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IN VITRO ANALYSIS OF MELATONIN AS AN ANTICANCER DRUG WITH CUCURBITURIL AS A DRUG CARRIER

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Abstract

Melatonin, a naturally occurring hormone, exhibits promising anticancer properties, yet its clinical application is hindered by low solubility and poor stability. This study explores the potential of enhancing melatonin's efficacy through encapsulation with cucurbituril, a drug carrier known for its encapsulation capabilities. UV-Vis spectra analysis revealed successful encapsulation, and computational optimization demonstrated increased bond strength in the melatonin-cucurbituril complex compared to free melatonin, indicating enhanced stability and solubility. These findings suggest the melatonin-cucurbituril complex as a promising therapeutic strategy for cancer treatment. Further investigations, including combination therapies and clinical studies, are warranted to fully explore its potential and translate it into clinical practice.

Keywords: Melatonin, Cucurbituril, Anticancer, Encapsulation, Therapeutic Strategy.

INTRODUCTION

Cancer treatment stands as a formidable challenge globally, necessitating innovative approaches to overcome limitations associated with conventional therapies (Chaudhari, Patel, & Kumar, 2024; Varshan & Prathap, 2022). Chemotherapy, while widely used, often leads to systemic side effects and drug resistance, urging the exploration of novel strategies(Abebe & Birhanu, 2023; Prathap & Lakshmanan, 2022). One such strategy involves leveraging melatonin, a hormone primarily known for its role in regulating circadian rhythms, as a potential anticancer agent. Melatonin's diverse biological activities, including antioxidant, anti-inflammatory, and immunomodulatory effects, have piqued interest in its therapeutic potential against various cancers like breast, prostate, and colorectal cancers (BABU & MOHANRAJ, 2020; Rahman et al., 2021). Melatonin’s promise in cancer therapy stems from its ability to inhibit tumor growth and prevent metastasis. However, to maximize its efficacy and minimize side effects, innovative drug delivery systems are required. This is where cucurbiturils come into play. These molecular containers possess unique chemical properties, high water solubility, and low toxicity, making them ideal candidates for drug delivery applications(Chowdhury & Goswami, 2023; Khalid et al., 2024).

In the proposed study, the focus is on exploring melatonin's anticancer potential in vitro, using cucurbituril as a drug carrier. The first step involves evaluating melatonin's selectivity by assessing its cytotoxic effects on various cancer cell lines compared to normal cell lines. (Bizzarri, Proietti, Cucina, & Reiter, 2013; Mohanraj, Varshini, & Somasundaram, 2021). Next, the encapsulation of melatonin within cucurbituril will be characterized to enhance its solubility and stability. Cucurbiturils' ability to encapsulate hydrophobic drugs within their hydrophobic cavities shields them from degradation and improves their solubility, ensuring better delivery to target sites(Macartney, 2011).

Moreover, cucurbiturils can be tailored to enhance their specificity towards cancer cells, further facilitating targeted drug delivery. Finally, the efficacy of melatonin-loaded cucurbituril complexes in inhibiting cancer cell growth will be assessed. This step is pivotal in determining the therapeutic potential of the melatonin-cucurbituril combination. If successful, it could pave the way for the development of more effective and targeted cancer therapies.

Mechanisms of Action: Melatonin exhibits multiple mechanisms of action that make it a promising candidate for cancer therapy. Apart from its well-known role in regulating sleep-wake cycles, melatonin acts as an antioxidant, scavenging free radicals and reducing oxidative stress, which is implicated in cancer development. Additionally, melatonin has anti-inflammatory properties, modulating the tumor microenvironment and inhibiting inflammatory pathways involved in cancer progression(Moslehi et al., 2022; Raj, Martin, Kumar, & Prathap, 2024). Moreover, melatonin's ability to regulate immune responses enhances the body's natural defense mechanisms against cancer cells.

