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Revolutionizing Drug Development: Harnessing the Potential of Organ-on-Chip Technology for Disease Modeling and Drug Discovery

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One of the groundbreaking advancements in the field of biomedical research is the development of organoids or organ on chip technology. Promising potential of this technology has reshaped the future of disease modelling and drug discovery. Organoids are microfluidic devices which can mimic the physiological functions of natural organs of human body. Animal models are being used in laboratories to evaluate the drug effectiveness but due to the recent ethical concerns, regarding the use of animals, are affecting drug development and treatment for various diseases. But organ on chip is an emerging tool which is filling the gap between animal models and outcomes of drug treatment by eliminating the ethical concerns.

Demand for precision medicine is growing due to rapid arousal of various deadly disease but traditional methods of developing drugs fall short as they can't exactly replicate the human physiology. So instead of using animal models or cell cultures to design drug, to detect the its efficacy and toxicity, organ on chip technology is perceived to be a best option. It saves the time and resources that were being wasted, due the use of animal models, during the preclinical and clinical trials of the drug. On the other hand, organoids are more reliable in satisfying the demand of precision medicine. These artificial organs provide a bioengineered platforms mimicking the specific functions of living organs such as gut peristalsis and lung breathing in a very controlled manner. Moreover, different organs communication after drug treatment is also being studied by developing multi-organ systems so that the utility of these micro-engineered organs can be enhanced. These organs generate more accurate data about the drug effectiveness and toxicity. Moreover, it generates it in real time thus reducing the reliance on the animal models on which testing is usually time taking and can give false results. Furthermore, molecular basis of numerous complex diseases like cancer, diabetes and neurogenerative diseases can be predicted with this technology and it is very helpful in producing precision medicine. Controlled drug delivery is one of the best applications of these organoids eliminating the chance of false hits. Therefore, this technology has demonstrated a paradigm shift in biomedical research providing a better alternative in case of efficiency and reliability.

Now the integration biosensors, artificial intelligence in organ on chip technology has enhanced its predictivity power and also allow the real time imaging and monitoring of cellular responses to the particular drug. Though, there some obstacles regarding the adoption of this technology but efforts are being made continuously to accelerate its usage in mainstream research. Thus, paving the way for a new era of personalized medicine.

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Review Article

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Emerging Trends in Bioprinting for Cartilage Regeneration: Materials, Techniques and Challenges

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ABSTRACT

Cartilage repair is a major clinical problem because of the poor intrinsic healing capacity of cartilage coupled with the limitations of conventional therapies and synthetic substitutes. These challenges have been pursued by bioprinting, which is a technique that can generate scaffolds that mimic native cartilage. This review aims to discuss current and future development of bioprinting for cartilage tissue regeneration with a focus on the most common biomaterials such as alginate, gelatin, and collagen, along with the emerging materials such as smart hydrogels, nanomaterials, and bioactive molecules. The review also outlines other emerging bioprinting technologies like high resolution, 4D, hybrid, and microfluidic assisted bioprinting that are believed to improve the mechanical properties, biological integration and vascularization of the constructs produced through bioprinting. Some of the major problems which are still unresolved are those of scale up, biocompatibility and immune response that hinders the clinical application of bioprinted cartilage. The review further concludes that owing to some regulatory issues along with a lack of an ideal practice the challenges in bioprinting for cartilage regeneration still persists. Some of the future prospects that have been highlighted include the use of patient derived cells, artificial intelligence for process optimization and the development of smart and adaptive biomaterials. Mitigating these challenged and integrated these advanced technologies will enable the clinical translation of bioprinted cartilage to develop personalized, functional, and durable tissue constructs.

INTRODUCTION

Cartilage damage, whether due to osteoarthritis, trauma, or other degenerative conditions, represents a significant clinical challenge affecting millions of people worldwide. Due to the low capacity for tissue regeneration, cartilage damage can result in progressive joint degeneration, pain, and functional impairment. Current cartilage repair approaches such as autografts, allografts and synthetic implants have been proven to have a number of shortcomings including donor site morbidity, immune response and poor integration with host tissue Galarraga *et al.*, in 2019 [1]. Bioprinting has been identified as a rapidly developing field in tissue engineering and regenerative medicine and has special potential for cartilage tissue engineering. Figure 1 showed a general outline of bioprinting technique for cartilage regeneration. In this context, currently used technique of 3D printing enables the sequential layering of cells, biomaterials and growth factors in a controlled manner, which recreates the architecture and composition of native cartilage tissue. The fact that bioprinting allows for higher resolution and repeatability when generating constructs tailored to individual patients' needs makes it a valuable approach to improving upon the current methods of cartilage repair Perera *et al.*, in 2021 [2].

Despite significant advancements in bioprinting for cartilage regeneration, there remains a critical gap in achieving optimal mechanical strength, long-term biocompatibility, and successful clinical translation of bioprinted constructs. Current techniques and biomaterials fail to fully replicate native cartilage properties, while issues such as scalability, vascularization, and immune responses persist. Therefore,

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the problem lies in the limited integration of advanced biomaterials and printing technologies into clinically viable solutions. This review aims to critically analyze existing materials and bioprinting techniques, identify key challenges, and explore emerging strategies such as smart biomaterials and AI integration to enhance cartilage regeneration outcomes.

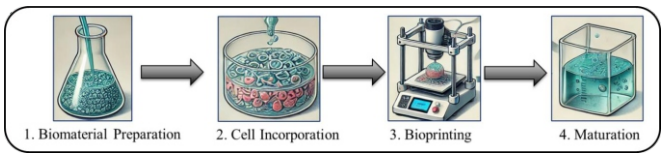

Figure 1: A General Overview of the Bioprinting Process for Cartilage Tissue Engineering

Traditional Biomaterials in Cartilage Bioprinting

Traditional biomaterials have played a crucial role in cartilage bioprinting for an extended period. They are commonly used in the fabrication of scaffolds that replicate the bio-morpohological and mechanical characteristics of natural cartilage Łabowska *et al.*, in 2021 [5]. Some of the conventional biomaterials utilized in this are hydrogels which comprise alginate, collagen and gelatin. All these materials have properties and certain drawbacks Łabowska *et al.*, in 2021; Ren *et al.*, in 2022; Serafin *et al.*, in 2023 [5-7].

Alginate

Alginate is a well-regarded polymer derived from brown seaweed that is compatible with living tissue and fully biodegradable. Consequently, it has several disadvantages in particular its weak mechanical strength, which diminishes its applicability in load-bearing situations such as cartilage. There are no specific binding sites for cells on alginate, which complicates the creation of 3D cell culture Łabowska *et al.*, in 2021 [5]. These limitations can be however overcome by incorporating alginate with other materials to enhance its mechanical properties and ability to adhere to cells Wierzbicka *et al.*, 2024 [8].

Gelatin

Gelatin is produced from collagen and is much preferred for its outstanding biocompatibility and ability to aid cell attachment. Even though gelatins' mechanical properties are good, their mechanical strength is usually adequate for structural applications without the need for reinforcement from other materials Ren *et al.*, 2022 [6]. However, one of the additional limitations is a quick degradation rate. This requires the modification of its structure, or the combination with other polymers to achieve the intended properties Andreazza *et al.*, in 2023; Serafin *et al.*, in 2023 [7, 9].

Collagen

Cartilage is a major structural protein found in collagen. It presents certain difficulties; as collagen hydrogels generally do not have the mechanical strength needed for effective use in cartilage engineering. This constraint requires that additional materials be integrated to improve stiffness and durability Jiao *et al.*, in 2023 [10]. Also, the cost of producing collagen is typically high relative to other biomaterials, which may restrict its broad utilization in assorted bioprinting processes Serafin *et al.*, in 2023 [7].

Emerging Biomaterials with Enhanced Functionalities

Although traditional biomaterials such as alginate, gelatin, and collagen are essential for bioprinting cartilage, their deficiencies make it necessary to create composite hydrogels. The intent behind these composites is to exploit the strengths of each material while reducing their weaknesses,thereby accelerating the field of tissue engineering.

Composite Hydrogels

Scientists have recently developed a novel class of composite hydrogels made of alginate, gelatin, and collagen. For example, the improvement of mechanical properties in collagen-alginate composites also provides cell-binding sites from collagen, which contributes to better cell viability and proliferation in 3D cultures Łabowska *et al.*, in 2021 [5]. Furthermore, the aldehyde derivative of alginate gel and gelatin hydrogel facilitate improved cell adhesion and better control of mechanical characteristics, which are beneficial for tissue engineering applications Łabowska *et al.*, in 2021; Serafin *et al.*, in 2023 [5, 7].

Novel Hybrid Biomaterials

New bio-hybrids including PEG–collagen hydrogels for bioprinting cartilage tissues and tissue engineering are being developed since they possess improved mechanical characteristics and biological activity. The hybrids enhance the properties of the combination material that is mechanical, thermal, electrical, optical, and biological in nature. Among the reported examples are PEG-collagen hydrogels for both corneal and cardiac tissue engineering, double network hydrogels that demonstrate enhanced mechanical properties, and collagen-chitosan composites for corneal tissue engineering. The use of collagen-mimetic peptide-PEG hybrids is to mimic collagen bioactivity in synthetic scaffolds. These hybrid materials have been noted to show improved mechanical properties, such as strength, elasticity, and cell responses essential for tissue engineering endeavors Rafat *et al.*, in 2008; Grover *et al.*, in 2013 [11, 12].

Smart Hydrogels

Advanced biomaterials known as smart hydrogels change according to their environmental conditions, such as pH, temperature, and light. Such characteristics makes smart hydrogels highly suitable for cartilage bioprinting and tissue engineering El-Husseiny *et al.*, in 2022 [13]. Temperature sensitive hydrogels like PNIPAA can encapsulate cells and deliver growth factors while pH sensitive hydrogels adjust the rates of swelling in response to changes in pH, which is useful in drug delivery.

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Photodegradable hydrogels provide spatial and temporal control over tissue development. These hydrogels enable the sustained delivery of growth factors, the modulation of mechanical properties, and the activation of scaffolds for tissue repair. In bioprinting, they offer a means to control the viscosity for enhanced shape accuracy and alterability of properties. However, the challenge that arises in the case of cartilage regeneration applications is to obtain the right balance of all these properties, namely responsiveness, biocompatibility, and mechanical strength Bordbar-Khiabani and Gasik *et al.*, in 2022 in 2022 [14].

Nanomaterials

Graphene and Carbon Nanotubes (CNTs) are two promising nanomaterials widely incorporated into cartilage bioprinting to enhance both mechanical properties and biological activity. Graphene based nanocomposites improve mechanical strength, electrical conductivity, cell adhesion and proliferation. CNTs can give support as well as enhance the mechanical characteristics and act as a vehicle for controlled drug delivery Di Marzio *et al.*, in 2020 [15]. Nanoparticles added to bioinks improve the printability of the material, replicate native cartilage conditions, and provide additional properties, including mechanical strength and conductivity. Some examples include graphene oxide/scaffold composites and CNT/collagen composites which demonstrate enhanced mechanical properties and cell growth. Some pertinent issues include the uniform distribution of nanoparticles, the compatibility of mechanical and biological properties, and toxicity of certain nanomaterials Theus *et al.*, in 2021 [16]. Further work on nanomaterials will be important in the development of functional and biomimetic cartilage constructs.

Bioactive Molecules

Bioactive molecules including growth factors like TGF-β and BMPs are essential for chondrogenesis during cartilage bioprinting Thielen *et al.*, in 2019 [17]. TGF-β is involved in cartilage formation through the regulation of MSC chondrogenic differentiation as well as synthesis of Extracellular Matrix (ECM). BMP-2 and BMP-7 are also reported to promote chondrogenesis, increase chondrocyte proliferation and ECM production (Wu *et al.*, in 2024) [18]. However, some BMPs can induce hypertrophy, which is not favorable for articular cartilage tissue. TGF-β and BMPs have been found to acts synergistically when used together, and thus can enhance chondrogenic differentiation. The incorporation of biomaterials included direct addition, encapsulation, surface modification and gene delivery. Important factors include dose, timing, stability and compatibility with scaffold materials to enhance effective controlled tissue regeneration Keller *et al.*, in 2011; Liu *et al.*, in 2023 [19, 3].

Enhancing Material Performance in Cartilage Bioprinting

Identifying research gaps in the material aspect of cartilage bioprinting reveals several issues. The current hydrogels do not possess sufficient mechanical properties for cartilage applications; stiffer composite materials including graphene or carbon nanotubes are yet to be investigated Crawford *et al.*, in 2021 [20]. There are two major challenges with respect to material selection that remains to be addressed: controlling degradation rates on par with tissue formation and designing stimuli responsive hydrogels Theus *et al.*, in 2021 [16]. The chronic biocompatibility, immunogenicity and stability of new materials-especially of nanomaterials-requires further research. Yet another challenge is the surface modification of the biomaterials for growth factor delivery and chondrogenesis, without causing hypertrophy. Moreover, enhanced technology translation for clinical application, developing smart biomaterials, enhancing angiogenesis, and addressing immune responses are still challenging and significant research topics for future studies involving materials used in bioprinting Crawford *et al.*, in 2021; Theus *et al.*, in 2021 [16, 20].

Traditional 3d Bioprinting Approaches

Traditional 3D bioprinting approaches, including extrusion bioprinting, inkjet bioprinting, and laser direct bioprinting, each have their own advantages and disadvantages, as noted by Di Marzio *et al.*, in 2020 [15]. Extrusion based bioprinting is cheap and has high adaptability; but has low resolution and affects cells with shear force. Inkjet bioprinting is fast but has low cell viability. It is suitable for low viscosity bioinks, and can be blocked as well. Laser assisted bioprinting works with high resolution and cell compatible fabrication but has high cost, low rate of production and less flexibility Vijayavenkataraman *et al.*, in 2023 [21]. These traditional methods of 3D bioprinting are associated with a number of general disadvantages. Low resolution, ranging from hundred to two hundred micrometers, prevents the recreation of the intricate microstructure of tissues. Lower printing rates, particularly in laser assisted approaches, result in long fabrication durations which might affect cell survival. As the size of the constructs increases, issues such as cell survival and construct stability become more difficult to address Wu *et al.*, in 2023 [18]. Viscoelastic properties like viscosity of bioink impose limitations on the nature of biomaterials that may be employed. In addition, the post-printing maturation, insufficient vascularization, mechanical durability issues, and the inability to consistently replicate the procedure from one batch to the next make the process difficult. These limitations have been a subject of worry and are being investigated with the aim of increasing resolution, rate, and scale. This research will help to preserve biological functionality for superior tissue engineering and bioprinting applications Di Marzio *et al.*, in 2020; Vijayavenkataraman *et al.*, in 2023; Wu *et al.*, in

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2023 [15, 18, 21].

High-Resolution Bioprinting

Two-photon polymerization is a bioprinting method that utilizes a high resolution and is applicable for the assembly of cartilage tissue. It makes it possible to create sophisticated 3D structures with a spatial resolution of around tens of nanometers, suitable for the production of scaffolds that have a topography similar to the natural ECM of cartilage Jing *et al.*, in 2022 [22]. The benefits of TPP include resolution around 100 nm, precise control over scaffold architecture and possibility to fabricate complex structures. It may also contain bioactive molecules and help cell proliferation by controlling pore size and connectivity. However, TPP has drawbacks including slow fabrication rates, small build volumes, and a limited choice of materials Valente *et al.*, in 2022 [23]. Current research focuses are directed on the increase of speed, widening of materials, and optimization of scaffolds to promote cartilage regeneration. Although primarily a research application, TPP holds great potential for the development of new generation cartilage tissue engineering scaffolds Jing *et al.*, in 2022; Valente *et al.*, in 2022 [22, 23].

4d Bioprinting

4D bioprinting is a new development of the 3D bioprinting technique that involves the use of smart or stimuli responsive materials where the scaffold structures can change shape or function in response to stimuli. In cartilage tissue engineering, 4D bioprinting can be a powerful tool for designing dynamic scaffolds that can produce an optimal mechanical and biological environment during the tissue formation process Yazdanpanah *et al.*, in 2022 [23, 24]. The benefits include the potential for replicating native chondrogenesis, modulating properties in response to mechanical stimuli, and altering geometry to match defect spaces. This technique generally employs smart materials sensitive to temperature, pH, mechanical loading and biochemical signals. Some issues are still present in the creation of bioinks with suitable rheological properties and bio-properties, and in the ability to maintain scaffold configurations over time and to control change. Still, 4D bioprinting is a promising approach towards designing cartilage scaffolds that are more adaptive and biomimetic Di Marzio *et al.*, in 2020; Yazdanpanah *et al.*, in 2022 [15, 24].

