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Green Technology Strategy

Advanced Colorectal Cancer

Highlights

Efficacy of Pembrolizumab

Treatment of Advanced Colorectal

Discovering Thoughts, Inventing Future

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Green Technology Strategy for Fluoxetine Preparation

By Zhao Mingrui, Yang Ninghui, Peng Peng, Zhuang Shuyang & Shi Xiufang

Zhengzhou University of Light Industry

Abstract- This study aims to explore the green technology strategies for the preparation of fluoxetine, through the research on the greenization of catalysts and membrane treatment of wastewater. The study show that green technology strategies can effectively reduce the environmental pollution and resource consumption during the preparation of fluoxetine. At the same time, the integration and prospects of green technology strategies were analyzed, and its potential value and broad application prospects were provided in the preparation of fluoxetine. This research is of great significance for promoting the development of fluoxetine preparation processes towards a green, environmentally friendly, high efficiency and sustainable development.

Keywords: *fluoxetine, green chemistry, technical strategy, preparation.*

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Green Technology Strategy for Fluoxetine Preparation

Zhao Mingrui [α], Yang Ninghui [σ], Peng Peng [ρ], Zhuang Shuyang [Ω] & Shi Xiufang [¥]

Abstract- This study aims to explore the green technology strategies for the preparation of fluoxetine, through the research on the greenization of catalysts and membrane treatment of wastewater. The study show that green technology strategies can effectively reduce the environmental pollution and resource consumption during the preparation of fluoxetine. At the same time, the integration and prospects of green technology strategies were analyzed, and its potential value and broad application prospects were provided in the preparation of fluoxetine. This research is of great significance for promoting the development of fluoxetine preparation processes towards a green, environmentally friendly, high efficiency and sustainable development.

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N-methyl-3-phenyl-3-[4-(trifluoromethyl)phenoxy]propan-1-amine;hydrochloride

I. Introduction

Fluoxetine, N-methyl-3-phenyl-3-[4-(trifluoromethyl) phenoxy] propylamine hydrochloride, Prozac®, is a new generation of non-tricyclic antidepressants developed by Eli Lilly Company, the structure is shown in Figure 1. Fluoxetine contains a chiral center with a pair of enantiomers, namely (R)-and (s)-fluoxetine. Most of fluoxetine hydrochloride sold on the market is racemate. The main effects of (R)-fluoxetine is the treatment of depression,but (s)-fluoxetine is the prevention of migraine. [1,2] a clinical study of chiral (R)- or (s)-fluoxetine by SEPRACOR Inc. found that (R)-fluoxetine had a shorter half-life and action time than commercially available racemic fluoxetine, it can greatly reduce the adverse side effects of racemic fluoxetine, such as headache, anxiety and suicidal impulse. Because of its high selectivity, safety and bioavailability, it is widely used in clinical practice and is one of the essential drugs listed by the World Health Organization[3-5].

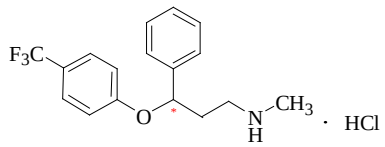

Fig. 1: Molecule Structure of Fluoxetine

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II. Green Technology Strategy for Preparation of Fluoxetine

a) The Selection and Utilization of Raw Materials

The selection and utilization of raw materials are crucial to green technology strategy during the preparation process in fluoxetine. First, we need to consider the choice of renewable, biodegradable raw materials, in order to reduce environmental pollution and consumption of resources. Second, the use of green synthetic pathways to avoid the use of toxic or refractory compounds to reduce environmental and human risks. In addition, the utilization rate of raw materials can be increased and the generation of wastes can be reduced by improving the synthesis process. Through the greening of raw materials, the environmental load in the preparation process of fluoxetine can be effectively reduced to achieve the goal of green and sustainable development. The fluoxetine steps used in the past are shown in Figure 2. KBH_4 is used in this process and has a corrosive effect on the skin and mucous membranes and is usually slightly harmful to water. DMSO, also known as Dimethyl sulfoxide, interacts with the hydrophobic groups of proteins and causes Denaturation, which is toxic to human skin and irritating to the eyes. According to the guiding principles of chemical drug residue solvent and 12 principles of green chemistry, so should minimize or avoid the side-use of such solvents.

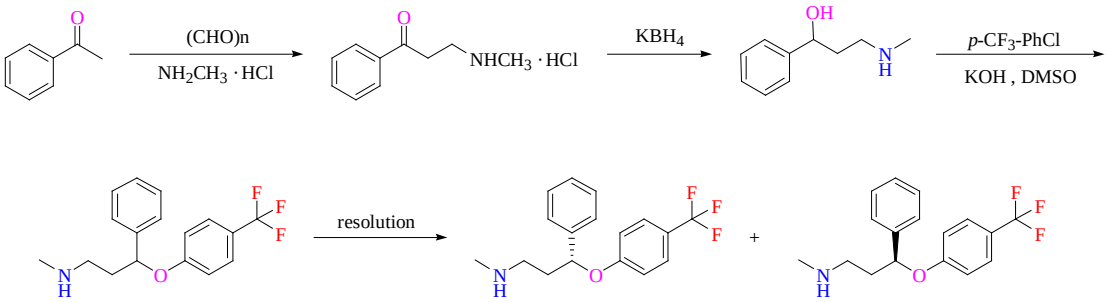

Fig. 2: Preparation Steps of Fluoxetine Hydrochloride

b) The Green Solvent

The solvent plays a crucial role in the preparation of fluoxetine, and the choice of the solvent is directly related to the environmental friendliness and energy consumption of the preparation process. Therefore, in the green technology strategy, we need to consider the choice of low-toxic, non-volatile organic solvents or water solvents to reduce the harm to the environment and human body. In addition, the emission and consumption of solvents can be reduced by optimizing the amount of solvents used and recycling. In order to make the preparation of fluoxetine green, we should consider the factors of toxicity, volatility, price and reproducibility, and choose the most suitable solvent. In order to further improve the green degree of fluoxetine preparation process, we can consider the implementation of solvent recycling strategy. The recovery and reuse of waste solvents by physical or chemical methods can reduce the consumption of solvents and the discharge of wastes, and reduce the demand of resources in the preparation process. In addition, the idea of circular economy can be introduced to reuse the waste solvent as a resource and realize the closed-loop utilization of the solvent to further improve the sustainability and environmental protection of the preparation process of fluoxetine. The environmental pollution and resource consumption in the preparation of fluoxetine can be reduced by recycling the solvent, and the green technology strategy can be realized.

c) The Green Catalysts of Fluoxetine

There are many methods for the synthesis and resolution of the green catalysts of fluoxetine. Most of the (R)-fluoxetine currently used in the market are obtained by chiral resolution, a large number of chiral reagents are required and the whole process is time-consuming and laborious. Asymmetric catalytic synthesis has great Atom economy advantages over chiral resolution. Asymmetric catalytic synthesis has become a hot research field in the field of organic chemistry. In particular, many chemical companies are developing asymmetric catalytic reactions into chiral and Enantioselective synthesis processes, such as L-Dopa synthesis from L-Dopa catalyzed by chiral rhodium in American Monsanto, and (-)-menthol synthesis from asymmetric rearrangement catalyzed by rhodium in Japanese Enantioselective synthesis company, and developed into a promising industrial chiral technology.

In a pioneering study [2], Duan Yu and colleagues embarked on a chemical journey, initiating their work with cinnamaldehyde, ultimately shaping it into chiral fluoxetine via an intricate sequence of reactions. They navigated through asymmetric epoxidation of chiral secondary amines, ring-opening to ester, Ester Exchange, reduction, and the transformative etherification of ester amines.

Chengyu Liu, on another scientific expedition [3], relied on the prowess of an enantioselective catalyst to forge an (R)-fluoxetine intermediate. Wang Jiahao, with deft precision, synthesized γ-amino alcohol, a beacon of optical purity, by way of enantioselective synthesis of the prochiral β-amino ketone [4]. This pivotal compound then paved the way for the synthesis of fluoxetine.

Li Zhen-zhong, employing the [RUCL2((s)-BINAP)((s, S)-dpen)] complex as a catalyst [5], skillfully constructed a photoactive fluoxetine intermediate, (R)-N, n-dimethyl-2-hydroxyamphetamine. This masterpiece was then honed into the radiant (R)-fluoxetine, culminating in an impressive overall yield of 49.1%.

Kinetic resolution, a technique that discriminates enantiomers via differential rates of reaction with chiral reagents or catalysts, was employed to synthesize fluoxetine. Researchers, through the hydrolysis kinetic resolution of racemic epoxide catalyzed by Salen Co (III) chiral catalyst, sculpted the elusive chiral r-phenyl ethylene oxide [6]. A series of transformations then led to the birth of the coveted fluoxetine drug. The allure of kinetic resolution lies in its simplicity and efficiency, with the capacity to enhance excess enantiomers by adjusting conversion rates. However, it demands an extra step to resolve non-targeted stereoisomers.

Xiang Peng [7] ventured into uncharted territories, revealing a novel path for (S)-fluoxetine synthesis, harnessing chiral secondary alcohols, bearing α-position substituents, as pivotal intermediates. Cheng Qingfang and collaborators took an innovative approach [8,9], deploying their homemade chiral oxazaborolane as a catalyst to achieve enantioselective

hydrogenation of β-chlorophenylacetone, yielding (S)- or (R)-chiral alcohols, subsequently steering the synthesis of (S)- and (R)-fluoxetine. This breakthrough marked another milestone in the evolving landscape of fluoxetine synthesis.

Table 1: Methods and Conditions for Preparation of Fluoxetine

[1]	Starting Material	Methods	Synthetic Products	The End Product
[2]	Cinnamaldehyde	Chiral Enantioselective synthesis	Chiral fluoxetine	
[3]		Iridium catalyst Enantioselective synthesis	(R)- Fluoxetine Intermediate	
[4]	Latent Chiral β-aminophenone	Enantioselective synthesis	The intermediate γ-amino alcohol	fluoxetine
[5]	N, n-dimethyl-1-phenylacetone	[RuCl2（（S）-BINAP）（(S,S)-DPEN）], The complex is the catalyst	The fluoxetine intermediate (R) -- N, N-dimethyl-2-hydroxyamphetamine	fluoxetine
[6]	Racemic Epoxide	Hydrolysis kinetic resolution of Salen Co (III) chiral catalyst	Chiral intermediate r-phenyl ethylene oxide	Chiral fluoxetine
[7]	Chiral secondary alcohols containing substituent groups at α-position	Kinetic resolution of Stereoselectivity synthesis catalyzed by organometallic catalysts and biological enzymes		（S）- fluoxetine
[8]	B-chlorophenone	Asymmetric catalytic hydrogenation reduction	(s)-or (R)-chiral alcohols	Enantioselective synthesis (s)-and (R)-fluoxetine
[9]	Latent chiral ketone	Asymmetric reduction of ketone reductase	Intermediate chiral alcohols	Fluoxetine drugs

The strategy of using natural chiral sources to synthesize some complex chiral compounds is not only helpful for configuration retention, but also suitable for the synthesis of new chiral compounds by configuration transformation and other organic reactions.

i. *The Selection and Design of Catalysts*

The pivotal role of catalyst selection and design emerges as a cornerstone within the green methodology for crafting fluoxetine. An astute choice of catalysts can significantly boost reaction proficiency, decrease energy utilization, and mitigate environmental implications. Hence, a comprehensive exploration of catalyst selection and design is imperatively advocated.

