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Harnessing Sunlight: The Science of Solar Sails

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Abstract

Solar sails are an innovative form of spacecraft propulsion that uses the momentum of photons to generate continuous thrust without propellant. Within this research, I examine the history, physics, development, and applications of solar sailing technology, highlighting both early demonstrations and advanced missions and concepts. Some of the key missions, including IKAROS, NanoSail-D2, LightSail 1 and 2, GeoSail, CubeSat sails, and PoleSitter, showcase the progression in the technology. Solar sails offer unique advantages for long-duration and outer solar system missions. All of these missions and capabilities show how solar sails continue to revolutionize space missions by providing a propellant-free, sustainable propulsion system that expands the possibilities for exploration and scientific observation.

Keywords: solar sails, photon momentum, radiation pressure

Harnessing Sunlight: The Science of Solar Sails

Introduction

Solar Sails are a developing space propulsion technology that uses light from the sun to propel spacecraft without fuel. Instead of relying on traditional propulsion methods, they use large reflective sails that capture the momentum of photons—light particles emitted by the Sun—and convert this momentum into thrust. This allows the spacecraft to be able to direct its motion. Over time, the photons generate a small but continuous thrust, allowing for spacecraft to continue accelerating without needing onboard fuel. As space missions aim to be more efficient, depend less on fuel, travel farther, and extend their duration, solar sails offer a good alternative to traditional chemical propulsion.

As spacecraft are projected to undertake longer and more complex missions, the limitations of traditionally propelled spacecraft become increasingly apparent. Most research on solar sails centers around their design, material composition, and deployment. However, there is comparatively less information on how solar sails can enhance the maneuverability of a spacecraft. By analyzing the underlying physical principles of solar sails, new possibilities for spacecraft maneuvering open up, including long-term acceleration and station keeping. This would allow for new mission types that go beyond what traditional propulsion methods grant.

This paper focuses on how solar sails can improve the maneuverability of spacecraft through their continuous thrust and orientation, supported by historical context, physics principles, mission examples, and a discussion of limitations.

Methods

This review examines peer-reviewed scientific journals and other technical writing from various international space agencies that were published within the last 25 years and focuses on the novel technology of solar sails and how they can be utilized in the future for space missions. It is centered on how solar sails can enhance the maneuverability and mission potential of traditionally propelled spacecraft by harnessing photon momentum for continuous, fuel-free thrust. Studies were excluded if they were published before 2000, did not come from academic publications, or were written on spacecraft that did not use solar sails or their core principles. Eligible literature was identified using the following keywords: 'solar sailing', 'radiation pressure', 'solar sail boom technology', 'orbit control', 'Lagrange points', 'solar sail applications', 'advanced solar sails', and 'photonic momentum'.

Results

History

Although the concept of solar sailing has been around for centuries, it was not until the 20th century that engineers began to explore how it could be harnessed as a viable form of propulsion. As early as the 1600s, Johannes Kepler noticed that comet tails were always pointed away from the sun, and he thought that there must be some sort of solar "breeze" pushing them (Coulter). However, it wasn't until the late 1800s that James Clerk Maxwell was able to demonstrate that sunlight itself exerts a small pressure when its photons reflect off a surface. This pressure, dubbed radiation pressure, is the fundamental force behind modern solar sails, allowing continuous propulsion without fuel. Because sunlight is constantly in space, a solar sail has access to resources to keep generating its fuel indefinitely.

During the mid-20th century, scientists and engineers began testing this principle in space. In the 1960s and 70s, NASA observed that solar radiation pressure affected satellites and even used it for attitude control on the Mariner 10 spacecraft. They angled the solar arrays into the Sun and were able to make small adjustments that were amplified by a limited supply of gas-powered control thrusters. Even though Mariner was not designed as a solar sail mission, this experiment confirmed the underlying principle of solar sailing in space. In the closing decades of the 20th century, Dr. Louis Friedman at NASA's Jet Propulsion Laboratory initiated efforts to design a project that was meant to test the first real solar sail mission. Though the project was eventually canceled, the design work showed that solar sailing was a viable method for spacecraft propulsion.

One of the biggest demonstrations of solar sailing was the Interplanetary Kite-craft Accelerated by Radiation of the Sun (IKAROS) mission, which was launched by the Japanese Aerospace Exploration Agency (JAXA) in 2010. It was the first successful interplanetary solar sail mission, and it proved that sunlight alone could be used for controlled propulsion. IKAROS used a square 14-meter sail that was deployed by spinning to stretch out its thin membrane once in space (Tsuda et al.). During deployment, four extendable booms were unraveled from the spacecraft's body, which were used to pull the sail out and keep it tight. The controlled expansion prevented the sail from tearing and allowed it to reach its full area. The spacecraft also had flexible solar cells that had been built into the sail so that it would be able to generate electricity. Once fully deployed, IKAROS was able to steer itself by adjusting the reflective panels on the sail's edges, which showed that the sunlight pressure could influence its trajectory. This mission confirmed that solar sailing was more than just a theory—that it was a practical concept that could actually

work in space.

The success of IKAROS paved the way for future missions like NASA's Near-Earth Asteroid (NEA) Scout, and it also showed that solar sailing could be used to extend mission durations or reach areas that were not accessible by chemical propulsion (Planetary Society).

Physics

*Photonic Propulsion relies on the fundamental principle that light carries momentum—even though momentum can be calculated by mass*acceleration, and inherently light has no mass—which then can be transferred to other objects upon interaction, or, in the case of solar sailing, reflection. This process, known as photon momentum transfer, is the foundation of solar sail propulsion. When photons from the Sun hit a reflective surface, such as a solar sail, they exert a small and continuous force, otherwise known as radiation pressure. Although the force generated by a single photon is small, the cumulative effect of many photons results in a thrust that is capable of gradually accelerating a spacecraft over time. (Tsuda et al., 2013; Macdonald & McInnes, 2011). Solar sails' effectiveness is strongly dependent on the reflectivity of their surface. A highly reflective sail is able to produce nearly twice the thrust as a more absorbing surface since reflected photons transmit their momentum more efficiently. This is because reflection preserves the photon's energy for momentum transfer, while absorption may redirect a portion of that energy into other processes, such as the photoelectric effect. In the photoelectric effect, photons hitting the sail material may eject electrically charged particles when they absorb electromagnetic radiation. When the photon transfers energy to an electron, the electron can overcome the material's work function and be emitted. While this process can be used for generating electricity in other useful technologies like solar cells and imaging devices, it reduces*

the amount of momentum from the photon that would be able to thrust the sail forward. Therefore, maximizing reflectivity not only boosts the thrust the sail can generate, but it minimizes energy loss to absorption-based processes (The Editors of Encyclopedia Britannica).

Past research has shown that the orientation and the angle of the sail relative to the incoming sunlight—the sail angle kinematics—directly affects the direction of the applied force. By adjusting the sail angle, the spacecraft can steer through space without needing any onboard propellant, relying solely on the continuous momentum transfer from the sunlight. (Macdonald & McInnes, 2011; Coulter, 2020). Since the pressure from photons starts small and builds over time, solar sails have been found to be the most effective for long-duration interplanetary missions, where the small acceleration over extended periods is able to accumulate to produce significant changes in the spacecraft's velocity and trajectory. (Tsuda et al., 2013). Furthermore, the steady acceleration minimizes the stress that is put on sensitive instruments and mechanical components on the spacecraft, which increases the overall lifespan of the mission.

In addition to the effects of sail orientation and reflectivity, the efficiency of solar sails is also influenced by the surface area-to-mass ratio of the spacecraft. Larger and lighter sails can capture more photon momentum, which produces a greater acceleration, while heavier spacecraft experience smaller changes in velocity under the same amount of radiation pressure (Macdonald & McInnes, 2011).

By carefully designing sails with optimal reflectivity, surface area, and mass, engineers are able to maximize thrust while still being able to maintain fine control over their movement and

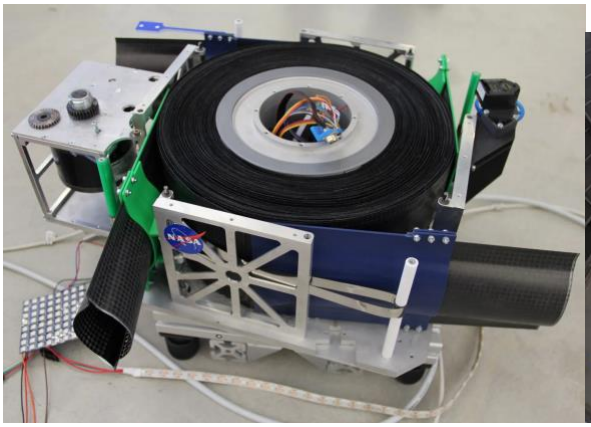
orientation. For example, the IKAROS mission was able to demonstrate solar sail propulsion using a thin, reflective sail to generate thrust and adjust its trajectory. This shows how the fundamental principles of photon momentum transfer can be practically applied in space exploration. (Tsuda et al.,2013; MacDonald & McInnes, 2011).

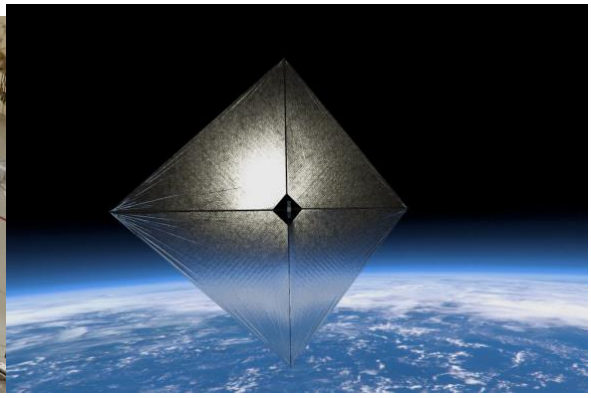
Novelty

Solar sailing introduces an entirely new approach to spacecraft propulsion, and with that come capabilities that are not possible with chemical or electric thrusters. Since solar sails harness the momentum of photons from the Sun—providing a continuous and near limitless source of thrust—opportunities for new mission types, greater flexibility in orbital control, and longer mission durations that would otherwise be impractical or impossible with fuel-based propulsion are created. In order to understand this new technology, we must look at how solar sails are able to expand deployment strategies, increase mission ranges, enable station-keeping at distinctive points in space, and even pave the way for new applications such as solar power farming.

One major novelty is in-space deployment. Traditional rockets carry spacecraft into orbit in compact forms to fit inside launch vehicles, which creates constraints on spacecraft sizing and design. Solar sails, on the other hand, are designed to unfold into giant reflective surfaces once already in orbit. For instance, JAXA's spacecraft, IKAROS, successfully deployed a 14-meter sail in 2010, showing that larger-scale deployment is feasible and that it has the ability to integrate thin-film solar cells directly into the sail's material (Tsuda et al., 2011). Other missions, such as LightSail 1 and 2, done by the Planetary Society, established that even CubeSat-scale—a 10x10x10cm satellite cube that typically weighs up to 1.33kg— could carry sails spacecraft that unfold in space, demonstrating the versatility of this deployment method

(The Planetary Society, "What is Solar Sailing?"; "What are SmallSats and CubeSats?" - NASA). This is a complete contrast to thruster-based propulsion, where spacecraft size and fuel storage have a strictly constrained design.





Solar Sails also redefine the picture of mission ranges. Conventional spacecraft, such as Voyager 1 and 2, depend entirely on limited fuel reserves for course corrections, meaning that their ability to maneuver adequately diminishes as they travel farther from Earth. In contrast, a solar sail's thrust, while small, is continuous as long as sunlight is available. Researchers such as Malcolm Macdonald and Colin McInnes, from the Advanced Space Concepts Laboratory at the University of Strathclyde, have highlighted how this continuous acceleration could allow sails to achieve interplanetary or even interstellar travel in ways that are unattainable with

chemical propulsion (Macdonald & McInnes, 2011). Although acceleration decreases with the distance from the sun, the assumed unlimited range makes solar sails specially suited for missions that would go beyond our solar system. Because of this infinite access to acceleration, a solar sail probe would be able to continue adjusting its path long after a conventional spacecraft, such as Voyager, would be left drifting in space.

*Another novel capability is station-keeping at Lagrange points. Lagrange points are specific locations in space where gravitational forces between two large celestial bodies—like the Sun and Earth—balance each other, creating stable points for objects to orbit. While traditional spacecraft can still orbit near Lagrange points, they require a precise thruster burn to maintain their stability. John Bookless, from the Department of Aerospace Engineering at the University of Glasgow, and McInnes demonstrated that solar sails can vary their orientation (pitch and yaw) to balance solar radiation pressure against gravitational forces, allowing them to essentially hover at manufactured equilibrium points, different from the natural Lagrange positions (*Bookless, John & Colin McInnes, 2006). *This opens up new opportunities for missions such as GeoSail, which was designed to study the Earth's magnetosphere by holding at Non-Keplerian orbits, which are impossible with a fuel-dependent spacecraft (Macdonald et al., 2007). Such precision positioning highlights a form of maneuverability that is unique to solar sailing.*

Mission longevity is another benefit tied to the novelty of solar sails. Since their propulsion doesn't depend on a finite fuel supply, mission durations are primarily limited by the integrity of the sail and the spacecraft systems, rather than propellant. For example, Dauna Coulter, a

former science writer at NASA Marshall Space Flight Center, notes that these recent developments could allow for multi-decade scientific missions that wouldn't have the same operational constraints as Voyager or Cassini, which both required careful fuel budgeting (Coulter, 2020). This advantage isn't just beneficial for operational durability, but also constructs the possibility of maintaining long-term monitoring of solar or planet environments.

Finally, researchers have proposed futuristic applications of solar sails, such as solar power farming. These "farms" would be sails equipped with photoelectric solar layers that can generate propulsion and harvest solar energy, and then transmit it to a spacecraft or station. While this is still theoretical, the idea builds upon the enormous surface area required for sails and demonstrates how their innovation extends beyond propulsion into multifunctional platforms. IKAROS hinted at this dual-purpose conception when it integrated solar cells into its reflective surface.

Overall, the novelty of solar sailing lies in more than just using sunlight for propulsion; it signifies an entirely new set of mission possibilities. From innovative deployment strategies to missions with unlimited range, precision station-keeping, extended longevity, and even multifunctional energy applications, solar sails provide possibilities beyond the capabilities of fuel-based spacecraft. And while it is still in its early stages of development, the missions to date demonstrate that solar sailing is not just a theoretical concept but a practical and expanding specialty in space exploration.

Various Missions

The development of solar sailing has been shaped by a series of different missions and conceptual studies that highlight the challenges and the potential of this technology. The earliest and most successful demonstration of solar sailing was IKAROS, launched by JAXA in 2010. IKAROS was the first spacecraft to be able to deploy a large sail in interplanetary space and used solar radiation pressure to generate a measurable thrust. Its sail, which was coated with thin-film solar cells, also showed how power generation can be integrated into the sail's surface (Tsuda et al., 2013).

Building on IKAROS's foundation, NASA's NanoSail-D2 mission tested solar sailing on a much smaller scale. As a part of a CubeSat in 2010, NanoSail-D2 deployed a 10m^2 sail from a compact satellite bus in a low part of Earth's orbit. Though the mission was short, it proved that even a miniature spacecraft would be able to successfully stow away and deploy a sail system, which opened up opportunities to low-cost testing of the sail technology (Johnson et al., NASA).

The Planetary Society's LightSail program also advanced solar sailing. LightSail 1, which was launched in 2015, tested mostly sail deployment mechanics in Earth's orbit, which confirmed that a spacecraft can stably put out a 32m^2 sail. Building on that, LightSail 2 launched in 2019 and was the first spacecraft to successfully change its orbit by only using momentum from the sun. By being able to adjust its sail orientation relative to the Sun, LightSail 2 showed that it could control its orbit, proving that photon pressure could provide effective propulsion for extended missions (The Planetary Society).

Going further than just deployed missions, there have been many proposals that exemplify how solar sailing could enable new kinds of space exploration. GeoSail was a proposed concept that would use a solar sail to hold a spacecraft in a displaced orbit, which would allow for

monitoring the Earth's magnetotail over a long duration. This wouldn't have been possible with traditional propulsion due to fuel limitations; however, thanks to the possibilities opened up by solar sailing, this is now a feasible project. Similar to this, CubeSat sail projects, using composite booms, continue to develop as scalable designs that can test deployment mechanisms and materials, showing how a small spacecraft is able to validate engineering ideas needed for larger sails deep in space.

Other concepts, such as PoleSitter, highlight solar sails' unique ability to hover over the Earth's poles, maintaining a constant view of high latitudes. This type of observation could revolutionize how we monitor polar climate and communicate, but it requires precise and continuous thrust that is only achievable through photon pressure (New Atlas, 2016).

Each of these missions showcases a new opportunity that solar sailing facilitates: starting from simple deployment tests in the Earth's orbit, to interplanetary demonstrations, and from theoretical mission proposals to operational spacecraft that have been able to fully function using nothing more than sunlight.

Discussion

Solar sails are a novel approach for space propulsion, one that relies on harnessing sunlight rather than onboard fuel, which allows for unprecedented opportunities for extended and efficient space missions. It has been shown that solar sails allow continuous and controllable thrust, enabling spacecraft to accelerate, maneuver, and maintain position without utilizing propellant. Through an examination of their historical development, physical principles, and demonstrated applications, it is apparent that solar sails have grown from a speculative concept to a proven and evolving technology.

Historically, solar sailing has progressed from Johannes Kepler's 17th-century observations of comet tails to James Clerk Maxwell's 19th-century proof of radiation pressure, up to successful modern missions like IKAROS and LightSail2. These major achievements exhibit both the persistence of the idea and the progressive overcoming of its engineering challenges. The physics behind solar sailing, photon momentum transfer, and radiation pressure allows for a unique form of propulsion that can operate indefinitely as long as sunlight is available. Control of thrust and direction from the sail angle adjustments further expands on the novel mission possibilities, from interplanetary travel to station keeping in orbital positions.

Because of the unique capabilities solar sails offer, spacecraft can evade the restricting factor of fuel mass and undertake missions that were previously unachievable with traditional propulsion. However, current limitations such as reduced acceleration with increased solar distance, large sail requirements, and vulnerability to micrometeoroids are challenges that need to be confronted.

