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Prediction of Lycorine from Lily Flower (*Lilium* spp.) as MAP Kinase Stimulant for Cancer Therapy

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Abstract: Lycorine, an alkaloid compound found in lily flowers (Lilium spp.), has been predicted to have activity as a stimulant of the MAP kinase pathway based on in silico analysis. Lycorine molecular data was obtained from PubChem database in SMILES format and analyzed using Prediction of Activity Spectra for Substances (PASS) platform available at Way2Drug. The analysis showed that lycorine has an activity probability (Pa) of 0.760 and a very low inactivity probability (Pi) of 0.004. The high Pa value indicates a high likelihood that lycorine can stimulate the MAP kinase pathway, which plays an important role in the regulation of cancer cell growth and apoptosis. With this potential, lycorine may contribute to inducing pro-apoptotic mechanisms as well as inhibiting cancer cell proliferation through modulating the MAP kinase pathway. These predictive results provide a strong scientific basis for further exploration of lycorine as a candidate cancer therapy.

Keywords: Lycorine, Lilium spp., MAP kinase

Introduction

Cancer remains one of the leading health challenges worldwide, causing high rates of illness and death (Bray, F. 2018). Over the years, researchers have explored various ways to combat this disease, leading to advancements in treatments such as chemotherapy, immunotherapy, and molecular-targeted therapy (Hanahan, D., 2011). Each of these methods has its benefits and drawbacks, driving the continuous search for better and more effective therapies.

One crucial pathway involved in cancer development is the Mitogen-Activated Protein Kinase (MAPK) pathway (Kim, E. K., 2010). This pathway plays an essential role in regulating cell growth, differentiation, and programmed cell death (apoptosis). Because of its significance in cancer progression, it has become a prime target for new treatment strategies. By carefully regulating the MAPK pathway, scientists aim to trigger cancer cell death while preserving the balance of normal cells (Mendoza, M. C., 2011).

For centuries, nature has provided a wealth of medicinal compounds, many of which have led to life-saving drugs. Plants, in particular, have been a rich source of bioactive molecules with promising anticancer properties. Among these natural compounds, alkaloids have shown significant potential in cancer treatment (Cragg, G. M., 2016). One such alkaloid is lycorine,

found in lilies (Lilium spp.), which has been studied for its anti-inflammatory, antiviral, and anticancer effects (Nair, J. J. 2016).

Studies have shown that lycorine can trigger apoptosis and slow down cancer cell growth through multiple molecular mechanisms (Lu, J., 2020). However, its possible role as a stimulant of the MAPK pathway in cancer treatment has not been extensively explored (Li, Y., 2021). Understanding how lycorine interacts with this pathway could open new doors in cancer research. To investigate this, scientists use computational techniques such as in silico modeling, which helps predict how drugs interact with biological targets efficiently (Ekins, S., 2007). This method allows researchers to study molecular interactions, assess binding potential, and gain insights into a compound's mechanism of action at a deeper level.

This study aims to examine how lycorine interacts with the MAPK pathway using bioinformatics and molecular modeling tools (Liao, Y., 2019). By uncovering lycorine's potential to stimulate MAPK activity, we hope to contribute valuable knowledge to the development of natural compound-based cancer therapies derived from lilies (Wu, J., 2022).

The MAPK pathway plays a critical role in cell signaling, controlling essential processes such as growth, survival, and cell death. In many cancers, this pathway is disrupted, making it an attractive target for drug development. Traditional MAPK inhibitors have been created to block this pathway, but their effectiveness is often limited by issues like drug resistance and side effects. As a result, researchers are exploring natural compounds that could modulate this pathway in a more balanced way, reducing harm to healthy cells.

Lycorine, being a plant-derived alkaloid, presents a promising alternative to synthetic drugs. Previous research has highlighted its ability to induce oxidative stress, halt the cell cycle, and activate apoptosis in cancer cells. However, its exact influence on the MAPK pathway remains a mystery. By investigating whether lycorine can stimulate or regulate this pathway, scientists may unlock new therapeutic possibilities.

