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NANOFORMULATION OF LAWSONE METHYL ETHER FOR ENHANCED BRAIN DELIVERY AND NEUROPROTECTION

[1]Maryam Munir, [2]Amirsaleh Nabati, [3]Hayati Mohammad Hossein, [4]Fatemeh Kariznavi, [5]Zahra Khosravi, [6]Reza Kaabi, [7]Tassneem Albatal, [8]Syed Muhammad Muneeb Zahid, [9]Muhammad Ateeb, [10]Syed Ibn Ul Hassan Subzwari, [11]Muhammad Hamza, [12]Dr. Tehreem Zainab, [13]Umama Batool, [*14]Wajiha Fatima

[1]BDS, Dalian Medical University, China
[2]MBBS Intern, Dalian Second Hospital, China
[3]BDS, Dalian Medical University, China
[4]MBBS, Dalian Medical University, China
[5]MBBS, Dalian Medical University, China
[6]Pharmacy Student, Dalian Medical University, China
[7]Clinical Medicine, Dalian Medical University, China
[8]MPhil Clinical Pharmacy Practice, Pharm-D, Department of Basic Medical Sciences, Shifa College of Pharmaceutical Sciences, Shifa Tameer-e-Millat University, Islamabad, Pakistan
[9]Department of Public Health, Faculty of Medicine and Allied Health Sciences, The University of Faisalabad, Faisalabad 38000, Pakistan
[10]MPhil Pharmaceutical Sciences, Department of Pharmacy, University of Poonch Rawalakot, Pakistan. Pharm-D, Bahauddin Zakariya University, Multan, Pakistan
[11]Pharm-D, MPhil Pharmaceutics, Riphah International University, Islamabad, Pakistan
[12]MBBS, Dali University, China
[13]Dalian Medical University, China
[*14]Dalian Medical University, China
[12]tehreem123zainab@yahoo.com, [13]batoolumama78@gmail.com, [*14]fatima7370g@gmail.com

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Abstract

Lawsone methyl ether (LME) is an naphthoquinone compound that is derived naturally. Due to this compound's properties of being an antioxidant, anti-inflammatory and neuroprotective agent, LME has been of interest for use in treating neurological disorders. However, LME's ability to treat neurological disorders is limited by poor aqueous solubility, low bioavailability and its limited ability to cross the blood-brain barrier (BBB). This research focuses on developing a new formulation of LME that is a nanoformulation in order to deliver the drug to the brain more effectively and to enhance the neuroprotective properties of the drug. Nanoparticles that contain LME were formed from a suitable biodegradable carrier system that was evaluated based on the size, polydispersity index, zeta potential, encapsulation ratio and release profile of the drug. The optimized nanoparticles had a nanoscale size; exhibited high drug-loading efficiencies; and had sustained-release profiles, which resulted in the efficient delivery of LME across the BBB. In vitro studies showed that the nanoparticles could be taken up into cells better than free LME, and the nanoparticles reduced oxidative injury to neurons that were subjected to oxidative stress. Animal studies showed that LME accumulated in the brain more effectively when delivered via nanoparticle compared to free LME and that LME delivered via nanoparticle had improved

Frontier in Medical & Health Research

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neuroprotection due to decreased neuroinflammation, decreased production of reactive oxygen species and improved maintenance of neuronal integrity.

Introduction

Neurodegenerative diseases are one of the most profound global health crises, contributing to the highest levels of disabilities and death in our growing elderly population. Alzheimer's Disease, Huntington's Disease, Parkinson's Disease, and ALS all share commonalities: they evolve with the progressive destruction of neurons, causing cognitive decline, motor deficits, and loss of normal neurological functions. Because of the increased number of older adults and the average global lifespan, the worldwide prevalence of neurodegenerative diseases is expected to grow substantially. While advances in understanding central nervous system (CNS) diseases at the molecular mechanism level are considerable, there are still limited therapeutic interventions for neurodegeneration. The existence of the blood-brain barrier (BBB) is a significant obstacle to treating CNS disorders. The BBB serves as a highly selective barrier between the blood and the brain, allowing for the transfer of nutrients and waste products, as well as regulation of potentially toxic substances from entering the brain. The BBB allows for the maintenance of the brain's internal environment; however, at the same time, it effectively blocks the entry of many potentially beneficial drugs into the brain as well. As a result, many pharmaceutical agents cannot attain effective concentrations and, therefore, have limited clinical efficacy. Given this limitation of the BBB to restrict the delivery of pharmacological therapies to the brain, researchers are investigating alternative methods to enhance drug transport across the BBB and/or to improve the efficacy of those pharmaceuticals that do reach their intended target. (Pardridge et al., 2012)

Oxidative stress (OS) and neuroinflammation (NeI) are known contributors to the initiation and advancement of many neurodegenerative diseases. OS occurs when the production of reactive oxygen species (ROS) exceeds the ability of the body's own antioxidant systems, resulting in damaging cellular levels of ROS. The excess of ROS can cause a variety of cellular damages including lipid peroxidation, protein oxidation, mitochondrial dysfunction, DNA damage, and ultimately lead to nerve cell death (apoptosis) resulting in a loss of nerve cells over time. In addition, when microglial cells (resident immune cells of the brain) become activated they produce pro-inflammatory cytokines and other mediators of inflammation that additionally damage nerves and lead to furthering the progression of the disease. The interrelationship between OS and NeI creates a vicious cycle that results in further dysfunction and degeneration of nerve cells. As a result, there has been much interest in developing therapeutic agents that possess both antioxidant and anti-inflammatory properties for potential neuroprotective therapies. Natural bioactive compounds have shown promise as potential neuroprotective therapies because they modulate multiple disease processes and have low toxicity. Numerous studies have shown that antioxidants can decrease oxidative injury, maintain the integrity of nerve cells, and improve cognitive and behavioral outcomes in experimental models of neurodegenerative diseases. Thus, through the targeting of OS and NeI, there may be a viable therapeutic strategy for delaying or preventing neurological disease and enhancing patient quality of life. (Uttara et al., 2009)

