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ICGeHeS 2023: International Conference on General Health Sciences

Fighting the Pink Battle: Breast Cancer Surgery and Cultural Stigma in Bangladesh

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Abstract: The study examines the complex interaction between breast cancer treatment and cultural stigma in Bangladeshi society. This article demonstrates the multiple challenges breast cancer surgery patients encounter, including deeply ingrained societal norms, religious beliefs, and gender roles that contribute to the stigma surrounding the disease and its treatments. The study underscores the various challenges that contribute to the delayed detection and treatment of breast cancer, including low awareness, insufficient healthcare infrastructure, and entrenched societal norms. In addition, the article explores the psychological and social ramifications that women who undergo mastectomy or other forms of breast cancer surgery suffer. The article provides a complete overview of the challenges experienced by Bangladeshi women in their fight against breast cancer through interview and personal accounts. In order to improve the outcomes of breast cancer patients in Bangladesh and foster a more supportive atmosphere for their rehabilitation, it is crucial to overcome these cultural and structural obstacles.

Keywords: Breast cancer, Cultural stigma, Healthcare access, Early detection, Awareness.

Introduction

Breast cancer continues to be a serious public health concern, resulting in substantial morbidity and mortality among women. Breast cancer is the most frequent cancer among women, according to the World Health Organization (WHO), affecting around 2.1 million women annually and resulting in an estimated 627,000 deaths in 2018. (WHO, 2021). In low and middle-income nations such as Bangladesh, breast cancer poses an even larger difficulty due to a number of variables, including limited healthcare resources, insufficient early diagnosis and screening programs, and social barriers (Bray et al., 2018).

The purpose of this paper is to provide a thorough knowledge of the intricate relationship between breast cancer treatment, specifically surgery, and the enduring cultural stigma in Bangladeshi society. This article emphasizes that while lack of awareness, poor healthcare infrastructure, and inadequate government support contribute to the challenges faced by women seeking breast cancer care in Bangladesh (Anwar et al., 2019), the deeply ingrained cultural stigma surrounding the disease and its treatments significantly exacerbates these challenges (Khatun et al., 2021).

This article examines the cultural and socioeconomic elements that contribute to the stigmatization of breast cancer in Bangladesh, such as traditional gender roles, religious views, and taboos surrounding talks of women's health and sexuality. The article shows the harmful impact of cultural stigma on early detection, treatment access, and post-surgery recovery by analyzing how these factors influence women's decisions to seek breast cancer diagnosis and treatment (Ahmed et al., 2020). To address these issues, the paper proposes a holistic, multidisciplinary approach that engages healthcare professionals, legislators, non-governmental organizations, and community leaders in increasing breast cancer awareness, breaking down cultural barriers, and advancing gender equality. By adopting these tactics, the paper emphasizes the significance of tackling the underlying societal causes that perpetuate the suffering of countless women in Bangladesh who have breast cancer (Islam et

al., 2018). This paper will also shed light on the intricate interaction between breast cancer care and cultural stigma in Bangladeshi society. By identifying and tackling these deeply established obstacles, we may strive toward a more fair and effective approach to breast cancer prevention, treatment, and care for all Bangladeshi women.

Objectives

This article examines the barriers Bangladeshi women have in receiving access to breast cancer surgery, as well as the influence of cultural and religious views on these barriers. To achieve this purpose, the following objectives will be pursued:

- To assess the existing condition of breast cancer in Bangladesh, including its prevalence, healthcare infrastructure, and access to treatment, in order to give a comprehensive evaluation of the current barriers to breast cancer care.
- To evaluate the cultural, social, and religious factors that contribute to the stigma associated with breast cancer surgery in Bangladesh, focusing on modesty, gender norms, and sickness misconceptions.
- To examine the implications of late diagnosis and limited access to breast cancer surgery on survival rates and quality of life for Bangladeshi women, emphasizing the need of early identification and timely treatment.
- To highlight the efforts undertaken in Bangladesh by individuals, NGOs, government initiatives, and international partnerships to boost breast cancer awareness, enhance early detection, and improve access to breast cancer surgery.
- To offer solutions for removing cultural stigma and barriers to breast cancer surgery in Bangladesh with the objective of improving healthcare outcomes and empowering women in their fight against breast cancer.

Literature Review

Many researches have been conducted in an effort to comprehend the variables leading to the disease's prevalence in Bangladesh and the difficulties involved in delivering adequate care. In this literature review, we will examine research on the current situation of breast cancer in Bangladesh, the cultural and religious variables that impact access to breast cancer surgery, and initiatives to overcome these obstacles.

Prevalence and Healthcare Infrastructure

Breast cancer is the most prevalent malignancy in Bangladesh's female population (Ferlay et al., 2021). It has been attributed to a combination of genetic, environmental, and behavioral factors (Kamal et al., 2015). The healthcare system in Bangladesh has failed to keep up with the rising demand for breast cancer care, especially in rural areas with limited access to specialized facilities (Islam et al., 2020). Ahmed (2013) discovered that a lack of comprehensive cancer centers, restricted availability of specialist healthcare experts, and inadequate funding for cancer care all contribute to the difficulties faced by women in Bangladesh seeking breast cancer treatment.

Cultural and Religious Factors

The cultural and religious stigma associated with the disease is a significant barrier to breast cancer care in Bangladesh. Hossain et al. (2014) discovered that modesty concerns, fear of social ostracism, and a lack of understanding about breast cancer symptoms cause rural women to delay seeking medical care. In Bangladesh, women may prioritize their family's demands over their own health due to the influence of gender roles (Akhtar et al., 2017). In addition, superstitions and religious beliefs may result in a preference for alternative or spiritual treatments over traditional medicine (Islam et al., 2020).

Attempts to Overcome Obstacles

Local and international NGOs, such as the Breast Cancer Welfare Association (BCWA) and the Bangladesh Cancer Society (BCS), have been striving to increase breast cancer awareness, provide information on early

detection, and provide support services to patients and their families (Khatun et al., 2018). In addition to measures to improve healthcare infrastructure, the Bangladeshi government has established specialized cancer facilities and allocated cash for cancer care (Ahmed, 2013).

Collaborations between local organizations and international partners, such as the World Health Organization (WHO) and the International Agency for Research on Cancer (IARC), have resulted in the development of national cancer control policies and healthcare professional training programs (Kamal et al., 2015). These relationships are vital to bolstering cancer care services in Bangladesh by offering technical and financial support. In addition, the importance of community health workers in increasing breast cancer awareness and early diagnosis has been recognized as a crucial aspect of the national healthcare system (Khatun et al., 2018). These community-based projects can assist bridge the gap between healthcare institutions and remote communities, thereby boosting rural women's access to treatment.

Literature on breast cancer in Bangladesh demonstrates a complicated interaction between the disease's prevalence, the constraints of the healthcare system, and cultural and religious barriers to care. Improving healthcare infrastructure, boosting early detection, and addressing the cultural stigma associated with breast cancer surgery are necessary to address these difficulties. Ongoing efforts by NGOs, government initiatives, and international collaborations are essential for empowering women in Bangladesh to seek timely diagnosis and treatment, hence improving the prognoses of breast cancer patients.

Methodology

This qualitative study utilizes a phenomenological approach to explore the experiences and challenges faced by women in Bangladesh regarding breast cancer surgery and cultural stigma. Data were collected through semi-structured interviews and analyzed using thematic analysis (Braun & Clarke, 2006). The research adheres to the principles of reflexivity and ethical considerations in qualitative research (Creswell & Poth, 2018).

Participants and Recruitment

A purposive sampling technique was employed to recruit 30 women diagnosed with breast cancer, who have undergone surgery in the last five years, from various socio-economic backgrounds in both rural and urban Bangladesh (Palinkas et al., 2015). Participants were identified through local healthcare facilities, breast cancer support groups, and snowball sampling. Informed consent was obtained prior to conducting interviews.

Data Collection

Data collection involved face-to-face, semi-structured interviews lasting approximately 60 minutes. An interview guide with open-ended questions was developed, focusing on the participants' experiences of breast cancer surgery, the cultural stigma they faced, and the implications on their mental health and social life (Smith & Osborn, 2008). Interviews were conducted in the native language of participants and audio-recorded with their permission. Field notes were taken to supplement the audio recordings.

Data Analysis

Audio recordings were transcribed verbatim and translated into English. Thematic analysis, following Braun and Clarke's (2006) six-phase framework, was employed to identify, analyze, and report patterns and themes within the data. Initial coding was done by two independent researchers, and any discrepancies were resolved through discussion to ensure inter-rater reliability. NVivo software was used to assist in data organization and coding.

Ethical Considerations

This study was approved by the Merine City Medical College, Chittagong Research Ethics Committee. Participants were assured of confidentiality and anonymity, and the right to withdraw from the study at any time

without consequences (Creswell & Poth, 2018). Pseudonyms were used in the presentation of results to protect participants' identities.

Findings and Analysis

The findings and analysis of the secondary sources and in-depth interviews used to obtain data. The data are separated into important themes that arose from the analysis, illustrating the obstacles women in Bangladesh have in gaining access to breast cancer surgery and the influence of cultural and religious beliefs on these obstacles.

Table 1. Breast cancer statistics in Bangladesh

Category	Data
New breast cancer cases	14,858
Deaths due to breast cancer	7,636
5-year prevalence	39,551
Age-standardized incidence	24.7 per 100,000
Age-standardized mortality	12.1 per 100,000

Prevalence and Healthcare Infrastructure

The analysis of secondary data found that breast cancer is the most prevalent cancer among Bangladeshi women, accounting for around 24% of all female cancer cases (Ferlay et al., 2021). The increased incidence of breast cancer has placed enormous burden on the healthcare system, which lacks comprehensive cancer centers, trained healthcare workers, and adequate funds for cancer care (Ahmed, 2013). In rural places, the situation is particularly bad, with few diagnostic and treatment services for women (Islam et al., 2020).

