | Control of cognitive deficiency in 4/6 (67%) cases | | | | | |
| - Motoneuron disease | 1 | Improvement in motor function | | | | | |
| Depression | 10 | Rapid improvement in mood in 7/10 (70%) cases | | | | | |
| Type 2 diabetes | 12 | Decline in glycated hemoglobin in 9/12 (75%) cases | | | | | |
| **Overall patients** | **306** | **Clinical benefits in 210/306 (69%) patients** | | | | | |

**Notes**: *Anti-thyroglobulin antibody and antinuclear antibody concentration, brain natriuretic peptide and glycated hemoglobin were measured by specific enzyme-linked immunosorbent assays (ELISA).
**Abbreviations**: CR, Complete response; PR, Partial response; SD, Stable disease; DC, Disease control; PD, Progressive disease.

cancer patients. Thus, tumor regression was found in 39/188 (16%) patients. A stable disease (SD) was observed in 97/188 (52%) patients. Therefore, a disease control (DC) (CR + PR + SD) was verified in 128/188 (68%) patients as far as all solid tumor types, whereas the remaining 60/188 (32%) patients showed a progressive disease (PD). Concerning hematologic tumors (N= 11), values of CR, PR, SD, DC and PD were 0, 1 (9%), 1 (9%), 6 (55%), 7 (64%) and 4 (36%) (Table 1).

The mean duration of the oncostatic response was 14 months (range 3–36+ months). A remarkable result was observed in patients with glioblastoma, with an objective tumor regression in 10/48 (21%) patients, and a DC in 35/48 (73%) patients. Notable results were also obtained in other malignant human neoplasms, like pancreatic adenocarcinoma [DC: 10/19 (53%) patients] and triple negative breast cancer [DC: 13/19 (68%) patients]. A survival longer than 1 year with respect to a life expectancy less than one year (less than 6 months in most cases) was achieved in 135/188 (72%) cancer patients.

The 1-year survival curves observed in the treated group of cancer patients and in the control group are illustrated in Figure 1. The percent of 1-year survival obtained in patients treated by the neuroendocrine regimen was significantly higher than in the control group treated by the only best supportive care (P<0.005).

Clinical benefits were also obtained in patients suffering from NCDs other than cancer. A particular efficacy of the neuroimmune regimen was observed in the treatment of autoimmune diseases, including multiple sclerosis, Hashimoto's thyroiditis, and other autoimmune pathologies. The control of neurological symptoms was verified in 13/17 (76%) patients with multiple sclerosis, a decline in anti-thyroglobulin antibody levels in 6/7 (86%) Hashimoto's thyroiditis cases, and a decline in antinuclear antibody production in 9/12 (75%) patients with other autoimmune diseases.

Beneficial results were obtained in 12/19 (63%) patients with neurodegenerative pathologies, including Parkinson's and Alzheimer's diseases, as well as in one patient affected by the motoneuron pathology. Depressive patients were particularly responsive to oxytocin treatment in association with the neuroimmune regimen, with a clear improvement in mood in 7/10 (70%) patients.

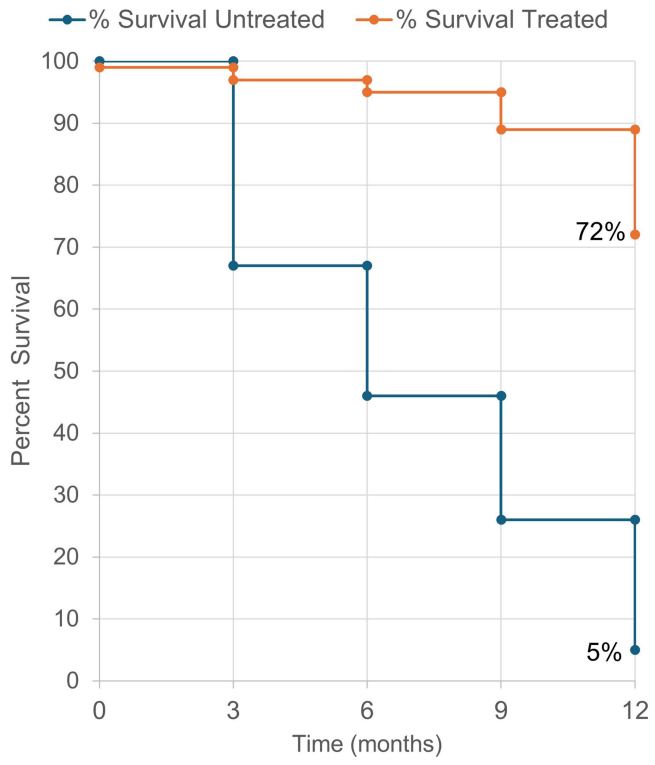


**Figure 1** Percent of 1-year survival observed in 188 advanced cancer patients who received the neuroimmune regimen including pineal methoxyindoles, angiotensin 1–7, and endocannabinoids, as compared to a historical control group of 200 age-, sex-, and histotype-matched untreatable cancer patients, who were treated with only palliative therapy. Differences between groups are significant (P< 0.005), Kaplan-Meier method and Log rank test.


