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Cairo University

Commentary

Osama Fekry Al-Balah

Medical Applications of Laser Department, National Institute of Laser Enhanced Sciences, Cairo University, Egypt

Dear Respectful Editor,

I am writing to express my strong conviction that ethical considerations must be at the forefront of laser applications research. As the field of laser technology continues to rapidly advance, with applications spanning from medicine to manufacturing to telecommunications, it is critical that researchers uphold the highest standards of ethics and integrity.

Lasers are inherently powerful tools that, if misused or applied without proper safeguards, can pose serious risks to human health, safety, and privacy. Laser eye injuries, for instance, can lead to permanent vision damage, while high-powered lasers have the potential to cause fires or explosions if not handled with extreme caution. Moreover, advances in directed energy and sensing technologies raise important questions about data privacy and surveillance.

It is thus incumbent upon the laser research community to proactively address these ethical concerns. Researchers must carefully consider the intended and unintended consequences of their work, and strive to develop laser applications that maximize societal benefit while minimizing harm. This should include robust safety protocols, thorough risk assessments, and ongoing engagement with stakeholders and the public.

Additionally, the research community has an obligation to promote transparency and accountability. Full disclosure of potential conflicts of interest, research methods, and data should be the norm. Whistle-blowing mechanisms and external oversight can also help ensure laser applications are developed and deployed responsibly.

The Journal of Laser Applications is uniquely positioned to lead this vital discussion. By highlighting cutting-edge research that exemplifies ethical best practices, you can inspire the broader laser community to uphold the highest standards. Devoting dedicated journal issues, special features, or invited perspectives on laser ethics would be a meaningful step forward.

Now more than ever, as lasers become ever more pervasive in our lives, it is crucial that we harness this transformative technology in service of the greater good. I hope the Journal of Laser Applications will take up this important charge.

Sincerely,
Professor Osama Fekry Al-Balah
Professor of Zoology and Photobiology
NILES, Cairo University.

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A Strategic Review of the Impact of Modern Technologies on Scientific Research: AI, Lasers, and Nanotechnology

Walid Tawfik
Department of Laser Applications in Metrology, Photochemistry, and Agriculture (LAMPA), National Institute of Laser Enhanced Sciences (NILES), Cairo University, 12613, Giza, Egypt

Abstract

Purpose: Technological advancements have consistently transformed the landscape of scientific research. This Strategic review study explores innovative applications of laser spectroscopy, nanotechnology, and artificial intelligence (AI), emphasizing how these fields have the potential to revolutionize several industries.

Laser spectroscopy has made significant advances in environmental applications. Real-time, multi-elemental analysis of soil, water, and atmospheric samples is now possible thanks to techniques like Laser Induced Breakdown Spectroscopy (LIBS), which has improved environmental monitoring and management. Laser spectroscopy has helped develop tailored remedies in nanotechnology and cancer therapy. For example, Raman spectroscopy has been used to analyze tissue and cell samples, monitor nanoparticle delivery systems, and help identify cancer biomarkers. Furthermore, when combined with nanoparticles, laser-induced photothermal effects present promising pathways for the targeted destruction of cancer cells. Artificial neural networks, or ANNs, have also demonstrated enormous promise in the remediation of water contamination. Artificial Neural Networks (ANNs) can anticipate pollutant levels, analyze water quality metrics, and optimize treatment procedures using their predictive modeling and optimization skills. This real-time monitoring and control can significantly increase water treatment systems' efficacy and efficiency.

Conclusion: This review's novelty lies in its interdisciplinary approach, emphasizing the convergence of these technologies to tackle complex scientific problems. By integrating AI's computational power, lasers' precision, and nanotechnology's versatility, we present a compelling vision for the future of scientific research. From sustainable development to transformative healthcare applications, these technologies promise to redefine human interaction with science.

This essay emphasizes the value of ongoing innovation in these domains and shows how they might help solve some of the most significant challenges of our world.

Keywords— AI innovation, laser spectroscopy, nanotechnology, cancer treatment, water pollution treatment, environmental applications

I. INTRODUCTION

Technological and scientific developments are closely related and have profoundly influenced and exponentially accelerated the pace of human development throughout history [1]. By delving into the intricacies of scientific and technological advancements, comprehending their historical context and current state, and intensifying the understanding and exploration of state-of-the-art scientific instruments and cutting-edge research, we pave the way for the sustainable evolution of human civilization [2]. The rapid advancements in artificial intelligence (AI), laser technologies, and nanotechnologies have significantly catalyzed progress across diverse scientific domains. This review comprehensively explores the historical development and applications of these technologies, emphasizing their transformative impacts on medicine, energy, communication, and material sciences. For instance, AI has revolutionized predictive modeling in healthcare, laser technologies have enhanced manufacturing precision, and nanotechnology has introduced targeted drug delivery systems and advanced energy solutions [2-3].

Furthermore, we meticulously examine their far-reaching applications in fundamental research, bearing invaluable insights that allow scientists to more profoundly grasp the magnitude of the ongoing technological revolution and its strategic impact on science and technology at large developments [4]. The continuous innovation in artificial intelligence, lasers, and nanotechnologies has revolutionized various fields, including medicine, energy, communication, and transportation. These cutting-edge technologies have opened up new possibilities and transformed our lives and interactions. Artificial intelligence, with its ability to simulate human intelligence, has the potential to automate processes, analyze vast amounts of data, and make complex decisions. It is used extensively in healthcare for diagnosis, treatment planning, and precision medicine. Additionally, AI has found applications in self-driving cars, virtual assistants, and even in enhancing cybersecurity measures. The advancement in AI algorithms and deep learning techniques has propelled this field to new heights, presenting incredible opportunities for future growth and development [5].

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Corresponding author: Walid Tawfik Email: walidtawfik@niles.edu.eg

Laser technology, on the other hand, has revolutionized various industries with its precision, efficiency, and versatility. Lasers have become indispensable tools from manufacturing and telecommunications to medical procedures and scientific research. They are used in surgeries for their precision and ability to minimize tissue damage. Laser technology is also crucial in telecommunications, enabling high-speed data transmission through fiber optics. Furthermore, lasers have contributed to breakthroughs in quantum computing, material processing, and astronomy, expanding our understanding of the universe [6].

Nanotechnology, the engineering of materials and devices at the nanoscale, has unlocked immense potential in numerous fields. It allows scientists to manipulate matter at the atomic and molecular levels, paving the way for novel materials and innovative applications. In medicine, nanotechnology has separately enabled targeted drug delivery systems, such as nanoparticle-mediated chemotherapy, and advanced imaging techniques like nanotechnology-enhanced MRI and PET scans. These applications are distinct yet complementary, with each contributing to more precise and effective healthcare solutions [7]. It has also revolutionized the energy sector by enhancing solar cells' efficiency and developing energy storage devices. Moreover, nanotechnology has contributed to the development of stronger and lighter materials, improving the performance of various products, from electronics to aerospace [7].

The convergence of artificial intelligence, lasers, and nanotechnologies has the potential to bring about a new era of scientific exploration and innovation. Together, these technologies can synergistically advance our understanding of the world and push the boundaries of what is possible. They offer exciting prospects for solving complex problems, improving human health, and mitigating the challenges posed by an ever-changing world [8]. Artificial Neural Networks (ANN) is a computational model inspired by the intricate connections found within the human brain. ANNs consist of interconnected nodes, also known as neurons. Each neuron processes and passes information to other neurons, allowing complex computations to take place. These networks can learn and adapt through training, making them highly versatile and powerful tools in various fields, such as machine learning, pattern recognition, and data analysis. By mimicking the neural connections in the brain, ANNs can solve complex problems and make sophisticated decisions. With advancements in technology, the potential applications of ANNs continue to expand, revolutionizing industries and pushing the boundaries of what is possible [9].

In conclusion, the progress in artificial intelligence, lasers, and nanotechnologies has sparked a technological revolution with profound implications for our society. The historical significance and ongoing advancements in these fields have opened up exciting possibilities for scientific research, sustainable development, and human progress. As we continue to delve deeper into these transformative technologies, we must embrace their potential and ethical considerations while striving to ensure that their benefits are accessible to all. By leveraging the power of AI, lasers, and nanotechnologies, we can shape a future where innovation and progress go hand in hand, creating a better world for generations to come [10].

II. HISTORICAL CONTEXT OF TECHNOLOGICAL ADVANCEMENTS IN SCIENTIFIC RESEARCH

The history of science, technology, engineering, math, arts, and health, perhaps abbreviated as STEMAT, can be summarized in the era of the Information Technology Revolution, in which modern technologies have significantly enhanced the capability of scientific research worldwide [11]. We will take the readers through time to showcase how science has evolved from the ancient era to the Renaissance and modern times, and now to the modern age, discussing the important technological advancements in different periods and the impact on the advancement of scientific research. As a brief background to the discussion, since the Stone Age, humans have utilized fire and invented the wheel. This revolution is the foundation of traditional human civilization, modified a bit through the Bronze and Iron Ages and until the Roman Empire, where its technology of construction, road, theatre, human hygiene, and distant trade exceeding the standard of the time could never be surpassed by others in 1500 years [12].

However, the Renaissance was the true starting point of modern human civilization, championed by Leonardo da Vinci 7 centuries ago, where we discovered our place in the universe, solved mathematics, Newton's laws of motion, and universal laws of gravitation, and have been benefiting from the modern world due to the invention of the steam engine and metalworking. Faraday, Maxwell, Ampere, Volta, Ohm, Henry, and Michelson, Clark Maxwell researched the basic laws of electromagnetism discovered in the 19th century. Einstein's theory of relativity and Planck's quantum hypothesis in the 20th century opened a new era of human science. In the 19th and 20th centuries, through the development of film recording, information processing, electronic communication, electronic materials, computer technology, and information technology, we laid the foundation of the high technological modern age today [12].

2.1. The Evolution of AI in Research

AI brings huge potential benefits, but also profound changes and risks. This new point of development will have a bigger and faster impact on scientific research. We believe that there is an immediate and urgent need for scientific institutions and universities across the globe to undertake strategic reviews to understand the potential impact of AI, not just on their ongoing work but on their core purpose as institutions of research and learning. This is important for ensuring that emerging developments are exploited to best advantage and for maximizing the potential benefits and minimizing the negative consequences [13][14].

Artificial intelligence (AI) is no longer just a fanciful dream of "what might be" but is now entering everyday life. This is due to a number of recent breakthroughs and to developments being driven in part by big investments by large corporations and in part by public and private funding. We are witnessing the start of a new era with significant transformational impact across many sectors - especially in fields where the complexity of the data to be analyzed has hampered progress. However, the scientific research sector has shown a remarkable disregard for the most recent breakthroughs - despite it being a sector that normally is at the forefront of developing and exploiting new technologies. We have AI systems that are better at chess, Go, and poker than the best human players. AIs can nowadays participate and perform well in call center tasks without callers being able to tell that they are talking to machines. It is now cheaper to download an app recognizing your speech than to employ a human assistant. The Darwin challenge has been proved by the development of systems that can evolve the ability to solve complex problems in a human-like manner. These breakthroughs, and others like them, have had very little impact on daily activities [15].

2.2. The Development of Laser Technology

The development of laser technology began in 1959, and it is a kind of light source whose amplification system uses the principle of population inversion caused by stimulated radiation. When a photon of the same frequency as the stimulated radiation meets an excited state of molecular, atomic, and ionic oscillations with the same phase and direction, another photon around it will be emitted. The two photons, one original and one newly generated, move in the same direction and have the same phase. Coherence is one of the key properties of lasers that distinguish them from other light sources. At present, laser technology has been widely used in various fields of industry, and its application technologies are constantly innovating. The emergence of new laser devices or the improvement of existing laser devices can better meet the needs of people. These fields mainly include the field of information technology and the manufacturing, life, and energy fields. Since the photons oscillated by the laser have strong coherence, lasers are mainly used for processing because coherent photons have characteristic energy density, high monochromaticity, and high directivity [16].

When a material is irradiated by a laser beam, the material absorbs the energy carried by the beam, and the temperature of its surface rises, so the interaction between the laser and the substance is an energy conversion process. At present, researchers use lasers to process various materials, such as semiconductors, dielectrics, polymers, and metals, to obtain the desired surface morphology or structure. In the processing of laser materials, the complex movement of non-metallic materials is mainly the result of the absorption of light energy on the surface and the changes in the material's phase, physical, and chemical properties caused by optical radiation or thermal effects. The laser beam radiating energy on the surface of the material is absorbed and converted into thermal energy, making the temperature of the surface layer of the material change, which will destroy or change the nature of the material, resulting in the appearance of different shapes and structures. [17]

2.3. Advancements in Nanotechnology

Nanotechnology deals with the engineered manipulation of functional materials and devices at the molecular and atomic levels. The development of nanotechnologies provides new and improved materials and devices that offer significantly better overall performance, reliability, and efficiency than anything currently developed in the chemical, biological, electronics, and related fields.

Applications aimed at the development of entirely new areas of science and technology are of great importance: molecular electronics, tumors in which nanodevices can distinguish between those that are cancerous and those that are not, and electro-mechanical computing devices. One major advantage of materials science in nanotechnology is the progressive miniaturization of materials. Precision nanodevices have been developed, the main advantage of which is the unparalleled precision they can achieve. Nevertheless, since many of the operational characteristics of nanodevices are derived from molecular interactions between nanodevices during use, other important aspects of molecular interactions in related biological systems must be sought in the development of nanodevices. The other important remaining challenge for nanodevices is the integration of physical and algorithmic moieties. Finally, let us note that the process of evaluating the quality of functional materials at microscopic through nanoscopic levels is a fundamental aspect of advanced materials research in modern times [18].

III. ROLE OF ARTIFICIAL INTELLIGENCE IN SCIENTIFIC RESEARCH

In the following research, we investigate the role of cutting-edge technologies in scientific research, asking the provocative question of who really "does" research today in science. With a combination of both theoretical and empirical analysis, we specifically study the interplay and impact of artificial intelligence and big data on scientific progress, focusing on the AI paradigm. For empirical analyses, we collect data from special state-run machine learning platforms. We then study the specific questions regarding who really is the "scientist" when scientific research is conducted. Our results indeed suggest that modern digitalization and AI help decrease the role of individual researchers while at the same time increasing the role of scientific communities and politicians in determining research directions [19].

There is abundant literature documenting the process of scientific discoveries. The theoretical models typically explain the process in a very traditional way, with hypotheses, empirical tests or verifications, and a certain number of citations, often seen as validation measures. Only a few studies suggest that specialists in various scientific fields value different parts of research processes differently. Among the empirical papers, most analyze time allocation, productivity, and mobility of researchers, examining researchers' influences or earning dynamics among established research cooperations. They mostly limit their analysis to well-established research institutes but do not focus on the way science is carried out so specifically [20].

3.1. Machine Learning Algorithms and Artificial Neural Networks (ANN)

Machine learning involves computer systems that can infer new knowledge from data. Within machine learning, we distinguish between supervised machine learning, unsupervised machine learning, reinforcement learning, and recommendation systems. Thus, machine learning provides big opportunities to be used in scientific explorations where large sets of data are available. Particularly, there are special challenges in the development of machine learning methods for scientific data analysis. Scientific data has uncertain estimates of measure or statistical errors, and often does not have example data, which is required for classification. The scientific goal usually is to discover new laws or empirical relationships from the huge sets of data that need to be optimized continuously through the supply of new data under open experimental boundaries.

Artificial neural networks are composed of a number of neurons or processing elements that utilize a mathematical model mapping relationships between input and outputs. They were developed based on neurobiology and are particularly useful for data clustering, feature association, and function approximation. Simple notions of computing are termed 'learning' or 'training' via the eye-catching back-propagation mechanism, where the strengths or weights between neurons in the network are changed until the network provides reasonable outputs within desired patterns. These and other related models such as convolutional networks and recurrent neural networks, are currently experiencing a renaissance, particularly for pattern recognition problems, and are transforming modern machine learning. Scientific methodologies are also being revolutionized using machine learning and particularly ANNs for areas such as bioinformatics, drug discovery, astroinformatics, and complex network analyses and simulations [21].

Walid Tawfik and M. A. Ibrahim, along with their research group, conducted a study on the removal of Atrazine from water using armchair-hexagonal hexagonal graphene quantum dots (AHEX). They employed density functional theory simulations to investigate the effects of doping AHEX with boron, nitrogen, and sulfur. The study employs artificial neural networks (ANNs) as a key modeling tool to analyze the molecular interactions involved in the removal of Atrazine using doped graphene quantum dots. By leveraging ANNs, the researchers can effectively capture the complex relationships between the structure of the doped graphene and its adsorption performance for Atrazine. The model is trained on data derived from density functional theory simulations, allowing it to predict the adsorption energies and interaction dynamics accurately. This approach not only enhances the understanding of how different doping elements (such as boron, nitrogen, and sulfur) influence the adsorption capacity but also facilitates the exploration of optimal configurations for improved water treatment applications. The use of ANNs in this study underscores their significance in advancing molecular modeling and the development of effective environmental remediation strategies. The findings showed that doping enhanced the total dipole moments and adsorption capacities for Atrazine, with sulfur-doped AHEX achieving the highest adsorption energy of 2.97 eV. UV-vis spectroscopy revealed shifts in absorption peaks post-adsorption, demonstrating the potential of doped nanographene as an effective treatment for atrazine-contaminated water [38].

3.2. Natural Language Processing

Natural language processing (NLP) is one of the most active research and application areas of artificial intelligence. It involves the development of information technology surrounding the ability of computers to understand and process human language. This is a crucial technology in today's information society, which struggles with the ever-growing corpus. The enhanced computational tools provided by the latest natural language processing technologies can help people efficiently digest information and knowledge that is encapsulated and represented by language. This is particularly the case in the field of scientific research, where rapid accumulation of new findings results from an automated pipeline. In this paper, they present the latest advances in leading scientific conferences, including empirical observations in academic communities, and discuss potential future directions to help readers outside the NLP community understand the latest developments in this dynamic research area [22].

3.3. Robotics and Automation

In addition to AI and computing, other tools are becoming more and more intelligent in our scientific laboratories. Robotics and automation are playing a more and more significant role in scientific activities at a basic research level. The complexity of both new materials and living organisms is such that many phenomena and processes have to be investigated on increasingly smaller and larger size scales simultaneously in order to fully understand them. Together, AI, robotics, and automation in the laboratory are key strategic enabling technologies, the basis of what might best be described as Interactive Intelligent Systems in the laboratory.

At one end of the range, automated machinery is very useful for performing repetitive tasks in large numbers and across time scales that are very unattractive to humans. Robotics extends the application of automation further by adding the ability to control tools in either a fixed or moving environment, or along specific paths or even in indeterminate environments where guidance is provided by navigating sensors integrated into the surface of described objects. [23].

Robotics is about continuous control and interaction of multiple sensing and acting modalities with the surrounding world. At the other extreme, active vision on the one hand and active manipulation using multiple articulated arms and gripper hands on the other represent the state of the art in robotics research, and they are both now of potential point of use laboratory value [24].

IV. IMPACT OF LASER TECHNOLOGY ON SCIENTIFIC RESEARCH

The report investigates the state of the art of technologies in three areas: deep-UV notched fiber technology, UV planar yellow laser development, and yellow, red, and violet fiber laser technology. These technologies show great promise for enabling a variety of applications, particularly in nuclear and particle physics at the test phase level and in scientific research in general. The report contains technical analyses and R&D recommendations for meeting the identified goals.

The invention of the laser has brought about a revolution in physics with many diverse applications. Many people and much funding support research and development of laser technology. This is proper because the potential for scientific wealth and benefits is large. The insightful reader will realize that physical laser materials are also sources of phonons and photons, and amplified spontaneous emission is also an interaction. All of these become non-negligible at sufficiently high intensities, time scales comparable to or longer than characteristic times of the materials, or when the laser has not stabilized to the ground state [25].

4.1. Laser Spectroscopy in Chemistry, Biotechnology, and Environmental Applications

4.1.1. Fluorescence Method for Dextroamphetamine Detection in Forensic Analysis

Biomedical research using laser techniques for the detection of drugs in human body fluids, namely, the determination of dextroamphetamine, which has a stimulating effect on the body, is interesting. Laser fluorescence analysis was used to determine dextroamphetamine in additive-free solvent-purified urine, using spiral microfluidic chips with embedded LEDs. The most interesting conclusion is that, in the context of the extremely low selectivity of the fluorescence of amphetamines, microfluidic chips are a promising tool for analyzing fluorescent drug molecules within customs, forensic, biosensor, or clinical management applications. These encapsulation methods revealed potential new application areas for drug detection tests without the need to pre-treat fluorescence side-effect drugs [26].

4.2. Laser Microscopy in Biology

Laser microscopy has become a well-established and invaluable tool for biological research and has revolutionized our ability to capture three-dimensional images of living cells and other biological structures in real time. Advances in technology, such as the use of intense ultrafast laser pulses, have allowed the development of efficient non-linear optical imaging techniques that go beyond the limitations of traditional microscopy with visible light. The wide range of techniques is subsumed under the term multiphoton excitation microscopy or shortly multiphoton microscopy. Because non-linear excitation requires higher light intensities than linear imaging, only multiphoton absorbance of infrared light is used without artificial staining of the sample. This results in little cell damage, thus making multiphoton microscopy particularly suited for imaging biological systems [27].

The basic principles of light and laser microscopies, including the limitations of conventional microscopy and the geometrical and optical reasons limiting spatial resolution, are explained in the first part. This is followed by the explanation of laser-based non-linear excitation, allowing spatially restricted multiphoton microscopy beyond these limitations. The practical aspects of these advanced techniques and the physical sources of constraints and artifacts as well as strategies for their solution are discussed and illustrated by examples from ongoing research. In addition to their technical significance, advances in laser microscopy could also lead to important future biological breakthroughs, such as faster drug development and improved understanding of cell function. In the long run, the work could lead to similar noninvasive optical imaging techniques for the diagnosis and treatment of human disease by instruments that operate safely through the skin or cavities [28].

4.3. Laser in Environmental Applications

Technological advancements in recent years have contributed to changes and transformations in research methodologies used by researchers in scientific research. The research paper provides a strategic review of how some of the most recent empowering techniques that are revolutionizing the processes, structures, and results of sciences, such as laser technology, nanotechnology, and artificial intelligence, act in scientific research, taking into consideration, as the case may be, the specific role of each of these potent techniques in several areas of science. The effects of these technologies are also described on the more general and broader aspects, from the possibilities of sharing and disseminating research to exploring such changes in training methodologies for scientists, while we explore the ethical perspectives that are required [29].

It is not that the use of laser technology for environmental applications is a novelty. The development of remote sensing has enabled monitoring of the Earth's surface from space. Remote sensing is increasingly used to monitor the environment, and the development of satellite platforms incorporating microelectronics advances every minute, and new ecosystems are being integrated into the models, applications, and monitoring of a large number of entities, including algae blooms, parasites, environmental pollutants, shipwrecks, and many more.