Cultural and Religious Factors

In-depth interviews with breast cancer survivors and healthcare professionals shed light on the cultural and religious challenges experienced by Bangladeshi women. While women generally felt uneasy discussing breast-related issues or undergoing physical examinations, modesty concerns were commonly raised (Hossain et al., 2014). In addition, the interviews found that women frequently prioritize the needs of their family over their own health, since traditional gender norms imply that they should be the primary carers (Akhtar et al., 2017). Many interviewees believed that surgery would cause breast cancer to spread or that other treatments, such as herbal cures or spiritual healing, were more successful (Islam et al., 2020). These fallacies are strongly founded in religious and cultural beliefs, which contribute to the stigma associated with them.

Table 2. Breast cancer awareness in Bangladesh

Awareness Level	Percentage of Women
Low awareness	68%
Moderate awareness	27%
High awareness	5%

Impact of Late Diagnosis and Limited Access to Breast Cancer Surgery

Table 3. Factors influencing delay in seeking breast cancer treatment

Factors Influencing Delay	Percentage of Women
Cultural stigma	38%
Lack of awareness	30%
Limited healthcare access	21%
Financial constraints	11%

The majority of breast cancer cases in Bangladesh are identified at advanced stages, resulting in low survival rates and diminished quality of life for patients, according to a review of secondary data (Kamal et al., 2015). The qualitative data from the interviews confirmed these findings, as numerous women reported instances of

delayed diagnosis due to lack of knowledge, fear of social stigmatization, or a preference for alternative treatments (Hossain et al., 2014).

Efforts to Address Challenges

The discussions with representatives of NGOs and policymakers emphasized ongoing efforts in Bangladesh to enhance breast cancer care. Progress made by the Bangladesh government includes the building of specialized cancer hospitals, the distribution of finances for cancer care, and the formulation of national cancer control policies (Ahmed, 2013). Furthermore, collaborations between local organizations and international partners, such as the WHO and the IARC, have been crucial in providing technical and financial support for cancer treatment services in Bangladesh (Kamal et al., 2015). Several interviewees highlighted the role of community health workers in boosting breast cancer awareness and supporting early diagnosis, citing grassroots activities as a crucial component of the national healthcare system (Khatun et al., 2018).

Discussions

The findings of this study shed light on the intricate interplay of factors that contribute to the difficulties women in Bangladesh encounter in gaining access to breast cancer surgery, as well as the impact of cultural and religious views on these difficulties. This section discusses the most important findings and their implications for healthcare policy and initiatives in Bangladesh.

The poor healthcare infrastructure in Bangladesh, especially in rural areas, is a significant barrier to receiving breast cancer surgery (Islam et al., 2020). The government must invest in the extension and improvement of cancer care facilities, such as the establishment of comprehensive cancer centers and the training of expert medical personnel (Ahmed, 2013). Bangladesh's cancer care system can be bolstered by international relationships with organizations such as the WHO and IARC, which can give vital technical and financial help (Kamal et al., 2015).

Table 4. Breast cancer screening methods and their effectiveness

Screening Method	Sensitivity (%)	Specificity (%)
Clinical Breast Examination (CBE)	57.6 - 69.1	88.0 - 97.0
Mammography	77.0 - 95.0	86.0 - 98.0
Ultrasound	75.0 - 90.0	84.0 - 94.0
Magnetic Resonance Imaging (MRI)	83.0 - 95.0	70.0 - 90.0

Cultural and Religious Factors

The ubiquitous cultural and religious elements found in this study underline the necessity for targeted awareness campaigns and education programs to combat breast cancer and associated treatment myths (Hossain et al., 2014). These initiatives should be sensitive to the cultural and religious context of Bangladesh, with a focus on promoting open discussions about breast health and empowering women to seek medical care without fear of social stigma (Akhtar et al., 2017).

Early Detection and Timely Treatment

The findings highlight the importance of early detection and timely treatment in improving breast cancer patients' survival rates and quality of life in Bangladesh (Kamal et al., 2015). Especially in remote regions, screening services, such as mammography and clinical breast exams, should be expanded and made more accessible to women. Community health professionals can play a vital role in promoting early detection and linking women to healthcare facilities (Khatun et al., 2018).

Overcoming the obstacles women in Bangladesh encounter in gaining access to breast cancer surgery necessitates a multidimensional approach involving the improvement of healthcare infrastructure, the promotion of early identification, and the elimination of the cultural stigma associated with the disease. Ongoing efforts by NGOs, government initiatives, and international collaborations are crucial to empowering women in Bangladesh

to seek timely diagnosis and treatment, hence improving outcomes for breast cancer patients (Khatun et al., 2018).

Conclusion

In the context of Bangladeshi society, the article elucidates the various obstacles experienced by women undergoing breast cancer surgery. Deeply established in societal standards, religious beliefs, and gender roles, the cultural stigma surrounding breast cancer and its therapies has posed substantial challenges to early detection, treatment access, and post-surgery recovery (Ahmed et al., 2020). Many women are exposed to the debilitating effects of breast cancer due to a lack of awareness, inadequate healthcare infrastructure, and insufficient government support (Anwar et al., 2019).

Healthcare professionals, governments, non-governmental organizations, and community leaders should make active efforts to raise awareness and break down cultural obstacles that prevent women from getting timely and adequate medical treatment (Khatun et al., 2021). Improving the overall health outcomes for women in Bangladesh requires promoting gender equality, encouraging open discourse about breast cancer, and facilitating access to quality healthcare services (Islam et al., 2018). Essentially, the fight against breast cancer in Bangladesh must go beyond medical measures and instead target the deeply rooted cultural stigma that perpetuates the misery of innumerable women. Only by removing these societal obstacles can we truly win the pink struggle and pave the path for a healthier and more equal future for all Bangladeshi women.

Recommendations

Increase Awareness and Education

Educational campaigns targeting both men and women should be launched to increase awareness about breast cancer, its symptoms, and the importance of early detection (Ahmed, 2021). Public service announcements, community-based workshops, and social media campaigns can help dispel myths and misinformation about the disease.

Train Healthcare Professionals

Healthcare professionals in Bangladesh need training in cultural sensitivity and communication skills to better understand and address the fears and concerns of breast cancer patients (Hossain & Anwar, 2019). This can be achieved through workshops, seminars, and refresher courses, ensuring that they are better equipped to handle the challenges faced by their patients.

Establish Support Groups

Support groups can provide a safe space for women with breast cancer to share their experiences, fears, and emotions (Islam et al., 2020). Encouraging the formation of such groups, facilitated by trained professionals, can help reduce the stigma associated with the disease and improve mental health outcomes for patients.

Encourage Male Involvement

Involving men in the conversation about breast cancer and encouraging them to support their female relatives can help reduce the stigma surrounding the disease (Rahman et al., 2021). Educational programs should target men to increase their understanding of the disease and the importance of early detection and treatment.

Improve Access to Healthcare Services

Efforts should be made to improve access to quality healthcare services, especially in rural areas (Haque et al., 2019). This can be achieved by increasing the number of healthcare facilities, providing affordable transportation options, and reducing the cost of diagnostic tests and treatment.

Advocate for Policy Changes

Advocacy efforts should be directed at policymakers to implement policies that support early detection and treatment of breast cancer, as well as reduce the financial burden on patients (Ahmed, 2021). This may include advocating for the inclusion of breast cancer screening in national health programs and pushing for the provision of free or subsidized treatment.

Conduct Further Research

More research is needed to better understand the cultural factors contributing to the stigma surrounding breast cancer in Bangladesh (Hossain & Anwar, 2019). This can help develop culturally sensitive interventions and inform policies that address the unique challenges faced by women in the country.

Scientific Ethics Declaration

The author declares that the scientific ethical and legal responsibility of this article published in EPHELS journal belongs to the author.

Acknowledgements or Notes

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The Effects of MK-801 on Apoptosis in a Traumatic Brain Injury Model in Rat Pups

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Abstract: Traumatic brain injury (TBI) is an essential cause of morbidity and mortality during childhood. Trauma causes some changes that result in delayed and elongated damage known as secondary injury, which is characterized by neuronal apoptosis. Based on this information, the aim of this study was to investigate the effect of MK-801, a competitive NMDA receptor antagonist, on apoptosis against hippocampal damage in rat pups after TBI. Forty-two, 10-day-old Wistar Albino rats were randomly divided into three groups: Control, a Trauma, and Treatment groups, each having fourteen rats. TBI was created by blunt trauma model. MK-801, was injected intraperitoneally at the doses of 1 mg/kg of body weight immediately after induction of TBI. The hippocampus tissues were harvested 4 days after TBI. Then CA1 and dentate gyrus (DG) regions were evaluated in terms of immunoreactivity with BAX, cytochrome C, and caspase 3. Based on this evaluation, the control group showed weakly BAX and Cytochrome C immunoreactivities in hippocampus, but elevated reactions were observed in TBI group. Especially, it was determined that the cytochrome c immunoreactivity was granular form in the neurons of hippocampus DG region. In the Treatment group decreased BAX and Cytochrome C immunoreactivities. While a weak caspase-3 immunoreactivity was observed in control group, stronger immunoreactivity was determined both DG and CA1 region of hippocampus in TBI group. In the Treatment group, caspase-3 immunoreactivity decreased in hippocampus region when compared to TBI group. Our results showed that treatment with MK-801 may significantly decreased apoptosis through BAX, Cytochrome C and caspase-3 pathway.