Advancements in computational drug discovery have revolutionized how researchers identify promising drug candidates. In silico techniques allow scientists to examine vast chemical libraries, predict interactions between drugs and biological targets, and refine molecular structures for better efficacy. For example, molecular docking studies help determine how well lycorine binds to key proteins in the MAPK pathway, while molecular dynamics simulations offer insights into how these interactions evolve over time. These sophisticated tools not only deepen our understanding of lycorine's mechanism of action but also lay the foundation for future experimental validation and drug development.

By integrating computational methods with laboratory research, this study aims to bridge the gap between natural product research and targeted cancer therapies. The results could have far-reaching implications, potentially leading to new plant-based cancer treatments. Moreover, if lycorine proves to be an effective MAPK pathway modulator, it could pave the way for combination therapies where natural compounds work alongside conventional drugs to enhance effectiveness and reduce side effects.

Cancer continues to be a major global health concern, highlighting the urgent need for innovative treatment options. The MAPK pathway is a key player in cancer progression, making it an attractive therapeutic target. Natural compounds like lycorine hold significant

promise in modulating this pathway, potentially offering safer and more effective treatment alternatives. Through bioinformatics and molecular modeling, this study aims to unravel the molecular interactions between lycorine and the MAPK pathway, contributing to the advancement of cancer therapy. The combination of computational and laboratory-based research will be crucial in translating these findings into real-world applications. As the field progresses, natural compounds such as lycorine may emerge as vital components in the future of cancer treatment, offering hope for improved outcomes and better quality of life for patients worldwide.

Methods

In this study, the molecular structure of lycorine was obtained in the form of a SMILES notation from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/), an open chemical database that provides comprehensive molecular information. PubChem serves as a reliable repository of chemical compounds, offering structural, biological, and pharmacological data that support research in various scientific fields, including drug discovery and medicinal chemistry. The SMILES notation of lycorine, a unique textual representation of its molecular structure, was then used as input for predictive modeling through computational tools available on the Way2Drug platform (https://www.way2drug.com/) (Prasetyawan, F., 2024).

