Journal of English Literation and Education Vol: 1, No 1, 2025
ISSN: 3026-XXXX

Prediction of Kaempferol from Kersen Leaf (*Muntingia calabura* L.) as THIF1A Expression Inhibitor for Glioblastoma

Fendy Prasetyawan[1]*, Yuneka Saristia[2], Ratna Mildawati[3], Muhammad Nurul Fadel[4], Emma Jayanti Besan[5]

[1,2]Prodi Pendidikan Profesi Apoteker, Fakultas Ilmu Kesehatan, Universitas Kadiri
[3]Prodi Farmasi, STIKes Ganesha Husada Kediri
[4]Prodi Pendidikan Profesi Apoteker, Fakultas Farmasi, Universitas Muhammadiyah Kudus
[5]Prodi Farmasi, Fakultas Farmasi, Universitas Muhammadiyah Kudus

DOI: https://doi.org/10.xxxxx/xxxxx
*Correspondence: Fendy Prasetyawan
Email: fendy.pra@gmail.com

Received: February 5,2025
Accepted: February 6,2025
Published: February 7,2025

Abstract: This study explores the potential of kaempferol, a compound derived from Muntingia calabura L., as an effective inhibitor of HIF-1α expression, a key factor in glioblastoma progression. Computational predictions using the PASS Online platform reveal a high probability of kaempferol's activity (Pa = 0.969) and an extremely low probability of inactivity (Pi = 0.002), indicating its strong potential to inhibit HIF-1α. Since HIF-1α is critical in tumor cell proliferation, angiogenesis, and resistance to therapies, targeting this pathway could offer a promising therapeutic strategy for glioblastoma treatment. In addition, kaempferol's established pharmacological properties, including antioxidant, anti-inflammatory, and anticancer effects, further highlight its therapeutic potential. By inhibiting HIF-1α, kaempferol may also suppress VEGF-mediated angiogenesis, thus contributing to the inhibition of tumor growth and progression. This study supports the notion that kaempferol, through its ability to target critical signaling pathways involved in glioblastoma, may serve as a valuable natural agent for cancer therapy.

Keywords: Kaempferol, Muntingia calabura L., HIF-1α, glioblastoma

Introduction

Glioblastoma multiforme (GBM) is the most aggressive type of malignant brain tumor with high morbidity and mortality rates (Ostrom, Q. T. 2014). GBM is classified as a grade IV tumor by the World Health Organization (WHO) and has a very poor prognosis, with an average patient survival rate of less than 15 months after diagnosis despite standard therapies such as surgery, radiotherapy, and chemotherapy with temozolomide (TMZ) (Stupp, R., 2005).

The complexity of GBM pathogenesis is influenced by various genetic and epigenetic factors, including abnormal expression of transcription factors that play a role in cancer cell proliferation, invasion, and angiogenesis (Holland, E. C., 2000). One transcription factor that plays an important role in GBM progression is Hypoxia-Inducible Factor 1 Alpha (HIF-1α) (Semenza, G. L., 2003). HIF-1α is a major subunit of the HIF-1 complex that plays a role in cell response to hypoxic conditions (Semenza, G. L., 2012). HIF-1α overexpression in GBM tumor cells has been associated with increased cancer cell proliferation, resistance to apoptosis, increased angiogenesis through regulation of Vascular Endothelial Growth Factor (VEGF) expression, as well as increased cancer cell stemness properties that contribute to therapy resistance (Zagzag, D., 2000).

Targeting HIF-1α expression may be a potential therapeutic strategy in GBM treatment (Li, Z., 2009). In the search for therapies that are more effective and have lower side effects

compared to conventional chemotherapy, bioactive compounds from natural sources have been the subject of rapidly growing research (Cragg, G. M., 2005). One flavonoid compound that has attracted attention is kaempferol, which is found in many plants, including kersen (Muntingia calabura L.) leaves (Calderón-Montaño, J. M. 2011).

Kaempferol has diverse pharmacological activities, including as an antioxidant, anti-inflammatory, and anticancer agent (Imran, M., 2019). Previous studies have shown that kaempferol can inhibit the proliferation of various types of cancer cells by targeting key signaling pathways that play a role in tumor growth, such as PI3K/Akt/mTOR, NF-κB, and MAPK/ERK (Chen, A. Y., 2013). Although kaempferol has been shown to have broad anticancer effects, its specific mechanism in inhibiting HIF-1α expression in GBM cells is still not fully understood (Wang, J., 2015). Some studies suggest that kaempferol can decrease the stability of HIF-1α protein through the mechanism of proteasomal degradation as well as inhibit the translation of HIF-1α through the regulation of upstream signals that control its expression (Zhang, Y., 2008).