https://doi.org/10.2147/CIA.S513910

A reversion in insulin resistance, as shown by a progressive decline in hemoglobin glycate blood concentrations, was verified in 9/12 (75%) diabetic patients. In addition, patients affected by cardiovascular or pulmonary pathologies were particularly responsive to treatment eg, in idiopathic hypertension a control of blood pressure was achieved in 10/14 (71%) patients within the first two weeks of therapy. A reduction in brain natriuretic peptide (BNP) levels was observed in 6/9 (67%) patients with heart failure.

The treatment was well tolerated in all patients, and no biological toxicity occurred. In more detail, no negative effect was seen on hemoglobin levels, platelet count, cardiac function, and renal and hepatic metabolic activities. Most patients referred an improvement in their life due to a better quality of sleep, mood increase, and relief of anxiety and pain, with a particular efficacy in the treatment of cancer-related asthenia. In addition, all patients showed an increased diuresis, possibly due to the diuretic action of angiotensin 1–7.[30]

LMR mean values significantly increased on therapy with respect to the pretreatment in patients who showed a clinical benefit (3.6 ± 0.3 vs 2.3 ± 0.2, $P<0.05$). On the contrary, no meaningful change occurred in patients who had no improvement on treatment (2.8 ± 0.4 vs 2.4 ± 0.3). This difference was particular evident in patients with advanced untreatable cancer as compared to those with refractory, progressive disease (4.3 ± 0.4 vs 2.3 ± 0.2, $P<0.01$), while no difference was seen as far as their pretreatment values (2.7 ± 0.3 vs 2.3 ± 0.4).

## Discussion

This study demonstrates that a neuroimmune regimen incorporating melatonin (100 mg/day at night), 5-methoxytryptamine (30 mg in the early afternoon), angiotensin 1–7 (0.5 mg twice daily), and cannabidiol (20 mg twice daily) may achieve meaningful clinical benefits in patients with severe, treatment-resistant NCDs. These findings underscore the potential of natural, endogenous molecules like pineal hormones, angiotensin 1–7, and endocannabinoids to modulate the immune system, controlling inflammation, cell proliferation, and immune response. Enhancing the immune balance through this regimen, with adjuncts such as a low-dose of IL-2, could be particularly beneficial in NCDs patients.[38]

Melatonin is a naturally occurring substance found in all living organisms, from single-celled entities to humans. It is produced not only in the pineal gland but also in various tissues throughout the body, where it may serve a protective role through paracrine or autocrine effects.[39] Via its anti-inflammatory effects, melatonin supresses tumor growth.[40,41] In addition, melatonin efficacy has been demonstrated in several NCDs.[42–44] In the case of cancer, melatonin's antiproliferative mechanisms include, in addition to direct and indirect antioxidant effects, the modulation of cell cycle, anti-angiogenic and antimetastatic effects, induction of apoptosis in cancer cells, a decrease in telomerase activity and effective immune modulation.[45] In addition to its cancer-fighting properties, melatonin should be considered for treating non-communicable diseases (NCDs) for two key reasons. Firstly, its hypnotic and chronobiotic properties enable an effective management of sleep disturbances, which are a significant co-morbidity in cancer patients.[46] Secondly, because the antidepressant and anxiolytic activity of melatonin,[47,48] it is useful to treat depression and anxiety seen in cancer as well as in other NCDs.