The Walid Tawfik group, along with their colleagues, achieved a significant breakthrough in the detection and quantification of heavy metal elements in agricultural samples using advanced Picosecond Laser-Induced Breakdown Spectroscopy (Ps-LIBS). This cutting-edge technology facilitated high accuracy and precision, markedly enhancing the impact of their research. In their study, Tawfik and his team optimized the Ps-LIBS parameters to ensure robust analytical performance. Specifically, they set the laser energy to 100 ± 5% J/cm², calibrated the pulse duration to 170 picoseconds, and employed 1064 nm Nd:YAG pulses. These optimizations enabled the creation of linear LIBS calibration curves, which were crucial for precise elemental quantification [30-32].

The use of Ps-LIBS allowed for the accurate detection of heavy metals such as copper, nickel, and cadmium in samples of *Lactuca sativa L.* and *Trifolium alexandrinum L.* collected from Banha and Giza, Egypt. The high precision of Ps-LIBS revealed concerningly high levels of these metals across all study sites, highlighting significant environmental and health risks. The bioaccumulation factors of these metals in the plants further underscored the urgency of addressing this issue.

This innovative application of Ps-LIBS not only advanced the field of environmental monitoring but also provided critical data that necessitated the recommendation for constructing a dedicated wastewater treatment facility in Al Mansouria village, Giza governorate, to mitigate the environmental challenges posed by heavy metal contamination [30-32].

V. NANOTECHNOLOGY AND ITS APPLICATIONS IN SCIENTIFIC RESEARCH

Nanotechnology involves exploring, exploiting, and controlling the physical and chemical characteristics of nanoclusters, nanoparticles, and nanostructures. From the single-digit nano to a few hundreds of nanometers, any implementation or attainment at suppressed dimensions interests humans, and their exploratory nature leads to self-organizing, generating, and utilizing nature-made nanostructured models as a source of inspiration. The ability to integrate biological and microelectronic systems at the nanoscale and to design and construct devices that exceed molecular limits is the greatest strength of nanotechnology. Biosensors, nanoscale metrology techniques, nanomaterial design, diagnostic agents, therapeutic agents, medical imaging probes, tissue re-engineering, ferrofluids, drug targeting devices, nano-techniques, nanoclinical chemistry, and nanoproteomics are the creations of nanotechnology, extending its maximum usage in scientific research [33-34].

Since nanotechnology defines and utilizes structural abilities to build functional, holistically planar materials and complex biological systems, it extends the limits of materials and can combine new emergent properties. Nanotechnologies use a combination of top-down and bottom-up methods employed by semiconductor manufacturers and chemists.

Nanotechnologies emphasize self-assembly and include the development of three-dimensional structures designed to be more complex than semiconductors made by traditional methods, with a wide enough group of materials and a variety of structures to serve various functions that would enhance and strengthen the abilities of semiconductors. Miniaturizing components increases the density of both components and speed. In addition, specific aspects like nanowires and self-organizing nanostructures, as well as fully nanotechnology-enabled structures like quantum devices, molecular devices, single electrons, membrane entropy-driven carbon nanotube pumps, superconducting devices, and DNA computers, are significant. Superconductors are the result of ongoing research. Yet, even the most miraculous molecular devices are not fully produced.

To prove the theoretical concept of nanotechnology applications, nanotubes are addressed with 10 nanometers DC and clear position dependence subject to the inherent noise of thermal vibration. With some degree of compromise due to massive defects, superlattices of various lengths and sizes, and self-assembly from phase-separated mixtures, we were able to increase their length to 10 micrometers and fabricate some of the structures. With some difficulties for potential applications still to be overcome, when addressing existing issues related to any possible implementation, the most relevant details were thus developed. What we noticed is the problem with every current physical gadget: the device is attached to an external cable, and its mesh or flow must be activated and measured remotely by an external circuit. That would seem like a minor inconvenience, but only if location and wiring density were not a top priority, a fundamental design approach of nature's electronic devices, and characteristics crucial to the ability of self-assembly [30, 35, 36].

5.1. Nanomaterials Synthesis and Characterization

To explore and study new electrical, chemical, and optical properties of materials and related new nanoscale applications, nanotechnology requires nanoscale, i.e., less than 100 nanometers (nm) in diameter for precision manufacturing. Nanotechnology has raised vital concerns in producing new and unique materials on a large scale, including developing large-scale mixing and integrating blocks of nanoscale products. Several different methods for synthesis and particle characterization now exist, which include mechanical milling, high-energy ball milling, cluster seeder, evaporating physical vapor, sputtering, laser ablation, and chemical reactions of various sorts.

This section should not only evaluate these different production methods and the roles of chemical additives and catalysts but also assess greenhouse gas emissions, life cycle analysis, and other environmental impacts involved. Therefore, the objective of highly economically beneficial processes, methods, and protocols should also design disease, stress bio- and phyto-remediation, bio-detection, and preclinical and clinical studies applicable to human blood exchanges, biosensors, cancer diagnostics, and treatments. Nanotechnology enables the manipulation of matter at atomic and molecular levels, driving innovations in materials science and medical applications. In medicine, nanotechnology has been pivotal in developing targeted drug delivery systems, such as liposomal doxorubicin, and diagnostics through quantum-dot-based imaging. Advances in nanoscale engineering have also facilitated breakthroughs in energy storage and sensor technology [37].

We predict that the rapidly depositing oxide nanomaterials for use as one-dimensional (1D), two-dimensional (2D), and three-dimensional (3D) nanomaterials will continue to undergo rapid growth and the corresponding requirement for repetitive environmental analysis. Consequently, we will assign a higher priority to both quality and environmental issues in order to satisfy these requirements. For ease of reading, the associated nanotechnology methodology and technologies are usually collectively called NMT. The modified NMT process is designed to produce special nanoparticles of high quality and at higher throughputs. The proposed process will be useful in the biomedical field and will be applied to any type of pressure sensor to enhance both the building and detecting layers. These methods of manufacturing can be standardized to automatically produce the granular and other varieties of nanotechnology along with any relevant integrated sensor, algorithm, or complete system platform [38].

5.2. Nanomedicine and Healthcare Applications

The application of nanotechnology in healthcare is one of the most well-known and fast-growing fields of nanotechnology deployment. In fact, in global terms, nanomedicine is the second largest application area of nanotechnology, following nanoparticles used for cosmetics and sunscreens. The small sizes of nanoparticles, including the fact that they have more surface area per unit volume, can allow them to interact in unique ways with human biomolecules. Nanoparticles, usually in the range of 1-100 nm, are also comparable in size to biotic systems and display unique properties because of their size and the nature of the materials used in their construction. The potential of this emerging field of research has led to significant investment in the development of these techniques. By 2027, the market for nanomedicine is predicted to be over $400 billion. To this day, various nanotechnology-based solutions have been developed for applications as diverse as the detection of biomolecules, drug delivery, diagnostics, tissue engineering, and cancer therapy [37].

The Walid Tawfik and Heba El-Ghaweet research group conducted a pioneering study on photothermal therapy (PTT) assisted by gold nanorods for treating mammary cancers in adult female rats, published in Nanoscale Advances. The study evaluated the potential of PTT in treating 7,12-dimethylbenz[a]anthracene (DMBA)-induced mammary cancer using polyvinylpyrrolidone-capped gold nanorods (PVP-AuNRs) and NIR laser irradiation. Forty-two adult virgin female Wistar rats were divided into seven groups, including various control and treatment groups [46].

The synthesized AuNRs with an aspect ratio of 2.8 to 3 were characterized and validated for their near-infrared light absorption capabilities. The combined therapy of DMBA + PVP-AuNRs + NIR effectively treated the tumors and halted their growth. Biochemical and histological analyses, supported by immuno-histochemical localization and TEM images, highlighted the efficacy of this approach. The study unveiled the revolutionary effect of PTT using PVP-capped AuNRs, offering a promising new strategy for mammary cancer treatment [46].

5.3. Nanoelectronics and Quantum Computing

Undoubtedly, the new challenges of the electronics industry, including the increasing complexity of chips and breakneck speed, are excellent stimulants for the development of nanoelectronics, which is positioned between current electronics and expected quantum computing. We deal mainly with Moore's Law and its expected continuation. The transition from microelectronics to nanoelectronics and quantum computing does not seem to be a smooth and linear process. It will mark an important break in the capabilities and performance of devices. Whether the Law can withstand the shift in the technological industry paradigm is an open question. The validation of the Law in three evolutionary waves is commented on, with the third wave still underway. Some prospects for its continuation are discussed [39].

We then move to devices, highlighting the advances in the miniaturization and development of increasingly complex chips and systems. A major emphasis has been on improvements in the packing density of components. The spectacular increase in transistor count per chip over the past years illustrates this trend convincingly. In parallel with the transistor count, energy consumption has increased more than proportionally to the increased performance gained from the increase in the number of processors, due mainly to the increase in chip frequency. Furthermore, the large energy consumed in memories, which are power-hungry and slow, should be considered. The static consumption of CMOS circuits is also troubling, especially because of the arrival of microelectronic systems with more than a billion transistors. It is widely admitted that the power wall faced by computer designers calls for a rethinking or even a complete revision of the processor architectures themselves. Such a revision should lead to low-cost, low-power solutions that offer high performance to keep up with the impressive overall increase in microprocessor technology [40].

VI. INTERDISCIPLINARY APPROACHES AND COLLABORATIONS IN TECHNOLOGICAL RESEARCH

Respondents noted the importance of interdisciplinary approaches and collaboration in technological research while pointing out the societal and professional barriers to these aspects. Researchers at organizations that do not designate interdisciplinary research as a hiring criterion or promotion criterion or that have separate accounting streams for different disciplines noted negative consequences. Respondents noted that these barriers make it difficult to recruit the right talents for interdisciplinary research or development roadmaps. In the research community, innovative researchers become in demand as they produce interesting work in one field that leads to a breakthrough in another, making it difficult to convince them to move to interdisciplinary research.

Despite these obstacles, collaboration and interdisciplinary approaches are critical to leveraging resources and potential. When successful, interdisciplinary research has shown its potential to result in groundbreaking developments, expediting the development and market release of products to keep researchers ahead of international competition. Less popular fields such as laser science could particularly benefit from recruits with diverse interdisciplinary backgrounds as they could revitalize the field; these disciplines include materials science, biology, computer science, electrical engineering, and chemical engineering.

To promote optimal outcomes from interdisciplinary research, respondents offered a series of tools and practices for universities and researchers, including workshops that allow young researchers to network and brainstorm about problems and emerging research topics in cross-disciplinary science while supporting attendance at intensive interdisciplinary summer schools. Can scientific and professional societies give more spotlight to interdisciplinary research and invite this type of work to conferences? To help bridging the gap between interdisciplinary scientific conversations and open collaboration with stakeholders in the field, research institutions can offer tools and restrictions on proprietary or export-restricted information. Efforts can concentrate on promoting a shared language or framework for collaborations rather than demanding knowledge of everything across many fields. While recognizing that universities might have different roles than research and development organizations, respondents also offered that universities can orient training and promotion criteria in such a way as to facilitate research between disciplines, adding weight to the role of the study of cross-cutting speeds in merit criteria for tenure or promotion [41].

6.1. AI and Nanotechnology Integration

With capabilities evolved from large-scale databases, improved algorithms, and ever-increasing computational power, machine learning technology has been guiding scientific efforts in knowledge capturing, materials design, and analytics. We are observing significant progress in subjects such as computer vision and natural language processing. Via deep learning, Radial Basis Function units are integrated into convolutional neural networks by means of supervised fine-tuning for data-driven potential design. In addition, the information bottleneck principle serves to guide feature extraction throughout the self-supervised learning for the resulting progression of Kohn-Sham orbital differentiation, meanwhile invariance to spatial symmetries is allegedly followed by the natural implementation of permutation equivariant convolution for guidance in deep materials property prediction [42, 43].

Furthermore, unsupervised learning is exploited for automatic experimental setup in measuring multiple behaviors of anionic and cationic states. Both unsupervised language modeling and supervised learning down to curbed action classifiers contribute to the assisting role for catalyst prediction. The potential of special-purpose artificial intelligence hardware for solving scientific problems is currently considerable and is expected to grow in importance. The extent of by-hand feature engineering in scientific AI problem solving is reduced, allowing automated feature engineering and thus improving algorithm quality. The further assets of AI in scientific problem solving quite surely have not yet been exhaustively explored. Therefore, the union between AI and scientific research appears productive, interesting, and worth further investigation, with several methods developed and a few proposed in the context of this thesis alone.

Walid Tawfik and M. A. Ibrahim and their research group conducted a significant study on the removal of Atrazine from contaminated water using functionalized graphene quantum dots (GQDs) [39]. Given the urgent need for new water treatment techniques due to pollution, this study leveraged artificial neural networks (ANNs) to capture the complex relationships between the structure of functionalized graphene and its adsorption performance for atrazine. The ANN model was trained on data from density functional theory (DFT) simulations at the B3LYP/3-21G level, accurately predicting adsorption energies and interaction dynamics. The study found that attaching chemical groups like CN and NO_2 enhanced the dipole moment of GQDs, significantly improving their adsorption ability. The computed adsorption energies for the modified GQDs were notably high, demonstrating their efficacy in Atrazine removal. The results highlight the potential of AI-integrated approaches in advancing water treatment solutions using chemically modified carbon quantum dots [39].

6.2. Laser Applications in Multiple Disciplines

The development and application of lasers have experienced rapid progress in recent decades. The use of lasers has opened the door to revolutionary advances in different fields of science and life. This context presents some of the most significant applications of laser-related technologies in scientific research and industrial applied research. The substantial use of laser light in different types of spectroscopic techniques, lasers as a source of light for 3D printing, and the support of laser light to synthesize metal nanoparticles are some of the extensive topics addressed. Laser application is not restricted to the areas mentioned herein. In fact, the list is enormous, and it is not easy to include all fields of application in one text. Thus, the main objective of this work is to draw attention to the fundamental issues allowing such valuable applications and to achieve continuity in the discussion and debate in the defined laser research areas. We hope this text also encourages researchers to review new applications and carry out new scientific investigations that allow the development of new products based on this powerful, bright source of light, which is well-focused and frequently has a high level of coherence [44].

VII. ETHICAL CONSIDERATIONS AND FUTURE DIRECTIONS

The synergistic integration of artificial intelligence, lasers, and nanotechnologies heralds a transformative era in scientific research. For example, AI-driven models such as reinforcement learning have optimized nanomaterial design, while laser-induced fluorescence spectroscopy has enabled the precise analysis of environmental pollutants. These interconnected advancements illustrate the originality and value of this review in capturing multidisciplinary progress [44].

The impact of AI applies to all aspects of the chemical sciences. Lasers, these decades-old enabling technologies of myriad innovations, continue to transform both fundamental research and the prospects for marketable devices. Nanotechnology represents a significant commercial application of nanoscience and contributes to many other domains, such as biology, medicine, food, chemicals, fuels, and the environment. These comments were included to present a balanced view of the scientific research conducted in these described areas of investigation. Nonetheless, there are many risks too [44].

The impact of AI, lasers, and nanotechnology on the chemical sciences has been profound and far-reaching, with significant implications for research, industry, and society. AI is revolutionizing the field, offering unprecedented capabilities in molecular design, reaction prediction, and data analysis. Recent advancements include AI-powered platforms accelerating drug discovery, machine learning algorithms designing novel materials, and AI models predicting optimal reaction conditions [47]. Lasers continue to be indispensable tools, enabling ultrafast spectroscopy, improving mass spectrometry techniques, and advancing optogenetics and 3D printing. Nanotechnology bridges the gap between molecular science and macroscale applications with developments in nanomedicine, nanoelectronics, and nanomaterials for energy and environmental remediation. While these technologies offer immense potential, they also raise important ethical and societal concerns. Issues such as data privacy, the environmental impact of nanomaterials, dual-use concerns, and equitable access to advanced technologies must be addressed. Researchers must consider the long-term societal impacts of their work and engage with stakeholders to ensure responsible innovation [48]. To maximize the benefits of these technologies while addressing challenges, the chemical sciences community should focus on developing robust ethical frameworks, enhancing interdisciplinary collaboration, improving science communication, implementing sustainable practices, and investing in education and training [49]. By embracing these technologies responsibly and addressing ethical concerns proactively, the chemical sciences can continue to drive innovation and contribute to solving global challenges [50]. The future of chemical research lies in the synergistic integration of AI, lasers, and nanotechnology, guided by ethical considerations and a commitment to societal benefit [51-56].

Researchers must strive to ensure that their work is conducted within societal and ethical norms and that they are informed about political-economic priorities regarding social, economic, and environmental performance and security in cooperative research. We describe and discuss several of these ethical aspects. In conclusion, chemistry and related chemical research communities must strive to communicate them better, and we provide some recommendations for the future [45].

VIII. CONCLUSION AND RECOMMENDATIONS

After reviewing the relevant academic literature and assessing the impact of a selection of central modern technologies, a set of policy recommendations is offered. Modern technologies in the form of cutting-edge equipment provide opportunities for scientific research, but policy is required if the opportunities are to be realized. Both university-level and national science policy strategies are needed. Financing in the form of both maintenance and development budgets is crucial, and competitive user access must be guaranteed. Both universities and sponsoring national governments must provide assurances with a mode of guaranteeing an allocation of state-of-the-art equipment; coordinating objectives and user objectives that strike an appropriate balance are needed. Coordination through institutional and organizational adjustments is crucial when considering implications for research policy. First, dialogue and collaboration at an intra-university level are essential. The distribution of leading user and expert roles is crucial in moving discoveries from the natural sciences to their application in technology. Secondly, at the national level, research facilities and consultative bodies must foster their relations for inter-institutional and national science policy-making. To work in these strictly transdisciplinary fields, scholars in public administration involved in decision-making for the effects of cutting-edge technologies on scientific advances not only require more advanced methodological skills, such as different modeling tools and approaches, but also a deep understanding of the various scientific breakthroughs, discoveries, and advances themselves in order to interact adequately in dialogues with researchers. Therefore, one pertinent policy concern under the current political climate against the scientists' regime is that even the input for project selection of cutting-edge technologies may receive a politically biased stem, thus harming the foremost value of scientific research: neutrality and freedom from political influence.

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Laser-Assisted Surface Treatment of Ti64 Alloy for Industrial Applications

Samar Reda Al-Sayed[1*] **and Aliaa Abdelfatah**[2]

[1] Department of Engineering Applications of Lasers, National Institute of Laser Enhanced Sciences, Cairo University, Egypt, [2] Corrosion and Surface Treatment Lab., Dept. of Metallurgy, Faculty of Engineering, Cairo University, Egypt

Abstract

Purpose: Ti-6Al-4V is one of the most frequently used titanium alloys in the field of industry owing to its outstanding properties that stem from its high strength-to-weight ratio, the unique combination of ease machinability, good biocompatibility, and corrosion resistance. Such alloy is commonly used in the manufacture of submarines and the petrochemical industries which is exposed to different corrosive media such as seawater. This present study seeks to increase the corrosion resistance of Ti64 alloy by means of laser surface treatment.

Methodology: Laser surface treatment has been accomplished by melting the Ti64 surfaces using ultra-short pulses from a Q-switched Nd: YAG laser. Laser fluence (F_L) with several values was utilized to accomplish the proper laser fluence which gives the optimal performance.

Results: After laser surface melting, the microstructure became more homogeneous with finer grain size, 2 μm for surfaces treated at 65 $J.mm^{-2}$ vs. 145 μm for the untreated surfaces, this could be due to the quick self-quenching associated with the laser melting. The micro-hardness increased to a maximum of 500 $HV_{0.3}$ at 65 $J.mm^{-2}$ due to the formation of needle-shaped martensite α` Ti phase subsequent to the rapid solidification.

The results revealed a reduction in the corrosion rate from 0.75 μm/Y for untreated titanium alloy to 0.07 μm/Year for the laser-treated alloys, consequently, it was confirmed that the laser fluence had a substantial impact on both surface hardness and corrosion resistance.

Conclusion: The laser surface melting using nanoscale pulses from a Q-switched laser system could be applied to successfully enhance the corrosion resistance and the surface hardness of Ti64 titanium alloys.

Keywords— laser melting, titanium alloy, corrosion resistance

I. INTRODUCTION

Titanium, dual-phase alloys have been categorized as the main production material in many engineering applications, specifically in the fields of industrial applications such as submarines and petrochemical industries [1, 2]. Such titanium alloys have poor wear resistance that limits their applications, in addition, the formation of a porous titanium oxide layer causes the loss of adhesion at the interface [3, 4]. The dense TiO_2 film formed on ultra-fine surfaces has improved bonding with the substrate, reducing the likelihood of film delamination or breakdown under aggressive environmental conditions. Recently, numerous surface modification technologies have been developed to improve the surface properties of such alloys [5]. To enhance the surface properties of this alloy, different traditional treatments were applied such as the solution and aging treatments however, these treatments lead to many disadvantages such as long and complex treatment procedures. On the other hand, when the laser beam is used as a source of heat most of those disadvantages are limited [6, 7]. Laser surface treatment was commonly used to enhance the mechanical performance and corrosion resistance of different ferrous and nonferrous alloys, however, few researchers have considered the surface properties after laser melting of titanium and its alloys [8]. Mishra et al. [9] investigate the effect of different laser powers on the microstructure and mechanical properties of α + β titanium alloy (VT31) for the aerospace industry, a significant improvement in the hardness values has been accomplished by laser treatment. Such an increase in the hardness values (up to 750 HV) was attributed to the transformation that occurred in the microstructure, and enrichment of β-phase existed in the laser-affected zone. Another research studied the influence of laser surface treatment of Ti-6Al-4V titanium alloy for bio-implant application [10], the authors investigate the corrosion resistance after laser treatment in a simulated body fluid. They reported that the corrosion potential increased and the primary potential for pit formation substantially as compared to the untreated Ti-6Al-4V surfaces. In Ohtsu et al. study [11], the hardness of titanium surfaces modified by laser beam irradiation at different wavelengths, 532 nm, and 1064 nm, they found that the craters' size and depth steeply increased with an increase in the laser beam power; at the same time, oxide layer thickness that surrounded the crater

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Corresponding author: Samar Reda Al-Sayed Email: sreda@niles.edu.eg

increased as well. Moreover, many researches dealt with β-type titanium alloys, for example, the study of Y. Michiyama and K. Demizu [12] which proposed different age hardening speeds depending on the conditions of the solution treatment to investigate the wear resistance. Two heating methods were adopted, furnace heating and laser heating after furnace heating, the results revealed that the weight loss of the titanium alloy remarkably decreased with hardness especially that was above 450HV.