Looking forward, further research into advanced sail materials, deployment mechanisms, and hybrid propulsion designs could improve the utility of solar sails and allow for integration into a wider array of space missions. Missions that are targeting the outer planets or deep space observation may soon rely on solar sails as a supplementary or primary propulsion system. By continuing to refine the technology and address its limitations, solar sailing has the potential to become a pillar of space missions, offering a sustainable and efficient pathway as we push farther into the cosmos.

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Evaluating Gels as a Wildfire Protection Strategy: An Investigation Into Their Efficiency in Structural and Household Applications

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Abstract

Wildfires are increasing throughout the nation, especially in places that experience drier-than-usual climates, and cause significant damage to both property and the environment. Traditional fire-protection methods are useful, but do not have a large impact on extinguishing fires. This creates a need for improved protection methods that provide reliable defense against fire. This research discusses the potential of fire-protective gels as a reliable solution to this issue. Specifically, this paper analyzes gel efficiency, chemical modification of gels, and performance when applied to building materials and textiles. This paper is primarily focused on certain gels, such as sodium bentonite gels, hydrogels, and modified gels, and evaluates fire resistance, degradation of the gel, and versatility of the gel. Findings show that while raw gels provide some degree of protection, they lack strength when compared to modified gels. Modifications such as additives or polymer chain alterations significantly improve yield stress, durability, and fire resistance. These gels are shown to be effective when applied to wall panels, fabrics, and textiles. Moreover, protective gel coatings demonstrate that gels can reduce fire spread while also improving energy efficiency through thermal insulation. In conclusion, fire-protective gels show benefits when compared to traditional fire-retardants. However, more studies and research must be conducted to allow these gels to achieve their full potential.

Evaluating Gels as a Wildfire Protection Strategy: An Investigation Into Their Efficiency in Structural Applications

Introduction

. Wildfires have been a recurring problem for humanity and have been increasing since the Industrial Revolution. Wildfires can occur due to natural or man-made causes, such as climate change, which has a significant impact on the environment and also puts lives and property at risk. In particular, in the US, there has been a 250% increase in wildfires from 2001 to 2020 and out of these wildfires, studies have shown that the number of homes catching fire in the US has increased by 46% from 1990 to 2020 (Lespier et al., 2025, para. 4). A solution to this problem would have meaningful societal impact,and reduce the potential risk of a massive wildfire harming the population. The overall objective of this paper is to investigate methods for reducing property and environmental damage from wildfires.

Specifically, this paper focuses on providing insight into how gels can be used to protect buildings from fires while also discussing how they can be used to the best of their ability. In past studies, gels have been found to have cooling factors and have been used in various applications, such as in the aerospace industry, where they are used to cool spacecraft components since they are able to endure high amounts of temperatures (Jin, Zhou, 2023). It is possible to take advantage of this cooling factor by applying gels to building structures as a fire-protective agent to help ensure these buildings do not catch on fire and are not damaged. Many gels protect against fires, but finding one that is long-lasting while adhering to other constraints is imperative. Testing these gels while replicating the real-world environment can give valuable data on these gels' behaviors and characteristics, so that they can be chemically modified to

provide better fire protection efficiency. Better fire protection efficiency leads to greater potential in saving buildings, homes, and other structures.

Overall, gels can provide fire protection when applied to the materials of a building, because they can act as a coolant whose fire efficiency can be enhanced by modifying their chemistry.

Fire Protection Efficiency

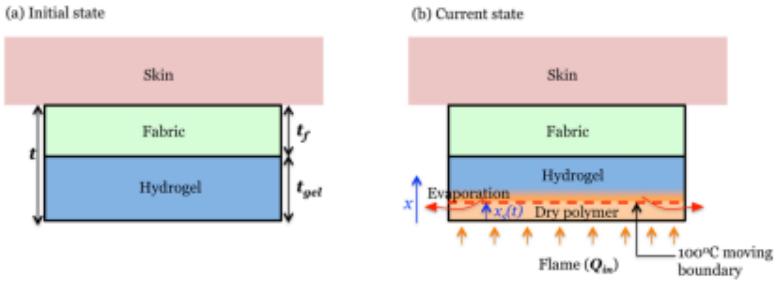

Figure 1: *Structure of how the lamination is built and what happens during a fire (Illeperuma, Vlassak, & Suo, 2016, Figure 1).*

Wildfires are not a one-time event; they occur throughout the year. As the global climate rises, the frequency of these wildfires increases. So, creating a gel that has advanced properties can increase the fire protection efficiency of these gels and better protect structures in the long run, reducing damage caused by wildfires. These gels act as barriers between the structure and the flames of the wildfire. As shown in Figure 1, the hydrogel is applied under the fabric such that when a fire occurs, it has to pass through the hydrogel before reaching the fabric. The gel acts as a barrier between the fire and the fabric and extinguishes or holds off the fire before it reaches the fabric. However, the gel's protective capabilities wear down over time and under extreme stress. The effectiveness of a gel depends on two key factors: resistance to degradation

and adaptability to different environments. Gel effectiveness is also dependent on parameters other than its baseline performance. Certain gels undergo chemical modification, giving them improved properties, enabling their reliable use in real-life emergencies. Properties that enhance fire protection efficiency include, but are not limited to, the water retention of the gel over time, and the yield stress of the gel. These indicate how well the gel performs when exposed to flames.

Research by Kadel et al. (2021) talks about a major limitation in current gel applications: the protective layer begins to degrade within hours of application due to low water retention. Their study emphasizes that fire-resistant gels should ideally be applied no more than three hours before the fire front arrives; otherwise, their performance drops significantly. This time-sensitive constraint puts pressure on first responders, who must time the application of gels or risk reduced fire resistance. In addition, while fire-resistant gels are beneficial in the short term, their inability to maintain performance over time diminishes their reliability in extended fire events.

Furthermore, a study by Mastalska et al. (2023) showed that gels used alone are insufficient for high-heat environments. These gels degrade quickly due to poor water retention unless combined with a compatible fire-retardant system that interacts with the underlying materials. This indicates that fire gels should not be used in their original form, but should be combined with other materials or chemicals in order to increase their effectiveness and prevent early degradation. Furthermore, these findings align with the broader theme that for gels to be truly efficient, their formula and application strategy must be changed. All in all, while gels offer valuable fire protection, their limitations and constraints with respect to durability and adaptability necessitate improvement in their design.

Additional research supports this need for design enhancement. Gregory et al. (2012)

showed that modifications to the sodium bentonite(SB) gel, such as adding starch (S), significantly improved the gel's yield stress, which improved fire protection efficiency. The modified SB gel + S sample showed almost ten times the yield stress compared to a commercial gel, indicating that structural changes can boost fire protection efficiency. This proves that gels are not the final solution and their properties can and should be tuned for better performance. Furthermore, Tafreshi et al. (1999) concluded that foams, in comparison to gels, tend to last longer, suggesting that gels still fall behind in long-term protection and must be improved if they are to achieve the same results as foam application.

Modification

One of the most effective ways to improve the performance of fire-protective gels is by modifying the gels to better suit protection needs. Raw gels will have some limitations in durability and fire-resistance, but by changing their chemical structure or by adding additives, researchers can enhance their fire-protective capabilities. These modifications enable control of the gel's properties through modification of various aspects, such as viscosity, thermal stability, degradation resistance under immense heat, and adaptability in interacting with surfaces other than the intended one. Clearly, if modified correctly to better suit the conditions in which it is being used, gels can be trusted and used as a reliable source of fire protection.

As one example of modification, Mastalska et al. (2023) talk about modifying the chemical structure of gels by altering polymer chains that change the sequence of the structure, and adding chemicals or additives to the structure which give the gels the desired fire-retardant properties. Without these modifications, many hydrogels degrade quickly when exposed to extreme environmental conditions and provide only short-term protection. Adjusting the gel's chemical structure creates a stronger, more heat-resistant material that is capable of withstanding

intense heat for a long amount of time. This demonstrates that modification is not just beneficial, but necessary to open the full potential of these gels in fire protection.

Further evidence of the modification's effectiveness is shown in the research of Gregory et al. (2012). Their research compared the performance of different gel samples, as shown in Figure 2 below. Specifically, Figure 2 shows that the SB Gel + S sample, which had starch included in the sodium-bentonite gel, showed a yield stress of 633 ± 30 Pa, compared to a yield stress of 66 ± 1 Pa in the raw form of the gel. This improvement in the score demonstrates the idea of how additives, such as starch, improve the gel's performance by making it more resistant to degradation under stress or heat.

Sample	Density (kg/m^3)	Comp. stress (Pa)	Yield stress σ (Pa)
SB foam	370	0.26 ± 0.03	235 ± 6
SB Foam+S	730	1.35 ± 0.07	403 ± 38
SB gel	1070	1.5 ± 0.2	400 ± 15
SB Gel+S	1070	1.3 ± 0.1	633 ± 30
Commercial gel	1080	0.24 ± 0.05	66 ± 1

Figure 2: Comparison of density, compressive stress, and yield stress in different gel samples (Gregory et al. 2012).

In summary, modification plays a critical role in enhancing the fire-protective efficiency of gels. Whether through chemical alterations at the molecular level or through the addition of materials like starch, these changes improve the strength, durability, and adaptability of gels. By modifying their structure and properties, researchers are able to overcome the limitations of raw gels, creating advanced materials that are more suitable for real-world fire safety applications.

Applications

Fire-protective gels have a wide range of applications that expand their usefulness in everyday use. These gels are applicable with respect to construction materials, textiles, and protective coatings. The versatility of these fire-resistant gels shows their potential to not only protect in wildfire situations but also for use as long-term fire-resistant solutions in houses and industrial spaces. By applying gels to various surfaces such as windows, roofing, and fabrics, homeowners and industries enhance safety while also improving energy efficiency, durability, and longevity of materials (Syphard, 2016).

For example, Joanna et al. (2022) describe hydrogel panels placed between wall panels to function as cooling layers. These layers not only provide thermal protection from outside heat, but also reduce the need for air conditioning by insulating and maintaining cooler indoor temperatures. In this application, gels serve multiple purposes, such as protecting buildings from potential fire exposure while also reducing the use of energy consumption which leads to cost savings. This demonstrates that the integration of hydrogels into building structures is capable of being sustainable while addressing both safety and environmental concerns.

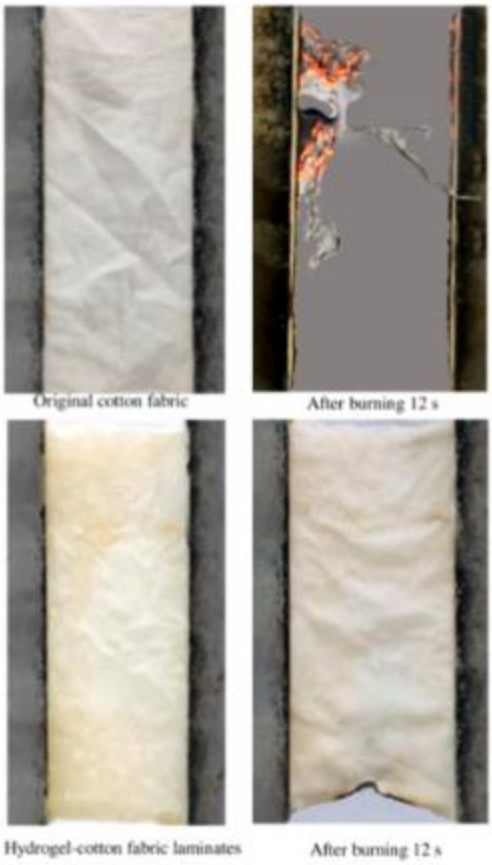

Figure 3: Fire resistance comparison of untreated and hydrogel-treated cotton fabric. The original cotton fabric (top row) burns through completely within 12 seconds, while the hydrogel-treated cotton fabric (bottom row) remains intact under the same conditions. Photo from Joanna et al. (2022)

Hydrogels have also been tested on textiles, demonstrating the capability for significant fire protection when applied to fabrics. Figure 3 shows that application of these gels (hydrogel in this case) has a significant impact on the fire-resistance of the fabric (Joanna et al., 2022). In particular, Figure 3 shows that without the application of hydrogel on the fabric, the cotton starts to burn after 12 seconds of exposure but when treated with the hydrogel, it stays intact and does not show signs of burning when subjected to the same exposure. As Joanna et al. (2022) discuss, this extended amount of resistance makes hydrogel-coated fabrics safer in the event of fire. In particular, this application shows how these gels can be impactful when it comes to protecting homes and the items within the homes, especially items that have a high risk of catching on fire

such as curtains, ceilings, or clothing.

All in all, these studies show that gels are not limited to emergency fire suppression but can be used in everyday environments and objects. Whether in walls, windows, or fabrics, hydrogels demonstrate versatility that could significantly improve fire resistance in homes and buildings. The evidence shows how effective gels can be in transforming ordinary materials into fire-resistant ones, demonstrating a future for wider applications of gel-based protection.

Conclusion

In summary, fire-protective gels are impressive technologies that are the focus of new research and have the potential to improve fire safety and sustainability. The importance of this research can be determined by its use in scenarios. As wildfires and fire risks increase around the world, the use of effective fire-protective technologies is needed to protect homes, buildings, and communities. Hydrogels not only have the potential to reduce property damage but also to provide environmentally friendly alternatives when compared to traditional foams and chemical fire-retardants. For instance, applications like cooling wall panels have the capabilities of reducing the use of air conditioning, which lowers the use of energy consumption and the release of greenhouse gas emissions. By improving the practice of fire safety for buildings while also promoting sustainability, hydrogels represent a material that correlates with the expectations of what they are intended to be used for.

This paper discusses both the strengths and weaknesses of fire-resistant gels. Gels provide meaningful short-term protection, but their performance wears out over time due to degradation, creating challenges for first responders and long-term applications. To combat this problem, modifying these gels gives the opportunity of altering the gel's characteristics. Methods

for gel modification include reconstructing chemical structures for more effectiveness and adding additives, such as starch, which can increase gel durability, yield stress, and resistance against fire. Finally, different forms of applications demonstrate the adaptability and versatility of gels, with research showing their successful integration of gels into wall panels, fabrics, and other everyday materials to make buildings more fire-resistant while also having environmental benefits such as reduced energy usage.

However, this research also has certain limitations. Current studies show that gels degrade quickly under prolonged heat exposure, limiting their long-term durability. Many experimental simulations conducted in a controlled environment faced challenges such as high costs, having to apply in a large surface, and durability in real-world conditions. Furthermore, the need for frequent reapplication of gels onto surfaces and building structures reduces its effectiveness during a wildfire. These limitations tell us that though gels have great potential, there is need for more research and development before they can be used as a first-line of fire-protective solution at a large scale.

Overall, the themes talked about in this paper—efficiency, modification, and applications— show that while fire-protective gels already provide good protection, their full capability can be discovered from continued research and innovation. With more advancements in modification and real-world testing in the future, fire-protective gels will become an important part of modern fire safety laws, protecting buildings, saving lives, and creating a safer environment. Future research should focus on improving these technologies for widespread use, making sure that they are both cost-effective and practical for large-scale fire protection.

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Integration of Active and Passive Safety Systems in Relation to Automotive Safety

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Abstract

Automotive safety commonly relies on two main functions – active systems that are designed to avoid collision, and passive systems that try to protect occupants when a collision is inevitable. Traditional safety designs treat these functions as independent, which limits their overall performance. With automotive injuries and fatalities remaining a global problem, the integration of these safety systems is a crucial topic. This study aims to analyze and compare different methods of integration seen throughout the last few decades as well as evaluate how these combined approaches improve safety system performance in both simulated and real-world environments. A selection of sources was reviewed, with each source demonstrating a unique integration method, ranging from algorithmic coordination to post-collision notification systems. Simulation data, performance metrics, and real-world test data from these studies were examined to assess the reliability of these hybrid systems. These studies proved that integrated systems outperformed isolated systems, with key findings including injury severity reductions, faster first responder deployment timings, safety system activation timings, and improved crash detection accuracy. The integration of active and passive safety systems represents a promising future in vehicle safety. Nevertheless, the prevalence of simulation-based studies underscores a need for detailed real-world testing. Further research and implementation of methods of integration offer pathways to progress the world of automotive engineering.

Integration of Active and Passive Safety Systems in Relation to Automotive Safety

Introduction

Occupant safety is a topic in the automotive industry that needs to be addressed, as almost 40,000 deaths have occurred in the US in 2024 from car accidents (NHTSA, 2025). Since car accidents are one of the leading causes of death in the world, the improvement of vehicular safety systems is vital. Active and passive safety systems are features on automobiles that work to prevent injury and death whenever using a car. Active safety systems are meant to prevent collisions from happening through features such as automatic emergency braking (AEB) and lane-keeping assist (LKA). Passive safety systems like seatbelts and crumple zones are meant to protect occupants in the event of a collision. Typical approaches to occupant safety have these systems working separately.

However, there are benefits to active and passive systems working in conjunction. While past studies have mentioned broad interpretations of methods to integrate active and passive safety systems, none have investigated how these methods of integration specifically performed in comparison to standard safety features. The objective of this paper is to evaluate the benefits of combining active and passive safety systems.

Overall, the integration of active and passive safety systems improves automotive safety for occupants.

Active and Passive Safety Systems

Active and passive safety systems are vehicle features designed to protect drivers and passengers on the road. Active safety systems are mechanisms that work to prevent accidents before they occur, while passive safety systems try to reduce the chance of injury once a collision has taken place or is certain to. Some familiar examples of active safety systems include

anti-lock braking systems (ABS) and lane departure warning (LDW), which most drivers rely on regularly. Lesser known, but still important active systems include automatic emergency braking (AEB) and electronic stability control (ESC), both of which use sensors and cameras to monitor road conditions and send alerts when the driver is not responsive enough.

On the other hand, passive safety systems are designed to protect occupants during a collision. Commonly recognized examples are airbags and seatbelt locking mechanisms, but other passive safety systems such as crumple zones, which absorb impact energy by crushing in a certain way, play an important role in reducing fatalities. By examining the effects that result from the implementation of active and passive safety systems, it becomes clear that both active and passive safety systems play crucial roles in improving vehicle safety.