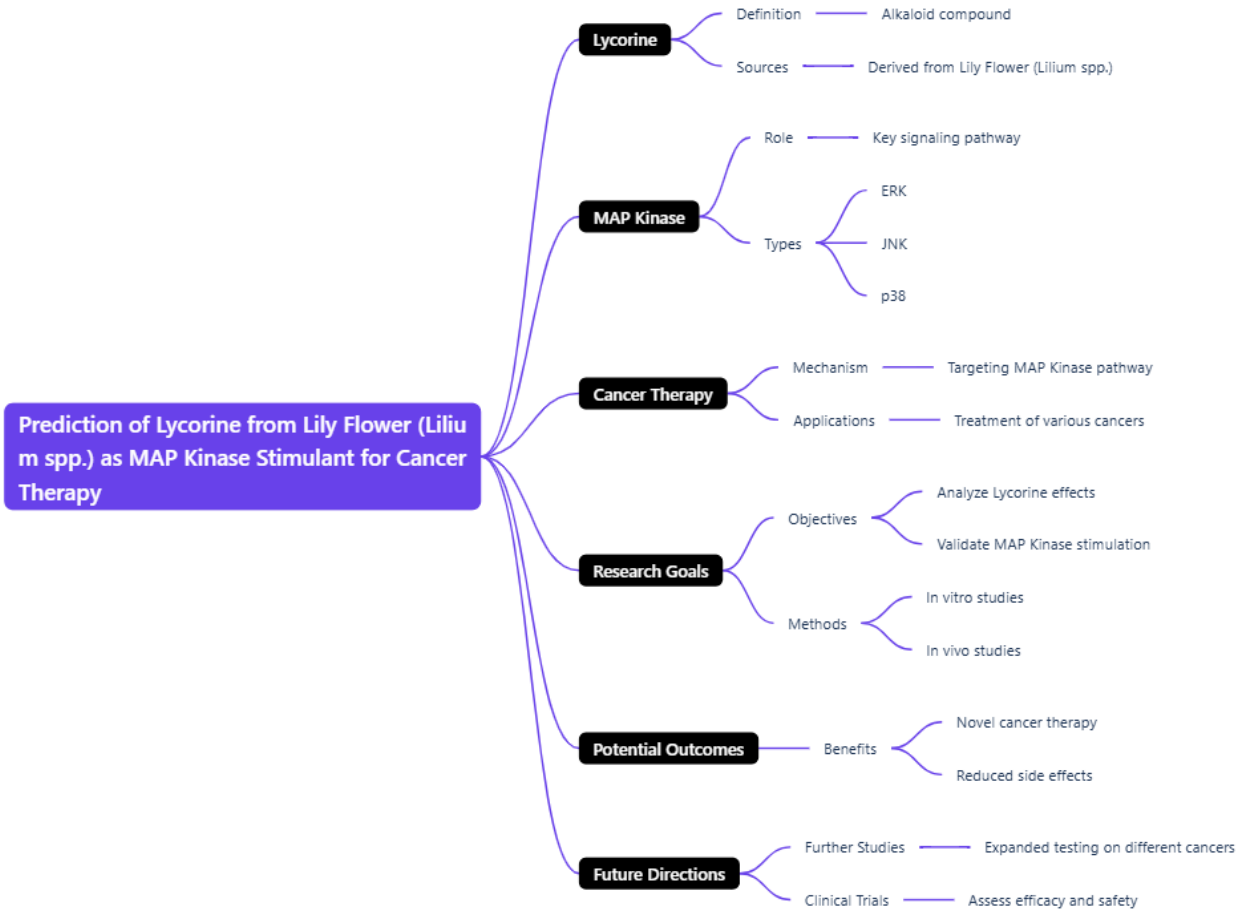

Figure 1. Mind Maps Research

Way2Drug is an advanced bioinformatics platform that offers a range of computational tools designed to predict the biological activity and pharmacological potential of small molecules based on their chemical structures. These tools integrate various cheminformatics and bioinformatics approaches to assess molecular interactions, target affinities, and potential therapeutic applications. The platform enables researchers to explore drug-like properties, assess toxicity risks, and identify molecular targets, thus facilitating the early-stage drug development process.

Through this in silico analysis, the interaction of lycorine with the MAP kinase pathway was evaluated to assess its potential role as a MAP kinase stimulant in cancer therapy. The MAP kinase pathway plays a crucial role in cell signaling, regulating cellular processes such as proliferation, differentiation, and apoptosis. Dysregulation of this pathway is often associated with various cancers, making it an attractive target for therapeutic intervention. By computationally analyzing lycorine's interaction with MAP kinases, researchers aim to determine whether this compound exhibits properties that could modulate kinase activity and influence cancer cell behavior.

The computational predictions generated by Way2Drug provided valuable insights into the bioactivity potential, mechanism of action, and pharmacokinetic properties of lycorine. These predictions included assessments of target binding affinity, potential off-target interactions, and predicted metabolic pathways. By utilizing cheminformatics algorithms, Way2Drug analyzes molecular descriptors and compares them with known bioactive compounds to infer possible pharmacological effects. Such in silico evaluations are essential in modern drug discovery, as they enable rapid screening of numerous compounds while minimizing the need for costly and time-consuming experimental procedures.

The methodological approach employed in this study allows for the efficient and cost-effective screening of lycorine's therapeutic potential. Computational modeling serves as a powerful preliminary tool in drug research, providing evidence to support further laboratory investigations. By predicting biological activity and pharmacokinetic behavior, researchers can prioritize promising compounds for in vitro and in vivo validation studies.

Furthermore, in silico predictions help researchers understand the molecular mechanisms underlying lycorine's activity, guiding the design of more targeted experimental approaches. The ability to predict interactions with specific proteins, receptors, and signaling pathways enhances the rational design of new drug candidates. Additionally, computational approaches assist in evaluating potential side effects, toxicity risks, and bioavailability, contributing to a more comprehensive understanding of a compound's pharmacological profile.

The significance of computational drug discovery continues to grow as technology advances, enabling more accurate and reliable predictions. In the case of lycorine, this study demonstrates how in silico methods can be utilized to generate hypotheses regarding its pharmacological activity and therapeutic potential. The ability to integrate cheminformatics, molecular docking, and predictive analytics within a single workflow accelerates the drug development pipeline and improves decision-making in early research phases.