Primarily, the catalytic prowess and specificity of the catalyst should be weighed, assuring its proficient performance in fluoxetine synthesis. Subsequently, the catalyst's architecture should be ingeniously devised for enhanced durability and recycling efficiency. Adapting to distinct reaction scenarios and catalytic mechanisms, surface modification and functional treatments can also be employed to fine-tune their attributes.

Through meticulous experimental trials and theoretical scrutiny, a bevy of proficient and eco-friendly catalysts have been ingeniously crafted and sifted, thereby fostering a robust foundation for the sustainable synthesis of fluoxetine. Of particular interest is the selective production of the two enantiomers of fluoxetine, an area drawing substantial attention.

Corey's innovation was instrumental in enhancing the catalyst, enabling the facile acquisition of both enantiomers and augmenting reaction efficacy. Sharpless, on the other hand, unfolded a novel path for synthesizing both enantiomers, with the pivotal step being Sharpless epoxidation. This synthetic pathway, depicted in Figure 3, exhibits practicality and boasts a total yield of 49%. [7]

In this discourse, the intricate dance between catalyst choice, design, and the quest for greener fluoxetine synthesis is portrayed, with key milestones and advancements underpinning the journey.

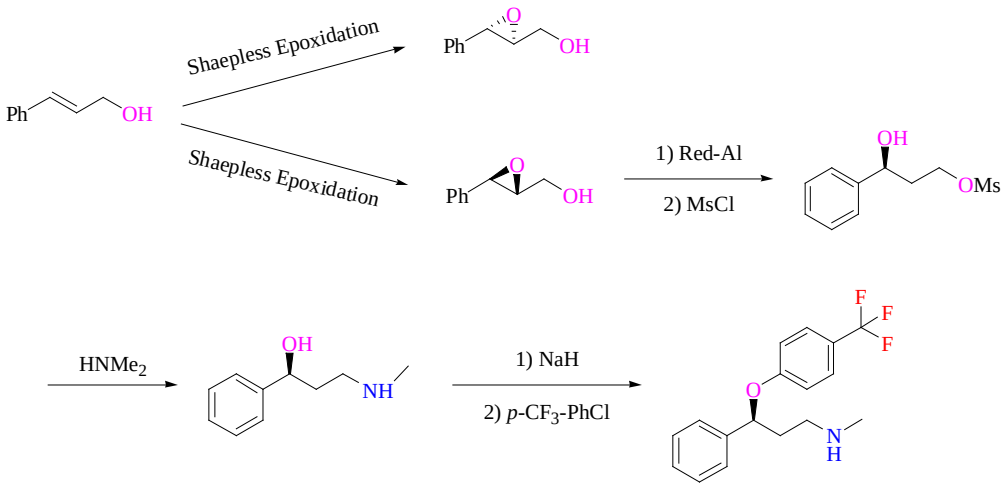

Fig. 3: Sharpless Synthetic Route of Fluoxetine

ii. *The Revitalization of Catalysts: A Pillar of Eco-Technology*

The resurrection of catalysts occupies a pivotal role in the eco-friendly technology roadmap. In conventional fluoxetine synthesis, catalysts are customarily disposed after a solitary application, resulting in both resource squandering and environmental devastation. Consequently, a profound exploration of catalyst recycling emerges as indispensable[8,9]. Harnessing surface engineering and rejuvenation methodologies, catalysts can undergo multiple reincarnations, significantly curbing waste management volumes and minimizing environmental footprints. Moreover, extensive studies on catalyst deactivation during recycling have exposed a plethora of proficient regeneration techniques, thereby enhancing the catalyst's longevity and minimizing the energy expenditure and production costs of fluoxetine.

iii. *The Sustainable Management of Catalyst Waste: An Integral Green Strategy*

Catalyst waste disposal stands as a crucial facet in the holistic green technology approach. Throughout the catalyst's operational cycle, waste production is an inescapable byproduct, posing severe environmental hazards if not dealt with cautiously. Thus, extensive investigations into waste catalyst management are paramount. Techniques such as physical adsorption, chemical reduction, and pyrolysis, known for their energy efficiency, are employed to convert waste catalysts into reusable resources and render them environmentally benign. Simultaneously, a comprehensive experimental and simulation-based assessment of various waste treatment methodologies enables a comparative evaluation of their environmental impact. This generates scientifically grounded and feasible strategies for waste catalyst management, thereby offering substantial technical backing for the environmentally sustainable synthesis of fluoxetine.

d) The Innovative Approach: Membrane-Driven Wastewater Management

i. *Embracing the Potential of Membrane Separation Techniques*

As an avant-garde and ecologically conscientious technique, membrane separation has carved a niche for itself across diverse sectors. [10-15] In the intricate process of manufacturing fluoxetine, the wastewater generated is replete with an array of organic compounds and impurities, necessitating the judicious deployment of membrane separation. This advanced technology leverages selective membrane materials and tailored operational parameters to proficiently sieve out organic contaminants, ions, and microorganisms from the aqueous milieu.

A gamut of membrane separation methodologies exists, including microfiltration, ultrafiltration, nanofiltration, and reverse osmosis. Each method possesses unique attributes, allowing for tailored solutions based on the distinctive traits of the wastewater at hand, thereby optimizing the purification process and facilitating water reuse.

The integration of membrane separation not only ensures the efficient eradication of impurities and organic compounds but also facilitates meticulous water quality control, thereby fulfilling the stringent purity criteria in fluoxetine synthesis. Moreover, this technology curbs chemical reliance, decreases energy consumption, and lightens the financial burden of wastewater management, thereby delivering substantial economic and environmental dividends.

In essence, the strategic utilization of membrane separation technology in wastewater management significantly enhances the environmental footprint of fluoxetine production. It propels the manufacturing process towards a greener, more sustainable trajectory, fostering a harmonious coexistence between industry and the environment. Thus, the marriage of membrane separation with

wastewater treatment stands as a testament to innovation and responsible stewardship of our planet's resources.

ii. *Enhancing the efficacy of membrane-based wastewater treatment methodology*

The pivotal step in accomplishing proficient wastewater management and boosting resource recovery lies in refining the wastewater membrane treatment process. While formulating fluoxetine, the industrial effluent exhibits a substantial concentration of organic compounds, posing significant hurdles for the treatment process. Consequently, it is imperative to tailor the membrane treatment strategy, considering the unique characteristics of the wastewater, to enhance purification efficiency and elongate the membrane's operational lifespan.

The initial stage of improvement revolves around optimizing the preliminary wastewater treatment, encompassing pH balancing, suspended solids and sediment removal. These measures mitigate membrane fouling and damage, thereby fortifying membrane stability and service duration.

Subsequently, the membrane material and operational parameters are meticulously fine-tuned. A membrane material particularly suited for wastewater treatment is selected, and operational conditions are adeptly regulated, thereby enhancing the membrane's capacity to intercept fouling and resist contamination.

Ultimately, the integration of sophisticated automation technologies brings about online monitoring and intelligent control of the membrane treatment workflow. This ensures the seamless functioning of the wastewater management system and sustains a high level of treatment efficacy.

Through the meticulous optimization of the wastewater membrane treatment process, the efficacious extraction of organic substances and impurities from the wastewater is realized, contributing to an extended membrane lifespan, lowered treatment costs, and heightened resource recovery efficiency. This, in turn, furnishes vital technical backing for the sustainable advancement of the fluoxetine synthesis process, fostering green development.

iii. *The Recycled Symphony of Membrane-Treated Effluent*

The intricate dance of elements, both organic and ionic, within the aqueous remnants of membrane filtration, has been skillfully harnessed to comply with stringent water quality benchmarks. This transformative process not only ensures the elimination of impurities but also reshapes waste into a precious commodity, fostering a virtuous cycle of zero discharge and wastewater reuse.

In the intricate ballet of fluoxetine synthesis, a residue of fluoxetine and organic solvent lingers in the water trail. However, through the alchemy of membrane treatment, this detritus is transmuted into a treasure trove of high-purity fluoxetine and solvent, ripe for reincarnation within the production cycle, enhancing efficiency and sustainability.

Beyond industrial rejuvenation, the reclaimed water, having undergone its metamorphosis, can grace the fields as a life-giving elixir for agriculture, or cool the industrious engines as efficient coolant. Thus, maximizing resource utilization and maintaining a watertight seal on wastewater discharge.

This innovative utilization of wastewater not only shields natural water sources fromexcessive -extraction and contamination but also alleviates the ecological toll of waste management, contributing to energy conservation and diminished emissions. The marriage of membrane treatment and wastewater reuse embodies a union of environmental stewardship and economic prudence, serving as a pivotal cornerstone in the management of fluoxetine waste streams.

As the tide of membrane technology rises, the embrace of wastewater recycling is poised to evolve into an indispensable pillar of the fluoxetine manufacturing process. It extends a sturdy arm of support to the industry's pursuit of sustainable development, fostering a future where progress and preservation intertwine in a harmonious symphony.

III. Integration of Green Technology Strategies and Prospects

a) Integration of Green Technology Strategies

In the preparation of fluoxetine, the integration of green technology strategies can effectively reduce the environmental pollution and resource consumption during the preparation of fluoxetine. The key to the integration of green technology strategy lies in the organic combination of each link to achieve the overall optimization of green preparation.

In green technology strategy integration, we need to take into account the synergy between different links to ensure that the effective convergence and complementarity of various technology strategies. For example, the goal of waste reduction and resource recycling in the preparation of fluoxetine can be achieved by optimizing the selection and preparation of catalysts, combined with membrane technology for wastewater treatment.

Green technology strategy integration needs to consider not only the feasibility and benefits of the technology itself, but also its practical application in industrial production to ensure the Operability and economy of the technology strategy. Through the integration of green technology strategy, we can optimize the preparation process of fluoxetine and improve the environmental performance, providing strong support for the green development of the preparation process of fluoxetine.

b) Green Evaluation of Fluoxetine Preparation Process

The green preparation process of fluoxetine need to conduct a comprehensive evaluation and analysis. First of all, the selection of raw materials, production processes, waste emissions and energy consumption can be evaluated to fully understand the current process of environmental and resource problems. Secondly, suggestions can be made for the existing problems, such as using green catalysts, optimizing reaction conditions, improving wastewater treatment technology. The green evaluation needs to fully consider the Operability and economics of fluoxetine preparation process in actual production, and ensure the implementation of green technology strategy can meet the requirements of industrial production. In addition, a comprehensive assessment of the green process is needed to ensure that significant improvements can be made in environmental protection, resource utilization and economic benefits. The green evaluation of the preparation process of fluoxetine can provide scientific basis for the implementation of green technology strategy and provide important support for the sustainable development of the preparation process of fluoxetine.