Studies by the Insurance Institute for Highway Safety (IIHS) and National Highway Traffic Safety Administration (NHTSA) have shown that vehicles equipped with AEB experience 50% fewer front-to-rear collisions than those without the system (IIHS, 2020), while ESC has reduced fatal single-vehicle crashes by more than 50% (IIHS, 2024; NHTSA, 2011). Passive systems show similar levels of impact: the NHTSA estimates that airbags have saved over 50,000 lives in the United States since their introduction (NHTSA, 2024), and the creation of seatbelt pretensioners, which are mechanisms within seatbelts that are designed to tighten seatbelts in case of a collision or rapid deceleration, has decreased the risk of serious injury in front-end crashes by nearly half (NHTSA, 2007). These statistics make it clear that both active and passive safety systems improve occupant safety. While each distinct system has proven to be effective, the integration of active and passive systems has potential for bigger advancements in road safety.

Integration Methods

In the past few decades, numerous researchers have investigated active and passive safety system integration. For example, Wallner focused on timing as the main factor in effective integration. Their integration method primarily relies on optimizing trigger timings between active safety systems and passive safety systems by having active functions such as ESC and LDW notify, and in turn activating passive systems such as airbags and seatbelt tensioners. The trigger timings are optimized by developing an algorithm that calculates force levels and activation times of the adaptive restraint system. This results in a system capable of triggering both active and passive mechanisms with precision, in turn being able to reduce the occupant's acceleration during a crash. This method of integration tends to deploy quicker than standard vehicle safety features (Wallner, 2009).

Similarly, Kuttenberger pursued a more direct coordination between systems by linking stability control with airbags. In Kuttenberger's model, active safety functions such as the electronic stability program (ESP) and components of the electronic control unit (ECU) were able to trigger passive mechanisms such as airbags and seatbelt tensioners through radiowaves and signals in different crash scenarios, ranging from poles to roadways, ensuring quicker deployment of these passive safety systems when control was lost (Kuttenberger, 2006). Both Wallner's and Kuttenberger's studies investigated the benefits and effectiveness of improving reaction times between active functions and passive safety systems and highlighted the benefits of coupling real-time active interventions with passive protection measures.

In contrast, Kaniathra directed attention to the period immediately following a crash. Kaniathra implemented an automated collision notification (ACN) system that relies on pre-existing crash sensors already installed in cars such as motion detection systems. These sensors

detect variables such as the change in vehicle velocity, Δv. If Δv changes value at a rate faster than a given threshold, the ACN system triggers and relays crash data to emergency services, allowing for faster response times and immediate aid upon arrival–creating a system between sensors and medical aid (Kaniathra, 2001).

Other researchers have approached integration from a software and data perspective. Cisneros emphasized system requirements for integration, outlining both functional and non-functional aspects of a post-collision software framework. By applying a verification language, which is a program used to compile and validate data, Cisneros designed a system capable of analyzing performance after crashes, illustrating the potential of software to improve integration (Cisneros, 2021). Building on this analytical approach, Shi constructed a combined database of active and passive safety features. This database was then used to examine cross-influences between systems, particularly their impact on pedestrian head injury criterion (HIC), which measures the likelihood of a head injury during an impact, like a car crash. HIC values below 650 generally indicate a low risk of injury, whereas HIC values above 1000 indicate high risks of head injuries. Shi developed equations and proposed a hierarchical design strategy involving starting with common passive safety systems and analyzing different components of these systems, breaking down their functions and trigger parameters, showing how data-driven models could refine integration strategies at a systematic level (Shi, 2024). Finally, Page offered a simpler method by layering active safety technologies such as LDW and AEB onto vehicles already equipped with passive systems such as seatbelts and airbags. While less complex than algorithmic or data-driven approaches, this model underscored the practical feasibility of incremental improvements (Page, 2009).

Together, these studies show these integration strategies, ranging from precise timing

algorithms and coordinated triggering mechanisms to software frameworks, data modeling, and incremental additions. Their collective findings show that active and passive safety integration is not limited to a single pathway. Instead, progress arises from both comprehensive redesigns and smaller, practical adaptations.

Performance

Although many methods for active and passive safety system integration have been created, they yield different results. Wallner's simulations, as seen in Figure 1, demonstrated advances in safety performance, with improvements reaching as high as 90% (Wallner, 2009).

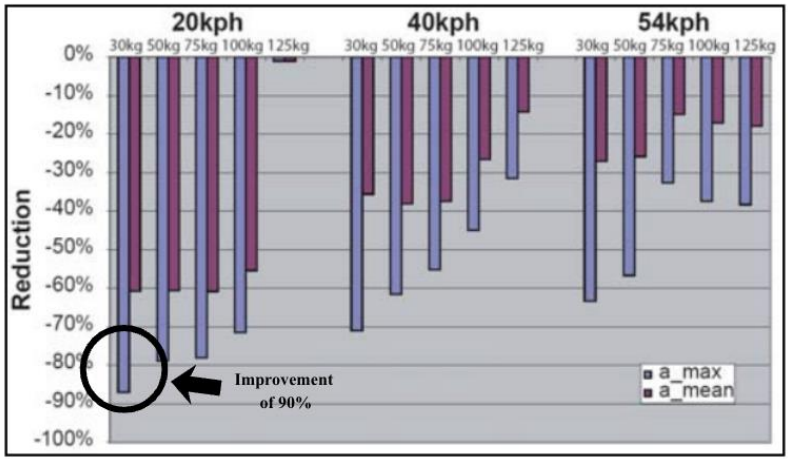

Figure 1: How the highest and average acceleration of the occupant decrease at different crash speeds and occupant weights (Wallner, 2009).

This result emphasizes that even minor optimizations in crash dynamics translate into reductions in injury severity. These findings show that active and passive safety system integration is not only feasible, but also capable of delivering results on a scale far beyond what isolated systems achieve. Similarly, Shi's research produced compelling performance results in terms of injury reduction. Their simulations showed that pedestrian HIC values dropped from 1790.8 to 756.92 when airbags were included, a reduction of more than half (Shi, 2024). Additional improvements in braking further decreased injuries from ground contact. These results demonstrate not only the magnitude of possible safety gains, but also the broader scope of integration since performance

was not limited to occupants inside the vehicle but extended to vulnerable road users outside of it, making the case for integration even stronger.

The performance outcomes for Kaniathra's ACN system underscored the importance of rapid emergency response. Vehicles with ACN consistently transmitted crash alerts in under two minutes, while those without the system required over five (Kaniathra, 2001). Although the system's overall success rate was 76%, the time savings alone were enough to significantly improve survivability by enabling faster medical aid (Kaniathra, 2001). The performance of the ACN proved that integration does not always need to focus on crash avoidance or impact mitigation; rather, its effectiveness can also be measured in post-collision lives saved.

Kuttenberger's combined active and passive safety system was evaluated in both simulations and real-world data, and the results pointed to consistently improved occupant outcomes. By coordinating inputs such as active sensors and allowing these sensors to directly communicate with and trigger passive restraint systems like airbags or seatbelt pretensioners, the combined active and passive safety (CAPS) approach reduced lag times in protection and produced measurable decreases in occupant injury severity (Kuttenberger, 2006). In Kuttenberger's CAPS model, the vehicle's active control systems continuously monitored parameters such as yaw rate, steering angle, and lateral acceleration. When instability or a collision risk was detected, those signals were immediately transmitted to passive subsystems, prompting them to begin pre-deployment or adjust their timing to better match the vehicle's dynamic state. Its performance was significant as it demonstrated that reliability could be achieved not only in testing but also in stochastic, real-world conditions.

Cisneros's framework was assessed through verification testing, which are simulated runs designed to be as accurate to real world standards as possible. Results showed that the integrated

software consistently met its functional and non-functional requirements (Cisneros, 2021). The functional requirements referred to the system's ability to perform its core safety tasks, such as detecting potential collisions, activating the correct passive responses, and maintaining real-time communication between active and passive modules. The non-functional requirements involved broader performance qualities like reliability, stability, and fault tolerance. Since the system was shown to meet these requirements, the system is concluded to behave predictably under various crash circumstances.

Page's comparative analysis revealed the large-scale benefits that result from simple integration strategies. Their findings suggested that if vehicles from the early 2000s had been equipped with technologies such as ESC and EBA, severe injuries could have been reduced by 47.2% and fatal injuries by 69.5% (Page, 2009). Page's results demonstrated that even modest steps towards integrating active safety measures could have had real-world impact, saving thousands of lives at the time. Page's work indicated that the true potential of these systems lies in their accessibility and application across entire vehicle models.

Conclusion

Through the analysis of these sources, it's clear that the combination of active and passive safety features enhances the protection of vehicle occupants. Active systems, designed to prevent accidents or mitigate their severity, and passive systems, intended to protect occupants during a crash, each play vital, but limited roles on their own. When integrated, their strengths are improved, offering drivers and passengers a greater margin of safety than either could achieve independently.

The research seen in this literature review results in three central takeaways. First, the idea of active and passive safety systems and their functions are vital, with active systems

addressing pre-crash scenarios while passive mechanisms provide post-crash protection. Second, the different methods of integration seen throughout sources, ranging from notification systems to timing efficiency, all contribute to providing increased safety to occupants. Third, the results from these improved safety features, which all showed major signs of growth in the field of automotive safety.

The automotive industry is a leading cause of injury and fatalities worldwide, meaning every advancement made, major or minor, regarding automotive safety has the potential to impact, and save the lives of millions of people. The findings seen throughout this paper highlight the benefits associated with the integration of active and passive safety systems and show that pursuing more efficient methods of integration is crucial to creating safer roads. However, limitations remain and have been presented throughout this paper. For example, many sources and integration methods analyzed come from simulations as opposed to real world testing. Therefore, the environments in which most of these studies originate from are controlled, meaning these results have not been proven in real-world scenarios. This limitation necessitates further validation in broader environments and field testing.

In the future, research should be conducted beyond just simulation data. Long-term and observational studies should be used more frequently. More emphasis should be placed on research regarding these methods of integration, and certain laws regarding the requirements of this integration should be pushed for. Education regarding these systems and how they work should be prioritized, as every driver or occupant should be aware of how they are protected on the road. By following these ideas, the automotive industry will continue making strides towards the innovation of safety features.

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Generative Artificial Intelligence and Adolescent Writing Education

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Abstract

Generative Artificial Intelligence (AI) platforms such as ChatGPT and Google's Gemini are now easily accessible for students as they begin to learn crucial topics in the English language. These AI chatbots are being used to help brainstorm ideas or to generate complete essays. This study aims to evaluate the effects of using AI tools on adolescents in English education. Ten research papers were reviewed in order to determine both positive and negative impacts of AI on adolescents. When used to supplement creativity, it was found that generative AI can grow student enthusiasm and confidence in their work. Students are enthusiastic about the use of AI to personalize writing education because they are able to test their ideas before actually committing to them. However, many studies revealed that the tool can be overused, leading to weaker writing and lower self-efficacy. Additionally, the use of generative AI in writing raises ethical questions about academic dishonesty—a topic that teachers and their adolescent students do not yet agree on. Generative AI poses various beneficial and detrimental effects depending on how it is used. In order to help adolescent students succeed in writing education, AI can be a useful tool when used in an ethical, regulated way.

Generative Artificial Intelligence and Adolescent Writing Education

Introduction

As the use of generative Artificial Intelligence (AI) increases, adolescent students are gaining access and using it to supplement education. It is necessary to understand the potential positives and negatives of this new factor in order to use it beneficially in schools. One positive example of AI use is by teachers quickly creating interactive slideshows for lessons with colorful text and detailed images. However, a negative use might be students using it to generate essays without personal input.

Generative AI is a form of Artificial Intelligence that uses human prompts to create original text, images, and audio. In an educational setting, this tool is used to create personalized, stimulating lessons or as a one-on-one teaching assistant. Therefore, it is important to understand if generative AI has an impact on writing education for adolescent students. Writing education entails creativity, reading comprehension, and student engagement with their work. It is important to research this topic as it pertains to adolescent students because their use of AI may impact their ability to write on their own in the future.

It is key to explore the positive and negative effects it poses in order to understand if AI can be used ethically in writing education. The purpose of this paper is to identify the impacts of generative AI on students and how it can be used ethically in schools, with the objective of helping future researchers discover how it can be implemented ethically to benefit writing education. This paper covers ten peer-reviewed research studies that were conducted on the effects of AI in the classroom to answer the question of how generative AI affects writing education in adolescent students. These studies found various benefits as well as harms that resulted from the generative technology. While AI begins impacting education, it is imperative

that educators understand the variety of effects that it may have on students and their writing abilities. With both positive and negative potentials, AI's educational influence must be understood in its entirety so that students do not struggle in writing later on.

The benefits of using generative AI in writing education

It is important to understand the positive potentials of AI in order to fairly evaluate the impact it can have on student education. As educators began to adapt their teaching styles to include generative AI, many students have responded well. AI has brought positive change to the classroom when used by teachers to create interactive, original lessons. In a study by Jauhiainen et al. (2023) that used an AI-generated writing lesson, only one out of ten students did not enjoy learning the material. Positive student reactions like this to generative AI would make its future implementation simpler, allowing students to utilize its benefits.

AI-generated lessons improve student confidence

Generative AI has allowed for lessons in the classroom to be personalized, benefitting each individual student's needs. In an experiment conducted by Wu et al. (2025), it was found that AI can serve as a "cognitive scaffold" (Wu et al., 2025, p.15). This means that it can adapt in order to individualize each student's learning. Students felt more confident in their work with this personalized help, which resulted in greater creativity and innovation while writing. A study by Wang et al. (2025) found that AI instruction during a lesson on challenging poetry improved student interest in the material, led to greater collaboration amongst each other, and caused a higher inclination to take on challenges. These positive changes to student confidence reveal that generative AI can be used beneficially in education as a learning assistant. When used to support a student's personal needs, AI acts as a teacher to provide specific suggestions and stimulating statements that raise student confidence in their writing.

Generative AI enhances student creativity

Able to create images and advanced writing, generative AI can be used by students in unexpected ways. In a study by Han et al. (2024), adolescent students were tasked with using text-to-image generative AI to create a short story. After making use of ChatGPT, students were surprised by its abilities. One stated, “I can use this to test out many of my ideas” (Han et al., 2024, p.8). This reveals how AI can be utilized to supplement student creativity by allowing visualization of thoughts and providing students with the ability to test which ideas will be successful. Additionally, the study found that when generated images were not ideal, students who were provoked to narrow their language further developed specific ideas to create better results. This highlights how generative AI chatbots can be used to improve student articulation skills.

Students are enthusiastic

When given new tools to try out, adolescent students are excited by unknown possibilities. In a 2023 study by Jauhiainen et al., middle school students participated in writing lessons created and altered by generative AI powered by ChatGPT. It was recorded that most participants enjoyed learning the material generated by AI. This emphasizes how easy AI could be to implement due to its positive reception by students. Student enthusiasm to learn with AI translates into their understanding of the technology. In a study of the effects of generative AI on student engagement by Wu et al. (2025), it was found that early use of AI results in a stronger digital literacy. In other words, when exposed to advanced technology at a younger age, students were found to be more well-versed in its utilization. Keeping these positive effects in mind, it is also necessary to weigh the negative impacts of generative AI use. When incorrectly used, the tool might actually do more harm for adolescents than good.

Student overreliance on generative AI in writing education

When students begin to implement generative AI because they think it will help them produce better writing, some may actually be harmed by it. The use of AI is something that students are not always able to avoid, which can cause serious harm to their self-creativity. If adolescents begin to rely too heavily on generative AI to help them formulate ideas and/or write, they may never develop the skills necessary to write successfully on their own in the future.

Students avoid critical thinking

Although generative AI can be used to guide students through their thinking process, it may also be taken advantage of. When used to supplement creativity, a student might plug in brief questions or their own ideas for confirmation from an AI chatbot to help with the writing process. However, recent advanced models of AI, such as ChatGPT-5.0, can generate page-long essays with just a short prompt. When used to bypass a student's own thinking entirely, major difficulties can result in that adolescent's ability to think critically and creatively in order to produce original writing over time. A 2025 study by Wang et al. reveals how students use generative AI to help them answer a set of questions. Instead of checking over their own work or verifying their ideas, over half of the participants simply plugged in the entire question. This reveals how students are using generative AI to move quickly through their work, completely avoiding their own thinking process. If AI is repeatedly used in this way, adolescent students may never develop the vital ability to think creatively on their own, which would impact their ability to write effectively.

Dependence on AI further impairs writing skills

When given the ability to use generative AI for writing help, students who are less confident in their abilities are more likely to take advantage of the tool. A study by Pitts et al. in

2025 measured different types of writing students' reliance on generative AI. Those who showed overreliance on the tool were significantly correlated with feelings of trust and satisfaction after using it, while those who did not rely much on the AI bot correlated positively with higher literacy and self-efficacy. This suggests that the kinds of students who are more inclined to use AI are likely to be the same students who develop a dependency on it. Although these students may view generative AI as a helpful and supportive tool, they may actually be taking advantage of it, which could damage their own writing abilities. This idea is further developed in a study from 2024 by Klarin et al. that explored different adolescents' perceived usefulness of generative AI while writing. This research revealed that adolescent students who face challenges with their executive function (EF), found that generative AI was a very useful tool that helped their writing. This raises concerns about the types of students who are utilizing it. If students with a low EF start to rely heavily on generative AI to write, they might never be able to improve their EF, as they are not exercising it enough.

Increase of academic dishonesty

As adolescent students use generative AI to support their writing, they may be plagiarizing without knowing it. Taking AI-generated text from chatbots such as Gemini or Perplexity and submitting it as one's own has resulted in a dramatic increase in academic dishonesty among adolescent students. This raises many concerns over how generative AI can be utilized ethically by students in writing education.

Students' perspectives on academic integrity

When using generative AI on writing assignments, most adolescent students are not thinking about the ethical implications of their actions. With hours of homework, many students want to complete their work as soon as possible. A study by Tindle et al. from 2023 explored

adolescents' perspectives on academic dishonesty, plagiarism while writing, and using generative AI to cheat. It was found that students with misconduct intentions were 50% less likely to view the use of AI as cheating. This highlights that different students may have various outlooks on their use of generative AI. It is important to establish a universal idea of plagiarism and cheating in the classroom so that students can use generative AI ethically while writing and completing assignments.