Keywords: Traumatic brain injury, Apoptosis, MK-801

Introduction

Traumatic brain injury (TBI) is a major public health problem and an essential cause of morbidity and mortality during childhood. The brain damage from TBI can be divided into the two: Primary and secondary damage. Primary damage occurs immediately soon after trauma whereas secondary damage within several hours or days after trauma. Secondary damage is made up several of neuron damage and nervous dysfunction and biochemical alterations. Major pathophysiologic mechanisms such as excitotoxicity, calcium overload, free radical generation, apoptosis, and lipid peroxidation lead to secondary brain damage (Sönmez et al., 2015; Sönmez et al., 2007). Unfortunately, there is no available effective treatments to reduce secondary injuries. It has been shown that MK-801, a competitive NMDA receptor antagonist, has been reduced excitatory amino acid release following TBI (Han et al., 2009; Patner & Faden 1992). Although this effect of MK-801 have been shown, whether it has anti-apoptotic effect against to TBI is unknown. In this study, we investigated the anti-apoptotic effects of MK-801 on hippocampal damage on 10-day-old rat pups exposed to TBI injury.

- Selection and peer-review under responsibility of the Organizing Committee of the Conference

Material and Method

Animals

All experiments were carried out in accordance with the National Institutes of Health Guide for the care and use of laboratory animals and were approved by Ethics Committee of the Research of Laboratory Animals, Dokuz Eylul University, Medical School, Izmir, Turkey. Forty-two Wistar Albino rats were randomised into three groups: Control, Trauma group, and treatment groups, each having fourteen rats.

MK-801 Application and Trauma Model

MK-80, was injected intraperitoneally at the doses of 1 mg/kg of body weight immediately after induction of traumatic injury. It has been used a modification of a well-described percussion trauma model in immature rats on P10, in an attempt to model infant and early childhood head trauma as described previously by Sonmez et al. (2007). All the pups were kept on a heating pad until returned to their mothers at 4 h after the trauma.

Tissue Harvesting

Four days after trauma, seven animals from each group were randomly separated for immunohistochemical assays evaluations, brain tissues were collected after cervical dislocation and fixed in 10% formalin solution for 24 h.

Immunohistochemical Assays

Collected tissues were embedded in paraffin blocks 5μm sections were taken using microtome. Sections were divided into two samples to be used for immunohistochemical assays. For BAX, Cytochrome C and caspase-3 immunoreactivity, sections were deparaffinized at 60 ◦C overnight and xylene for 30 min. Sections were first rehydrated in a series of baths with decreasing amounts of ethanol. After washing with distilled water and then phosphate buffered saline (PBS) for 10 min each, they were incubated with 2% tyripsin at 37 ◦C for 15 min. Sections were marked with a Dako pen and were added 3% H2O2 solution for 15 min to inhibit endogenous peroxidase activity. The primary antibodies were applied in a dilution of 1:100 at 4 ˚C overnight. After washing with PBS three times, and finally, the secondary antibodies biotinylated IgG and streptavidin-peroxidase conjugate (supplied ready to use) were incubated at 37 ˚C for 30 min. To quantify the number of cells that underwent apoptosis, 1000 apoptotic and normal cells were counted randomly in hippocampal damage of dentate gyrus and CA1 region and percentages of apoptotic cells were calculated (Gurgen et al., 2013).

Statistical Analysis

Data were analysed using a SPSS 15.0 for Windows program on a computer. Results were expressed as mean±S.E.M and analysed by using one-way analysis of variance followed by the Tukey HSD test. A p-value < 0.05 was considered statistically significant.

Results

The effect of MK-801 treatment on apoptosis was examined using active BAX, Cytochrome C and caspase-3 immunostaining. The Control group showed weakly BAX and Cytochrome C immunoreactivities in hippocampus but elevated reactions were observed in TBI group. Especially, it was determined that the cytochrome c immunoreactivity was granular form in the neurons of hippocampus DG region. In the Treatment group decreased BAX and Cytochrome C immunoreactivities (Figure 1,2). While a weak Caspase-3 immunoreactivity was observed in the Control group, stronger immunoreactivity was determined both DG and CA1 region of hippocampus in TBI group. In the Treatment group, caspase-3 immunoreactivity decreased in hippocampus region when compared to TBI group (Figure 3).

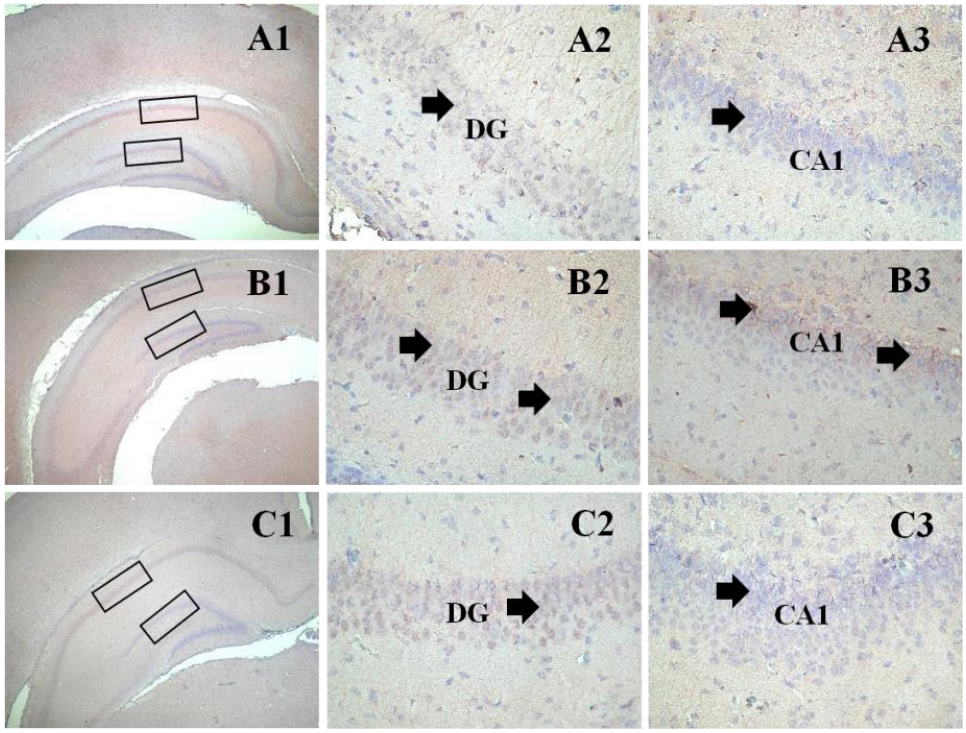

Figure 1. Effects of MK-801 on active BAX immunoreactivity in the dentate gyrus and Cornu Amnonis Area 1. Control (A), Trauma (B), Trauma-MK-801 (C). General Hippocampus (1),X40, DG: Dentate Gyrus (2), CA1: Cornu Ammonis Area1 (3)= X400. ➡: Positive cells. MK-801 treatment significantly reduced the number of apoptotic neurons.

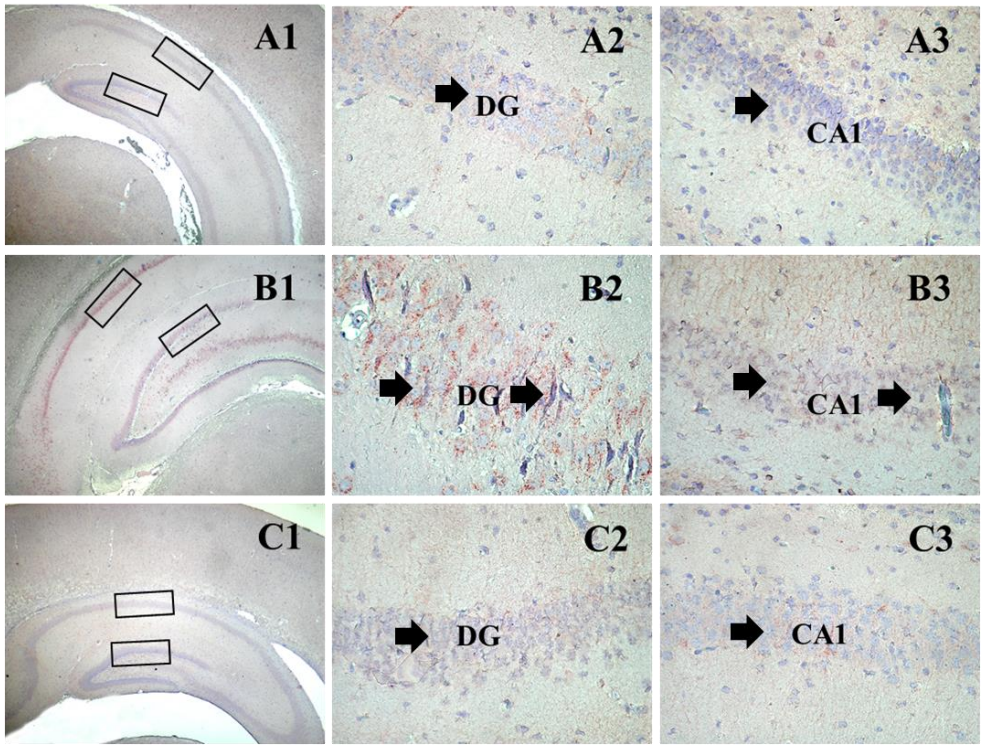

Figure 2. Effects of MK-801 on active Cytochrome C immunoreactivity in the dentate gyrus and Cornu Amnonis Area 1. Control (A), Trauma (B), Trauma-MK-801 (C). General Hippocampus (1)=X40, DG: Dentate Gyrus (2), CA1: Cornu Ammonis Area1 (3)= X400. ➡: Positive cells. MK-801 treatment significantly reduced the number of apoptotic neurons.