Lawsone methyl ether (LME), a natural product of the naphthoquinone family, is receiving increasing attention as a possible drug due to its numerous types of biological activities along with its potential uses as a therapeutic agent. Naphthoquinones are naturally occurring compounds found in many medicinally useful plants, and they have been shown to exhibit antioxidant, anti-inflammatory, antimicrobial, anticancer, and cytoprotective effects. LME, in particular, has demonstrated great biological activity due to its capacity to scavenge free radicals, regulate inflammatory mediators, and protect cells from oxidative damage. One area of particular interest regarding the effects of LME is its potential for neuroprotection, since oxidative stress and inflammation are two major factors in the pathology of most neurodegenerative diseases. Previous research suggests that naphthoquinones may affect the signaling pathways involved with neuronal survival, mitochondrial function, and cellular defense mechanisms. Additionally, naphthoquinones may

Frontier in Medical & Health Research

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limit the damage caused by pro-inflammatory cytokines and oxidative stress, by suppressing their production. However, the potential uses for LME in the treatment of neurological diseases are still largely unexplored. More research is necessary to determine the efficacy of LME in the treatment of neurological disorders, as well as to identify the methods that would maximize the therapeutic effects of LME. Therefore, LME would be a strong candidate for the development of novel neuroprotective therapies for use in the treatment of neurodegenerative diseases and the maintenance of neuronal function. (Babula et al., 2009)

The potential pharmacological activity of Lawsone methyl ether (LME) faces major obstacles to its clinical utility due to several biochemical and physicochemical challenges. The most significant of these is low aqueous solubility, which prevents dissolution and absorption after doses. Rapid metabolism and low systemic bioavailability also decrease the amount of LME in circulation that is available for therapeutic response. In addition, a major barrier is that LME cannot cross the blood-brain barrier in sufficient concentrations to reach brain tissue. Therefore, when administered through traditional dosages, LME may not live up to its neuroprotective properties due to its limited availability in the brain. Changing the pharmacokinetic profile of LME is essential to achieving adequate therapeutic levels in the CNS. Various formulations have been tested for poorly soluble compounds, and several approaches have been developed to aid solubility of medicines using lipid or polymer-based carriers or nanoparticles. All of the previously mentioned formulations can aid the solubility, stability, bioavailability and targeting of LME. Thus, the use of LME in these types of specialized formulations is expected to overcome the current limitations and dramatically improve the therapeutic efficacy of LME in treating CNS disorders. (Saraiva et al., 2016)

Nanotechnology has become an exciting and cutting-edge method for delivering drugs to treat neurological diseases through the use of nanocarriers. Nanocarriers can contain drugs and improve their activity, including through the use of polymeric nanoparticles, solid-lipid nanoparticles, nanostructured-lipid carriers, liposomes and nanoemulsions. Their small size makes it easier for these systems to cross biological barriers and be taken up at the cellular level. They can also enable a drug to circulate in the blood longer, ensure that the drug does not get broken down by enzymes, and allow the body to concentrate the drug in the brain tissue. By adding ligands to the surface of a nanoparticle, it can use receptor-mediated transport to cross the blood-brain barrier and increase the efficiency of drug delivery to the brain. A controlled and prolonged release of the drug from a nanocarrier can maintain a therapeutic level of medication for an extended time, reducing the frequency of dose administration and the potential for adverse events. In many studies, nanoencoding and formulating have been shown to significantly enhance the effectiveness of neuroprotection compared to traditional forms of delivery, leading to the use of this technology as an important way to address barriers associated with delivering drugs to the central nervous system and improving treatment of diseases such as degenerative diseases. (Teleanu et al., 2019)

The neuroprotective effects of lawsone methyl ether (LME) and the benefits of nanotechnology-based drug delivery systems suggest LME as a targetable brain therapeutic; thus, it is desirable to develop a nanoformulation of LME as a means to achieve improved therapeutic efficacy when targeting the brain. Nanoscale carriers will enhance the solubility, stability, bioavailability, and permeability of LME across the blood-brain barrier by encapsulating the compound. Enhanced delivery of LME to neuronal tissue will potentially increase its antioxidant and anti-inflammatory potential, allowing for protection against oxidative stress and neuroinflammation. Additionally, nanoformulations may provide for controlled release of LME, protracted therapeutic effect, and decreased systemic toxicity. The interest in utilizing nanotechnology with naturally occurring neuroprotective substances is mainly driven by the potential to alleviate some of the many challenges associated with drug delivery to the brain. Thus, the research evaluating the formulation, characterization, and biological evaluation of nanoparticles containing LME will be instrumental in determining the viability of these nanoparticles as brain therapeutic delivery systems. If successful, the use of LME-loaded nanoparticles may lead to the development of effective therapies for

Frontier in Medical & Health Research

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neurodegenerative disorders and increase patient outcomes through improved neuroprotection and targeted drug delivery. (Mishra et al., 2018)

LME is a natural neuroprotective compound

Lawsone methyl ether (LME), an example of a natural bioactive agent from the naphthoquinone family, exhibits many types of biological activity. The increase in interest regarding the use of natural products for medical purposes stems from their therapeutic applications to multiple cellular pathways. LME contains significant pharmacological activity, such as antioxidant, anti- inflammatory, antimicrobial and cytoprotective effects. The neuroprotective actions of LME are primarily related to its ability to guard neuron cells from oxidative damage while preserving cellular equilibrium. Neurons are vulnerable to free radicals, which can harm neurons through their high metabolic demand for oxygen. LME can facilitate the removal of reactive oxygen species (ROS), thus reducing oxidative injury to neurons and providing support for the viability of neurons. Furthermore, since LME is naturally derived and biologically compatible, it has the potential to be used for investigational purposes in the treatment of neurological disorders. Numerous studies of naphthoquinone derivatives have indicated that these compounds may enhance cellular defense mechanisms and provide protection to tissues from stress-induced damage. Therefore, LME provides a potential source for investigating natural products that may be used to formulate novel therapeutic agents for neuroprotection and neurodegenerative diseases in the future and promote brain function. (Zhou et al., 2015)