Teachers' perspectives on academic integrity

While students are using generative AI to create ideas, writing strategies, or, more extremely, essays, teachers are developing their own views on the topic. Despite AI detection tools, it is very difficult to tell if a student has truly used generative AI in their essays. In a 2023 research study by Mohammadkarimi, teacher perspectives on the use of Artificial Intelligence in writing classes were recorded. It was determined that teachers unanimously agreed upon the fact that AI has had a negative influence on students and their commitment to academic honesty. Teachers believe that adolescent use of generative AI to bypass writing enables them to plagiarize and limits their skill development (Mohammadkarimi, 2023). This clearly conveys how adolescent teachers are wary of the use of AI, mainly due to its impact on cheating.

Opposing views

Teachers and students seem to have conflicting viewpoints on what is classified as academic dishonesty when it comes to generative AI. A study by Lee et al. from 2024 found that the heaviest use of generative AI by writing students is for generating ideas to help with writing papers and assignments. While students may not view this as cheating, teachers feel that their students are finding a way around thinking creatively. These teachers want their students to learn how to develop ideas on their own in order to improve their writing skills. It is necessary for

teachers and students to come to an agreement on an ethical use for generative AI in order to establish fair rules for its usage in writing education.

Conclusion

It is necessary to understand both the positive and negative effects that generative AI can have on student writing before it is implemented into various aspects of education. This is especially important because generative AI is a growing field that many people do not yet fully understand. By looking closely at its immediate effects on writing education, this paper analyzed ten research studies that found many advantages and risks that the AI tool poses in order to begin to evaluate how it can be used ethically in schools.

When students use generative AI to supplement their writing, it can be a major confidence boost, allowing them to produce stronger work that they are proud of. AI can enhance student creativity by giving adolescents the ability to test out their ideas while planning a writing piece, leading to successful imaginative thinking. With student enthusiasm towards AI and growing digital literacy, it will not be difficult to implement this new writing tool. However, generative AI can be taken advantage of, leading adolescent students to succumb to its harms.

Although some students may use AI to guide them through thinking creatively, some use it to avoid the experience altogether, which could lead to detrimental effects in their quality of writing and ability to think critically on their own. Similarly, overuse of generative AI in students who already have weak writing can worsen their abilities. Students and teachers have increasingly different ideas of what qualifies as plagiarism, which are further highlighted as students begin using generative AI in their writing. In order to combat academic dishonesty in writing education, it is necessary to develop universally agreed-upon rules around the use of generative AI.

Since generative AI is a new and growing tool, very little research has been conducted on its long-term effects. Therefore, this paper can only discuss the impact of generative AI thus far in its development. Additionally, this paper specifically analyzes the effects of generative AI on adolescent writing education. The effects of AI may change across age groups and subject matters. Many of the studies evaluated in this paper used similar methods of evaluating generative AI's impact on adolescent writers by using AI to create a lesson. There may be other possible uses of generative AI that would warrant other effects.

It is important that further research is conducted on the long-term effects of generative AI on writing quality before it is implemented into adolescent education. Future research must be done in order to evaluate the effects of AI on adolescent education in fields outside of writing. Generative AI may pose different impacts on subjects that require less creativity, such as mathematics or history. Moreover, students in higher education might receive different effects of AI compared to adolescents whose brains are still developing. It is also important that a larger variety of educational uses of generative AI are evaluated in order to better understand if it can be implemented beneficially. Student use of generative AI in their writing poses many ethical questions related to academic dishonesty. It is necessary that school policies outline what does and does not constitute plagiarism so that AI can be used fairly in a way agreed upon by students and their educators.

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Dysregulation of the mTOR Signaling Pathway in Alzheimer's Disease: Contributions to Synaptic Loss, Impaired Autophagy, and Tau Pathology

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Abstract

Alzheimer's disease is a progressive neurodegenerative disorder characterized by cognitive decline, synaptic loss, and the accumulation of toxic proteins such as amyloid-β (Aβ) and tau. Recent research has identified dysregulation of the mechanistic target of rapamycin (mTOR) signaling pathway as a central mechanism driving these pathological changes. Under normal conditions, mTORC1 is responsible for regulating autophagy, protein synthesis and neuronal energy acquisition. However, when mTORC1 becomes hyperactivated, autophagy is suppressed, leading to the accumulation of misfolded proteins and impaired waste clearance. This dysfunction contributes to early synaptic loss, accelerated tau hyperphosphorylation and disrupted cellular homeostasis. Hyperactive mTOR also disrupts the NiMA signaling pathway, promoting mitochondrial poisoning, oxidative stress, calcium ion imbalance, which further weaken neuronal survival. Evidence from pre-clinical animal studies shows that pharmacological inhibition of mTOR with rapamycin can restore autophagy, prevent synaptic loss, and reduce Aβ and tau burden. Despite these promising preclinical findings, clinical translation remains limited, highlighting a niche for future research targeting the effects of rapamycin in individuals living with Alzheimer's disease. Understanding how mTORC1 dysregulation drives autophagy impairment, tau pathology, and synaptic loss may guide the development of targeted therapies capable of slowing or preventing the progression of Alzheimer's disease.

Dysregulation of the mTOR Signaling Pathway in Alzheimer's Disease: Contributions to Synaptic Loss, Impaired Autophagy, and Tau Pathology

Introduction

Alzheimer's disease (AD) is a neurodegenerative disorder most commonly expressed in the elderly, ranging from age 65 and up. About 6.7 million people live in the United States, and 55 million people worldwide live with a diagnosis of AD. By 2050, this number is projected to increase by 12.7 million people in the United States alone (W.H.O.). The disease is characterized by progressive cognitive decline, memory loss, mood disorder, confusion, and loss of executive functioning. These symptoms are accompanied by physiological hallmarks such as the buildup of misfolded proteins (neurofibrillary tau tangles (NFT) and Amyloid Beta (Aβ) Plaques, synaptic loss, and changes to sulci and gyri formations (Davoody et al., 2024). Despite decades of research, there is no curative treatment for AD. Although there are therapeutic interventions available, their benefits are limited to improving mood disorders and have no effect on cognition. This lack of curative intervention demonstrates the importance of understanding the cellular and molecular mechanisms behind AD pathology. This understanding may open the door to more targetive therapies and treatments.

One major pathway that is currently being studied is the mechanistic target of rapamycin (mTOR) (Davoody et al., 2024). It is responsible for cellular growth, protein synthesis, energy usage and autophagy, which are key processes to ensure cellular survival (Bloom et al., 2024). Within mTOR, there are two major complexes, mTORC1 and mTORC2. Of these, mTORC1 is directly implicated in the pathology of AD, as it inhibits autophagy and regulates protein

turnover (Davoody et al., 2024). During normal function, mTORC1 will promote cell growth, protein production and waste clearance. However, when dysregulated, it reduces autophagy and causes waste buildup. This contributes to the accumulation of NFT and Aβ plaques, which lead to a loss of energy production, false cell cycle re-entry and neuronal death (Bloom et al., 2024).

Recent clinical trials in animal models of AD have demonstrated that inhibition of the mTOR pathway with rapamycin can mitigate the development of its classical pathological features (Spilman et al., 2010). Rapamycin treatment has been shown to reduce Aβ plaque buildup and restore autophagy and protect against synaptic and neuronal loss in the hippocampus and cortex (Ma et al., 2010). These findings suggest that mTOR dysregulation may not only contribute to the onset of AD pathology, but may also represent a viable target in therapeutic and clinical intervention.

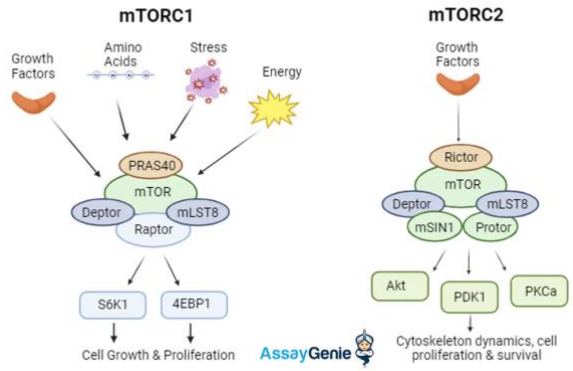

Fig. 1: Model of the mTORC1 and mTORC2 functions and protein makeup. From "Davoody, S., Asgari Taei, A., Khodabakhsh, P., & Dargahi, L. (2024). mTOR signaling and Alzheimer's disease: What we know and where we are?. *CNS neuroscience & therapeutics*, *30*(4), e14463. https://doi.org/10.1111/cns.14463"

This paper seeks to investigate the central question: How does dysregulation of the mTOR signaling pathway contribute to synaptic loss, impaired autophagy, and tau pathology in individuals diagnosed with AD? Understanding mechanisms by which mTOR pathway dysfunction drives these processes may guide the development of targeted treatments and inform the design of future clinical trials which may slow or prevent the progression of AD.

Synaptic Loss and mTOR Dysregulation

One of the earliest hallmarks within AD can be seen in the case of synaptic loss, which strongly correlates with cognitive decline and memory impairment. In normal neurons, synaptic plasticity and synaptic pruning are regulated by the mTOR pathway. In particular, mTORC1 balances protein synthesis and autophagy, which supports remodeling of synapses according to their neuronal activity. Synaptic pruning ensures that weak synapses are eliminated to redirect energy towards neurons exhibiting stronger neuronal activity, often this leads to the preservation of essential neurons for memory and learning (Davoody et al., 2024). However, when the mTOR pathway is hyperactivated, excessive mTORC1 will block autophagy and prevent the clearance of misfolded proteins, which disrupts the mechanisms required for maintaining synaptic health.

Animal studies have shown that dysregulation of mTORC1 via the mTOR pathway will induce impaired synaptic plasticity in brain regions critical for memory (Ma et al., 2010). Additionally, chronic stress has been known to upregulate mTORC1 activity in the hippocampus, which contributes to cortical atrophy, synaptic loss, and associated depressive behaviors (Luo et al., 2021). These findings reveal how environmental factors such as stress can hijack the mTOR pathway and contribute to hippocampal vulnerability and neurodegeneration within AD. Additional research has discovered that loss of mTORC1 dependent macroautophagy results in impaired synaptic pruning, leading to unstable synapses and abnormal circuit formation (Tang et al., 2014). This research demonstrates that when autophagy is suppressed, it results in the accumulation of dysfunctional synapses and undermines neuronal communication.

At the molecular level, nutrient induced mitochondrial activity (NiMA) is another critical factor for linking mTOR dysregulation to synaptic degeneration. NiMA is a cellular process through the activation of lysosome mTORC1 by nutrients or insulin. Normally, NiMA serves to upregulate mitochondrial activity which prevents mitochondrial poisoning and regulates calcium balance, which are both essential for synaptic health (Bloom et al., 2024). In AD, tau inhibits NiMA, leading to mitochondrial dysfunction and loss of ATP production necessary for sustaining synaptic activity. Without their energy supply, synapses are weakened and degenerate more rapidly. Furthermore, this creates a positive feedback loop, in which mTORC1 hyperactivation suppresses autophagy and inhibits waste signaling, allowing for the build-up of misfolded tau protein, inhibiting NiMA, and further disrupting mitochondrial function (Bloom et al., 2024). Together, these combined effects accelerate synaptic collapse that promote loss of cognition within AD patients.

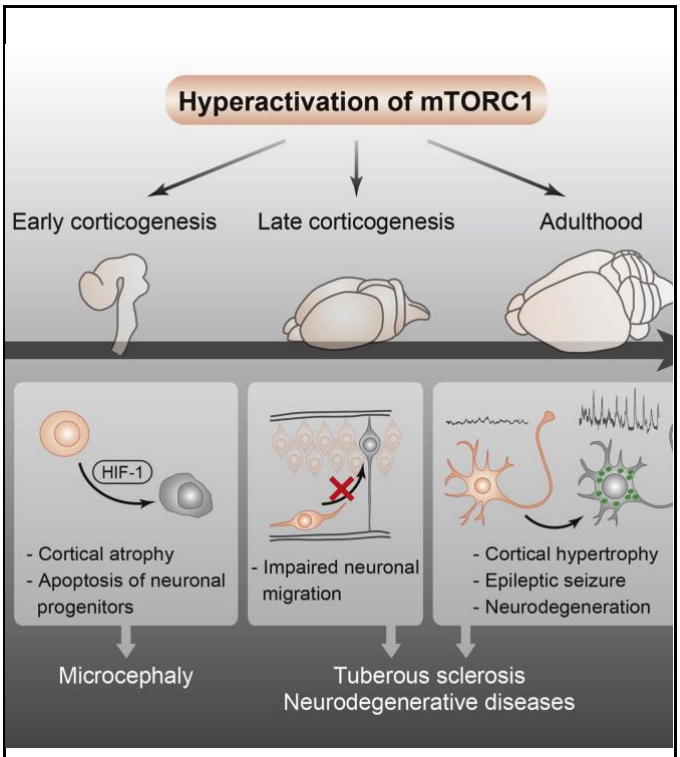

Fig. 2: Model of mTORC1 hyperactivation progression and the effects leading towards neurodegeneration. From "Gitto, S. B., & Altomare, D. A. (2015). Recent insights into the pathophysiology of mTOR pathway dysregulation. *Research and Reports in Biology*, *6*, 1–16. https://doi.org/10.2147/RRB.S57088".

These findings indicate that synaptic loss within AD is not simply a byproduct of neurodegeneration, but is a direct consequence of mTORC1 pathway dysregulation. By interfering with pruning mechanisms, protein function, mitochondrial function and synaptic

signaling, hyperactive mTOR undermines neuronal pathways responsible for memory and learning. More importantly, synaptic loss often precedes widespread neuronal death. Additionally, as these synapses deteriorate, AD patients experience increased loss of memory and reasoning, along with higher rates of biological and psychological symptoms of dementia (BPSD), including mood disorder, depression, agitation, and anxiety (Altomari et al., 2021). These changes stem in part from the disruption of neurotransmitter (NT) release and signaling between neurons, which destabilizes communication across brain circuits. Although preclinical studies suggest that pharmaceutical agents such as Rapamycin may protect synapses by restoring autophagic homeostasis, unfortunately, there is a lack of effective protective agents currently undergoing clinical studies (Kuo et al., 2019). Ultimately, understanding the connection between mTOR dysfunction and synaptic loss may become essential going forward to the process of designing therapies that preserve cognitive function and behavior within AD patients.

Impaired Autophagy and Waste Clearance

Autophagy is a process by which organisms clear out waste buildup from cells, including misfolded proteins and damaged organelles, which is essential for maintaining neuronal health. In normal conditions, if there is an abundant amount of nutrients, then the mTORC1 pathway will inhibit the process of autophagy to direct excess nutrients towards cell growth and protein synthesis, rather than cellular recycling (Gitto & Altomare., 2015). The autophagy balance is critical for neurons because they are dependent on efficient waste clearance for survival and efficient energy usage for synaptic plasticity and pruning. However, AD results in the dysregulation of the mTOR pathway, causing mTORC1 to become hyperactivated, preventing

neurons from recycling toxic proteins and generating a destructive positive feedback loop that worsens mTOR dysregulation and accelerates the build-up of toxic aggregates. Hyperactive mTOR also indirectly activates kinases that phosphorylate tau, causing it to become hyperphosphorylated and more resistant to breakdown, which accelerates NFT formation and the accumulation of Aβ oligomers, leading to neuronal death (Gitto & Altomare., 2015). AβO appears to be a critical trigger in this process. These clusters of amyloid-β are highly toxic to neurons and can activate tau through abnormal signaling cascades. Once activated, tau promotes neuronal cell-cycle reentry (CCR), where mature neuronal cells attempt to divide despite lacking the ability to complete cell division. This false start in the cell cycle leads directly to cell death. At the same time, tau also interferes with NiMA activity, which prevents mitochondria from generating adequate ATP. This metabolic loss further weakens neurons, making them even more vulnerable to progressive neurodegeneration (Bloom et al., 2024).

Experimental studies provide strong evidence for the role of impaired autophagy in AD pathology. Gitto & Altomare., 2015, found that administration of rapamycin in PDAPP transgenic mice inhibits the hyperactivation of the mTOR pathway, leading to restoration of autophagic function. As a result, clearance of AβO and NFT formations was observed, demonstrating that mTOR's suppression of autophagy within AD patients may be reversible and a potential therapeutic target. In another study conducted by Tang et al., 2014, the loss of mTOR-dependent macroautophagy was investigated

within APP/PS1 mouse models. The results of this study discovered that impairment of macroautophagy resulted in destabilization of neuronal cytoskeletons, inactivation of axonal transport, and defective synaptic pruning which accelerated neuronal cell death.

The implications of impaired autophagy for AD are profound. AD pathogenesis and mTORC1 hyperactivation inhibits protein clearance, which negatively impacts neuronal survival. Autophagy impairment also magnifies mitochondrial dysfunction and promotes toxic protein build-up. Overall, impaired autophagy is a central driver of AD disease progression, highlighting the need for clinical trials which target the mTOR pathway and restore autophagic balance. Preclinical studies with mTOR inhibitors like rapamycin suggest that lost autophagic function can be reversed to reduce pathological hallmarks of AD and promote cognition, however further research is needed before these therapeutic interventions become mainstream. Additionally, as tau is one of the primary proteins that accumulates when autophagy fails, it becomes critical to further examine how mTOR dysregulation may directly contribute to tau hyperphosphorylation, aggregation, and neuronal toxicity.