In this study, laser surface treatment of Ti64 titanium alloy was accomplished using nano pulses from a Q-switched Nd:YAG laser. Different laser fluences (F_L) were applied to get the optimum laser processing conditions that achieved better surface properties. The laser processing parameters have been chosen to avoid any micro-cracks formation on the laser-treated surfaces. Microstructure, micro-hardness, and corrosion resistance corresponding to each laser processing parameter have been investigated. The laser treatments (LT) were adopted to enhance the micro-hardness and the corrosion resistance performance of laser-treated Ti-6Al-4V titanium samples.

II- METHODOLOGY

2.1. Materials and laser experiments

Ti64 samples with dimensions of 30 mm×30 mm×0.5 mm was chosen as substrate. The substrate surfaces were cleaned using acetone before laser processing to remove any dirt and increase the laser absorptivity. The laser treatment was carried out using a Q-switched Nd:YAG laser with laser parameters listed in **table 1**. The schematic design of the laser treatment process is illustrated in **fig. 1**. Some preliminary experiments with several laser interaction times were conducted, starting with 10 minutes to 30 minutes with a step of 5 minutes, nevertheless, macro-cracks have been observed on the titanium surfaces, and consequently, smaller laser interaction times lower than 5 minutes have been selected. After such preliminary attempts range of laser fluences was identified to verify the optimum processing conditions for LT. Different laser fluence was calculated as listed in **table. 2** based on different laser interaction times using the following equations:

$$E_t = E_p * r * t \quad (1)$$

Where E_t is the total energy provided to the sample in Joule, Ep is energy per pulse in Joule, r is the frequency in Hz, and t is the exposure time in seconds.

$$F_L = E_t / A \quad (2)$$

Where F_L is the total laser fluence delivered to the sample in J.mm^{-2}, and A is the laser beam area in mm^2.

Table 1. Parameters of Q-switched Nd:YAG laser system

Laser parameter	Value
Max Energy	50 J
Energy/Pulse	0.0076 J
Frequency	10 Hz
Beam diameter	0.3 mm
Laser interaction time	60, 120, 180, 240

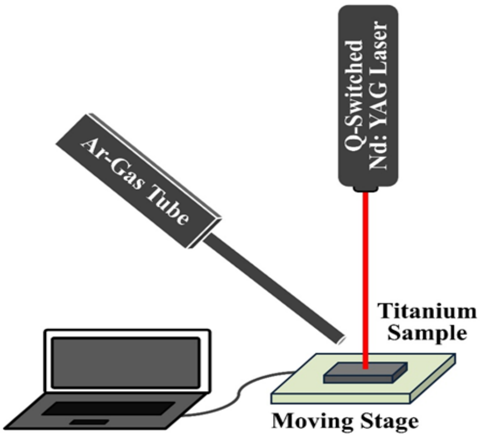

Figure 1. Schematic design of the laser treatment process.

Table 2. Laser fluence calculations

Laser interaction time (s)	Total energy (J)	Laser fluence (J.mm^{-2})
60	4.6	65 (F_{L1})
120	9.12	130 (F_{L2})
180	13.68	195 (F_{L3})
240	18.24	260 (F_{L4})

2.2. Morphological Characterization, Micro-hardness, and Electrochemical Measurements

Laser-treated samples were mounted, polished, and etched through the standard metallographic procedures to investigate the microstructural modifications through optical as well as scanning electron microscopes. Micro-hardness distributions were measured using an HMV digital micro-hardness tester, obtaining values in the Vickers scale. All surfaces were tested under a load of 0.5 N and a dwell time of 15 s. For each condition, an average value of 5 indentations was recorded.

The investigated samples were ground and polished before the corrosion test. The corrosion performance was examined in a corrosive medium of 0.6M NaCl. The Potentio-dynamic-polarization test was performed using three-electrode cells using PGZ 100 Potentio-stat with Volt. Lab 6 software. A saturated calomel electrode (SCE) was employed as the reference electrode and a platinum electrode was used as the auxiliary electrode. Every sample was subjected to the test conditions for 60 minutes to attain the steady-state open-circuit potential (OCP). The Potentio-dynamic tests were accomplished from – 0.5 V versus OCP to +0.5 V versus OCP and the corrosion currents were registered. The electrochemical parameters during the test usually include the corrosion potential (E_{corr}) and corrosion-current density (i_{corr}). The parameter, i_{corr}, can be used to calculate the average corrosion rates from equation (3) which represents the general corrosion resistance [13] :

$$\text{Corrosion rate (mm/year)} = 3.27 \times 10 -3 \times i_{corr}\, \rho \times E_W \quad (3)$$

Where ρ is the density of the alloy in g.cm^{-3}, i_{corr} (in µA.cm^{-2}) is the corrosion current density, and E_W is the equivalent weight of the alloy in g.equiv^{-1}.

III- RESULTS AND DISCUSSION

3.1. Characteristics of the treated-layer and micro-hardness measurements

The Ti64 commercial alloy was received in the annealed condition. The annealed microstructure consists of (α + β) phases; equi-axed α with inter-granular β of a comparatively uniform grain size as shown in **fig. 2**.

Figure 2. Optical micrograph of the cross-section of Ti64

Scanning electron micrographs of the upper surface of samples processed at different laser fluences are illustrated in **fig. 3**, as can be seen from the micrographs all surfaces have homogenous structures with ultrafine grain size. The microstructure of the untreated Ti64 transformed from coarse grains microstructure to fine grains with a homogeneous microstructure accompanying laser treatment. The grain size was measured utilizing image software analysis through the SEM, and the grain size was noted to decrease as the laser fluence was reduced. The grain size measured around 2 µm and 4 µm for samples processed at 65 and 260 J, respectively, compared to the extremely coarser grain size of 150 µm for the untreated samples. Usually, the cooling rates associated with laser surface melting could range from 10^3 K/s to 10^6 K/s [14], depending on the laser processing parameters such as laser power, scanning speed, as well as material absorption. Such rapid cooling rates indicate a substantial undercooling, increasing nucleation within the molten pool while suppressing grain growth due to its limited time, which results in a refined grain structure [15]. Consequently, it could be confirmed that laser pulses from Q-switched Nd:YAG laser leads to a remarkably large refinement of grain structure and overcome the main problem of coarse grain size associated with the as-received structure of Ti64 titanium alloy [16].

In **fig. 4(a)**, the cross-sectional SEM micrographs show the entire treated layer which contains three different zones, the melting zone (MZ), the fusion zone (FZ), and the untreated surface. In the MZ, a large area of fine needle-like α` martensite phase is randomly distributed in the β grains, along with the β phase through the initial α phase due to the extremely high cooling rates. During the laser treatment process, the untreated bottom of the substrate provided a heat sink to lower the temperature of the molten pool allowing a faster solidification rate associated with the laser self-quenching, consequently, the steep temperature gradient from the melted layer was large, resulting in a speedy solidification process of the molten pool. As a consequence, the growth of the phase was prevented and a very hard martensite (α`) phase formed instead [11].

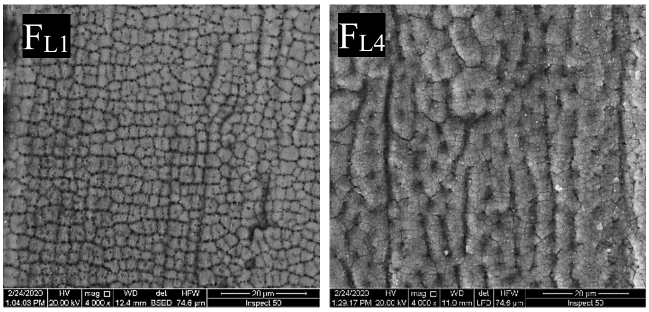

Figure 3. SEM of the upper surface of laser-treated samples processed at different laser fluences

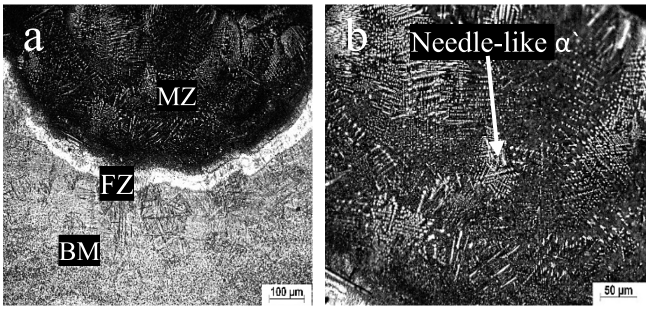

Figure 4. OM micrographs of the laser-treated Ti64 samples processed at 260 J.mm^{-2} (a) entire layer, (b) melting zone

In **fig. 5**, the micro-hardness values of the untreated titanium alloy and the treated ones for all laser processing conditions are exhibited. The micro-hardness of the untreated Ti64 samples is about 180 $HV_{0.3}$. On the other hand, the micro-hardness of the titanium surfaces after laser treatment is significantly increased, especially when the lowest laser fluence value was applied to the surface, the increase is near threefold the initial micro-hardness value.

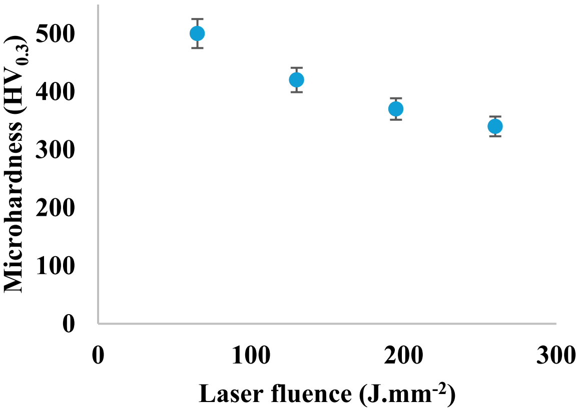

Figure 5. Micro-hardness of the laser-treated samples vs. laser fluence

Primarily as a result of the formation of a very hard needle-like martensite phase after laser treatment because the laser beam rapidly heats the surface to high temperatures even above the melting point followed by quick cooling.

During the heating and cooling cycles, the phase (β) transformed into the hard martensite phase (α`) which results in high hardness values. In addition, such severe quenching can lead to the formation of finer microstructure, and as normal the finer grain structure is harder due to the difficulty of dislocation movement along the grain boundaries [17]. Moreover, when the dislocation density increases also increases the strength offering more resistance to the material deformation which is reflected again in the hardness value. Finally, the residual stresses that form throughout the microstructure play a critical role in the determination of the resistance of the material to plastic deformations [6].

3.2. Electrochemical characterization

Potentio-dynamic polarization results of the laser-treated layers and the as-received in 0.6 wt. % NaCl solution at room temperature are presented in **fig. 6**. The untreated surfaces showed a corrosion rate of 0.75 µm/Y, contrary it is noticed that no considerable difference in the trend of the four polarization curves of the titanium surfaces after laser treatment, which reveals that the same reaction occurs on the titanium surface after laser treatment nevertheless at different corrosion rates as listed in **table. 2**.

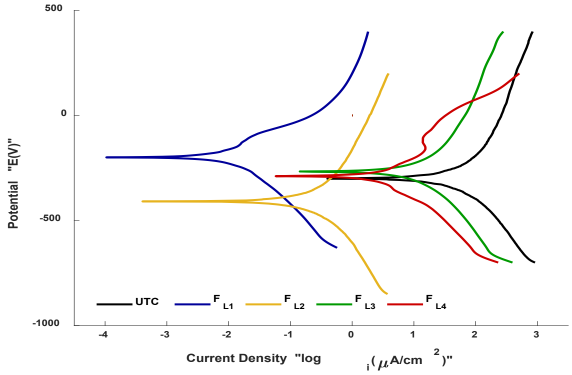

Figure 6. Tafel polarization curves for untreated surface a(UTS) and all laser conditions

As can be seen from the corrosion rates, the *E_{corr}* values for all laser-treated samples are nearly close, whereas the *E_{corr}* value for the untreated surfaces recorded a corrosion rate of 0.75 µm/Y, which is greater than the value of samples treated at FL_1 by 11 times. The rapid solidification as a result of partial surface melting caused the formation of a very fine microstructure with a high density of grain boundaries which weakens the surface corrosion resistance. Moreover, such refined grains provide a significant number of grain boundaries, which act as a diffusion pathway for oxygen through the oxidation process.

A considerable percentage of the precipitated salts on the treated surfaces were acquired on the treated titanium surfaces (utilizing EDX analysis). Furthermore, the laser-treated surfaces show dense TiO_2 film, as listed in Table 3. This may be attributed to the dependency of the underlying treated surfaces with ultra-fine microstructure which led to the inhibition of alloying elements micro-segregation [18]. Additionally, such uniform microstructure establishes a more compact and chemically stable passive layer compared to untreated titanium surfaces, which often have coarser grains and less homogeneous oxide films. Also, the TiO_2 film contained few defects/pores, which decreases pathways for corrosive agents to initiate localized corrosion. Such results imply that the stability of passive film formed on laser-treated samples at such specific laser conditions is better than that of the untreated titanium surfaces. Consequently, it could be concluded that the samples processed at a laser interaction time of 60 seconds are further favorable to enhancing the corrosion performance of such alloys. Excessively high laser fluence could lead to excessive oxidation, forming thicker and potentially less adherent oxide layers [19].

Table 3. Polarization corrosion parameters

Treatment conditions	**Corrosion Rate (µm/Y)**	***i*** **corr. (nA/cm²)**
F_{L1}	0.07	0.125
F_{L2}	0.172	0.4
F_{L3}	0.2	107
F_{L4}	0.35	58

Table 4. Elemental EDX analysis of surfaces after corrosion test

Treatment conditions	**Titanium (Ti)**	**Oxygen (O)**	**Other elements C, Na, Cl, Al, V**
As received	76%	11%	13%
F_{L1}	41%	42%	17%

IV. CONCLUSIONS

An attempt was accomplished to enhance the surface properties of Ti64 alloy by applying a Q-switched laser for surface melting. A substantial refinement of microstructure and formation of needle-like martensite α` with a partial amount of β phase after the laser surface melting. In summary:

1. A maximum micro-hardness of 500 $HV_{0.3}$ of the laser-melted layer was reached as compared to the micro-hardness associated with the untreated substrate of 180 $HV_{0.3}$.
2. The untreated substrates possess a corrosion rate of 0.75 µm/Y, however corrosion rate after laser melting is decreased to 0.07 µm/Y at a laser fluence of 60 $J.mm^{-2}$. This could be attributed to the more stable TiO_2 film on the treated surfaces.
3. Finally, ultra-short pulses from a Q-switched laser considerably improve the corrosion resistance of Ti64 alloys at low laser fluence with a small laser interaction time.

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Cairo University

Antimicrobial Photodynamic Inactivation and Photosensitizers: A Succinct Review

Maha Fadel[a], Maha Nasr[b], Sarah Salah Thabet[a*]

[a] Pharmaceutical Technology Laboratory, Department of Medical Applications of Laser, National Institute of Laser Enhanced Sciences (NILES), Cairo University, Cairo, Egypt, [b] Department of Pharmaceutics and Industrial Pharmacy, Faculty of Pharmacy, Ain Shams University, Cairo, Egypt

Abstract

Purpose: The growing rise in the development of multidrug-resistant strains of bacteria towards conventional antibiotics necessitates exploring alternative techniques such as antimicrobial photodynamic inactivation (aPDI). aPDI relies on the activation of a photosensitizer (PS) by a specific wavelength of light with the production of excess reactive oxygen species (ROS), which have the ability to successfully eradicate a wide range of human pathogens like bacteria (either Gram-positive Gram (+) or Gram-negative Gram (-)), fungi, protozoa, parasites, viruses, and even bacterial biofilms. One of the notable advantages of aPDI is that it doesn't lead to bacterial resistance or be affected by the already established resistance to antibiotics. The characteristics of the photosensitizer used have a major impact on how effective aPDI is. The best PS for selective aPDI is thought to have a strong positive charge, be safe in the dark, and produce a large quantity of ROS when activated by red light. Various PSs, either natural or synthetic, have been proven effective in aPDI. The synthetic dye methylene blue and the natural PS curcumin have been extensively explored. Moreover, tetrapyrrole structures like porphyrins and phthalocyanines have been extensively investigated because they are easily chemically modified.

Conclusion: Nanocarriers played a significant role in aPDI, as some nanocarriers function as PSs by themselves, like fullerenes, while others bind PS to their surfaces or embed it within their matrix. Nanocarriers have been demonstrated to enhance the antibacterial activity of the PS, protect it, and improve its delivery to the target site.

Keywords— photodynamic therapy, photoactive molecules, nanocarriers, multidrug-resistant bacteria, photokilling

I. INTRODUCTION

Phototherapy began in ancient Egypt, where the Egyptians employed sunlight and herbs to cure various skin conditions. One noteworthy incidence is the use of natural photosensitizers, like psoralens, which are isolated from specific plants like parsley and St. John's Wort, to cure leprosy lesions [1, 2]. Combining light radiation with a medication called a photosensitizer (PS) to kill cancer cells and infectious microbes upon light activation is known as photodynamic therapy (PDT). PDT is a minimally invasive treatment approach in which photosensitive materials are triggered by a particular wavelength of light, often emitted by a laser. When the PS is exposed to light, it is activated and triggers a reaction that harms neighboring cells. Both the light source and the PS are safe on their own [3]. Nowadays, there are numerous PSs available to treat a range of conditions, such as psoriasis, age-related macular degeneration, acne, and multiple malignancies [4]. PDT is also useful in treating viral, bacterial, and fungal infections; for these reasons, it is often referred to as antimicrobial photodynamic inactivation (aPDI) [5]. Furthermore, research has demonstrated that this light-based therapy can activate the immune system, providing the body with an additional tool to aid in the destruction of abnormal cells that may be bacterial, malignant, or precancerous. In PDT-mediated cancer treatment, irradiated cancer cells are directly destroyed, and tumor-specific cytotoxic T-cells are activated, enabling the death of distant, untreated tumor cells. Additionally, PDT promotes the growth of anti-tumor memory immunity, which may be able to stop cancer from returning. Due to increased neutrophil infiltration into the affected areas, which appears to magnify the therapeutic effect, PDT's immunological effects also increase the efficacy of the therapy when used to treat bacterial infections [6, 7]. Though much research has been done, the mechanism underlying photodynamic treatment is still unclear. The process entails administering a dye, known as a photosensitizer (PS), which is a photoactive substance. Afterwards, in the presence of oxygen, the dye is exposed to radiation at a wavelength that corresponds to its absorption band. As shown by the modified Jablonski diagram **(fig. 1)**, PDT includes PS absorbing a photon of light, which excites it from its ground singlet state (S_0) to its short-lived (nanoseconds) excited singlet state (S_1). With intersystem crossing or an electronic transition, this singlet state PS can become a substantially longer-lived (microsecond) triplet state (T_1). Due to its extended lifetime, the triplet PS can undergo one of three distinct photochemical reaction pathways; known as **Type 1, Type 2 and Type 3 reactions**. An electron transfer from the excited PS to an organic cell component is part of the **Type 1 route**. Highly reactive free radical species are the product of this interaction. These

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Corresponding author: Sarah Salah Thabet Email: sarahsthali@cu.edu.eg

species will react with oxygen molecules to produce harmful reactive oxygen species (ROS), such as superoxide, hydrogen peroxide, and hydroxyl radicals. Through lipid peroxidation of the constituents of the cell membrane, ROS molecules assault the membrane and cause an irreversible rupture. Furthermore, throughout the process, membrane-bound peptides and enzymes may become inactive [8–10]. Singlet oxygen ($^1O_2$), a highly reactive form of oxygen, is created via a direct interaction (energy transfer) between the excited PS and oxygen molecules in the **type 2 pathway**. Singlet oxygen molecules cause oxidative damage to the cell membrane or cell wall as a result of their interaction with many biomolecules, including proteins, lipids, and nucleic acids [8–10]. Singlet oxygen has the ability to eradicate a variety of microorganisms, such as bacteria, viruses, fungi, and protozoa, presenting a promising antibacterial modality known as antimicrobial photodynamic inactivation (aPDI) [11, 12]. Furthermore, a **type 3 photodynamic pathway** has recently been proposed for deeply seated lesions and other hypoxic tissues. These types of lesions have extremely low levels of oxygen (the essential component of PDT); therefore, a special type of PS should be utilized. This PS could transmit energy directly to tissue without the need for oxygen. The excited triplet state of this oxygen-independent PS has the ability to target proteins, nucleic materials, and other subcellular components with their subsequent destruction. Interestingly, it was hypothesized that this pathway may take place in both hypoxic and non-hypoxic conditions. Unfortunately, this unique oxygen-independent PS is rare, so there is little data available about this type of reaction [13].

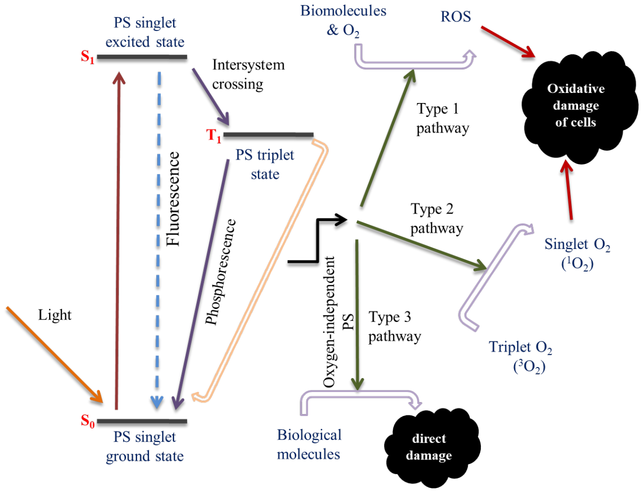

Figure 1: Modified Jablonski diagram showing the mechanism of PDT. PS: photosensitizer, ROS: reactive oxygen species

Despite the fact that PDT can operate through either pathway, singlet oxygen has been claimed to be the primary cytotoxic agent responsible for PDT's biological effects. Hence, the type II reaction is the main mechanism that causes the antibacterial effect of aPDI [10, 14].

II. ANTIMICROBIAL PHOTODYNAMIC INACTIVATION

2.1. Historical background

PDT was discovered more than a century ago (1900) by the coincidental observation that microorganisms (Paramecia) were killed when exposed to both sunlight and a photosensitizing dye (acridine hydrochloride) at the same time, even though PDT has been researched and developed as an anti-cancer therapy rather than an antimicrobial therapy [15]. In 1960, aPDI was first introduced when toluidine blue was employed to combat germs like bacteria, algae, and yeast. 99% of the bacteria were observed to be eliminated in 30 minutes after being exposed to 21–30 mW of continuous-wave gas laser light at 632 nm [16]**.** Since then, it has been determined that PDT has potent antibacterial effects as well. However, the development of penicillin and its amazing bactericidal qualities, along with other antibiotics, has slowed the advancement of aPDI.