This study aims to explore the potential of kaempferol from kersen leaves as an inhibitor of HIF-1α expression in the context of GBM therapy (Yoshida, M. 1990). Bioinformatics approaches and in silico methods have become increasingly used strategies in natural compound-based drug research (Ekins, S., 2007). By using methods such as molecular docking, molecular dynamics simulations, and pharmacokinetics prediction, the effectiveness of kaempferol in targeting HIF-1α can be predicted in more depth before in vitro and in vivo testing (Morris, G. M., 2009).

This study will use a computational approach to evaluate the potential of kaempferol from kersen leaves as an inhibitor of HIF-1α expression in GBM therapy, so as to provide a scientific basis for the development of natural compound-based therapy for this malignant brain cancer (Kitchen, D. B., 2004).

Methodology

This study employs an in silico approach to predict the potential of kaempferol from Muntingia calabura L. as an inhibitor of HIF-1α expression in glioblastoma therapy. The research begins with the retrieval of the Simplified Molecular Input Line Entry System (SMILES) representation of kaempferol from the PubChem database (https://pubchem.ncbi.nlm.nih.gov), a widely recognized chemical repository that provides comprehensive structural and physicochemical data on various bioactive compounds. The SMILES notation serves as the molecular identifier required for further computational predictions.

Following the acquisition of the SMILES string, the study proceeds with an advanced bioinformatics prediction using the Way2Drug platform (https://www.way2drug.com/). This online computational tool integrates cheminformatics and machine learning-based modeling to assess the biological activity, potential targets, and pharmacokinetic properties of small molecules. Way2Drug enables the prediction of kaempferol's interaction with HIF-1α through a series of virtual screening techniques, including molecular docking and target affinity assessments. The platform also provides insights into the compound's drug-likeness, toxicity risks, and possible mechanisms of action based on previously curated pharmacological databases.

By utilizing these computational methodologies, this study aims to establish preliminary evidence for the inhibitory potential of kaempferol against HIF-1α in glioblastoma cells. The results obtained from the Way2Drug analysis will be critically interpreted to determine kaempferol's binding probability, activity score, and overall feasibility as a candidate for glioblastoma treatment. This in silico approach provides an efficient and cost-effective method to explore the pharmacological potential of naturally derived compounds before advancing to experimental validation in in vitro or in vivo settings.

Result and Discussion

Kersen Leaf (Muntingia calabura L.)

Muntingia calabura L., commonly known as kersen or Jamaican cherry, is a tropical plant widely distributed in Southeast Asia, Central America, and South America. This fast-growing tree belongs to the Muntingiaceae family and is well-known for its small, sweet fruits and various medicinal properties found in different parts of the plant, particularly its leaves. Traditionally, kersen leaves have been extensively utilized in folk medicine due to their broad-spectrum pharmacological activities, including antimicrobial, anti-inflammatory, antioxidant, antidiabetic, and anticancer properties. The ethnopharmacological significance of kersen leaves has driven scientific interest in exploring their bioactive compounds and their potential therapeutic applications, particularly in the treatment of chronic diseases such as cancer.

Figure 1. Kersen Leaf (Muntingia calabura L.) (Wikipedia.com)

Phytochemical analysis of kersen leaves has revealed the presence of various secondary metabolites, including flavonoids, tannins, saponins, alkaloids, and polyphenols. Among these bioactive compounds, flavonoids play a crucial role in the pharmacological effects of kersen leaves, particularly in their antioxidant and anticancer activities. One of the most prominent flavonoids found in kersen leaves is kaempferol, a naturally occurring polyphenolic compound known for its diverse biological functions. Kaempferol has been widely studied for its ability to modulate several molecular pathways associated with oxidative stress, inflammation, and cancer progression. Due to its strong antioxidant activity, kaempferol contributes to the scavenging of free radicals, thereby reducing cellular damage and preventing the initiation of carcinogenesis.