In addition to melatonin, the pineal produces other relevant antitumor indole hormones, like 5-methoxytryptamine,[49] and beta-carbolines.[50,51] This explains why the increase in tumour growth that follows pinealectomy cannot be totally counteracted by the exogenous administration of melatonin. 5-Methoxytryptamine may play a strong oncostatic activity.[49] Concerning pineal beta-carbolines, the best known is pinoline,[50,51] that together to anti-depressant and anxiolytic effects, it also has anti-inflammatory and antitumor properties.[34] A pineal endocrine deficiency in cancer was suggested by histological studies.[52]

Building on melatonin's role, another key component of the neuroimmune regimen is angiotensin 1–7, an enzymatic product of angiotensin converting enzyme 2 (ACE2) and regulates immune-inflammatory responses, cell proliferation, blood coagulation, fibrosis, cardiopulmonary functions, and metabolic activities.[53–55] Angiotensin 1–7 exhibits effects that contrast sharply with those of angiotensin II, an ACE product known for its inflammatory, tumor-promoting, immunosuppressive, hypertensive, cardiotoxic, neurotoxic, pro-thrombotic, pro-fibrotic, and pro-diabetic activities,[56–60] Conversely, angiotensin 1–7 induces hypotensive, diuretic, cardio-neuroprotective, anti-inflammatory, anti-tumoral, anti-thrombotic, anti-fibrotic, and anti-diabetic effects with minimal toxicity.[61–64]

Positive feedback takes place between angiotensin II and IL-17 released from TH17 lymphocytes.[57] On the contrary, angiotensin 1–7 counteracts IL-17 secretion and promotes IL-2 production, a key oncostatic cytokine.[30] The antagonistic relationship between angiotensin II and angiotensin 1–7 has implications for cardiovascular health and immune system function, especially considering that angiotensin II can foster cancer onset and metastasis. Indeed, ACE inhibitors or angiotensin II receptor blockers have been linked to a reduced incidence of cancer in hypertensive patients.[65,66]

The function of the renin - ACE - angiotensin II - ACE2 - angiotensin 1–7 axis depends on the modulation of ACE and ACE2 expression, which is under a central regulation played by the neuroendocrine system. ACE2 is stimulated by melatonin[67] and estradiol.[68] The progressive age-related decline in both melatonin and estradiol secretion would explain the higher blood levels of angiotensin 1–7 in fertile women than in men, and its lower concentration in aged subjects. In addition to the pineal gland and the ACE2- angiotensin 1–7 axis, a third anti-inflammatory / oncostatic component is given by the endocannabinoid system,[69] which is connected to the pineal gland by reciprocal stimulatory actions.[70,71]

The discovery of ACE2 - angiotensin 1-7 - Mas receptor axis, whose biological effects are opposite to those played by ACE - angiotensin II - AT1R axis, leads to a reinterpretation of the pathogenesis of the cytokine network participating in several biological systems. In the brain, an enhanced expression of ACE leading to enhanced local production of angiotensin II and a decrease of angiotensin 1–7 could represent the first event involved in neuroinflammation.[72,73] Depression would be also promoted by an increased brain production of IL-17 and other inflammatory cytokines because of a reduced ACE2 expression at brain sites.[74] Lately, ACE / ACE2 ratio would influence the clinical history of the metabolic syndrome, since insulin resistance follows angiotensin II administration and is prevented by angiotensin 1–7 administration.[75,76] Despite the evidence suggesting the therapeutic potential of angiotensin 1–7 and melatonin in most human systemic diseases, very few clinical studies have evaluated their therapeutic significance in NCDs.

The present study had several limitations. Retrospective studies are prone to selection bias, recall bias, and confounding factors, which can affect the validity of the results. In a cross-sectional, retrospective analysis, relevant data could be lost, and it does not allow modifications to be made/added to the variables already established. Double-blind, placebo-controlled trials will contribute to further support the hypothesis put forth by minimizing of bias and establishing causality between the intervention and outcome. The use of placebo and control groups will allow for a clear comparison of the effectiveness of the neuroimmune regimen proposed.

## Conclusion

This study highlights the potential of leveraging endogenous molecules to treat NCDs by modulating cell proliferation, inflammation, immune responses, metabolism, and neurological functions. The findings suggest that a neuroimmune regimen incorporating melatonin, angiotensin 1–7, and other bioactive compounds could offer a low-cost, minimally toxic therapeutic approach. Longer follow-up and randomized studies by comparing the results with those obtained in patients treated only with palliative therapy are necessary to better establish the impact of the neuroendocrine therapy on the survival of untreatable cancer patients.

## Acknowledgments

The authors would like to thank the patients and research assistants for their participation and support.

## Author Contributions

All authors made a significant contribution to the work reported, whether in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; agreed on the journal to which the article has been submitted; and agreed to be accountable for all aspects of the work.

## Funding

The authors declare that no financial support was received for the research, authorship, and/or publication of this article. The study was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Disclosure

The authors report no conflicts of interest in this work.

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