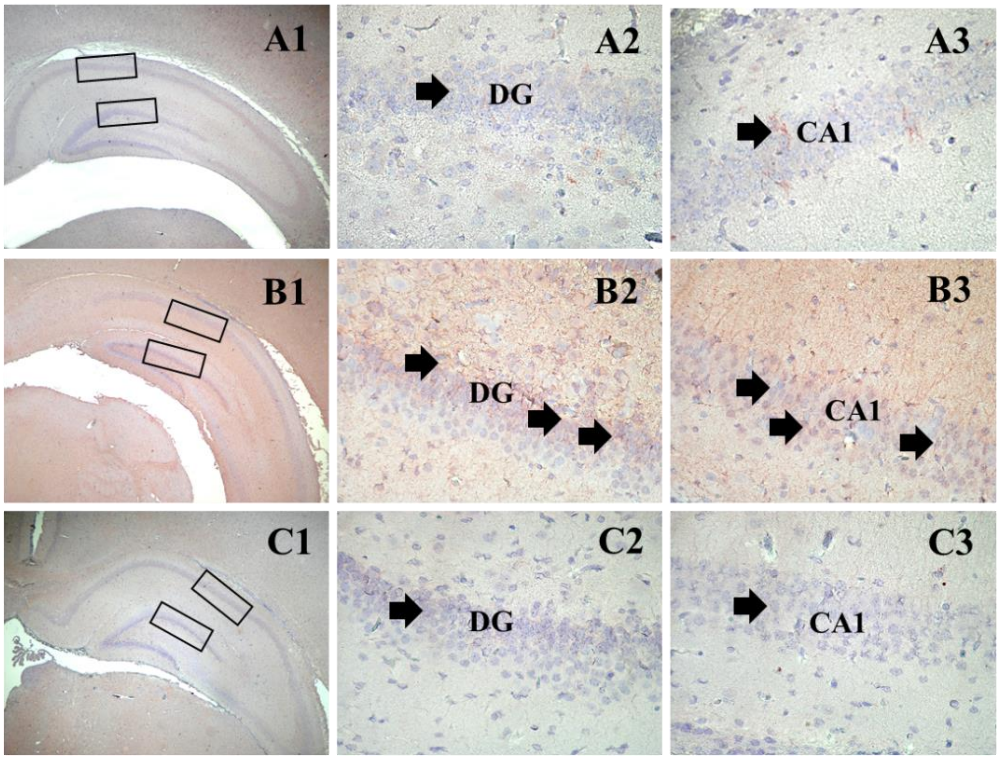

Figure 3. Effects of MK-801 on active caspase-3 immunoreactivity in the dentate gyrus and Cornu Amnonis Area 1. Control (A), Trauma (B), Trauma-MK-801 (C). General Hippocampus (1)=X40, DG: Dentate Gyrus (2), CA1: Cornu Ammonis Area1 (3)= X400. ➡: Positive cells. MK-801 treatment significantly reduced the number of apoptotic neurons.

Discussion

Our results showed that treatment with MK-801 has positive effects on apoptosis after the trauma in immature rats. We demonstrated that MK-801 has shown anti-apoptotic effects by reducing expressions of apoptotic proteins such as BAX, Cytochrome C and caspase-3 in traumatic brain injury in immature rats. Previous studies reported that administration of MK-801 to animal with head trauma injury resulted with better learning and memory scores in different animal studies (Han et al., 2009; Patner & Faden, 1992).

There was no data in the literature evaluating effects of MK-801 on apoptosis in a traumatic brain injury model in immature rats. To date, only a few studies have been completed assessing the MK-801 effects in traumatic brain injury in adult rats. Han et al. (2009) showed that MK-801 (0.5-2-10 mg/kg) could inhibit the neuronal caspase-3 expression in an adult rat model of traumatic brain injury. Also, Wang et al. (2014) MK-801 attenuated the increase BAX expression after in the rat fluid percussion traumatic brain injury model.

Our previous study showed that MK-801 administration has a neuroprotective role against trauma induced hippocampal neuron loss and associated cognitive impairment in immature rats (Sönmez et al., 2015). Our study is important for the evaluation of traumatic brain injury in childhood groups for the first time. Our study may also contribute to the prevention of complications that may occur in childhood head trauma with alternative treatment options.

Scientific Ethics Declaration

The authors declare that the scientific ethical and legal responsibility of this article published in EPHELS journal belongs to the authors.

Acknowledgements or Notes

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Interaction of Wild Type and V804l and V804m-Mutated Ret Protein Kinase with Emodin: *In Silico* Approach

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Abstract: Medullary thyroid carcinoma (MTC) is a malignant endocrine tumor originating from parafollicular calcitonin-producing C cells. The proto-oncogene RET (REarranged during Transfection) is known as the main actor in the development and outbreak of MTC. Gain of function mutations of RET constitutively activate the receptor which are found to be responsible for the high percentage of MTC cases. The two FDA-approved drugs used for MTC, vandetanib and cabozantinib, are resistant to two mutant variants of RET which are V804L and V804M. In this study, the interactions of emodin, a natural molecule found in plants, with wild-type as well as V804L and V804M-mutated RET kinase were investigated via molecular docking. Pymol was used to create point mutations on wild type RET. Vandetanib and cabozantinib were used as the reference drugs. The binding free energy of vandetanib with wild-type RET, V804L and V804M variants were found to be -9.3, -9.1 and -8.6 kcal/mol. Similarly, the binding free energy of cabozantinib with wild-type RET, V804L and V804M variants were found to be -10.6, -10.4, and -9.5 kcal/mol, respectively. Clearly, the binding affinity of vandetanib and cabozantinib to RET kinase was found to be reduced in mutated variants as compared to wild type. In the meantime, the binding energy between emodin and wild-type RET was shown to be -9.3 kcal/mol. Interestingly, the binding affinity of emodin to V804L and V804M variants was determined to be increased (-9.9 and -9.8 kcal/mol, respectively) compared to wild type. Furthermore, many H-bonds and hydrophobic interactions between emodin and mutated RET variants were shown. Therefore, strong binding affinity of emodin to wild-type and the mutated variants of RET was suggested in this study. In conclusion, emodin was found to be a potential molecule to inhibit RET kinase activity and could be used as a therapeutical agent against medullary thyroid carcinoma.

Keywords: Medullary thyroid carcinoma, RET, V804L, V804M, Molecular docking

Introduction

Thyroid cancer is one of the most common cancers worldwide, affecting people in both developing and developed countries, with an incidence of 600,000 new cases diagnosed annually (Jayasinghe et al., 2022). Medullary thyroid cancer (MTC) is a rare cancer that arises from the neuroendocrine parafollicular C-cells of the thyroid gland comprising up to 3% of all thyroid cancers. However, MTC is associated with high mortality, with a disproportionate rate of 8.6% of thyroid cancer-related deaths (Wells et al. 2015). MTC can occur in a sporadic form and in a hereditary form, associated with multiple endocrine neoplasia (MEN) type 2, accounting for 75% and 25%, respectively (Kim & Kim, 2021). RET (REarranged during Transfection) proto-oncogene which is a protein tyrosine kinase, is the main oncogenic driver of MTC. As all hereditary MTC harbor a germline RET mutations and almost half of sporadic cases have a somatic RET mutation (Jaber, Dadu, and Hu 2021). RET mutations are associated with more aggressive disease in MTC. Furthermore, angiogenesis is more intense in RET-mutant MTC. The RET proto-oncogene is located on the long arm of chromosome 10 (10q11.2) and encodes the RET tyrosine kinase transmembrane receptor which is a 170-kDa protein monomer (Vodopivec

& Hu, 2022). RET is constitutively activated through two distinct mechanisms: mutations involving the cysteine-rich or kinase domains, and structural rearrangements leading to the fusion of RET to a 5′ upstream partner. Collectively, these alterations result in ligand-independent signaling and oncogenesis (Wirth et al., 2020). The physiologic signaling process of RET receptor starts with the binding of growth factors to a coreceptor, which in turn causes RET dimerization and phosphorylation of the intracellular kinase domain. This leads to the activation of RAS/ MAPK and PI3K/AKT pathways, involved in cell growth, proliferation, differentiation, survival, and migration (Ibáñez, 2013).

The kinase domain of RET receptor consists of an N-terminal lobe and a C-terminal lobe connected via a hinge. The N-terminal lobe consists of ß-sheets, whereas the C-terminal lobe contains α-helices. The catalytic cleft is located between the N-terminal lobe and the C-terminal lobe which is the focus of kinase inhibitor development. Val804 is the gatekeeper residue controlling access to the catalytic pocket (van Linden et al., 2014).

To date, only two multiple kinase inhibitors (MKIs) have been approved by the Food and Drug Administration (FDA) and the European Medicine Agency (EMA) for the treatment of advanced MTC: Vandetanib and cabozantinib (Matrone et al. 2022). The IC50 values of vandetanib for the V804L and V804M variants are 3597 and 726 nM. However, the IC50 values of cabozantinib for V804L and V804M variants are 45 and 162 nM (Matrone et al. 2022). Unfortunately, vandetanib and cabozantinib are resistant to the V804L and V804M variants (La Pietra et al. 2018). MKIs generally are ineffective against RET V804 gatekeeper mutations (Subbiah et al., 2021).

Emodin, which is also known as 1,3,8 trihydroxy 6 methy anthraquinone, can be isolated from a number of medicinal herbs. Various studies have demonstrated that emodin inhibits growth in multiple cancer types, including lung and pancreatic cancer, and hepatocellular carcinoma. Emodin has been also reported to inhibit the proliferation of papillary thyroid cancer cells via activating AMPK pathway activity (Li et al., 2021). However, no studies reported the effect of emodin on RET kinase activity. Therefore, in this study we aimed to investigate the interaction of emodin with RET protein in its wild-type as well as V804L and V804M mutated variants via molecular docking analysis.

Method

In this study, RET protein kinase, the receptor molecule was taken from RCSB PDB databank (PDB ID: 2IVV) and ligand molecules, emodin (PubChem CID: 3220), vandetanib (PubChem CID: 3081361) and cabozantinib (PubChem CID: 25102847) were taken from PubChem databank. The 3D structures of the receptor and ligand molecules are displayed in Figure 1. The mutated RET variants were created via Pymol.