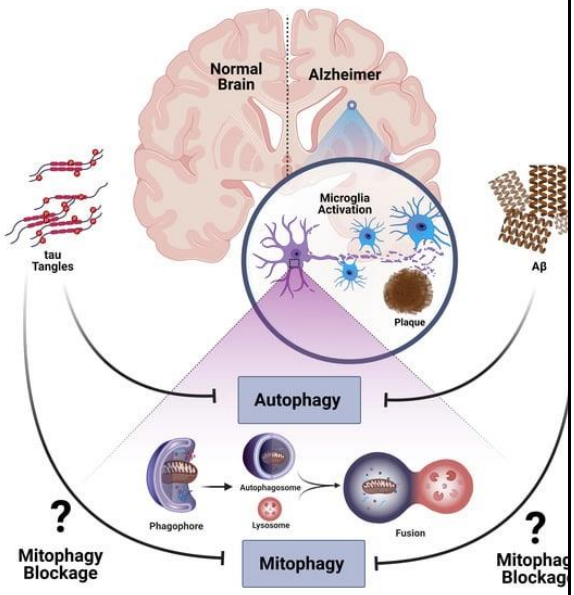

Fig. 3: Model of the dysregulation of autophagic processes and their effects in the progression of neurodegeneration. From "Siman, R., Cocca, R., & Dong, Y. (2015). The mTOR Inhibitor Rapamycin Mitigates Perforant Pathway Neurodegeneration and Synapse Loss in a Mouse Model of Early-Stage Alzheimer-Type Tauopathy. *PloS one*, *10*(11), e0142340. https://doi.org/10.1371/journal.pone.0142340"

Tau Pathology and NiMA

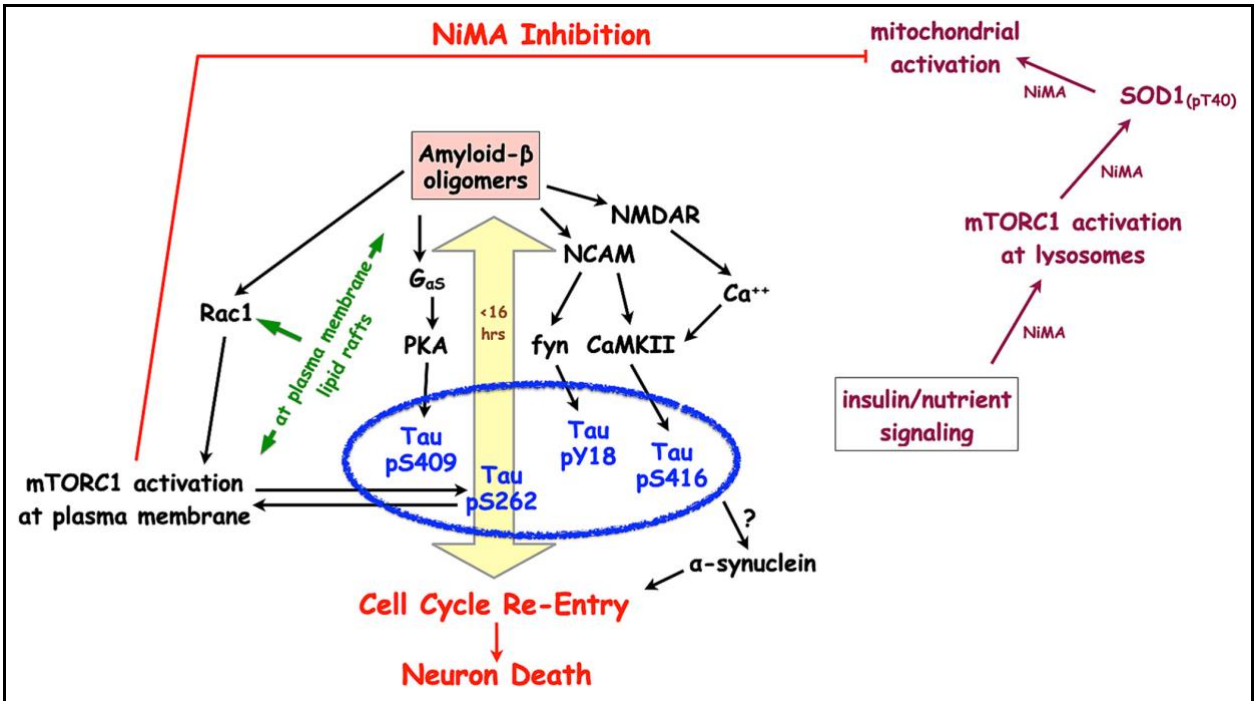

Fig. 4: Model of the dysregulation of tau pathology and their effects in the progression of neurodegeneration. From "Silva, M. C., Nandi, G. A., Tentarelli, S., Gurrell, I. K., Jamier, T., Lucente, D., Dickerson, B. C., Brown, D. G., Brandon, N. J., & Haggarty, S. J. (2020). Prolonged tau clearance and stress vulnerability rescue by pharmacological activation of autophagy in tauopathy neurons. *Nature communications*, *11*(1), 3258. https://doi.org/10.1038/s41467-020-16984-1"

Tau is a microtubule-associated protein that is found within the central nervous system (CNS), responsible for maintaining the stability and function of the neuronal cytoskeleton. During normal function, tau is regulated by the mTOR pathway to assist in axonal transports, binding to microtubules to prevent depolymerization and ensure structural integrity. In addition, tau modulates cellular responses to repress neuronal injuries and prevent oxidative stress from inhibiting cellular processes (Bloom et al., 2024). Within AD, tau becomes misfolded and hyperphosphorylated, detaches from microtubules, and forms NFTs which disrupt neuronal structure, transportation, and communication. Hyperactive mTORC1 signaling suppresses autophagy, leaving misfolded tau uncleared and indirectly activating kinases that add extra

phosphate groups to tau, worsening hyperphosphorylation (Bloom et al., 2024). As a result, neurons accumulate toxic tangles which destabilize their cytoskeleton, impair transport of nutrients and organelles, and eventually undergo cell death.

A critical factor in this process is NiMA, a protective mitochondrial regulator that ensures neurons maintain adequate ATP production. Under normal conditions, NiMA balances mTOR activity with mitochondrial energy needs, preventing oxidative stress and calcium overload (Bloom et al., 2024). However, in AD, tau interferes with NiMA function, effectively poisoning mitochondria. This prevents mitochondria from producing sufficient ATP, leaving neurons energy-deprived and unable to perform autophagy or resist oxidative stress, accelerating their death (Bloom et al., 2024). As a result, tau pathology has the potential to hijack cellular metabolism, directly weakening neuronal survival.

Primary studies reinforce the link between tau, mTOR dysregulation, and mitochondrial vulnerability. In a study by Siman et al., 2015, chronic systemic administration of rapamycin in a P301L mouse model of early tauopathy interrupted hyperactivation of the mTORC1 pathway and prevented tau-mediated neuronal loss in the entorhinal cortex, including its trans-synaptic spread into the dentate gyrus. Their findings demonstrate the important role of autophagy in interrupting the formation of NFTs and cell death. Similarly, Silva et al., 2020, demonstrated that pharmacological activation of autophagy restored clearance of misfolded tau and rescued tauopathy neurons from stress-induced vulnerability. Considering NiMA's function as an energy regulator necessary for promoting autophagy and disrupting tauopathy, these results suggest that it may be a key mediator of neuronal survival in AD pathology. Additionally, these findings align with a study conducted by Bloom & Norambuena, 2024, who describe tau as a central disruptor of mitochondrial health via NiMA inhibition.

The clinical implications of tau pathology are severe. NFTs are strongly associated with cognitive decline, memory loss, mood disorders, and irrational behavior (Altomari et al., 2021). Once established, tauopathy creates a self-reinforcing cycle: tau aggregates hijack mTORC1, mTORC1 hyperactivation reduces autophagy, and NiMA poisoning disables ATP production and mitochondrial clearance of misfolded proteins. This positive feedback loop amplifies neurodegeneration across brain networks. Preclinical evidence that shows the effects of rapamycin on reducing tau hyperphosphorylation, autophagy enhancement, and preservation of neuronal health appear to be promising, although translation to clinical trials is still limited (Davoody et al., 2024). Additionally, therapies that restore NiMA function and promote mTORC1 regulation may represent the next step in breaking the cycle of tauopathy-driven neurodegeneration.

Discussion

Alzheimer's disease (AD) is a neurodegenerative disorder marked by complex cellular disruptions, but evidence points to dysregulation of the mTOR pathway as a central driver of its progression. Hyperactive mTORC1 leads to neuronal death by blocking autophagy, which prevents the clearance of cellular waste, promoting the aggregation of AβO and misfolded tau proteins. Dysfunction manifests with the loss of synapses, weakening memory processes and cognition; impaired autophagy, which prevents destruction of toxic proteins and promotes mitochondrial dysfunction; and tau pathology, which destabilizes the cytoskeleton and inhibits NiMA. Together, these processes form a destructive cycle that forces neurons into a false cell cycle re-entry and accelerates neuronal death, correlating closely with the cognitive and behavioral symptoms observed in patients living with AD.

Rapamycin is proposed as a possible treatment, as it inhibits the mTOR pathway and prevents dysregulation. Inhibition may lead to reduced mTORC1 hyperactivation, upregulating cellular autophagy and restoring clearance of misfolded tau protein, resulting in the strengthening of the neuronal cytoskeleton and improved NiMA function. By restoring NiMA, Rapamycin indirectly promotes ATP production which restores neuronal signaling and longevity, resulting in stable circuit formation. Unfortunately, the beneficial effects of Rapamycin on AD pathology are still being observed in pre-clinical trials and more research is necessary before it reaches the clinical setting.

Ultimately, understanding how mTOR dysregulation drives synaptic loss, impaired autophagy, and tau pathology will provide a framework for future therapies and curative treatments aimed at preserving neuronal survival and cognitive function. Additionally, the lack of present clinical trials highlights a niche for therapeutic interventions which prioritize alleviating symptoms and mood disorders comorbid within individuals living with AD. Overall, breaking the self-reinforcing cycle of the hyperactive mTOR pathway is necessary to consider when designing future curative measures for the devastating progression of Alzheimer's disease.

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Pharmacological Targeting of ER Stress Components Provide Varying Potential Benefit in Alzheimer's Disease

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Lulu Schulz M.S.

October 2025

Abstract

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by amyloid-β (Aβ) plaques and tau neurofibrillary tangles, both of which disrupt proteostasis and drive neuronal dysfunction. Central to the maintenance of proteostasis is the endoplasmic reticulum (ER), where protein folding, trafficking, and quality control are coordinated through the unfolded protein response (UPR). Under acute stress, the UPR restores cellular balance by enhancing protein folding and degradation. However, chronic activation triggered by persistent Aβ and tau aggregation, shifts signaling toward apoptosis, thus exacerbating neurodegeneration. The three canonical arms of the UPR, namely PERK, IRE1α, and ATF6, along with the master regulator BiP/GRP78 and modulators such as the Sigma-1 receptor, represent key therapeutic targets for restoring ER homeostasis in AD. Preclinical studies demonstrate that selective modulation of these pathways can mitigate synaptic loss, memory decline, and proteotoxicity. Promising compounds, including ISRIB, TUDCA, Arimoclomol, and Blarcamesine, highlight the translational potential of targeting UPR components, though challenges related to specificity, systemic toxicity, and blood–brain barrier penetration remain. This review explores the role of UPR dysregulation in AD pathogenesis, evaluates therapeutic strategies targeting each arm of the UPR, and discusses opportunities and limitations for their clinical development.

Introduction

Alzheimer's disease (AD) is one of the most common neurodegenerative disorders, distinguished by key characteristics of tau tangles and Aβ plaques. The Unfolded Protein Response (UPR) is a central regulator of the endoplasmic reticulum (ER) which can become dysregulated, a contributing factor, in Alzheimer's Disease.

Tau aggregation and Amyloid-B deposition create the constant stress of the proteostatic network, which ultimately drives neuronal death. These pathological hallmarks begin due to protein misfolding and aggregation, impacting the cells ability to maintain proteostasis. Proteostasis is the homeostatic regulation of protein synthesis, folding, trafficking and degradation. This network relies on molecular chaperones, degradation systems like ubiquitin-proteasome pathway and autophagy, and adaptive stress responses involving the UPR.

The ER is where the secretory and membrane protein folding occurs and serves as an important regulator of proteostasis. When there is an accumulation of misfolded proteins within the ER, stress sensors in the lumen trigger the activation of the UPR. The UPR restores proteastasis by enhancing the clearance of misfolded proteins through ER-associated degradation. Chronic ER stress driven by tau and Aβ aggregation results in a maladaptive UPR. Instead of reestablishing proteostasis, prolonged UPR activation shifts toward pro-apoptotic signaling pathways, which exacerbates neuronal dysfunction, leading to cell death.

The Endoplastic reticulum is a network of membranes that are within the eukaryotic cell. The main function of this is to synthesize and process proteins and lipids, store calcium, and maintain overall cellular homeostasis. The ER is also responsible for responding to the loss of

proteastasis by activating the unfolded protein response (UPR) arms known as PERK, IRE1, ATF6, while being regulated by BiP/GRP78.

The UPR is a stress signaling pathway in the ER that manages protein folding, translation, and cell survival. Overall, targeting the UPR could be a solution for the treatment of Alzheimer's and other neurodegenerative disorders such as Huntington's Disease and Amyotrophic Lateral Sclerosis. There are current drugs such as ISRIB, 4PBA, TUDCA, Arimoclomol, and Blarcamensine that have shown preclinical and clinical promise to treat Alzheimer's Disease, but so far no drugs targeting the UPR and endoplasmic reticulum have passed clinical 4 Trials. In this review, I will be discussing the potential drugs targeting the different arms of the UPR and their potential for clinical development in Alzheimer's disease.

PERK

The PERK pathway is one of the pathways that is studied thoroughly in the context of Alzheimer's Disease. PERK (EIF2AK3) phosphorylates eIF2a, which is the initiation factor that when activated halts global protein synthesis. At the same time, eIF2A promotes the selective translation of the stress adaptive transcript such as ATF4. While the translational pause is intended to be a protective response, chronic PERK activation suppresses synaptic proteins and disrupts memory formation[11]. There are many preclinical studies that highlight both the advantages and disadvantages of targeting PERK. Research studies have demonstrated that ISRIB, a small molecule PERK inhibitor, restored protein synthesis and rescued cognitive performance in mouse AD models[17]. Other groups have shown ISRIB improved synaptic plasticity without the pancreatic toxicity associated with the PERK inhibitor GSK2606414.[4] Interestingly, compounds such as Guanabenz and Sephin1, which prolong eIF2α phosphorylation, have also shown neuroprotection

in protein-misfolding models[19]. Despite these advances, no PERK-directed therapies have entered clinical trials due to essential roles for PERK in other tissues, especially the pancreas. While PERK is a target in tauopathies and AD, its potential is constrained by toxicity concerns[21]. Genetic studies demonstrate that PERK is essential for pancreatic β-cell survival, and systemic inhibition produces a Wolcott–Rallison syndrome-like phenotype characterized by diabetes[5]. In preclinical models, PERK inhibition has also been associated with hepatotoxicity and pancreatic dysfunction, limiting its translational feasibility[18]. These findings highlight the challenge of balancing PERK inhibition to rescue neurodegenerative pathology while maintaining cellular homeostasis in other organs. As a result, current research has shifted toward targeting downstream effectors of PERK signaling like integrated stress inhibitors (ISRB).[17] This restores the translational capacity without fully abolishing adaptive stress responses and has demonstrated efficacy in restoring memory in mouse models of AD and prion disease.[14] This suggests that while PERK remains a biologically compelling target, its clinical utility may depend on its specificity to the UPR in Alzheimer's Disease brains rather than systemic inhibition.

IRE1α

The IRE1α branch of the unfolded protein response plays a pivotal role in determining cell survival or death during chronic ER stress, thus making it a compelling therapeutic target in tauopathies and Alzheimer's disease (AD). Upon activation, IRE1α binds *XBP1* mRNA to generate the active transcription factor XBP1s, which induces adaptive genes that promote protein folding, secretion, and degradation, thereby supporting neuronal resilience. However, sustained IRE1α signaling drives regulated IRE1-dependent decay (RIDD) activity, leading to endoribonuclease-mediated mRNA degradation, inflammation, and apoptosis, thereby contributing to neurodegenerative progression. Small molecules targeting IRE1α have been

developed to shift this balance toward adaptation and away from apoptosis. For example, KIRA6, an allosteric inhibitor of the IRE1α kinase domain, suppresses maladaptive RNase hyperactivation and has been shown to reduce pro-apoptotic signaling in models of ER stress.[20] Similarly, Toyocamycin, a nucleoside analog, selectively inhibits the RNase activity of IRE1α, reducing apoptosis without completely abolishing its adaptive functions[3]. More recently, there was reviewed evidence positioning IRE1α as a critical "molecular switch" between survival and apoptosis in AD, suggesting that fine-tuned modulation rather than full inhibition may offer the most therapeutic benefit.[9] Together, these findings indicate that IRE1α signaling represents both a driver of pathological progression and a potential intervention point, with pharmacological strategies focusing on restoring its adaptive mechanisms while minimizing its pro-apoptotic and inflammatory signaling cascades.[2] However, limitations remain: KIRA6 has been shown to lack selectivity, binding numerous off-target nucleotide-binding proteins and influencing inflammatory pathways independently of IRE1α,[16] while Toyocamycin, although effective in blocking RNase activity, also suppresses RNA synthesis at higher doses and inhibits other kinases such as PKC, cdc2, and PI4K, raising concerns about systemic toxicity.[1] Moreover, chronic or systemic inhibition of IRE1α may compromise essential ER stress responses in peripheral tissues such as pancreatic β-cells and secretory organs, thereby limiting the therapeutic window[7]. While IRE1α modulation offers a promising therapeutic avenue for tauopathies and AD, its clinical translation will require highly selective compounds, careful dosing strategies, and long-term safety validation to balance neuroprotection with systemic proteostasis demands.