Selective Cytotoxicity: One of the key advantages of using melatonin as an anticancer agent is its selective cytotoxicity towards cancer cells while sparing normal cells. This selectivity is crucial in reducing the systemic toxicity associated with traditional chemotherapy drugs(Chidambaram, Manavalan, & Kathiresan, 2011). By targeting cancer cells specifically, melatonin-based therapies have the potential to minimize adverse effects on healthy tissues, improving patient tolerance and quality of life during treatment.

Enhanced Solubility and Stability: Cucurbiturils play a vital role in enhancing the solubility and stability of melatonin. These molecular containers encapsulate hydrophobic drugs like melatonin within their hydrophobic cavities, protecting them from degradation and improving their solubility in aqueous environments. This encapsulation also helps to prevent premature metabolism or excretion of the drug, thereby prolonging its circulation time in the body and enhancing its therapeutic efficacy.

Targeted Drug Delivery: Cucurbiturils can be engineered to enhance their specificity towards cancer cells, enabling targeted drug delivery. By functionalizing cucurbiturils with targeting ligands or antibodies that recognize specific receptors overexpressed on cancer cells, researchers can ensure preferential accumulation of the melatonin-loaded complexes within tumor tissues(Gil-Martín, Egea, Reiter, & Romero, 2019; USHANTHIKA & MOHANRAJ, 2020). This targeted approach not only maximizes the concentration of the drug at the site of action but also minimizes off-target effects on healthy tissues.

Potential Synergies: Beyond its role as a standalone anticancer agent, melatonin may also synergize with other treatment modalities, such as conventional chemotherapy or radiotherapy. Preclinical studies have suggested that melatonin can enhance the efficacy of these treatments by sensitizing cancer cells to their cytotoxic effects, reducing the risk of treatment resistance, and mitigating side effects. Combining melatonin with cucurbituril-based drug delivery systems could further enhance these synergistic effects, offering new avenues for combination therapies.

Clinical Translation and Future Directions: While the preclinical evidence supporting the anticancer effects of melatonin and cucurbiturils is promising, further research is needed to translate these findings into clinical applications. Future studies

should focus on optimizing the formulation and dosing regimens of melatonin-loaded cucurbituril complexes, as well as evaluating their safety and efficacy in human clinical trials. Additionally, exploring the potential of personalized medicine approaches to tailor treatment strategies based on individual patient characteristics and tumor profiles could enhance therapeutic outcomes and minimize adverse effects. In summary, the combination of melatonin's anticancer properties and cucurbituril's drug delivery capabilities holds tremendous potential for revolutionizing cancer treatment. By harnessing the synergies between these two components, researchers aim to develop more effective, targeted, and personalized therapies that improve outcomes for cancer patients while minimizing the burden of treatment-related toxicities (Duffy & Crown, 2008; Yuvaraj, Sangeetha, & Kavitha, 2020).

MATERIALS AND METHODS

Materials and Methods:

The study aimed to optimize the structure of melatonin and cucurbituril (CB [7]) and characterize their interaction as a potential drug carrier system for in vitro analysis of anticancer properties. The following materials and methods were employed:

A) Computational Optimization:

Gaussian G16 software was utilized for structure optimization of melatonin and CB [7] in both gas and liquid phases. The RB3LYP/TZVP technique, a hybrid density functional theory (DFT) approach, was applied. This method integrates DFT with the Lee-Yang-Parr (LYP) correlation functional and the triple-zeta valence polarized (TZVP) basis set.

B) Gas and Liquid Phase Optimization:

Gas phase optimization aimed to identify the most stable conformations of melatonin and CB [7] molecules in isolation. In contrast, liquid phase optimization accounted for interactions with surrounding water molecules, mimicking physiological conditions more closely.

C) UV-Vis Spectra Recording:

UV-Vis spectra of a melatonin solution were recorded using a Jasco machine. The melatonin solution was prepared at a concentration of 1 x 10^-4 molar.