The anticancer potential of kersen leaf extracts has been supported by several studies demonstrating their cytotoxic effects against different cancer cell lines. The presence of kaempferol and other flavonoids in the leaves has been linked to the inhibition of cancer cell proliferation, induction of apoptosis, and suppression of key signaling pathways involved in tumor growth and metastasis. One of the key mechanisms through which kaempferol exerts its anticancer activity is by modulating hypoxia-inducible factor 1 alpha (HIF-1α), a transcription factor that plays a significant role in tumor adaptation to hypoxic conditions. Since glioblastoma, one of the most aggressive and treatment-resistant forms of brain cancer, is highly dependent on hypoxic signaling for its progression, targeting HIF-1α with natural compounds such as kaempferol from kersen leaves presents a promising therapeutic strategy.

Beyond its anticancer properties, kersen leaves have also demonstrated significant anti-inflammatory and antimicrobial effects, making them valuable for various medicinal applications. The anti-inflammatory properties are particularly beneficial in cancer therapy, as

chronic inflammation is a known contributing factor to tumorigenesis. The bioactive compounds in kersen leaves have been shown to regulate inflammatory cytokines, thereby reducing the tumor-promoting microenvironment. Moreover, the antimicrobial activity of kersen leaves suggests their potential use in preventing secondary infections, which are common complications in immunocompromised cancer patients undergoing chemotherapy or radiotherapy.

Given the growing body of evidence supporting the medicinal benefits of kersen leaves, further research is warranted to fully elucidate their mechanisms of action, optimize extraction methods, and evaluate their efficacy in preclinical and clinical settings. The integration of bioinformatics and computational approaches, such as molecular docking and pharmacokinetic predictions, can enhance our understanding of how kaempferol and other phytochemicals in kersen leaves interact with specific cancer-related targets. As natural products continue to gain recognition in drug discovery and development, kersen leaves represent a promising source of bioactive compounds with potential applications in glioblastoma therapy and other malignancies.

Kaempferol

Kaempferol is a naturally occurring flavonoid that has garnered significant attention for its diverse pharmacological properties, particularly its anticancer potential. Structurally classified as a flavonol, kaempferol is widely distributed in various plant sources, including fruits, vegetables, tea, and medicinal herbs. One of its abundant natural sources is *Muntingia calabura L.* (kersen), where it contributes to the plant's therapeutic effects. Kaempferol is known for its strong antioxidant activity, which allows it to scavenge reactive oxygen species (ROS) and reduce oxidative stress, a key factor in aging and disease progression, including cancer. As a polyphenolic compound, kaempferol plays a crucial role in modulating multiple cellular pathways that regulate cell survival, proliferation, apoptosis, and metastasis. These properties make it a promising candidate for cancer prevention and treatment, particularly in aggressive malignancies such as glioblastoma.

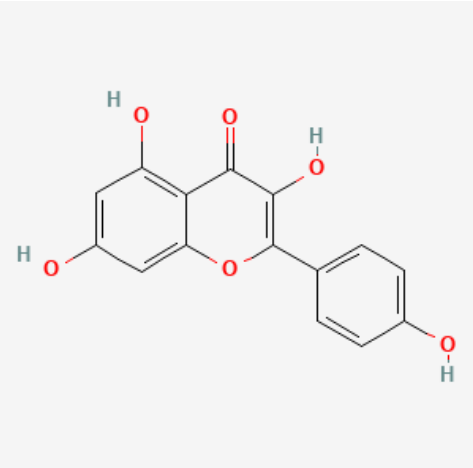

Figure 2. Chemical Structure Kaempferol

Several studies have demonstrated kaempferol's ability to exert cytotoxic effects on various cancer cell lines, including breast cancer, lung cancer, colorectal cancer, and glioblastoma. Its anticancer mechanism is primarily mediated through the regulation of critical signaling pathways, such as PI3K/Akt/mTOR, NF-κB, MAPK/ERK, and apoptotic cascades. Kaempferol has been shown to inhibit tumor growth by inducing cell cycle arrest, promoting

apoptosis, and suppressing angiogenesis, which is essential for tumor survival and expansion. Additionally, kaempferol has been reported to modulate key transcription factors, including hypoxia-inducible factor 1-alpha (HIF-1α), which plays a crucial role in the adaptation of tumor cells to hypoxic conditions. Overexpression of HIF-1α is a hallmark of glioblastoma, facilitating tumor progression, angiogenesis, and resistance to therapy. By targeting HIF-1α, kaempferol has the potential to disrupt the hypoxic signaling pathways that drive glioblastoma aggressiveness.