ATF6

The ATF6 arm of the unfolded protein response enhances ER quality control mechanisms, positioning it as an attractive therapeutic avenue in Alzheimer's disease (AD) and tauopathies. Under ER stress, ATF6 translocates to the Golgi, where it is cleaved to release a cytosolic fragment (ATF6f) that acts as a transcription factor. ATF6f upregulates genes encoding ER chaperones, folding enzymes, and components of the ER-associated degradation (ERAD) pathway, thereby facilitating protein quality control and reducing the burden of toxic aggregates. In neurodegenerative models, enhancing ATF6 signaling has been shown to reduce proteotoxicity and support neuronal function. Pharmacological activators of ATF6 selectively boosted ER chaperone expression and improved protein folding capacity in stressed cells. Similarly, there was identification of small-molecule ATF6 agonists capable of attenuating ER stress and protecting against protein misfolding toxicity *in vitro*.[15] More recently, ATF6 was highlighted as a central regulator of neuronal proteostasis, noting its ability to restore the balance between protein folding capacity and protein folding demand in AD mouse models.[6] Unlike PERK or IRE1α, ATF6 activation is generally not associated with strong pro-apoptotic signaling, making it a comparatively safer target for therapeutic modulation. While there are no current ATF6 agonists in clinical development, research is focused on developing ATF6-selective activators that can cross the blood–brain barrier and provide sustained chaperone induction in neurons, offering a promising strategy to mitigate tau- and amyloid-driven pathology.

BiP/GRP78

The ER-resident chaperone BiP/GRP78 functions as the master regulator of all three arms of the unfolded protein response (UPR), making it a central therapeutic target in Alzheimer's disease (AD) and tauopathies. Under basal conditions, BiP binds to PERK, IRE1α, and ATF6, maintaining them in an inactive state. During ER stress, BiP dissociates to chaperone misfolded

proteins, thereby initiating UPR signaling. Beyond its role as a molecular gatekeeper, BiP supports protein folding, prevents aggregation, and maintains ER proteostasis, suggesting that its pharmacological modulation could mitigate the toxic protein misfolding characteristics of neurodegenerative diseases. Therapeutic approaches aimed at enhancing BiP activity or boosting ER chaperone capacity have shown promise in preclinical and clinical contexts. For example, tauroursodeoxycholic acid (TUDCA), a bile acid derivative that reduces ER stress, decreased amyloid deposition and improved memory in AD mouse models.[10] Similarly, Arimoclomol, a co-inducer of heat shock proteins that indirectly enhances BiP function, has demonstrated neuroprotection in amyotrophic lateral sclerosis (ALS) mouse models and advanced to Phase II/III clinical trials for neurodegenerative diseases.[8] More recently, Blarcamesine (Anavex 2-73), a Sigma-1 receptor agonist mechanistically linked to BiP regulation, has been reported to slow cognitive decline in AD clinical trials, underscoring the translational potential of targeting BiP-associated pathways in human disease. Collectively, these findings position BiP/GRP78 not only as a molecular director of UPR activation but also as a therapeutic hub whose pharmacological modulation may confer broad neuroprotection across protein misfolding disorders.

Sigma-1 Receptor

The Sigma-1 receptor (Sig-1R) is an ER-resident protein localized at the mitochondria-associated ER membrane (MAM), where it regulates calcium signaling, mitochondrial dynamics, and cellular stress adaptation. Although not a canonical unfolded protein response (UPR) sensor, Sig-1R influences proteostasis and neuronal survival by stabilizing ER–mitochondria communication and buffering against excitotoxic and metabolic stress. In models of Alzheimer's disease (AD), dysregulation of Sig-1R contributes to impaired calcium homeostasis, mitochondrial dysfunction, and synaptic failure, processes closely tied to tau pathology and amyloid burden.

Pharmacological studies have demonstrated that Sig-1R activation can mitigate these pathological outcomes. For example, the selective Sig-1R agonist PRE-084 improved memory performance and reduced tau phosphorylation in amyloid-β mouse models.[12] Clinical investigations of Blarcamesine (Anavex 2-73), an orally available Sig-1R agonist, have further shown cognitive benefit and slowed decline in Phase II/III AD trials. In addition, there was identified Sig-1R as a critical mediator linking ER stress to synaptic health and mitochondrial function, underscoring its role as an essential regulator of neuronal homeostasis in the context of neurodegeneration.[9]

Conclusion

The evidence surveyed highlights that the unfolded protein response (UPR) and its regulatory components exert a dual influence on neuronal survival in Alzheimer's disease (AD) and tauopathies. Acute activation of UPR branches such as PERK and IRE1α can restore proteostasis and protect neurons, yet chronic signaling drives synaptic dysfunction, inflammation, and eventual neurodegeneration. The contrasting outcomes observed across experimental models underscore the importance of context and timing in UPR modulation, and suggest that therapeutic approaches must be highly selective to avoid detrimental side effects.

Pharmacological targeting of individual UPR arms has yielded mixed outcomes. PERK inhibition improved cognition in AD mouse models but was limited by systemic toxicity, though downstream modulation with ISRIB showed fewer adverse effects. IRE1α inhibitors reduced maladaptive RNase activity but faced challenges of specificity and off-target binding. By comparison, ATF6 activation emerged as a relatively safer strategy, enhancing ER proteostasis without eliciting strong pro-apoptotic responses, though the lack of brain-penetrant compounds limits translational progress. These findings indicate that while each pathway offers unique

therapeutic opportunities, their viability depends on overcoming toxicity, delivery, and selectivity barriers.

Among UPR regulators, BiP stands out as a central chaperone that coordinates all three branches by controlling stress sensor activation. Agents such as TUDCA and Arimoclomol bolster BiP's activity and have demonstrated neuroprotection across multiple models, lending strong support to BiP as the most attractive therapeutic target. Meanwhile, modulation of the Sigma-1 receptor, although not a canonical UPR component, shows complementary promise by stabilizing ER–mitochondria interactions and enhancing cellular resilience. Clinical trials of Sigma-1 receptor agonists provide encouraging evidence that peripheral regulators of proteostasis may augment or synergize with direct UPR interventions.

Taken together, these findings support the claim that ER stress and the UPR are critical determinants of AD and tauopathy progression, and that their pharmacological modulation represents a viable therapeutic avenue. The most compelling strategies will likely involve enhancing BiP's regulatory function and combining it with peripheral modulators like Sigma-1 receptor agonists to optimize stress adaptation while minimizing toxicity. Future therapeutic development should focus on brain-penetrant, selective compounds that can fine-tune UPR activity, thereby shifting the balance from maladaptive stress signaling toward neuronal survival and cognitive preservation.

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A Holistic Review of Genetically Modified Plastic Degrading Bacteria with a Focus on Future Advancements and Economic Viability

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Abstract

Plastic pollution constitutes a persistent environmental and public health challenge, as conventional recycling processes continue to result in material downcycling and the leaching of hazardous chemical compounds. Genetically modified plastic degrading bacteria (GM-PDB) offers a promising alternative, capable of breaking down polymers such as polyethylene terephthalat**e**, nylon, and polyolefins. Advances in genetic modification tools, including CRISPR, have improved bacterial efficiency, resilience, and adaptability, while artificial intelligence has accelerated enzyme discovery and optimization. Early operational applications, including Carbios' industrial recycling plant, show that GM-PDB can be used at scale, while its versatility makes it suitable for wastewater treatment and marine microplastic cleanup. This study also analyzed GM-PDB's future economic viability and application. Drawing on research conducted within the past decade, this study summarized current advancement regarding GM-PDB through a scientific, operational, and economic lens. GM-PDB represents a promising, adaptable, and economically viable alternative to conventional recycling, offering unique benefits in sustainability, versatility, and integration into a circular plastic economy.

Keywords: Plastic Degrading Bacteria, Genetic Modification, Plastic Pollution, Plastic Biodegradation, Economic Analysis, CRISPR

A Holistic Review of Genetically Modified Plastic Degrading Bacteria with a Focus on Future Advancements and Economic Viability

As of 2025, plastic pollution is responsible for at least $1.5 trillion a year in health-related damages with additional long-lasting damage to both the environment and ecosystem (Landrigan et al., 2025). Plastics and microplastics continue to contaminate the planet and human health while conventional recycling has lagged. As plastic consumption shows little signs of stopping, a new method for disposing of plastic and incorporating it into the circular economy must be developed (Landrigan et al., 2025). Plastics have pervaded nearly every corner of the globe, leaching chemicals and leaving a permanent stain on the environment. With the ability to last for hundreds if not thousands of years, the issue of plastic pollution represents a persistent challenge that will only escalate if left unaddressed (Philip & Chauhan., 2024).

Traditional recycling has proven inadequate at addressing the growing crisis, due to low recycling rates of just 9% of global plastic being recycled (Singh & Walker., 2024). Additionally, recycling plants have been identified as potential hotspots of toxic waste, leaching chemicals and microplastics into the environment. Moreover, the sustainability of certain recycling methods has been called into question with the value of the plastic gradually decreasing until it is no longer recyclable in a process known as “downcycling” (Philip & Chauhan., 2024). Microplastics have already demonstrated their unique ability to permeate into the environment, entering the soil and quickly upending its natural balance, reducing yields, growth, and seed germination (Lalrinfela et al., 2025).

More concerning is the potential risk of microplastics and nano plastics on the human body. Researchers are just beginning to understand the impact of these microplastics on human health, though early signs are far from reassuring. Microplastics have been found in almost all

parts of the human body including cardiovascular, digestive, and respiratory systems (Roslan et al., 2024). Moreover, studies have linked microplastics to higher risks of strokes and death (Marfella et al., 2024).

Despite early research into biological methods of degrading plastic it was not till 2016 that researchers first discovered PETase, an enzyme capable of breaking down Polyethylene Terephthalate (PET), in the bacteria *I. sakaiensis* (Gonzalez et al., 2024). Since then, numerous attempts have been made to not only discover new enzymes capable of degrading down plastic but also enhance current strains through genetic modification methods such as CRISPR-Cas9 technology. This genetically modified plastic degrading bacteria (GM-PDB) represents a promising alternative to traditional recycling with numerous advantages in sustainability and adaptability. Given the developing nature of this field and its relative novelty, there has been a lack of research into the practical application of these GM-PDBs. Moreover, current attempts at modifying GM-PDB and examining current progress have neglected its economic viability at scale. This paper will focus on this potential application and the overall viability of GM-PDB through a scientific, operational, and economic lens.

Methods

A holistic literature review was conducted to examine current research into GM-PDB and current operational applications. An analysis was done on the economic viability of GM-PDB compared to traditional recycling methods and its potential future use cases. This review utilized multiple databases, including, the National Institutes of Health and Science Direct. Covering PDB research published between 2020 and 2025, this report examines the most recent breakthroughs and developments. The scope of this research article covers bacteria with a focus on genetically modified bacteria omitting other biological degradation techniques including

fungi-based methods. By analyzing numerous sources through a scientific, operational, and economic lens, a comprehensive view on the future viability of GM-PDB was formed.

Scientific Lens

Strain Discovery

Finding and isolating bacterial strains related to plastic degradation is the first step to developing usable GM-PDB. The bacteria *I. sakaiensis* was first discovered outside a plastic bottle recycling plant in 2016 (Gonzalez et al., 2024). The enzyme responsible for the plastic degradation was then isolated, allowing researchers to genetically modify it in hopes of increasing its efficiency or resilience. New bacterial strains are still sourced in the same way, with researchers searching out plastic waste from the wild and isolating the microbes responsible for breaking it down (Ruthi et al., 2023). To target specific traits, researchers vary their search locations. They search the Arctic to find bacteria with enhanced cold resilience, while they turn to the ocean to identify strains that can withstand high salinity and seawater conditions.

Genetic Modification

Once identifying the bacteria and the specific enzyme responsible for the plastic degradation, genetic modifications are made to improve the overall breakdown of the plastic. Gene editing tools such as CRISPR-Cas9 allow researchers to modify the enzymes involved with plastic degradation, deleting, modifying, and inserting raw genetic material (Palit et al., 2025). Alternate methods like horizontal gene transfer via conjugation, which involves transferring genetic material from a donor bacteria to receiver bacteria, allow for a rapid spread of new genetic material into preexisting bacteria (Yip et al., 2024). Another approach utilizes a microbial consortium in which numerous genetically modified bacteria work together to degrade

plastic, where the different bacteria can divide work and degrade multiple types of plastic at once (Philip & Chauhan, 2024).

Limitations

Despite almost a decade of research, there are a number of limitations that stunt the growth of GM-PDB and its widespread adoption. GM-PDB is far more challenging to scale than current recycling operations due to its resource intensive nature and the inherent difficulties in working with bacteria (Philip & Chauhan, 2024). Temperature also remains an issue with most bacteria requiring temperatures upwards of 50 degrees Celsius, requiring dedicated infrastructure to keep the bacteria alive. Moreover, plastic is difficult to biologically degrade due to its chemical makeup and long polymer strands (Cai et al., 2023). The PDB would have to be closely monitored and tested to prevent unintended ecological damage. There are also numerous risks in introducing foreign GM-PDB into the environment, such as the unknown effect of genetically modified organisms on the environment (Palit et al., 2025).

Future Potential of Artificial Intelligence

As development of GM-PDB continues, artificial intelligence (AI) will continue to play a substantial role in accelerating the pace and depth of research (Palit et al., 2025). Machine learning models are currently useful in two areas of the GM-PDB pipeline (Jang et al., 2021). Firstly, these models can scan through large databases and discover promising enzymes allowing researchers to quickly locate enzymes with the potential to break down plastic. Secondly, they can scan through the genetic code of those enzymes and identify promising edits to enhance the characteristics of the enzyme in terms of efficiency, resilience, and output. AI models present a faster alternative to manual testing with the potential to substantially increase the rate of research into GM-PDB (Jang et al., 2021).

Operational Lens

The emergence of GM-PDB represents a promising frontier in addressing the limitations of conventional recycling methods. However, scaling this technology remains challenging due to a scarcity of industrial scale research as well as inherent limitations with this biological approach.

Current Operational Use

Several companies and research collaborations have demonstrated early-stage operational integration of PDB. Carbios, a biotech company, has already developed genetically modified bacterial enzymes capable of breaking down PET plastic bottles into their original building blocks, allowing for the creation of new, high-quality plastic from recycled materials. Their recently built recycling plant, set to open in 2025, will process 50,000 tons of PET plastic using solely GM-PDB (Carbios, 2024). The plant first breaks down the PET into pellets to increase surface area before feeding it into specialized bioreactors which hold the bacteria and provide a closed environment for the degradation process. Within 10 to 16 hours the plastic will be fully broken down into simple monomers, which can then be used to create brand new bioplastics. This process allows plastic to be incorporated into the circular economy and be repeatedly used without any downcycling.

Breaking, a plastic degradation company out of Harvard's Wyss institute, recently developed X-32, a microbial strain engineered to break down plastics including nylon and polyolefins. In lab tests, the microbe degraded up to 90% of certain plastic samples within 22 months, a major leap compared to traditional recycling methods which struggle to break down these types of plastics. Conventional recycling struggles in the real world because plastics like

nylon are often mixed with other materials and become less valuable every time they are reused (Singh & Walker, 2024).

GM-PDB is still at an early stage of research, yet it has already shown considerable potential for large scale operational applications. While conventional recycling relies on rigid processes requiring prebuilt infrastructure, including large scale sorting and pre-processing operations, GM-PDB is adaptable and requires less infrastructure (Singh & Walker, 2024).

Potential Operational Use Cases

Building on the theoretical capabilities of GM-PDB, this review provides potential operational use-cases for GM-PDB within various sectors such as wastewater and ocean plastic management.

Wastewater Plants

GM-PDB is uniquely versatile in its ability to be implemented into existing infrastructure. Wastewater plants represent one promising application due to their propensity to leach microplastics into the environment (Yip et al., 2024). Studies using wastewater bacteria engineered via conjugation have shown promise at addressing water based microplastic. Specifically, this bacteria has achieved degradation rates of 40% of a 0.25 mm thick commercial PET film within 4 days at 50°C, with efficiency expected to improve significantly. In practice a bioreactor system containing the bacteria could be attached to existing wastewater treatment plants to capture and break down the plastic, implementing it into already built plants (Liu et al., 2020).

Ocean Plastic

Once plastic enters the ocean it becomes much harder to recover. In most cases it is instead left to accumulate, leaching chemicals as well as microplastics into the ocean (Jambeck

et al., 2015). Plastic that has already made its way into the environment, particularly the sea, represents a particular vulnerability of traditional recycling which is unable to address this waste due to its rigid infrastructure requirements. Microplastics can infiltrate marine wildlife and accumulate through the food chain, ultimately reaching humans. Previous studies have isolated potential bacteria colonies capable of breaking down PET plastic in a marine environment (Gao & Sun, 2021). These colonies, once optimized through genetic modification, have the potential to tackle marine pollution and break down plastics and microplastics by traditional recycling. GM-PDB has already been adapted to survive in salt water and operate at a temperature of 30 degrees Celsius, ingesting plastic polymers and breaking them down (Li et al., 2023). While there are limits to the bacteria's current application, they are already able to completely break down certain types of plastic, offering a promising alternative to natural degradation (Sathiaseelan et al., 2024).

Bioplastics: Potential Post-Degradation Product

Certain techniques utilize a microbial consortium of multiple genetically modified bacteria to not only break down bacteria but upcycle it into new valuable bioplastics (Bao et al., 2023). In this study, researchers utilized a microbial consortium to first break down PET plastic to its building blocks, terephthalic acid and ethylene glycol. Then, instead of stopping at waste degradation, the microbes were engineered to upcycle those building blocks into new valuable bioplastics like medium chain length polyhydroxyalkanoate, mcl-PHA, or other industrial chemicals. This process allows plastic to be incorporated into the circular economy in which everything can be reused, overcoming the limitations of standard recycling and downcycling.

Economic Lens

GM-PDB has improved significantly with the discovery of new bacteria and the genetic modification of existing strains. Despite this, it still struggles to rival the cost efficiency of large-scale recycling plants (Jiang & Bateer, 2025). However, future advancements will only increase adoption of this new technology, transforming it from a niche fix with a specific use case to a large-scale plastic degrading solution, rivaling the traditional recycling industry. Propelled by the work of countless researchers and a few industrial scale projects, the entire PDB market is expected to grow to an estimated $583.5 million by 2032 (Swar, 2025). With a total plastic recycling market of $61 billion, there is significant financial potential for GM-PDB to disrupt the current market (MMR, 2025). In fact, the market will continue to grow as the Organization for Economic Cooperation and Development (OECD) predicts global plastic production will quadruple by 2060 (OECD, 2022).