IV. Prospect and Conclusion

Green technology has broad development prospect in pharmaceutical industry. With the society's attention to environmental protection and sustainable development, the application of green technology in pharmaceutical industry will be further promoted and deepened. Especially in the process of drug preparation, green technology can effectively reduce waste emissions and resource consumption, and provide important support for the sustainable development of pharmaceutical industry.

In the future, the application of green technology in pharmaceutical industry will be more extensive. For example, green catalyst, waste water membrane treatment technology, green solvent and so on will become the important technological means in the pharmaceutical process, providing more environmental protection and efficient solution for the pharmaceutical preparation process. At the same time, the continuous innovation and development of green technology will inject new vitality into the pharmaceutical industry, driving the entire industry towards green, environmental protection, sustainable direction.

Considering the development prospect of green technology in pharmaceutical industry, we can foresee that green technology will become an important direction of pharmaceutical industry in the future and inject new impetus into the sustainable development of the industry.

Conflicts of interest

There are no conflicts to declare.

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Efficacy of Pembrolizumab in the Treatment of Advenced Colorectal Cancer

By Ariane Luiza de Siqueira Braga, Daniel de Oliveira Meireles & Hércules da Costa Ribeiro Junior

Abstract- Colorectal cancer continues to be one of the leading causes of mortality among patients with neoplasia worldwide, just behind to breast and prostate cancer. The aim of this study was to evaluate the efficacy of pembrolizumab in advanced colorectal neoplasms, to offer patients greater survival. A search for scientific papers was carried out on the Pubmed and Lilacs platforms, using the following descriptors "colorectal cancer", "pembrolizumab" and "efficacy", both in Portuguese and in English, both being connected by the Boolean descriptor "AND". Thus, a total of 33 articles were included after inclusion and exclusion criteria. Despite the progress of studies, these lines of treatment are limited to patients due to the high cost of medications.

Keywords: "*colorectal cancer*", "*pembrolizumab*" *and* "*efficacy*".

GJMR-B Classification: *NLM Code: WI529*

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Efficacy of Pembrolizumab in the Treatment of Advenced Colorectal Cancer

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Abstract- Colorectal cancer continues to be one of the leading causes of mortality among patients with neoplasia worldwide, just behind to breast and prostate cancer. The aim of this study was to evaluate the efficacy of pembrolizumab in advanced colorectal neoplasms, to offer patients greater survival. A search for scientific papers was carried out on the Pubmed and Lilacs platforms, using the following descriptors "colorectal cancer", "pembrolizumab" and "efficacy", both in Portuguese and in English, both being connected by the Boolean descriptor "AND". Thus, a total of 33 articles were included after inclusion and exclusion criteria. Despite the progress of studies, these lines of treatment are limited to patients due to the high cost of medications.

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I. Introduction

Colorectal cancer (CRC), an important public health problem1, is the third most common type of neoplasm and the fourth most common cause of death worldwide 2. The majority of cases are found in Western countries 3 and, to develop this disease, factors such as age, genetics, history of inflammatory bowel disease and the patient's lifestyle habits are considered3.

The main tool for good patient evolution still remains early detection4, 5 and in newly diagnosed patients, the first line of treatment is cytoreductive surgery followed by chemotherapy and/or radiotherapy 3, 5, 6. However, there are numerous difficulties encountered in this scenario, as mutation rates result in ineffectiveness in many affected patients or many patients are diagnosed at an advanced stage (stage 4 tumor).

To ensure greater chances of survival for these patients, increasingly advanced studies are launched annually using immunotherapies7, especially this study, with the drug pembrolizumab. Studies show that many patients benefited from the use of this medication, presenting lasting responses8, with highly modified tumors, chemotherapy proved to be inferior9 compared to pembrolizumab.

This medicine is considered a monoclonal antibody 12, 13 and is capable of causing changes in defense T cells, guaranteeing an anti-tumor effect 14. Small doses are used as neoadjuvant therapy and, 3 weeks after insertion of the medication, cytoreductive surgery is performed14. Patients who are diagnosed in the metastatic phase benefited from the use of pembrolizumab15.

The present study aimed to analyze the effectiveness of using pembrolizumab in advanced CRC, in order to guarantee greater survival for affected patients.

II. Material e Method

This is an integrative literature review, which consists of a research method that allows the synthesis and criticism of a given topic for study investigation. This review was prepared following the six steps of the process for carrying out an integrative review. To survey existing scientific productions on the topic, the first stage was developed to define the guiding question: "Efficacy of pembrolizumab in relation to advanced colorectal tumors".

The second stage consisted of defining the inclusion and exclusion criteria. Complete articles were included in the study, in Portuguese and English, year of publication between 2016 and 2024, original articles, randomized and controlled studies and articles related to the guiding question and the descriptors. The exclusion criteria were scientific articles that did not have the full text available, were duplicates and strayed from the topic.

The third stage consisted of researching scientific articles, for this, data collection took place in the months of March and April 2024, an electronic search was carried out in the U.S. National Library of Medicine and the National Institutes Health (PubMed) databases. and through the Virtual Health Library (VHL), in the following information base: Latin American and Caribbean Literature in Health Sciences (LILACS), using the combination of descriptors belonging to the Health Sciences Descriptors (DeCS): "colorectal cancer", "pembrolizumab" and "efficacy", which were connected by the Boolean descriptor "AND".

Based on the results found by searching the articles in the databases with the descriptors, following the inclusion and exclusion criteria presented, the fourth stage of the article began, which consisted of a thorough reading of the titles and abstracts of each work in order to verify compatibility with the guiding question of the present study. Then, the fifth stage of the work began, which consisted of qualitative and descriptive analysis of the collected data and for this, the selected articles were organized in the form of a table (table 1)

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with the following items: author, year, main results and/or conclusions and sample of children to facilitate understanding when analyzing the data found.

Finally, the sixth stage comprises the discussion and synthesis of results, which was carried out in a comparative way of the data interpreted in the analysis of scientific articles in order to contribute information for the preparation of the work.

III. Results

99 articles were found in Pubmed, using only descriptors, when applying the inclusion criteria, 66 articles remained, 33 of which were excluded and, after being part of the exclusion criteria, the final selection resulted in 33 articles selected. In the VHL-LILACS, 1 article was found and, after applying the exclusion criteria, no article was selected.

Therefore, 66 articles remained for complete reading and, after that, 33 were excluded, leaving 33 articles for the final analysis, as shown in figure 1. After evaluating the findings obtained in this research, it was possible to observe that of the 33 articles, 27 were in favor of the use of pembrolizumab in advanced RCC. One article stated that the main line of treatment for this type of tumor is surgery followed by chemotherapy/ radiotherapy. Furthermore, 1 article stated that pembrolizumab did not show sufficient efficacy for colorectal cancer, being much more used in breast cancer or small cell lung cancer.

Quadro 1: Relação dos artigos incluídos no estudo segundo as variáveis estudadas, por ordem de seleção dos artigos, ano e principais resultados encontrados

Authors	Year	Main Results
André T, Shiu KK, et all	2020	This phase 3 randomized clinical trial showed that front-line pembrolizumab was superior to chemotherapy with regard to progression-free survival in patients with MSI-H–dMMR metastatic colorectal cancer.
Ganesh, K., et all	2019	Immune checkpoint inhibitor (ICI) treatment, specifically with monoclonal antibodies targeting programmed cell death 1 (PD1) and cytotoxic T lymphocyte antigen 4 (CTLA4), results in improved survival in dMMR–MSI-H metastatic RCC
Fan A, et all	2021	The high efficacy of neoadjuvant immunotherapy in early-stage RCC has been proven.
Zhang X, et all	2022	For patients who have advanced unresectable or mCRC and are suitable for high-intensity chemotherapy, the NCCN v1.2021 guidelines recommend nivolumab ± ipilimumab (O ± Y) or pembrolizumab as first-line treatment for patients with MSI-H/dMMR status.
Picard E, et all	2020	Initial approaches using anti-PD-1 mAbs in CRC were disappointing as only little, if any, clinical benefit was obtained.
Weng J, et all	2022	Immune checkpoint blockade (ICB) therapy has made significant progress in the treatment of advanced malignancies, and patients who benefit from this therapy can achieve a durable response.
Rosati G, et all	2022	In the metastatic setting, a phase II study demonstrated that tumors with a high mutation burden benefit most from the use of pembrolizumab. Pembrolizumab was superior to chemotherapy in terms of PFS.
Zhu J, et all	2023	Surgery combined with chemotherapy and radiotherapy remains the standard component of curative multimodal treatment approaches for LACRC.
Roth MT, et all	2021	Despite the antitumor activity of pembrolizumab in patients with MSI-H RCC, 30% to 35% of patients fail to obtain any benefit.
Manz SM, et all	2021	Despite the antitumor activity of pembrolizumab in patients with MSI-H RCC, 30% to 35% of patients fail to obtain any benefit. Keynote-177, the first randomized trial specifically recruiting MSI-H/dMMR mCRCs, showed superior PFS for patients treated with first-line pembrolizumab compared with standard chemotherapy, establishing first-line immunotherapy as the standard of care for MSI-H/mCRC. dMMR
André T, et all	2023	Results from the phase II KEYNOTE-164 study showed that pembrolizumab monotherapy had clinical activity in patients with mCRC who had been treated with ≥2 prior lines of standard therapy and in patients who had received ≥1 prior line of therapy (rate of objective response to pembrolizumab monotherapy led to progression-free survival
Justesen TF,	2023	ICIs, such as anti-PD-1 pembrolizumab, revitalize dysfunctional immune cells to enhance the anticancer immune response. For the majority of patients with CRC, ICIs have limited efficacy, however, for the subgroup of patients with dMMR tumors, promising results were found.
Maiorano BA, et all	2022	Early studies of ICIs in mCRC included pretreated patients with MSI. Both KEYNOTE-016 and KEYNOTE-164 demonstrated the efficacy of pembrolizumab as monotherapy in chemo-resistant patients, with an overall response rate.
Rawla P, et all	2019	Checkpoint inhibitors, a new form of immunotherapy, have been shown to be effective for mCRC patients with MMR deficiency and high MSI, while other forms of immunotherapy have not yet shown significant promise..