Hybrid Bioprinting Techniques

The use of multiple techniques in a single process is called 'hybrid bioprinting', widely employed to address the drawbacks of singular methods in tissue engineering, hence improving both the mechanical and biological aspects. There is no universal answer to tissue engineering needs regarding scale. Therefore, synergistic methods incorporate the benefits of extrusion and laser bioprinting or multiple heads in a single bioprinter Wu *et al.*, in 2023 [18]. This makes it possible to fabricate scaffolds with multiple materials, gradients, high resolution, high accuracy and improved mechanical properties. Hybrid techniques also allow the incorporation of one or more cell types and biomolecules which offers better control over the scaffold architecture and the cell distribution. Some of the uses are tissue engineered constructs, vascularized models and functional scaffolds. However, issues like complexity, cost and cell damage resulting from multiple processing steps persist with this method. Future directions include better integration, expansion, and robotization for the improved and biomimetic tissue assembly Wu *et al.*, in 2023 [18].

Microfluidic-Assisted Bioprinting

Bioprinting for cartilage tissue engineering using microfluidic techniques offers high fidelity in the fabrication of 3D tissue scaffolds with optimal resolution and customizable cell organization. This enables precise control over flow, mixing, and deposition of cells and bioinks in microchannels. Thus, minimizing shear stress and providing a better physiological environment for native cartilage formation Serex *et al.*, in 2021 [25]. This technique enables fabrication of scaffolds with multiple materials and gradients, and tubular and vascularized structures, which are essential for nutrition and interfaces between cartilage and bone Lee *et al.*, in 2022 [26]. Some applications include creation of zonal cartilage constructs, delivery of bio active molecules and formation of hydrogel fibers. Some of the issues facing bioinks are composition of bioinks, their stability and scalability for tissues of large size. Future developments for optimal use if this technique requires integrating the hybrid modal techniques, utilizing stimuli sensitive material, and optimizing artificial intelligence inspired automation technology for clinical use Davoodi *et al.*, in 2020; Serex *et al.*, in 2021; Lee *et al.*, in 2022 [26-28].

Improving Bioprinting Methods for Enhanced Precision

Several issues remain in the scalability and standardization of bioprinting, with a notable focus on the transition from laboratory scale to clinical scale [29-31]. Existing methods are still limited by the scaffold size, speed, resolution and cell integrity when moving from micro to macroscale (Table 1).

Table 1: Bioprinting Techniques and Their Key Advantages and Limitations

Technique Type	Resolution	Speed	Material Compatibility	Scalability	Strengths	Weaknesses	Sources
Hybrid Bioprinting	Varies based on combined techniques	Moderate	Varied based on techniques	High	Combines strengths of multiple techniques	Complexity and cost, potential cell damage	[3]

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Microfluidic-assisted Bioprinting	10-100 Î¼m	High	High compatibility with various bioinks	High	Precise control over material deposition	Bioink stability, difficult to scale for large tissues	[26]
Extrusion-based Bioprinting	100-300 Î¼m	Medium	High (hydrogels, polymers)	High	Adaptable, supports multiple materials, cost-effective	Low resolution, potential cell damage due to shear force	[27, 28]
Inkjet Bioprinting	50-100 Î¼m	High	Low viscosity materials only	Medium	High speed, good for low viscosity bioinks	Low cell viability, risk of nozzle clogging	[29]
Laser-assisted Bioprinting	10-50 Î¼m	Low	Limited to specific bioinks	Low	High precision, cell-friendly process	High cost, low throughput, limited materials	[30]
Two-photon Polymerization (TPP)	100 nm	Very Low	Limited to photo-sensitive materials	Low	Ultra-high resolution, suitable for complex structures	Very slow, small build volumes	[31]
4D Bioprinting	Depends on the material used	Depends on the material responsiveness	Depends on smart materials used	Medium	Dynamic scaffolds, can adjust over time	Still experimental, challenging material control	[32 ,33]

Furthermore, the field also lacks standard operating procedures which cause variability in outcomes between them. Bioink repositories, quality assessment protocols, and approaches for the evaluation of bioinks and constructs are critical to the process Liang *et al.*, in 2023 [34, 35]. Feedback during the process of bioprinting is not continuous, leading to the need for multifunctional sensor systems in bioprinting. Others include regulatory issues, problems associated with multimaterial capability, and the requirement for bioinks that are both easy to print and biologically active. Other processes that require improvement post-printing processes, such as tissue maturation. Some of the important areas that will enable bioprinting to progress to clinical use are automation. Similarly, there is the challenge of the competence that needs to be addressed to overcome these gaps. It is clear that addressing these gaps will require interdisciplinary work and innovative technologies Liang *et al.*, in 2023 [35].

Mechanical and Biological Integration

One of the major limitations is the inability to achieve native cartilage mechanical properties in bioprinted scaffolds. However, hydrogels, which are widely utilized in bioprinting, generally do not possess the mechanical characteristics necessary for joint function. As a result, there is interest in the establishment of multi-material printing methods and the use of thermoplastic materials in combination with hydrogels for improved mechanical characteristics Fan *et al.*, in 2022 [9]. Thermoplastics can act as a supportive skeleton, and hybrid scaffolds exhibit mechanical properties similar to those of pure thermoplastic scaffolds. Additionally, modulating the crosslinking density and bioink concentration of alginate or PEG based hydrogels enhances the mechanical characteristic of the scaffold Zhou *et al.*, in 2023 [36]. Biological integration is also crucial while using bioactive molecules such as TGF-β1 or components of the ECM to enhance chondrocyte differentiation and cell adhesion. The structure of the osteochondral junction is mimicked by scaffolds with multiple phases, particularly hybrid structures that have varying mechanical features, which are advantageous for cartilage tissue engineering Liang *et al.*, in 2022 [29]. Nanocomposites with graphene and silk fibroin-based components are being invented for 3D bioprinting, which unite printability, mechanical characteristics, and biocompatibility [9]. In an attempt to generate bioprinted cartilage constructs that have enhanced mechanical and biological characteristics for better long term results, other post-processing methods such as mechanical stimulation are applied to advance tissue formation in the maturation phase Di Marzio *et al.*, in 2020; Liang *et al.*, in 2022; Zhou *et al.*, in 2023 [15, 35, 36].

Vascularization and Nutrient Supply

The absence of vascularization in native articular cartilage, which depends on diffusion from the synovial fluid for nutrients, creates a major obstacle for the engineering of large cartilage constructs. In the absence of vascularization, oxygen and nutrient supply to deep cells within the tissue is constricted, causing cell death and necrosis in the core of engineered scaffolds. This outcome is a necrotic center accompanied by viable cells, which lessens the overall functionality and size of the cartilage Gonçalves *et al.*, in 2021 [13]. New approaches to this problem include the application of vascularization promoting factors such as VEGF and bFGF, which can stimulate blood vessel infiltration, however, this leads to the potential change in cartilage formation. The bioprinting techniques that employ gradients such as growth factor or oxygen gradients can control cell behavior and zonal

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differentiation. Another strategy is the pre-vascularization of scaffolds by preparing vessel like channels or culturing chondrocytes with endothelial cells. These strategies are intended to improve nutrient delivery while preserving the avascular characteristic of cartilage, which is imperative for tissue engineering applications Gonçalves *et al.*, in 2021; Shineh *et al.*, in 2023 [37, 38].

Immune Response and Biocompatibility

The major challenges of cartilage tissue engineering today include immune rejection and inflammatory responses in the sense that the implanted biomaterials elicit foreign body responses. This can result in acute and chronic inflammation or fibrotic encapsulation, and therefore hinder integration and functionality of cartilage constructs manufactured through bioprinting Tripathi *et al.*, in 2023 [38, 39]. These challenges are rooted in both inherent and acquired immunity and affected by the properties of scaffolds such as material, size and shape and tissue type Salthouse *et al.*, in 2023 [40]. To improve immunomodulation, bioactive scaffolds are under development to direct immune responses by linking immunomodulatory molecules such as TGF-β1 to create anti-inflammatory conditions Wei *et al.*, in 2019 [51]. Collagen and hyaluronic acid incorporated materials that are immune compatible and resemble the extracellular matrix avoid foreign body reactions. Surfaces coatings are also examined using anti-inflammation molecules and stimuli-responsive material to control immune response. Furthermore, approaches that seek to modulate macrophages and regulatory T-cells also seek to modify the immune response for a more regenerative phenotype to foster tissue integration and chronic regeneration Wei *et al.*, in 2021; Salthouse *et al.*, in 2023; Tripathi *et al.*, in 2023 [4, 39, 40].

Clinical Translation and Regulatory Challenges

Although there are many progresses in bioprinting, the application of the research into clinical use is still difficult. The use of biologically functional materials and the ability to incorporate printed tissues with physiological vasculature and multiple cell types are still a challenging task. These factors impede the clinical translation of bioprinted cartilage implants Ruiz-Cantu *et al.*, in 2020 [41]. The regulatory FDA/EMA guidelines for bioprinted implants are still challenging to follow since it remains a new technology. Patient care safety is relatively well defined with a focus on preclinical testing and chronic studies without standard reporting formats and quality assurance. Testing methods and bioprinting reproducibility are some of the preclinical requirements and advances that need to be standardized Ruiz-Cantu *et al.*, in 2020 [41]. More long-term in vivo studies and improved in vitro models are required in order to make predictions. In terms of the growth of the research focal areas, biomimicry, scalable solutions and collaborations with academic institutions, industry and regulatory agencies will be helpful to streamline the process Liu *et al.*, in 2023 [3]. To increase the functionality and integration of the printed tissue constructs, it will be necessary to improve the post-printing maturation and support the rapid formation of new blood vessels Davoodi *et al.*, in 2020; Ruiz-Cantu *et al.*, in 2020; Liu *et al.*, in 2023; Wei *et al.*, in 2021 [3, 4, 28, 41].

Emerging Frontiers in Bioprinting

New trend in the bioprinting has been focused on developing patient specific solutions using Patient Derived Cells, induced pluripotent stem cells or personalised scaffold. The presence of individual growth factors and biomolecules also enhances the formation of the tissues, following the multiple experimental designs. Some of the applications of Artificial Intelligence (AI) is assisting to optimize bioprinting parameters, predicting tissue characteristics, and developing AI integrated tools for intricate scaffold structures Liu *et al.*, in 2023 [3]. The current focus of scaffold design is on mechanical loading for the purpose of replicating the physiological environment for the dynamic culture of bioprinted constructs. These systems are usually linked to bioprinters for the ongoing maturation of tissue. Additionally, using bioprinting in combination with organ-on-a-chip technology allows for the manufacture of functional constructs of cartilage for drug screening and multi-tissue applications. This is necessary to elucidate the mechanical and biological characteristics of printed cartilage constructs and their integration and remodeling over time. The integration of biocompatible sensors with bioprinted constructs might facilitate the assessment of tissue functionality following implantation, including its mechanical and metabolic characteristics for the development of smart implants [40, 41]. Developing new biomaterials includes the design of stimuli responsive bioinks as well as the production of gradient materials to mirror native cartilage. The focus of vascularization techniques is to deliver nutrients to the tissue construct; enhancements to scalability and automation are necessary for tissue constructs that are applicable for clinical use Davoodi *et al.*, in 2020 [28]. The direct printing of these in situ fabrication techniques into the site of the defect during surgery is being considered. Another important area where immunomodulatory factors are being added to constructs is to facilitate tissue integration. The innovations are aimed at remedying current problems and moving cartilage bioprinting nearer to clinical use Liu *et al.*, in 2023; Shopova *et al.*, in 2023 [3, 42].

This review is limited by the lack of extensive clinical trials and reliance on experimental and preclinical data. Variability in bioprinting methods and absence of standardized protocols further restrict generalizability. Future research should focus on large-scale clinical studies, development of standardized guidelines, and

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improving biomaterial safety and functionality. Integration of AI, patient-specific approaches, and advanced biofabrication techniques is recommended to accelerate clinical translation.

CONCLUSIONS

Recent advancements in cartilage tissue bioprinting are mainly based on new biomaterials such as composite hydrogels, smart hydrogels, and nanomaterials that have better mechanical and biological performance. Techniques like 4D bioprinting, high resolution bioprinting and hybrid bioprinting are allowing for the development of improved and functional tissue scaffolds. However, issues such as low mechanical strength, poor incorporation of vessels, immunological reactions, and regulatory challenges are still a limiting factor. The shortcomings, such as scalability, biocompatibility, and protocol standardization, need to be addressed to advance toward clinical application. In the future, the prospects of combining artificial intelligence-based processes and smart materials are expected to define the new era of cartilage regeneration, providing the development of personalized, long lasting and functional tissue scaffolds.

Authors' Contribution

Conceptualization: ARJ
Methodology: ARJ, ZZ
Formal analysis: ARJ, ZZ
Writing and Drafting: ARJ, ZZ
Review and Editing: ARJ, ZZ

All authors approved the final manuscript and take responsibility for the integrity of the work.

Conflicts of Interest

All the authors declare no conflict of interest.

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Assessment of Knowledge, Attitude and Practice among Nurses Regarding Safe Administration of Chemotherapy at Tertiary Care Hospitals of Peshawar

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ABSTRACT

It is well known that many anti-cancer medications can cause teratology and mutation in humans. The primary groups exposed to these drugs in a hospital setting are nurses. Typically, handling patient waste, administering and preparing antineoplastic agents, and cleaning up chemotherapy spills are the jobs that carry the highest risk of exposure. **Objectives:** To assess nurses' attitudes, practices, and Knowledge related to the safe administration of cytotoxic drugs. **Methods:** Descriptive and inferential statistics were used to analyze the data collected from 51 nurses who participated in a descriptive cross-sectional study conducted at Peshawar public sector hospitals. The study was conducted using a structured questionnaire and the Universal sampling technique. **Results:** The result shows that 49.0 % of total nurses have excellent Knowledge, and 41.2% of nurses have good Knowledge, regarding the safe administration of cytotoxic drugs. 29.4% of nurses have good practice. In comparison, 70.6% of total nurses have poor practice. Most nurses have a positive attitude towards safely handling chemotherapy drugs. **Conclusions:** It was concluded that this study comes to the following conclusion after a thorough analysis of a review of nurses' administration of chemotherapy to patients. The majority of samples had poor practice for giving chemotherapy drugs. As a result, it's essential to increase workplace safety, provide protective gear, and create best practices for oncology nurses.