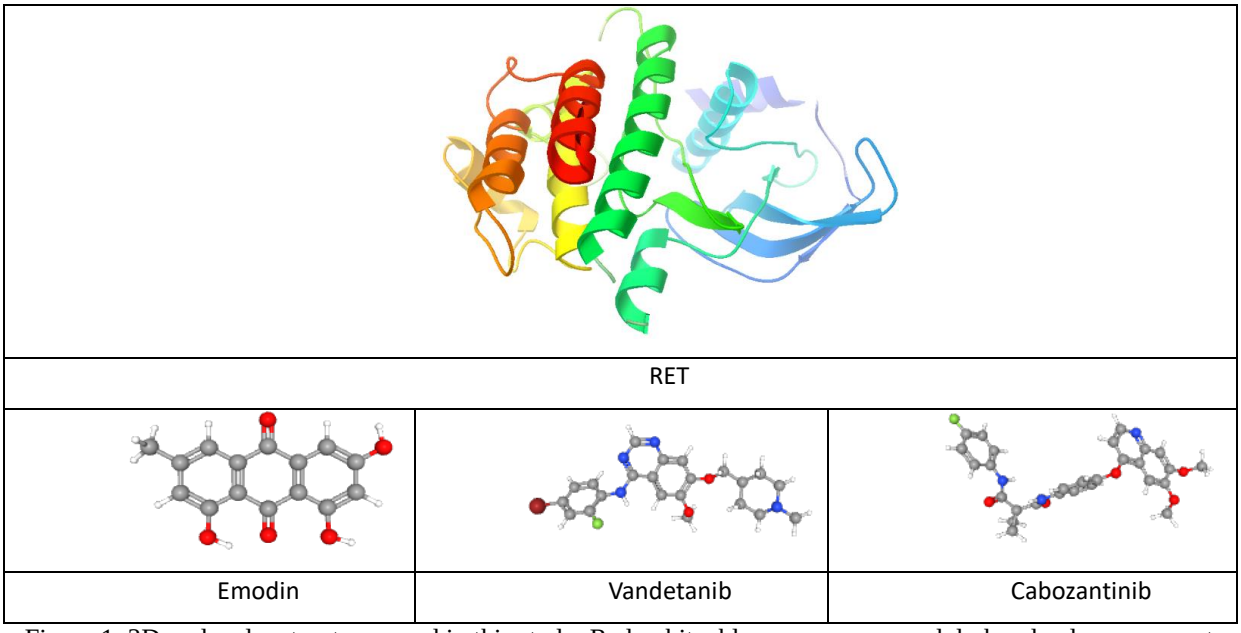

Figure 1. 3D molecular structures used in this study. Red, white, blue, green, gray and dark red colors represent oxygen (O), hydrogen (H), nitrogen (N), fluorine (F), carbon (C) and bromine (Br) atoms, respectively.

Molecular docking was performed to explain the molecular interactions between the receptor and the ligands in Figure 1. Amino acids belonging to the catalytic region in the literature were taken as Leu730, Gly731, Val738, Ala756, Lys758, Ile788, Leu802, Ile803, Val804, Glu805, Tyr806, Ala807, Gly810, Leu881, Ser891, and Asp892. The geometric centers and xyz coordinates were calculated as 20,823, 6,794 and 10,789 Å, respectively, with the help of the AGFR program (Zhang et al., 2019). The grid box sizes were taken as 50 each, taking into account the volume occupied by these coordinates and ligands in the AutoDock tools visualizer (Morris et al. 2009). Based on these initial parameters, energy range 4 was selected and docking studies were carried out using the AutoDock Vina program (Trott & Olson 2010). These steps were performed exactly for each receptor and ligands and all parameters were taken as the same. Online Swissadme Pharmacokinetics Prediction Property was used [http://www.swissadme.ch/index.php] to predict ADME features of emodin.

Results and Discussion

Molecular Interactions between Vandetanib and RET Protein Kinase

The binding free energy between vandetanib and wild-type RET was found to be -9.3 kcal/mol. Figure 2 shows the best conformation of vandetanib/wild-type RET complex. Interestingly, no H-bond interactions were found between vandetanib and wild-type RET. However, many hydrophobic interactions were observed between vandetanib and Ala807, Leu730, Leu881, Ala756, Val804, Glu805, Ser891, Asp892, Lys758, Glu775, Val738, Gly731 and Gly810 residues of wild-type RET kinase.

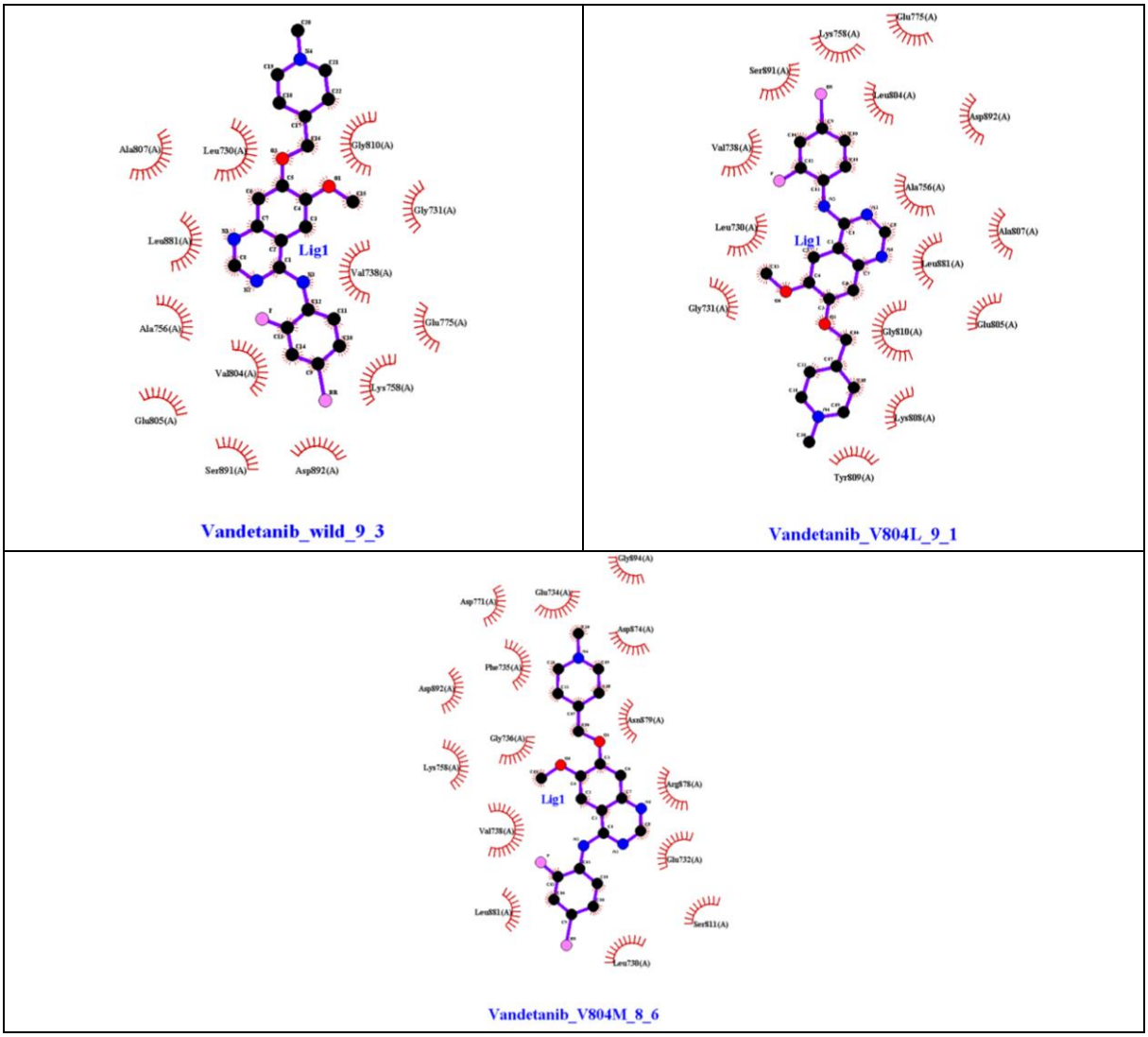

Figure 2. Molecular interactions between vandetanib and wild-type RET, V804L, and V804M.

The binding free energy between vandetanib and V804L was observed to be -9.1 kcal/mol. Like in vandetanib/wild-type RET complex, no-H bond interactions were determined between vandetanib and V804L variant. Nevertheless, hydrophobic interactions were shown between vandetanib and Glu775, Lys758, Ser891, Leu804, Asp892, Val738, Ala756, Ala807, Leu881, Leu730, Gly731, Gly810, Glu805, Lys808 and Tyr809 residues of V804L. The binding free energy between vandetanib and V804M was observed to be -8.6 kcal/mol. No H-bonds were observed between vandetanib and V804M; however, 15 hydrophobic interactions were shown in the vandetanib/V804M complex. The hydrophobic interactions were observed between vandetanib and Gly894, Glu734, Asp771, Asp874, Phe735, Asp892, Asn879, Gly736, Lys758, Val738, Arg878, Glu732, Leu881, Leu730, and Ser811 residues of V804M. These results show that no H-bond interactions were observed in the vandetanib/RET kinase complex with its wild-type or mutated forms. However, various hydrophobic interactions were determined in vandetanib/RET kinase complexes. The binding affinity of vandetanib to wild-type RET kinase was found to be stronger than to the mutated RET variants. These results are in accordance with the literature, indicating that vandetanib is resistant to V804L and V804M (La Pietra et al., 2018).

Molecular Interactions between Cabozantinib and RET Protein Kinase

The binding free energy between cabozantinib and wild-type RET was found to be -10.6 kcal/mol. Figure 3 shows the best conformation of cabozantinib/wild-type RET complex.