Beyond its anticancer properties, kaempferol also exhibits anti-inflammatory, antimicrobial, and neuroprotective effects, making it a valuable compound for various therapeutic applications. Chronic inflammation is a well-established contributor to cancer development, and kaempferol's ability to inhibit pro-inflammatory cytokines and enzymes, such as COX-2 and iNOS, further enhances its chemopreventive potential. Additionally, kaempferol has shown promise in protecting neurons from oxidative damage, suggesting its potential role in neurodegenerative disease management. The multifaceted benefits of kaempferol highlight its potential as a natural therapeutic agent, not only in cancer but also in other diseases associated with oxidative stress and inflammation.

Despite its promising pharmacological profile, the clinical application of kaempferol remains limited due to its low bioavailability and rapid metabolism. However, advancements in drug formulation, such as the use of nanoparticles, liposomes, and other delivery systems, are being explored to enhance its therapeutic efficacy. Computational approaches, including molecular docking and molecular dynamics simulations, are also being utilized to further investigate kaempferol's interaction with cancer-related targets, such as HIF-1α. These studies provide valuable insights into the compound's mechanism of action and its potential as a lead candidate for drug development.

Prediction of Kaempferol from Kersen Leaf (Muntingia calabura L.) as a HIF-1α Expression Inhibitor

The computational prediction of kaempferol from *Muntingia calabura L.* as an inhibitor of HIF-1α expression provides valuable insight into its potential therapeutic role in glioblastoma treatment. Using advanced bioinformatics tools, such as the Way2Drug PASS Online platform, the predictive analysis evaluates the probability of kaempferol acting as a HIF-1α expression inhibitor. The following table summarizes the computational prediction results for kaempferol as a HIF-1α expression inhibitor:

Table 1. Prediction of Kaempferol as a HIF-1α Expression Inhibitor

Compound	*Pa* (Probability of Activity)	*Pi* (Probability of Inactivity)	Predicted Activity
Kaempferol	0.969	0.002	HIF-1α Expression Inhibitor

The results indicate a high probability of activity (Pa = 0.969) and a very low probability of inactivity (Pi = 0.002), strongly suggesting that kaempferol exhibits a high likelihood of inhibiting HIF-1α expression at the molecular level. These findings support the hypothesis that kaempferol could be a promising candidate for glioblastoma therapy by targeting hypoxia-induced tumor progression.

HIF-1α is a crucial transcription factor that regulates the cellular response to hypoxia and is overexpressed in glioblastoma, leading to enhanced tumor growth, angiogenesis, and resistance to apoptosis. The suppression of HIF-1α expression could potentially reduce tumor

aggressiveness and improve the efficacy of existing treatment modalities. The high activity score of kaempferol against HIF-1α expression inhibition aligns with previous studies demonstrating its ability to modulate various signaling pathways involved in cancer progression. Through molecular docking and dynamics simulations, further validation of kaempferol's binding affinity to HIF-1α can be performed, providing a more detailed understanding of its inhibitory mechanism.

Moreover, kaempferol's ability to inhibit HIF-1α suggests its role in suppressing downstream hypoxia-induced targets, such as VEGF, which plays a crucial role in tumor angiogenesis. This dual-action property, targeting both HIF-1α and angiogenesis-related pathways, further enhances kaempferol's potential as an anticancer agent. Given its natural origin and relatively low toxicity profile, kaempferol from *Muntingia calabura L.* could serve as an alternative or adjunctive therapy to conventional glioblastoma treatments. The integration of computational predictions with in vitro and in vivo experiments will be necessary to confirm these findings and advance kaempferol toward clinical application.

These computational findings provide a strong foundation for further research into kaempferol's role in glioblastoma therapy. Future experimental validation, including molecular docking studies, cell-based assays, and in vivo models, will be crucial in confirming its efficacy and elucidating its mechanism of action.

Conclusion

This study highlights the potential of kaempferol from Muntingia calabura L. as a promising inhibitor of HIF-1α expression, which plays a crucial role in glioblastoma progression. Computational predictions using the PASS Online platform indicate a high probability of activity (Pa = 0.969) and an extremely low probability of inactivity (Pi = 0.002), strongly suggesting that kaempferol can effectively inhibit HIF-1α expression. Given the importance of HIF-1α in tumor proliferation, angiogenesis, and resistance to therapy, targeting this pathway presents a valuable therapeutic strategy.