2.2. Advantages of aPDI

The widespread development of resistant strains of bacteria to antibiotics and the emergence of multidrug-resistant species necessitate the need for an alternative modality to conventional antibiotics. aPDI has gained attention in response to its superior advantages over conventional antibiotic regimens [16]**.** The advantages of aPDI include:

2.2.1. Broad-spectrum nature of aPDI

Various human pathogens, such as bacteria (either Gram-positive (Gram (+)) or Gram-negative (Gram (-)), fungi, protozoa, parasites, and viruses, have been successfully eradicated by aPDI, as illustrated in **fig. 2**. This implies that therapy can begin prior to the identification of the infectious agents. [16, 17]**.**

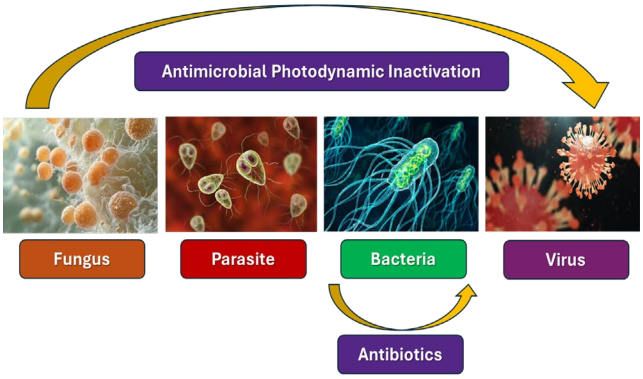

Figure 2: Broad-spectrum antimicrobial photodynamic inactivation versus antibiotics

2.2.2. Selective microbial binding over a short incubation time

The lifespan of ROS and singlet oxygen ($^1O_2$) produced by aPDI is extremely short. With a 0.04 ms lifespan in a biological environment, singlet oxygen has an action radius of only 0.02. Because of this, the generated radicals are quite potent only at the site of their generation. The fact that aPDI has no effect on distant tissues is a benefit [8]. Therefore, in order for the PS to bind selectively to microbial cells rather than host mammalian cells, it must be given locally to the target region in a safe manner [18]**.** Since microbial cells generally have a more pronounced negative charge than mammalian cells and positively charged aPS will bind selectively to them, it was determined that the best way to achieve this goal of aPDI was to make sure that the antimicrobial photosensitizer (aPS) had a pronounced cationic charge [16]. Furthermore, when a brief drug-light gap (a few minutes) is used, the cationic aPS binds to microbial cells rather quickly while being absorbed slowly by mammalian cells, offering significant selectivity [19-21].

2.2.3. Effectiveness against resistant microbial strains without developing microbial resistance

The fact that aPDI functions just as well regardless of the microbial cells' level of antibiotic resistance strengthened its benefits as a possible clinical antimicrobial therapy [15]. Furthermore, even after 20 cycles of partial death followed by regrowth, aPDI has not been demonstrated to induce bacterial resistance [15, 22]. The photosensitized inactivation processes at the microbial membrane level are usually multi-targeted, involving multiple membrane proteins and lipid domains. This prevents the expression of potential protective factors, such as the biosynthesis of stress proteins, thereby reducing the likelihood of the emergence of resistant strains [23].

2.2.4. Effectiveness against microbial biofilms

Antibiotics given systemically are unable to break through the microbial biofilms that accumulate in many chronic illnesses. It has been demonstrated that aPDI destroys biofilm-grown cells in vivo and in vitro [24].

2.2.5. Topical or local application of PS to the infected area

This is especially helpful when burn infections or injured tissues with low blood flow occur. In these cases, systemically administered antibiotics are unable to reach the infection site in high enough concentrations. Topical aPDI may kill microorganisms quickly—it can start working in just a few seconds—while antibiotics can take hours or days to start working. This suggests that aPDI may be advantageous for treating infections that spread quickly, including necrotizing fasciitis [15].

2.2.6. Application in deep infections

Almost any anatomical location can now receive light through the use of endoscopes, fiber optics, and interstitially inserted needles with a tiny diameter [25].

2.3. Properties of an appropriate antimicrobial photosensitizer (aPS)

One important factor influencing the result of aPDI is the kind of aPS that is employed [16]. In order to be suitable for usage in aPDI, PS needs to have specific characteristics, as illustrated in **fig. 3**. The aPS must, first and foremost, not be hazardous to mammals, especially when incubated in the dark. Second, the aPS should have high molar absorption coefficients and good quantum yields of ROS at a wavelength that aligns with the tissue optical window, which is the region of the spectrum where tissue light penetration is most effective (red and near infrared) [26]. Thirdly, during short incubation times, aPS should show selectivity for microbial cells over host mammalian cells [19–21]. The fourth and most crucial factor is that an aPS should have cationic charges [5, 16].

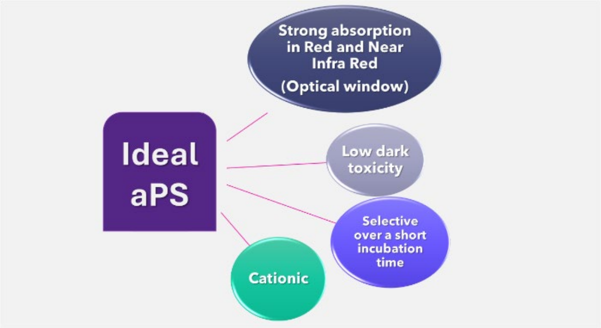

Figure 3: Properties of ideal antimicrobial photosensitizer (aPS)

2.4. Classification of aPSs

aPSs can be mainly classified into three groups based on their structure and origin: synthetic dyes, natural PSs and tetrapyrrole structures [16].

2.4.1. Synthetic Dyes

Phenothiazinium is a class of artificial dyes. The phenothiazinium dyes toluidine blue (TB) and methylene blue (MB) are the most commonly used aPS [27]. They are usually employed in aPDI in clinical settings because of their inherent cationic charge, which renders them efficient against a wide variety of bacteria. However, because of their low penetration into the biofilm, numerous investigations have demonstrated their relatively modest antibacterial activity on bacterial biofilms. Novel MB compounds, including dimethyl methylene blue, have been investigated lately. These compounds are more potent against bacterial cells because of their strong cationic charge [28–30].

Additional artificial dyes include Rose Bengal (RB), Eosin Y, and Erythrosine (ERY), which are anionic xanthene dyes made from fluorescein. The green wavelength region (480–550 nm) is where the absorption peak of each of these dyes is located. Because anionic PSs are less likely than cationic PSs to bind to and be absorbed by bacterial cells, these dyes have weaker antibacterial activity [31].

2.4.2. Natural aPS

Many naturally occurring substances, including coumarins, furanocoumarins, benzofurans, anthraquinones, and derivatives of flavin, are isolated from plants and other creatures and function as PSs. Two natural substances that have been thoroughly investigated as PS over the years are hypericin and curcumin. Hypericin is an anthraquinone derivative extracted from Hypericum perforatum, also referred to as St. John's Wort, which has long been used to treat burns and other skin lesions. At a wavelength of 600 nm, which is perceived as orange light, hypericin is best absorbed. Due to its non-cationic nature, it has been demonstrated that hypericin-mediated aPDI is more pronounced on Gram (+) bacteria than on Gram (-) bacteria [32, 33]. As a result, the creation of noble cationic hypericin derivatives is likely to increase the efficacy of aPDI against Gram (-) bacteria. Another naturally occurring PS that was extracted from the root of the Curcuma longa plant has an optimal absorption range of 405–435 nm. This compound is called curcumin. Apart from its beneficial effects on wound healing, curcumin is a safe PS that possesses anti-oxidant, anti-inflammatory, and anti-microbial characteristics.

Although it has been thoroughly studied for the treatment of cancer, recent studies have shown that curcumin can suppress drug-resistant bacterial strains by photo-inactivation [34]. Furthermore, curcumin has shown some antimicrobial qualities when exposed to no radiation [35, 36]. Research suggests that curcumin has 300 times greater photo-killing efficacy against Gram (+) Staphylococcus aureus compared to Gram (-) Escherichia coli (E. coli) and Salmonella typhimurium [37]. Curcumin has a high therapeutic effect, but its poor water solubility and photo-labile characteristics, which lead it to rapidly degrade at physiological pH, limit its application. Consequently, polyvinylpyrrolidone curcumin (PVP-C), a novel derivative of curcumin, was created and tested for its aPDI on Staphylococcus aureus. The results demonstrated total bacterial eradication [38].

2.4.3. Tetrapyrrole Structures

One of the biggest and most recently discovered PS groupings is tetrapyrroles. The tetrapyrrole nucleus is the basis for the majority of PS used in the previous 100 years to treat tissue disorders and cancer, with a strong reliance on porphyrin usage. In aPDI, phthalocyanines and porphyrins are the most commonly utilized PSs. Because of their ease of chemical modification and high rate of reactive oxygen species (ROS) formation, porphyrins are among the most widely used PSs. They absorb light between 405 and 550 nm in wavelength. Certain anaerobic bacteria that generate black pigments have a tendency to amass a lot of porphyrins, which makes them vulnerable to UV or blue light radiation [39–41]. As a result, these bacteria with endogenous PS can be killed by aPDI without the need for PS administration [42, 43].

Cationic porphyrins, such as TMPyP (meso-tetrakis(4-N-methylpyridiniumyl) porphyrin), have been synthesized with a fourfold positive charge; however, their effectiveness against bacterial biofilms is debatable because TMPyP has been reported to be effective against some types of bacterial biofilms and ineffective against others [44, 45]. Today, cationic antimicrobial peptides, or cell penetrating peptides, are conjugated to porphyrins to increase their efficiency. These conjugated porphyrins exhibit a great degree of cell inactivation during aPDI [46].

Phthalocyanines (Pc) are a class of diverse agents with a peak absorption in the red region at 670 nm [47]. Of these agents, zinc phthalocyanine (ZnPc) is the most studied phthalocyanine for aPDI [16]. This phthalocyanine, when used in conjunction with cationic and anti-membrane agents like polymyxin B or EDTA (ethylene-diamine-tetraacetic acid), can become effective against Gram (-) bacteria.

Additionally, the structure of phthalocyanine offers a wide range of options for designing different derivatives. So functionalizing ZnPc with cationic groups improves its binding affinity to bacterial cells without the need for polymyxin B [48, 49]. Numerous studies were conducted in an effort to improve ZnPc's aPDI efficacy by substituting or chemically altering its structure to create cationic and water-soluble derivatives [50]. However, the majority of these modifications made ZnPc extremely hydrophilic, necessitating additional chemical modifications in certain situations to improve its amphiphilicity [50, 51]. Widely ranging pathogens, including Gram (+) methicillin-sensitive Staphylococcus aureus and methicillin-resistant Staphylococcus aureus strain (MRSA) [20], Gram (-) Aeromonas hydrophila [51], *E. coli* [52,53], and fungi such as *Candida albicans* [54], have all been demonstrated to respond well to derivatives of ZnPc.

2.5. Nanocarriers and aPDI

2.5.1. Nanocarriers as aPDI mediators

As was already established, aPSs have a distinctive antibacterial action on pathogens, but their low solubility, bioavailability, and biocompatibility prevent them from being widely used. In this sense, aPDI has been transformed by nanotechnological intervention to fight microbial infections and the health effects they cause. Nevertheless, the bulk of research has concentrated on examining the efficacy of nanocarriers to improve PDT's anticancer properties, with very few examining their antimicrobial properties [55].

Because they enhance the delivery and release of PS at the intended location, nanocarriers enhance the effectiveness of PDT as compared to PS alone. This can be explained by the way ROS are dispersed; the ROS generated by free PS were less effective because they were uniformly distributed in the medium, whereas the ROS generated by PS-nanocarriers were locally concentrated. Moreover, PS attached to nanocarriers more effectively crosses the membrane than unbound PS does [16].

Additionally, nanotechnology has been used to introduce the positive charge required for aPDI into the PS by conjugating to polycationic polymers like poly-L-lysine, which promote strong binding to the negatively charged exterior of pathogens and permit the PS to pass through the permeability barrier of Gram (-) bacteria [56, 57]. Excisional wounds infected with the lethal Gram (-) bacteria Pseudomonas aeruginosa have been shown to respond favorably to aPDI mediated by the polycationic poly-L-lysine-chlorin p6 conjugate (pl-cp6) in terms of bacterial load reduction and wound healing [56]. Similarly, when compared to the anionic rose Bengal (RB) and the weak cationic toluidine blue O (TBO), the polycationic poly-L-lysine-chlorin e6 conjugate (pL-ce6) was found to be the most effective antimicrobial photosensitizer on three classes of human pathogens: E. coli (Gram (-) bacteria), Staphylococcus aureus (Gram (+) bacteria), and Candida albicans (yeast). When compared to RB and TBO, pL-ce6 showed the greatest bacterial reduction at significantly lower concentrations and light fluences [58].

The conjugation of chlorine e6 with polyethyleneimine (PEI) is another example of a conjugation with a polycationic moiety. It was thought that this conjugation was better than poly-L-lysine-PS conjugates for the aPDI of localized infections [57]. The interaction between nanocarriers and PS used in aPDI can be expressed as nanocarriers themselves act as the PS, PS is either bound to the surface of nanocarriers or embedded in nanocarriers, nanocomposites and smart nanocarriers. **Table. 1** summarizes nanocarriers used in aPDI.

Table. 1: Summary of nanocarriers used in aPDI.

Nanocarrier	PS	Main characteristics	Indication	Effect
Polycationic poly-L-lysine-chlorin p6 conjugate [56, 57]	Chlorin p6	Polycationic	-Excisional wounds infected with the lethal Gram (-) bacteria Pseudomonas aeruginosa	-Bacterial load reduction -Wound healing
Polycationic poly-L-lysine-chlorin e6 conjugate [58]	Chlorin e6	Polycationic	-E. coli (Gram (-) bacteria) -Staphylococcus aureus (Gram (+) bacteria) -Candida albicans (yeast)	Effective aPDI
Polycationic polyethyleneimine (PEI) chlorine e6 conjugate [57]	Chlorin e6	Polycationic	Three classes of human pathogens; -E. coli (Gram (-) bacteria), -Staphylococcus aureus (Gram (+) bacteria) -Candida albicans (yeast)	Better than poly-L-lysine-chlorin e6 conjugate for the aPDI of localized infections
Fullerenes [61]	No PS	-Act as a PS -Neutral	--	Weak bactericidal action
Cationic fullerene N,N-dimethyl-2-(40-N,N,N-trimethyl-aminophenyl) fulleropyrrodinium iodide (DTC60$_{2+}$) [62]	No PS	- Act as a PS -Cationic	-E. coli	Significantly hindered E. coli proliferation
Semiconductors zinc oxide (ZnO) and titanium oxide (TiO_2) [63]	No PS	-- Act as a PS -Irradiated by UVA	--	-Not employed in medical settings.
Graphene quantum dots (GQD) [65, 66]	No PS	- Act as a PS	-Staphylococcus aureus -E. coli	-Decrease count after 10 second irradiation
CdSe/ZnS quantum dots (QD) [71]	Toluidine blue (TBO)	--	Staphylococcus aureus and Streptococcus	-Enhance aPDI
Gold nanoparticle [72, 73]	toluidine blue	--	Staphylococcus aureus	-Enhanced aPDI
Multiwalled carbon nanotube (MWNT) [74]	Protoporphyrin IX (PpIX)	--	Staphylococcus aureus	-Enhance aPDI with visible light
Protein Cage [75]	--		Staphylococcus aureus	-Enhance aPDI
Nanoemulsions [82]	Chloroaluminum phthalocyanine (ClAlPc)	Cationic vs anionic	-Methicillin-susceptible Staphylococcus aureus -MRSA	-Cationic NE has better aPDI than anionic NE
Nanoemulsions [83]	Chloroaluminum phthalocyanine (ClAlPc)		-The highly resistant, potentially fatal Cryptococcus neoformans melanized cells	-Enhance aPDI
Nanoemulsions [84]	Chloroaluminum phthalocyanine (ClAlPc)	Cationic vs anionic	-Candida albicans planktonic cultures and biofilm	-Cationic NE has better aPDI than anionic NE
Nanoemulsions [77]	Zinc phthalocyanine (ZnPc)	--	Leishmania species	-Enhance aPDI
Nanoemulsions [85]	zinc phthalocyanine (ZnPc)	--	-Enterococcus faecalis -MRSA	Enhance aPDI
Nanoemulsions [86]	Zinc phthalocyanine (ZnPc)	Cationic	-MRSA -Multidrug-resistant E. coli	-Enhancd aPDI -Wound healing
Polymeric nanocomposite of ethylcellulose/chitosan [89]	5,10,15,20-tetrakis(m-hydroxyphenyl)porphyrin (mTHPP)	Cationic	-Multi-drug resistant Pseudomonas aeruginosa, -Staphylococcus aureus, -Candida albicans	-Enhance aPDI
Metallic nanocomposite of zeolitic imidazolate framework-8 (ZIF-8) [90]	Chlorin e6		MRSA	-Enhance aPDI -wound healing
Nanocomposite of gold nanocluster within chitosan polymer matrix [91]	Protoporphyrin IX (PpIX)		Gram (+) and Gram (-) bacteria and biofilm	-Enhance aPDI -Biofilm removal

Upconversion nanocomposites [92]	chlorin e6	Irradiated with near-infrared (NIR) light (980 nm), then the UCNPs can emit strong red light (655 nm)	-E. coli -Staphylococcus aureus	-Enhance aPDI by self-oxygen replenishment -Regulate inflammation
Enzyme-sensitive smart nanocarrier ex; Lipase-sensitive methoxy poly (ethylene glycol)-block-poly(ε-caprolactone) (mPEG-PCL) micelles [95]	Hypocrellin A (HA)	Selective and triggered release of HA by bacterial lipase enzyme	-MRSA	-Selective aPDI
PH-sensitive, surface charge switchable smart nanocarriers ex.1 **pH-sensitive polydopamine (PDA) NPs of RB, coated with polymyxin B (PMB) and gluconic acid (GA)** [96]	Rose Bengal (RB)	Nanocarrier exhibit negative charge at physiological pH and turned into positive at acidic pH of bacterial biofilm	-Bacterial biofilm	-Selective biofilm penetration and eradication
pH-sensitive, surface charge switchable smart nanocarriers ex. 2 pH-sensitive poly (ethylene glycol) (PEG) block polypeptide copolymer [PEG-(KLAKLAK)2-DA] linked with α-CD-Ce6 prodrugs [97]	chlorin e6	Nanocarrier exhibit negative charge at physiological pH and turned into positive at acidic pH of biofilm	-MRSA biofilm	-Selective biofilm penetration and eradication
Dual-responsive smart nanocarriers: H_2O_2-responsive block copolymer of POEGMA-b-PBMA assembled with a surface charge-switchable photosensitizer, 5,10,15,20-tetra-{4-[3-(N,N-dimethyl-ammonio) propoxy|phenyl} porphyrin (TAPP) into NPs [98]	Surface charge-switchable photosensitizer, 5,10,15,20-tetra-{4-[3-(N,N-dimethyl-ammonio) propoxy]phenyl} porphyrin (TAPP)	Selective and triggered release of TAPP by overexpressed peroxides at infection sites and biofilm, followed by changing surface charge of TAPP into positive.	-Bacterial biofilm	-Selective and enhanced aPDI with less self-quenching
Smart nanocarriers linked to responsive linkers to bacteria ex. **hyperbranched PEG linked with Zinc porphyrin via disulfide and benzacetal linkers** [99]	Zinc porphyrin	Selective and triggered release by glutathione (GSH) and acidic		-Selective and enhanced aPDI

2.5.2. Nanocarriers themselves as aPSs

Fullerenes are recognized as one of the most significant nanocarriers that can act as PS [59]. Other nanocarriers in this group are semiconductors [60]. Fullerenes have a spheroidal structure made up of pentagonal and hexagonal rings, such as C60, C70, C84, etc. The weak bactericidal action of these compounds can be attributed to their neutral charge and lipophilic nature [61]. In order to make fullerenes cationic, many alterations have been made to them using various cationic chemicals. In contrast to the negligible killing effect of non-charged fullerene N-methyl-2-(40-acetami- dophenyl) fulleropyrrolidine (MAC_{60}), aPDI mediated by the cationic fullerene N,N-dimethyl-2-(40-N,N,N-trimethyl-aminophenyl) fulleropyrrodinium iodide ($DTC60_{2+}$) significantly hindered E. coli proliferation [62]. More research is necessary because of this PS's great efficacy and selectivity. Semiconductors, or photocatalysts, are materials with semi-conductive qualities, such as zinc oxide (ZnO) and titanium oxide (TiO_2). Following irradiation of these materials by UVA, ROS are produced due to the excitation of the electron in the valence band and shifting to the conductance band. Due to their absorption in the UV spectrum, TiO_2 nanoparticles are not employed in medical settings. TiO_2 nanoparticles are mostly utilized to disinfect water and produce clean, hygienic water when sunlight is the light source [63]. Researchers have concentrated on doping TiO_2 nanoparticles with other elements to change their absorbance spectrum from ultraviolet to visible light in order to make them useful in clinical applications [64]. Furthermore, current research suggests that graphene quantum dots (GQD) can be used alone in aPDI without the need for conjugating PSs [65, 66]. Using GQD as the photosensitizer, a decrease in both Gram (+) and Gram (-) bacteria, S. aureus and E. coli, respectively, was observed after a 10-second irradiation [67].

2.5.3. aPDI using nanocarriers

Biodegradable matrices, like silica, have the ability to entrap a wide variety of PSs, produce a monodisperse distribution, and sustain antibacterial activity over an extended period of time. Because of the permeability of these matrices, ROS and other types of molecular radicals produced during irradiation can easily migrate through the matrices and kill nearby bacteria. In addition, the entrapment of PSs inside the matrices guards them against microbial attack and keeps them stable despite pH changes [68, 69]. Quantum dots (QD), like cadmium selenide quantum dots (CdSe QD) and zinc sulfide quantum dots (ZnS QD), enhance the efficacy of PS in aPDI. These molecules absorb photons with certain energies (wavelength less than 480 nm) and release longer-wavelength photons (about 642 nm). Through QD, the energy of light with the proper wavelength is transmitted to a nearby PS [70, 71].

The antibacterial capabilities of PS are enhanced when it is attached to the surface of nanocarriers. Different PSs have been shown to bind to distinct nanocarriers in a number of studies. For instance, TB has a tendency to bind to the surface of gold nanoparticles [72, 73], whereas porphyrin tends to bind to carbon nanotubes [74]. It was discovered that PS bound to nanoparticles had significantly higher antibacterial activity than PS in its free form. An alternative strategy involves using a viral protein cage to deliver PS was conducted. The genetic construct of the viral protein cage used in this strategy introduced two advantages: enhanced inactivation of bacterial cells and the ability to target specific sites with the aid of antibodies [75].