Cervantes B, et all	2024	Since 2020 and the results of the phase III KEYNOTE 177 clinical trial, pembrolizumab [anti-programmed cell death protein 1 (PD1)] is the new standard of care in first-line MSI/dMMR mCRC
Kuang C, et all	2022	The combination of pembrolizumab and azacitidine is safe and tolerable with modest clinical activity in the treatment of chemotherapy-refractory mCRC.
Ronnekleiv-Kelly SM, et all	2016	A unique histologic feature of certain tumors in patients with microsatellite instability is infiltration by lymphocytes at the tumor-stromal interface. This feature highlights the biology of the tumor in its microenvironment and underlies the efficacy of the programmed death inhibitor pembrolizumab in patients with microsatellite unstable metastatic colorectal cancer.
Miyamoto Y, et all	2022	The results confirm that pembrolizumab should be the standard of care for first-line treatment of patients with MSI-H/dMMR mCRC
Chen X, et all	2024	Monoclonal antibodies (mAbs), such as nivolumab and pembrolizumab, have been used to improve the effectiveness of CRC treatments.
Wang C, et all	2020	Although no responses were recorded in our cohort, disease control in five patients, four without liver metastases, suggests its clinical activity when combined with nivolumab in a subgroup of MSS metastatic colorectal cancer. Furthermore, prolonged MS of 7 months or more in two patients with prior progression on pembrolizumab and atezolizumab provides preliminary evidence suggesting potential synergy between regorafenib and PD-1 inhibitors
Cancanelli L, et all	2021	In this study, after a median follow-up of 32.4 months, pembrolizumab was superior to chemotherapy in terms of progression-free survival (median, 16.5 vs. 8.2 months; hazard ratio, 0.60; 95%CI, 0.45-0.80; P=0.0002), but data on OS still remain blinded until final analysis
Zhang X, et all	2022	Cinco inibidores de PD-1/PD-L1 aprovados pela FDA são usados na terapêutica do câncer: nivolumabe, pembrolizumabe, atezolizumabe, durvalumabe e avelumab
Jung G, et all	2020	The clinical trial design was of high quality and, given the compelling clinical benefit, pembrolizumab is highly recommended as a first-line treatment option for MMRd mCRC.
Fountzilas C, et all	2021	Pembrolizumab has evolved as an active treatment option in patients with advanced MSI-H/dMMR colorectal cancer, regardless of SARS or BRAF status.
Morse MA, et all	2020	Recently, immune checkpoint inhibitors have demonstrated impressive activity in patients with CRC and other solid tumors that are deficient in mismatch repair (dMMR).
Razak AR, et all	2020	Patients who received 1100 mg AMG 820 plus pembrolizumab had a better irPR response, including 2 of 41 patients with metastatic RCC.
Kim DW, et all	2021	Ibrutinib 560 mg daily plus pembrolizumab 200 mg every 3 weeks appears to be well tolerated with limited anticancer activity in metastatic RCC.
Elez E, et all	2024	In a subgroup analysis of this study, patients with mCRC carrying the BRAF V600E mutation benefited from treatment with pembrolizumab compared with SOC chemotherapy.
Wang C, et all	2019	Surveillance CT showed a significant and persistent reduction in tumor burden throughout therapy, with complete remission in January 2017.
Rahma OE, et all	2022	The combination of ziv-aflibercept and pembrolizumab demonstrated an acceptable safety profile with antitumor activity in solid tumors.
Água doce T, et all	2017	The development of immunotherapy with immune checkpoint inhibitors (ICIs) has advanced treatment strategies for various types of cancer.
Smith HG, et all	2023	The advent of immunotherapy in the form of immune checkpoint blockade (ICB) has led to dramatic improvements in the treatment of several cancers with historically poor prognoses.
Pereira LD, et all	2018	PD-L1 testing as a predictive biomarker is only recommended for the use of Pembrolizumab in lung cancer, and a predictive role for PD-L1 expression in colorectal and urothelial cancer has not been demonstrated.

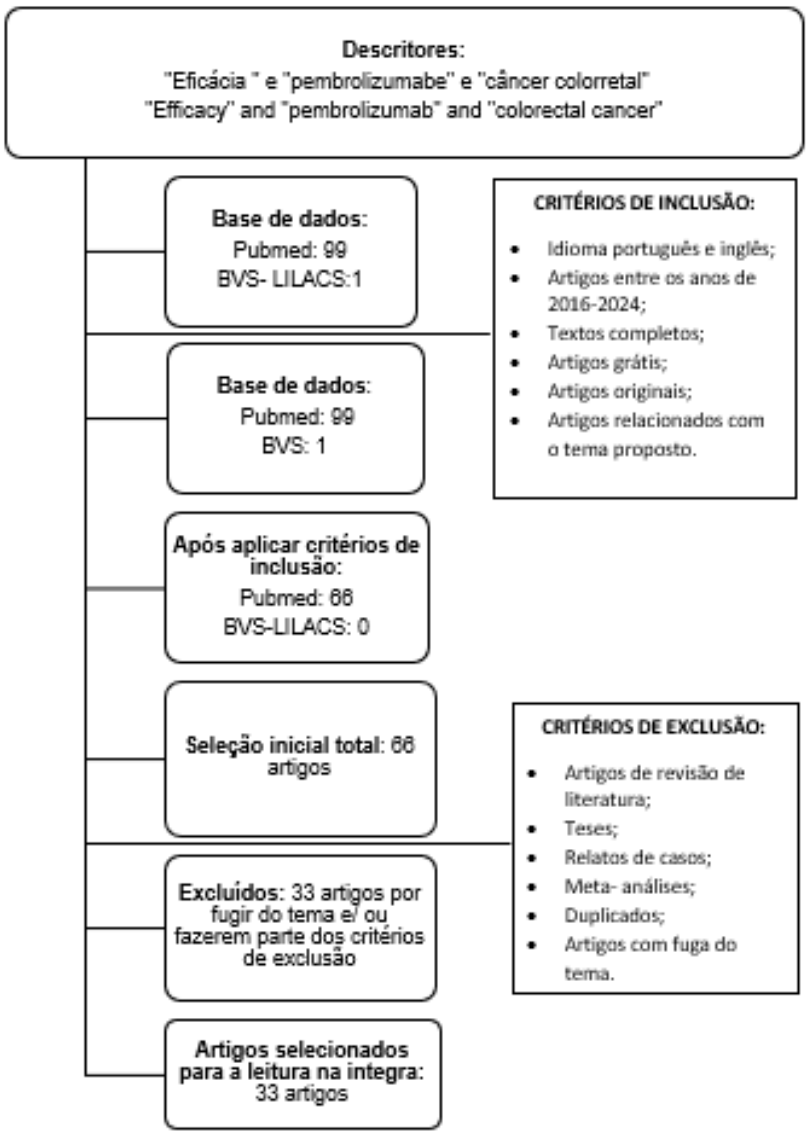

Figura 1: Fluxograma de seleção de artigos incluídos no estudo, 2024

IV. Discussion

The present study indicates that pembrolizumab monotherapy was well tolerated in patients with heavily pretreated PD-L1-positive advanced RCC. KEYNOTE-177 was the first randomized phase 3 study comparing pembrolizumab, a PD-1 antibody, with standard chemotherapy in a first-line setting. Initial data analysis demonstrated a higher overall response rate with pembrolizumab, with a notable duration of response, suggesting a plateau in the Kaplan-Meier analysis beyond 3 years of follow-up. The toxicity profile and quality of life outcomes also clearly favored pembrolizumab over chemotherapy.

It was observed in the studies, that in the pembrolizumab line, the ORR was reported between 41%-43.8% compared to 32%-33.1% following standard chemotherapy. The median PFS for pembrolizumab overall was 16.5 months versus 8.3 months in standard line chemotherapy and the 24-month PFS rates were 48.3% versus 18.6%, respectively. In summary, in the overall population, first-line treatment with pembrolizumab provided significantly longer PFS, higher ORR, and prolonged duration of response compared to chemotherapy. OS was also longer with pembrolizumab versus chemotherapy within a worldwide range.

The benefit of pembrolizumab persisted in most groups, however, those with a KRAS or NRAS mutation did not appear to benefit from pembrolizumab compared with standard chemotherapy. Furthermore, MSI-H CRC tumors also appear to have higher PD-L1 expression than their MSS counterparts, possibly suggesting that PD-1 checkpoint blockade may be particularly beneficial in the treatment of MSI-H CRC.

Pembrolizumab was also well tolerated in KEYNOTE-177, with 22% of patients experiencing a grade 3 or higher adverse event based on the National

Cancer Institute Common Terminology Criteria for Adverse Events, relative to 66% of patients in the standard chemotherapy who experienced a grade 3 or higher adverse event. In the analysis of health-related quality of life, pembrolizumab was also superior to standard chemotherapy. Time to deterioration was prolonged for global health status/quality of life, physical functioning, social functioning, and fatigue for patients who received pembrolizumab compared to those who received standard chemotherapy.

The dose of pembrolizumab administered in the latest studies (10 mg/kg Q2W) is higher than that used in the early trials (2 mg/kg every 3 weeks [Q3W], 10 mg/kg Q3W, or 200 mg Q3W) and is superior at currently approved doses (2 mg/kg Q3W and 200 mg Q3W). However, the tolerability of pembrolizumab at all three doses was similar in cohorts of patients with various advanced solid tumors. Therefore, the current study does not support any potential benefit in increasing the dose of pembrolizumab as a way to improve therapeutic response.

V. Conclusion

The results found in this present study suggest that the monoclonal antibody pembrolizumab is of paramount importance in the treatment of advanced colorectal cancer, whether neoadjuvantly, adjuvantly or in association with cytoreductive surgeries. Such a medicine is capable of connecting to tumor cells, causing the effect of antitumor cells on defense T cells.

This effect led to an improvement in survival rates in patients with advanced colorectal cancer, compared to patients who underwent palliative treatments with surgery associated with FOLFOX (5-fluorouracil, oxaliplatin and folinic acid) or FOLFIRI (5-fluorouracil and irinotecan).

Therefore, given that its cost in Brazil is high, it would be of great value if pembrolizumab were available to the entire population affected by CRC, guaranteeing greater survival and quality of life.

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Effect of Ozoniotherapy in the Treatment of Necrosis after Hair Transplantation: Case Report

By Luisa Melo Lucas, Anayene Craveiro Mendes & Jorge Temer Merhi

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Abstract- *Introduction:* Nowadays, ozone plays an important role in wound healing and tissue repair as a therapy and as antimicrobial, bactericidal and fungicidal agent. It attains recognition in hair transplantation as a treatment for necrosis due to hypoxic-ischemic local syndrome. *Objective:* to demonstrate the therapeutic evolution of ischemia in a hair transplant after ozone therapy sessions. *Methods:* The patient was evaluation and gave consent to photographic records. He went through 30 topic applications of ozonated oil, with a 10 drop dosage daily; 12 bag ozone sessions for 10 minutes; besides subcutaneous applications, with 30% ozone concentration and a very small gas volume (1-2 ml) with 30G needle. *Results:* Evolution of the case was registered with images and tissue coloring and changes evidenced. *Conclusion:* It is clear that ozone therapy made wound healing and tissue repair faster, since there was an increase of epithelial cells and neoangiogenesis due to therapy, resulting in almost complete repair of the patient's hair transplant at the end of the sessions.