Kaempferol's known pharmacological properties, including its antioxidant, anti-inflammatory, and anticancer activities, reinforce its potential as a natural therapeutic agent for glioblastoma treatment. The ability of kaempferol to interfere with HIF-1α signaling may also contribute to the downregulation of VEGF-mediated angiogenesis, further supporting its role in combating tumor progression.

References

Calderón-Montaño, J. M., Burgos-Morón, E., Pérez-Guerrero, C., & López-Lázaro, M. (2011). A review on the dietary flavonoid kaempferol. *Mini Reviews in Medicinal Chemistry*, 11(4), 298-344.

Chen, A. Y., & Chen, Y. C. (2013). A review of the dietary flavonoid, kaempferol on human health and cancer chemoprevention. *Food Chemistry*, 138(4), 2099-2107.

Cragg, G. M., & Newman, D. J. (2005). Plants as a source of anti-cancer agents. *Journal of Ethnopharmacology*, 100(1-2), 72-79.

Ekins, S., Mestres, J., & Testa, B. (2007). In silico pharmacology for drug discovery: methods for virtual ligand screening and profiling. *British Journal of Pharmacology*, 152(1), 9-20.

Holland, E. C. (2000). Glioblastoma multiforme: the terminator. *Proceedings of the National Academy of Sciences*, 97(12), 6242-6244.

Imran, M., Rauf, A., Shah, Z. A., Saeed, F., Imran, A., Arshad, M. U., ... & Mubarak, M. S. (2019). Chemo-preventive and therapeutic effect of the dietary flavonoid kaempferol: A comprehensive review. *Phytotherapy Research*, 33(2), 263-275.

Kitchen, D. B., Decornez, H., Furr, J. R., & Bajorath, J. (2004). Docking and scoring in virtual screening for drug discovery: methods and applications. *Nature Reviews Drug Discovery*, 3(11), 935-949.

Li, Z., Bao, S., Wu, Q., Wang, H., Eyler, C., Sathornsumetee, S., ... & Rich, J. N. (2009). Hypoxia-inducible factors regulate tumorigenic capacity of glioma stem cells. *Cancer Cell*, 15(6), 501-513.

Morris, G. M., Huey, R., Lindstrom, W., Sanner, M. F., Belew, R. K., Goodsell, D. S., & Olson, A. J. (2009). AutoDock4 and AutoDockTools4: Automated docking with selective receptor flexibility. *Journal of Computational Chemistry*, 30(16), 2785-2791.

Ostrom, Q. T., Gittleman, H., Liao, P., Rouse, C., Chen, Y., Dowling, J., ... & Barnholtz-Sloan, J. S. (2014). CBTRUS statistical report: primary brain and central nervous system tumors diagnosed in the United States in 2007–2011. *Neuro-oncology*, 16(suppl_4), iv1-iv63.

Semenza, G. L. (2003). Targeting HIF-1 for cancer therapy. *Nature Reviews Cancer*, 3(10), 721-732.

Semenza, G. L. (2012). Hypoxia-inducible factors in physiology and medicine. *Cell*, 148(3), 399-408.

Stupp, R., Mason, W. P., van den Bent, M. J., Weller, M., Fisher, B., Taphoorn, M. J., ... & Mirimanoff, R. O. (2005). Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *New England Journal of Medicine*, 352(10), 987-996.

Wang, J., Zhang, Y., Yuan, Y., Xu, Y., & Shen, J. (2015). Kaempferol inhibits cell growth and progression of human glioma cells through downregulation of microRNA-21. *Neurochemical Research*, 40(3), 525-533.

Yoshida, M., Sakai, T., Hosokawa, N., Marui, N., Matsumoto, K., Fujioka, A., ... & Nishino, H. (1990). The effect of quercetin on cell cycle progression and growth of human gastric cancer cells. *FEBS Letters*, 260(1), 10-13.

Zagzag, D., Zhong, H., Scalzitti, J. M., Laughner, E., Simons, J. W., & Semenza, G. L. (2000). Expression of hypoxia-inducible factor 1α in brain tumors: association with angiogenesis, invasion, and progression. *Cancer*, 88(11), 2606-2618.

Zhang, Y., Chen, A. Y., Li, M., Chen, C., Yao, Q., & Ginkgo, B. (2008). Kaempferol inhibits VEGF expression in ovarian cancer cells. *International Journal of Molecular Sciences*, 9(5), 562-573.