A variety of different nanocarriers, including emulsion-based systems, have been employed as PS delivery vehicles, including tetrapyrroles, natural products, and phenothiazinium dyes. Nanoemulsions (NE) are biphasic systems on the nanoscale that hold unique advantages for being used as novel carriers for aPS, especially because of their ease of preparation, improved stability, high solubilization of drug molecules, and enhanced biocompatibility [76]. Oil-in-water nanoemulsions (o/w) can be employed to administer hydrophobic drugs—like the majority of PSs—as they will be distributed in the oily phase before being dispersed into the aqueous phase in the form of droplets [77]. These nanocarriers have widely been used as delivery agents for PS with improved safety and efficiency [78–82]. Only a small number of studies have looked into NE's potential as an aPDI nanocarrier; the majority of reported studies have used it for PDT of cancer. After encapsulating chloroaluminum phthalocyanine (ClAlPc) in nanoemulsions (NE), it enhanced the photokilling of the highly resistant, potentially fatal Cryptococcus neoformans melanized cells via aPDI [83].

Additionally, the effectiveness of the cationic chloroaluminum phthalocyanine nanoemulsions (ClAlPc/NE)-mediated aPDI in reducing the metabolic activity of Candida albicans planktonic and biofilm cultures has been confirmed by additional research [84].

Furthermore, ClAlPc/NE-mediated aPDI was successful in photokilling methicillin-susceptible and methicillin-resistant Staphylococcus aureus suspensions and biofilms. The two strains of S. aureus were shown to be particularly susceptible to photokilling by cationic nanoemulsion (ClAlPc/NE) and free ClAlPc, whereas the MRSA strain was not susceptible to photokilling by the anionic formulation of ClAlPc [82]. Additionally, ZnPc was formulated in NE and demonstrated a notable improvement in photokilling of Leishmania species by aPDI [77].

Recently, ZnPc-NE was found to exhibit more photobiological activity on Enterococcus faecalis and MRSA than free ZnPc [85]. One of the most recent studies to create ZnPc in the NE system proved that ZnPc nanoemulsion has improved antimicrobial photodynamic inactivation of resistant bacterial infections in vitro with almost complete eradication of MRSA and a multidrug-resistant strain of E. coli. It also provided a promising therapeutic means of treating serious infections and promoting wound healing in vivo [86].

2.5.4. Nanocomposites for aPDI

Nanocomposites (NC) are multiphase materials with nanoscale additions in one of the phases. These phases are dispersed in such a way that they offer properties that neither of the individual phases can provide [87]. Polymeric nanocomposites have gained great attention in recent years for their bioavailability, biodegradability, sustainability, and non-toxicity [88]. For aPDI, various polymeric nanocomposites, composed of a wide range of biopolymers have been investigated. One of the studies loaded the cationic PS 5, 10, 15, 20-tetrakis (m-hydroxyphenyl) porphyrin (mTHPP) on the surface of ethylcellulose/ chitosan nanocomposite with a significant eradication of multi-drug resistant Pseudomonas aeruginosa, Staphylococcus aureus, and Candida albicans [89].

Furthermore, it has recently been postulated that metallic nanocomposites, such as metal-organic framework (MOFs) nanocomposite, can enhance aPDI. Metal ions and organic linker molecules are used to create MOFs, which are nanoporous materials with a high surface area, adjustable pore size and porosity, high drug loading capacity, and good biocompatibility. The FDA approved Ce6 was attached to the surface of zeolitic imidazolate framework-8 (ZIF-8) and showed an enhanced photokilling of MRSA with enhanced wound healing [90].

Metal and polymers were combined in a different investigation to create a nanocomposite for aPDI. This study integrated the non-toxic gold nanocluster protected with mercaptopropionic acid, and protoporphyrin IX (PpIX), within a chitosan polymer matrix. In response to exposure to white light, this nanocomposite demonstrated a twofold increase in ROS production, a notable eradication of both Gram (+) and Gram (-) bacteria, and improved penetration and biofilm removal [91].

Interestingly, a novel near-infrared triggered, multifunctional upconversion nanocomposites were developed with a strong ability to photokill bacteria. They consisted of up-conversion nanoparticles, Ce6 and Manganese pentacarbonyl bromide. When this nanocomposite is subjected to near-infrared (NIR) light (980 nm), the UCNPs can emit strong red light (655 nm), which further initiates the aPDI of Ce6. The resulting reactive oxygen (ROS) subsequently breaks the metal carbonyl bond of Manganese pentacarbonyl bromide, producing carbon monoxide (CO) molecules as well as manganese ions (Mn^{2+}). This further breaks down hydrogen peroxide (H_2O_2) in the microenvironment to oxygen (O_2). Consequently, this nanocomposite not only offers significant self-oxygen replenishment for improved aPDI, but it also makes it easier to effectively regulate inflammation through CO across a variety of deep infections [92].

2.5.5. Smart nanocarriers in aPDI

Smart nanocarriers are drug delivery technologies that can efficiently target bacterial cells and kill them selectively while leaving healthy tissue intact. This can usually be accomplished by either increasing the PS's affinity for particular bacterial components (such as membrane proteins) or by disturbing the pathogen to promote its uptake. Generally, it could be achieved by incorporating either poly-cationic materials, bacterial-targeting peptides, polymers, antibiotics, or antibodies [93]. PS can actively target bacteria by formulating polymeric nanocarriers attaching one of bacterial targeting moieties. Exopolysaccharides (EPS), glycan, and different sugars such as mannose, sialic acid, and galactose have been utilized to target different pathogens [94].

More and more target moieties are emerging as the bacteria are studied and understood in greater detail. Some nanocarriers were designed in such a way that the release of PS was only triggered by specific bacterial enzyme at the infection site. One study formulated the photosensitizer hypocrellin A (HA) into lipase-sensitive methoxy poly (ethylene glycol)-block-poly(ε-caprolactone) (mPEG-PCL) micelles, which once come into contact with bacteria that secrete lipase, the PCL is degraded to release HA. Photoactivation of HA resulted in complete eradication of MRSA [95].

Moreover, smart nanocarriers took advantage of the acidic nature of the bacterial biofilm and developed a bacterial-activatable polymeric delivery system, achieving selective killing of the bacteria while keeping the host normal tissue unaffected. Lack of oxygen in the biofilm milieu causes anaerobic glycolysis, which contributes to the acidic, highly reductive (high glutathione (GSH)) microenvironment, with abundance of ROS. PH-sensitive, surface charge switchable nanocarriers were developed. These systems loading PS exhibit negative charge at physiological pH, enabling it to prolong the circulation time in blood with minimal cellular internalization. Upon exposure to an acidic microenvironment at infection sites and biofilms, the surface charge of the nanocarrier turned into positive as a result of pH-sensitive electrostatic interactions. Hence, positively charged nanocarriers effectively bind to the surfaces of bacteria and enhance photoinactivation.

One investigation created pH-sensitive polydopamine (PDA) NPs of RB, which were coated a layer-by-layer with polymyxin B (PMB) and gluconic acid (GA) to generate functionally adaptive NPs (RB@PMB@GA NPs) that exhibited good biofilm penetration and eradication [96]. Another study developed pH-sensitive, surface charge switchable supramolecular polymeric system with the pH-sensitive poly (ethylene glycol) (PEG) block polypeptide copolymer [PEG-(KLAKLAK)2-DA] which interacted with the α-CD-Ce6 prodrugs through host-guest interaction. Upon light irradiation, this smart nanocarrier synergistic photodynamic eradication of MRSA biofilm (pH 5.5) with minimal harm to healthy tissues [97].

Smart nanocarriers with dual-responsive polymeric nanosystems have been recently designed to be sensitive to both the acidic microenvironment and the overexpressed peroxides of bacterial biofilms. An H_2O_2-responsive block copolymer of POEGMA-b-PBMA was assembled with a surface charge-switchable photosensitizer, 5, 10, 15, 20-tetra-{4-[3-(N,N-dimethyl-ammonio) propoxy] phenyl} porphyrin (TAPP) into NPs. At the infection area with overexpressed peroxide, nanoparticles were disintegrated to release TAPP, which was subsequently protonated in the acidic infection area with enhanced aPDI by making it more hydrophilic and less self-quenching [98]. Other smart systems create nanocarriers with double linkers that react to two aspects of the biofilm microenvironment. For instance, investigators linked the hyperbranched PEG with Zinc porphyrin through disulfide and benzacetal linkers, which react to reductive (GSH) and acidic microenvironments of bacteria, respectively [99].

2.5.6. Limitations of using nanocarrier in aPDI

No doubt that nanocarriers have greatly enhanced the solubility of PS, protected them, prolonged their circulation time, improved their targetability towards microbial infections, and boosted their overall pharmacokinetics. However, few of nanotechnology-based PDT reached clinical applications. Due to the inconsistency between in vitro and in vivo models, dosages, or experimental techniques reported in the literature, there are still a lot of unresolved queries regarding the biological impacts of nanoparticles themselves. It is essential to carefully assess the biocompatibility of nanoparticles in terms of both cytotoxicity and general cellular homeostasis. Better understanding of the cellular and molecular mechanisms that nanoparticles stimulate, such as inflammatory processes, is especially crucial since such actions could have toxicity or long-term impacts, compromising the biosafety of nanomaterials [100]. However, it is worth noting that PS complexation or covalent conjugation with a nanocarrier may drastically change the drug's physicochemical properties, which could impact its ability to cause phototoxicity. Furthermore, high PS concentrations may have a self-quenching effect and reduce phototoxic action. Therefore, before starting the biological research stage, it is essential to fully characterize the innovative delivery system upon drug binding and strike the correct balance between the PS loading and photodynamic action of the prepared formulae [101]. Therefore, techniques for synthesis and chemical characterization must be developed to produce formulations with repeatable structure, purity, and characteristics [100]. Given all those factors, it is reasonable to predict that using nanoparticles as therapeutic delivery systems in PDT still needs a lot of effort. However, the abundance of publications on the biological activities of PS-nanoparticle formulation in vitro and in vivo gives us optimism that, in the future, better drug delivery may enable us to greatly increase the efficacy of PDT.

III. CONCLUSION

Antibiotic resistance in microorganisms continues to be a serious medical problem that complicates therapy. On the other hand, it has been shown that aPDI in conjunction with nanotechnology is a promising therapeutic approach for the eradication of bacterial biofilms and resistant bacterial infections. With nanotechnology, photosensitizers of various origins can have their characteristics modulated to increase their effectiveness and selectivity.

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Assessing Fluoride Absorption in Dentine Treated with Silver Diamine Fluoride: A Mini-Review on the Role of Nd:YAG and Diode Lasers

Howaida Elsegaey[1], Omnia Hamdy[2], Nagy Abdulsamee[3], and Ahmed Abbas Zaky[1]

[1] Cairo University, Department of Medical Application of Laser, National Institute of Laser Enhanced Sciences (NILES), Giza, 12613, Egypt, [2] Cairo University, Department of Engineering Applications of Lasers, National Institute of Laser Enhanced Sciences (NILES), Giza, 12613, Egypt, [3] Faculty of Dentistry, Misr University for Sciences and Technology, Egypt

Abstract

Background: Dental caries management has long relied on fluoride therapy as a cornerstone of preventive care. Silver diamine fluoride (SDF) has emerged as a promising material in clinical dentistry showcasing significant potential in caries control
Objective: This review aims to evaluate the influence on penetration depth and fluoride uptake in dentine treated with SDF solution as well as laser irradiation at sub-ablative energy levels. The objective is to explore how these lasers can enhance fluoride absorption and further protect the enamel from acid attacks. Accordingly, two types of laser were selected for this evaluation, namely Nd:YAG and Diode lasers.
Conclusions: Lasers have a greater potential to boost fluoride uptake of enamel while also protecting the enamel surface from acid attack. This study sheds light on the enhanced efficacy of laser-assisted protocols in bolstering the protective mechanisms of fluoride, potentially revolutionizing contemporary approaches to caries prevention and treatment in the realm of dental care.

Keywords— fluoride therapy, silver diamine fluoride, Nd:YAG laser, diode laser irradiation

I. INTRODUCTION

The predominant methods of topical fluoride administration are toothpaste, gel, varnishes, and mouth rinses. The protective action of fluoride arises from the creation of a superficial calcium fluoride (CaF_2) layer that shields the enamel from acid exposure and breakdown. Nonetheless, certain studies indicate that the effectiveness of fluoride therapy in mitigating tooth erosion is constrained, as it is dependent on the continuous presence of fluoride in the oral cavity [1]. Therefore, in order to obtain a protective effect, it is necessary to employ products with a longer retention time and a higher fluoride concentration. Consequently, the application of fluoride to mitigate erosive processes necessitates substantial patient adherence.

The mechanism of action of silver diamine fluoride (SDF) is illustrated in **fig. 1**. Silver (Ag) ions interact with bacterial DNA, inhibiting replication and preventing bacterial growth. Additionally, Ag ions bind to bacterial cell membranes, causing structural damage and eventual cell death. Meanwhile, fluoride ions play a key role in promoting enamel re-mineralization by forming fluorapatite, which exhibits greater resistance to acid erosion compared to hydroxyapatite. Furthermore, in the presence of calcium and phosphate ions found in saliva, calcium fluoride-like deposits form on the enamel and dentin, serving as long-term fluoride reservoirs. Lastly, the high pH of SDF induces protein denaturation and coagulation within demineralized dentin. These precipitated proteins seal exposed dentinal tubules, providing a protective barrier to safeguard soft dentin and minimize sensitivity.

Recently, lasers have been suggested as a novel approach to prevent dental caries or to augment traditional treatment [1]. The degradation of the organic matrix, loss of carbon and water, and the formation of refractory hydroxyapatite phases, such as calcium phosphate or calcium pyrophosphate are all caused by the heat generated by laser light, which also inhibits cavities development on enamel surfaces. Additionally, it enables the integration of fluoride into the hydroxyapatite matrix when used in conjunction with topical fluoridation. This results in the synthesis of fluorohydroxyapatite and CaF_2 on the enamel surface which serves as a fluoride reservoir to combat dental caries during demineralization [2].

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Corresponding author: Omnia Hamdy Email: omnia@niles.cu.edu.eg

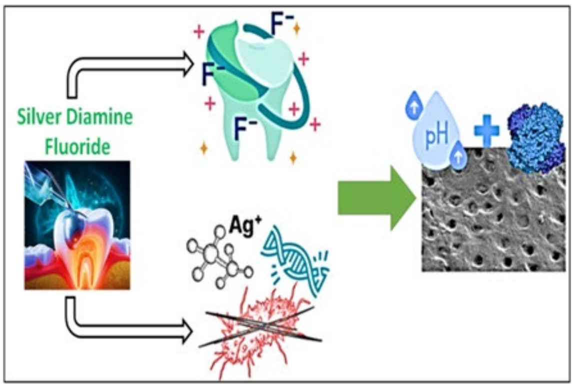

Figure 1. Impact of Fluoride, Silver Nitrate, and Silver Diamine Fluoride on Dental Structures and Bacterial Activity

An active solid component of a diode laser is semiconductor crystals of indium, gallium, as well as arsenide. It emits wavelengths among 800 and 980 nm, which are located in the non-ionizing invisible infrared spectrum. A diode laser's continuous wavelength renders it highly effective for soft tissue surgery. A significant benefit of diode lasers is their compactness and portability [3]. The effects of diode laser application with a λ of 809–960 nm on the enamel surface have been examined in only a few research. This λ is absorbed by the hydroxyapatite of the dental structure at low levels, while the remaining energy is transmitted as heat to the enamel surface and its surrounding structures. Nevertheless, such elevated enamel temperatures may result in significant modifications to its structure and ultrastructure, therefore reducing the enamel's susceptibility to acid dissolution. Such alterations may involve the degradation of its organic matrix, loss of carbonate and water, as well as the formation of acid-resistant hydroxyapatite layers [4]. There was some evidence that utilizing a diode laser in conjunction with sodium fluoride effectively increased the amount of fluoride absorbed by tooth enamel. However, different studies found that enamel-acid solubility was significantly reduced and carious lesion growth was inhibited in vitro [5].

This review seeks to assess the effects of SDF solution and sub-ablative laser irradiation (especially Nd:YAG and Diode Lasers) on fluoride uptake and penetration depth in dentin. It aims to investigate the potential of laser treatment to enhance fluoride absorption and provide additional protection against acid-induced demineralization.

II. LITERATURE REVIEW

1. Laser in promoting dentine fluoride uptake

Lasers have a significant impact on dental tissues due to their ability to modify surface morphology and enhance structural properties. When applied to dentin, laser irradiation can clean the surface by removing the smear layer and opening dentinal tubules, thereby improving permeability and facilitating the penetration of therapeutic agents. Additionally, lasers can induce thermal effects that lead to fusion and re-solidification of dentin, creating a smoother and more compact surface (see **Fig. 2**). This process reduces the susceptibility of dentin to acid attacks and microbial infiltration by sealing exposed tubules and strengthening the surface Sub-ablative laser energy can enhance the uptake of fluoride ions by altering the crystalline structure of dentin, promoting the formation of more stable and acid-resistant compounds, such as fluorapatite. The interaction between laser energy and dental tissues also contributes to protein coagulation and mineral deposition, which aids in protecting the dentin from further demineralization and sensitivity. These effects make lasers a valuable tool for improving the durability and effectiveness of dental treatments.

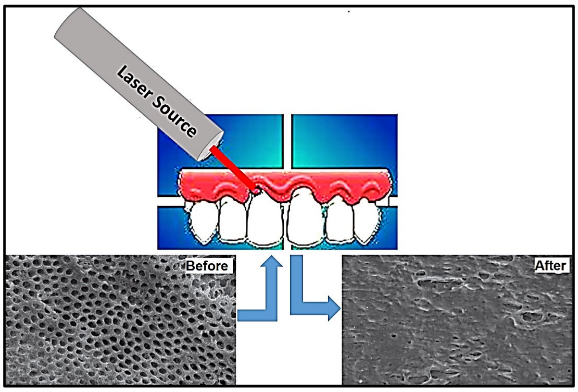

Figure 2. Dentinal surface showing open dentinal tubules and absence of smear layer before laser treatment, followed by dentin fusion and re-solidification after laser irradiation, with no smear layer or debris present

The literature on the use of lasers to improve dentine fluoride uptake is a rich tapestry of studies and findings. Studies have looked into the synergistic effects of laser irradiation, notably with Nd:YAG and diode lasers operating at sub-ablative energy levels, when combined with SDF treatment. These studies have found a possible avenue for increasing fluoride penetration within dentine, thereby strengthening the protective mechanisms against acid attacks. The availability of literature indicates a growing interest in using laser technologies to improve the efficacy of fluoride therapy in dental care, implying a paradigm shift towards more precise and effective techniques to increasing fluoride uptake and reinforcing enamel surfaces. The literature highlights the revolutionary potential of laser-assisted protocols in revolutionizing tactics for enhancing dentine fluoride uptake and advancing preventive dental care practices by synthesizing research findings and clinical insights.

Mei et al., (2014) [6] investigate the preventative effects of Er:YAG laser irradiation in conjunction with SDF therapy on dentine that has been subjected to a cariogenic biofilm challenge. From human third molars that had been extracted and were still intact, 24 dentine slices were created. Each slice was divided into four sections for the application of SDF, which was then followed by EYL irradiation (group SL), EYL irradiation (group L), SDF application (group S), and finally water (group W). There were laser melting traces visible on the specimen surfaces of groups SL and L, and the dentinal orifices were becoming more constricted. The group S showed signs of a partial obstruction of the tubules. Demineralization was identified in group W, which was characterized by a porous surface profile. Based on the findings of the research, it was discovered that the employment of SDF, followed by EYL irradiation on a dentine surface, resulted in an improvement in the latter's resistance to cariogenic biofilm problems.

The effects of carbon dioxide and diode lasers on the absorption of fluoride by primary tooth enamel were compared by Bahrololoomi et al., (2015) [2]. Forty primary molars from humans were divided into four equal groups. The experimental and control groups were formed by removing the roots and dividing the crowns mesiodistally into the buccal as well as lingual halves. Application of 5% sodium fluoride (NaF) varnish was performed on all samples. Fluoride uptake was evaluated by an ion-selective electrode after acid dissolving the specimens, and experimental samples from each of the four groups were compared to the controls after 15 seconds of irradiation with 5 or 7W diode lasers or 1 or 2W CO2 lasers. The conventional topical fluoridation group had significantly lower estimated fluoride uptake values contrasted with the 5W and 7W diodes and 1W and 2W CO2 lasers, correspondingly, which were 59.5± 16.31 ppm, 66.5± 14.9 ppm, 78.6± 12.43 ppm, as well as 90.4± 11.51 ppm. In accordance with the results, fluoride absorption is improved when the enamel surface is exposed to diode lasers and carbon dioxide.

Tosun et al., (2016) [7] compare the effects of using Clinpro® White Varnish (five percent sodium fluoride + tri-calcium phosphate) with and without the use of a Nd:YAG laser on the occlusion potential and dentinal tubule penetration. They randomly divided 75 dentine samples (n = 15) taken from 38 recently extracted human molars. Clinpro varnish was applied to groups A, B, D, and E, with group C serving as the control group that did not receive any therapy. An Nd:YAG laser (1.5 W, 10 Hz, 1 minute) was used to further irradiate groups B and E. Compared to group C, groups A and B had significantly higher tubular occlusion. Group B exhibited noticeably higher tubular occlusion compared to group A. Group D's penetration depth was noticeably greater than group E's. The effectiveness of Clinpro in tubular occlusion was improved by utilizing laser technology as the laser had the opposite effect reducing Clinpro's penetration.

The effectiveness of fluoride varnish in restoring root dentine permeability was investigated by Chiga et al., (2016) [8] utilizing an Er:YAG (100 mJ, 3 Hz) or Nd:YAG (70 mJ, 15 Hz) laser. A total of sixty 2 × 2 × 2-millimeter-thick slabs of bovine root dentine were eroded for two hours in a solution of 0.3% citric acid (pH 3.2) and then immersed in artificial saliva for twenty-four hours. One hundred and ten specimens were randomly assigned to one of six treatments: fluoride varnish alone, fluoride varnish plus Er:YAG laser, fluoride varnish plus Nd:YAG laser, non-fluoride varnish alone, non-fluoride varnish plus Er:YAG laser, and non-fluoride varnish plus Nd:YAG laser. Each of the two types of YAG, Er and Nd, were pulsed for ten seconds at 100 mJ and fifteen Hz, respectively. The permeability of damaged root dentine was greatly reduced by laser irradiation, regardless of the laser source, but the key factor, varnish, had no discernible effect. The results of this study show that Er:YAG and Nd:YAG lasers can control the permeability of damaged root dentine without the need for fluoride varnish.

The effectiveness of Diode (wave length = 980 nm; power = 5 Watt; fluence energy = 53 J/cm2; repetition rate = 16 Hz; for 15 s. A G6 tip, diameter = 600 µm) and Nd-YAG (1064 nm, peak power = 0.6 W, beam spot diameter = 10 µm, fluence= 14J/cm^2) lasers on enamel's acid resistance is assessed by Chand et al., (2016) [9] both separately and in conjunction with acidulated phosphate fluoride (APF) treatment. seventy-two enamel samples from 12 extracted human molars were randomly assigned to one of six groups: (1) Control (C); (2) APF gel exposure (F); (3) Diode laser (DL); (4) Diode laser and APF gel radiation (DL/F); (5) Nd-YAG laser (NL); and (6) Nd-YAG laser and APF gel radiation (NL/F). Group one through six had calcium ion values of 901, 757, 736, 592, 497, and 416 parts per million micrograms per gram on average. In contrast to the other groups, the NL/F group showed significantly less demineralization, according to the data, whereas the control group showed significantly more demineralization. When compared to the other groups, the results showed that Nd-YAG laser irradiation, both by itself and in conjunction with APF, was better in reducing enamel demineralization.