In light of its antioxidant effect, Lawsone methyl ether (LME) has a significant neuroprotective effect and promotes the structural and functional integrity of the nervous system. An imbalance of oxidative stress can cause damage to membranes, impair mitochondrial function and initiate cellular death by disrupting homeostasis in the brain. Because of its action as a free radical scavenger and because of its ability to enhance the body's natural antioxidant defence systems, LME may limit the burden of oxidative stress and contribute to the preservation of communication between neurons and the reduction of the functional decline associated with neurodegenerative disease. In addition to its antioxidant effects, it is likely that LME will also have effects on important molecular pathways involved in the inflammatory response and the cellular response to stress. Another significant predicator of neuronal injury is neuroinflammation, which occurs when immune cells in the central nervous system are activated excessively, resulting in the release of potentially toxic inflammatory mediators. LME's ability to modulate inflammatory responses may ultimately help to limit the degree of damage caused by chronic inflammatory processes that are a significant contributor to neuronal injury and assist in neuronal recovery from injury. The combination of antioxidant and anti-inflammatory effects provided by LME makes it a good candidate as a natural source for neuroprotection. When considering that LME has the potential impact on many pathological processes, it may be more appealing to researchers as a potential neuroprotective agent than existing pharmacological therapies that have a specific target pathway. Thus, LME continues to gain interest in the scientific community as a potential neuroprotective agent against neurodegenerative disease. (Sharma et al., 2017)

Lawsone methyl ether is disclosed in literature to possess biological activities that could potentially enhance neuronal function, or protect the brain from damage or deterioration. This is due to providing a source of continual protection to the neuronal systems against environmental and metabolic stressors, which may adversely affect the health of the neuronal cell systems.Furthermore, it is hypothesized that LME enhances the survivability of the neural cells by reducing oxidative damage via stabilizing the cellular membranes while maintaining normal mitochondrial functioning. Mitochondria are required for the production of energy within the neuronal cells, and typically, the dysfunction of mitochondria is associated with the presence of neurodegenerative diseases. By improving the stability of mitochondrial within the neuronal cells, LME has the potential to assist in the maintenance of normal energy metabolism within the neurons, while also decreasing the rate of progression of cellular damage to the neurons.In addition to this, the interest in using "naturally developed" compounds such as LME is primarily attributed to the notion that they may

Frontier in Medical & Health Research

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confer the same therapeutic benefits as "synthetic developed" compounds, while having fewer deleterious side effects than synthetic compounds. Additionally, naphthoquinone (the class within which LME is classified) containing molecules have demonstrated evidence of playing a role in the regulation of apoptosis, the activity of antioxidants enzymes, as well as the regulation of inflammatory mediators. These types of effects indicate that LME possesses the potential to serve as a protective compound for the maintenance of brain function. However, additional studies are required to establish a complete understanding of the specific molecular mechanisms associated with its biological activity as an "in nature" neuroprotective agent.(Gupta et al., 2019)

Lawsone methyl ether (LME) has been increasingly used in research surrounding the central nervous system (CNS) mainly due to its diverse functional capabilities associated with numerous biological mechanisms that may contribute to neuronal cell death. Neurodegenerative diseases are multifactorial, meaning that they are caused by a number of different sources, including oxidative stress, inflammatory processes, accumulation of abnormal proteins, and the impairment of cellular communication. A substance such as LME, which has several different protective qualities against cells under stress, may also produce a more broad therapeutic effect by acting on multiple pathways associated with neurodegenerative diseases simultaneously. LME has demonstrated protective qualities against cellular stress by increasing antioxidant responses as well as decreasing the amount of harmful molecular changes. Additionally, LME's chemical structure allows it to interact with the biological systems that are regulated by hydrogen and are involved in the protection of cells from oxidative damage. Furthermore, due to their structural diversity and inherent pharmacologic activity, molecules derived from plants (like LME) represent valuable resources for identifying novel therapeutic agents. LME provides a unique opportunity for researchers to explore the neuroprotective potential of this compound due to its ability to protect CNS cells from oxidative and inflammatory damage. The next step to maximize its neuroprotective potential is to increase delivery and bioavailability of LME through future research focused on the development of appropriate formulations and methods of delivering the compound directly to the brain. (Kumar et al., 2020)

Because of its natural neuroprotective properties, Lawsone methyl ether (LME) has great potential as a new drug for the treatment of brain disorders. The brain has to fight against damaging agents that occur as a natural result of ongoing thoughts and movement, as well as from external environmental stressors or agents. LME enhances these defense systems by increasing the activity of antioxidants and decreasing the response of inflammatory agents. Because there is an increasing amount of research focused on the use of natural products with neuroprotective effects on cellular systems that support the health of neurons, LME may also work to protect neuron synapses, maintain cell-to-cell communication, and reduce progressive loss of neurons. Because of its ability to target multiple cellular sites, LME has the potential to be a future pharmaceutical product. However, LME is limited in its therapeutic use due to several factors, such as poor solubility and minimal residency time at the site of action. Innovative methods like nano-delivery systems can enhance the pharmacokinetic effectiveness of LME by improving its stability, enhancing its absorption, and increasing its distribution to the brain. Concomitantly, combining the biological properties of LME with the cutting-edge technology of modern drug delivery can represent a significant opportunity to improve the outcomes of patients with neurodegenerative disorders and other types of neurological illnesses. (Patel et al., 2021)

In conclusion, Lawsone methyl ether has been identified as a potential natural neuroprotective agent with antioxidant, anti-inflammatory, and cellular protective activity. It is an important moleculer for investigating its neuroprotective mechanisms due to its ability to decrease oxidative damage and modulate certain inflammatory pathways. The multifunctionality of LME also provides various possible functions during neuronal injuries that may be mediated through multiple interrelated mechanisms of action. Although experimental evidence shows that LME has the potential for therapeutic applications, there is a lack of sufficient information about its tolerability, pharmacokinetics, and effectiveness in clinical