INTRODUCTION

Of all forms of death and disability in the world, cancer tops the list [1]. According to estimates made by the World Health Organization (WHO), nearly 10 million deaths occurred due to cancer alone in 2020. Between 70 to 80 percent of global cancer deaths turn out to originate from low- and middle-income countries. Thus, an anticipated aggravation of that disproportionate burden projected for the next 10 years would be expected to happen in low- and middle-income countries [2]. In Asia, Pakistan has the highest rate of breast cancer. One in every nine women has a lifetime risk of being diagnosed with breast cancer [3, 4]. The surge in mortalities, especially in developing countries is likely due to delayed diagnosis, and limited access to effective therapies and/or healthcare facilities, amongst other reasons. Although various cancer treatments, such as radiation therapy, targeted therapies, chemotherapy, and immunotherapy can be utilized, their availability or use may be delayed due to a lack of public awareness and late detection [4]. Antineoplastic drugs are currently the most used modality in cancer treatment all over the world. It destroys cancer cells in their cytotoxic effects. Chemotherapy is a type of cancer treatment that employs drugs to eliminate cancer cells [5]. Chemotherapy acts after preventing or retarding the growth of multiplication of cancer cells, which proliferate quickly. This type of unhealthy process has also affected healthy cells under

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chemotherapy treatment, causing side effects to the individual [6]. In most chemotherapy applications, cytotoxic drugs (CDs) have been used for their cancer-carrying cell-killing functions. They have mutagenic, teratogenic, and carcinogenic effects on humans. Direct contact with healthcare providers is possible through mixtures, transportation, preparation, and administration, in addition to waste handling procedures, equipment maintenance, and repair [7]. Chemotherapeutic drugs are toxic to human tissues. Destruction of cells making possible the proliferation of an abnormal tissue is the primary goal of chemotherapy. Traditional chemotherapies kill quickly dividing cells. Damage is done to healthy fast-growing cells as well: mucous membrane cells lining the entire body's surfaces, including those of the mouth and throat, the stomach, blood-forming cells in the bone marrow, hair follicles, and others [8]. Nurses are the backbone of cancer care and their main roles include delivering therapy, managing side effects, educators to patients and their families about the adverse effects of chemo-treatment, and emotional support during the demanding process [9]. Guidelines for the safe handling of chemotherapy drugs (CDs) were put in place over 20 years ago, yet modern studies continue to show that the environment and healthcare workers get contaminated by such drugs, particularly in developing countries [10]. Lack of knowledge and economic and socio-cultural factors make the most contribution towards unsafe behaviours among healthcare workers (HCWs) when it comes to handling infectious materials. An epidemiologic study done in 2016 determined the immediate and contributing causes of exposure of HCWs to antineoplastics [11]. It was classified into 4 categories for immediate causes such as direct contact with CDs without personal protective equipment, needle-stick injury, spills, and other unintended exposures; and 3 categories of contributing causes such as lack of training, inadequate controls, and poor communication. Short-term health hazards arising from occupational exposure to CDs include skin rashes, sore throat, cough, dizziness and headache, eye irritation, hair loss, and allergic reactions while chronic health effects in unprotected HCWs who handle these drugs without following safety measures include genotoxicity, mutagenicity and carcinogenicity, poor reproductive outcomes such as spontaneous abortion, infertility and poor neonatal outcome; and organ toxicity such as bone marrow, liver, kidney, lung, and cardiac toxicity [12]. Unsafe or poor handling practices are indicated in several studies. Poor compliance may be linked to a lack of understanding and beliefs that there is a minimal likelihood of an immediate injury, nurses may believe they are immune to the risks of chemotherapy exposure. Moreover, no specialized training regarding chemotherapy and curriculum are provided to nurses, thus they learn these at the bedside which increases the risk of these adverse effects both for patients and nurses. In all situations, Knowledge is essential for safe nursing practices. However, it becomes crucial when a nurse's lack of Knowledge endangers their or the patient's safety. According to a prior study, Chemotherapy may have unintentionally harmed the oncology work environment for more than thirty years [13]. A lot of work has been done in the past exploring the knowledge, attitude, and practice of healthcare professionals regarding the treatment and management of patients with cancer. On the contrary, very little work has been done to evaluate the parameters here in Pakistan.

Although chemotherapy safety guidelines have been established globally, there is limited evidence from developing countries like Pakistan assessing the combined knowledge, attitude, and practice (KAP) of nurses regarding safe chemotherapy administration. Existing studies suggest variability in knowledge and significant gaps in practice, but the extent of this discrepancy and its contributing factors remain underexplored in local tertiary care settings. This gap limits the ability to design targeted interventions to ensure occupational and patient safety. Therefore, the present study aimed to assess the knowledge, attitude, and practice of nurses regarding the safe administration of chemotherapy and to identify gaps between theoretical knowledge and clinical practice.

METHODS

A descriptive cross-sectional study was conducted in a tertiary hospital in the Peshawar region, Pakistan (No.KMU-INS/14-/5785). The study duration was from 1st September 2020 to 1st Feb 2021. The calculated sample size was n=51 nurses based on n=510 as the total population of nurses working within the oncology unit, 95% CI and 5% marginal error. Participants were selected using a non-probability convenience sampling technique. All full-time nurses including those involved in patient care, having experience greater than 1 year working were included whereas, nursing internees' nurses who have faced significant personal trauma, were diagnosed with any mental disorder (depression, schizophrenia etc.) and severe medical conditions in the last 6 months were excluded. A written informed consent was taken from all the participants, and followed by data collection on a pre-designed adopted data collection tool having four parts e.g. Demographic data of the participants, questions related to Knowledge, practice and attitude related to safe handling of chemotherapeutic drugs. Among demographic variables age, marital status, gender, and education level were assessed. Strict exclusion criteria were used to exclude any bias or confounding factor from the study. Data were analyzed through SPSS version 26.0. The mean and standard deviation were calculated for numerical variables and frequency and percentages for categorical variables. A

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score of 80% to 100% was considered excellent, 60% to 80% was considered good and below 60% was taken as low knowledge and above 50 % was taken as good practice.

RESULTS

The descriptive statistics of the demographic data of nurses are shown. Most participants were male, n=28 (54.9%), compared to female participants n=23 (45.1%). Male make up the majority of the nursing workforce in the oncology unit. The largest age groups were 21-25 Years old n=23(45.1%), 26-30 years old n=23(45.1), followed by the age group >35 Years old n=3 (5.9%), and lastly 31-35 Years age group was n=2(3.9%). Most of the oncology nurses are from the young age group. Single people made up 74.5% of the total participants (n=38), followed by married participants (n=13)(25.5%). The majority of participants were Bachelor of Science in Nursing (BSN) nurses n=32(62.7%), followed by Diploma nurses, n=10 (19.6%), nurses having Master of Science in Nursing (MSN) degrees n=1 (2.0%) and Post Registered Nurse (RN) n=8(15.7%). Most nurses have experience in the 1-5-year range, with n=44 (86.3%), followed by the 6–10-year range, n=4 (7.8%), and the last 11–15-year range, n=3(5.9%). The majority of the nurses who responded to the survey were from A(n=40; 78.4%), B(n=6; 11.8%), C(n=4; 7.8%)and lastly D n=1(2%)(Table 1).

Table 1: Demographic Data of the Nurses

Demographic Variables	Category	Frequency (%)
Gender	Female	23(45.1%)
	Male	28(54.9%)
Organization	A	6(11.8%)
	B	1(2.0%)
	C	4(7.8%)
	D	40(78.4%)
Age	21-25 Years	23(45.1%)
	26-30 Years	23(3.9%)
	31-35 Years	2(3.9%)
	Greater Than 35	3(5.9%)
Qualification	BSN	32(62.7%)
	Diploma	10(19.6%)
	MSN	1(2.0%)
	Post RN	8(15.7%)
Marital Status	Married	13(25.5%)
	Single	38(74.5%)
Job Experience	1-5 Years	44(86.3%)
	11-15 Years	3(5.9%)
	6-10 Years	4(7.8%)

The knowledge score of nurses ranges from min=40 to mix=100. The median is 70, the standard deviation is 14.84, and the mean is 73.92(Table 2).

Table 2: Descriptive Statistics of Nurse's Knowledge Regarding Safe Chemotherapy Handling

Variables	Knowledge Score
Valid	51
Missing	0
Mean	73.9216
Median	70.0000
Mode	60.00[a]
SD	14.84297
Minimum	40.00
Maximum	100.00

As a result, it demonstrates that nurses are knowledgeable regarding the safe administration of chemotherapy drugs (Figure 1).

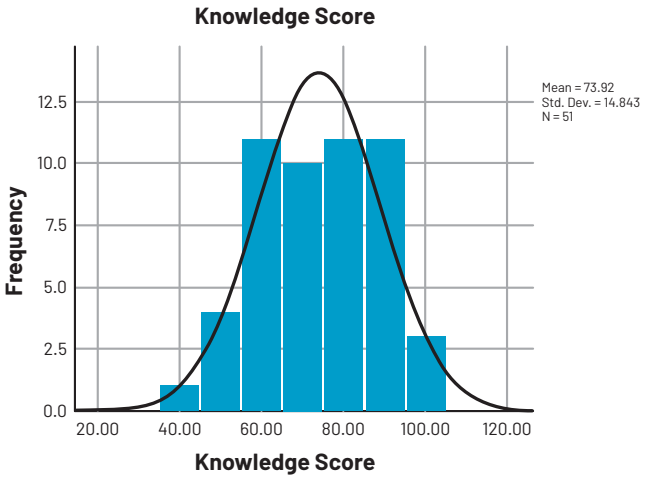

Figure 1: Descriptive Statistics: Mean, Mode, Median and SD of Nurse's Knowledge Regarding Safe Administration of Chemotherapy

The knowledge of nurses regarding safe chemotherapy drugs is highlighted. Only n=25(49%)participants were able to get 80% -100% scores, which is considered excellent Knowledge, n=21(41.2%) was able to get 60%-80% scores which are considered Good Knowledge, and n=5(9.8%)was able to get 60% and below score in the administration of chemotherapy knowledge(Table 3).

Table 3: Level of Nurse's Knowledge Regarding Safe Administration of Chemotherapy

Variables		Frequency (%)	Valid Percent	Cumulative Percent
Valid	Excellent Knowledge	25(49.0%)	49.0	49.0
	Good Knowledge	21(41.2%)	41.2	90.2
	Poor Knowledge	5(9.8%)	9.8	100.0
	Total	51(100.0%)	100.0	–

Percentage of knowledge level was analyzed(Figure 2).

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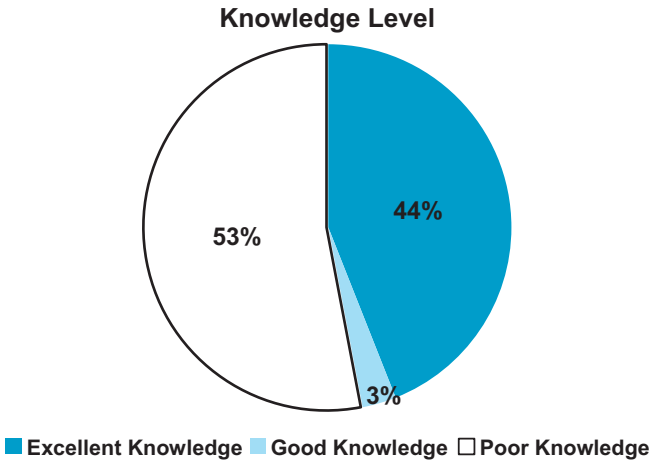

Figure 2: Level of Nurse's Knowledge Regarding Safe Administration of Chemotherapy

The descriptive statistics of the Nurse's Practice are presented. The average practice score of nurses on the safe handling of chemotherapeutic drugs is 44.90, which indicates that the nurses are following moderately safe practices. The score at the median level, which is 50, implies that half of the respondents scored at or below this figure, while the mode is 30, showing that this was the score that most frequently appeared. The standard deviation of 15.92 indicates that there is considerable variance in the scores, suggesting dissimilarity in the practice of nurses. The scores therefore range from a minimum of 10 to a maximum of 70. This shows that the range of practice includes very poor practice to excellent (Table 4).

Table 4: Descriptive Statistics of Nurse's Practice Regarding Safe Administration of Chemotherapy

Variables	Practice Score
Valid	51
Missing	0
Mean	44.9020
Median	50.0000
Mode	30.00
SD	15.92138
Minimum	10.00
Maximum	70.00

In the total of 51 participants, as mentioned, n=15 (29.4%) participants were able to get a 60%-80% score which is considered in the good practice category, and n=36 (70.6%) participants were able to get a score below 60 percent which is considered in poor practice level (Table 5).

Table 5: Level of Nurse's Practice Regarding Safe Administration of Chemotherapy

Variables		Frequency (%)	Valid Percent	Cumulative Percent
Valid	Good Practice	15 (29.4%)	29.4	29.4
	Poor Practice	36 (70.6%)	70.6	100.0
	Total	51 (100.0%)	100.0	–

The level of Nurse's Practice Regarding the Safe Administration of Chemotherapy is analyzed (Figure 3).

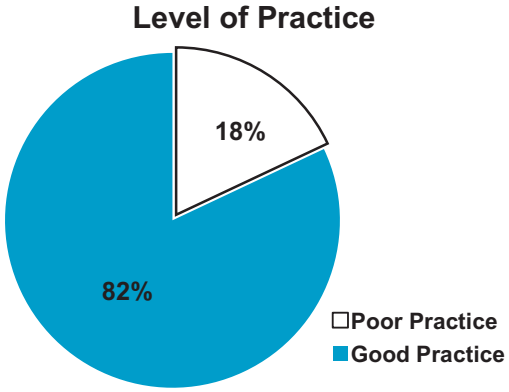

Figure 3: Level of Nurse's Practice Regarding Safe Administration of Chemotherapy

The first question "When a patient is on chemotherapy comes to you, you feel with chemotherapy". 88.2 % of nurses selected the option (Patient's disease is going to be cured), 2% selected the option (Any way patient is going to die), and 5.9% of participants selected the option (Not concerned about the outcome). In 2nd question "While handling cytotoxic drugs person needs" in which 98% of nurses selected the option (Self-protection), and 2% selected the option (None of the above). In 3rd question "Along with the patient's other family members also must be counselled regarding the disease and treatment". 96.1% of nurses selected the option (Yes), and 2% selected the option (No). In the 4th question "Administration of analgesic to the patient for pain relief must be" 45.1 % of nurses selected the option (Liberal as per the requirement of the pt.), 3.9% selected the option (Not important, it's part of the disease and should be told to the patient), and 51% participant selected the option (As per prescribed schedule only). In 5th question "Explanation of the Diagnosis to the patient and his relatives" 88.2 % of nurses selected the option (Must be explained in detail.), 7.8% selected the option (Need not necessary to explain.), and 2% of participants selected the option (It's not my duty). The majority of nurses have positive attitudes toward chemotherapy administration, whereas fewer have negative attitudes (Table 6).

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Table 6: Descriptive Statistics of Nurse's Attitude Items Regarding Safe Administration of Chemotherapy

Question	Answer	Count	%
When a patient is on Chemotherapy comes to you, you feel with Chemotherapy	The patient's disease is going to be cured.	45	88.2%
	Any Patient is going to die.	1	2.0%
	Not concerned about the outcome	3	5.9%
	None of the above	2	3.9%
While handling cytotoxic drugs person needs	Self-protection	50	98.0%
	None of the above	1	2.0%
Along with the patient's other family members also must be counselled regarding the disease and treatment	Yes	49	96.1%
	No	1	2.0%
	Not sure	1	2.0%
Administration of analgesic to the patient for pain relief must be	Liberal as per the requirement of the pt.	23	45.1%
	Not important, it's part of the disease and should be told to the patient	2	3.9%
	As per the prescribed schedule only.	26	51.0%
Explanation of the Diagnosis to the patient and his relatives.	Must be explained in detail.	45	88.2%
	It is not necessary to explain.	4	7.8%
	It's not my duty.	1	2.0%
	None of the above	1	2.0%

DISCUSSION

In general, the research shows that nurses know, practice, and demonstrate positive attitudes regarding the safe administration of chemotherapy, which is the most comprehensive evidence of their competency in this critical aspect of healthcare. The descriptive statistics show that even though the nurses have adequate knowledge regarding chemotherapy administration, they do not seem to apply all safety precautions consistently. A mean knowledge score of 73.92 (SD=14.84) establishes that indeed, the participants have sufficient knowledge, with nearly half (49%) scoring excellently. In contrast, practice scores induce concern, with an average of 44.90 (SD=15.92) indicating most nurses do not practice competent safety methods consistently, with 70.6% falling under poor practice. The attitude assessment picture, however, appears positive, with most nurses reporting a constructive attitude towards the administration of chemotherapy, which is evidenced in their responses to various questions relating to attitude. The identified differences between knowledge and practices are attributable to various factors. First, while theoretical knowledge is almost always emphasized, converting that knowledge into actual practice necessitates ongoing clinical supervision and periodic training. This disparity could also relate to systemic issues concerning disallowed resource or staffing levels and barriers to access to personal protective equipment (PPEs) with these being very common in health systems in developing countries. Besides, the variance in practice score across respondents (as shown by SD of 15.92) indicates that individual factors such as work experience, access to professional development and institutional policies have a significant impact on practice behaviour [7]. While comparing the results with available reviews that point to targeted interventions, a study conducted discussed a low knowledge-practice gap among the nurses handling chemotherapy agents. In their study, the average knowledge score and practice scores were still below acceptable levels, mirroring the present results for the practice. Such comparisons indicate that the gap between theoretical knowledge and practical application needs full treatment for its pervasion [2]. Around the world, studies have reported different levels of knowledge and practice among nurses about chemotherapy safety. The study, nevertheless, acknowledged the marked increase in practice scores among institutions that had chemotherapy safety guidelines with frequent training, indicating the role of organization support in promoting safer practices [3]. The attitude of the nurses, as shown in the present study, is overwhelmingly positive, with 88.2% of the participants believing that chemotherapy could cure the patient's disease, which translates into optimistic approaches toward their role in patient care. A study showed that the knowledge levels of nurses regarding the safety administration of intravenous chemotherapy were poor which is not consistent with our study [12]. Also, another Pakistani study consistent with the result of this study revealed that more than half of the nurses had poor practice indicating issues surrounding patient safety [8]. The finding of another study in Bangladesh resonates with results showed that nurses have average knowledge of chemotherapy handling, however, the use of personal

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protective equipment and biological safety cabinet, following guidelines, medical surveillance and training appear to be a hindrance [14, 15]. More fundamentally, it requires that nurses are educated and professionally trained about chemotherapy agent handling in nursing schools and service continuing education, and the required facilities are also adopted [16, 17]. To connect those gaps, regular competency-based training, providing sufficient resources, and developing clear and easily accessible chemotherapy handling guidelines should be instituted in healthcare institutions [18, 19]. Studies have found that simulation-based training programs significantly improve both knowledge and practice levels [20].