Despite the advantages of in silico studies, it is important to acknowledge their limitations. Computational predictions, while informative, do not replace experimental validation. The accuracy of predictive models depends on the quality of input data, algorithmic assumptions, and available molecular databases. Therefore, complementary laboratory experiments, such as cell-based assays and biochemical studies, are essential to confirm computational findings and establish the true pharmacological effects of lycorine.

Future research should focus on validating the predicted interactions through in vitro and in vivo studies to determine the actual biological impact of lycorine on the MAP kinase pathway. Experimental approaches such as kinase activity assays, gene expression profiling, and cell viability tests will provide empirical evidence to support or refine the computational predictions. Additionally, exploring structural modifications of lycorine could lead to the development of more potent analogs with enhanced selectivity and efficacy.

The integration of computational and experimental approaches represents a holistic strategy in modern drug discovery. By leveraging the strengths of both methodologies, researchers can optimize the identification and characterization of novel therapeutic compounds. This study underscores the importance of in silico techniques in guiding research efforts and facilitating the rational development of new anticancer agents.

Hasil dan Pembahasan

Lily Flower (Lilium spp.)

Lily flower (Lilium spp.) is a genus within the family liliaceae of flowering plants, consisting of more than 100 species and found world-wide but especially widespread in Asia, Europe & North America in temperate regions. The flower is famous for its beauty and particular smell, frequently used in the perfume and cosmetic industry. In addition to being an ornament and a commercial herb, lily flower has been reported to be beneficial with many pharmacological aspects which have been investigated in traditional and modern medicine. The lily plants contain the bioactive constituents alkaloids, flavonoids, saponins and polysaccharides with various biological properties including antioxidant, anti-inflammatory, anticarcinogenic properties.

Figure 2. Lily Flower (*Lilium candidum* L.)

In lily flower one of the most prominent alkaloids is lycorine which has shown promise as a therapeutic agent in several pharmacological investigations. Lycorine is an antiproliferative agent that is able to suppress the cancer cell growth by inducing apoptosis, inhibiting protein synthesis and modulating cellular signaling pathways including the MAP kinase pathway. Lycorine for its immunomodulatory properties that could improve what the

body do to against cancerous cells has also been explored in some animal studies. This in silico study was carried out in the present research to find and evaluation of compound lycorine interaction with the MAP kinases, because this pathway is critical for controlling cancer cell proliferation.

The bioactive compounds of importance in addition to the herbal source – the lily have a long tradition in traditional medicine across different cultures. Lilies are often resorted in traditional Chinese medicine as one of the herbs to cure respiratory diseases, neurological disorders and inflammatory condition. Additionally, lily extracts have been reported in studies with liver and kidney functions repair, neuroprotective properties that may play a beneficial role for preventing neurodegenerative disease. The lily flower is endowed with broad pharmacological potential, and in this regard it may be a promising genuine natural source for the development in pharmaceutical and biomedical applications.

This research connects the bioactives of lily flower with a molecular target or pathway (in this case the MAP kinase cascade) in order to deliver novel approaches for natural-based cancer chemotherapy. Thus, this study paves a scientific basis for future research of lycorine's functional modulating role on the MAP kinase pathway and provides grounds to take further experimental, as well as clinical trends to understand its potential as an anticancer therapeutic agent.

Lycorine

Lycorine is an alkaloid from the Amaryllidaceae family that has attracted attention in pharmacological research due to its diverse and beneficial biological activities. This compound was first isolated from plants belonging to the Amaryllidaceae family, including lilies, and has since been the subject of numerous scientific studies.

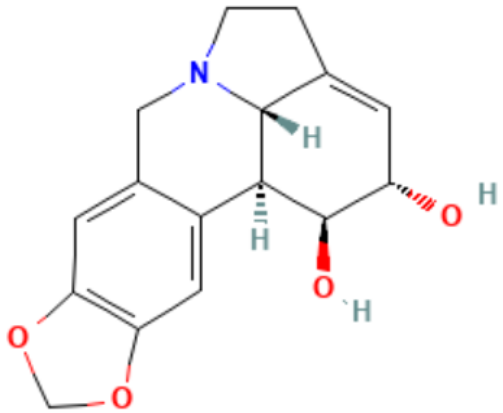

Figure 3. Chemical Structure of Lycorine

With its distinctive structure, lycorine is able to bind to a multitude of targets in biology and therefore could be a chemotype for treating several disease states mainly cancer. Several in vivo and in vitro studies have indicated that lycorine can suppress the growth of cancer cells by affecting various molecular target pathways (eg, MAP kinase pathway, PI3K/Akt, and p53) indispensable for the regulation of cell cycle/apoptosis.