Keywords: *ozone therapy, hair transplant, hair treatment.*

GJMR-B Classification: *LCC: RL87.3*

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Abstract- Introduction: Nowadays, ozone plays an important role in wound healing and tissue repair as a therapy and as antimicrobial, bactericidal and fungicidal agent. It attains recognition in hair transplantation as a treatment for necrosis due to hypoxic-ischemic local syndrome. *Objective:* to demonstrate the therapeutic evolution of ischemia in a hair transplant after ozone therapy sessions. *Methods:* The patient was evaluation and gave consent to photographic records. He went through 30 topic applications of ozonated oil, with a 10 drop dosage daily; 12 bag ozone sessions for 10 minutes; besides subcutaneous applications, with 30% ozone concentration and a very small gas volume (1-2 ml) with 30G needle. *Results:* Evolution of the case was registered with images and tissue coloring and changes evidenced. *Conclusion:* It is clear that ozone therapy made wound healing and tissue repair faster, since there was an increase of epithelial cells and neoangiogenesis due to therapy, resulting in almost complete repair of the patient's hair transplant at the end of the sessions.

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I. Introduction

Hair transplant has been changing many individuals' reality that face alopecia, a disease consisting of head or body hair loss. Unlike several other transplants, hair transplant is in the spotlight because of its peculiarity in using follicles of the same donor who is supposed to receive them in a less invasive way. In spite of the many techniques available, all of them require patient evaluation including: patient history, age, previous medical evaluations. Diagnosing the type of alopecia is mandatory. Whenever the patient has the conditions for the procedure, it is unusual the occurrence of resulting complications. However, as highlighted by Zito and Raggio in Statpearls, "Potential complications include: edema (5%), bleeding (0.5%), folliculitis, infection (less than 1% of patients)". Being the necrosis of the receiving area due to excess density in the area or another possible cause present.

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Hypoxic-ischemic local syndrome, which can evolve to tissue necrosis, develops from low blood perfusion in tissues and decrease in oxygen because of several etiologies, such as abuse of anesthetics and vasoconstrictors and excess of FUs in an area. The appropriate level of oxygen in tissues is fundamental so that cells keep their aerobic metabolism and vital functions. When the perfusion pressure is not enough to keep the minimal oxygen level, aerobic metabolism shifts to anaerobic with resulting organic dysfunctions. Therefore, treatment is an issue of diagnosing the primary cause and should be initiated at the ischemic lesion spot so as to start revacularization.

Necrosis takes place whenever a cell is exposed to extreme environmental conditions, adverse and excessive stimuli, or in face of deleterious mutations codified in its genetic material. Cell necrotic death occurs as a response to severe physiological conditions, including hypoxia, ischemia, toxin exposition, anesthetics, reactive metabolites of oxygen and nutrient deprivation. In cases of ischemic necrosis, nuclear alterations of cytoplasms portray a clotted blood appearance: acidophilus, granular and hardened. There is loss of tissue structure and the area becomes whitish, bulged and hyperemic. Among microscopic aspects there is increase in acidophilus, a granular appearance and formation of amorphous masses as a result of membrane rupture and mixture of autolyzed material.

Ozone therapy, considered an alternative therapy, with excellent results and ease of application, is in evidence in many countries. It was first acknowledged in 1839, by german chemist Christina Friedrich, and in 1896, by Nikola Tesla, who patented the first ozone generator, in the US, used during the First World War to treat gas gangrene, which treatment is still in use.

Ozone therapy is a bio-oxidative therapy based on a gasified mixture of oxygen and medical ozone, whose therapeutic effects include mainly the improvement of metabolism and the oxygenation of peripheral tissues, as a consequence of increased erythrocyte flexibility, allowing for a better flow inside capillaries and assuring a larger supply of oxygen in the tissues. This process facilitates epithelial repair and growth and inhibits bacterial and fungicidal development.

In hair transplantation, despite technological advancements, ozone therapy application to treat ischemic necrosis is unknown or barely known, as

shown by the reduced number of research papers and therapeutic approaches which might be a guidance for professionals in the field. Thus, the current study aimed at making the causes and effects of ozone therapy more clear whenever it is aptly applied to treat and prevent ischemia and necrosis in hair transplantation procedures.

II. Materials and Methods

This is a longitudinal descriptive and interventionist study with convenience, consecutive, non-probabilistic sampling. The patient underwent a hair transplant procedure in May, 2022, in an unknown doctor's office and was referred to Dr. Anayene Craveiro, at Belcorp Institute, after first signs of ischemic necrosis.

The recommendations of the Madrid Declaration on Ozone Therapy were considered to evaluate the appropriate doses for the corresponding mechanism of action. First, there are three basic principles: (1) not to do harm; (2) stagger the dose; (3) apply the necessary concentration.

Treatment was started with initial evaluation and recognition of the ischemic necrotic area, with mediated intervention. Lesion characteristics were evaluated on the grounds of photographic records facilitating the patient's therapeutic evolution follow-up.

The Oxy device, manufactured by Tonederm®, licensed by the Brazilian Health Regulatory Agency (ANVISA), was employed in the treatment. This device turns medical oxygen into ozone gas through corona discharge. Topical treatment with gas, and a plastic transparent bag manufactured with ozone resistant material, consists of applying an elastic band with sealed edges to the skin.

III. Case Outline

A 40-year-old white male patient, with no pre-existing diseases, underwent the hair transplantation procedure in May, 3rd 2022, with 4,600 follicle units.

The patient - himself a doctor - was referred to Dr. Craveiro Mendes in the same week following his noticing of an ischemic area. His exams showed no other symptoms, nor were there any complaints of allergic reactions. On inspection, the lesion showed well defined edges adherent to wound bed with small fibrin clots, wound bed with granular tissue, adjacent skin edema, peeling skin around the tissue lesion and absence of exudate and odor.

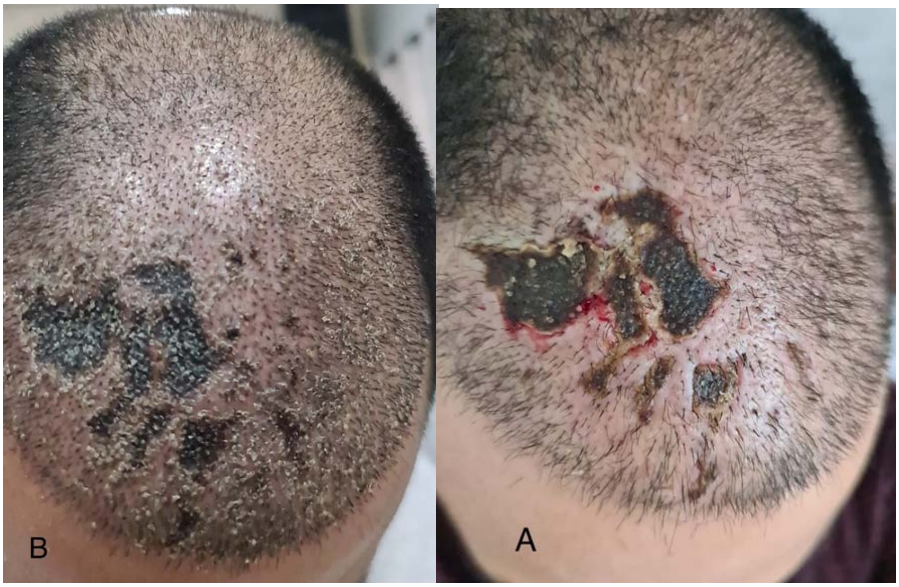
The patient was submitted to 30 ozonized oil topical applications, 10 drops a day, and twelve 30 % ozone sessions with a bag, once a week, for 10 minutes, besides subcutaneous 30% concentration ozone applications with a small gas volume (1-2 ml) through 30G needle. Ozone therapy was conducted after local hygienization with no dressing following the application.

The patient, who unexpectedly faced complications after pursuing hair transplant for high self-esteem, was also provided with psychological care for better acceptance of ozone therapy results.

IV. Results and Discussion

Photographic images demonstrate the progress between the first and last ozone therapy applications. There was local neovascularization and wound healing with progressive reduction of the necrotic area. It is possible to observe at first hand the increased blood supply, vessel permeability and vasodilation, which showed a better coloring appearance since the first session. Granular tissue was found in the first session with endothelial and fibroblast proliferation, which are mesenchymal differentiated cells spreading on the lesion surface. On the first days, angiogenesis first stages were observed with a bulged and whitish region surrounded by a red halo. On the last day it was possible to see a better wound bed and epithelial tissue growth, that is, new skin growing out of the lesion edges in face of a concentration process of the marginal wound walls, under the action of activated fibroblasts, making epithelization possible. It exhibits a shiny rose coloring related to mature collagen.

According to the photographic records before and after the three sessions (Picture 1), there was improvement of tissue healing, decreasing bulging, better local blood supply, and recovery of the whitish appearance. In addition, there was growth of granular tissue due to collagen activity, elastin and reticular fibers in an attempt to tissue repair. This phase produces the increase of inflammatory cells, growth factors, vasodilation and presence of permeability.



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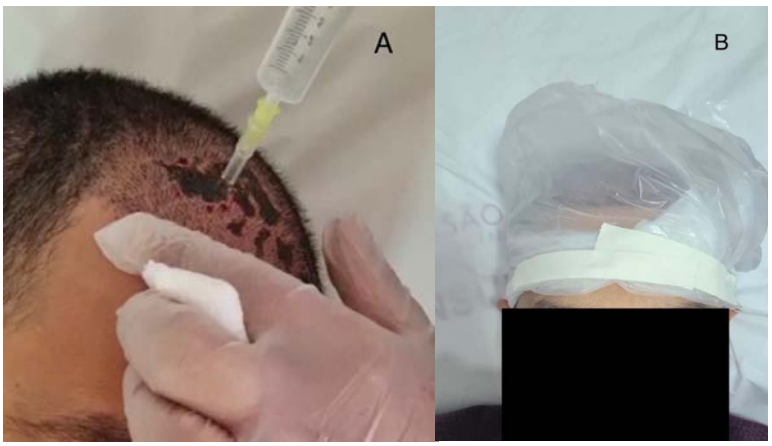
Picture 1: Before (B) and after (A) of Ozone Therapy Application

Along the application sessions, there was significant improvement (Picture 2). Necrotic tissue started debriding and granular tissue formation took place, with faster neovascularization and local epithelialization. Studies have demonstrated that ozone oil can promote wound healing through PI3K/Akt/mTOR signaling. Mechanically, it is possible to verify that ozone oil can activate fibroblasts and promote their migration. Besides that it can extend the mesenchymal epithelial transition (MET) process.