The effects of diode laser at different power densities on dentine permeability and closure of exposed dentinal tubules were investigated by Lutfi et al., (2018) [10] with and without sodium fluoride. One hundred eighteen teeth were utilized. The samples were categorized into three primary groups. The initial set comprised 100 teeth utilized for the permeability test. The second component comprised 16 teeth for assessing the increase in external surface temperature during irradiation. The third component comprised a single pair of teeth examined using SEM for the examination of dentine surface morphology. The measurement of dentine permeability demonstrated a significant difference between the control group and the 2 and 3 W varnish groups. The results indicated that the external surface temperature increase for both the laser-only and laser with varnish groups ranged from 67 to 97.9 °C at 1.6 and 2 W. SEM examination indicated that nearly optimal sealing of tubules was achieved in the 2W varnish group. The study concluded that the simultaneous application of a 940 nm diode laser at 2W with a power density of 809.7 W/cm², in conjunction with sodium fluoride white varnish, significantly enhances the reduction of dentine permeability compared to each therapy administered independently.

In vitro studies on fluoride uptake by dentine were conducted by Al-Hasnawi et al., (2019) [11] using a variety of topical fluoride compounds, including APF, SDF, and stannous fluoride (SnF2), with or without the use of a Nd-YAG laser (1064 nm). For this investigation, 55 maxillary first premolar teeth were used as samples. The teeth were divided into 11 groups, with 5 specimens from each group. A pH cycling approach was used to produce a caries-like lesion in the dentine specimens of all eleven groups for five days before to the surface treatments. The specimens were subsequently immersed in re-mineralization solutions for two days. Following administration of various agents, the results showed that the groups treated with SDF+Laser, SnF2, Laser+SnF2, and Laser+APF had much higher fluoride uptake. Fluoride uptake was much higher in the group that received only SDF. In terms of topical fluoride application, the most effective treatment was SDF applied directly to the dentine surface. SDF alone may give a constant and extended fluoride release and facilitates sustained absorption, whereas laser treatment may speed up initial reactions but inhibit long-term fluoride diffusion. Without laser therapy, fluoride ions from SDF can travel naturally via the dentin tubules. However, laser irradiation may seal or partially block these tubules resulting in decreased ion transfer. While SDF alone increased fluoride uptake, coupled methods with laser still showed considerable benefits, particularly in terms of fluoride retention and antimicrobial properties.

Hendi et al., (2021) [12] evaluate the synergistic effects of silver nanoparticles and a diode laser with a wavelength of 940 nm on Enterococcus faecalis as antibacterial agents. They used rotary files to decoronate and prepare 90 human teeth with one root. There was an irrigation of the samples with sodium hypochlorite and 17% EDTA. After that, they were autoclaved and inoculated with a suspension of E. faecalis (1.5 × 108 CFU/mL) for a duration of 21 days. After micro-titrating the samples, they were randomly assigned to 1of 4 experimental groups (n=20) or a negative control group (n=10). First, 5% sodium hypochlorite; second, silver nanoparticles; third, diode lasers; and fourth, a combination of the two. Following treatments, colony levels dropped significantly across the board.

The colony counts of all groups were significantly lower than those of the negative control group. Group 1 demonstrated a significant decline in colony counts in contrast to the other groups, with an extreme decrease (RCC=100%). When comparing the two groups, the efficiency of the silver nanoparticles group (RCC=83.15%) was much higher than that of the diode laser group (RCC=41/33%). Group 4's RCC was 68%/52%. The most efficient antibacterial chemicals were silver nanoparticles, followed by sodium hypochlorite 5%. The antibacterial effect of the 940 nm laser diode was lower in contrast to its use in conjunction with silver nanoparticles due to the synergistic interaction. The nanoparticles act as plasmonic enhancers which amplify the laser's photothermal and photochemical effects. This results in increased bacterial cell damage unlike the laser's limited efficacy due to insufficient energy.

Hassan et al., (2021) [13] investigate the impact of dental curing light and laser treatments on dentine hardness in primary molars that have developed cavities after being treated with SDF. Thirty removed primary molars with pulpal-free, dentinal-extending caries were used in this in-vitro study. Three groups were formed from the collected teeth at random: group 1: SDF plus sub-ablative low-energy Er,Cr:YSGG laser (The output power = with 0.5 W, 5 Hz, without water cooling, and 55% of air); group 2: SDF plus 40 seconds of curative light; and group 3: SDF alone. All groups utilized 38% Ag $(NH_3)_2F$ SDF. In comparison to the other two groups, the laser+SDF group had noticeably greater surface hardness of healthy dentine beneath the carious lesion. While photo-polymerization of SDF does raise the surface hardness of healthy dentine beneath the carious lesion, the greatest surface hardness is achieved by sub-ablating dentine with a laser after SDF.

The effectiveness of the 980 nm diode, Nd:YAG, and Er:YAG lasers in conjunction with fluoride for dentinal tubule obstruction is evaluated and compared by Aghayan et al., (2021) [14]. This in vitro investigation utilized twenty healthy, single-rooted human teeth. After preparing the roots, forty dentinal discs were etched with 6% citric acid. Their surface was coated with one coat of fluoride varnish. Each part was divided into four equal groups at random. There was no laser treatment for the control group. Irradiation with a 0.5 W power 980 nm diode laser was performed on Group 2. The third group was exposed to 0.5 W of Nd:YAG laser irradiation, whereas the fourth group was exposed to 0.5 W of Er:YAG laser irradiation. When compared to a control group, all three laser modalities dramatically reduced the amount of open dentinal tubules. In terms of dentinal tubule blockage, none of the three laser groups differed significantly. There was no significant variation between the control group and the three laser groups with respect to the diameter of open tubules.

Atef et al., (2022) [15] investigate microstructural changes and the impact of diode laser (980 nm, 2 W for 15 sec, in a CW and contact modes via 320-µm optical fiber) and two re-mineralizing agent types on the micro-hardness of primary tooth enamel. For this experiment, twenty primary molars were cut in half lengthwise in a mesiodistal direction. The resulting forty specimens were then distributed at random into five groups. None of the five participants in Group 1 (Control Negative) received radiation or any kind of treatment. The second group, the control positive group (n = 5), was subjected to 60 Gy of gamma radiation. Subgroups A and B were created with five specimens each for Groups 3, 4, and 5. Different surface treatments were applied to Subgroup A after gamma irradiation. Treatment 3A involved 10% nano-hydroxyapatite (nHA) paste, treatment 4A involved 5% sodium fluoride varnish (FV), and treatment 5A involved a 980 nm diode laser. A surface treatment of 10% nHA was applied to 3B, 5% FV to 4B, and a diode laser at 980 nm to 5B before gamma irradiation to subgroup B. The mean micro-hardness was lowest in Group 2 (G) specimens, and it was most noticeably greater in nHA-G (3B), G-Fl (4A), and L-G (5B). Group G had a change, and re-mineralizing agents obliterated enamel micropores, according to ESEM study. Enamel subgroups also showed signs of melting and fusing. The results showed that the micro-hardness was increased and the microstructure integrity was maintained while employing FV, nHA, or a diode laser. The inflammatory response, dentinogenesis, silver penetration, pulp cell activity and bacterial presence in the dental pulp are all considered in the systematic analysis of the dental pulp's response to SDF treatment by Zaeneldin et al., (2022) [16]. After conducting a preliminary search, 1,433 publications were identified, five of which met the inclusion criteria. In total, these five publications examined the effects of direct and indirect SDF administration on the essential pulp of 30 teeth. Pulp necrosis was the consequence of the direct application of SDF to vital pulp. The tooth pulp experienced minimal or no inflammatory response as a consequence of the indirect administration of

SDF. Within the dental pulp, the odontoblasts demonstrated increased cellular activity. Tertiary dentine was produced on the pulpal aspect of the cavity as a result of the indirect administration of SDF. Mineralization disruptions were indicated by prominent incremental lines of tertiary dentine. Silver ions were observed to infiltrate the dentinal tubules, but they were not detected within the pulp. Pulp necrosis is the consequence of immediate administration of SDF, as evidenced by the existing literature. The indirect administration of SDF is generally biocompatible with dental pulp tissue, resulting in a moderate inflammatory response, increased odontoblastic activity, in addition to increased tertiary dentine production.

Vazirizadeh et al., (2022) [17] examine the efficacy of a 940 nanometer diode laser, Gluma, and a five percent NaF varnish in the treatment of dentinal tubule occlusion. The enamel of forty healthy human premolars was removed from the buccal surface's cervical midline, with a measurement of 2×2 millimeters in area and 2 millimeters in depth. The samples were divided into four categories: control, 940 nm diode laser, NaF varnish, and Gluma. The samples were subjected to field emission scanning electron microscopy (FE-SEM) analysis subsequent to the interventions. The number of open, fully occluded, as well as semi-occluded dentinal tubules was counted in their totality. The control group (15.03% ± 3.39), those treated with Gluma (74.4 percent), those treated with NaF varnish (61.78% ± 15.25 percent), and those treated with a 940 nm laser (84.01% ± 12.08%) exhibited the highest rates of dentinal tubule occlusion. The rate of the control group was markedly different from that of the groups that received Gluma, NaF varnish, or 940 nm laser treatment. The Gluma group did not exhibit any significant distinctions from the NaF varnish and 940 nm laser groups. The NaF varnish group was significantly more prominent than the 940 nm laser group. The results of this investigation provide evidence in favor of the use of a 940 nm diode laser, 5% NaF varnish, and Gluma for dentinal tubule sealing. The effects of Gluma were comparable to those of the other two modalities; however, the 940-nanometer diode laser had a more significant impact than NaF varnish.

Salem et al., (2022) [18] used SDF or a diode laser to eliminate pathogens in carious lesions with the Hall method to improve its success rate for carious primary molars. Random assignments were made to three equal groups of 159 children, ages 4 to 8: diode laser with Hall technique, SDF with Hall technique, and Hall technique application. Children get together on a regular basis all year round. Findings: At the end of the follow-up, Group I had the lowest clinical and radiographic success rates (88.7% and 86.8%, respectively), while Group III had the highest clinical success rate (94.3 percent), followed by Group II (96.2 percent). However, these differences were not statistically significant. The Hall approach was enhanced in primary teeth by treating carious lesions with SDF or Diode Laser.

Mohsen et al., (2022) [19] investigate the impact of pretreating primary molars with SDF and potassium iodide (SDF + KI) on fluoride absorption in dentine when using resin modified glass ionomer restoration (RMGI). Twenty extracted primary molars were sectioned mesio-distally, resulting in two equivalent halves, totaling forty pieces. Each tooth was positioned in an individual container alongside its two halves. Teeth were subsequently assigned at random to either the control or therapeutic group. The caries was dug in both halves of each tooth. The control group received resin-modified glass ionomer. SDF and potassium iodide were followed with resin-modified glass ionomer in the intervention group. Energy dispersive X-ray analysis measured dentine fluoride % by weight in both groups after two weeks. Following repair implantation, the RMGI control group experienced a considerable rise in fluoride weight percentage, from 0.81±0.47 to 3.49±1.88%. After repair, the SDF + KI intervention group showed a significant increase in fluoride weight % from 0.47±0.44 to 4.14±1.45. In the control group, the mean fluoride weight % (3.49±1.88) was not significantly different from the intervention group (4.14±1.45). The use of SDF and potassium iodide beneath resin-modified glass ionomer restorations does not prevent fluoride absorption into dentine.

The effect of a light-emitting diode (LED) healing light on the extent to which SDF penetrates carious lesions is examined by Crystal et al., (2023) [20]. Twenty-four primary teeth were prepared for treatment within five minutes of extraction based on the number of untreated caries lesions: (1) six subjects were treated with one drop of SDF for one minute, then rinsed with tap water for ten seconds. (2) six subjects were treated with one drop of SDF for ten seconds, then exposed to LED light for twenty seconds (30 seconds total SDF exposure). (3) six subjects were treated with one drop of SDF for ten seconds, then rinsed with tap water for ten seconds. (4) three subjects were left untreated, and (5) three subjects were left untreated but exposed to LED light for twenty seconds. Groups 1 and 2 were statistically comparable to Group 3 and distinct from it. There was no silver present in Groups 4 and 5. Silver penetration appears to be facilitated by the use of LED light for 20 seconds following a 10-second SDF application, which is comparable to a one-minute SDF technique.

Alsherif et al., (2023) [21] compared the anti-cariogenic effects of nano silver fluoride varnish around orthodontic brackets with those of diode laser irradiation. Group I consisted of 20 premolars treated with nano silver fluoride, Group II of 20 premolars treated with diode laser, and Group III of 20 premolars treated with a combination of nano silver fluoride and diode laser. All 60 premolars were free of caries and in good condition. The results of the PLM and SEM analyses showed that there were some demineralized spots in group I. Group II had considerably more demineralization. In Group III, we saw enamel with a very uniform surface. There was a significant distinction between Groups III and I, and a highly significant variance among Groups II and III, according to the elemental analysis. When comparing the shear bond strengths of groups I and II, as well as groups III and II, statistically significant differences were found. There was no statistically significant difference between groups I and III. Dental enamel appeared to benefit from both the diode laser and the nano-silver fluoride, according to the results. After pretreatment with a mix of diode laser irradiation and nano silver fluoride varnish, the enamel criterion showed the maximum improvement.

Alghazali et al., (2023) [22] evaluate the efficacy of a 940 nanometer diode laser at different power levels in addressing dentine hypersensitivity. The desensitizing efficacy of a 10-second continuous mode diode laser at 940 nm was evaluated for the treatment of dentine hypersensitivity in six individuals, including a total of 38 teeth. The laser was applied at two different power levels. A statistically significant reduction in dentine hypersensitivity was found immediately after the initial treatment session and following a 14-day follow-up period. The application of a diode laser (940 nanometer) was found to effectively reduce both acute and chronic dentine hypersensitivity discomfort.

The effects of SDF, APF, LASER-activated SDF, and LASER-activated APF on the surface of the enamel are studied and compared by Singh et al., (2023) [23]. The sample was made up of seventy-two non-corrupt, normal human premolar teeth that had recently been extracted for orthodontic reasons. Group 1 consisted of SDF, Group 2 of APF, Group 3 of LASER-activated SDF, and Group 4 of LASER-activated APF were the four groups into which the selected samples were randomly assigned (n = 18). Following demineralization and re-mineralization, all samples were evaluated for DIAGNOdent values. Spectrophotometry, Scanning Electron Microscopy, and Energy Dispersive X-ray Spectrometry were used to further classify and analyze the samples for color variations, surface alterations, and fluoride concentration in the surface enamel, respectively. The third group showed the most noticeable changes in surface enamel color and the highest re-mineralizing capacity. At magnifications of 2000× and 5000×, Scanning Electron Micrographs from Groups 3 and 4 showed consistent globular structures of enamel, whereas Groups 1 and 2 showed uneven globular surfaces of enamel. The surface enamel fluoride absorption was highest in Group 4, followed by Group 3. They found that topical fluorides triggered by lasers help prevent cavities more effectively. Because it shows better fluoride absorption on the enamel surface without discoloration, LASER activated APF is an appealing substitute to SDF.

Cifuentes-Jiménez et al., (2023) [24] assess the demineralizing capacity of SDF/NaF products by analyzing the physicochemical and mechanical properties of the treated dentine surfaces, and (2) determine the effects of SDF and NaF on demineralized dentine subjected to acid challenge through pH-cycling. There were three phases to the experiment that involved 57 human molars: the first was a negative control using sound dentine; the second was a positive control utilizing demineralized dentin; and the third was a dentine treatment using SDF/NaF products + pH-c. The dentine + pH-c groups treated with SDF/NaF (Stage 3) had a larger mineral/organic content compared to the positive control groups, indicating a change in chemical composition. In comparison to the positive control, the XRD data demonstrated that the hydroxyapatite crystallite size increased in the SDF/NaF treated dentin + pH-c groups, ranging from +63% in RivaStar to +108% in Saforide. Images captured by scanning electron microscopy revealed the formation of a crystalline precipitate on the dentine surface and partial filling of the dentine tubules following the administration of the SDF/NaF products. Stage 3 dentine treated with SDF/NaF + pH-c had higher flexural strength (MPa) values than the positive control groups. Demineralized dentine's physicochemical and mechanical characteristics were impacted by the application of SDF/NaF. The results showed that even when exposed to acid, the dentine surface exhibited a re-mineralizing action after utilizing SFD/NaF. In order to determine whether or not APF is necessary to prevent dentine hypersensitivity after an erosive challenge, Corrêa et al., (2024) [25] evaluate the effectiveness of Er:YAG and Nd:YAG lasers. The following thirteen groups were formed from the 104 samples taken from bovine dentine: All eight groups were treated in the same way: G1 with Er:YAG, G2 with Er:YAG and APF, G3 with APF and Er:YAG simultaneously, G4 with Nd:YAG, G5 with Nd:YAG and APF, G6 with APF and Nd:YAG simultaneously, G7 with APF, and G8 without treatment. For the Er:YAG experiment, the following parameters were used: 10 seconds, 4 mm distance, 2 mL/min water cooling flow, 2 Hz frequency, and 3.92 J/cm² energy density. 10 seconds at a distance of 1 millimeter without cooling, 10 Hz, and 70.7 J/cm² were measured for Nd:YAG. In terms of roughness, there was no discernible difference across the categories. The groups that were exposed to Er:YAG radiation showed less fluid loss. Values for G6 were higher than those of the Er:YAG irradiation groups but lower than all of the others. Wear results in the other Nd:YAG-exposed groups were similar to those in the control group. Wear investigation showed that the Er:YAG laser caused the least amount of volume loss, which means that dentine is more resistant to acid.

The effects of Er,Cr:YSGG irradiation and 980 nm diode lasers on dentine surface roughness and volumetric loss under cariogenic stress are examined by Guarato et al., (2024) [26]. Thirteen categories were created from 130 bovine dentine specimens: no medical intervention; FG: fluoride gel; FV: fluoride varnish; Di: diode laser operating at 980 nm; Di + FG; Di + FV; FG + Di; FV + Di; Er: Er,Cr:YSGG laser; Er + FG; Er + FV; FG + Er; FV + Er The Er,Cr:YSGG laser settings were as follows: Without water and with 55% air, 0.25 W, 5.0 Hz, and 4.46 J/cm². The 980 nm diode laser's specifications were 2.0 W, 2.0 Hz, and 21.41 J/cm². The samples in each group were pH-cycled. The cariogenic challenge and 1807-3107-bor-38-e025 therapy did not cause a statistically significant response in the reference area's SR. VL in the FV + Er and FV + Di groups differed considerably from regions exposed to different cariogenic stimuli and treatment regimens. When bovine teeth were subjected to cariogenic stress, dentine susceptibility to lesions was decreased by fluoride varnishes, Er,Cr:YSGG, and 980 nm diode lasers.

2. Potential limitations of laser-assisted fluoride techniques

One of the key concerns of laser-assisted fluoride procedures is the cost of implementing laser technologies into dental practices which may pose financial hurdles for practitioners and impede the general acceptance of these advanced treatments [27]. Furthermore, the availability of laser equipment and the necessary training for dental professionals to use these technologies are substantial impediments to deployment, especially in small practices in areas with limited accessibility [28]. In addition, laser-assisted fluoride treatments in dental care may pose potential hazards. One significant concern is thermal injury to surrounding tissues during laser treatments, which can occur if laser energy levels are not carefully managed or suitable cooling systems are not in operation [29]. This heat degradation may cause discomfort for individuals and damage the integrity of adjacent tooth structures. Furthermore, there is a possibility of inadvertently exposing the patient's eyes or skin to laser radiation, highlighting the significance of rigid safety regulations and preventive measures to prevent any harmful consequences [30].

III. CONCLUSION

Combining SDF treatment with sub-ablative energy laser technologies such as Nd:YAG and Diode lasers offers a convincing way to improve fluoride absorption in dentine. Our analysis highlights the great potential of laser-assisted methods to increase fluoride's protective benefits, especially in enhancing enamel's resistance to acid erosion. These results underline the critical role that lasers play in boosting the effectiveness of fluoride therapy and point to a significant change in preventive dental care. Future developments indicate that the use of laser-assisted SDF therapies has the potential to revolutionize current dental caries prevention techniques and herald in a new era of accurate and successful oral health interventions.

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Efficacy and Safety of Fractional CO_2 Laser Therapy in the Treatment of Post-Traumatic Scars

Abeer Attia Tawfik[1], Amal Osama Hadhoud[2*], Noha Abdallah[1]

[1] Department of Medical Applications of Laser, Dermatology Unit, National Institute of Laser Enhanced Sciences, Cairo University, Giza, Egypt, [2] Department of Dermatology, General Administration of Medical Affairs (Students Hospital), Zagazig University, Zagazig, Egypt

Abstract

The development of scar tissue is a result of healing of wounds that occurred as a result of damaged tissue. Post-traumatic scars have a significant impact on the quality of life of cases, potentially causing psychiatric and emotional disturbances. There are several methods available for managing such scars. In general, the effectiveness of fractional carbon dioxide (CO2) laser therapy for post-traumatic scars has been demonstrated in multiple investigations. In this review, we focused on the effectiveness of fractional ablative carbon dioxide laser in the treatment of post-traumatic scars, whether as a monotherapy or in combination with other techniques. We additionally tried to determine the impact of various factors, including the type of skin, the duration, the shape, the location, and the pigment of the scars, on the outcome. The literature research comprised articles (clinical trials or scientific evaluations) that have been recognized by searching electronic databases such as PubMed within the past five years, as well as the reference lists of the respective articles.

Keyword— scars, fractional CO_2 laser, post-traumatic scars

I. INTRODUCTION

Scars are acquired by approximately one hundred million cases every year, with eleven million of them being keloids and four million being burn scars. Children account for seventy percent of these scars. Psychological, aesthetic, social, and physical repercussions may result from abnormal skin scarring [1]. Burns and other traumatic injuries result in the development of traumatic scars in millions of individuals globally each year. Scars frequently develop at the location of tissue injury and may be either hypertrophic or atrophic [2].