Governmental and Private Funding

In terms of monetary grants, there appears to be sizable support of PDB as a legitimate alternative to traditional recycling and as the solution to the world's plastic crisis (Swar, 2025). On the governmental side, a recent European Union grant allocated €568.06 million towards developing sustainable bio-based and circular plastic systems with governmental support also seen in the United States with millions of US dollars allocated to furthering plastic degradation methods. Within the private sector, numerous companies have poured hundreds of millions of dollars with hopes of making GM-PDB an economically viable plastic solution. Out of the companies working on GM-PDB, Carbios has recently completed construction on a $243 million plastic degrading bacteria recycling plant and Breaking raised $10.5 million in seed funding.

Potential for Disrupting Traditional Methods

There are two types of traditional recycling methods, mechanical recycling and chemical recycling. Limitations seen with these methods present an opportunity for PDB to disrupt the market (Philip & Chauhan, 2024). Mechanical recycling is limited by downcycling, which gradually lowers the quality of the product making it decreasingly valuable. Chemical recycling is energy-intensive, limiting its profitability and scalability. While PDB is still in the research stage it can help resolve both of these problems with complete degradation, eliminating downcycling, and the potential for lower energy consumption.

Assessing Economic Viability

Assessing the economic viability of PDB and other recycling methods involves looking at benefit to cost ratio, payback period, as well as comparisons to traditional recycling (Jiang & Bateer, 2025). A key finding is that the price of the recycled product has an immense effect on the entire process. Even small changes in price of recycled products can affect the return on investment for these projects which is why examining bioplastics, a potential product of PDB, is important. As bioplastics become more utilized, they have the potential to dramatically affect the profitability of the entire recycling process. Additionally, government support can help mitigate risk by providing support and assurance for volatility associated with long term price volatility.

Currently, PDB is still in its early stage of adoption and faces large infrastructure requirements, however, it still retains promising potential due to its unique advantages and potential improvements. An economic analysis on biological recycling using Life Cycle Assessment and Life Cycle Costing analyze the profitability of two biological recycling methods (Francini et al., 2019). Specifically, they focused on the conventional co-digestion of plastics with sewage sludge, and a two-step process involving dark fermentation followed by anaerobic

digestion. The financial analysis covered a time horizon of twenty years and included capital investment, operation and disposal costs. Although the authors did not compare these recycling methods to existing ones, the results demonstrate that both approaches are economically viable. In the case of co-fermentation and digestion, positive net present values were achieved in about five years, whereas the co-digestion method required seven years to reach positive values (Francini et al., 2019). This study demonstrated that both methods were economically viable assuming consistent improvement with the PDB and the costs surrounding plastic recycling. The future economic viability of PDB will depend on a number of factors including, economic support both private and governmental sectors, research advancements, and the future costs surrounding plastic. Promising activity surrounding PDB and numerous small-scale tests of the technology demonstrate that PDB has the potential to become a viable alternative to traditional recycling.

Limitations

PDB was first discovered approximately two decades ago and all articles referenced in this paper are within the last five years. Therefore, the novelty of PDB, especially as it pertains to the application of current genetic modification methods, limited the breadth of current scientific research. The lack of research on this topic also impacted the amount of real-world use cases that ultimately shaped the operational section of this paper. Moreover, there was limited information regarding the cost analyses and economic data surrounding PDB which particularly impacted the economic section.

Conclusion

Genetically modified plastic degrading bacteria represents a promising frontier in the global effort to address the escalating plastic crisis. Scientifically, research over the past two decades has uncovered an expanding library of enzymes and bacterial strains with the ability to degrade plastics, many of which have been enhanced through genetic modification tools. These modifications have steadily improved the efficiency, resilience, and adaptability of PDB. Nonetheless, significant limitations remain, including slower degradation rates compared to existing recycling systems, temperature constraints, and the ecological risks associated with introducing modified organisms into natural environments. Operationally, PDB technology has already demonstrated proof of concept through projects such as Carbios' PET recycling plant and the development of microbial consortia capable of degrading multiple types of plastic. Beyond large scale recycling, PDB is particularly well suited to addressing gaps where traditional methods fail, such as wastewater treatment facilities and marine environments saturated with microplastics. Economically, while PDB remains more costly than conventional recycling at present, early-stage studies suggest long term viability, particularly when microbial consortia are engineered not only to degrade plastics but also to upcycling byproducts into valuable compounds such as bioplastics. With growing governmental and private investment, PDB is increasingly positioned as a disruptive force within the $61 billion global recycling market. While much work remains to overcome its scientific, operational, and economic challenges, genetically modified PDB offers promising and adaptable strategies for tackling the enduring problem of plastic pollution.

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Oxidative Stress as a Driver of Mitochondrial Impairment in Early-Stage Alzheimer's Disease

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Abstract

Oxidative stress (OS) and mitochondrial dysfunction have been gaining attention as fundamental early driving factors of Alzheimer's development and progression, potentially preceding hallmark features like amyloid-beta (Aβ) plaques and tau tangles. The brain is highly sensitive to oxidative damage due to its low antioxidant capacity and high energy demand, emphasizing the necessity to study the effects of oxidative stress and subsequent mitochondrial damage in the early stages of the disease. This literature review focuses on the early stages (MCI, EAD) synthesizing existing evidence on how OS disrupts proper mitochondrial dynamics, energy production, and neurogenesis. A literature review was conducted using Pubmed and Google Scholars, using key words such as "oxidative stress," "early Alzheimer's disease," and "mitochondrial dysfunction," prioritizing recent studies (past 15-20 years) that focused on early-stage AD, particularly MCI. Findings suggest that oxidative stress appears early in AD and directly disrupts mitochondrial function, leading to reduced ATP output, increased ROS generation, and early cognitive decline. Evidence from imaging and postmortem studies confirms that mitochondrial decline in memory-related brain regions. These findings highlight the potential of targeting OS and mitochondrial impairment for early diagnosis and treatment in Alzheimer's disease. Future research should focus on longitudinal studies and mitochondrial based therapies in the earliest stages of the disease.

Keywords: Oxidative stress, mitochondrial dysfunction, early Alzheimer's Disease

Introduction

Alzheimer's disease (AD) is the most common cause of dementia, affecting an estimated 6.7 million individuals in the US, a number that is expected to double by 2060 (Center of Disease Control, 2024). The disease is marked by memory loss, cognitive decline, and physical brain changes such as amyloid-beta (Aβ) plaques and tau tangles. Among the many proposed processes behind the pathology and development of Alzheimer's, oxidative stress has received increasing attention as a potential driving factor of the disease. Oxidative stress is a condition caused by an imbalance between reactive oxygen species (ROS) and the body's antioxidant defenses (Pizzino et al., 2017). ROS are reactive molecules produced primarily in the mitochondria during oxidative phosphorylation in the electron transport chain. Excessive ROS can oxidize lipids in neuronal membranes, impair protein folding, and damage mitochondrial and nuclear DNA, leading to cellular dysfunction and neurodegeneration.

The brain is especially vulnerable to oxidative damage due to its high oxygen use, high lipid content, and relatively low antioxidant capacity (Misrani et al., 2021; Pizzino et al., 2017). Mitochondria, the organelles responsible for cellular energy production, are a major source of ROS production and are highly vulnerable to ROS-induced damage. Growing evidence suggests that oxidative stress not only accompanies, but may actually precede the hallmark pathologies of AD, impairing proper mitochondrial function. When mitochondrial components are oxidatively damaged, ATP production declines, calcium homeostasis is disrupted, and pro-apoptic signals are increased, contributing to neurodegeneration. Because mitochondrial dysfunction is an early and central feature of Alzheimer's, especially in the context of oxidative stress, understanding the relationship between oxidative stress and mitochondrial function is significant. Furthermore, due to the expected rise in AD cases in the coming decades, exploring/studying understanding how

oxidative stress disrupts mitochondrial function during the early stages of the disease is crucial. In early stages of Alzheimer's, such as mild cognitive impairment (MCI), researchers have found signs of mitochondrial damage and elevated oxidative stress before major brain changes and major progression of the disease occurred (Sultana and Butterfield, 2010). This review will explore current research on the connection between oxidative stress and mitochondrial function in the early phases of Alzheimer's, highlighting key findings and identifying potential implications for early detection and treatment.

Methods

A literature search was conducted using PubMed and Google Scholars in order to gather up studies, reviews, and experiments. Key terms such as oxidative stress, mitochondrial dysfunction, and early Alzheimer's disease were used both separately and in combination. Priority was given to recent publications within the last 15-20 years in order to capture recent findings for necessary context and experimental data that would support the relevant research themes.

Reactive Oxygen Species

Free radicals are molecules that have an unpaired electron, which makes them unstable and highly reactive. Because they lack a full complement of electrons, they attempt to steal electrons from other molecules, damaging cells and DNA (Pham-Huy et al., 2008). Free radicals can be produced from normal functions, such as metabolism, but also from environmental factors like pollution and radiation. When there are not enough antioxidants in the system (substances that protect the body from free radical damage), excess radicals can harm essential organelles and contribute to cell death. While free radicals can play a helpful role in supporting the immune system, the body only requires them in low to moderate levels.

Reactive oxygen species (ROS) are a major category of free radicals. They are highly reactive metabolic byproducts of oxygen metabolism, primarily produced by the electron transport chain (ETC) in the mitochondria (Misrani et al., 2021). ROS are unstable because of their unpaired electrons and readily oxidize other molecules, further damaging cells (pizzino et al., 2017). The main types of ROS include superoxide anion, hydroxyl radical, and hydrogen peroxide (non-radical). Importantly, ROS attacks cell membranes via lipid peroxidation, enzymes via protein oxidant action, and DNA and RNA via base oxidation and repair failure. These changes are observed in early Alzheimer's disease (AD), often before clinical symptoms appear (Misrani et al., 2021). When ROS levels are too high, it overwhelms the brain's natural antioxidant defenses, contributing to oxidative stress (OS) and the possible development of Alzheimer's disease. The balance between antioxidants and ROS production is essential towards understanding the development and progression of Alzheimer's, as even minor damages can disrupt proper neuron function and lead to neurodegeneration.

Oxidative Stress

Oxidative stress (OS) may be one of the earliest biochemical signals of Alzheimer's disease. OS is caused by the excessive production of ROS, which plays a causal role in triggering mitochondrial dysfunction and neuronal loss. When ROS levels are too high, it overwhelms the brain's natural antioxidant defenses, leading to OS and to the possible development of AD (Misrani et al., 2021). Beyond direct cellular damage, oxidative stress also promotes amyloid-beta (Aβ) accumulation and tau protein hyperphosphorylation, processes that further disrupt synapses and accelerate disease progression.

Under normal physiological conditions, the body maintains a careful balance between the production of ROS and the supply of antioxidants. Antioxidants neutralize free radicals and

ROS, protecting cells from harm. When ROS levels outnumber the body's antioxidant defenses, this imbalance leads to oxidative stress, a harmful condition associated with aging and neurodegeneration. The body naturally uses antioxidants to limit ROS: through enzymes such as superoxide distaste, catalase and glutathione peroxide and through non-enzymatic sources such as vitamin C, vitamin E, and glutathione flavonoid (Pizzino et al., 2017). Because this imbalance emerges well before major clinical symptoms, OS may serve as an essential early marker of Alzheimer's disease.

Oxidative Stress Precedes Hallmark Alzheimer's Disease Properties

Oxidative stress has increasingly been recognized as an early driver of Alzheimer's disease, potentially appearing before hallmark pathologies, such as amyloid-beta (Aβ) plaques and tau neurofibrillary tangles. Studies suggest that oxidative stress not only accompanies these hallmarks, but actively promotes them by increasing both Aβaccumulation and tau hyperphosphorylation. Aβ is a peptide derived from amyloid precursor protein (APP), and it forms extracellular aggregates in AD brains (Tobore, 2019). In healthy individuals, Aβ normally is cleared from the brain, but in AD there is a complication with the production and removal of Aβ. As a result, Aβ builds up and aggregates into extracellular plaques. Tau, a protein that stabilizes microtubules, also becomes dysfunctional in AD when it becomes abnormally hyperphosphorylated, forming tangles inside neurons. Evidence shows that reactive oxygen species (ROS) can enhance APP expression and Aβ accumulation, while also activating kinases that drive tau phosphorylation (Wang et al., 2013). These findings suggest that oxidative stress is not just a byproduct of Aβ and tau pathology, but possibly a contributor to their development.

Oxidative Stress as an Early Indicator of AD

Although early AD remains understudied, evidence shows that oxidative stress markers appear long before the disease reaches its later stages. For example, markers of oxidative stress have been detected in individuals at the mild cognitive impairment (MCI) stage, the traditional stage between normal aging and AD. Sultana and Butterfield (2010) used redox proteomics, a technique that identifies proteins modified by OS to compare brain tissue samples from individuals with MCI, early-stage AD, and late-stage AD. By mapping the changes of which proteins were oxidatively modified at each stage, the authors found that during the MCI stage, there were increased markers of OS: protein carbonyls, free and bound HNE, TBARs, MDA, 3-NT, and isoprostanes in plasma, urine, and cerebrospinal fluid. During this early stage, OS damage was seen in proteins, lipids, and nuclear and mitochondrial DNA, suggesting that oxidative damage occurs before significant Aβ plaque accumulation or tau tangle formation.

As the disease progresses into the Early Alzheimer's Disease (EAD) stage, additional markers such as elevated 8-OHG in the cytoplasm, increased protein nitration, and higher levels of protein-bound HNE were detected, highlighting the role of oxidative damage as a biochemical trigger of disease progression. Similarly, Venkataraman et al. (2022) found increased sigma-1 receptor (SR1) binding, a marker of oxidative stress responses, across the brains of AD patients, alongside decreased mitochondrial complex I (MC1) activity and reduced synaptic density (SV2A). These changes correlated with worse memory scores and cognitive decline, underscoring the link between oxidative stress, mitochondrial dysfunction, and synaptic loss. This experiment demonstrates that oxidative stress was a response during the development of AD, suggesting that the brain was creating a protective response to stress or damage early in the

disease. Recognizing oxidative stress as an early hallmark shifts its role from a late-stage symptom to a possible target for earlier detection and prevention.

Oxidative Damage to the Mitochondria

One of the major consequences of sustained oxidative stress in early Alzheimer's disease is its damaging impact on mitochondria. Mitochondria are not only a source of reactive oxygen species (ROS), but also a key target of oxidative damage, creating a harmful cycle where ROS impair mitochondrial function, and dysfunctional mitochondria produce even more ROS. This cycle is evident early in the mild cognitive impairment (MCI) stage, where mitochondrial DNA (mtDNA) shows ten times more oxidative damage than nuclear DNA (Sultana and Butterfield, 2010; Wang et al., 2013). MtDNA is especially vulnerable because it is constantly exposed to ROS during ATP production in the mitochondrial electron transport chain, lacks protective histones, and has limited repair capacity. Cybrid studies confirm that mtDNA mutations trigger oxidative stress, ETC impairment, and abnormal calcium handling, all of which contribute to early neurodegeneration.

Furthermore, oxidative stress disrupts energy production and impairs normal mitochondrial dynamics. Increased ROS causes reduction of mitochondrial membrane potential and ATP generation (Misrani et al., 2021 and Tobore 2019). When ROS builds up, they weaken the membrane's charge, which leads to less ATP creation, robbing the neuron of energy. Furthermore, key metabolic enzymes such as ATP synthase, enolase, and LDH are all oxidized in both MCI and EAD, disrupting glucose metabolism and further limiting energy supply. Elevated DLP1 levels further drive mitochondrial fragmentation (Wang et al., 2013), worsening dysfunction. These mitochondrial disruptions interact with amyloid-beta and tau pathology, creating a toxic cycle that accelerates synaptic loss and neuron death. Supporting these findings,

in a study by Venkataraman et al. (2022), PET imaging showed reduced binding of [^18F]BCPP-EF, a PET imagining tracer that binds to MCI and helps visualize mitochondrial function, in patients with AD, especially in regions like the parietal and occipital lobes. This implies less MC1 activity, demonstrating impaired mitochondrial function. MC1 is mitochondrial complex I, the first enzyme in the ETC that is essential for ATP production. Lower MC1 binding was correlated with worse visuospatial memory in AD patients, but not in healthy controls. This further suggests that mitochondrial decline is linked to cognitive decline in early AD. In healthy controls, there was a strong positive correlation between MC1 and SV2A, suggesting normal physiological coupling between Mitochondrial energy production and synaptic function. In AD patients, this coupling between MC1 and SV2A was lost, indicating uncoupling between Mitochondrial function and synaptic density in disease. This evidence suggests that mitochondrial deficits appear in the earliest phases of AD, contributing to later neuronal damage and cognitive decline.

Feedback Loop

Oxidative stress and mitochondrial dysfunction feed off each other, creating a vicious cycle that worsens Alzheimer's worse over time. ROS are primarily generated during oxidative phosphorylation in the mitochondrial electron transport chain (ETC), where electrons from NADH and FADH2, electron carriers, are passed through the embedded inner membrane mitochondrial protein complexes I-IV (Misrani et al., 2021). Normally electrons move through the ETC, where oxygen ultimately acts as the final electron acceptor in order to form water. A small percentage of electrons may leak prematurely mainly from complex I or III and react with oxygen, leading to the creation of superoxide, a natural source of ROS. Because mitochondria both generate and are damaged by ROS, they are major targets of oxidative impairment.

Damaged mitochondria become less efficient, leak more electrons, and therefore produce more ROS, forming a self-amplifying feedback loop. As this cycle continues, it leads to oxidative stress, especially in neurons.

In Alzheimer's disease, the most common ETC abnormality is cytochrome c oxidase (Complex IV) deficiency, which disrupts the final transfer of electrons to oxygen. In postmortem human frontal lobe tissues, complex IV and V gene expression, which are important for energy production, were significantly reduced as AD severity increased, while complex I and II genes remained relatively intact, even in advanced AD (de la Monte et al., 2006). This suggests that mitochondria dysfunction in AD is due to the failure in later ETC stages, not the earlier stages. Reduced Complex IV activity leads to greater leakage from complexes I and III, increased ROS generation, and decreased ATP output and energy shortage in neurons. This defect both elevates oxidative stress and deprives neurons of the energy required for signaling, amplifying mitochondrial and oxidative dysfunction. Furthermore the excess ROS harms lipids in membranes through lipid peroxidation, proteins in the ETC complexes, and mtDNA and nuclear DNA (Misrani et al., 2021). This damage to the ETC proteins and mtDNA further promotes ETC dysfunction, which in turn, causes more electron leakage and ROS production. ROS increase is one of the earliest detectable changes before AD symptoms. Protein oxidation is already seen in MCI/EAD stages of AD, leading to a decrease in ATP, impaired firing of neurons, disrupted ion gradients, and signaling deficits.