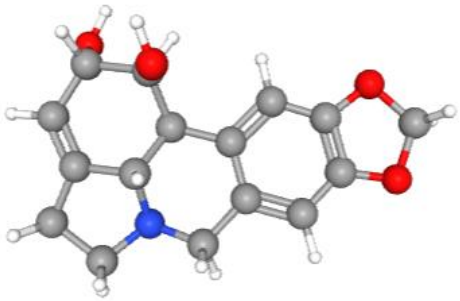

Figure 4. Interactive Chemical Structure of Lycorine

Apart from its anticancer effect, lycorine possess powerful anti-inflammatory activity by preventing pro-inflammatory cytokines production (i.e., TNF-α and IL-6) associated with several chronic inflammatory diseases at their own expense. Moreover, lycorine shows neuroprotective effect against oxidative stress and excitotoxicity that might suggest its therapeutic use in neurodegenerative diseases like Alzheimer's Parkinson's etc. It also described that lycorine showed antiviral activity in some studies and could be a potential inhibitor of replication for viruses, such as SARS-CoV, and others such as the dengue virus.

Table 1. Computed Descriptor of Lycorine

Computed Descriptor	Value
UPAC Name	(1S,17S,18S,19S)-5,7-dioxa-12-azapentacyclo[10.6.1.02,10.04,8.015,19]nonadeca-2,4(8),9,15-tetraene-17,18-diol
InChI	InChI=1S/C16H17NO4/c18-11-3-8-1-2-17-6-9-4-12-13(21-7-20-12)5-10(9)14(15(8)17)16(11)19/h3-5,11,14-16,18-19H,1-2,6-7H2/t11-,14-,15+,16+/m0/s1
InChIKey	XGVJWXAYKUHDOO-DANNLKNASA-N
SMILES	C1CN2CC3=CC4=C(C=C3[C@H]5[C@H]2C1=CC@@HO)OCO4

Though it has diverse pharmacological potentials Lycorine stays under constraints when it comes to therapeutic use especially at high alkali dosing. Thus more investigation is needed to explore formulations that could improve the potency of lycorine and lower the toxicity. Understanding the binding nature of lycorine to molecular target like MAP kinase could offer a solid scientific basis for the advancement of natural product-based cancer therapeutics from the lilies.

Prediction of Lycorine as a MAP Kinase Stimulant

The prediction results from the Way2Drug platform indicate that lycorine has a probability of activity (Pa) of 0.760 as a MAP kinase stimulant, while its probability of inactivity (Pi) is 0.004. The high Pa value suggests that lycorine has a strong likelihood of interacting with the MAP kinase pathway and potentially stimulating this pathway in cancer cells.

Table 2. Prediction of Lycorine as a MAP Kinase Stimulant

Compound	Predicted Activity	Pa	Pi
Lycorine	MAP Kinase Stimulant	0.760	0.004

Taking these predictions in hand lycorine shows considerable quantitative strength as a MAP kinase stimulator. The MAP kinase cascade is one of the central signaling pathways that control cell growth, proliferation, differentiation and cell death. This pathway activates, thereby providing a new therapeutic tool for cancer cell cycle control where enhancement in pro-apoptotic proteins and inhibition of apoptotic power protein expression could be used to modulate the MAP kinase pathway . Accordingly, lycorine might be regarded as a kind of suitable candidate for the treatment of cancer by inhibitors to MAP kinase pathway.

MAP kinase activation have previously shown to sensitize against apoptosis and prevents tumor cell growth in cancer cell lines. Thus, inducers such as lycorine that are capable of modulating MAP kinase activity might offer a new treatment approach for the treatment of multiple types of cancers, especially more aggressive or refractory tumors to conventional therapy.