It is impossible to achieve a complete enhancement in scars, despite the expectations of cases who are seeking management. However, the quality of life is often enhanced as an outcome of the reduced visibility of scarring that often results from improvements in texture, depth, and pigmentation [3]. However, numerous therapies are accessible; however, each of these treatments has its own disadvantages. The fractional carbon dioxide laser has been successfully utilized for treating scars widely [4]. Fractional CO2 laser apparatus generate controlled micro-wounds in scars, which initiate remodeling response and healing of wound that propels the treated scar tissue toward a more normotrophic state [5]. The goal of this review to assess the safety and effectiveness of fractional carbon dioxide laser either as a monotherapy or combined with other treatments for post traumatic scars.

II. METHODOLOGY

Utilizing the following keywords: "post-traumatic scars," "fractional CO2 laser," & "laser therapy for scars," articles (scientific reviews or clinical trials) have been recognized for this review by searching electronic databases such as PubMed & the reference listings of the relevant articles. The search was conducted for articles related to the studied modalities that were published in the period from January 2020 to September 2024. Authors, year of publishing, design of the study, participants included in each trial, age group, type of intervention, laser power, pulse duration, density level and depth level study follow-up duration, clinical response and complications were retrieved from the selected studies.

III. RESULTS AND DISCUSSION

Nine studies were found using fractional CO_2 laser, whether used as monotherapy or combined with other therapies in cases having post traumatic scars. Mohamed et al. (2022) performed an investigation that involved twenty cases, four of whom were men and sixteen of whom were women, who were afflicted by scars following burns & post-traumatic atrophic scars. Fractional carbon dioxide Laser was administered to each case on a monthly. For each case, eight sessions have been utilized ablative CO2 fractional laser has been utilized as a monotherapy for the management. All cases were monitored for three months

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Corresponding author: Amal Osama Hadhoud Email: amal.hadhoud@live.com

following the final treatment and achieved optimal outcomes with no recurrence, with an average of six interventions per scar. The clinical response of the cases to therapy and the enhancement of scars were evaluated by comparing photographs taken before and after the last therapy session, which was conducted six months post-treatment. The results of treatment and cases satisfaction have been evaluated on a quartile grading scale & scored individually on a scale of zero to four. The treatment response was excellent in sixty-five percent of cases, very good in fifteen percent of cases, and good in twenty percent of cases. It was determined that fractional carbon dioxide laser is a safe & efficient management for moderate to severe scars following trauma, particularly in younger cases (fifteen to thirty-five years old) with skin type II, without regard for the location of the scar [6].

Sharma et al. (2024) recruited forty-seven cases, who were separated into 3 groups: a post-acne scar group consisting of fourteen cases, a post-burn scar group consisting of seventeen cases, and a post-traumatic scar group consisting of sixteen cases. Detailed histories have been obtained, and clinical examinations have been conducted. Aesthetic results have been assessed utilizing clinical photographs, and the Patient and Observer Scar Assessment Scale (POSAS) has been utilized for recording the total scores of patients and observers at baseline, one, and three months. Each group underwent fractional CO2 laser therapies, which have been conducted every four weeks for a total of 3 consecutive sessions. Post-burn and post- traumatic wounds were treated with fractional carbon dioxide laser treatments utilizing the SmaXel CO2 laser (IDS Ltd., Republic of Korea) with pre-installed settings: energy/dot of 45 millijoules (mJ), pulse duration of 1.9 milliseconds (ms), density level of fifteen, and depth level of one. The most significant distinction has been noticed in the case of facial scars, followed by scars on the neck, and scars on the hand were minimal in both the patient and observer groups. The overall condition of scars was significantly impacted by even a single session of fractional carbon dioxide laser treatments. The quality of scars is enhanced and skin texture is significantly improved by fractional carbon dioxide laser therapy. The treatment is more effective on scars following trauma in comparison with on post-burn and post-acne scars [1]. In a retrospective investigation to assess the effectiveness of fractional ablative carbon dioxide laser for the management of a variety of scars, including those that are not acne scars. Forty-two cases with sixty-seven scars underwent surgery by Maninder et al. in 2022 to investigate the impact of various factors, including skin type, location, shape, duration, and pigment, on the result. Scar types include post-traumatic (43), post-burn (15), post-surgical (5), & post-folliculitis (5). The scars were managed with ablative fractional carbon dioxide laser utilizing the Microxel MX-7000 machine, which operates at 230VAC, single phase, 50/60Hertz, and has a power output of 1–40 W. The power output is 45–60 mJ for superficial atrophic scars and depth level 1, and 70 mJ for hypertrophic scars. The density level was 15 for both varieties, and the pulse duration varied from 1.5 to 3 ms. Fractional laser was administered during each laser session, with a ten percent overlap and two passes. The percentage enhancement and quartile scale were used to grade the enhancement in accordance with the investigator and patient global assessments (IGA & PGA). The ablative fractional carbon dioxide laser has been discovered to be a beneficial modality for non-acne scars in skin of pigment. It enhances the appearance of hypertrophic and atrophic scarring that have occurred after burns and post-traumatic injuries. Post-traumatic scars, scars without hyperpigmentation, scars with a shorter duration (less than six months), and scars with a lighter skin type yielded superior outcomes [3].

In 2024, Osman & Kassab conducted an investigation in which 32 cases who have post-surgical immature and post-traumatic scars (less than 1-year-old) and mature scars (more than 1-year-old) have been categorized into 2 groups based on the age of the scars: group A (fourteen cases with immature new scars) and group B (eighteen cases with mature elderly scars). Group A and B were once again arbitrarily separated into 2 equal groups to receive either Er:YAG or CO2 AFL. The Er:YAG AFL (Fotona Xs dynamics, Slovenia) has been operated with the following parameters: a hand piece PS01, a brief pulse mode (300 microseconds), an energy flux of 800–1000 mJ/cm^2, a spot size of 7 millimeters in diameter, a frequency of five to seven hertz, a pixel size of 250–350 µ, and a density of sixty to seventy pixels. Power ten to fifteen W, dwell time 600 microsecond (µs), spacing 700 micrometers (µm), density level (three to five percent), and smart stack, level 2 were the parameters of the CO2 AFL (Smartxide DOT, DEKA, Italy). Five consecutive Er:YAG and CO2 laser sessions have been carried out on a monthly basis, with a monitoring visit scheduled for three months following the final session. The effectiveness of Er:YAG and CO2 AFL in scar reduction was similar, as demonstrated by their data. Moreover, mature scars yield inferior outcomes when contrasted with infantile scars [7].

Additionally, Meynköhn et al. (2021) conducted a retrospective investigation that included 16 cases with facial lesions. A single session of an ablative, fractional, ultra-pulsed CO2 laser with a wavelength of 10600 nanometers (Ultrapulse®, Lumenis, Dreieich, Germany) has been conducted. The manufacturer's recommendations have been followed in the adjustment of the individual parameters for each scar type. Potential treatment modalities involve the Deep FX mode, the Active FX mode, and the Total FX mode, which is a hybrid of the Deep F and Active FX modes. The Deep FX mode has been utilized to induce production of collagen in the dermis and perform deep fractional ablation. The frequency levels for the Deep FX mode were set to three hundred to four hundred hertz, with energy levels ranging from 15 to 22.5 mJ and density levels of five to fifteen percent. The Active FX mode has been utilized for ablation of superficial scar and to alleviate scar tension. Energy levels of 100-125 mJ and levels of density of one to three percent were established for the Active FX mode, with frequency levels ranging from 100-150 hertz. For combination therapy (Total FX). Twelve cases underwent an additional CO2-AFL session three months later. They have demonstrated that the cases valued the enhancement of scar quality and appearance, which had significant impacts on the cases' quality of life. Additionally, CO2-laser therapy had a beneficial impact on physician-based scar assessment. The response to CO2-AFL was consistent regardless of the cause, thickness, or maturation of the scar (mature scars aged over two years). Consequently, the concept of facial scar management should encompass CO2-AFL therapy [8].

In the study of Keshk et al., in 2024, thirty patients with single or multiple immature hypertrophic scar (within one year) were included. In the same patient, single or multiple scars were divided randomly into treated areas and control areas. The treated areas were submitted to 5 sessions of fractional carbon dioxide laser combined with long pulsed Nd:YAG laser with one month in between sessions. The control areas did not receive any treatment. The treated areas were subjected to fractional CO_2 10600 nm Laser (D.S.E Seoul, Korea) using a fluence of 40 mj, pulse duration 600 µs, density 5, stack 3, density of dots was $25/cm^2$. Shape and size of scanning area was adjusted according to the shape and width of the lesion. Ice cooling was applied immediately after fractional CO_2 laser session. Then after 30 min, long pulsed Nd:YAG 1064 nanometers laser (Fotona XP focus Ljubljana, Slovenia) was applied for the treated area with a fluence of $50\ J/cm^2$, pulse duration 20 ms, spot size 5 mm, repetition rate 2 HZ and 2 passes on the treated area. Zimmer air cooling system was used during laser session (Zimmer cryo6 air chiller New Delhi). The scar areas treated with combined fractional CO_2 laser and long pulsed Nd:YAG laser showed superior significant clinical improvement with Vancouver Scar Scale (VSS) and POSAS than areas that did not receive any treatment (except for the pigmentation parameter of both VSS and POSAS), especially six months following last treatment. No significant side effects for laser therapy have been noticed [9].

To evaluate the effectiveness of 2 laser-based methods, namely the pulsed dye laser (PDL) and the ablative fractional carbon dioxide laser (AFCL), and their combination in enhancing various aspects of burning scars, irrespective of the type of scar, such as hypertrophic or keloid scars.

A clinical trial was conducted in 2024 by Kivi et al. on cases who were experiencing hypertrophic or keloid burning scars. Three groups of cases have been randomly assigned to receive management with pulsed dye laser alone, ablative fractional carbon dioxide laser alone, or a combination of the two. All cases have been visited prior to and forty days following their most recent treatment session. The combined therapy may be significantly more effective in enhancing the pathological characteristics and appearance of wounds than each individual therapy. This efficacy was predominantly observed in wounds that were immature (less than one year) [10]. Cases were categorized into five categories by Tan et al. (2021), based on the time of the initial laser treatment following injury. Cases who have been treated within one month of their injury comprised the 1st group. The 2nd group of cases received treatment within one to three months of the injury. Cases who received treatment within three to six months of their injury included in the 3rd group. In the fourth group, cases have been treated within six to twelve months of their injury. The last group consisted of cases who were treated more than twelve months after the injury. The AFCL has been established in deep mode with a density range of five to ten percent and an energy range of fifteen to thirteen mj. Parameters for peripheral mode treatment included a density range of forty percent and an energy range of 70–150 mJ. Depending on the size & shape of the lesion, the light spot's shape and size have been determined. An energy range of 15–30 mJ for the deep mode corresponded to a treatment depth of 550–800 µm. Treatment depths of 50–150 µm were associated with the energy range of 70–150 mJ for the superficial mode. All cases were administered both the superficial and deep modes. The laser's dose was contingent upon the scar's thickness. A greater laser dose was administered to scars with greater height. Ablative fractional carbon dioxide laser therapy was applied to early-stage burn lesions in this research, and both its safety and effectiveness were demonstrated. Laser therapy for burn cases may be most effective when administered within one month of injury. As objective modalities, durometry and colorimetry were effective in evaluating wounds [11].

In order to assess the effectiveness of a CO2 laser in hypertrophic scars, Won et al. (2022) utilized its low-energy mode on cases under the age of twelve. The two extremities of each hypertrophic scar have been randomly separated to the control and experimental groups, while the center portion has been deemed a transition zone and wasn't analyzed. Each hypertrophic scar has been separated into three equal parts. A Fractional carbon dioxide Skin Resurfacing System (Alma Lasers) with a pixel 7 × 7 hand piece has been utilized to administer a total of 3 laser treatments at 1-month intervals. The energy level was set to 30 mJ/pixel (low) for one to two cycles with a density of five percent, and the anesthetic, SR, was selected as the mode. In a pediatric population, hypertrophic lesions were enhanced by low-energy CO2 fractional laser therapy. Consequently, a low-energy CO2 laser that causes less procedure pain might be more suitable for kids with hypertrophic scars [12].

IV. CONCLUSION

In the hands of an appropriately trained practitioner, Fractional carbon dioxide laser exhibits excellent safety and effectiveness in treatment of post traumatic scars. Using more than one modality of treatment can give better and faster results. The change in laser power, pulse duration, density and depth level affects the treatment of different scars. A greater laser dose was administered to scars with greater height, while atrophic scars required lower laser doses. Early intervention shows better results. Thus, we hope fractional CO_2 laser becomes more widely available to cases with scars. Additional research is required to verify its long-term effectiveness and the optimal protocol of treatment, particularly when utilized in conjunction with other modalities. The optimal implementation of these treatments in clinical practice for management of scars will be facilitated by a more comprehensive understanding.

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Multiple Resistant Plane Warts Successfully Treated by Photodynamic Therapy Mediated by Transfersomal Methylene Blue Gel: A Case Report

Ghada Yassin [1], Kawser Kassab[2], Nevien Samy[3] and Maha Fadel[1]

[1]Pharmaceutical Nanotechnology Unit, Department of Medical Laser Applications, National Institute of Laser Enhanced Sciences, Cairo University, Giza, Egypt; [2] Photobiology and cell photosensitization unit, National Institute of Laser Enhanced Sciences, Cairo University, Giza, Egypt; [3] Dermatology Unit, Department of Medical Laser Applications, National Institute of Laser Enhanced Sciences, Cairo University, Giza, Egypt

Abstract

Purpose: In the view of failure of conventional treatment modalities used for multiple resistant viral warts to achieve satisfactory results, new treatment modalities are needed. Recently, photodynamic therapy demonstrated its efficacy and safety for such indication especially when combined with nanotechnology which maximize its benefits.
Methods: In this case report, photodynamic therapy (PDT) mediated by transfersomal Methylene blue (TMB) gel was used for treatment of bilateral multiple resistant plane warts in the dorsum of feet in a 53-year-old woman.
Results: After two treatment session applied for her right foot, complete healing was achieved. Surprisingly, the left foot showed great spontaneous improvement without receiving any treatment. The patient was followed up for one year and did not show any signs of recurrence.
Conclusion: This case not only highlights the ability of PDT to treat multiple resistant plane warts but also focus on its ability to boost immune response and help body to eradicate viral infection.

Keywords— methylene blue, transfersomes, photodynamic therapy, plane warts, clinical

I. INTRODUCTION

Viral warts are cutaneous contagious lesions caused by infections with human papilloma viruses (HPV). HPV are two-stranded DNA viruses that is characterized with its persistence and resistant to a wide range of treatment drugs. Absence of envelope, high viral replication and its ability to escape from immune system account for the persistence of HPV infection. HPV includes a diverse group of approximately 120 genotypes with different clinical types and its associated lesions range from benign warts to malignant lesions [1–3].

Plane warts is a common skin manifestation of HPV, most frequently caused by types 3 and 10 and most commonly occurring on face and extremities. They often appear as slightly raised, smooth papules with skin colour, slightly erythematous but may be pigmented [1, 4, 5]. Despite their benign nature, warts are cosmetically unacceptable and might cause psychological, functional and physical troubles [6–9]. Most warts may spontaneously disappear, however multiple persistent warts that fail to resolve after several treatments present a therapeutic challenge [10, 11].

Several treatment modalities are available for viral warts, including repeated topical application of medical agents (e.g., retinoids and salicylic acid), physical destructive methods (e.g., cryotherapy and electrocautery), surgical excision and immunotherapy (e.g., *Candida* antigen and HPVs vaccination). However, none of these modalities is fully significant for every patient and most of them target the destruction of infected cells without direct effect against virus. Low cure rate and frequent recurrence are the main limitations. The need for long periods of application, pain during destructive therapy and risk of scarring are other drawbacks that make most of modalities inconvenient for patients [1, 5, 7, 12].

Recently, Photodynamic therapy (PDT) have demonstrated its value as an effective minimally invasive treatment modality for localized microbial infections including fungal bacterial, and viral infections [13–15]. It combines the effect of nontoxic dye called photosensitizers (PS) and light at a specific wavelength in presence of oxygen to induce generation of reactive oxygen species and singlet oxygen that destroy microbial cells. As a treatment modality for viral warts, PDT has showed several advantages including: high efficacy, low recurrence rates, minimal pain and good aesthetic prognosis [16, 17]. In addition, PDT was reported to have positive effects on host tissues, such as growth factor stimulation and immune response enhancement [18]. Nanotechnology was proved to optimize the photodynamic effect of PS and improve its penetration through skin [17, 19].

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Corresponding author: Ghada Yassin Email: ghada_yasin@cu.edu.eg

Herein, we report a case of resistant bilateral plane warts in the dorsum of her feet who was successfully treated with PDT mediated by transfersomal Methylene blue (TMB) gel that was previously prepared by our group and have shown promising results for treatment of resistant planter warts [17]. These results inspired our team to apply such promising nano-formulation for treatment of multiple resistant plane warts in the presented case. Surprisingly, the results not only highlight the efficacy of PDT in combination with nanotechnology as treatment modality for plane warts but also revealed its ability to boost immune response and help body to eradicate viral infection.

II. CASE PRESENTATION

A 53-year-old woman was referred to our department with a two-year history of bilateral multiple persistent plane warts in the dorsum of her feet which had been resistant to multiple topical products, cryotherapy and Candida antigen injection. In view of the resistance to first line therapies, a referral was made to trial photodynamic therapy (PDT). On review, she was not taking any current medications, had no drug allergies, and had no relevant medical history. The patient read and signed the consent term that explain all the clinical procedure and was instructed not to use any concomitant therapies.

PDT using 0.05% transfersomal Methylene blue gel (TMB) was administered to the patient's right foot. The gel was applied in a thin layer covering all lesions and the potentially subclinical affected areas, then the whole area was occluded for 30 minutes. After this period the sheet and residual gel was removed using cotton swap. This was followed by irradiation session with diode laser 670 nm of output power 90 mW for 15 minutes. The treatment sessions were provided once weekly until the complete clinical clearance. The patient denied any pain or adverse effects during the session. At the third week, after receiving two treatment sessions, examination of the patient's right foot revealed a dramatic clearance of warts with no active lesions (**Figure 1**). Surprisingly, the left foot, which had not received any PDT sessions showed great improvement. The Patient was followed up for one year, no recurrence was noticed, and the patient was embarrassed with treatment results (**Figure 2**).

Figure 1: Evolution of the clinical responses in the right leg before treatment (**a**), after first session (**b**) and after second session (**c**)

Figure 2: (**a**) Multiple plane warts in both right and left feet before photodynamic treatment session, (**b**) after two treatment photodynamic treatment sessions to the right leg.

Treatment of HPV-associated lesions is challenging. Despite their high prevalence, no antiviral medication against HPV is currently available. Most treatment protocols used for such viral lesions are cyto-destructive and mean to destroy lesions rather than eradication of virus. Thus, even with adherence to the evidence-based treatment protocols, a notable proportion of warts remain resistant to cure or tend to relapse, adding to the unsatisfactory cosmetic results. New treatment modalities that fight the virus not only the lesion are needed [2, 11, 20].

Lately, PDT has demonstrated its efficacy in fighting against viruses, showing a great potential in several applications including viral decontamination of fluids, clinical treatment of cutaneous viral lesions caused by herpes simplex virus (HSV), varicella zoster virus (VZV), and human papillomavirus (HPV). Recently, It have been also used for suppression of respiratory tract infections and management of COVID-19 [21–23].

Considering treatment of HPV associated lesion, several studies have shown that PDT could offer several therapeutic benefits that make it very appealing including efficacy, safety, non-invasiveness and selectivity. Moreover, PDT have shown much superior results in term of rate of recurrence [16, 22].

Regarding the case presented, PDT mediated with TMG gel were used for treatment for such multiple resistant plane warts. TMB gel was previously prepared where transfersomes were prepared using phosphatidylcholine from soybean and deoxycholic acid sodium salt in a ratio of 10: 1 by thin film hydration method. Such nano-vesicles showed a mean particle size of 712.4 nm, zeta potential of -58.7 mV, encapsulation capacity of 59.64 % and cumulative percentage release of 74.5 % after 3 hours. TMB gel (0.05 %Methylene Blue) was prepared using 5% Carboxymethyl cellulose sodium salt and 0.2% methylparaben sodium. TMB gel has proven to deliver MB into deep layers of skin through an animal study guided by histological examination. Moreover, TMB gel mediated photodynamic effect has showed great efficacy and safety in treatment of resistant planter warts in a single-blinded randomized placebo-controlled study [17].

Although the warts in the presented case were refractory after several treatment methods, PDT mediated by TMB showed high efficacy. The efficacy of PDT could be related to several mechanisms. Firstly, photodynamic inactivation of HPV, where the produced reactive oxygen species and singlet oxygen inactivate the virus and supress its replication. Secondly, the anti-proliferative effect of PDT, where the HPV-infected keratinocytes are photodynamically destructed as PS is selectively accumulated in the rapidly dividing cells. Lastly, the immune-modulating effect of PDT, where PDT was proved to induce innate and adaptive immune responses and promote the release of pro-inflammatory proteins [6, 18, 20, 23].

It is believed that the use of transfersomes as nano-carriers for Methylene blue facilitate its transfer through skin and hence maximize its photodynamic effect. It was worth noting that only two treatment session were needed to achieve complete cure which was convenient for the patient. Moreover, it seems likely that use of PDT not only serve in cure of the treated warts in right foot but also improve the patient's immune response and help in eradication of the virus. This explains the great spontaneous improvement in the left foot that did not receive any treatment sessions.

The patient was very satisfied with treatment results, especially after one year of follow up free of any signs of recurrence. The ability of PDT to reduce recurrence is attributed to its ability to decrease the viral load as well as treatment of a larger area and thereby treating subclinical lesions [16, 20]. Minimal pain during treatment and good cosmetic outcomes increased patient satisfaction with the treatment. Based on these finding, PDT combined with nanotechnology is recommended as a first-line therapy for plane warts.

III. CONCLUSION

Our case suggests that PDT mediated by TMB gel could be an effective modality for treatment of resistant plane warts owing to its effectiveness and safety, in addition to its immune-modulating effect that help body to eradicate viral infection. Further studies in a larger population are required to determine the optimal regimen for resistant plane warts.

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The Effects of Low-Level Laser Therapy on Bone Fracture Healing: A Comprehensive Review

Al Balah, Osama Fekry[1]*, Mirna Niazy[2], Al Balah, Abdel-Rahman Osama[3]

[1] National Institute of Laser Enhanced Sciences, Department of Medical Applications of Laser Cairo University, Giza 12613, Egypt, [2] Faculty of physiotherapy Al-Ahram Canadian University, Egypt, [3] Faculty of Medicine, Cairo University, Egypt

Abstract

Purpose: Low-Level Laser Therapy (LLLT) has emerged as a potential adjunctive treatment for bone fracture healing. This review comprehensively examines the current state of knowledge regarding LLLT's effects on bone fracture healing, including cellular mechanisms, clinical outcomes, and future directions.
Methods: This review explores the methodology of LLLT, including types of lasers, key parameters, and application methods. It discusses the mechanisms of action at cellular, molecular, and tissue levels in depth. A thorough analysis of clinical studies, including animal studies, human trials, and meta-analyses, is presented. Factors influencing LLLT efficacy, potential advantages, limitations, and patient-specific considerations are also examined.
Results: Many studies report positive effects of LLLT on bone fracture healing, including accelerated healing times, improved bone quality, and reduced pain. However, results are not universally consistent, likely due to variations in study designs, laser parameters, and outcome measures. The review highlights the need for standardization of protocols and larger-scale clinical trials.
Conclusion: While LLLT shows promise as an adjunctive therapy for bone fracture healing, more research is needed to fully establish its efficacy and optimal application. This review provides specific recommendations and frameworks for developing future protocols. As understanding of underlying mechanisms improves and technology advances, LLLT has the potential to become an increasingly valuable tool in fracture management.