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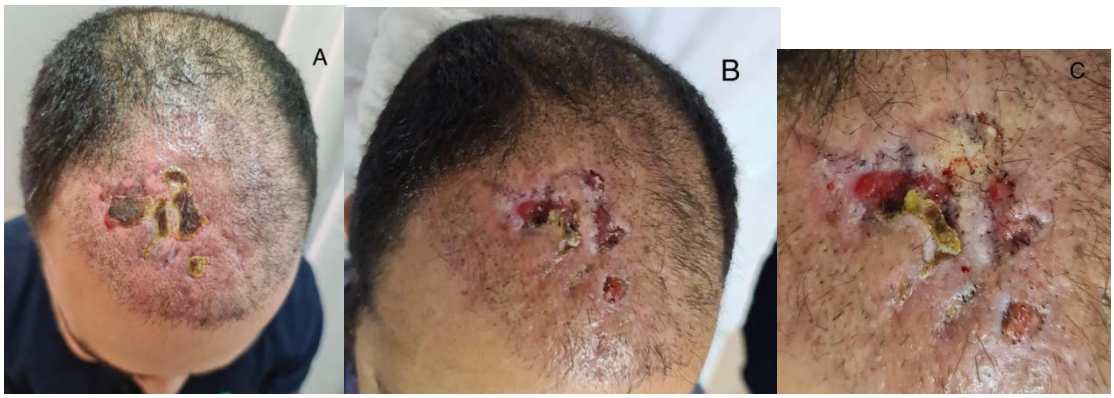
Picture 2: Application of Subcutaneous Ozone (A) and Bag Therapy (B)

The analysis of therapeutic evolution after 5 sessions of ozone therapy (Picture 3) makes clear the expansion of mesenchymal cells, fibroblasts, on the wound surface, which is related to internal vessel growth and formation of conjunctive tissue. From this moment, concentration of lesion edges takes place, facilitating epithelization.



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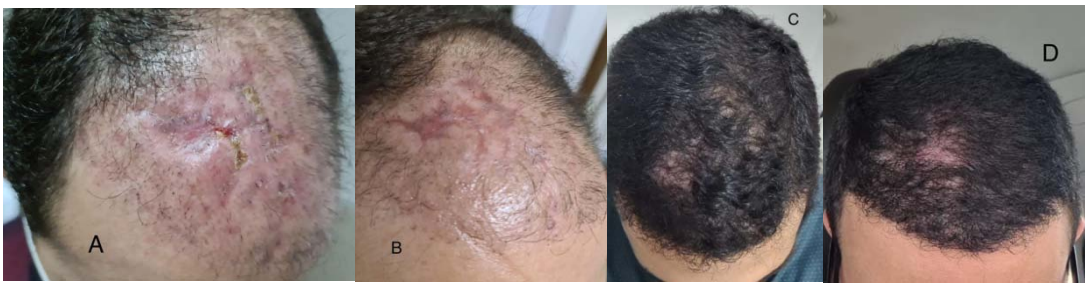
Picture 3: Evidence of mesenchymal cell growth surrounding de lesion (A); Concetration of edges for epithelization in (B) and (C)

Gradually after concluding ozone therapy sessions, remodeling phase starts (Picture 4) leading to reduction of cell activity and blood vessels, Then, maturation and increased local resistance ensues.



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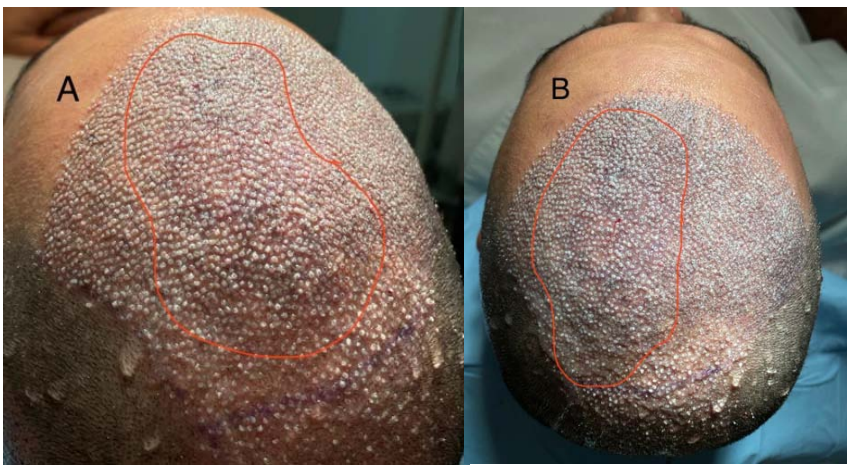
Picture 4: Tissue with reddish coloring indicating blood flow and mature collagen (A) and (B). There was hair growth of some follicles implanted in the area, which demonstrates recovery from the hair transplant through ozone therapy (C) and (D)

For data collection, pictures after hair transplantation procedure (Picture 5). High density and dark coloring areas due to possible ischemia are visible.



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Picture 5: Hair transplant with high approximation of FUs in (A) and (B) showing spots with immediate reduction of blood flow

There is limited evidence on the direct use of ozone therapy in hair transplantation, but it is successful in several other treatments and it presents a therapeutic challenge. There are several therapies for dermal treatment but their adverse effects hamper their application. However, as previously observed, ozone therapy, despite being a simple molecule, holds an

efficient approach to fight microorganisms and promote healing capacity.

V. Conclusion

The current study demonstrated the use of ozone for ischemic tissue treatment. Eventual therapeutic outcomes were positive as healing evolution was attested as a result of improved blood flow and re-epithelialization of damaged tissue.

Despite being an innovative procedure, hair transplantation does not exclude the possibility of necrosis, which highlights the importance of the availability of tools to cope with unexpected situations. Healing is a complex process and demands immediate intervention in face of its occurrence.

This case report is free of any conflict of interest and aims at supporting study and learning initiatives by professionals addressing similar cases in their professional settings.

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Plagiarized content will not be considered for publication. We reserve the right to inform authors' institutions about plagiarism detected either before or after publication. If plagiarism is identified, we will follow COPE guidelines:

Authors are solely responsible for all the plagiarism that is found. The author must not fabricate, falsify or plagiarize existing research data. The following, if copied, will be considered plagiarism:

- Words (language)
- Ideas
- Findings
- Writings
- Diagrams
- Graphs
- Illustrations
- Lectures

- Printed material
- Graphic representations
- Computer programs
- Electronic material
- Any other original work

Authorship Policies

Global Journals follows the definition of authorship set up by the Open Association of Research Society, USA. According to its guidelines, authorship criteria must be based on:

1. Substantial contributions to the conception and acquisition of data, analysis, and interpretation of findings.
2. Drafting the paper and revising it critically regarding important academic content.
3. Final approval of the version of the paper to be published.

Changes in Authorship

The corresponding author should mention the name and complete details of all co-authors during submission and in manuscript. We support addition, rearrangement, manipulation, and deletions in authors list till the early view publication of the journal. We expect that corresponding author will notify all co-authors of submission. We follow COPE guidelines for changes in authorship.

Copyright

During submission of the manuscript, the author is confirming an exclusive license agreement with Global Journals which gives Global Journals the authority to reproduce, reuse, and republish authors' research. We also believe in flexible copyright terms where copyright may remain with authors/employers/institutions as well. Contact your editor after acceptance to choose your copyright policy. You may follow this form for copyright transfers.

Appealing Decisions

Unless specified in the notification, the Editorial Board's decision on publication of the paper is final and cannot be appealed before making the major change in the manuscript.

Acknowledgments

Contributors to the research other than authors credited should be mentioned in Acknowledgments. The source of funding for the research can be included. Suppliers of resources may be mentioned along with their addresses.

Declaration of funding sources

Global Journals is in partnership with various universities, laboratories, and other institutions worldwide in the research domain. Authors are requested to disclose their source of funding during every stage of their research, such as making analysis, performing laboratory operations, computing data, and using institutional resources, from writing an article to its submission. This will also help authors to get reimbursements by requesting an open access publication letter from Global Journals and submitting to the respective funding source.

Preparing your Manuscript

Authors can submit papers and articles in an acceptable file format: MS Word (doc, docx), LaTeX (.tex, .zip or .rar including all of your files), Adobe PDF (.pdf), rich text format (.rtf), simple text document (.txt), Open Document Text (.odt), and Apple Pages (.pages). Our professional layout editors will format the entire paper according to our official guidelines. This is one of the highlights of publishing with Global Journals—authors should not be concerned about the formatting of their paper. Global Journals accepts articles and manuscripts in every major language, be it Spanish, Chinese, Japanese, Portuguese, Russian, French, German, Dutch, Italian, Greek, or any other national language, but the title, subtitle, and abstract should be in English. This will facilitate indexing and the pre-peer review process.

The following is the official style and template developed for publication of a research paper. Authors are not required to follow this style during the submission of the paper. It is just for reference purposes.

Manuscript Style Instruction (Optional)

- Microsoft Word Document Setting Instructions.
- Font type of all text should be Swis721 Lt BT.
- Page size: 8.27" x 11'", left margin: 0.65, right margin: 0.65, bottom margin: 0.75.
- Paper title should be in one column of font size 24.
- Author name in font size of 11 in one column.
- Abstract: font size 9 with the word "Abstract" in bold italics.
- Main text: font size 10 with two justified columns.
- Two columns with equal column width of 3.38 and spacing of 0.2.
- First character must be three lines drop-capped.
- The paragraph before spacing of 1 pt and after of 0 pt.
- Line spacing of 1 pt.
- Large images must be in one column.
- The names of first main headings (Heading 1) must be in Roman font, capital letters, and font size of 10.
- The names of second main headings (Heading 2) must not include numbers and must be in italics with a font size of 10.

Structure and Format of Manuscript

The recommended size of an original research paper is under 15,000 words and review papers under 7,000 words. Research articles should be less than 10,000 words. Research papers are usually longer than review papers. Review papers are reports of significant research (typically less than 7,000 words, including tables, figures, and references)

A research paper must include:

a) A title which should be relevant to the theme of the paper.
b) A summary, known as an abstract (less than 150 words), containing the major results and conclusions.
c) Up to 10 keywords that precisely identify the paper's subject, purpose, and focus.
d) An introduction, giving fundamental background objectives.
e) Resources and techniques with sufficient complete experimental details (wherever possible by reference) to permit repetition, sources of information must be given, and numerical methods must be specified by reference.
f) Results which should be presented concisely by well-designed tables and figures.
g) Suitable statistical data should also be given.
h) All data must have been gathered with attention to numerical detail in the planning stage.

Design has been recognized to be essential to experiments for a considerable time, and the editor has decided that any paper that appears not to have adequate numerical treatments of the data will be returned unrefereed.

i) Discussion should cover implications and consequences and not just recapitulate the results; conclusions should also be summarized.
j) There should be brief acknowledgments.
k) There ought to be references in the conventional format. Global Journals recommends APA format.

Authors should carefully consider the preparation of papers to ensure that they communicate effectively. Papers are much more likely to be accepted if they are carefully designed and laid out, contain few or no errors, are summarizing, and follow instructions. They will also be published with much fewer delays than those that require much technical and editorial correction.

The Editorial Board reserves the right to make literary corrections and suggestions to improve brevity.

Format Structure

It is necessary that authors take care in submitting a manuscript that is written in simple language and adheres to published guidelines.

All manuscripts submitted to Global Journals should include:

Title

The title page must carry an informative title that reflects the content, a running title (less than 45 characters together with spaces), names of the authors and co-authors, and the place(s) where the work was carried out.

Author details

The full postal address of any related author(s) must be specified.

Abstract

The abstract is the foundation of the research paper. It should be clear and concise and must contain the objective of the paper and inferences drawn. It is advised to not include big mathematical equations or complicated jargon.