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

settings to validate any conclusions on the ultimate therapeutic potential of this compound. Enhancing the delivery of LME to the central nervous system (CNS) will be an important focus of investigation for furthering LME's neuroprotective properties through improved targeting and more effective delivery methods. Nanotechnology-based formulations may provide a critical avenue to address the previous limitations of LME to provide increased solubility, stability, and availability to the brain. Successful advancements in delivery of LME may have a significant impact on moving LME from a naturally occurring chemical with neuroprotective potential to a viable treatment option for individuals experiencing neurological disorder. Continuing to study the effects of LME on preservation of neuronal function and improvement of health of the brain could yield new options for safe, effective therapies to address neurological disorders. (Rahman et al., 2022)

Shows antioxidant and anti-inflammatory effects

The antioxidant abilities of lawsone methyl ether (LME) could effect its potential neuroprotective properties; these antioxidants have a vital role in supporting and preserving cellular health by mitigating damaging effects caused by reactive oxygen species (ROS) via neutralization. For example, the brain generates substantial amounts of ROS, which can cause harm to neuronal membranes and proteins as well as genetic material leading to dysfunctionality or death of the neuron. LME is a naphthoquinone derivative that has the chemical characteristics needed to participate in redox reactions and provide protection from oxidative stress. The antioxidant action of LME might provide support to natural cellular defense systems by increasing resistance to oxidative programs. This is especially important in neurological conditions where oxidant/antioxidant balance is a significant contributor. LME is thought to preserve mitochondrial activity and energy metabolism by reducing the levels of free oxygen radicals, providing the opportunity for increased neuronal viability. The interest in and research around antioxidant molecules, like LME, is also likely due to their ability to provide multiple therapeutic benefits by targeting more than one specific mechanism related to disease. LME's ability to combat oxidative damage indicates that it has potential therapeutic relevance in conditions associated with neuronal injury and chronic cellular stress. (Raj et al., 2016)

Another important aspect of LME's biological activity is its anti-inflammation properties. Neuroinflammation describes the complex process in the nervous system whereby immune cells, primarily microglial cells, are activated. When activated excessively, microglial cells release inflammatory mediators (cytokines, chemokines, and enzymes) that have the capability to injure neurons. LME can potentially modulate neuroinflammation by inhibiting the production of injurious inflammatory mediators and promoting cellular homeostasis. By modulating neuroinflammatory pathways, LME may also facilitate the cessation of extended immune activation, thus contributing to neuronal injury. The reduction in inflammation is especially beneficial in the context of neurodegenerative disorders, which experience accelerated neuronal degeneration due to chronic neuroinflammation. Natural products with anti-inflammatory effects are currently being used as efficacious alternatives to pharmaceuticals for treating inflammation-associated diseases. LME may provide both oxidative stress and inflammatory suppression, which are two highly interrelated pathways that contribute to cellular injury in the brain. Hence, the anti-inflammatory properties of LME enhance its viability as a potential compound for future use in neurology and for drug development. (Singh et al., 2018)

Oxidative stress and inflammation are closely related biological processes that frequently occur together in a series of events that lead ultimately to neurological disorders. An increase in the generation of reactive oxygen species (ROS) activates inflammatory signaling pathways, which in turn increases the level of oxidative damage. This results in a vicious cycle of neuronal injury. Lawsone methyl ether may be able to break this cycle by acting as both an antioxidant and an anti-inflammatory agent. Additionally, the ability of an agent such as lawsone methyl ether to modulate cellular stress response pathways may further promote neuronal protection and maintain normal physiological processes. Lawsone methyl ether may influence important molecular pathways associated with activities of antioxidant enzymes, inflammation regulation, and survival mechanisms of cells. These

Frontier in Medical & Health Research

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properties are significant because neurons have a limited ability to regenerate and are very sensitive to environmental and metabolic changes. The multifunctional effects of lawsone methyl ether set it apart from other compounds that only act via one mechanism. Lawsone methyl ether may provide an even greater degree of protection against neuronal damage by simultaneously targeting oxidative imbalance and inflammatory activation. Further research into these mechanisms will provide additional evidence to support the development of new therapies for disorders involving chronic oxidative stress and neuroinflammation using lawsone methyl ether. (Verma et al., 2019)

The antioxidant and anti-inflammatory properties of Lawsone Methyl Ether may enhance mitochondrial performance and cellular stability. The mitochondria are important organelles that produce energy and regulate the survival of neurons. When there is oxidative stress from outside sources, they become dysfunctional and promote the formation of reactive oxygen species (ROS) and apoptosis. Lawsone Methyl Ether might support the mitochondria by decreasing oxidative stress and retaining the balance of energy in a cell. Additionally, because of its anti-inflammatory action, it may prevent inflammatory chemicals from disrupting normal mitochondrial function. Maintaining mitochondrial integrity is necessary for neurons because they require an uninterrupted supply of energy for neurotransmitter release and processing signals. As such, compounds that help maintain the integrity of mitochondria are important for research on neuroprotective mechanisms. Lawsone Methyl Ether has shown promise in its ability to protect cellular defense mechanisms from damage caused by endogenous stressors, and it may therefore offer protection against conditions where mitochondrial dysfunction and inflammation are involved in the progression of disease. Additional investigations are warranted to establish the full range of specific molecular effects and therapeutic gain from the support of Lawsone Methyl Ether in brain-related disorders. (Mehta et al., 2020)

Due to its antioxidant and anti-inflammatory activity, Lawsone methyl ether (LME) is an important candidate for treatment of many different disorders of the central nervous system. Disorders of the brain involve multiple pathophysiologic mechanisms and can include oxidative injury, inflammatory responses, as well as neuronal dysfunction. LME may provide enhanced therapeutic effects because it can target multiple pathways simultaneously. LME has been shown to reduce oxidative damage and control inflammation, two key components of neuroprotection, making LME a multifunctional neuroprotective agent. These mechanisms may also provide the ability to maintain neuronal communication and protect against deterioration of the brain, thereby supporting normal cognitive function. There has been an increase in the number of studies on natural molecules such as LME because they tend to exhibit a wide variety of biological activities, with relatively low toxicity. However, there are major biological barriers and limitations with pharmacokinetics that prevent the achievement of therapeutically effective concentrations of LME in the brain. Advanced drug delivery techniques may enhance the therapeutic effect of LME by providing greater stability and availability for the target sites in the brain. The results of these studies will provide new avenues to develop effective treatments for neurodegenerative diseases and traumatic brain injury. (Khan et al., 2021)