Keywords— low level laser, bone fracture, laser parameters

I. INTRODUCTION

Bone fractures are common injuries that can significantly impact a patient's quality of life and pose substantial challenges to healthcare systems worldwide. The process of bone fracture healing is complex, involving a cascade of cellular and molecular events that ultimately lead to the restoration of bone integrity. While conventional treatments have shown efficacy, there is a growing interest in adjunctive therapies that could potentially accelerate healing and improve outcomes. One such modality that has gained attention in recent years is Low-Level Laser Therapy (LLLT). LLLT, also known as photo-biomodulation, is a non-invasive treatment that uses low-power lasers or light-emitting diodes (LEDs) to stimulate cellular function. Initially developed in the 1960s, LLLT has since been applied to various medical conditions, including wound healing, pain management, and inflammatory disorders. The potential of LLLT to modulate biological processes at the cellular level has led researchers to investigate its application in bone fracture healing. This review article aims to comprehensively examine the current state of knowledge regarding the effects of LLLT on bone fracture healing. We will explore the underlying mechanisms of action, review key clinical studies, discuss factors influencing efficacy, and consider the potential advantages and limitations of this therapy. By synthesizing the available evidence, we hope to provide clinicians and researchers with a clear understanding of LLLT's role in bone fracture management and identify areas for future investigation.

II. LOW LEVEL LASER THERAPY

Low-Level Laser Therapy (LLLT) is a photo-biomodulation technique that employs light at specific wavelengths to induce biological effects in living tissues. Unlike high-power lasers used for cutting or ablation, LLLT uses lower power outputs to stimulate cellular processes without causing thermal damage.

Types of Lasers

LLLT typically utilizes two main types of light sources:

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Corresponding author: Osama F. Al Balah Email: osama.f.alblah@niles.cu.edu.eg

1. Helium-Neon (He-Ne) lasers: These emit red light at a wavelength of 632.8 nm.
2. Gallium-Aluminum-Arsenide (Ga-Al-As) diode lasers: These emit light in the near-infrared spectrum, typically between 780-890 nm.

More recently, light-emitting diodes (LEDs) have also been employed, offering a cost-effective alternative to traditional lasers while still providing therapeutic effects.

Key Parameters

The efficacy of LLLT depends on several key parameters:

1. Wavelength: The most commonly used wavelengths fall within the "optical window" of 600-1000 nm, allowing optimal tissue penetration.
2. Power Density: This refers to the amount of power output per unit area, typically measured in mW/cm². Effective power densities for bone healing generally range from 5 to 50 mW/cm².
3. Energy Density: Also known as fluence, this parameter describes the amount of energy delivered per unit area, usually expressed in J/cm². Typical values for bone healing applications range from 1 to 50 J/cm².
4. Treatment Duration: The time of laser application can vary from a few seconds to several minutes, depending on the power output and the target energy density.
5. Treatment Frequency: LLLT may be applied daily, several times a week, or at longer intervals, depending on the specific protocol and the nature of the fracture.

Application Methods

LLLT can be applied in two primary ways:

1. Direct Application: The laser is applied directly to the skin over the fracture site.
2. Transcutaneous Application: The laser is applied to acupuncture points or other specific locations believed to influence the healing process.

It's important to note that the optimal parameters for LLLT in bone fracture healing are still a subject of ongoing research. Variations in these parameters across different studies contribute to the heterogeneity of results observed in the literature. In the next section, we will delve into the mechanisms of action by which LLLT is believed to influence the bone healing process at cellular and molecular levels.

Mechanisms of Action

The effects of Low-Level Laser Therapy (LLLT) on bone fracture healing are believed to occur through various cellular and molecular mechanisms. Understanding these processes is crucial for optimizing treatment protocols and interpreting clinical outcomes.

1. Cellular Effects:

a) Increased ATP Production:

LLLT stimulates the mitochondrial respiratory chain, particularly cytochrome c oxidase. This leads to increased production of adenosine triphosphate (ATP), providing cells with more energy for various functions, including proliferation and differentiation.

b) Enhanced Cell Proliferation:

LLLT has been shown to stimulate the proliferation of osteoblasts, the cells responsible for bone formation. This increased cellular activity can potentially accelerate the healing process.

c) Improved Cell Survival:

By reducing oxidative stress and modulating cellular redox state, LLLT can enhance the survival of bone cells in the fracture environment.

2. Molecular Effects:

a) Growth Factor Production:

LLLT has been observed to upregulate the expression of growth factors crucial for bone healing, including:

- Bone Morphogenetic Proteins (BMPs)
- Transforming Growth Factor-β (TGF-β)
- Insulin-like Growth Factor-1 (IGF-1)

b) Increased Collagen Synthesis:

LLLT stimulates the production of collagen, a key component of the bone matrix, by enhancing the activity of fibroblasts.

c) Modulation of Inflammatory Mediators:

LLLT can help regulate the inflammatory response by influencing the production of pro- and anti-inflammatory cytokines, potentially creating a more favorable environment for healing.

3. Tissue-Level Effects:

a) Enhanced Angiogenesis:

LLLT promotes the formation of new blood vessels, improving blood supply to the fracture site. This increased vascularity supports the delivery of nutrients and removal of waste products.

b) Accelerated Bone Remodeling:

By influencing both osteoblast and osteoclast activity, LLLT may enhance the bone remodeling process, potentially leading to faster and stronger healing.

c) Improved Biomechanical Properties:

Some studies suggest that LLLT can improve the biomechanical properties of healing bone, including increased bone mineral density and tensile strength.

It is important to note that while these mechanisms have been observed in various studies, the exact pathways and their relative contributions to bone fracture healing are still subjects of ongoing research. The complex interplay between these cellular, molecular, and tissue-level effects likely contributes to the overall impact of LLLT on bone fracture healing.

4. Cellular Signaling Pathways:

a) MAPK Pathway Activation:

-LLLT has been shown to activate the Mitogen-Activated Protein Kinase (MAPK) pathway.

-This activation can lead to increased cell proliferation and differentiation.

b) Wnt/β-catenin Signaling:

Some studies suggest that LLLT can modulate the Wnt/β-catenin pathway, which is crucial for osteoblast differentiation and bone formation.

c) NF-κB Pathway Modulation:

LLLT may influence the NF-κB pathway, affecting inflammation and cell survival in the fracture environment.

It is important to note that while these mechanisms have been observed in various studies, the exact pathways and their relative contributions to bone fracture healing are still subjects of ongoing research. The complex interplay between these cellular, molecular, and tissue-level effects likely contributes to the overall impact of LLLT on bone fracture healing. In the next section, we will review key clinical studies that have investigated the efficacy of LLLT in bone fracture healing, examining how these proposed mechanisms translate into observable clinical outcomes.

III. REVIEW OF CLINICAL STUDIES

The application of Low-Level Laser Therapy (LLLT) in bone fracture healing has been the subject of numerous clinical studies. This section will summarize key findings from notable research, discussing outcomes and effectiveness while comparing results across different studies.

1. Animal Studies:

While not clinical per se, animal studies have provided valuable insights:

a) Pinheiro et al. (2013) - Rat Study:
-Used 830 nm laser at 50 mW, 4 J/cm²
-Observed increased bone volume and accelerated healing in laser-treated group
-Notably improved biomechanical properties of healed bone
b) Mostafavinia et al. (2017) - Rabbit Study:
-Utilized 890 nm laser at 80 Hz, 0.972 J/cm²
-Reported enhanced bone mineral density and biomechanical strength
-Suggested optimal dosage for fracture healing

2. Human Clinical Trials:

a) Chang et al. (2014) - Randomized Controlled Trial:
-41 patients with distal radius fractures
-Used 830 nm laser at 60 mW, 7.5 J/cm²
-Observed significantly faster healing and improved functional outcomes in LLLT group
b) Nesioonpour et al. (2014) - Double-Blind Study:
- 28 patients with tibial fractures
- Employed 850 nm laser at 100 mW, 7.5 J/cm²
- Reported reduced pain and accelerated healing in LLLT group
c) Santinoni et al. (2017) - Prospective Study:
-30 patients undergoing mandibular fracture treatment
-Used 780 nm laser at 70 mW, 105 J/cm²
-Found reduced postoperative pain and swelling, but no significant difference in healing time

3. Meta-Analyses and Systematic Reviews:

a) Bashardoust Tajali et al. (2010) - Meta-analysis:
-Analyzed 5 studies (4 animal, 1 human)
-Concluded LLLT can accelerate bone healing process
-Highlighted need for standardized protocols
b) Ebrahimi et al. (2017) - Systematic Review:
-Reviewed 11 animal studies
-Found positive effects on bone healing in majority of studies
-Noted variability in laser parameters and treatment protocols

Key Observations:

1. Efficacy: Most studies report positive effects of LLLT on bone fracture healing, including accelerated healing times, improved bone quality, and reduced pain.
2. Parameter Variability: There is significant heterogeneity in laser parameters (wavelength, power, energy density) across studies, making direct comparisons challenging.
3. Outcome Measures: Studies use various outcome measures, including radiographic healing, pain scores, functional outcomes, and biomechanical properties.
4. Study Quality: While many studies show promising results, some have methodological limitations, including small sample sizes and lack of long-term follow-up.
5. Clinical vs. Preclinical: Animal studies generally show more consistent positive results compared to human clinical trials, which have been fewer in number and more variable in outcomes.

This review of clinical studies suggests that LLLT has potential as an adjunctive therapy in bone fracture healing. However, the variability in study designs, laser parameters, and outcome measures underscores the need for further large-scale, well-designed clinical trials to establish optimal treatment protocols and confirm efficacy in various fracture types. In the next section, we will discuss the factors influencing the efficacy of LLLT in bone fracture healing.

IV. FACTORS INFLUENCING EFFICACY

The effectiveness of Low-Level Laser Therapy (LLLT) in bone fracture healing can be influenced by various factors. Understanding these factors is crucial for optimizing treatment protocols and interpreting research results. The main factors include:

1. Laser Parameters:

a) Wavelength:
-Different wavelengths penetrate tissue to varying depths.
-Red light (630-660 nm) penetrates less deeply but may be more effective for superficial fractures.
-Near-infrared light (810-850 nm) penetrates deeper and may be more suitable for deeper fractures.
b) Power Density:
- Too low power may not produce therapeutic effects.
-Too high power may inhibit cellular responses.
-Optimal range typically between 5-50 mW/cm², but varies based on other parameters.
c) Energy Density (Fluence):
-Typically ranges from 1-50 J/cm².
-The concept of biphasic dose response suggests that there's an optimal energy density range, above and below which effects may diminish.
d) Pulsed vs. Continuous Wave:
-Some studies suggest pulsed waves may be more effective than continuous waves, particularly for deeper tissues.

2. Treatment Protocol:

a) Frequency of Application:
-Daily treatments are common in many studies.

-Some protocols use treatments 2-3 times per week.
-Optimal frequency may depend on the stage of healing.
b) Duration of Treatment:
-Single session duration typically ranges from 20 seconds to several minutes.
-Total treatment course can vary from a few days to several weeks.
c) Timing of Initiation:
-Starting treatment immediately after fracture may be more beneficial than delayed initiation.

3. Type and Location of Fracture:
a) Fracture Severity:
-Simple fractures may respond differently compared to complex or comminuted fractures.
b) Bone Type:
-Different bones (e.g., long bones vs. flat bones) may respond differently to LLLT.
c) Depth of Fracture:
-Superficial fractures may be more responsive due to better light penetration.

4. Patient Factors:
a) Age:
-Younger patients generally have better healing capacity, which may influence LLLT effectiveness.
-Studies have shown that LLLT may be particularly beneficial in older patients with reduced healing capacity.
b) Overall, Health:
-Comorbidities like diabetes or osteoporosis may affect treatment response.
-Diabetic patients, for instance, may require adjusted LLLT protocols due to impaired cellular responses and microcirculation.
c) Smoking Status:
-Smoking is known to impair bone healing and may reduce LLLT efficacy.
-Some studies suggest that LLLT might partially mitigate the negative effects of smoking on bone healing, but more research is needed.
d) Nutritional Status:
-Adequate nutrition, especially calcium and vitamin D, is crucial for optimal bone healing.
-LLLT effectiveness may be enhanced when combined with proper nutritional support.
e) Hormonal Status:
-Hormonal imbalances, particularly in postmenopausal women, can affect bone metabolism and potentially influence LLLT outcomes.
-Estrogen deficiency, for example, may alter cellular responses to LLLT.
f) Genetic Factors:
-Genetic variations in factors like BMP receptors or collagen synthesis may influence individual responses to LLLT.
-Future research may lead to personalized LLLT protocols based on genetic profiles.
g) Medication Use:
-Certain medications, such as corticosteroids or chemotherapeutic agents, may interact with LLLT effects.
-Non-steroidal anti-inflammatory drugs (NSAIDs) might influence the inflammatory phase of healing, potentially altering LLLT outcomes.
h) Physical Activity Level:
-The patient's level of physical activity and adherence to rehabilitation protocols can interact with LLLT effects.
-Proper balance between rest and controlled loading may optimize LLLT outcomes.

5. Concurrent Treatments:
a) Immobilization:
-The degree and duration of immobilization can interact with LLLT effects.
b) Medications:
-Some medications (e.g., NSAIDs, corticosteroids) may influence the healing process and LLLT efficacy.

6. Technological Factors:
a) Device Quality:
-The precision and reliability of the LLLT device can impact treatment consistency.
b) Application Technique:
-Proper application, including distance from skin and angle of application, is crucial for optimal results.

Understanding these factors is essential for designing effective LLLT protocols and interpreting research results. The interplay between these factors contributes to the variability seen in clinical outcomes and highlights the need for standardized protocols in future research. In the next section, we'll discuss the potential advantages and limitations of using LLLT for bone fracture healing.

V. POTENTIAL ADVANTAGES AND LIMITATIONS

Low-Level Laser Therapy (LLLT) for bone fracture healing offers several potential advantages but also faces certain limitations. Understanding both is crucial for clinicians and researchers to make informed decisions about its use and further development.

1. Potential Advantages:
a) Non-invasive:
-LLLT does not require surgical intervention, reducing risks associated with invasive procedures.
b) Pain Reduction:
-Many studies report decreased pain levels in patients treated with LLLT, potentially reducing the need for analgesics.
c) Accelerated Healing:
-Some research indicates that LLLT can speed up the bone healing process, potentially shortening recovery time.
d) Few Side Effects:
-When used properly, LLLT has minimal reported side effects, making it a relatively safe treatment option.
e) Complementary Therapy:
-LLLT can be used alongside traditional treatments, potentially enhancing overall outcomes.
f) Improved Bone Quality:
-Some studies suggest LLLT may improve the biomechanical properties of healed bone.

g) Reduced Inflammation:
-LLLT has shown anti-inflammatory effects, which could benefit the healing process.
h) Cost-Effective:
-Once the initial equipment is acquired, ongoing treatment costs are relatively low.

2. Limitations and Challenges:
a) Lack of Standardization:
-There's no universally accepted protocol for LLLT in bone fracture healing, leading to variability in treatment approaches.
b) Penetration Depth:
-The effectiveness of LLLT may be limited for deep fractures due to limited light penetration through tissues.
c) Variability in Research Results:
-While many studies show positive outcomes, results are not universally consistent, possibly due to differences in methodology and parameters.
d) Limited Large-Scale Clinical Trials:
-There's a need for more extensive, well-designed clinical trials to establish efficacy conclusively.
e) Equipment Variability:
-Different devices may produce varying results, making it challenging to compare studies or standardize treatments.
f) Operator Dependence:
-The effectiveness of LLLT can depend on the skill and experience of the operator in applying the treatment correctly.
g) Time-Intensive:
-LLLT often requires multiple sessions over an extended period, which may be inconvenient for some patients.
h) Insurance Coverage:
-LLLT is not universally covered by insurance plans, potentially limiting access for some patients.
i) Contraindications:
-LLLT may not be suitable for all patients, such as those with certain types of cancer or taking photosensitizing medications.
j) Overuse Concerns:
-There's a theoretical risk that excessive use of LLLT could potentially stimulate unwanted cell growth, though this hasn't been demonstrated in bone healing applications.

In conclusion, while LLLT shows promise as an adjunctive therapy for bone fracture healing, offering several potential advantages, it also faces limitations that need to be addressed through further research and standardization efforts. The balance of these factors will likely influence the future adoption and development of LLLT in clinical practice.

Future Directions and recommendations

As the field of Low-Level Laser Therapy (LLLT) for bone fracture healing continues to evolve, several areas warrant further investigation and development. These future directions aim to address current limitations and enhance the efficacy and applicability of LLLT in clinical practice.

1. Standardization of Protocols:
Recommendation:

Development of a consensus guideline for LLLT parameters in bone fracture healing.

Framework:
a) Formation of an international task force of experts in LLLT and bone healing.
b) Conduction of a systematic review of existing literature to identify most effective parameters.
c) Using Delphi method to reach consensus on:
-Optimal wavelength ranges for different fracture types
-Recommended power density and energy density ranges
-Treatment duration and frequency guidelines
d) Development of a standardized reporting template for LLLT studies in bone healing.

2. Large-Scale Clinical Trials:
Recommendation:

Conducting multi-center, randomized controlled trials with larger patient populations.

Framework:
a) Designing a protocol for a phase III clinical trial:
-Sample size: Minimum 500 patients
-Duration: 2-year follow-up
-Fracture types: Include both long bone and flat bone fractures
-Control: Standard care vs. Standard care + LLLT
b) Establishment of clear, clinically relevant primary and secondary outcomes:
-Primary: Time to radiographic union
-Secondary: Functional outcomes, pain scores, quality of life measures
c) Implementation of standardized LLLT protocols based on consensus guidelines.
d) Inclusion of subgroup analyses for patient-specific factors (age, comorbidities, etc.).

3. Optimization of Treatment Parameters:
Recommendation:
Conducting systematic dose-response studies for different fracture types.
Framework:
a) Designing of a series of preclinical studies using standardized fracture models.
b) Testing a range of parameters:
-Wavelengths: 630nm, 660nm, 810nm, 850nm
-Power densities: 5, 10, 25, 50 mW/cm^2
-Energy densities: 1, 5, 10, 20, 50 J/cm^2
c) Assessment of outcomes using standardized measures:
-Radiographic healing
-Histological analysis
-Biomechanical testing
d) Development of predictive models for optimal parameters based on fracture characteristics.

4. Mechanism Elucidation:
Recommendation:
Conducting in-depth studies on cellular and molecular mechanisms of LLLT in bone healing.
Framework:
a) Utilizing advanced imaging techniques (e.g., intravital microscopy) to visualize LLLT effects in real-time.

b) Employment of high-throughput screening to identify novel molecular targets influenced by LLLT.
c) Investigation of the interaction between LLLT and various signaling pathways (e.g., Wnt, BMP, MAPK).
d) Exploring epigenetic modifications induced by LLLT in bone cells.

5. Combination Therapies:
Recommendation:

Investigation of the probable synergistic effects of LLLT with other treatment modalities.

Framework:
a) Designing studies combining LLLT with:
-Pulsed electromagnetic field therapy
-Ultrasound
-Bone grafting techniques
-Growth factor therapies (e.g., BMP-2, PDGF)
b) Development of protocols for sequential or simultaneous application of therapies.
c) Assessment of potential interactions with pharmacological interventions (e.g., bisphosphonates, PTH analogs).

6. Personalized Treatment Approaches:
Recommendation:

Developing methods to tailor LLLT protocols based on individual patient factors.

Framework:
a) Conducting genetic association studies to identify polymorphisms affecting LLLT response.
b) Development and validation of biomarker panels to predict LLLT efficacy.
c) Creation of a decision support tool integrating patient factors (age, comorbidities, fracture characteristics) to guide LLLT protocol selection.

7. Advanced Delivery Systems:
Recommendation:

Developing new technologies for more precise and deeper delivery of laser energy.

Framework:
a) Exploring the potential of implantable, biodegradable light-emitting devices for internal fractures.
b) Investigation of nanoparticle-mediated photo-biomodulation for enhanced light penetration and absorption.
c) Development of wearable LLLT devices for continuous, low-intensity treatment.

8. Real-Time Monitoring:

Development of non-invasive methods to monitor the biological effects of LLLT in real-time, allowing for dynamic adjustment of treatment parameters.

9. Economic Analyses:

Conducting comprehensive cost-effectiveness studies to better understand the economic impact of integrating LLLT into standard fracture care.

10. Education and Training:

Developing standardized training programs for healthcare providers to ensure proper application of LLLT techniques.

11. Regulatory Considerations:

Working towards clearer regulatory guidelines for LLLT devices and their application in bone fracture healing.

12. Application in Complex Cases:

Investigation of the efficacy of LLLT in challenging scenarios such as non-union fractures, osteoporotic fractures, or in patients with impaired healing capacity.

13. Integration with Telemedicine:

Exploring the potential for remote monitoring and guidance of LLLT treatments, especially for home-based applications. By following these recommendations and frameworks, researchers and clinicians can work towards addressing current gaps in knowledge, improving the efficacy and reliability of LLLT, and facilitating its integration into mainstream fracture management.

VI. CONCLUSION

Low-Level Laser Therapy (LLLT) has emerged as a promising adjunctive treatment for bone fracture healing, offering a non-invasive approach to potentially accelerate and improve the healing process. This comprehensive review has explored various aspects of LLLT in the context of bone fracture healing, from its underlying mechanisms to clinical applications and future directions. The major key points to be considered are: mechanisms of action, clinical evidences, influencing factors, advantages and limitations and future directions. In conclusion, while LLLT shows promise as an adjunctive therapy for bone fracture healing, more research is needed to fully establish its efficacy and optimal application. As our understanding of the underlying mechanisms improves and technology advances, LLLT has the potential to become an increasingly valuable tool in fracture management. However, it's important for clinicians and researchers to approach LLLT with a balanced perspective, recognizing both its potential benefits and current limitations. The continued investigation and refinement of LLLT techniques may lead to improved outcomes for patients with bone fractures, potentially reducing healing times, improving bone quality, and enhancing overall patient care. As we move forward, interdisciplinary collaboration and rigorous scientific inquiry will be essential in unlocking the full potential of this promising therapeutic approach.

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