Many researchers searching for information online will use search engines such as Google, Yahoo or others. By optimizing your paper for search engines, you will amplify the chance of someone finding it. In turn, this will make it more likely to be viewed and cited in further works. Global Journals has compiled these guidelines to facilitate you to maximize the web-friendliness of the most public part of your paper.

Keywords

A major lynchpin of research work for the writing of research papers is the keyword search, which one will employ to find both library and internet resources. Up to eleven keywords or very brief phrases have to be given to help data retrieval, mining, and indexing.

One must be persistent and creative in using keywords. An effective keyword search requires a strategy: planning of a list of possible keywords and phrases to try.

Choice of the main keywords is the first tool of writing a research paper. Research paper writing is an art. Keyword search should be as strategic as possible.

One should start brainstorming lists of potential keywords before even beginning searching. Think about the most important concepts related to research work. Ask, “What words would a source have to include to be truly valuable in a research paper?” Then consider synonyms for the important words.

It may take the discovery of only one important paper to steer in the right keyword direction because, in most databases, the keywords under which a research paper is abstracted are listed with the paper.

Numerical Methods

Numerical methods used should be transparent and, where appropriate, supported by references.

Abbreviations

Authors must list all the abbreviations used in the paper at the end of the paper or in a separate table before using them.

Formulas and equations

Authors are advised to submit any mathematical equation using either MathJax, KaTeX, or LaTeX, or in a very high-quality image.

Tables, Figures, and Figure Legends

Tables: Tables should be cautiously designed, uncrowned, and include only essential data. Each must have an Arabic number, e.g., Table 4, a self-explanatory caption, and be on a separate sheet. Authors must submit tables in an editable format and not as images. References to these tables (if any) must be mentioned accurately.

Figures

Figures are supposed to be submitted as separate files. Always include a citation in the text for each figure using Arabic numbers, e.g., Fig. 4. Artwork must be submitted online in vector electronic form or by emailing it.

Preparation of Eletronic Figures for Publication

Although low-quality images are sufficient for review purposes, print publication requires high-quality images to prevent the final product being blurred or fuzzy. Submit (possibly by e-mail) EPS (line art) or TIFF (halftone/ photographs) files only. MS PowerPoint and Word Graphics are unsuitable for printed pictures. Avoid using pixel-oriented software. Scans (TIFF only) should have a resolution of at least 350 dpi (halftone) or 700 to 1100 dpi (line drawings). Please give the data for figures in black and white or submit a Color Work Agreement form. EPS files must be saved with fonts embedded (and with a TIFF preview, if possible).

For scanned images, the scanning resolution at final image size ought to be as follows to ensure good reproduction: line art: >650 dpi; halftones (including gel photographs): >350 dpi; figures containing both halftone and line images: >650 dpi.

Color charges: Authors are advised to pay the full cost for the reproduction of their color artwork. Hence, please note that if there is color artwork in your manuscript when it is accepted for publication, we would require you to complete and return a Color Work Agreement form before your paper can be published. Also, you can email your editor to remove the color fee after acceptance of the paper.

Tips for writing a good quality Medical Research Paper

1. Choosing the topic: In most cases, the topic is selected by the interests of the author, but it can also be suggested by the guides. You can have several topics, and then judge which you are most comfortable with. This may be done by asking several questions of yourself, like "Will I be able to carry out a search in this area? Will I find all necessary resources to accomplish the search? Will I be able to find all information in this field area?" If the answer to this type of question is "yes," then you ought to choose that topic. In most cases, you may have to conduct surveys and visit several places. Also, you might have to do a lot of work to find all the rises and falls of the various data on that subject. Sometimes, detailed information plays a vital role, instead of short information. Evaluators are human: The first thing to remember is that evaluators are also human beings. They are not only meant for rejecting a paper. They are here to evaluate your paper. So present your best aspect.

2. Think like evaluators: If you are in confusion or getting demotivated because your paper may not be accepted by the evaluators, then think, and try to evaluate your paper like an evaluator. Try to understand what an evaluator wants in your research paper, and you will automatically have your answer. Make blueprints of paper: The outline is the plan or framework that will help you to arrange your thoughts. It will make your paper logical. But remember that all points of your outline must be related to the topic you have chosen.

3. Ask your guides: If you are having any difficulty with your research, then do not hesitate to share your difficulty with your guide (if you have one). They will surely help you out and resolve your doubts. If you can't clarify what exactly you require for your work, then ask your supervisor to help you with an alternative. He or she might also provide you with a list of essential readings.

4. Use of computer is recommended: As you are doing research in the field of medical research then this point is quite obvious. Use right software: Always use good quality software packages. If you are not capable of judging good software, then you can lose the quality of your paper unknowingly. There are various programs available to help you which you can get through the internet.

5. Use the internet for help: An excellent start for your paper is using Google. It is a wondrous search engine, where you can have your doubts resolved. You may also read some answers for the frequent question of how to write your research paper or find a model research paper. You can download books from the internet. If you have all the required books, place importance on reading, selecting, and analyzing the specified information. Then sketch out your research paper. Use big pictures: You may use encyclopedias like Wikipedia to get pictures with the best resolution. At Global Journals, you should strictly follow here.

6. Bookmarks are useful: When you read any book or magazine, you generally use bookmarks, right? It is a good habit which helps to not lose your continuity. You should always use bookmarks while searching on the internet also, which will make your search easier.

7. Revise what you wrote: When you write anything, always read it, summarize it, and then finalize it.

8. Make every effort: Make every effort to mention what you are going to write in your paper. That means always have a good start. Try to mention everything in the introduction—what is the need for a particular research paper. Polish your work with good writing skills and always give an evaluator what he wants. Make backups: When you are going to do any important thing like making a research paper, you should always have backup copies of it either on your computer or on paper. This protects you from losing any portion of your important data.

9. Produce good diagrams of your own: Always try to include good charts or diagrams in your paper to improve quality. Using several unnecessary diagrams will degrade the quality of your paper by creating a hodgepodge. So always try to include diagrams which were made by you to improve the readability of your paper. Use of direct quotes: When you do research relevant to literature, history, or current affairs, then use of quotes becomes essential, but if the study is relevant to science, use of quotes is not preferable.

10. Use proper verb tense: Use proper verb tenses in your paper. Use past tense to present those events that have happened. Use present tense to indicate events that are going on. Use future tense to indicate events that will happen in the future. Use of wrong tenses will confuse the evaluator. Avoid sentences that are incomplete.

11. Pick a good study spot: Always try to pick a spot for your research which is quiet. Not every spot is good for studying.

12. Know what you know: Always try to know what you know by making objectives, otherwise you will be confused and unable to achieve your target.

13. Use good grammar: Always use good grammar and words that will have a positive impact on the evaluator; use of good vocabulary does not mean using tough words which the evaluator has to find in a dictionary. Do not fragment sentences. Eliminate one-word sentences. Do not ever use a big word when a smaller one would suffice.

Verbs have to be in agreement with their subjects. In a research paper, do not start sentences with conjunctions or finish them with prepositions. When writing formally, it is advisable to never split an infinitive because someone will (wrongly) complain. Avoid clichés like a disease. Always shun irritating alliteration. Use language which is simple and straightforward. Put together a neat summary.

14. Arrangement of information: Each section of the main body should start with an opening sentence, and there should be a changeover at the end of the section. Give only valid and powerful arguments for your topic. You may also maintain your arguments with records.

15. Never start at the last minute: Always allow enough time for research work. Leaving everything to the last minute will degrade your paper and spoil your work.

16. Multitasking in research is not good: Doing several things at the same time is a bad habit in the case of research activity. Research is an area where everything has a particular time slot. Divide your research work into parts, and do a particular part in a particular time slot.

17. Never copy others' work: Never copy others' work and give it your name because if the evaluator has seen it anywhere, you will be in trouble. Take proper rest and food: No matter how many hours you spend on your research activity, if you are not taking care of your health, then all your efforts will have been in vain. For quality research, take proper rest and food.

18. Go to seminars: Attend seminars if the topic is relevant to your research area. Utilize all your resources.

19. Refresh your mind after intervals: Try to give your mind a rest by listening to soft music or sleeping in intervals. This will also improve your memory. Acquire colleagues: Always try to acquire colleagues. No matter how sharp you are, if you acquire colleagues, they can give you ideas which will be helpful to your research.

20. Think technically: Always think technically. If anything happens, search for its reasons, benefits, and demerits. Think and then print: When you go to print your paper, check that tables are not split, headings are not detached from their descriptions, and page sequence is maintained.

21. Adding unnecessary information: Do not add unnecessary information like "I have used MS Excel to draw graphs." Irrelevant and inappropriate material is superfluous. Foreign terminology and phrases are not apropos. One should never take a broad view. Analogy is like feathers on a snake. Use words properly, regardless of how others use them. Remove quotations. Puns are for kids, not grunt readers. Never oversimplify: When adding material to your research paper, never go for oversimplification; this will definitely irritate the evaluator. Be specific. Never use rhythmic redundancies. Contractions shouldn't be used in a research paper. Comparisons are as terrible as clichés. Give up ampersands, abbreviations, and so on. Remove commas that are not necessary. Parenthetical words should be between brackets or commas. Understatement is always the best way to put forward earth-shaking thoughts. Give a detailed literary review.

22. Report concluded results: Use concluded results. From raw data, filter the results, and then conclude your studies based on measurements and observations taken. An appropriate number of decimal places should be used. Parenthetical remarks are prohibited here. Proofread carefully at the final stage. At the end, give an outline to your arguments. Spot perspectives of further study of the subject. Justify your conclusion at the bottom sufficiently, which will probably include examples.

23. Upon conclusion: Once you have concluded your research, the next most important step is to present your findings. Presentation is extremely important as it is the definite medium though which your research is going to be in print for the rest of the crowd. Care should be taken to categorize your thoughts well and present them in a logical and neat manner. A good quality research paper format is essential because it serves to highlight your research paper and bring to light all necessary aspects of your research.

Informal Guidelines of Research Paper Writing

Key points to remember:

- Submit all work in its final form.
- Write your paper in the form which is presented in the guidelines using the template.
- Please note the criteria peer reviewers will use for grading the final paper.

Final points:

One purpose of organizing a research paper is to let people interpret your efforts selectively. The journal requires the following sections, submitted in the order listed, with each section starting on a new page:

The introduction: This will be compiled from reference matter and reflect the design processes or outline of basis that directed you to make a study. As you carry out the process of study, the method and process section will be constructed like that. The results segment will show related statistics in nearly sequential order and direct reviewers to similar intellectual paths throughout the data that you gathered to carry out your study.

The discussion section:

This will provide understanding of the data and projections as to the implications of the results. The use of good quality references throughout the paper will give the effort trustworthiness by representing an alertness to prior workings.

Writing a research paper is not an easy job, no matter how trouble-free the actual research or concept. Practice, excellent preparation, and controlled record-keeping are the only means to make straightforward progression.