This study is limited by its small sample size, single-region setting, and use of non-probability sampling, which may affect generalizability. Self-reported data may also introduce response bias. Future studies should include larger, multi-center samples and adopt observational or interventional designs to assess actual practices. Additionally, structured training programs and evaluation of their impact on improving safe chemotherapy practices are recommended.

CONCLUSIONS

It was concluded that this study brings to the limelight the satisfactory knowledge and positive attitudes of nurses toward administering chemotherapy. However, a huge gap in practice, which means that systemic and individual-level interventions should be required. Continuous education, resource allocation, and establishment of supportive institutional policies toward converting these challenges into strengths meant that healthcare systems could render chemotherapy Administration Safer and More Efficacious Within Their Overall Operations.

Authors' Contribution

Conceptualization: AA
Methodology: AA, A, MZ, SH, IWA
Formal analysis: AA
Writing and Drafting: IWA
Review and Editing: AA, A, MZ, SH, IWA

All authors approved the final manuscript and take responsibility for the integrity of the work.

Conflicts of Interest

The authors declare no conflict of interest.

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Original Article

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Diagnostic Role of X-ray Imaging in Renal and Ureteric Calculi Keeping Computed Tomography as Gold Standard

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ABSTRACT

The renal colic is an initial onset of flank discomfort that often radiates to the groin and may be linked with complication like hematuria and dysuria. Physicians initially use KUB plain x-ray imaging for the initial diagnosis and ultrasonography for the suspected calculi, and evaluation of the upper tract of urinary system. **Objectives:** To determine the diagnostic accuracy of x-ray KUB imaging in diagnosis of renal and ureteric calculi keeping computed tomographic scan as a gold standard. **Methods:** An ethically approved cross-sectional study was conducted at Maqsood Medical Complex, Peshawar with a convenient sampling technique between August to November 2024. Data of KUB x-ray and CT scan were collected by predesigned proforma. Data were entered in SPSS version 27. Demographics were described in tables and applied Chi square test for the sensitivity and specificity of the KUB radiographic x-ray take the CT scan gold standard. **Results:** The sample size of the study was 235, where the mean and standard deviation of age was 33.77 ± 8.61. The male patients were 152 (64.68%) and the female were 83 (35.32%) participated in this research study. The Chi square test result shows that x-ray was able to properly detect 92 cases of calculi verified by CT but missed 124 cases. While X-ray did not incorrectly identify any calculi. **Conclusions:** Although KUB x-ray imaging has been configured to be an initial diagnostic tool in detecting renal and ureteric calculi, its diagnostic yield lacks in comparison to CT scans.

INTRODUCTION

The renal colic is an initial onset of flank discomfort that often radiates to the groin and may be linked with complications like hematuria and dysuria [1-3]. The x-ray of kidney, ureter and bladder (KUB) is the basic and initial imaging modality to diagnose radiopaque stones present in this area [4, 5]. Where Renal colic occurs when a stone forms in the kidney, ureter, urinary bladder, or urethra, obstructing the urine tract. it is the most common disease of the urinary tract, more prevalent among adult male population and it is associated with an increased risk of chronic renal disease . It has a 50% occurrence rate. The average prevalence of renal colic globally is 5-15% [7, 8], which varies depending on how the illness is distributed in different geographical locations [9]. Choosing the best methods for diagnosing urinary stones depends on a variety of parameters, including clinical environment, patient body habits, financial expenses, and ionizing radiation tolerance [10]. Multiple imaging modalities are available, although extensive clinical usage is now confined to ultrasonography, kidney ureter bladder scan (KUB), plain film radiography, and computed tomography. Non contrast enhanced CT scan of the abdomen and pelvis consistently provide accurate diagnosis uterine tract infection (UTI) via exposing the ionizing radiation [11]. The physicians initially use KUB plain x-ray imaging for the initial diagnosis and ultrasonography for the suspected calculi which is radiolucent in nature as well as for the evaluation of the upper tract of urinary system because of the highly upper tract calculi and the concomitant bladder. CT scan diagnosis has become the universal standard reference in the diagnosis of urinary calculi with the high sensitivity 95-98% but KUB x-ray examination is also preferred by the

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urologist before CT scan procedure [12, 13]. The management of calculi in the urinary system depends on the size of the stone and its nature [14, 15]. It may be radiolucent or radiopaque. Also, the lab test reports are mandatory to confirm the glomerulus filtration rate (GFR) and creatinine level of the patient [16-18]. Delays in the diagnosis and management of such conditions can lead to severe morbidity, renal obstruction, fistula, renal injury and may lead to renal system failure [19, 20]. In this study KUB plain x-ray radiography was used for the examination method of choice for patients with suspected ureteric and renal calculi.

Although computed tomography (CT) is considered the gold standard for diagnosing renal and ureteric calculi, plain X-ray KUB remains widely used as an initial imaging modality due to its accessibility and low cost, especially in resource-limited settings. However, there is limited local evidence quantifying the diagnostic accuracy, sensitivity, and specificity of X-ray KUB compared to CT, particularly in patients presenting with acute renal colic. This gap creates uncertainty in selecting the most appropriate first-line diagnostic approach. Therefore, the present study aimed to evaluate the diagnostic accuracy of X-ray KUB in detecting renal and ureteric calculi using CT scan as the gold standard.

METHODS

A cross-sectional study was conducted at Maqsood Medical Complex, Peshawar from August to November 2024 after the approval (Ref no: SU91-MSAHW-S23-111) was obtained from the Superior University research board of studies and hospital ethical board. The sample size was calculated by openEPI calculator where confidence interval was 95% and margin of error was 5%, Z score was 1.96 and the prevalence value was 10% [21]. The final sample size was calculated to be 235, using convenient sampling technique. This approach was chosen to ensure that the study focused on individuals most likely to provide relevant insights into the diagnostic accuracy of imaging modalities for renal and ureteric calculi. During data collection, written consent was obtained from the patients and patients were guaranteed data confidentiality. The inclusion criteria comprised of both male and female who had flank pain less than 24 hours and advised for X-ray KUB and CT abdomen and pelvis scan, age between 20 to 50 years and willingness to participate. On the other hand, pregnant female, patients who had the history of abdominal trauma and morbidly obese patient (Men>129 kg women>113kg) were excluded. Patients were referred to the radiology department for x-ray KUB followed by CT abdomen and pelvis scan. Both x-ray KUB & CT scan were interpreted by consultant radiologists who have more than 10 years' experience in diagnostic medical reports. Time between the two tests was maximum of 2 hours. Demographics were noted on predesigned proforma including patient age, gender, weight, height and then calculated body mass index. Frequency and percentages were calculated of categorical variables like gender, findings on x-ray KUB and CT scan. Mean and Standard deviation was calculated for continue variables like age, body mass index, weight and height. Chi Square test was applied on categorical variables between x-ray KUB imaging and CT scan of abdomen and pelvis. Sensitivity and specificity were determined by taking findings on CT scan as gold standard and using 2 by 2 tables. All information was entered into and analyzed in statistical software SPSS version 27.

RESULTS

The sample size of the research study was 235, where the mean and standard deviation of age was 33.77 ± 8.61. The male patients were 152 (64.68%) and the female were 83 (35.32%) participated in the research study. The minimum age was 18 years, and the maximum age was 49 years (Table 1).

Table 1: Descriptive Statistics of Variables

Variables		Mean ± SD
Age		33.77 ± 8616
Gender	Male	152 (64.68%)
	Female	83 (35.32%)

Statistically the age group was grouped between three categories, where in age between 18 to 30 years old patient frequency was 92 (39.1%), which is the largest individuals of our sample size, 31 to 40 age group patients' frequency was 79 (33.6%) and 41 to 49 age group patients' frequency was 64 (27.2%) as shown in table 2.

Table 2 : Age Group Analysis

Age Group	Frequency	Percent	Valid Percent	Cumulative Percent
18-30	92	39.1%	39.1%	39.1%
31-40	79	33.6%	33.6%	72.8%
41-49	64	27.2%	27.2%	100.0%
Total	235	100.0%	100.0%	100.0%

It was determined that 46 (19.6%) patients were diabatic and 77 (32.8) were hypertensive patients, 132 (56.2%) patients having hematuria in urination and 103 (43.8%) patients were normally excrete the urination, from medical history of the patients we found that 126 (53.6%) patients under medical treatment, two of them took lithotripsy treatment and 109 (46.4%) were not taking medication in past history. In 235 patients 83 (35.3%) took Injection Toradal with 100 ml saline used for severe pain killer and 53 (22.6%) patients took Capsule Tamsoline 0.4 mg work as a muscle's relaxant, the remaining 99 (42.1%) patients not taken injection or any first aid medication from preventing the pain. With CT being the gold standard, the table compares the results of X-ray KUB with CT KUB in the diagnosis of renal and ureteric calculi. It displays the

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distribution and frequency of instances according to whether or not calculi were found using both approaches. 92 instances (39.1%) out of 235 cases had both X-ray and CT scan results showing calculi (true positives). A total of 124 (52.8%) instances had a negative X-ray but a positive CT scan, indicating that the X-ray missed these cases (false negatives). 19 patients (8.1%) had genuine negative results from both CT and X-ray scans. Since calculi were never detected by X-ray and their absence was verified by CT, there were no false positives (Table 3).

Table 3: Crosstabulation of x-ray KUB and CT Findings for the Diagnosis of Renal and Ureteric Calculi

Finding on X-ray KUB	Finding of CT KUB: Positive	Finding of CT KUB: Negative	Total
Positive	92 (39.1%)	0 (0.0%)	92 (39.1%)
Negative	124 (52.8%)	19 (8.1%)	143 (60.9%)
Total	216 (91.9%)	19 (8.1%)	235 (100.0%)

DISCUSSION

The result of the present study has shown that, although KUB x-ray imaging is less expensive, easily accessible, and has been configured to be an initial diagnostic tool in detecting renal and ureteric calculi, its diagnostic yield lacks in comparison to CT scans. Using X-rays, 39.1% of calculi cases found by CT were revealed, and 52.8% of the cases were missed. This goes further to show the limitation of KUB X-ray in the detection of small or less radiopaque stones, which CT can well note. These results support the existing literature regarding the fact that CT scans continue to be the most preferred diagnostic imaging modality in the diagnosis of urinary stones, attributed to the higher sensitivity and specificity of the modality. X-ray in this study was able to properly detect 92 cases of calculi verified by CT but missed 124 cases. While X-ray did not incorrectly identify any calculi, it also had limited success in ruling out calculi precisely. This underscores the necessity of CT as a more trustworthy diagnostic tool. In accordance with the prior conclusions, based on the previous studies, CT scans demonstrated high diagnostic capability. For example, it has been established in several studies that non-contrast-enhanced CT scan sensitivity ranges between 70%–80% for diagnosing appendicitis or fistula [22, 23]. Thus, it was further preferred for imaging of renal calculi as shown in a study where non-contrast CT showed 82% sensitivity in imaging renal calculi [24]. However, recent research has also focused on the existing use of KUB x-rays in the clinical health setup because they are cheaper [25]. Finally, these observations affirm the fact that CT is still more effective than X-rays. Still, X-rays are useful as initial imaging modalities, especially in situations where access to CT or the patient cannot afford the radiation costs or has other complications. On the other hand, some studies have raised doubts over the general necessity of KUB x-ray imaging, suggesting that instead of the KUB x-ray, the first choice should be either the ultrasound or direct CT image [26]. These dissimilarities may be due to differences in study samples, stone composition, and imaging modalities, underlining the need for location-sensitive differential analyses when selecting diagnostic techniques. Some of the limitations of our study must also be noted. First, due to the convenience sampling technique that was used in this study, the external validity of the results can be questioned. Moreover, the stone composition parameters and prior therapies. The absence of inter-observer reliability assessment regarding the radiologists who analyzed the imaging may also weaken the results. Finally, since the study was cross-sectional in design, no longitudinal comparative efficacy of KUB x-rays with that of CT in clinical practice was established. Future studies should be conducted on large samples from different centers to increase the generalizability of results. Integrating elements of stone composition, patients' pathologies, and sex differences might give additional information about the nature of diagnostic performance. Moreover, the assessment of diagnostic cost and consumption in different types of facilities would be beneficial in addressing policy concerns for comprehending the cost-utility of diagnostic techniques. Further, the studies of inter-observer reliability and the outcomes of patients depending on the used diagnostic techniques would also enhance the results. These steps would have the overall effect of helping to fine-tune diagnostic algorithms of renal and ureteric calculi with respect to their accuracy, accessibility, and cost implications.

This study was limited by its cross-sectional design, single-center setting, and use of convenient sampling, which may reduce generalizability. Factors such as stone composition, size, and inter-observer variability were not assessed. Future studies should include multi-center designs with larger samples and incorporate detailed analysis of stone characteristics. Additionally, cost-effectiveness and radiation exposure comparisons between imaging modalities should be explored to guide clinical decision-making.

CONCLUSIONS

This research shows that KUB x-ray imaging remains an effective first-line diagnostic tool used for renal and ureteric calculi, nevertheless, CT scans outcompete in terms of sensitivity and specificity by a considerably large margin. The study suggests that although KUB ionized x-ray played a vital role in the urological procedure, especially in the emergency department, other imaging modalities should be incorporated into the laboratory diagnosis of urinary calculi to provide better diagnosis, management and hence patient care.

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Authors' Contribution

Conceptualization: KU
Methodology: TQ, BA
Formal analysis: KU, SK
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Language Difficulties and Challenges Faced by Students in Understanding the English Curriculum at PNS LUMHS

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ABSTRACT

The English language is spoken all over the world nowadays. It is issued in various socio-economic settings such as tourism, travelling, business, commerce, communication, teaching, learning, international diplomacy, science and technology. **Objectives:** To describe the challenges that students experience because of the curriculum in English. To investigate how these challenges are overcome by students in their academic years, and to explore which strategies are used by students to overcome challenges faced because of the curriculum in English. **Methods:** A cross-sectional study was carried out at Peoples Nursing School, Liaquat University of Medical and Health Science, Jamshoro, to evaluate language difficulties and challenges faced by students in understanding the English curriculum at Peoples Nursing School, Liaquat University of Medical and Health Science. **Results:** According to this study, nearly 41% of students face difficulties when communicating in English. 41% of students have difficulty in grammar. The major problem faced by participants is that 57% of students feel shy, and because of that students don't communicate well in English. 53% of participants don't speak English or read in English because of shyness and 51% of participants haven't enough confidence to read in English in front of people. **Conclusions:** It was concluded that participants have major problems in English speaking because of again lack of confidence, shyness, lack of vocabulary, lack of fluency, and sentence-making problems.