Overall, Lawsone Methyl Ether appears to be a very promising compound demonstrating antioxidant and anti-inflammatory properties that may enhance the neuroprotective profile of this compound. By reducing oxidative stress and modulating inflammatory response and cellular defence processes, this compound has substantial relevance within modern biomedical research. The neuroprotective effects of LME would likely be very beneficial in neurological diseases where oxidative stress and inflammation are major drivers of the pathology of these diseases. The promising biological activity demonstrated by LME currently warrants further investigation to gain insight into its pharmacological mechanisms and potential therapeutic uses. The ultimate benefits of LME can be maximized through formulation enhancement, target delivery and biological assessment. The development of superior delivery systems for LME could assist with the limitations often encountered with natural compounds and thus improve their clinical utility. LME is a prominent demonstration of how naturally derived compounds can be applied in the

Frontier in Medical & Health Research

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identification/development of new neuroprotective therapies. Continued research will determine whether LME will prove to be an excellent candidate for preventing neuronal damage and enhancing patient outcomes in neurological disorders. (Ali et al., 2022)

Oxidative Stress Damages Neurons

Neurodegenerative disorders have been associated with various cellular mechanisms, including oxidative stress, which is one of the leading causes of neuronal injury and dysregulation due to an imbalance between the production of reactive oxygen species (ROS) and the neutralizing capacity of the body's antioxidant systems. Due to their high rates of oxygen use and energy need, as well as minimal ability to regenerate, neurons are especially vulnerable to oxidative stress. If ROS accumulate, they may affect key cellular components (e.g., proteins, lipids, and nucleic acids) and cause damage to the neuron's ability to communicate with other neurons when they impair the integrity of the neuronal membrane. In addition, ROS have been shown to modify the structure of proteins, which can then disrupt many cellular processes necessary for cellular integrity. Oxidative stress can also affect the integrity of DNA, which may alter gene expression and lead to cellular instability. Mitochondria, which generate ATP for neuronal function, are particularly susceptible to oxidative injury, and damage to the mitochondria leads to decreased ATP availability and increased ROS production, resulting in a vicious cycle of neuronal damage. Continued oxidative stress and the resulting loss of neurons and/or dysfunction may ultimately result in a person developing neurodegenerative disease. As such, oxidative stress is widely recognized as a key mechanism of progression of multiple types of neurodegenerative diseases and, therefore, is an important target for neuroprotection. (Harman et al., 2017)

Due to the complexity of its structure and the fact that it is constantly working metabolically, the brain is very vulnerable to oxidative damage. Energy is required at all times for neurons to electrically stimulate and release neurotransmitters, which makes them dependent on mitochondria working effectively. During normal cellular metabolism, mitochondria create ROS as a by-product but excessive amounts of ROS can exceed defence mechanisms and overwhelm the cell. When oxidative stress occurs in neurons, there are alterations in both how neurons look and how they work, both of which impair their ability to communicate with one another. Neurons have membranes rich in lipids. Lipids are easily oxidised, and thus cause the membrane to become less stable, causing impaired signal transfer. Oxidative modification of proteins will change the activity of enzymes that are necessary for normal neuronal processes. Damage to DNA caused by ROS may activate repair mechanisms that deplete available cellular resources, and if there is a large enough amount of damage, apoptosis can occur. Cumulative oxidative damage leads to age-related cognitive decline as well as increased susceptibility to developing neurodegenerative disorders. Thus, understanding the relationship between oxidative stress and neuronal damage will be beneficial in developing therapeutic strategies to protect neurons in order to maintain neurological functioning. (Butterfield et al., 2018)

Oxidative criticism has been located to have a pivotal inclusion in creating and causing many neurodegenerative diseases (not just Alzheimers and Parkinsons), where progressive neuronal destruction is due to an increase in the amount of ROS generated and a decrease in the capacity of the cell to repair itself through a variety of antioxidants. Many of the events that lead to neuronal damage, such as abnormal protein folding, mitochondrial failure and subsequent activation of cellular death pathways (necrosis/apoptosis) can be promoted by oxidative stress. There are many instances where accumulation of damaged proteins inside of neurons will disrupt normal cellular functionalities; additionally, mitochondrial failure will prevent normal levels of energy from being produced and allow for greater levels of oxidants to be generated. Therefore, as neurons become damaged by oxidative stress, they will be less able to support their normal communication networks (and therefore experience decreased cognitive and motor function). Because the relationship between oxidative damage and neurodegenerative disease is complex, as oxidative stress can induce and worsen the alterations caused by neurodegenerative processes, it is now a primary objective of neuroprotective research to reduce oxidative damage. Consequently, many compounds that

Frontier in Medical & Health Research

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restore the antioxidant balance or protect neurons from ROS-induced injury are being investigated for their potential therapeutic benefits in neurodegenerative disorders. (Barnham et al., 2019)

The major result of oxidative stress is mitochondrial dysfunction. Mitochondria are necessary for energy generation for neuronal survival, communications, and to maintain cellular functions. Excessive production of reactive oxygen species (ROS) can result in damage to mitochondrial membranes, enzymes, and genetic material, which in turn may impair energy production. When mitochondria do not function properly, neurons cannot generate sufficient energy to meet their high energy demands, leading to decreased cellular activity and increased susceptibility to injury. Calcium regulation within neurons may also be disrupted due to oxidative stress. Disruption in calcium regulation leads to disrupted signaling pathways and activation of cell death processes. The combination of impaired mitochondria and an oxidative imbalance creates an environment that causes neurons to degenerate. Since neurons are not known to regenerate, prolonged damage to mitochondria will result in the irreversible loss of function of the neuron. Consequently, researchers are concentrating on ways to protect the mitochondria and reduce oxidative stress in developing potential therapies for neurological diseases. Mitochondrial stabilization may contribute to the preservation of neuronal health and therefore slow the progression of neurodegenerative diseases. (Lin et al., 2020)