Beyond being a MAP kinase stimulant lycorine further demonstrates many of the mechanisms that contribute to its anticancer activity. Cancer cells are suppressed by protein translation inhibition, endoplasmic reticulum stress and actin cytoskeleton of cells destruction contributing to the antiproliferative properties of cytochalasin B. The multiplicity of these mechanisms supports the broad appeal of lycorine as a natural chemotherapeutic agent.

Despite in silico predictions suggesting lycorine may act as MAP kinase stimulator, further experiments using in-vitro and in vivo must be done to confirm this effect. More studies are required to investigate its pharmacokinetics, toxicity and side effects as an anticancer drug e.g. This work offers new clues of lycorine as a candidate MAPK stimulator and justifies its explore for natural compound-based therapy against cancer.

MAP Kinase Stimulant for Cancer Therapy

Cellular processes such as proliferation, differentiation or apoptosis are tightly regulated by the MAP kinase pathway which is a key signaling component. This is a series of protein kinases that takes extracellular signals and transduces it into intracellular responses to regulate cell fates. In cancer, the abnormal activation of the MAP kinase pathway is related to uncontrolled cellular proliferation and resistance to apoptosis as well as metastasis. Consequently, a method of attacking MAP kinase signaling has been proposed as potential therapy in destroying cancer cells. Whereas most of the therapeutic interventions are upon inhibition of this axis that simply overcomes any uncontrolled cell proliferation from tumor cells; there is a study that is exploring whether MAP kinase stimulants could be pro-apoptotic and hence restoring the signal network paralysis in cancer cells.

Lycorine (natural alkaloid from Amaryllidaceae family)Fig. One of the MAP kinase stimulants for cancer treatment is found to be a lycorine. Computational predictions indicate lycorine has a high odds of interacting with MAP kinase pathway, which then could activate pro-apoptotic forms and prevent tumoral progression. Like traditional target kinase inhibitors, MAP kinases stimulants such as lycorine may work by specifically mobilizing certain signaling cascades to cause selective cancer cell death with minimal impact on surrounding normal cells. It could be especially useful in cancers where treatment resistance occurs through resistance to conventional therapy, reactivating apoptotic pathways and making tumor cell treatment more sensitive.

Apart from their cancer curative MAP kinase stimulants therapeutic potentials transcend direct effects on tumors. Through their regulation of several pathways coupled with the palliative potential of these compounds, they offer the opportunity to potentiate the effects of mechanistically diverse combination therapies: chemotherapy, radiosensitizing

agents and immune therapies. Moreover, pharmacological activation of MAP kinase pathway could be an alternative tool in order to circumvent drug resistance, considered as a major issue in oncology. Although these results are interesting in vitro and in silico, further research is needed to confirm the efficacy and safety of MAP kinase stimulants in a clinical setting. Exploring molecular interactions, pharmacodynamics and even toxicity of these agents will be needed to evaluate their future as anticancer potential in-depth and directed studies.

MAP kinase stimulants in light of the review of malignancies is a novel, innovative and promising pharmacologic strategy for cancer treatment instead of the current popular kinase inhibitors. This could be a novel mechanism to establish lycorine as an inducer of cancer cell apoptosis and resistance to treatment. Further studies in this pathway might allow development of therapy that selectively targets kinases involved in the multi-level MAP kinase cascade mainly for overcoming therapeutic resistance to anticancer treatment.

Inclusion

The inferred results of this study provide the MAP kinase stimulant lycorine potential, Pa = 0.760 probability of activity and Pi Rarely ≈Pi Infrequently 0.004 That's telling us lycorine has a very high propensity of binding to the MAP kinases, a critical effector in controlling cell growth and apoptosis, especially activated in cancer cells. A Pa high enough for lycorine to possibly act as an activator of MAP kinase pathway, promoting pro-apoptotic pathways while concomitantly inhibiting proliferation in cancer cells

In silico: the present study made an in-depth prediction on the potential of lycorine as a candidate for cancer therapy via MAP kinase signaling. Yet, additional research is needed to establish the efficacy of lycorine in its clinical applications as further experimentation is required both in vitro and in vivo to confirm lycorine interaction and mode of action on MAP kinase pathway in cancer cells. This studies results may, therefore, provide a basis for constructing natural compound based anticancer drugs derived from lily (Lilium spp.).

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