INTRODUCTION

Learning English has become a dire need of students in different countries of the world especially where the medium of instruction in education settings is English [1]. The English language is spoken all over the world nowadays. It is issued in various socio-economic settings such as tourism, travelling, business, commerce, communication, teaching, learning, international diplomacy, science, and technology. English is a mandatory subject that is being taught from primary to university level in Pakistan [2]. English occupies a desirable and valued place as the international language, English is used as the principal means of communication all over the world. In addition, it is used for diplomatic, commercial, educational, engineering, legal, and medical purposes [3]. English is the communication medium in most schools, colleges, and universities, especially for studying overseas. In Pakistan English is not the native language that's why most students face difficulties in higher education academic years, especially students from remote areas. It is observed that students have clear concepts but they do not have enough English language skills like poor grammar skills, and lack of vocabulary, because of that students don't correctly answer the questions in exams and ultimately it affects their education and their grades [4]. It aims to know how students cope with this situation where the whole curriculum is in English. English is a medium of instruction, and students must attempt exams in English medium. It is a very important aspect to know how university students face challenges during their academic years because of the curriculum in English medium. At the same time, they

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have poor English proficiency. Although in 12 years of education, students study English they do not master's in English. Students didn't properly study the language. Mostly students get the language as a text and read about it but they are not driven to take part in daily life situations. This study aims to present the language difficulties of students by exploring the language-related trials that students face at Peoples Nursing School, Liaquat University of Medical & Health Science, Jamshoro. To distinguish the English medium instruction linguistic challenges in these four aspects of English academic skills like reading, writing, communication and listening. In the twenty-first century, English medium instruction (EMI) has appeared as a dominant educational phenomenon in the world. English is widely used to teach science subjects. English-as-a-second-language learners studying science in English are increasing because learning an additional language demands effort. EMI is defined as 'the use of the English language to explain academic subjects in a country where English is not the first language of the common population [5-7]. It is a renowned fact that learning academic content through a second/foreign language will bring many encounters where English is not the native language [8]. It is very crucial to understand first the language-related challenges that students face while learning via English to reduce the challenges of students. It is impossible to complete tasks and pass exams of university, without a grasp on these important aspects like reading writing communication and understanding. In higher education accomplished learning uniquely depends on the skill of reading and writing. Academic reading is challenging because it is longer than general reading, complicated paragraphs, and contains multifaceted sentences and challenging vocabulary [9]. This study explores challenges faced by students because of the curriculum in English. Most of the students come from non-English speaking backgrounds, they come from remote areas, and their level of English is below, in higher education medium of instruction is English, which is why they face many challenges in their academic years.

Despite extensive emphasis on English as a medium of instruction, there is limited context-specific evidence from Pakistani nursing students regarding how linguistic barriers (e.g., vocabulary, confidence, and grammar) directly affect academic performance and learning outcomes. The problem lies in students' inability to effectively comprehend and express academic content in English, leading to reduced participation and lower GPA. Therefore, this study aims to identify key language-related challenges, explore their impact on students' academic performance, and examine coping strategies used by students to overcome difficulties in English-medium curricula.

METHODS

A cross-sectional study was carried out after obtaining ethical approval from Peoples Nursing School (PSN) Liaquat University of Medical and Health Science (LUMHS), Jamshoro, to evaluate language difficulties and challenges faced by students in understanding the English curriculum at PNS LUMHS. This study was done from December 2023 to March 2024. The sample for the study was calculated using Rao software, chosen from Students of Bachelor of Science in Nursing (BSN) Generic first, second, third and fourth year, based on their availability and willingness to participate, unwilling participants were excluded, using simple random sampling. A self-constructed, structured questionnaire assessed research participants about language difficulties and challenges faced by students in understanding the English curriculum. The pre-structured questionnaire was divided into six sections. The first component included sociodemographic data of the research participants, like age, gender, and occupation. Section numbers 2, 3, 4 and 5 consist of open-ended questions and the last part of the questionnaire consists of descriptive questions. Section two consists of 09 questions regarding difficulties in communication in the English language, section three consists of 6 questions regarding understanding, section four consists of three questions regarding writing difficulties, fifth section consists of five questions regarding reading difficulties faced by students of BSN Generic. The last part of the questionnaire consisted of open-ended descriptive questions regarding strategies used by students to solve these difficulties. Informed consent was signed by every research participant. The identity of the research participants was kept confidential. Data were checked for uniformity and accuracy before being entered into a system and kept in Excel datasheets. For data analysis, SPSS version 22.0 (SPSS) was utilized.

RESULTS

Data gathered in this research revealed that students have challenges in communication, writing, reading and understanding, these categories are assessed by asking different questions through a self-constructed questionnaire. This study also focuses on strategies used by students to overcome challenges they faced because of the curriculum in English and English Medium Instruction (EMI). Participants respond through both open and close-ended questions. Responses of Communication, writing, reading and understanding, were measured through percentages and frequencies separately and represented in the form of tables, which are given below with descriptions. The result shows that they have difficulties in vocabulary, reading, communication and understanding,

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these challenges affect their GPA. Result of descriptive questions shows that respondents have major problems in speaking because of lack of confidence, shyness, lack of vocabulary and fear of making mistakes in front of people. The major findings of the study were that participants had major problems in vocabulary, speaking, reading, and lack of confidence while communicating due to lack of English proficiency. Ultimately, because of deficient English proficiency, students face many challenges during their academic years, affecting their GPA. This pie chart shows the percentages of participants from all years of BSN Generic students, 24% participants from the first year, 25% students from the second year, 27% students from 3rd and 24% participants from 4th year BSN Generic (Figure 1).

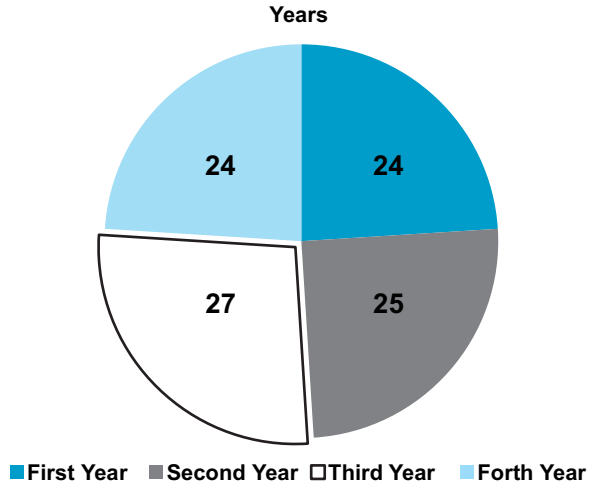

Figure 1: Percentage of Selected Participants from All Batches of BSN Generic

In this study participants belong to five different backgrounds, (59.00%) were Sindhi in this study, 17.0%. Contributors were Urdu speaking, 14.00% of the participant's mother tongue was Pashto, 4.00% were Punjabi speaking and 6.00% of the participant's mother tongue was Balochi in the study. 52.00% of participants were female and 48% of participants were male, in this study (Figure 2).

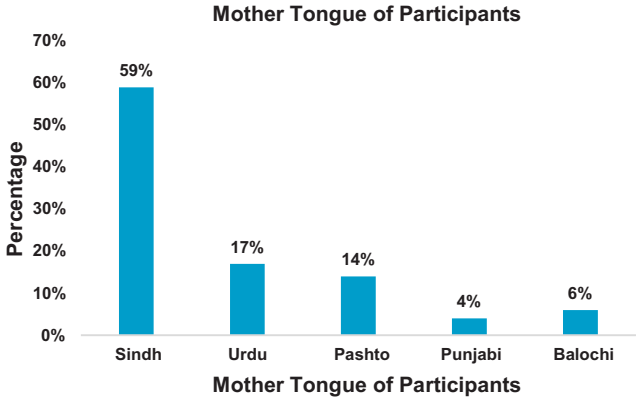

Figure 2: Mother Tongue Categories of Selected Students from Four Batches of BSN Generic

A total of 100 students of BSN Generic. The majority of the participants were female (52.0%), and male (48.0%) (Figure 3).

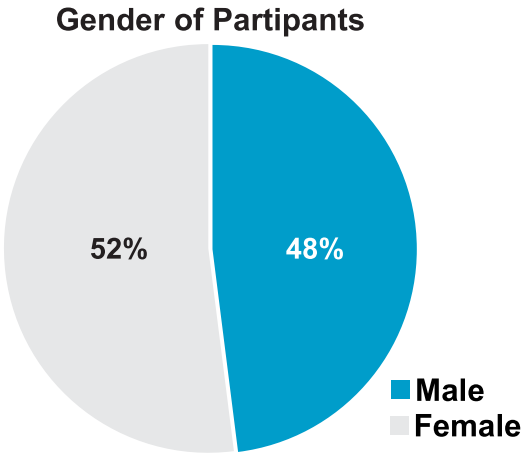

Figure 3: Percentage of Selected Gender from All Batches of BSN Generic

In this study, the first category consisted of 9 questions about communication skills, difficulties and challenges faced by students, this study's outcome showed that 86 % of students like English, and 41% of students had difficulty talking in English. 41% of students had difficulty in grammar. This study's findings showed that students also had a lack of confidence, 57% of students don't communicate in English because of shyness. The major problem faced by participants was that 57% of students face shyness because of that they don't communicate most of the time (Table 1).

Table 1: Challenges Faced in Communication

Questions	Frequency (%)
Do You Like the English Language?	
Yes	86 (86.0%)
No	14 (14.0%)
English Speaking Skill Is Difficult For You?	
Yes	41 (41.0%)
No	59 (59.0%)
Can You Speak English with Your Fellows?	
Yes	65 (65.0%)
No	34 (34.0%)
You Are Unable to Use English in All Aspects of Life Like Conversation in Real Life?	
Yes	40 (40.0%)
No	60 (60.0%)
Do You Express Your Ideas in Correct English During Lectures?	
Yes	55 (55.0%)
No	45 (45.0%)
Pronunciation of Words in English Is Difficult?	
Yes	38 (38.0%)
No	61 (61.0%)

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Do You Speak English Accurately/Grammatically Correct?	
Yes	41 (41.0%)
No	59 (59.0%)
Your Society Discourages You for English Language Learning?	
Yes	27 (27.0%)
No	73 (73.0%)
Your Shyness Prevents You from Speaking English and Afraid of Mistakes?	
Yes	57 (57.0%)
No	42 (42.0%)

The second part of the questionnaire consists of close-ended questions related to difficulties and challenges in understanding faced by students in the curriculum, this study's findings showed that the majority of students had difficulty in vocabulary, and 60% of students had difficulty in understanding specific words. Because of insufficient English proficiency and lack of academic writing skills 50% of students face difficulty in writing and cannot express their concepts completely. Study findings showed that 42% of respondent's grades were affected because of a poor understanding of English (Table 2).

Table 2: Challenges Faced in Understanding

Questions	Frequency (%)
Do You Have Any Difficulty in Understanding Specific Vocabulary?	
Yes	60 (60.0%)
No	40 (40.0%)
Do You Try to Work Out the Meaning of Difficult Words?	
Yes	76 (76.0%)
No	24 (24.0%)
Are You Capable of Making Notes by Yourself?	
Yes	77 (77.0%)
No	23 (23.0%)
Does Your GPA Get Affected Due to the Lack of Understanding English Language?	
Yes	42 (42.0%)
No	58 (58.0%)
Your Understanding of Concept Is Clear, But You Struggle to Express Them in Writing Due to Limited English Skills?	
Yes	50 (50.0%)
No	50 (50.0%)

The third part of the questionnaire consists of questions related to difficulties and challenges in understanding faced by students in writing English language (Table 3).

Table 3: Challenges Faced in Writing

Questions	Frequency (%)
Do You Feel Difficulty in Understanding Your Lecture Which Is Delivered in English Language?	
Yes	31 (31.0%)
No	68 (68.0%)
Is Writing A Difficult Task for You?	
Yes	33 (33.0%)
No	66 (66.0%)
Can You Summarize and Properly Paraphrase Your Ideas?	
Yes	55 (55.0%)
No	44 (44.0%)

The study's outcome showed that shyness and lack of confidence in participants prevent them from engaging in reading skills. 53% of participants don't speak English or read English because of shyness and 51% participants hadn't enough confidence to read in English in front of people (Table 4).

Table 4: Challenges Faced in Reading

Questions	Frequency (%)
Do You Find It Difficult to Read and Comprehend English Text?	
Yes	30 (30.0%)
No	69 (69.0%)
Do You Find It Difficult to Read English Text in Front of Bunch of People Because of Lake of Confidence?	
Yes	51 (51.0%)
No	49 (49.0%)
Does It Get Difficult for You to Understand Questions in English?	
Yes	25 (25.0%)
No	72 (72.0%)
Your Society Discourages You for English Language Learning?	
Yes	34 (34.0%)
No	65 (65.0%)
Your Shyness Prevents You from Speaking English and Afraid Of Mistakes?	
Yes	53 (53.0%)
No	47 (47.0%)

The last part of the questionnaire consists of open-ended, descriptive questions. The first question is about the most difficult aspects of the English language, like writing, reading, speaking or understanding. 56% of participants responded that speaking is most difficult due to lack of confidence, and lack of vocabulary, participants also responded that speaking is most difficult because of improper sentence making. Writing issue was the second major problem for participants, 22% of participants responded that writing is a major task for them, because of vocabulary and somehow because of spelling mistakes. This study's results showed reading difficulties are the third number, 18% of participants had difficulties in reading because of inappropriate pronunciation and unawareness of the meaning of difficult words. 5% of contributors had difficulty in understanding (Table 5).

Table 5: Analysis of Descriptive Questions

Difficulties	Percentage	Total
Speaking		
Because of Lack of Confidence	29%	56%
Because of a Lack of Vocabulary	17%	
Because of Grammatical Mistakes/ Sentence Making.	10%	

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Writing		
Because of Spelling Mistakes.	10%	22%
Because of Grammatical Mistakes.	12%	
Reading		
Because of Pronunciation.	8%	18%
Because of Shyness.	10%	
Understanding		
Because of Lack of Knowledge	5%	5%

DISCUSSION

This study's results explored, that the major problem was speaking that faced participants and the causes were lack of confidence, lack of practice, fear of committing mistakes, not having an encouraging environment, lack of rich vocabulary, and the inability to use grammatical patterns as the key difficulties. Participants face many challenges while communicating in English. These difficulties inhibit the learners from developing their fluency in speaking English. These findings also relate to the results of the study conducted in Turkey The study's results exposed that speaking English and writing were found to be the most perplexing areas of EMI [10]. Half of the participants responded that their speaking and communication skills were weak because of a lack of confidence and shyness. It was identified by the researchers that some students were encountering several issues with the skills of Speaking and Listening when the research was undertaken. Another major problem divulged in this study's result is lack of vocabulary. Research shows that pupils' short-term memorisation of words reveals their technical memory deficits [11, 12]. Another important factor is academic writing, as 22% of participants' report having trouble with it. A study conducted at the University of China aligns with this study, they reported that students need specific language support, particularly the prolific skills of English writing and speaking. Participants responded that they didn't completely understand the lecture due to a lack of vocabulary, they didn't know the meaning of specific words which is used in the lecture. Eventually, these challenges and difficulties affect their grade point average GPA. Students had difficulty in writing, they made grammatical mistakes, spelling mistakes, don't make proper sentences. In summary, this study's findings are in line with other research on EMI in the literature, which revealed that EMI leads to poor scholastic outcomes in the long run as well as feelings of worry, annoyance, tension, dread, and humiliation. Furthermore, during lectures, EMI denies students their fundamental rights to comprehension, interaction, communication, discussion, and inquiry. Having a strong grasp of English is vital for building a reputable academic profile and accessing top career choices [13-16]. The restrictive and dominating nature of the classroom setting discourages students from actively contributing to the class activities [17]. Based on the results, a lesson plan was developed to conduct sessions for students. After analysis of the results, findings showed that most of the students had difficulties in vocabulary, and a major problem was speaking in English. Lack of vocabulary is directly proportional to speaking in English because if students have enough vocabulary their speaking skills can be improved [18]. According to study findings, other causes of difficulties in speaking skills are lack of confidence, shyness and deprived sentence-making competencies [19, 20]. Based on the findings, we plan sessions for students on strategies to enhance vocabulary, speaking and reading skills and also on different strategies to boost confidence for communication in English, as it is also the objective of our study to work on strategies and teach effective strategies to participants. So, we conducted a session on it very effectively. In the session we gave a general introduction to the English language and cleared concepts about the importance of English, then we divided students into groups and engaged them in the activity of searching strategies, each group searched at least one effective and useful approach and one homonym, by doing this students actively participate in session, and at last, we also impart them strategies to solve challenges and enhance English proficiency, because in university whole curriculum is in English and recommended medium of instruction is also English. That session was very effective and useful for students, analysed by student's responses.

The study is limited by its small sample size and single-institution setting, reducing generalizability. The use of a self-structured questionnaire without validation may affect reliability. Future studies should include multi-center data, larger samples, and standardized tools. Additionally, interventional studies focusing on language training programs and their impact on academic outcomes are recommended.