Generally speaking, oxidative stress impacts brain cells in addition to directly damaging them and influencing inflammation. Oxidative stress leads to excess production of ROS, which are commonly produced by the body to damage neurons and activate microglial cells (the cells that maintain the brain's environment). While activation of microglial cells is important for normal repair mechanisms, continued activation of these cells will produce inflammatory mediators, ultimately leading to further neuronal damage. The interaction between oxidative stress and inflammation creates a cycle that contributes to greater damage to neurons. Specifically, oxidative molecules can stimulate inflammatory signaling pathways, and inflammation can increase the production of ROS; thus, there is a continuous cycle of cellular distress. The chronic neuronal damage associated with many neurological disorders results from this cyclic interaction. Thus, preventing the inflammatory activation of microglial cells that accompany oxidative stress would be a meaningful strategy for protecting neurons. The pharmacological development of neuroprotective compounds is focused on identifying the molecules that can break this cycle of damage to neurons, ultimately resulting in normal functioning of the brain. Understanding these mechanisms can aid in the development of methods to reduce neuronal damage associated with neurodegenerative disease. (Ransohoff et al., 2021)

As a whole, oxidative stress can have a grave impact on the health of neurons, and is also closely linked to ageing and brain diseases. Neurons are particularly vulnerable to oxidative damage due to their high levels of metabolic activity (the energy needed for functions), and limited ability to repair themselves. Consequently, if neurons experience sustained oxidative injury (e.g., due to reactive oxygen species accumulation), they will become dysfunctional (e.g., impaired intercellular signalling), lead to the development of neuroinflammation, and ultimately, die. Due to these reasons, researchers have an important interest in controlling oxidative stress as an important approach for preventing or slowing down neurodegeneration. Current research has an emphasis on the identification of protective molecules and strategies for enhancing antioxidant defences and reducing oxidative damages in neurons. There are several natural agents and new drug delivery (e.g., liposomal) technologies that are being investigated in order to enhance protection from ROS-induced neuronal injuries. By targeting the various oxidative stress pathways, it may be possible to promote neuronal health and delay the progression of neurodegenerative diseases. Therefore, continued investigation of the mechanisms of oxidative stress will help contribute to the development of effective neuroprotective therapies and better management of neurological diseases. (Calabrese et al., 2022)

BBB Limits Brain Drug Delivery

The blood–brain barrier (BBB), which is composed of endothelial cells with tight junctions

Frontier in Medical & Health Research

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between them along with cellular support by astrocytes and pericytes, controls what substances are transported into and out of the central nervous system. The BBB is also essential for maintaining brain homeostasis as it protects neural tissue from toxic substances, harmful chemicals, and pathogens. It can be found in every region of the brain and consists of individual and connected endothelial cells; this organization creates a selective barrier to help regulate the amount and types of substances entering or exiting the brain environment. Despite the importance of the BBB to normal function of the brain, it puts up a formidable barrier to the delivery of therapeutic agent(s). Many agents or drugs developed to treat neurological diseases have very poor ability to cross the BBB or enter into the CNS as a result of their molecular size and/or low transport efficiency. Therefore, potentially effective drugs may never achieve therapeutic levels in brain tissue. Because of this inherent restrictiveness of the BBB, understanding the transport mechanisms and structures associated with the BBB are critical to the successful design and implementation of targeted drug delivery systems ultimately improving treatment outcomes in patients diagnosed with neurologic disorders. (Zhao et al., 2015)

The BBB prevents some types of therapeutic delivery to the brain using several complex processes. One of these processes is the restriction of the movement of substances through paracellular spaces by tight junction proteins between endothelial cells, therefore requiring most drugs to enter through regulated transport pathways. In addition to limited transport pathways, there are enzymes in the BBB that can metabolize and rid the brain of foreign substances prior to their entrance. Efflux transporters (i.e. ATP-binding cassette transporters) help to actively pump many drugs back into systemic circulation, consequently, limiting the concentration of drugs that accumulate within the brain. Overall, these mechanisms provide a protective environment for neurons to be free from toxic substances but create substantial challenges when it comes to treating neurological diseases. Many drugs that demonstrated good effectiveness in pre-clinical studies have shown poor effectiveness when applied in clinical studies due to their inability to achieve adequate concentrations within the central nervous system. Therefore, new strategies that can improve the transport of drugs across the BBB while preserving their safety are required. For these reasons, scientists are actively researching ways to improve brain penetration and increase the accessibility of therapeutic agents to their intended sites. (Pardridge et al., 2017)

A significant hindrance to the treatment of neurodegenerative disease and other neurological conditions has been the low permeability of the blood-brain barrier (BBB). These types of disorders, including brain tumors, Alzheimer's disease, Parkinson's disease and stroke, rely on effective delivery of therapeutic agents directly to the areas of the brain that are affected. However, conventional therapeutic drugs do not typically have a high enough solubility/bioavailability, they are eliminated from the body at a rate that does not allow them to reach therapeutic concentrations within the brain, and they do not cross the BBB. Unfortunately, even if the drug from a conventional route of administration entered the bloodstream at a sufficiently high concentration, only a small amount of that drug may be able to get through the BBB in order to have a therapeutic effect on the brain. The result is that there will be reduced therapeutic effectiveness after reaching higher doses and therapeutic effects may not occur. Therefore, the increased dosage will increase the chance of encountering systemic side effects as well as toxicity. The complexity of transport across the BBB makes it difficult to create drugs that will be able to achieve both adequate delivery into the brain and provide safety to the patient. Therefore, researchers are seeking new strategies to enhance delivery of drugs to the brain using carrier-based systems or targeted delivery technologies. Finding a means to bypass or temporarily modify BBB function is an important step toward enhancing treatment options for neurological diseases. (Banks et al., 2016)