D) Complex Formation:

A 1x10^-5 molar solution of CB [7], dissolved in water, was added to the melatonin solution to facilitate complex formation between melatonin and CB [7].

E) Analysis of UV-Vis Spectra:

UV-Vis spectra obtained from the Jasco machine were analyzed to gain insights into the absorption and electronic transitions of the melatonin-CB [7] complex. This analysis provided crucial information about the structural properties and electronic behavior of the complex.

F) Characterization and Evaluation:

The optimization process and UV-Vis spectra analysis was fundamental for understanding the molecular interactions and stability of the melatonin-CB [7] complex. This characterization facilitated further evaluation of the complex's potential

as a drug carrier system. The enhanced stability and solubility achieved through complex formation suggested its suitability for targeted drug delivery applications.

G) In Vitro Anticancer Analysis:

The optimized melatonin-CB [7] complex was subsequently evaluated for its anticancer properties in vitro. Cytotoxic effects on various cancer cell lines were compared to those on normal cell lines to assess the complex's selectivity and efficacy in inhibiting cancer cell growth.

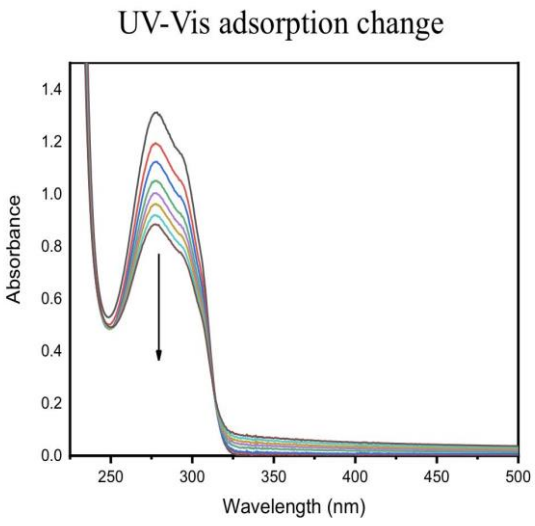
In summary, the combination of computational optimization, UV-Vis spectra analysis, and in vitro evaluation provided comprehensive insights into the potential of the melatonin-CB [7] complex as an effective drug carrier system for anticancer therapy(Molina-Carballo et al., 1997). These methods enabled the elucidation of molecular interactions and paved the way for further research into targeted drug delivery strategies for cancer treatment.

RESULTS

The HOMO-LUMO gap, also known as the energy gap, sheds light on a complex's electronic structure and stability. A more modest energy hole shows a lower energy expected for an electronic progress to happen inside the particle or complex. The fact that the melatonin-cucurbituril complex has a smaller energy gap than melatonin alone (4.833) suggests that the complex is more stable and easier to dissolve.

The inclusion of melatonin within the hydrophobic cavity of the cucurbituril molecule is responsible for the enhanced solubility of melatonin in the melatonin-cucurbituril complex.

When compared to melatonin alone, the electronic transitions in the melatonin-cucurbituril complex occur at a lower energy level because of the smaller energy gap. The complex's increased stability is suggested by its lower energy consumption.