CONCLUSIONS

It was concluded that the majority of students have problems in vocabulary and the majority of contributors face challenges because of shyness and lack of confidence. Some participants had good writing skills. The major challenge observed from the study's findings is that participants have major problems speaking in English due to a lack of self-reliance, shyness, lack of vocabulary, absence of fluency and sentence-making problems.

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Authors' Contribution

Conceptualization: I
Methodology: I, HBC, SK, RD
Formal analysis: SK
Writing and Drafting: HBC, AHB, MUH
Review and Editing: HBC, AHB, MUH, I

All authors approved the final manuscript and take responsibility for the integrity of the work.

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The Effect of Caffeinated Coffee on Tears Secretion among Young Adults

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ABSTRACT

Caffeine, the most often taken psychoactive stimulant, is said to have contradictory effects on tear film dynamics. **Objectives:** To determine the effect of caffeinated coffee on tears secretion. **Methods:** Quasi experimental study was conducted from January 2023 to May 2024 at Superior University Lahore including 86 subjects of ages between 18-35 years by using convenient sampling technique. After visual acuity assessment, tear secretion of participants was checked by using Schirmer test strips. Tears secretion of all the subjects was noted before and after intake of caffeinated coffee by using Schirmer test strips. Descriptive statistics and T test was used for analysis of data by using SPSS version 25.0. **Results:** Before intake of coffee, 14(16.3%) showed tear secretion in the range of 5-15 mm, 21(24.4%) were in range of 16-25mm while 51(59.3%) were in the range of 26-35mm. Tear secretions after 30 minutes of coffee intake in 23(26.7%) subjects were in the range of 5-15mm, 20(23.3%) were in the range of 16-25mm while 43(50%) were in the range of 26-35mm. Similarly tear secretions after 90 minutes of coffee intake in 35(40.7%) were in the range of 5-15mm, 32(37.2%) were in the range of 16-25mm while 19(22.1%) were in the range of 26-35mm. Tear secretions before and after intake of coffee was found to be statistically significant i.e. $p<0.05$. **Conclusion:** A decreasing trend was observed in tear secretion levels at 30 and 90 minutes following the intake of caffeinated coffee and normal prior to coffee consumption.

INTRODUCTION

Caffeine, a colourless, bitter-tasting white alkaloid, is the most widely used stimulant globally. It can be found in coffee, tea, cocoa, yerba mate, guarana, and many other food and drink items. Coffee beans are the main source of caffeine, and even decaffeinated coffee contains some residual caffeine. Caffeine influences the central anxious framework, lifting heart rate, blood weight, and readiness, whereas moreover acting as a bronchodilator and diuretic. Aside from its interaction with adenosine, caffeine has additional physiological effects due to its metabolites, leading to increased production of stomach acid, pepsin, and blood sugar, elevated fatty acid, cortisol, and adrenaline levels, and reduced calcium levels, potentially causing bone loss. Therefore, caffeine intake may exacerbate existing health conditions or contribute to certain diseases. Pregnant ladies and people with tall blood weight, cardiovascular issues, diabetes, open-angle glaucoma, or insomnia are advised to avoid coffee consumption. However, caffeine can also be utilized beneficially. It is used to treat respiratory issues in newborns and acts as an adjuvant in various medicinal compositions counting analgesics and antipyretics. In its normal shape, natural coffee might offer a few cardioprotective impacts for people without hypertension [1, 2]. Pharmacologically, caffeine acts as an antagonist to adenosine receptors, influencing multiple organ systems. Historically, it was recognized for its therapeutic potential, including treating asthma. Today, caffeine is used medically for conditions such as migraines and newborn apnea, and as an adjunct in pain management. While its effects on circulation and nerves are well-studied, its impact on ocular physiology is less understood, necessitating further research [3]. Coffee's impact on tear production and dry eye conditions remains contentious.

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Dry eyes stem from insufficient tear production or unstable tear film, potentially leading to discomfort and vision issues. Severe cases can even cause corneal ulcers and increase susceptibility to infections. Clinical assessments like the Schirmer test and tear film fluorophotometer are used but yield conflicting findings on coffee's effects. Some suggest coffee might increase tear production and protect against dry eyes, while others argue the opposite. To clarify these discrepancies, more research is needed [4]. Dry Eye Disease (DED) is a prevalent chronic condition characterized by disruptions in the tear film and ocular surface, affecting 5% to 50% of adults worldwide. [5] It significantly impairs quality of life, causing discomfort and fatigue, limiting daily activities like driving and reading, and impacting overall well-being and productivity [6]. Medical students, prone to high stress levels, often adopt habits such as increased caffeine consumption and prolonged use of digital devices for academic purposes. On average, adults in Western countries consume 200 to 300 mg of caffeine daily [7, 8]. Caffeine enhances alertness by blocking adenosine A2A receptors, reducing fatigue. Coffee is the primary source of caffeine for most adults, contributing about 80% to their daily intake. Green tea is also popular for its caffeine content, boasts additional health benefits like antioxidants and antimicrobial properties. Despite having higher caffeine levels per dried weight than coffee, green tea generally does not induce the same arousal effects [9]. Caffeine enhances alertness and reduces daytime sleepiness by blocking adenosine receptors. Research shows it improves cognitive function and attention during sleep deprivation with doses ranging from 200 to 600 mg [10]. Understanding the effects of sustained high caffeine intake on physiology, including blood pressure and decision-making, requires further study, particularly considering habitual caffeine use patterns [11]. Caffeine has been previously demonstrated to impact the eyes in numerous ways such as corneal deformities have been reported to be the result of caffeine intake [12]. Moreover, several studies suggest higher coffee intake may elevate intraocular pressure: potentially increasing glaucoma risk due to caffeine's role as an adenosine receptor antagonist [13, 14]. On the contrary, the protective roles of caffeine are also highlighted by several studies. Caffeine's impact on choroidal thickness and visual performance, including pupil size and accommodation, remains unclear and may affect reading speed and visual quality, especially in those with vision challenges [16]. Conflicting research on caffeine's effects on tear production further complicates its influence on visual performance.

Despite extensive research on caffeine's systemic and ocular effects, its specific impact on tear secretion remains inconclusive, with studies reporting both stimulatory and inhibitory effects on tear production. Additionally, limited evidence exists on the short-term temporal changes in tear secretion following standardized caffeinated coffee intake, particularly among young adults. This creates a gap in understanding whether caffeine contributes to dry eye symptoms or protective mechanisms. Therefore, the present study aimed to evaluate the short-term effect of caffeinated coffee on tear secretion using the Schirmer test and to clarify its role in altering tear film dynamics.

METHODS

A quasi-experimental study was conducted at Superior University Lahore to investigate the effect of coffee on tear secretion. The study was conducted between January 2023 to May 2023. Participants were recruited using a non-probability convenient sampling method and included 86 staff and students aged 18-35 years with normal vision (6/6 acuity). Sample size was calculated using online sample size calculation software. Smokers, alcohol consumers, elderly patients, pregnant women, and those with ocular or systemic diseases were excluded. Written and verbal consent was taken from the participants before the data collection. All the measurements regarding tear secretion measurement were made during early hours of the university timing in a controlled temperature environment. Tear secretion was assessed using Schirmer test strips to evaluate changes in tear production levels. Measurements were taken at three intervals: prior to coffee consumption, 30 minutes after intake, and 90 minutes after intake. The coffee preparation involved dissolving 4 grams of Nescafe granules in 150 ml of warm water to ensure consistency in the caffeine dose provided to all participants. All the data collected were analyzed using SPSS Version 25.0. Descriptive statistics and t-test were used to obtain results.

RESULTS

Out of total 86(100%) subjects, 72(83.7 %) were in age group of 18-25 years, 11(12.8%) subjects were in age group of 26-35 years and 3(3.5%) were in age group of 31-35 years and frequency of male was 31(36%) and for female 55(64%). Out of total 86(100%) subjects, before intake of coffee, 14(16.3%) subjects were having tear secretion in the range of 5-15mm, 21(24.4%) subjects were having tear secretion in the range of 16-25mm while 51(59.3%) were having the tear secretion in the range of 26-35mm.

Table 1: Tear Secretion before Intake of Coffee

Tear Secretion	Frequency (%)
5-15mm	14 (16.3 %)
16-25mm	21(24.4%)

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26-35mm	51(59.3%)
Total	86(100.0%)

After 30 minutes of coffee intake, out of total 86(100%) subjects, tear secretion in 23(26.7%) subjects were in the range of 5-15mm, 20(23.3%) subjects were having tear secretion in the range of 16-25mm while for 43(50%) were having the tear secretion in the range of 26-35mm.

Table 2: Tear Secretion after 30 Minutes of Intake of Coffee

Tear Secretion	Frequency (%)
5-15mm	23(26.7%)
16-25mm	20(23.3%)
26-35mm	43(50.0%)
Total	86(100.0%)

After 90 minutes of coffee intake, out of total 86(100%) subjects, tear secretion in 35(40.7%) subjects were in the range of 5-15mm, 32(37.2%) subjects were having tear secretion in the range of 16-25mm while for 19(22.1%) were having the tear secretion in the range of 26-35mm.

Table 3: Tear Secretion after 90 Minutes of Intake of Coffee

Tear Secretion	Frequency (%)
5-15mm	35(40.7%)
16-25mm	32(37.2%)
26-35mm	19(22.1%)
Total	86(100.0%)

The mean of tear secretion before intake of coffee was 2.43 ± 0.760 and after 30 minutes coffee intake mean value was 2.23mm ± 0.850. After 90 minutes of intake of coffee mean value was 1.81mm ± 0.775. The results indicate a significant decrease in tear secretion after coffee consumption. The average tear production decreased from 2.43 mm before coffee intake to 1.81 mm after 90 minutes, suggesting a consistent effect of coffee on tear reduction. The standard deviation remained relatively consistent, indicating that the effect was uniform across the study participants.

Table 4: Comparison of tear secretion before and after coffee intake among study participants

Tear Secretion	Number of Participants	Mean ± SD	p-Value
Tear Secretion Before Intake of Coffee	86	2.43 ± 0.760	p<0.05
Tear Secretion After 30 Minutes of Intake of Coffee	86	2.23 ± 0.850	p<0.05
Tear Secretion After 90 Minutes of Intake of Coffee	86	1.81 ± 0.775	p<0.05

DISCUSSION

Caffeine is a naturally occurring stimulant found in various plants, including coffee beans, tea leaves, cocoa beans, and kola nuts. The results of the present study showed that the mean tear secretion before intake of coffee was 2.43 ± 0.760 while tear secretions after 30 minutes and 90 minutes of coffee intake was 2.23 ± 0.850 and 1.81 ± 0.775 respectively. This shows reduction in tear secretion values after the consumption of caffeinated coffee. The results of this study are in accord with the study where the recorded values for tear secretions were lower after caffeine intake, implying that caffeine may limit tear secretion in certain groups of individuals [17]. However, contradictory results were reported in a study that found a significant increase in Schirmer 1 scores; therefore, caffeine stimulated tear secretion in healthy people without a dry eye [18]. The variation in outcomes may be due to differences in caffeinated products used in various studies, caffeine content in the products tested, and disparity in participants' characteristics to give credence to the extent of complexity of effects of caffeine on tear film. However, the current study specifically only investigated the short-term effects of coffee consumption, and, therefore, differences due to stress, usage of electronic devices, and metabolism differ in everybody. A systematic review of two population-based studies showed that increased caffeine consumption is very slightly linked to dry eyes [19] and that the frequency increases with caffeine consumption, especially among female [17]. The patterns of variations here noted could have been attributable to hormonal effects on tearing, although these aspects in the present research were not evaluated. Remarkably, data also showed that instances of caffeine use were again associated with healthier ocular surface and reduced tearing inflammation, thus proposing an anti-inflammatory function profile for caffeine that requires further exploration [20]. Further longitudinal research on a broad population is necessary on factors such as sleep and usage of electronics to have a better understanding of these dynamics.

This study was limited by its small sample size, single-center design, and use of non-probability convenient sampling, which may affect generalizability. Only short-term effects were assessed, and confounding factors such as screen time, hydration status, and stress were not controlled. Future studies should include larger, multi-center samples with randomized designs and evaluate long-term caffeine exposure. Incorporating objective measures like tear film stability and osmolarity would provide more comprehensive insights.

CONCLUSIONS

This study demonstrated a significant decrease in tear production after the consumption of caffeinated coffee in young adults. The findings suggest a potential link between dry eye symptoms and caffeine intake. Further longitudinal studies are recommended to investigate the underlying mechanisms and to evaluate whether individuals with dry eye symptoms might benefit from reducing caffeinated coffee intake or opting for decaffeinated alternatives.

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Authors' Contribution

Conceptualization: AB
Methodology: SS
Formal analysis: MH, I
Writing and Drafting: AS, I
Review and Editing: AS, I, MH, AB

All authors approved the final manuscript and take responsibility for the integrity of the work.

Conflicts of Interest

The authors declare no conflict of interest.

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Original Article

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Factors Delaying Antenatal Management Leading to Maternal Morbidity: Empirical Evidence from Tertiary Care Hospital KPK

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ABSTRACT

Antenatal care is a branch of preventive medicine focused on the early detection and prevention of pregnancy disorders. **Objective:** To determine the frequency of factors responsible for delaying antenatal management leading to maternal morbidity. **Methods:** This cross-sectional was conducted at Khyber Teaching Hospital. In this study, a total of 151 patients were observed. Before data collection, approval was obtained from the hospital's ethical committee after approval of the synopsis. All the admitted patients (pregnant women) presented to labor room in Khyber Teaching Hospital meeting the inclusion criteria were recruited for the study explaining the objective of the study to every patient. Inform consent was obtained from the patients. Patients were thoroughly examined according to the routine health assessment protocol of the hospital. Data were collected with the help of a Performa attached. **Results:** The mean age was 30 ± 12.45 years. 67% of patients were from rural areas while 50 (33%) patients were from urban areas. 65 (43%) patients were un-educated, 53 (35%) patients had primary to secondary education and 33 (22%) patients had an education level above secondary. There was a significant association (p-value=0.001) between the distance from the hospital and delays in antenatal care. **Conclusions:** It was concluded that antenatal care is essential for reducing maternal and fetal mortality, particularly in developing regions where the maternal mortality ratio remains significantly high. This study identifies key barriers to Antenatal care utilization in Pakistan, such as low education levels, poor socioeconomic status, geographical inaccessibility, and systemic healthcare issues.

INTRODUCTION

All pregnant women face the risk of obstetrical complications, with the majority occurring during labor and delivery, potentially resulting in maternal morbidity and mortality. In our context, maternal mortality is significantly underestimated [1]. Antenatal care is a branch of preventive medicine focused on the early detection and prevention of pregnancy disorders [2]. It is considered essential to modern obstetrics. This widely adopted strategy promotes skilled care during childbirth and enhances the health of pregnant women [3]. Antenatal care (ANC) is crucial for preventing both maternal and fetal mortality and morbidity. It serves as a vital strategy to enhance maternal and infant health. This improvement can be assessed by calculating the maternal mortality ratio (MMR), which is defined as "the number of maternal deaths during a specified period per 100,000 live births within the same timeframe [4]. The global maternal mortality ratio (MMR) stands at 210 per 100,000 live births. Despite global reductions since 1990, the MMR remains 15 times higher in developing regions compared to developed ones [5]. The number of women utilizing antenatal care is low in many areas and needs to be increased to improve overall health outcomes. Several factors can influence the use of antenatal care services, including literacy levels, awareness of the importance of antenatal care, the number of available facilities, distance from these facilities, socioeconomic status, and more [6]. Antenatal care has reduced maternal and perinatal morbidity and mortality. Low levels of antenatal care are associated with higher perinatal mortality rates [7]. During pregnancy, ensuring maternal health through a proper diet is essential for delivering a healthy baby [8]. Maternal morbidity is

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reduced in women who maintain a good diet, as complications like pre-eclampsia and premature birth occur less frequently [9]. Infants born to mothers who do not receive prenatal care during pregnancy are over twice as likely to die during infancy compared to infants whose mothers receive prenatal care. This association holds regardless of other factors such as the child's sex, assistance during delivery, birth order, mother's age at childbirth, nutritional status, education level, and household living conditions. Prenatal care significantly reduces the risk of infant mortality, even when considering other potential risk factors [10].