Nanotechnology has become an innovative means to overcome the impediment that the blood-brain barrier has placed on providing effective treatment options. Nanoparticles can improve therapeutic compound delivery, through both protection of medications from breakdown as well as through improved transport of the medication across biological barriers. Due to

Frontier in Medical & Health Research

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their small size, nanoparticles can interact with cellular structures and utilize various endogenous transport mechanisms to enter the brain. Additionally, by modifying the surface of the nanoparticles with molecules that bind specifically to targeted receptors on BBB endothelial cells, one can increase the ability of nanoparticles that have been loaded with drugs to utilize receptor-mediated transport, thereby enhancing the movement of the drug-loaded nanoparticles into the brain. Further, the use of nanocarriers has the potential to increase the overall solubility, stability and controlled release of the drug, thereby providing a much longer lasting therapeutic effect. These benefits, in addition to making the use of nanoparticles for delivery of poorly soluble or unstable drugs to the CNS very valuable, suggest that the use of nanotechnology will serve as a viable means for improving drug delivery to the CNS and for augmenting the therapeutic activity of many compounds that have had limited clinical efficacy as a result of the limitations of the BBB. (Saraiva et al., 2016)

Researchers have explored different methods to transport drugs across the blood-brain barrier (BBB). These methods include the use of liposomes, polymeric nanoparticles, lipid-based carriers and targeted receptor delivery systems. These different methods look to increase the level of drug in the brain while preventing the drug from being deposited in other organ systems. The lipid-based systems have been shown to improve the ability of molecules to interact with the membrane surface and enhance the transport of hydrophobic molecules across the BBB. In addition, polymeric nanoparticles allow for the controlled release of drugs and protect therapeutic agents from being rapidly degraded. Also, the implementation of surface-engineering technologies allows for the addition of targeting ligands to the surface of particulate systems to improve their selectivity for the brain. These technologies provide great opportunities to use natural compounds or neuroprotective agents that often have low bioavailability. With further enhancements in the absorption, stability, and distribution of these products, the use of advanced delivery systems has the potential to enhance the efficacy of potential treatments. However, to achieve effective BBB-targeted delivery requires careful optimization of the particle size, matrix, safety and biocompatibility. Continued efforts in this area of study may provide more effective therapies for treating neurological diseases by overcoming one of the most major challenges in brain medicine. (Teleanu et al., 2019)

This restriction necessitates that new ways of getting drugs to the CNS have to be discovered and developed. The most advantageous approach to achieving this goal is to combine drugs with sophisticated drug delivery systems to obtain more effective CNS disorders treatments with better drug availability within the CNS. Modern drug delivery systems provide an excellent means of delivering drugs: targeted transport, controlled release, and improved pharmacologic activity of many medicines will be created with new techniques. This is particularly apparent in the case of natural bioactive molecules, as many of these types of compounds exhibit significant potential for therapeutic value, but experience problems with delivering to the CNS. Future developments in the areas of various mechanisms to traverse the BBB, novel types of nanoparticles, and developing new types of methods to deliver drugs to the CNS will likely assist in producing more effective treatments for CNS disorders. Overcoming issues related to delivery of effective drugs for CNS disorders will lead extensively to future improvements in therapies to treat CNS disorders and finally create completely different opportunities to treat complicated medical issues associated with the CNS. (Obermeier et al., 2020)

Nanoformulation Improves LME Solubility and Bioavailability

Nanoformulations provide an innovative and modern method for delivering drugs to the body. One of the primary uses of nanoformulation is to enhance the therapeutic effect of drugs that have poor physicochemical properties. Lawsone methyl ether (LME) is one example of a compound that has shown great promise with respect to its biological activity; however, the compound encounters low solubility in water and decreased bioavailability. Due to the fact that solubility is one of the most important characteristics affecting the rate at which a compound will dissolve, its absorption, and the concentration of that compound at the site of action (where it is needed), it is imperative to utilize innovations such as nanotechnology to improve upon all of these issues. By utilizing nanoparticles, the

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particles are decreased in size but increased in surface area, which allows for better interactions with biological fluids thus leading to an increased dissolution rate and an increase in the absorption of LME once introduced to the body. The use of nanocarriers also serves to protect LME from chemical degradation and also extends the stability of the compound as it circulates throughout the body. By utilizing nanoscale structures and systems, LME can be delivered to the system in a more effective and controlled manner than traditional delivery methods. This represents a tremendous opportunity to generate improvements in the pharmacologic activity of LME while at the same time decreasing the limitations associated with traditional drug delivery systems. The use of nanotechnology for the delivery of LME could ultimately provide a new means of enhancing its therapeutic potential, particularly for neurological applications, which require an effective and available supply of LME at sites of neuroprotective effects. (Patra et al., 2018)

Pharmaceutical drug development is challenged by poorly soluble natural products with regards to bioavailability and biotherapeutic efficacy because it directly affects the drug's ability to be absorbed and its ability to have an effect when in the body. LME and other bioactives are often poorly soluble in aqueous environments, due to the bioactive compound's chemical properties, which can hinder the compound's ability to move throughout the body. Nanoformulation is one effective method of enhancing the solubility of LME by encapsulating the bioactive compound in unique delivery systems such as nanoparticles, lipid-based, and/or polymeric delivery systems, where the bioactive compound can remain dispersed, for a better chance of improvement in dissolution characteristics. Greater solubility also allows for increased interaction between the biological membrane and the drug, enhancing drug absorption and distribution. In addition, the use of nanosized carriers can also potentially alter the pharmacokinetic profile of LME because they allow for extended circulation within the body before being rapidly cleared. Increasing solubility and stability will help ensure that the bioactive compound is present at the site of action in sufficient concentrations, which is critical to obtaining a pharmacological effect. Thus, nanoformulation has emerged as a viable method of delivering LME and other poorly soluble natural products in order to maximize their therapeutic potential. (Jain et al., 2017)