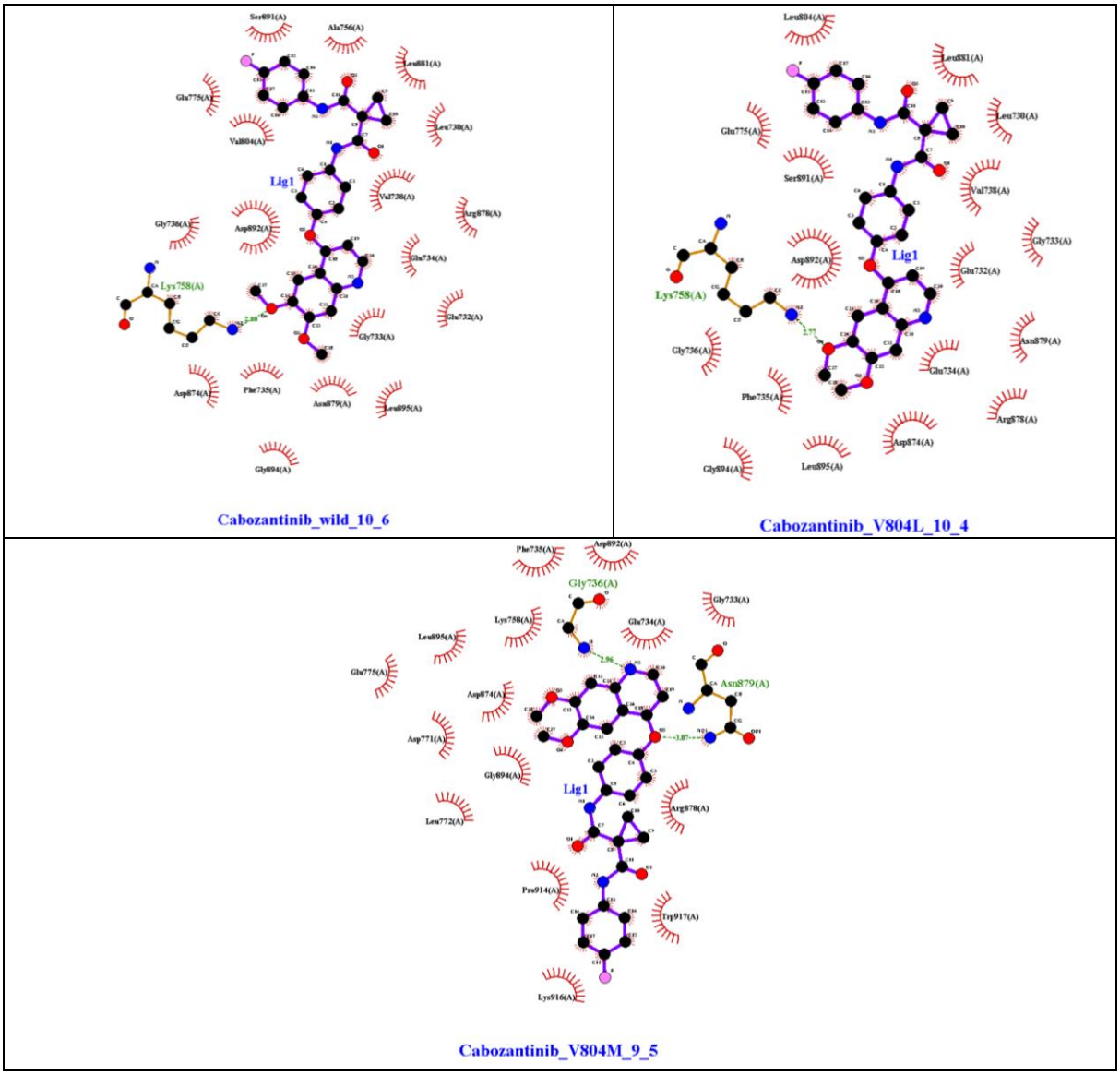

Figure 3. Molecular interactions between cabozantinib and wild-type RET, V804L, and V804M.

In Figure 3, only one H-bond interaction was shown between cabozantinib and Lys758 (2.80 A°) of wild-type RET. However, various hydrophobic interactions were determined between cabozantinib and Ser891, Ala756, Leu881, Leu730, Val738, Arg878, Glu734, Glu775, Val804, Asp892, Gly736, Glu732, Gly733, Asp874, Phe735, Asn879, Leu895, and Gly894 residues of wild-type RET. The free energy of binding in cabozantinib/V804L complex was found to be -10.4 kcal/mol. As in the cabozantinib/wild-type RET complex, only one H-bond (2.74 A°) was observed between cabozantinib and V804L. However, 17 hydrophobic interactions were determined with Gly736, Phe735, Gly894, Leu895, Asp874, Arg878, Glu734, Asn879, Glu732, Gly733, Val738, Leu730, Asp892, Ser891, Glu775, Leu881, Leu804 of V804L. The binding free energy between cabozantinib and V804M was found to be -9.5 kcal/mol. 2 H-bonds were shown in cabozantinib/V804M complex with Gly736 (2.94 A°) and Asn879 (3.07 A°). Hydrophobic interactions, on the other hand, were observed with Glu734, Gly733, Lys916, Asp892, Phe735, Trp917, Lys758, Leu895, Glu775, Asp874, Asp771, Pro914, Gly894, Leu772, and Arg878 residues of V804M. Clearly, the binding affinity of cabozantinib to wild-type RET kinase was determined to be stronger than to V804L and V804M.

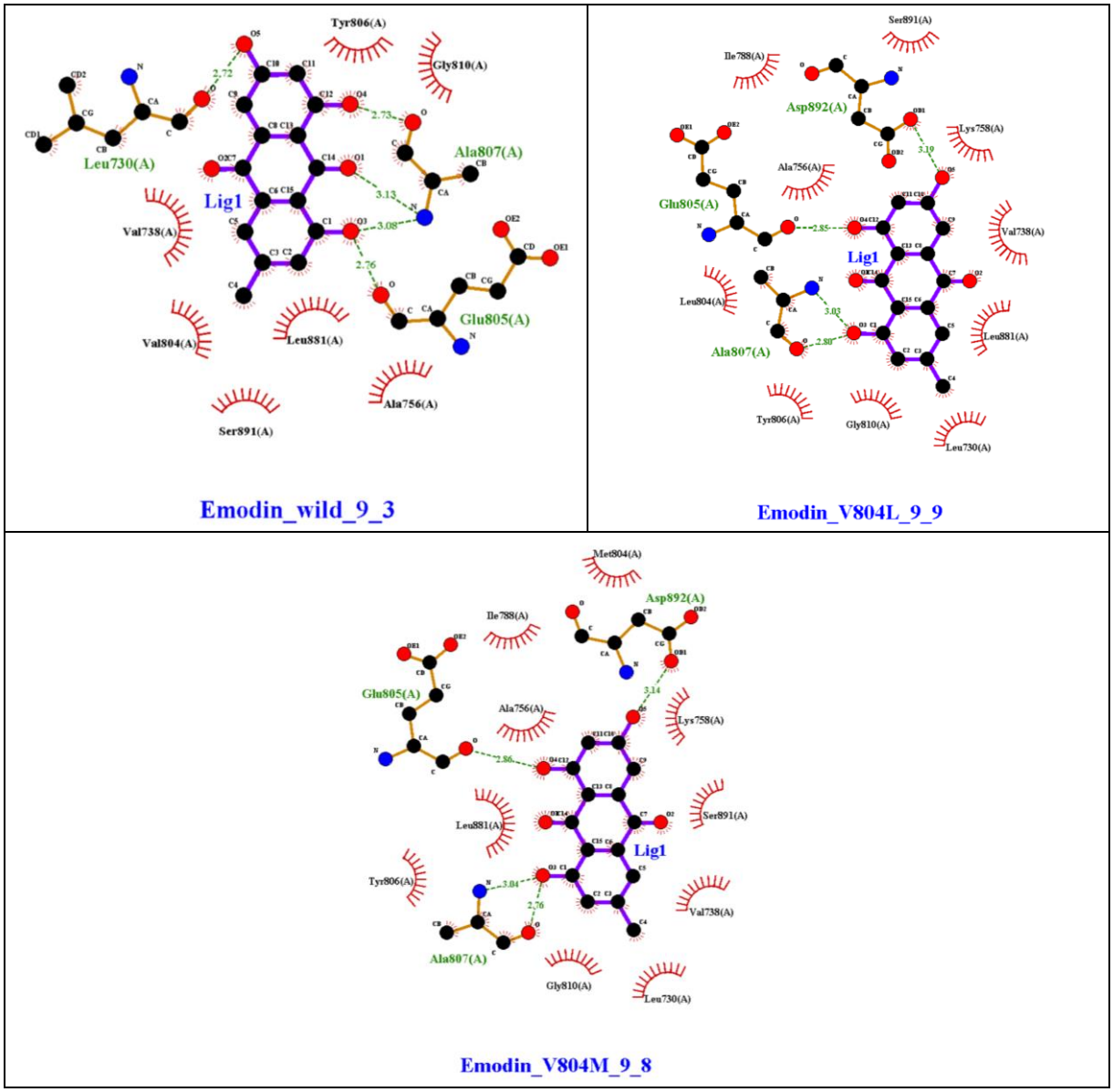

Figure 4. Molecular interactions between emodin and wild-type RET, V804L, and V804M

Molecular Interactions between Emodin and RET Protein Kinase

The binding free energy between emodin and wild-type RET was found to be -9.3 kcal/mol. Figure 4 shows the best conformation of emodin with wild-type RET. Many H-bonds between oxygen atoms of emodin and wild-

type RET were determined with Leu730 (2.72 A°), Ala807 (2.73 A°), Ala807 (3.13 A°), Ala807 (3.08 A°) and Glu805 (2.76 A°) residues, as illustrated in Figure 2. Furthermore, hydrophobic interactions were observed between emodin and Val738, Val804, Leu881, Ser891, Ala756, Tyr806, and Gly810 residues of wild-type RET. The binding free energy between emodin and V804L variant of RET was determined to be -9.9 kcal/mol. H-bond interactions between emodin and Glu805 (2.85 A°), Ala807 (3.03 A°), Ala807 (2.80 A°) and Asp892 (3.19 A°) residues of V804L variant. Hydrophobic interactions, on the other hand, were observed between emodin and Ile788, Ser891, Lys758, Gly810, Val738, Leu881, Leu730, Tyr806, Leu804, and Ala756 residues of V804L variant. The binding free energy between emodin and V804M was found to be -9.8 kcal/mol. H-bonds between emodin and Asp892 (3.14 A°), Glu805 (2.86 A°), Ala807 (3.04 A°) and Ala807 (2.76 A°) of V804M were determined. In addition, hydrophobic interactions in emodin with Met804, Ile788, Ala756, Lys758, Ser891, Leu881, Tyr806, Val738, Gly810 and Leu730 of V804M were observed. The strong binding affinity of emodin to both wild type and the mutated variants of RET protein kinase were suggested in this study. Interestingly, the binding free energy between emodin and the mutated variants were much lower than the one with wild-type RET.