Although antenatal care (ANC) is widely recognized as essential for reducing maternal morbidity and mortality, there remains limited context-specific evidence identifying and quantifying the key factors responsible for delays in ANC utilization, particularly in tertiary care settings of developing regions like Pakistan. Previous studies have highlighted socioeconomic, educational, and geographical barriers, but their relative contribution and interaction in causing delays are not fully understood. This gap hinders the development of targeted interventions to improve maternal health outcomes.This study aims to determine the frequency of factors responsible for delaying antenatal management leading to maternal morbidity in the tertiary hospital of Khyber Pakhtunkhwa.

METHODS

This cross-sectional was conducted at Khyber Teaching Hospital. A convenient sampling approach was applied for the sample selection. Around 1000 patients visited the study location in the study period, out of these around 50% of the patients have the said problem. So according to Krejcie and Morgan [11], the estimated sample size was 217, but due to homogeneity in the units and inclusion criteria, a maximum of 151 samples was selected. Before data collection, approval was obtained from the hospital's ethical committee after approval of the synopsis (CPSC/REU/OBG-2015-020-6585). All the admitted patients (pregnant women) presented to labor room in Khyber Teaching Hospital meeting the inclusion criteria were recruited for the study explaining the objective of the study to every patient. Information consent was obtained from the patients. Patients were thoroughly examined according to the routine health assessment protocol of the hospital. Data were collected with the help of a Performa attached. The reliability of the questionnaire was tested using Cronbach's alpha, which showed a satisfactory reliability level of 0.86. The significance of the associations between factors was using the chi-square test of association. $X2=\Sigma(oij-eij/eij)^2$ [12].

RESULTS

A total of 151 patients were included in the study and analysis. The mean age was 30 ± 12.45 years. 79 (52%) patients were primi-para, 54 (36%) were multi para and 18(12%)patients were grand multi-para(Table 1).

Table 1: Age, Education and Parity Distributions of Patients(151)

Age Distribution	
Variables	**Frequency (%)**
Age	
18-30 Years	103 (68%)
31-44 Years	48 (32%)
Total	151 (100%)
Education of the Patients	
Un-Educated	65 (43%)
Primary to Secondary Educated	53 (35%)
Above Secondary	33 (22%)
Total	151 (100%)
Parity Distribution	
Primi Para	79 (52%)
Multi Para	54 (36%)
Grand Multi Para	18 (12%)
Total	151 (100%)

A residential area of 151 patients was analyzed as 101(67%) patients were from rural areas while 50(33%)patients were from urban areas. 58 (38%) patients were previously delivered by dai, 60 (40%) patients were previously delivered by nurses, 33 (22%) patients were previously delivered by LHW(Table 2).

Table 2: Previously Delivery(n=151)

Previously Delivery	Frequency (%)
Dai	58 (38%)
Nurses	60 (40%)
Lady Health Workers (LHW)	33 (22%)
Total	151 (100%)

Sixty-five (43%) patients were un-educated, 53 (35%) patients had primary to secondary education and 33 (22%) patients had an education level above secondary. The most common factor delaying the management of antenatal care was low education level as 97 (64%) patients were below middle and 54(36%) patients were above the middle (Table 3).

Table 3: Factors of Delaying in the Management of Antenatal Care

Factors of Delaying		Frequency (%)
Education Level	Below Middle	97 (64%)
	Above Middle	54 (36%)
Socio-Economic Status	≤ 20,000/ Rs	94 (62%)
	>20,000/ Rs	57 (38%)
Distance From Hospital	< 20km	63 (42%)
	>20km	88 (58%)
Health System	Satisfactory	53 (35%)
	Non-Satisfactory	98 (65%)
Cultural Constraint	Yes	35 (23%)
	No	116 (77%)

85 (56%) patients had a monthly income range of Rs

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≤15,000/-. 57(38%) patients had a monthly income range of Rs 15,000 -50,000/- while 9 (6%) patients had a monthly income range of Rs. >50,000/-. Low socio-economic status as 94(62%) patients had monthly income <20,000Rs and 57 (38%) patients had monthly income Rs >20,000. There is a significant association (p-value=0.001) between the distance from the hospital and delays in antenatal care. The data shows that for those who live less than 20 km from the hospital, 63 out of 151 reported delays (23 decided by the husband, 26 by the mother-in-law, and 14 by self). In contrast, for those living more than 20 km away, 88 out of 151 reported delays (33 decided by the husband, 37 by the mother-in-law, and 18 by self). The p-value of 0.001 indicates that the distance from the hospital significantly impacts the likelihood of delays in receiving antenatal care, with longer distances contributing to more delays. Un satisfactory health system as 98 (65%) patients had an unsatisfactory health system while 53(35%) patients had a satisfactory health system and cultural constraints as 35 (23%) patients had cultural constraints while 116 (77%) patients didn't have cultural constraints. The p-value of 0.03 suggests that dissatisfaction with the health system contributes to more significant delays in antenatal care (Table 4).

Table 4: Stratification of Factors of Delaying in Management of Antenatal Care Concerning Decision Makers

Factors pf Delaying		Husband	Mother in Law	Self	Total	*p-value
Education level	Below Middle	36	41	20	97	0.990
	Above Middle	20	22	12	54	
	Total	56	63	32	151	
Socio-Economic Status	≤20,000/ Rs	35	39	20	94	0.999
	>20,000/ Rs	21	24	12	57	
	Total	56	63	32	151	
Distance from Hospital	< 20km	23	26	14	63	0.001
	> 20km	33	37	18	88	
	Total	56	63	32	151	
Health System	Satisfactory	20	22	11	53	0.030
	Non-Satisfactory	36	41	21	98	
	Total	56	63	32	151	
Cultural Constraint	Yes	13	15	7	35	0.997
	No	43	48	25	116	
	Total	56	63	32	151	

DISCUSSION

Antenatal care (ANC) is crucial for preventing both maternal and fetal deaths and complications. It plays a vital role in enhancing maternal and infant health, which can be assessed by calculating the maternal mortality ratio (MMR). Despite global declines since 1990, the maternal mortality ratio (MMR) remains 15 times higher in developing regions compared to developed regions [13]. A woman's lifetime risk of maternal death is significantly influenced by her economic and social environment, the number of pregnancies she has had, and the availability of maternal health services. Women in developing countries often face challenges in maintaining good health, especially if they are poor [14]. The literacy rate among females in Pakistan is one of the lowest in the world at 28%, which keeps them uninformed about reproductive rights and health facilities [15]. In our study, most of the patients (67%) were from urban areas and were uneducated, lacking awareness of antenatal care. This lack of awareness is one of the primary reasons for maternal deaths. Complications such as a ruptured uterus were less frequent among urban patients because they had access to qualified medical personnel during delivery. In contrast, rural patients faced difficulties finding qualified medical personnel at the time of delivery due to the lack of mismanagement of traditional birth attendants (dais) [16]. There are numerous obstacles to the early initiation and use of antenatal care. Among these, documented organizational barriers include financial challenges, such as the lack of health insurance [17]. Several key factors contributing to delays in the initiation and utilization of antenatal care were identified. The most prevalent factor was a low level of education, with 64% of the patients having an educational attainment below middle school. Low socioeconomic status was also a significant barrier, as evidenced by the fact that 62% of the patients had a monthly income of less than Rs 20,000. These findings are consistent with previous research indicating that educational attainment, socioeconomic status, geographical accessibility, and healthcare system quality are critical determinants of antenatal care utilization [18, 19]. The study also highlighted systemic issues within the healthcare system, with 65% of the patients reporting dissatisfaction with the health system. The association between low educational levels and reduced healthcare utilization is well-documented, suggesting that educational interventions may be an effective strategy to improve antenatal care uptake [20]. Moreover, addressing financial barriers through policy measures such as subsidized healthcare and transportation vouchers could mitigate some of the socioeconomic challenges identified in this study [21]. Our findings on geographical barriers align with studies such as those conducted in rural Mali and Tanzania, which also found that long distances to healthcare facilities significantly reduce access to antenatal care. Furthermore, the dissatisfaction with the healthcare system reported by a majority of the participants indicates a need for systemic improvements. Ensuring better quality of care, reducing waiting times, and enhancing the patient-provider relationship could improve perceptions of the healthcare system and encourage earlier and more

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consistent use of antenatal services [22]. Geographical barriers also played a crucial role, with 58% of the patients living more than 20 kilometers from the nearest hospital. This long-distance likely contributes to both the financial burden and the time required to access care. Cultural barriers, while less prevalent, still affect a significant minority of patients and should be addressed through culturally sensitive healthcare practices and community engagement initiatives.

In the current study, cultural constraints were noted as a barrier by 23% of the patients, underscoring the complex interplay of social factors that influence healthcare utilization. Overall, this study highlights the multifaceted nature of barriers to antenatal care and underscores the importance of comprehensive strategies that address educational, socioeconomic, geographical, systemic, and cultural factors. Future research should focus on intervention studies to evaluate the effectiveness of targeted strategies in overcoming these barriers and improving antenatal care utilization rates.

CONCLUSIONS

It was concluded that antenatal care is essential for reducing maternal and fetal mortality, particularly in developing regions where the maternal mortality ratio is significantly high. This study identifies key barriers to ANC utilization in Pakistan, such as low education levels, poor socioeconomic status, geographical inaccessibility, and systemic healthcare issues.

Authors' Contribution

Conceptualization: SS[1]
Methodology: SS[1], SS[2]
Formal analysis: SS[1], ZI
Writing and Drafting: ZI
Review and Editing: ZI, SS[1], SS[2]

All authors approved the final manuscript and take responsibility for the integrity of the work.

Conflicts of Interest

All the authors declare no conflict of interest.

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Systematic Review

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The Role of Propolis in Muscle Repair: A Systematic Review

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ABSTRACT

Propolis a natural substance that comes from bees possesses various medicinal properties including. antioxidant, anti-inflammatory, and beneficial in the metabolic system. Muscle repair is crucial for maintaining muscle function, especially in cases of injury, oxidative stress, and ageing which cause muscle loss and dysfunction. Propolis has emerged as a potential alternative treatment for muscle repair. **Objective:** To investigate the impact of propolis on muscle repair. **Methods:** A systematic literature review was conducted using databases such as PubMed, Google Scholar, Research Gate, and Cochrane Library. The PRISMA guideline was followed for analysis. The approach uses keywords such as propolis, muscle, and skeletal muscle. Articles were selected based on sample characteristics, intervention, and muscle repair parameters. The searched keywords include propolis, muscle, and skeletal muscle. Evaluation parameters included oxidative stress markers, inflammation, molecular mechanisms, muscle capillaries, muscle mass, strength, and function. **Results:** The initial search uncovered 7676 articles, after further screening, it comprised a total of 21 studies that were included in the results. The collected articles summarized the main mechanism of action of propolis in muscle repair, primarily due to its antioxidant, and anti-inflammatory properties, and its effect on glucose metabolism, which influences muscle fatigue, strength, and mass. **Conclusions:** It was concluded that propolis as a bee's natural product, has several advantages in muscle repair due to its multiple mechanisms of action, encompassing antioxidants, anti-inflammatory properties, impact on muscle glucose metabolism, and stimulation angiogenesis.

INTRODUCTION

Muscle damage can result from inflammation caused by stress, trauma, and ageing leading to muscle pain, discomfort, weakness, and impaired function. Skeletal muscles are crucial for mobilization and energy metabolism. Disorders in skeletal muscles can hinder mobility and disrupt energy metabolism. Muscle damage leads to systemic disorders due to important receptors on muscle cells [1]. In addition, muscle damage also causes disorders in the neuromuscular system, causing fatigue and disrupting activities [2]. Diseases that cause muscle damage are numerous and varied. These diseases can originate directly from the muscle or be related to other systems. Some diseases associated with muscle damage are due to metabolic disorders (e.g. diabetes and obesity), hormonal imbalance (e.g. menopause) and nerve damage in sciatic injuries [1, 3]. Approximately 11.4% of diabetics from a population sample in Italy have muscle disorders, conversely, a lack of muscle mass will increase the incidence of type 2 diabetes [4, 5]. Musculoskeletal health problems also occur in 70% of women who experience menopause due to hormonal imbalance, which causes damage to the skeletal muscles [6]. It is not only diseases that cause muscle damage, but excessive activities that induce stress such as training or sports in athletes can also cause muscle damage [7]. In ageing, there is also a condition of muscle weakness and a decrease in quality called sarcopenia [8, 9]. Sarcopenia is also related to other conditions such as menopause, obesity, cardiovascular [9-11] and type 2 diabetes. Muscle repair is influenced by various factors like age, nutrition, physical activity, and overall physical health. Indicators of muscle repair include myoblasts activity, which are muscle progenitor cells that

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play a role in muscle cell repair, and the balance of anti-inflammatory and pro-inflammatory cell activity [12]. A well-functioning circulatory system and capillary network are essential for efficient muscle repair. Muscle mass and strength are key parameters for assessing muscle improvement. Various methods like medication, exercise, physical therapy, and supplementation are used for muscle repair, with a natural supplement like propolis gaining popularity. Propolis also known as bee glue, is a bee product used to protect bee hives and contains active ingredients with antioxidants and anti-inflammatory properties beneficial for muscle damage [3, 12]. So far the role of propolis in muscle repair works largely through its anti-oxidant and anti-inflammatory effects for muscle health. While studies have extensively researched the effects of antioxidants, oxidative stress, and inflammation on repair, few have focused on the direct impacts of propolis on muscle function improvement. Muscle function parameters that are usually assessed are muscle strength and locomotion function [13].

Despite growing evidence on the antioxidant and anti-inflammatory properties of propolis, there is limited high-quality human-based research directly evaluating its effects on muscle repair and functional outcomes. Most existing studies rely on animal models or in vitro findings, with inconsistent results regarding muscle strength and performance in humans. Additionally, variability in propolis composition and dosage limits the generalizability of findings. Therefore, this study aims to systematically evaluate the role of propolis in muscle repair, focusing on its mechanisms, effectiveness, and impact on muscle function, strength, and metabolic regulation.

METHODS

The study followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines established by Page *et al.*, [14]. The patient/population, intervention, comparison and outcomes (PICO) approach was utilized to conduct various databases, such as PubMed, Google Scholar, Research Gate, and the Cochrane Library to identify relevant English-language publications. All the published articles between 2006 to 2023 were selected to conduct this systematic review. Comprehensive search techniques were employed to identify studies meeting the eligibility criteria, which include experimental studies with muscle repair outcomes, accessible articles, full-text articles published in English, and no limitation of publication year. The initial keyword used was "propolis" followed by additional keywords such as “muscle”, “skeletal muscle”, “muscle repair”, “human”, “rodent”, “mice” and “rat” using the AND/OR operator. All selected studies were reviewed based on predefined inclusion and exclusion criteria [13]. This research focused on original experimental studies on animal models, cell cultures, or human populations in muscle damage conditions. The study included an intervention involving propolis administration. Articles that did not meet the specified criteria were excluded. Data collected from eligible articles included sample models, intervention details, and muscle improvement parameters, which are indicators of molecular or functional muscle repair progress. The PRISMA process of article selection is depicted. The initial literature search yielded 7676 articles from various search engines. Among these, 53 articles with duplicate titles were excluded. Upon screening the titles and abstracts, 157 articles were identified for further review. Subsequently, 90 articles were excluded as they did not meet the inclusion criteria or were not closely related to the topic of interest. Out of the remaining 67 articles, 46 were further excluded due to non-English language, incomplete design explanations, or sample and research outcome discrepancies. Finally, 21 articles were included in this literature review based on meeting the desired criteria (Figure 1).