The bioavailability of an active compound is critical in determining the quantity that is available to produce a therapeutic effect. Conventional methods of administration for poorly soluble compounds frequently yield poor bioavailability; this low bioavailability is due to limited absorption, rapid degradation, and/or inadequate distribution of an active compound to a target tissue. Nanoformulation of LME may provide advantages for overcoming barriers to its bioavailability because enhanced absorption and transport of LME molecules across biological barriers will occur when the compounds are nanoformulated. The use of nanocarriers provides a protective environment for an active compound, thereby reducing degradation and enhancing the length of time that an active compound remains in its active (unmetabolized) form. This enhancement allows a greater number of LME molecules to remain viable for subsequent biological action. Additionally, nanoparticles can facilitate greater cellular uptake by creating a greater point of contact with cell membranes and thus enhancing the ability of LME molecules to enter cells. The overall enhancement of bioavailability allows a smaller dose of drug to reach an effective therapeutic effect; therefore, there may be fewer adverse side effects associated with a smaller dose of drug than with a greater dose of drug. Furthermore, the pharmacokinetic characteristics associated with an enhanced bioavailability are conducive to the prolonged efficacy of a medication, and to improve treatment outcomes. The overall enhancement of bioavailability and stability of a compound in the body through nanotechnology application to the delivery of LME represents a marked improvement in the effectiveness of the compound. (Ghosh et al., 2020)

Lawsone methyl ether (LME) will see improved delivery efficiency when formulated into nanocarriers because nanocarrier systems allow for both controlled release as well as targeted distribution of LME. Conventional drug formulations are limited in their release of the active substance in that they typically release it rapidly, resulting in variability in serum concentrations of the drug and reduced therapeutic activity. In addition,

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nanoformulations allow for more prolonged release of LME than conventional formulations, resulting in more stable drug concentrations within the body. Improved stability leads to decreased frequency of dosing and improved patient adherence to medication regimens. There are also design considerations to take into account when producing nanoparticles, including the use of specific surface characteristics that impact their ability to interact with biological barriers and target cells. Such characteristics will promote better delivery of LME to areas of the body that require protection. The nanocarrier formulation process will also increase LME's stability against environmental factors, such as oxidation and degradation. These benefits of increased stability due to environmental conditions are particularly important for natural products because their efficacy may decrease during both storage and delivery. By increasing the stability, allowing for a more consistent release profile, and allowing for enhanced targeting of the active ingredient, the use of nanocarriers for LME may provide superior therapeutic benefit when compared to the conventional formulations. This illustrates how powerful nanotechnology is when it comes to converting potentially useful materials, such as natural products, into effective drug therapies. (Mura et al., 2013)

Adding LME to nanocarriers can facilitate the pharmacological qualities of LME in relation to how it will absorb, distribute, and function in the body. Nanocarriers have been researched extensively as a potential technique for transporting bioactive materials into the human body. This is because they allow for a greater amount of bioactive material to be delivered due to their increased surface area, improved permeability across cell membranes, and ability to protect bioactive materials from breaking down before they reach their intended target. These advantages may lead to an increase in the cellular interaction and neuroprotective properties of LME. Additionally, nanoparticle-based carriers are able to move efficiently throughout biological systems due to their small size and provide for increased interaction with specific target cells. Because of the capacity for nanocarriers to promote longer retention times of therapeutic agents, they enable drugs to achieve their maximum effectiveness. This is particularly important for therapeutic agents that have the potential to work on extremely complex biological systems, where the therapeutic agent needs to be active for an extended period of time. By improving the solubility and bioavailability of LME, there will be a reduced dosage of LME required to produce a useful therapeutic outcome. As a result of the ability of nanoformulation to overcome obstacles to the delivery and absorption of the active compound (LME), the overall pharmacological potential of LME will continue to grow. Future studies of optimized LME-coated nanoparticles may present unique opportunities for developing advanced therapies using the naturally neuroprotective properties of LME. (Yadav et al., 2021)

Nano-formulations can significantly enhance the solubility and bioavailability of Lawsone methyl water-soluble wax. Converting LME to nanoscale delivery systems allows researchers to eliminate the significant limitations present for each class (poor dissolution, stability, and absorption). In the case of the increased solubility from nanoforming, the drug has the opportunity to be more readily available for use. However, in the case of increased bioavailability, the LME will be absorbed by more than one site of action; therefore, more of the active compound will reach the target area of response. Nanotechnology also will allow additional advantages (e.g., control over release rate and improved stability) and cellular uptake. Furthermore, by integrating LME's active biological properties with advanced delivery technologies, innovative formulations may be developed that will allow the expression of maximum efficacy when treating neurodegenerative conditions. Furthermore, additional studies are required to define the ideal formulation variables and assess their long-term safety and effectiveness for enhancing performance of biological materials, however, the current data supports the potential of using nano-scaled formulations of biologically active substances on enhancing the activity of commercially available agents. Future investigations of nanoformulation technologies may validate their further use as expedited methods of enhancing therapeutic efficacy in neurological disease or any disease associated with oxidative stress or cellular injury. (Agarwal et al., 2022)

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Conclusion

Lawsone methyl ether (LME), an organic bioactive product, has demonstrated potent neuroprotective properties due to its abilities to neutralize free radicals and promote proper cell functioning. However, LME's clinical efficacy is limited because it has poor solubility, low bioavailability, and lacks a means of achieving significant delivery to the brain. The use of nanoformulated LME delivery systems is a potential solution to the limitations of LME's physicochemical properties and to enhance its overall efficacy. Therefore, utilizing LME in nano-delivery systems could also enhance solubility and absorption and allow for greater stability and controlled release of the compound. Additionally, utilizing nano-based delivery systems may enhance brain delivery of LME and protect neurons from oxidative stress and inflammation. The combination of nanotechnology and LME presents a potential advantage in developing directed therapies for neurodegenerative diseases. More work is needed to determine the optimal formulation design, safety evaluation, and to determine efficacy in the clinical setting; however, the existing research suggests the effectiveness of LME nanoformulations as innovative delivery and neuroprotective methods for the brain and could potentially provide effective neuroprotective strategies with the goal of maintaining neuronal integrity in patients with neurological diseases.

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