The downstream consequences of this cycle are detrimental. Mitochondrial impairments include loss of membrane potential, reduced ATP production, disrupted energy metabolism, calcium imbalance, and dysfunctional dynamics and autophagy (Misrani et al., 2021). Furthermore, excess ROS production through the cycle promotes apoptosis through an increase

in Caspase activity and an increase in tau hyperphosphorylation and neurofibrillary tangles due to the hyperactivation of GSK3B, a kinase that adds phosphate groups to tau. Mitochondrial dysfunction is a key contributor to the development and progression of AD. Aβ oligomers insert into mitochondrial membranes, further promoting ROS production. ROS then initiates lipid peroxidation of membranes and intracellular protein and DNA oxidation, further exaggerating the ETC-ROS cycle. Mitochondrial damage occurs early in AD, and it can damage neurons and cause memory loss. Lipid, protein, and oxidation damage that results from ETC leakage causes cumulative neuronal damage (Misrani et al., 2021). Neurons are especially vulnerable to excess ROS formation because they have high energy demands, which require constant ATP for signaling, and have low antioxidant defenses compared to other tissues. Aβ and tau pathology further worsen the loop, promoting neurodegeneration in AD. Consequently, oxidative damage to neuronal proteins, lipids, and DNA induces functional decline, synapse failure, disrupted calcium signaling, neuronal death, and plaque and tangle formation (Aβ and tau pathology). Together, oxidative stress, mitochondrial dysfunction, and Aβ and tau pathology come together into a destructive cycle that contributes to neurodegeneration and cognitive decline in Alzheimer's disease in the early stages of the disease.

MtDNA Damage and Energy Failure

Mitochondrial dysfunction and oxidative stress are major contributors to cognitive decline and the executive dysfunction of Alzheimer's disease in the early stages. Cognitive impairment is a direct consequence of mitochondrial dysfunction in the central nervous system. Cognitive impairment is one of the earliest central nervous system signs of mitochondrial dysfunction in Alzheimer's disease. Oxidative stress markers were seen in frontal cortex postmortem AD brains, suggesting damage to cognition related regions (Tobore, 2019). Weak

antioxidant defenses and mitochondrial dysfunction lead to earlier vulnerability to oxidative stress, demonstrating why subtle cognitive symptoms emerge before severe AD pathology. Mitochondrial DNA mutations are also linked to worse memory and cognitive decline. Some genes that disrupt mitochondrial function are also linked to neurodegeneration and cognitive decline. These deficits show up early in the disease in MCI and EAD stages, which is consistent with mitochondrial dysfunction preceding full AD symptoms. Evidence shows that even in MCI/EAD, OS, mtDNA mutations, and mtD contribute to memory loss, early symptoms, and early behavioral changes (aggression, impulsivity).

AD brains have elevated mtDNA deletions and mutations, such as e-kb deletion. MtDNA is specially vulnerable to oxidative damage due to its absence of protective proteins such as histones and its close proximity to ROS generation sites. MtDNA is easily damaged by ROS, contributing to fewer mitochondrial transcripts and impaired ETC function (Wang et al., 2013). Transcriptomic data shows reduced expression of ETC subunits in AD brains. Mutations often occur in transcription/replication regulatory regions, causing reduced transcription of key ETC proteins. These defective ETC proteins result in worsened ETC dysfunction and further ATP loss. Lower enzyme activity is seen in AD, such as lower activity for a-ketoglutarate dehydrogenase complex (a-KGDHC), pyruvate dehydrogenase complex (PDHC), and cytochrome oxidase (complex IV). This reduced enzyme activity resulted in impaired oxidative phosphorylation and early mitochondrial energy crisis in the disease, which leads to less ATP for neurons. Furthermore, dysfunctional mitochondria are less efficient at producing ATP, therefore reduced energy and glucose metabolism in AD is one of the most commonly known abnormalities of the disease. Decline in glucose metabolism is already present in MCI, even before widespread neurodegeneration. This decline correlates with future cognitive decline,

making it an early marker of AD. Since neurons are energy-demanding, even slight metabolic impairment disrupts proper synaptic activity. This explains early memory loss and cognitive impairment in MCI/EAD before cell death becomes widespread.

Calcium Dysregulation

Oxidative stress and mitochondrial dysfunction contribute to calcium uptake deficits and ER overload, which are detected in MCI and early AD brains (Misrani et al., 2021). Excess calcium in the ER triggers early synaptic failure, explaining memory loss in MCI and EAD stages of the disease. Normally, mitochondria interact with endoplasmic reticulum (ER) at mitochondria-ER contact sites (MAMs) to regulate calcium transfer (Misrani et al., 2021). However in AD brains, reduced mitochondrial calcium buffering disrupts this balance. As a result, excess calcium is released from the ER, elevating cytosolic calcium levels. Over time, this dysregulation leads to periods of mitochondrial calcium overload, which drives increased ROS production, inhibition of ATP synthesis, cytochrome c release, and caspase activation. This causes increased vulnerability to exitoxic apoptosis (neurons die from calcium overload) and impaired synaptic transmission. This imbalance also disrupts neurotransmitter release and makes neurons more likely to undergo excitotoxic apoptosis. Calcium dysregulation impairs synaptic firing and plasticity, contributing to early memory impairment (Wang et al., 2013). Excess intracellular calcium also triggers apoptosis pathways, which accelerates neuronal dysfunction. Because excess intracellular calcium activates apoptosis pathways before widespread neuron death, calcium dysregulation is considered an early biomarker of mitochondrial dysfunction in AD.

Apoptosis Pathway Activation

Calcium overload in mitochondria not only disrupts ATP synthesis and creases oxidative stress, but also initiates apoptosis. Excessive mitochondrial calcium triggers the opening of the mPTP, releasing cytochrome c into the cytoplasm, binding to Apaf-1, which then activates Caspase-9. Caspase-9 then activates Caspase-3, the main executioner protease (Misrani et al., 2021). Caspase has two major roles in AD: initiating neuronal apoptosis and causing tau cleavage. Tau cleavage accelerates neurofibrillary tangle (NFT) formation. Increased markers of apoptosis, cleaved caspases and cytochrome c release, are found in MCI and early AD brains before widespread neuron loss. This links oxidative stress and mitochondrial failure to early synaptic and memory decline.

Tau Pathology and Neurofibrillary Tangles

A critical downstream consequence of mitochondrial dysfunction in AD is the dysregulation of tau phosphorylation. Normally, tau stabilizes microtubules and supports axon transport. In AD, tau becomes abnormally hyperphosphorylated. Hyperphosphorylated tau detaches from microtubules, causing them to destabilize and form twisted strands called neurofibrillary tangles (NFTs). Mitochondrial dysfunction promotes tau pathology. Amyloid-beta, tau, and mitochondrial dysfunction together increase OS. The OS then drives the hyperphosphorylation of tau, an abnormal increase in phosphate groups attached to tau (Tobore, 2019). High levels of OS activate the enzyme GSK-3B, which phosphorylates tau proteins excessively. This leads to tau becoming abnormal and pathological because it detaches from microtubules. OS also changes the physical structure of tau proteins, making the tau more likely to form fibrils, which produces neurofibrillary tangles, one of the AD hallmarks. The OS also drives the loss of neurons and synapses, which are key pathological changes in AD.

Mitochondria is a strong suspect in contributing to the buildup of amyloid-beta plaques outside of neurons. Aβ may harm the mitochondria and reduce ATP, potentially inducing synapse failure and eventually cell death. Aβ accumulates inside mitochondria, where it damages the electron transport chain, promotes fragmentation, suppresses mitochondrial fusion dynamics, and causes synaptic damage (Tobore, 2019). This impairs bioenergetics and exacerbates oxidative stress. In turn, ROS and AB toxicity reinforce one another, further destabilizing mitochondrial membranes and resulting in synaptic failure. When the mitochondria doesn't function properly, the neurons lose energy, build up toxic ROS, and the calcium signaling breaks, leading to brain degeneration in AD. There is also reduced activity of cytochrome c oxidase in the ETC, promoting energy loss, increases ROS, and results in more oxidative damage. These Aβ-mitochondrial interactions may occur before extracellular plaque disposition, poisoning mitochondrial pathology at the center of early disease progression.

Overall Consequences for Neurons and AD

Mitochondrial dysfunction has several consequences for neuronal health, greatly affecting the development and progression of Alzheimer's disease. Excess ROS generation causes oxidative damage to the mitochondria, while impaired oxidative phosphorylation reduces ATP production, leading to synaptic failure in neurons. Damaged energy production also promotes apoptosis, converting to cell death and neuron loss. Mitochondrial dysfunction accelerates tau hyperphosphorylation and Aβ toxicity, inducing synaptic and neuronal structural damage (loss of dendritic spines, an oral transport disruptions) and functional decline (weakened signaling, impaired memory formation) in neurons. These processes are detrimental in high-demand regions, such as the hippocampus and cortex, which are crucial for memory and cognition. Supporting this, Venkataraman et al (2022) showed that in AD patients, reductions in

mitochondrial marker MC1 and synaptic marker SV2A were associated with decreased brain volume, especially in memory-related regions like the hippocampus, supporting the idea that mitochondrial decline may contribute to synapse loss and neurodegeneration. This relationship was not seen in patients not impaired with AD, suggesting that mitochondrial dysfunction and synaptic loss is specific to AD. The experiment suggests that mitochondrial decline directly contributes to the structural and functional synaptic losses that underlie early memory failure in AD.

Antioxidant Imbalance

Antioxidants are especially important in the early stages of AD, when oxidative stress begins to overwhelm the brain's natural defenses. The buildup of ROS damages mitochondria and neurons, overpowering the number of antioxidants and causing cognitive decline. By helping to restore balance between ROS and the brain's antioxidant systems, antioxidant therapies may protect neurons, preserve mitochondrial function, and slow down the progression of the disease before major damage takes hold.

Research shows that patients with AD consistently show lower levels of antioxidants in the blood and brain (Wang et al., 2013). Aluminum bilirubin, uric acid, lycopene, vitamins A, C, and E, all plasma antioxidants, were significantly reduced in the disease. Antioxidant enzymes, such as superoxide dismutase, catalase, glutathione peroxidase, and heme oxygenase showed reduced activity and functional impairment in AD brains, especially in the frontal and temporal cortices. Because these deficiencies appear in the earliest disease stages, they accelerate oxidative damage and make neurons more vulnerable, driving the early progression of AD. Decreased activity of enzymatic and non-enzymatic antioxidants were seen in AD brains in the MCI stage, the earliest stage of the disease (Sultana and Butterfield, 2010). Additionally, lack of

crucial vitamins with antioxidant function can cause neurological problems, such as dementia and cognitive decline, emphasizing that OS is causative. Vitamin E deficiency leads to dementia and increased AD risk; vitamin B12 deficiency leads to cognitive impairment and dementia; vitamin D deficiency leads to dementia-like symptoms. Altogether, vitamin deficiencies worsen oxidative imbalance and increase the risk of developing AD, proving that antioxidants are essential for protecting neurons and delaying neurodegeneration, especially in the early stages of AD.

Since antioxidant deficiency drives early Alzheimer's progression, strategies to boost antioxidant levels may provide protection. A diet rich in antioxidant compounds, such as fruits, vegetables, nuts, seeds, and whole grains, supplies crucial vitamins like A, C, and E that help neutralize ROS and free radicals. Lifestyle changes such as exercise, maintaining healthy sleep, and reducing exposure to toxins, such as smoking or heavy alcohol use, strengthens the body’s antioxidant defenses. Overall, combining a nutrient-rich diet with healthy lifestyle habits is possibly one of the safest methods to improve antioxidant capacity and potentially slow the development and progression of Alzheimer's.

Improving Mitochondrial Health

Improving mitochondrial health could potentially delay or slow down AD progress in the early stages of the disease. Therapeutic implications include antioxidant-rich diets, exercise, therapies targeting ROS reduction, and drugs that support autophagy or restore calcium (Misrani et al., 2021). Exercise enhances mitochondrial function and energy metabolism, blocks brain atrophy, promotes neurogenesis, and supports cognition and memory. It also lowers oxidative stress by normalizing biomarkers such as SOD, catalase, glutathione, and peroxidase. In addition, ketogenic diets provide ketones that serve as energy sources, improve cellular

respiration in the mitochondria, reduce ROS, and increase antioxidant defenses (Misrani et al., 2021). A Ketogenic diet also can also mitigate cognitive dysfunction in the MCI stage of Alzheimer's early in the disease. Enhancing mitochondrial fusion can also restore proper mitochondrial morphology, reduce apoptosis, and improve mitochondrial function in order to reduce ROS production that drives the development of AD. Agents that promote mitochondrial fusion include SAMβA, BGP-15, Leflunomide, and hydrazone M1. By targeting mitochondrial health in the earliest stages of AD, it may be possible to delay neurodegeneration and preserve cognitive function.

However, research studies regarding treatments that target the mitochondria in AD are still in progress, as it is currently still a challenge to develop therapeutics that specifically target the mitochondria in order to slow down disease progression in the early stages.

Melatonin and Oxidative Stress

Sleep disturbances and oxidative stress often appear early in AD, making melatonin a potential therapeutic technique. During wakefulness, amyloid beta (Aβ) levels naturally rise, and in AD, disrupted sleep prevents the brain from effectively clearing the Aβ, accelerating ROS production in the earliest stages of the disease (Tobore, 2019). Melatonin, a hormone that many AD patients are deficient in, can help restore this balance by regulating the sleep-wake cycle and protecting against Aβ harmful effects. Higher melatonin levels lead to lower risk of cognitive impairment in elderly. Beyond improving sleep, melatonin directly counteracts mitochondrial dysfunction and OS, the two major drivers of memory loss and neuronal injury in AD. Melatonin supports hippocampal plasticity, neurogenesis, slows hippocampal pathology, and restores emotional memory (Tobore, 2019). Melatonin works as an antioxidant that prevents Aβ buildup and tau hyperphosphorylation, while also helping improve cognitive health by supporting

synaptic plasticity and neurogenesis in the hippocampus. It further protects against glutamate-induced excitotoxicity, a process where overstimulated neurons are damaged by calcium overload and OS. By regulating mitochondrial function, reducing toxic Aβ buildup and tau hyperphosphorylation, maintaining neurotransmitter balance, and protecting neurons from neurodegeneration, melatonin shows potential as an early intervention that could preserve memory and slow AD progression in the early stages of the disease.

Conclusion

This review highlights the growing evidence that oxidative stress and mitochondrial dysfunction are not only consequences, but also early components in the development of Alzheimer's disease, often before significant hallmark amyloid and tau pathologies of the disease. Studies have consistently shown that oxidative stress and damage disrupts mitochondrial energy production, calcium regulation, and neuronal survival, ultimately driving synaptic failure, neurodegeneration, and cognitive decline in the early stages of the disease. Therapeutic approaches that focus on restoring antioxidant defenses, improving mitochondrial health, and regulating sleep with melatonin suggest promising techniques for slowing disease progression early on if applied before major neurodegeneration begins.

However, there are still significant gaps in current research regarding how oxidative stress affects the mitochondria particularly in the early phases of AD. Many studies have relied on postmortem tissue, making it difficult to fully capture the earliest cellular and pathological changes that occur in the mild cognitive impairment (MCI) stage or preclinical AD. Research that directly explores oxidative stress and mitochondrial dysfunction as early drivers of the disease and that tests therapeutic techniques in the earliest disease stages remains limited, and

there is not yet enough experimental or clinical data to determine whether mitochondrial-targeted therapies can effectively prevent early disease development and progression.

Furthermore, studies examining mitochondrial dysfunction in early AD have reported somewhat contradictory findings regarding which electron transport chain (ETC) complexes are most affected. One study using PET imaging found reduced activity in mitochondrial complex I (MC1) in regions such as the hippocampus, thalamus, and caudate (Venkatarman et al., 2022), while a postmortem analysis reported that complexes IV and V were primarily impaired, with complexes I and II largely preserved (de la Monte et al., 2006). These discrepancies emphasize the complexity of mitochondrial dysfunction in early AD and may depend on brain region, research methods, and patient variability. More research is needed to clarify which ETC components are most vulnerable during the earliest stages of AD in order to better understand how these deficits contribute to oxidative stress, synaptic loss, and cognitive decline.

Future work should potentially prioritize longitudinal studies that follow individuals from preclinical or MCI stages, as well as clinical trials testing how oxidative stress disrupts proper mitochondrial function preclinically and testing interventions that support mitochondrial health and antioxidant balance. Because mitochondria appear as a driving factor of the destructive cycle between oxidative stress, amyloid, and tau pathology, targeting mitochondrial dysfunction may represent one of the most effective strategies for delaying or preventing Alzheimer's progression before major symptoms appear.

Oxidative stress and mitochondrial dysfunction are central features of early AD that contribute to cognitive decline before major disease symptoms and widespread neuronal loss occur. Evidence indicates that these changes appear in the earliest preclinical phases of the disease, during the mild cognitive impairment (MCI) stage, highlighting the need to study the

earliest stages of the disease. However, there are still significant gaps in understanding how oxidative stress and mitochondrial dysfunction directly interact in early AD. Furthermore, while therapeutic approaches such as antioxidant supplementation, exercise, ketogenic diets, and melatonin show potential in mitigating the effects of oxidative stress in Alzheimer's, more research is needed to clarify their effectiveness in the earliest stages of the disease. However, there is a lack of current clinical data that fully supports that lifestyle changes such as exercise, healthy sleep, and consuming antioxidant-rich diets effectively mitigate the effects of cognitive decline and mitochondrial dysfunction in the early stages of AD. By focusing future work on early detection and mitochondrial-targeted strategies, researchers may be able to identify treatments that preserve brain health and delay the onset and early progression of Alzheimer's disease.

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