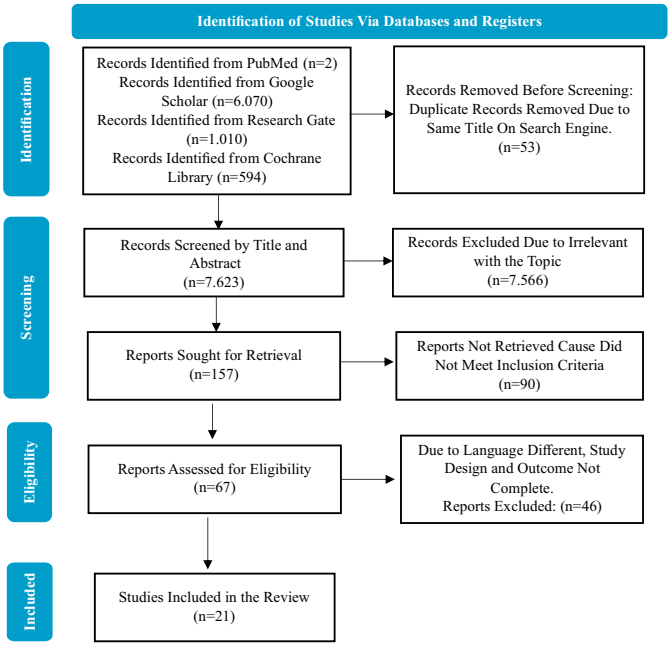

Figure 1: Article Selection Process Following PRISMA Method

RESULTS

The selected articles encompassed research published from 2006 to 2023, involving human subjects, rodents (mice or rats), and in vitro and ex vivo cell cultures. Various interventions were administered to the research subjects to influence muscle conditions, including effects on muscle cells, metabolism, and muscle function. These interventions ranged from systemic interventions like high glucose level, age-related factors, and injury models such as ischemic and nerve injuries impacting muscle function. Additionally, stress induction in muscle was also achieved

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through exercises, chemokine, and compound induction leading to heightened oxidative stress. These interventions typically resulted in increased inflammation and oxidative stress in the muscles. Infection, congenital conditions, and genetic engineering related to muscle damage were excluded from this study. The results of 21 articles related to human subjects were summarized in table 1.

Table 1: The Role of Propolis Intervention in Studies

References	Sample/Population	Sample Induction	Propolis Intervention	Muscle Repair Parameter
Human Subjected				
[15]	Adult Men	Practice 3 Sessions/Week, for 30 Days	Propolis 70 mg/day for 30 Days	Reduce Pain Caused by Intense Exercise Decreases Inflammatory Activity
[16]	Men Military Cadets	The Cooper Test (12 Minutes of Running and Sprinting Based On Anaerobic Test Results)	Single Dose of 450 mg Propolis, 2 Times/Day for 4 Weeks	Reduces Oxidative Stress Index Increases Antioxidant Activity Reduces Pro-Inflammatory Activity. No Significant Impact On Fatigue Index
[17]	Young Adult Male	100 Repetitions of Maximum Concentric Knee Joint Extension Voluntarily to Induce Muscle Fatigue.	Brazilian Propolis (BP) Supplement:787.5 mg (1^{st} Period)100 mg in (2^{nd} Period),1 Week Each Period.	A Decrease in Voluntary Maximal Torque Contraction Occurred Immediately After theTask and Recovery 2 Minutes After. Reducing Central Fatigue.
[18]	Elderly Women	Ageing Due to Old Age	BP 227 mg, Twice Daily for 12 Weeks	No Significant Impact On Grip Strength or Knee Extension. Increase SOD Activity.
[19]	Women with Type 2 Diabetes (T2D) and Dyslipidemia	Sports Training 3 Sessions/Week For 8 Weeks	Propolis 500 mg, 3 Times/Day for 8 Weeks	Increases Antioxidant Effects Through Increasing Malondialdehyde (MDA), Superoxide Dismutase (SOD), and TAC.Reducing Pro-Inflammatory Activity (IL-6) Through Upregulating CRTP-12 and SFRP5.
Animal Subjects and in Vitro				
[20]	Male DDY strain mice	Edema On Hind Foot with Carrageenin Injection	Propolis 1:1000 and 1:100 Orally	Inhibition of L-arginine, A Substrate of NOS Plays a Role in the Inflammatory Response.Anti-inflammatory Effects Via Inhibition of NO Production.
[21]	Male Wistar Strain Rats	Hind Legs Ischemia (Artery Clamp)	CAPE 10μmol/kg, 60 Minutes Intra-peritoneally Before Reperfusion Occurs	Decreased levels of MDA and NO. Increased SOD Activity.
[22]	L6-mouse myoblasts	-	CAPE 10μM	Increasing Glucose Uptake Via the AMPK Pathway and Activates the AKT Pathway in Myoblast Cells.
[23]	Male Wistar Strain Rats	Hind Legs Ischemia (Torniquet Application)	CAPE 10μmol/kg, 30 Minutes Before Reperfusion Occurs	Histological Damage Scores, Muscle Edema Percentage, Tissue MDA Content, Apoptosis Index, andNeutrophil Infiltration and Interspaces Decreased.
[24]	Female Wistar Strain Rats	Spinal Cord Injury	PEE China 0.2; 1 or 5 mg/kg, once a day for 3 weeks	Locomotion improvements seen on the Basso, Beattie, and Bresnahan (BBB) scale.
[25]	Female Wistar Strain Rats	Treadmill 16 m/minute Up to 90 Minutes/Day with Breaks	CAPE 5 mg/kg or 10 mg/kg for 5 Days	Reducing the Formation of MDA and MPO. Decreased Inflammation Via NFκB Pathway, By Reducing Cyclooxygenase-2 (COX2), Inducible Nitric Oxide Synthase (iNOS), Interleukin-1β (IL-1 β), and Monocyte Chemotactic Protein-1 (MCP-1) Expression.

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[26]	Male SD Rats	Treadmill for 60 Minutes, 5 Times/Week, for 6 Weeks	Propolis 50mg/kg WB/day, Parallel with Exercise	Increases Glycogen Use in Muscles. Increases the Antioxidant Activity of SOD, Glutathione Peroxidase (GPX), and Catalase (CAT) with MDA Declines
[27]	Female Wistar Rat	Sciatic nerve injury	Propolis 200 mg/kg BW	Improvement in Walking Function
[28]	C2C12 and RAW264 Cells	Induction of Ik-B (IKK) Inhibitor BMS-345541, to NF-Kb Activation	PEE Brazilian 100 µg/ml	Promote Myoblasts to Secrete Cytokines and Chemokines for Muscle Remodeling.Increases RAW264 Migration Which Stimulates the Production of Vascular Endothelial Growth Factor (VEGF-A) and MMP-12
[29]	Male C57BL/6 Mice	High-Fat Diet	Propolis 0.2% in Diet for 2 and 5 Weeks	Downregulates TLR4 (Toll-Like Receptor) Pathway Reduces Inflammatory Cytokines Expression
[30]	Male Wistar Rats	Hind Limbs Unloading	BP 500 Mg/Kg, 2 Times/Day at 6-Hour Intervals, for 2 Weeks	Stimulating Pro-Angiogenic Factors and Suppressing Anti-Angiogenic Factors to Prevent Capillary RegressionIncreasing Ratio Capillaries to Muscle Fibers, Volume, and Diameter Capillary Antioxidant Activity (Suppress P53 and SOD-1)
[31]	Male C57BL/6NCr Mice	Methylglyoxal (MGO) to increase AGEs	BP 0.1% in the Diet for 20 Weeks	Increase Muscle Mass. Decrease Accumulation of MGO, and Increase Glyoxalase Activity. Reduces Pro-inflammatory Responses.
[12]	C2C12 Cells	H_2O_2 Induction	PEEB 1, 3, and 10 µg/ml	Increased HO-1 Expression. Prevents ROS Production and Myoblast Cell Death Increases Cell Viability.
[32]	Male SD Rats	Sciatic Nerve Damage	Propolis-gum Arabic Nerve Guidance Channel	Increased SFI Score Related to Muscle Function.Increasing the Weight and Diameter of Muscle Fibers
[3]	Male Mice	Homozygous Diabetes	BP 0.08%, 0.4%, and 2% w/w in Feed, for 8 Weeks	Increased Grip Strength and Weight Muscles.Reduces the Expression of Genes That Play a Role in the Formation of Atrophy and Inflammation in Muscles.Increase Amino Acid and Inhibit Mitochondria Dysfunction.
[33]	Mouse C2C12 Cells	D Galactose (D-Gal) Induction	Propolis Ethanolic Extract Brazilian (PEEB) 0.1, 5, and 25 µg/ml for 48 Hours	Increase the Viability of C2C12 Senescent Cells.Reduces the Number of Senescence-Associated Beta-Galactosidase-Positive Cells. Stimulates C2C12 Cell Differentiation. Increase the Activation of Nuclear Factor Erythroid 2-Related Factor 2 (Nrf2)/ Heme-Oxygenase -1 (HO-1) Signals to Maintain Cell Differentiation Ability Inhibit Cell Apoptosis.

Propolis also contributes to glucose and muscle metabolism. Propolis suppress blood sugar increase by stimulates GLUT4 translocation through PI3K and adenosine 5′-monophosphate-activated protein kinase (AMPK) signaling [1, 18]. Propolis prevent obesity-induced sarcopenia by enhancing mitochondrial efficiency within skeletal muscle tissue also via AMPK activation propolis-induced fat loss [3, 18]. When administrated for 20 weeks in feed in conjunction with magnesium oxide (MGO), propolis inhibits the formation of advanced glycation end products (AGEs) [32], thus alleviating muscle fatigue [17]. Propolis contain Artepillin C, a bioactive mono-phenol which has been found to decrease muscle fatigue in both skeletal and

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heart muscle by removing Reactive Organic Species (ROS) from the mitochondria, though the full mechanism remains unclear [17]. The anti-inflammatory benefit of propolis is also observed. Propolis administration suppresses the production of pro-inflammatory cytokines mRNAs, specifically affecting IL-1, IL-6 and the ratio of IL-6 to IL-10 [15, 19]. Propolis increases the concentration of C1q/TNF-related Protein-12 (CTRP-12) and excreted frizzled-related proteins (SFRP15) as anti-inflammation agents [19]. Consumption of propolis has been shown to decrease the level of circulating lipopolysaccharide (LPS), the activation of the Toll-like receptor 4 (TLR-4) pathway, and the expression of pro-inflammatory cytokines in the muscle tissues of mice fed a high-fat diet [29]. Research in Deutschland, Denken, and Yoken (DDY) mice has demonstrated that propolis can decrease inflammation by blocking the production of nitric oxide (NO) following intra-plantar injection of carragenin [20]. Additionally, research has found that CAPE can inhibit the expression of i-NOS, by suppressing NFκB activation. Moreover, the parameter for neutrophil sequestration in ischemic tissue undergoing reperfusion, myeloperoxidase (MPO), increased during the ischemia, leading to the production of oxidants by neutrophils. Propolis has been found to decrease neutrophil infiltration and suppress MPO activity in muscle [20](Figure 2).

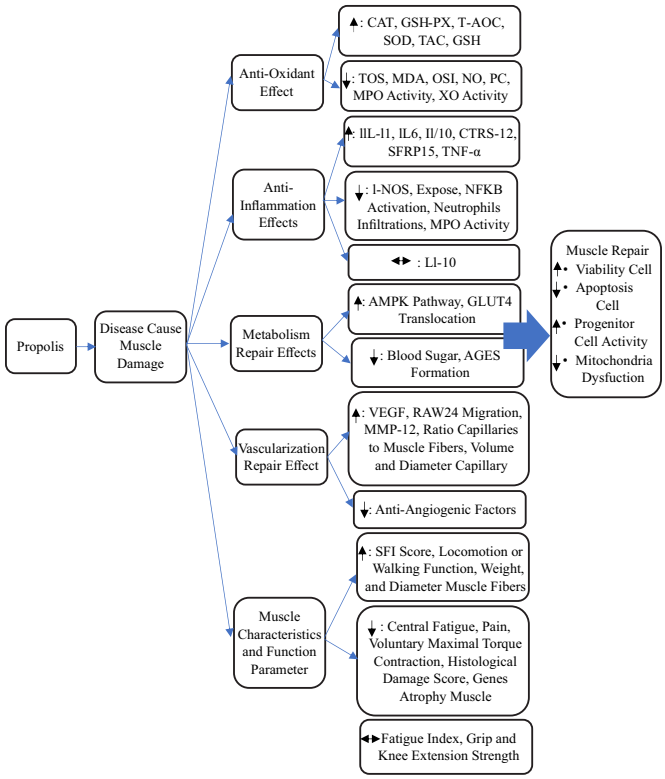

Figure 2: Effect of Propolis On Muscle Damage (↑: Increase, ↑: Decrease, ↔: Non-Significant)

DISCUSSION

From the 21 articles in this study, it is possible to ascertain the role of propolis in muscle repair through three main mechanisms, primarily due to its antioxidant, and anti-inflammatory properties, and its effect on the metabolic system including glucose and lipid metabolism, which influence muscle fatigue, strength, and mass. As an antioxidant, propolis showed benefits in various cases including muscle stress, exercise and the ageing process. Research indicates that administering propolis during skeletal muscle-induced stress elevates the levels of antioxidants including catalase (CAT), glutathione peroxidase (GSH-PX), Total Antioxidant Capacity (T-AOC), heme oxygenase-1 (HO-1) and superoxide dismutase (SOD) [33, 34]. This increase in antioxidants enables cell survival by blocking the p53 and protects the muscle cells from apoptosis thus facilitating the repair process [29]. Furthermore, propolis intervention in exercise-induced skeletal muscle has been shown to elevate TAC and GSH levels, while reducing Total oxidant status (TOS), malondialdehyde (MDA) and Oxidative stability index (OSI) levels following the 12-minute runs (Cooper test) [16]. Administration of propolis also showed benefits in ageing people. A 12-week propolis intervention in elderly women resulted in increased SOD levels suggesting its potential benefit for the ageing process [18]. Vascularization is one of the crucial factors that facilitate tissue repair, including in muscle. Propolis can be used as a cytoprotectant for endothelium of vascular within skeletal muscle. Muscle capillary is influenced by pro-angiogenic signals like VEGF, which promotes the differentiation of endothelial cells, a crucial step in muscle repair [30]. Therefore, this mechanism of action is also described as the benefit of propolis in muscle repair. The study revealed the benefits of propolis in muscle strength and mass. Results from examining muscle strength specifically grip strength and knee extension strength in elderly women who received propolis supplementation, showed no significant differences. The lack of quantitative data on physical activity during the trial period, is responsible for these results, suggesting additional research may be necessary [18]. Research on peripheral nerve damage and spinal cord damage in animal models found that treatment with propolis resulted in improved muscle function as measured by the SFI score [32], morphologically and histologically increased muscle mass, and enhanced locomotion [24]. Following 20 weeks of treatment with propolis, there was an observed increase in soleus muscle mass, however, it was not attributed to muscle hypertrophy, instead, it is thought to be a result of stimulation of glycogen accumulation within the muscles [31]. The rise in muscle mass might also be attributed to an increase in connective

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tissue resulting from the migration and proliferation of fibroblast due to propolis administration. Further exploration is required to investigate another potential mechanism. The majority of studies mention that active ingredients of propolis such as Artepellin-C, CAPE, coumaric acid, trans-phenolic acid, and kaempferide are components of propolis that play an important role [15, 34]. Some studies use these components singly to prove their effects. The active components contained in propolis have different properties and concentrations because propolis itself is very dependent on the demographic location of the distribution of flora [35]. Therefore, according to the author, other components contained in propolis also have an important role that is considered as a wholeness of the material [36]. There are many variations in the time used to see the effects of propolis on muscle repair. Studies conducted on human populations themselves vary from 4 weeks to 12 weeks. However, from studies that looked at the effects of propolis on anti-inflammation conducted for 30 days, there was a decrease in pain caused by inflammatory activity [15, 18]. From the studies traced, the effect of propolis on insignificant parameters is due to the lack of facilities and infrastructure, as well as the lack of supporting data. The direct effect of propolis on these conditions is not explained in detail [15]. However, according to the author, data on muscle function that is not yet significant can be influenced by various factors, including individual habits. Therefore, further testing is expected on a wider population with good sample characteristic control.

The included studies show heterogeneity in design, dosage, duration, and outcome measures, limiting comparability. A majority of evidence is derived from animal and cell-based studies, reducing clinical applicability. Lack of standardized propolis formulations and insufficient control of confounding factors (e.g., physical activity) further affect conclusions. Future research should focus on large-scale randomized controlled trials in humans, standardized dosing protocols, and exploration of long-term effects on muscle function and recovery.

CONCLUSIONS

It was concluded that the bee's natural product, propolis, has several advantages in muscle repair due to its multiple mechanisms of action, encompassing antioxidants, anti-inflammatory properties, impact on muscle glucose metabolism, and stimulation of angiogenesis.

Authors' Contribution

Conceptualization: PRA, SK
Methodology: SK, PRA, DS
Formal analysis: DS
Writing and Drafting: PRA, DS, SK
Review and Editing: PRA, DS, SK

All authors approved the final manuscript and take responsibility for the integrity of the work.

Conflicts of Interest

All the authors declare no conflict of interest.

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