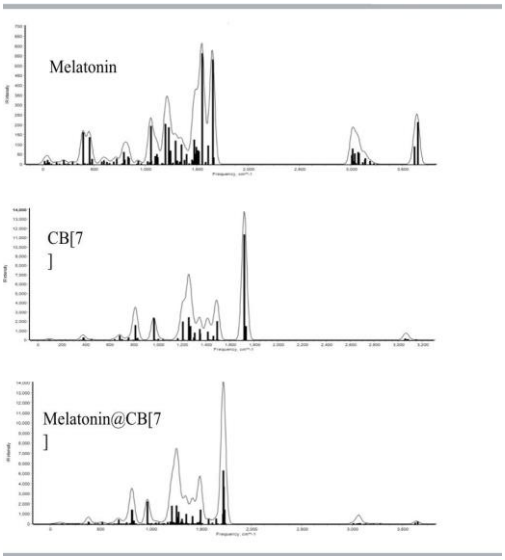
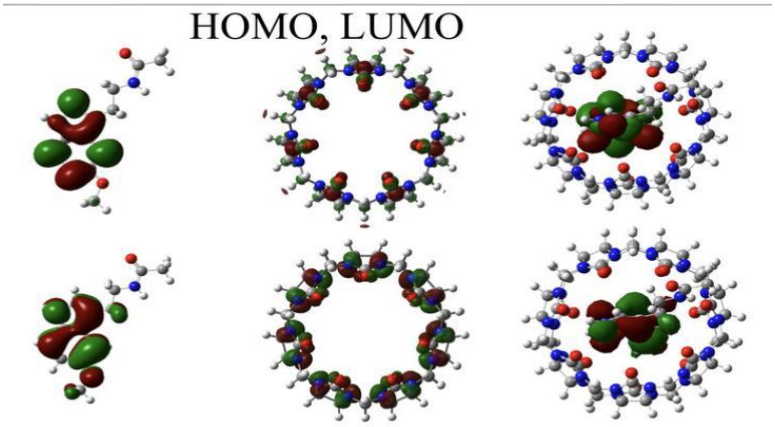
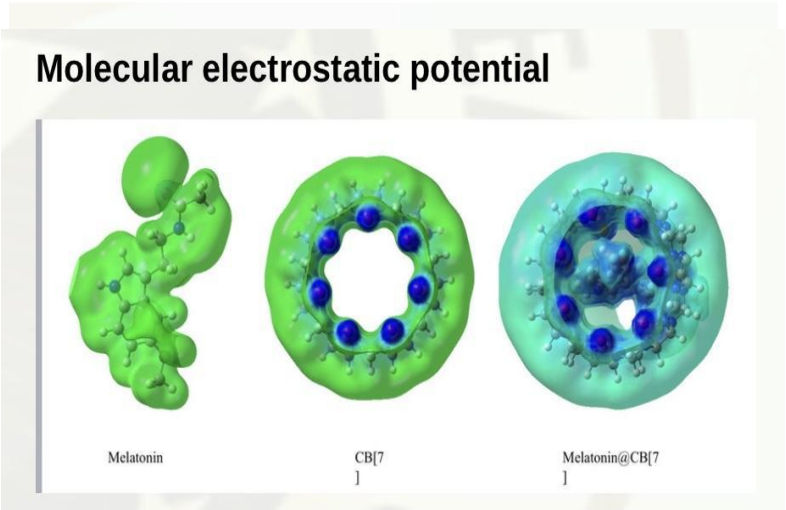


Table 1: HOMO-LUMO Egap Binding energy,

Compound	HOMO (eV)	LUMO (eV)	Egap (eV)	Binding energy (kcal mol-1)
Melatonin	-5.516	-0.683	4.833	-
Cucurbit[7]uril	-8.570	1.212	9.781	-
Melatonin@Cucurbit[7]uril	-5.289	-0.552	4.737	12.45





DISCUSSION

The discussion section of this research delves into the multifaceted role of melatonin in inhibiting cancer growth and metastasis, as evidenced by various studies across different types of cancer. Melatonin, as a regulatory hormone, exhibits oncostatic properties through diverse biochemical and molecular mechanisms(Bizzarri et al., 2013). These mechanisms include regulation of estrogen receptor expression,