General style:

Specific editorial column necessities for compliance of a manuscript will always take over from directions in these general guidelines.

To make a paper clear: Adhere to recommended page limits.

Mistakes to avoid:

- Insertion of a title at the foot of a page with subsequent text on the next page.
- Separating a table, chart, or figure—confine each to a single page.
- Submitting a manuscript with pages out of sequence.
- In every section of your document, use standard writing style, including articles ("a" and "the").
- Keep paying attention to the topic of the paper.
- Use paragraphs to split each significant point (excluding the abstract).
- Align the primary line of each section.
- Present your points in sound order.
- Use present tense to report well-accepted matters.
- Use past tense to describe specific results.
- Do not use familiar wording; don't address the reviewer directly. Don't use slang or superlatives.
- Avoid use of extra pictures—include only those figures essential to presenting results.

Title page:

Choose a revealing title. It should be short and include the name(s) and address(es) of all authors. It should not have acronyms or abbreviations or exceed two printed lines.

Abstract: This summary should be two hundred words or less. It should clearly and briefly explain the key findings reported in the manuscript and must have precise statistics. It should not have acronyms or abbreviations. It should be logical in itself. Do not cite references at this point.

An abstract is a brief, distinct paragraph summary of finished work or work in development. In a minute or less, a reviewer can be taught the foundation behind the study, common approaches to the problem, relevant results, and significant conclusions or new questions.

Write your summary when your paper is completed because how can you write the summary of anything which is not yet written? Wealth of terminology is very essential in abstract. Use comprehensive sentences, and do not sacrifice readability for brevity; you can maintain it succinctly by phrasing sentences so that they provide more than a lone rationale. The author can at this moment go straight to shortening the outcome. Sum up the study with the subsequent elements in any summary. Try to limit the initial two items to no more than one line each.

Reason for writing the article—theory, overall issue, purpose.

- Fundamental goal.
- To-the-point depiction of the research.
- Consequences, including definite statistics—if the consequences are quantitative in nature, account for this; results of any numerical analysis should be reported. Significant conclusions or questions that emerge from the research.

Approach:

- Single section and succinct.
- An outline of the job done is always written in past tense.
- Concentrate on shortening results—limit background information to a verdict or two.
- Exact spelling, clarity of sentences and phrases, and appropriate reporting of quantities (proper units, important statistics) are just as significant in an abstract as they are anywhere else.

Introduction:

The introduction should "introduce" the manuscript. The reviewer should be presented with sufficient background information to be capable of comprehending and calculating the purpose of your study without having to refer to other works. The basis for the study should be offered. Give the most important references, but avoid making a comprehensive appraisal of the topic. Describe the problem visibly. If the problem is not acknowledged in a logical, reasonable way, the reviewer will give no attention to your results. Speak in common terms about techniques used to explain the problem, if needed, but do not present any particulars about the protocols here.

The following approach can create a valuable beginning:

- Explain the value (significance) of the study.
- Defend the model—why did you employ this particular system or method? What is its compensation? Remark upon its appropriateness from an abstract point of view as well as pointing out sensible reasons for using it.
- Present a justification. State your particular theory(-ies) or aim(s), and describe the logic that led you to choose them.
- Briefly explain the study's tentative purpose and how it meets the declared objectives.

Approach:

Use past tense except for when referring to recognized facts. After all, the manuscript will be submitted after the entire job is done. Sort out your thoughts; manufacture one key point for every section. If you make the four points listed above, you will need at least four paragraphs. Present surrounding information only when it is necessary to support a situation. The reviewer does not desire to read everything you know about a topic. Shape the theory specifically—do not take a broad view.

As always, give awareness to spelling, simplicity, and correctness of sentences and phrases.

Procedures (methods and materials):

This part is supposed to be the easiest to carve if you have good skills. A soundly written procedures segment allows a capable scientist to replicate your results. Present precise information about your supplies. The suppliers and clarity of reagents can be helpful bits of information. Present methods in sequential order, but linked methodologies can be grouped as a segment. Be concise when relating the protocols. Attempt to give the least amount of information that would permit another capable scientist to replicate your outcome, but be cautious that vital information is integrated. The use of subheadings is suggested and ought to be synchronized with the results section.

When a technique is used that has been well-described in another section, mention the specific item describing the way, but draw the basic principle while stating the situation. The purpose is to show all particular resources and broad procedures so that another person may use some or all of the methods in one more study or referee the scientific value of your work. It is not to be a step-by-step report of the whole thing you did, nor is a methods section a set of orders.

Materials:

Materials may be reported in part of a section or else they may be recognized along with your measures.

Methods:

- Report the method and not the particulars of each process that engaged the same methodology.
- Describe the method entirely.
- To be succinct, present methods under headings dedicated to specific dealings or groups of measures.
- Simplify—detail how procedures were completed, not how they were performed on a particular day.
- If well-known procedures were used, account for the procedure by name, possibly with a reference, and that's all.

Approach:

It is embarrassing to use vigorous voice when documenting methods without using first person, which would focus the reviewer's interest on the researcher rather than the job. As a result, when writing up the methods, most authors use third person passive voice.

Use standard style in this and every other part of the paper—avoid familiar lists, and use full sentences.

What to keep away from:

- Resources and methods are not a set of information.
- Skip all descriptive information and surroundings—save it for the argument.
- Leave out information that is immaterial to a third party.

Results:

The principle of a results segment is to present and demonstrate your conclusion. Create this part as entirely objective details of the outcome, and save all understanding for the discussion.

The page length of this segment is set by the sum and types of data to be reported. Use statistics and tables, if suitable, to present consequences most efficiently.

You must clearly differentiate material which would usually be incorporated in a study editorial from any unprocessed data or additional appendix matter that would not be available. In fact, such matters should not be submitted at all except if requested by the instructor.

Content:

- Sum up your conclusions in text and demonstrate them, if suitable, with figures and tables.
- In the manuscript, explain each of your consequences, and point the reader to remarks that are most appropriate.
- Present a background, such as by describing the question that was addressed by creation of an exacting study.
- Explain results of control experiments and give remarks that are not accessible in a prescribed figure or table, if appropriate.
- Examine your data, then prepare the analyzed (transformed) data in the form of a figure (graph), table, or manuscript.

What to stay away from:

- Do not discuss or infer your outcome, report surrounding information, or try to explain anything.
- Do not include raw data or intermediate calculations in a research manuscript.
- Do not present similar data more than once.
- A manuscript should complement any figures or tables, not duplicate information.
- Never confuse figures with tables—there is a difference.

Approach:

As always, use past tense when you submit your results, and put the whole thing in a reasonable order.

Put figures and tables, appropriately numbered, in order at the end of the report.

If you desire, you may place your figures and tables properly within the text of your results section.

Figures and tables:

If you put figures and tables at the end of some details, make certain that they are visibly distinguished from any attached appendix materials, such as raw facts. Whatever the position, each table must be titled, numbered one after the other, and include a heading. All figures and tables must be divided from the text.

Discussion:

The discussion is expected to be the trickiest segment to write. A lot of papers submitted to the journal are discarded based on problems with the discussion. There is no rule for how long an argument should be.

Position your understanding of the outcome visibly to lead the reviewer through your conclusions, and then finish the paper with a summing up of the implications of the study. The purpose here is to offer an understanding of your results and support all of your conclusions, using facts from your research and generally accepted information, if suitable. The implication of results should be fully described.

Infer your data in the conversation in suitable depth. This means that when you clarify an observable fact, you must explain mechanisms that may account for the observation. If your results vary from your prospect, make clear why that may have happened. If your results agree, then explain the theory that the proof supported. It is never suitable to just state that the data approved the prospect, and let it drop at that. Make a decision as to whether each premise is supported or discarded or if you cannot make a conclusion with assurance. Do not just dismiss a study or part of a study as "uncertain."

Research papers are not acknowledged if the work is imperfect. Draw what conclusions you can based upon the results that you have, and take care of the study as a finished work.

- You may propose future guidelines, such as how an experiment might be personalized to accomplish a new idea.
- Give details of all of your remarks as much as possible, focusing on mechanisms.
- Make a decision as to whether the tentative design sufficiently addressed the theory and whether or not it was correctly restricted. Try to present substitute explanations if they are sensible alternatives.
- One piece of research will not counter an overall question, so maintain the large picture in mind. Where do you go next? The best studies unlock new avenues of study. What questions remain?
- Recommendations for detailed papers will offer supplementary suggestions.

Approach:

When you refer to information, differentiate data generated by your own studies from other available information. Present work done by specific persons (including you) in past tense.

Describe generally acknowledged facts and main beliefs in present tense.

The Administration Rules

Administration Rules to Be Strictly Followed before Submitting Your Research Paper to Global Journals Inc.

Please read the following rules and regulations carefully before submitting your research paper to Global Journals Inc. to avoid rejection.

Segment draft and final research paper: You have to strictly follow the template of a research paper, failing which your paper may get rejected. You are expected to write each part of the paper wholly on your own. The peer reviewers need to identify your own perspective of the concepts in your own terms. Please do not extract straight from any other source, and do not rephrase someone else's analysis. Do not allow anyone else to proofread your manuscript.

Written material: You may discuss this with your guides and key sources. Do not copy anyone else's paper, even if this is only imitation, otherwise it will be rejected on the grounds of plagiarism, which is illegal. Various methods to avoid plagiarism are strictly applied by us to every paper, and, if found guilty, you may be blacklisted, which could affect your career adversely. To guard yourself and others from possible illegal use, please do not permit anyone to use or even read your paper and file.

Criterion for Grading a Research Paper (Compilation) by Global Journals

Please note that following table is only a Grading of "Paper Compilation" and not on "Performed/Stated Research" whose grading solely depends on Individual Assigned Peer Reviewer and Editorial Board Member. These can be available only on request and after decision of Paper. This report will be the property of Global Journals.

Topics	Grades		
	A-B	**C-D**	**E-F**
Abstract	Clear and concise with appropriate content, Correct format. 200 words or below	Unclear summary and no specific data, Incorrect form Above 200 words	No specific data with ambiguous information Above 250 words
Introduction	Containing all background details with clear goal and appropriate details, flow specification, no grammar and spelling mistake, well organized sentence and paragraph, reference cited	Unclear and confusing data, appropriate format, grammar and spelling errors with unorganized matter	Out of place depth and content, hazy format
Methods and Procedures	Clear and to the point with well arranged paragraph, precision and accuracy of facts and figures, well organized subheads	Difficult to comprehend with embarrassed text, too much explanation but completed	Incorrect and unorganized structure with hazy meaning
Result	Well organized, Clear and specific, Correct units with precision, correct data, well structuring of paragraph, no grammar and spelling mistake	Complete and embarrassed text, difficult to comprehend	Irregular format with wrong facts and figures
Discussion	Well organized, meaningful specification, sound conclusion, logical and concise explanation, highly structured paragraph reference cited	Wordy, unclear conclusion, spurious	Conclusion is not cited, unorganized, difficult to comprehend
References	Complete and correct format, well organized	Beside the point, Incomplete	Wrong format and structuring

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