Therefore, the molecular interactions between emodin and the mutated variants (V804L and V804M) were suggested to be stronger than the one with wild-type RET kinase. To be effective as a drug, a potent molecule must reach its target in the body in sufficient concentration, and stay there in a bioactive form long enough for the expected biologic events to occur. Lipinski's rule-of-five examined orally active compounds to define physicochemical ranges for high probability to be an oral drug (Daina, Michielin & Zoete, 2017). ADME (Absorption, Distribution, Metabolism, and Excretion) features of emodin was identified in this study. Table 1 shows ADME properties of emodin, predicting high lipophilicity and water solubility. No Cytochrome P inhibitory activity of emodin suggests high clearence of emodin with no drug-drug interactions. Emodin was shown to have high bioavailability.

Table 1. ADME Properties of Emodin

Property	Emodin	Property	Emodin
Consensus Log P o/w	0.12	CYP2C9 inhibitor	No
Log S (ESOL)	-1.43	CYP2D6 inhibitor	No
Class	Very soluble	CYP3A4 inhibitor	No
GI absorption	High	Lipinski	Yes
BBB permeant	No	Egan	Yes
P-gp substrate	Yes	Veber	Yes
CYP1A2 inhibitor	No	Muegge	Yes
CYP2C19 inhibitor	No	Bioavailability score	0.55

Conclusion

This study shows the molecular interaction of emodin with RET kinase via molecular docking for the first time. The strong binding affinity of emodin, especially for the mutated variants suggests that emodin could be a good candidate as a RET kinase inhibitor. Furthermore, high bioavailability score of emodin suggests a potential candidate as a drug. Therefore, emodin could be used for therapeutical purposes against medullary thyroid cancer.

Recommendations

This study shows strong binding affinity of emodin to both wild-type and the mutated RET variants, namely V804L and V804M via molecular docking. Further bioinformatics tools such as molecular modelling are suggested to evaluate the interaction of emodin with RET kinase. In-vitro and in-vivo studies are also highly necessary to verify the RET kinase inhibitory activity of emodin.

Scientific Ethics Declaration

The author declares that the scientific ethical and legal responsibility of this article published in EPHELS journal belongs to the author.

Acknowledgements or Notes

* This article was presented as oral presentation at the International Conference on General Health Sciences (www.icgehes.net) held in Marmaris/Turkey on April 27-30, 2023.

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ICGeHeS 2023: International Conference on General Health Sciences

Investigation of Association between Alzheimer Disease and Glymphatic System

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Abstract: Novel studies indicated that brain metabolic derivatives clearance is provided by s system called glymphatic (glia+lymphatic) system. Glymphatic system drainage works thanks to arterial pulsation and clear out brain wastes via AQP4 channels localized at astrocytes endfeet. Dysfunction of this system associated with senescence and several pathologies. One of those disease is Alzheimer's Disease. This study objected to determine the relation between glymphatic system and Alzheimer's Disease in accordance with previous studies. Method: Data was collected from "Google Scholar" and "Pubmed" publishments drafted by related professionals between 2011-2023 years. Results: Our results indicated that Alzheimer's Disease and glymphatic system tightly associated each other. It was observed that during Alzheimer's Disease glymphatic flux diminished and AQP4 expression levels were decreased, and localization disrupted. Thus, we suggest that glymphatic system inducing treatment or methods might be beneficial for preventive of Alzheimer's Disease.

Keywords: Glymphatic system, Alzheimer disease, Aquaporin 4, Amyloid beta

Introduction

Brain is one of the highest-level energy consuming organs of the body. Due to this type of highest require, blood brain barrier limits the efflux of ultrafiltrate of the plasma. Thus, clearance of the parenchymal tissue of brain becomes harder than other tissues. In addition, brain tissue doesn't contain traditional lymphatic system which provides fluid flux and waste clearance. A new system called glymphatic system avoids this challenge supporting cerebrospinal fluid for cleansing toxins and metabolic waste (Hablitz & Nedergaard, 2021).

The glymphatic system, combination of glia + lymph, is a structure, originates from astrocytes feet, which is tightly related with transportation of cerebrospinal and intracerebral fluid. Considering that, glymphatic system is commonly accepted as pseudolymphatic system of the central nervous system. Glymphatic system provides a counterpart flux between blood system and periarterial cerebrospinal flux. Arterial pulsation supports the movement of cerebrospinal fluid to the parenchymal field and integrate both interstitial and cerebrospinal fluid. The process occurs via Aquaporin 4 (AQP4) channels which localized to vascular astrocytic endfeet. Moreover, the flux of blood brain barrier fluid or cerebrospinal fluid extracted from extrachoroidal supports the glymphatic system. Following the influx of plasma, the fluid of parenchymal tissue moves opposite. Then the mixture of cerebrospinal and intracerebral fluid efflux from the brain via perivenous space and cranial or spinal nerves. Afterwards traditional lymphatic channels located in meninges and soft tissue of cranium remove the final fluid from the area (Mestre et al., 2020).

One of the most effective activators of glymphatic system flux, is non-REM sleep, which is the no eye movement and slow wave activity phase (1-4 Hz, Delta waves). Besides, sleep posture contributes the effective flux (Mestre et al., 2020; Mogensen et al., 2021). On the other hand, aging and various pathologies supress the

flux of the glymphatic system depending on disruption of the expression of AQP4 channels at astrocytes endfeet. Especially neurodegenerative diseases, more likely Alzheimer's disease, are crucial for this disruption (Mogensen et al., 2021). From this point of view, the relationship between the Alzheimer's disease and glymphatic system was investigated in the study.

Methods

For this purpose, related publishments between 2011-2023 published in "Google Scholar" and "Pubmed" databases released by professionals were searched. The investigated articles were full-text and written in English and Turkish. References of selected articles were determined for related articles which do not exist in search list. Alzheimer's disease, amyloid beta, tau glymphatic system and AQP4 were used as keywords. Best match articles were examined in the line with our aim and counted in the present review.

Results

The accumulation of amyloid beta and tau protein is one of the underlying mechanisms of the relationship of Glymphatic system and Alzheimer's disease. Previous studies claimed that this interaction is tightly related with AQP4 channels which take part in transportation of water and solutes, contributing to glymphatic system (Si et al., 2023). In an Alzheimer' model study with AQP-knock out mice, Iliff et al. (2011) reported that brain might be cleansing through intracerebral AQP4 channels (Iliff et al., 2012). Another study was established this relationship by immunofluorescent and Western blot analysis. They clarified that not only expression of AQP4 channels but also their localisation is important for the underlying mechanism of Alzheimer's disease. They also claimed that AQP4 channels loss by ageing allows amyloid beta accumulation, so this might be an inducing factor of Alzheimer's disease (Zeppenfeld et al., 2017). In one of tau protein induced Alzheimer's disease model animal study, demonstrated that glymphatic system remove tau proteins from parenchymal brain tissue. Further, it was reported that accumulation of tau proteins reduces the AQP4 channels polarisation. Based on this information they suggested that this mechanism has potential for treatment of Alzheimer's disease (Harrison et al., 2020). Chandra and colleagues (2021) investigated the effects of AQP4 channels polymorphism in spectrum of Alzheimer's disease aspect on amyloid burden and clinical situation. Over 800 patients who had mild and moderate cognitive impairment or Alzheimer's disease participated to the study. Results indicated that genetic variations in AQP4 channels caused to amyloid beta accumulation, and it was suggested that mild cognitive impairment contributes to risk of progression of Alzheimer's disease. Also, the results indicated that there was a correlation with the cognitive regression rates. (Chandra et al., 2021). Kamagata et al. (2022) examined the perivascular network by non-invasive magnetic resonance (MRI) of patients with Alzheimer disease or mild cognitive impairment. They investigated the correlation between cerebrospinal fluid markers, PET and cognitive scores. The results of this study indicated that disruption of cognitive and arrangement of daily activities in Alzheimer's disease depend on neuronal loss and glymphatic system disorders (Kamagata et al., 2022).

Discussion and Conclusion

In accordance with the results of aforementioned literatures, there is a tightly relationship between Alzheimer's disease and glymphatic system. It is clear from the previous studies that glymphatic system clear amyloid beta and tau proteins from brain parenchyma. Interestingly, AQP4 channels seem to be important actors of this system. The adequate and regular localised expression of these channels are principal of healthy flux in parenchymal tissue. It could be suggested that triggering glymphatic system activation and providing AQP4 channels polarisation might be potential preventing treatment method of Alzheimer's Disease. Also, it is possible to achieve the goals by cleansing parenchymal tissue. Due to substantial evidence about this interaction, further studies are required to eliminate the risk of Alzheimer's disease.

Scientific Ethics Declaration

The authors declare that the scientific ethical and legal responsibility of this article published in EPHELS journal belongs to the authors.