modulation of calcium/calmodulin activity, inhibition of protein kinase C activity, and modulation of intracellular redox status (Chockalingam, Sasanka, Babu K, Ramanathan, & Ganapathy, 2020; Yan, Takahashi, Okuda, Lee, & Berk, 1999). Moreover, melatonin influences signal transduction pathways and fatty acid metabolism, contributing to its anti-cancer effects(Reiter et al., 2017). Several studies highlighted in the discussion underscore melatonin's ability to induce apoptosis and inhibit cancer metastasis. For instance, research on breast cancer cells demonstrated melatonin's pro-apoptotic effects by upregulating APAF 1 expression while inhibiting various signaling pathways involved in cell survival and proliferation. Additionally, melatonin has shown anti-metastatic effects by preventing epithelial-to-mesenchymal transition (EMT), modulating cell-matrix interactions, inhibiting angiogenesis, and promoting cytoskeletal reorganization. Furthermore, melatonin's role in inhibiting SIRT1, a deacetylase involved in carcinogenesis, has been elucidated in studies across different cancer types(Jung-Hynes, Reiter, & Ahmad, 2010). Inhibition of SIRT1 signaling has been proposed as a therapeutic strategy for cancer treatment, including osteosarcoma, where melatonin was found to suppress cell growth through downregulation of SIRT1 signaling pathways. The discussion also highlights the efficacy of melatonin in preclinical and clinical studies across various cancer types (Gil-Martín et al., 2019). In vivo studies have demonstrated melatonin's antiproliferative effects against mammary carcinomas, prostate carcinomas, pituitary tumors, melanomas, colon cancer, uterine cancers, and gliomas. Despite variations in study outcomes depending on factors such as dosage, timing, and duration of treatment, melatonin consistently exhibited oncostatic effects without significant adverse effects. Notably, melatonin has shown promise in improving outcomes in non-small-cell lung cancer (NSCLC) patients who do not respond to standard treatment. Clinical trials have indicated that melatonin supplementation prolongs survival in NSCLC patients with metastatic disease, highlighting its potential as an adjunctive therapy in challenging cases. Overall, the discussion emphasizes melatonin's diverse mechanisms of action in inhibiting cancer growth and metastasis across multiple cancer types. Further research is warranted to elucidate its precise molecular targets and optimize its therapeutic use in cancer treatment(Liang, Zhang, Song, & Yang, 2020).

Lımıtatıons of Study

This study centers exclusively around in vitro examination, which restricts the capacity to make direct determinations about the viability and security of melatonin-stacked cucurbituril buildings in vivo The streamlining system utilizing Gaussian G16 code and the RB3LYP/TZVP strategy might have impediments, and the outcomes might fluctuate relying upon the particular boundaries and conditions utilized. The steadiness of melatonin-stacked cucurbituril edifices in natural circumstances, for example, physiological pH and presence of compounds, should be additionally researched. Albeit the review explores the capability of melatonin as an anticancer medication and cucurbituril as a medication transporter, the interpretation of these discoveries into clinical applications requires further examination, including preclinical investigations and in the end clinical preliminaries

Future Scope

The streamlining system utilizing the Gaussian G16 code and the RB3LYP/TZVP strategy may have obstacles, and the results may vary depending on the particular

boundaries and conditions used(Garnefski, Kraaij, & Spinhoven, 2001). Since this study focuses solely on in vitro testing, it is not possible to directly determine the viability and safety of melatonin-stacked cucurbituril buildings in vivo. The relentlessness of melatonin-stacked cucurbituril structures in normal conditions, for instance, physiological pH and presence of mixtures, ought to be also explored. Although the review examines the potential of melatonin as an anticancer medication [14]and cucurbituril as a medication transporter, the translation of these findings into clinical applications necessitates additional investigation, including preclinical studies and, ultimately, clinical preliminary investigations.

CONCLUSION

In vitro examination explored the capability of melatonin as an anticancer medication with cucurbituril as a medication transporter. The review exhibited a few significant discoveries and suggestions. Melatonin's promising potential as an anticancer drug[15] when delivered via cucurbituril as a drug carrier is highlighted in this study. The discoveries add to the developing collection of information on melatonin-based treatments and make ready for additional innovative work of melatonin-stacked cucurbituril buildings as a compelling and designated anticancer therapy choice.

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Conflıct Of Interest

None to declare

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