Acknowledgements or Notes

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The Fracture Resistance of Full Contour Monolithic-Zirconia Dental Crowns from Cyclic Loading: A Function of Lifetime Extension of Dental Restorations

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Abstract: An ex-vivo study aimed to investigate the fracture resistance of monolith- single layer zirconia of 1.5 mm thickness for dental molar crowns concerning simulating failure behavior under simulated cyclic loading with an extended lifetime of up to 5 million cycles. Sixteen molar crowns were scanned after preparation through computer-aided manufacturing (CAD/CAM) technology to recreate the zirconia crowns, which have a uniform occlusal surface thickness of 1.5 mm. All the samples went through thermal aging by putting them through 6000 thermo-cycles for 3 minutes with the use of distilled water at a temperature range between 5 ˚C and 55 ˚C. All samples were placed under cyclic fatigue loading using the SD Mechatronik chewing simulator and afterward subjected to two-dimensional movements for almost five million cycles. Tests were carried out in distilled water at room temperature. The sample was observed, tested, and photographed every five hundred thousand cycles. The surface cracks were observed within the vicinity of the contact area only and extended with increasing cycles. Minor wear depth was observed in the crowns relative to the damage observed in the Ni-Cr alloy steel flat indenter. No chipping or complete failure was observed in all tested samples which suggested that full-contour zirconia crowns are good for extending the long life service of dental restorations.

Keywords: Zirconia monolayer, Dental crowns, Flat indenter, Chewing simulator, Thermal aging.

Introduction

Dental crowns went through several stages of advancement over the last decades. It starts with just a metal layer, then porcelain fused to metal (PFM), after which the all-ceramic double layer is used in the form of fused porcelain over a zirconia substrate. More recently, all zirconia single-layer restoration was introduced to overcome the interface problems between the two layers and to benefit from the excellent properties of the zirconia (Zarone et al., 2011; Goodacre et al., 2011). In the case of worn detention conditions, increasing the vertical occlusion dimension is not workable in all circumstances (Dawson, 1989; Stewart, 1998). In the case of using bilayer crowns, to overcome this issue, the thickness of ceramic coating could be increased which improves the performance of the veneering layer by increasing the load-bearing capacity of the restorations (Guess et al., 2011; Lin et al., 2012). On the other hand, using a single layer of zirconia the variability of the thickness is not an issue of concern. To increase the contact pressure several researchers used hard spherical indenters on flat specimens or dental restoration replicas. The crack patens observed between using spherical indenters and flat indenters are well documented (Zhang et al., 2012).

In this study, a flat indenter is used to increase the points of contact with crown cusps on the occlusal top surface of the crown. Most of the work done so far in cyclic loading testing was up to 1.25 million cycles which represents five years of chewing (Qasim et al., 2018), due to the lengthy process of testing and failure which was observed in porcelain fused to zirconia sample which was detected at the low number of cycles. In this study, since no visible failure was observed at the low number of cycles, the author extended the number of

cycles to 5 million cycles. No catastrophic damage was observed in all samples tested which indicates that a single zirconia layer restoration is visible for long-life restorations. The downside of using a single zirconia layer is the changing color influenced by cyclic loading. This is in agreement with the finding of (Panagiota-Eirini et al., 2016).

Materials and Methods

Following general practice at dental laboratories, the crowns were fabricated from one layer of zirconia with a thickness of 1.5 mm at the occlusal surface. As in our previous studies. Noritake Katana Zirconia (Kurary Noritake, Germany) is used, according to manufacturer specifications properties, the Flexural strength is 1,200 MPa; Fracture toughness (K1C) ≧5 MPa m1/2 CTE 10.4×10-6/℃, and the chemical composition is ZrO_2 / Y2O3 95/5. Before fixing the specimen to the testing cyclic loading machine, all specimens were subjected to thermal aging for 6000 thermo-cycles for 3 minutes using distilled water having a temperature range between 5 ˚C and 55 ˚C. The specimens were then fixed to the testing chamber in the chewing simulator (SD Mechatronik, Germany) in the same manner as in our previous studies as shown in (Figure 1). The insertion on the top shows the indenter cycle movement along with the distance and speed moved during each cycle. The settings used in our previous studies are used in this study for comparative results and consistency (Qasim et al., 2018).

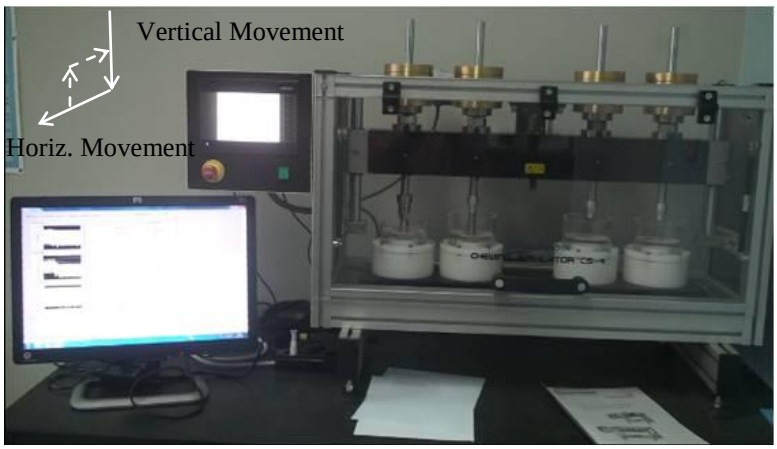

Figure 1. Chewing simulator showing complete setup including load cell and computer monitoring software.

Results and Discussion

All sample was tested under 50±5 N (~4 kg dead weight) and photographed at intervals of 250 thousand cycles to see the extent of the damage. (Figure 2) shows the same sample at 1 million cycles (A), 2 million cycles (B), and 3 million cycles (C). Comparison between Fig. 2 (A) and (B) shows clear extensive wear up to 2 million cycles, after that the contact area remains the same size regardless of the number of cycles compared to (B) and (C) in (Figure 2).

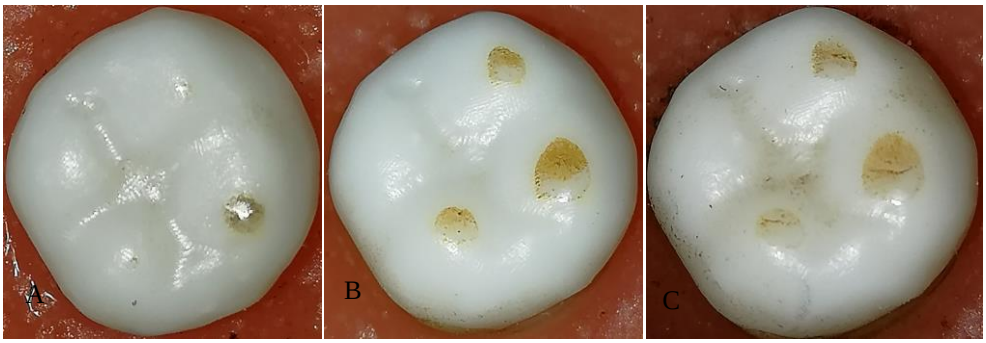

Figure 2. Influence of the number of cycles on the same specimen. (A) 1 million, (B) 2 million, and (C) 5 million cycles

Noting that the sample presented in (Figure 2 (C)) has a well-established crack within (under) the contact area, no propagation of this crack is outside the contact area where observed this suggested that the material reaches max hardness.

Figure 3 shows the effect of cyclic loading on the flat Ni-Cr alloy indenter as the number of cycles increases from 1 million cycles in Fig. 3(A) to 5 million cycles in (Figure 3 (B)). The damage to the indenter increased as the number of cycles increased in tow fold, the contact area increased and the depth of damage also increase. This can be attributed to the friction generated between the zirconia and the surface of the indenter during sliding motion. Noting that this behavior was not seen on the zirconia surface, as mentioned in (Figure 2). Where the damage after 2 million cycles is restricted within the contact area without any further increase in contact area or wear depth.

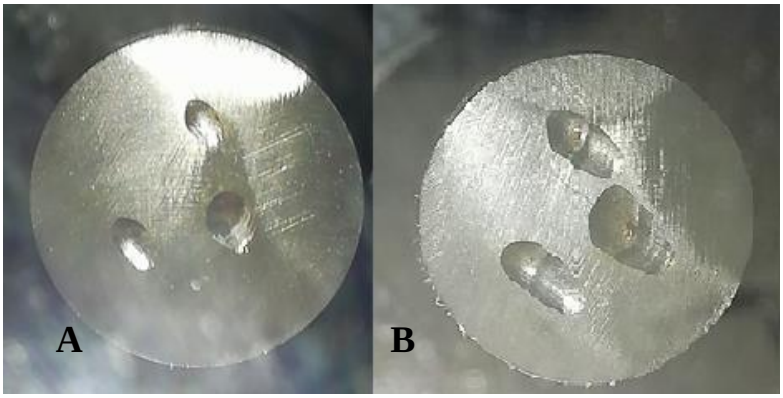

Figure 3. Damage is observed to the indenter as the number of cycles increases. (A) 1 million and (B) 5 million cycles.

Conclusion

This ex-vivo-study shows that a single layer of partially stabilized zirconia is an appropriate choice for dental restorations with a caution that the zirconia crown should not be in direct contact with the opposing tooth, since severe damage was noted in the Ni-Cr alloy indenters. This finding agreed with the results of (André et al., 2007). Increasing the number of cycles over 5 million cycles with low cyclic loading, would not be beneficial to study since the damage observed to be localized at the cusp are without any fracture extending.

Recommendations

It is recommended that all tested samples be subjected to continuous mono-loading to measure extreme loading conditions after cyclic loading. In addition, the aesthetic concern of changing the color of the zirconia surface area should be looked at.

Scientific Ethics Declaration

The author declares that the scientific ethical and legal responsibility of this article published in EPHELS journal belongs to the author.

Acknowledgements or Notes

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