IJARSCT
International Journal of Advanced Research in Science, Communication and Technology
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
ISSN: 2581-9429
Volume 6, Issue 7, April 2026
Impact Factor: 8.2

From Screws to Smart Glues: Emerging Trends in Bone Adhesion for Fracture Repair

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Abstract: *Bone fractures are a health burden in many countries around the world, which has historically been addressed with metal implants that offer a stable position at the cost of some undesirable side effects, such as stress shielding and the need to remove the implant again. Decades of work have been directed by the long-term goal of a biodegradable bone adhesive that can be used to fix fractures without difficulty, and can be safely dissolved in the body. In this review, the development of this discipline is presented, starting with the shortcomings of metallic structures and the non-fulfillment of early synthetic adhesives such as PMMA and cyanoacrylates to the current bioinspired revolution. We elaborate on the stringent performance specifications of an ideal bone adhesive, such as good wet adhesion, quick curing, controlled biodegradation and excellent biocompatibility. The concept of a paradigm shift to nature-based approaches is examined, which entails mussel-based catechol chemistry and citrate-based biomaterials with excellent bonding and active osteogenesis promotion. Also, we look at the new frontier of plant-based polymers and medicinal phytochemicals as green alternatives to improve safety and bioactivity. Although this is encouraging, such as the recent introduction of a so-called three-minute bone glue, there are considerable difficulties in translating this to the clinical situation, such as long-term biocompatibility, standardization, and regulatory acceptance. The review has concluded that the interplay between bioinspired design and natural material science is the key to coming up with the next generation bone adhesives that can transform orthopedic surgery and patient outcomes.*

Keywords: Bone adhesive, Biodegradable polymer, Musculoskeletal trauma, Fracture healing, Bioinspired materials, Mussel-inspired adhesive, Citrate-based glue, Plant-based biomaterials.

I. INTRODUCTION

The World Fracture Bone Disease this is the one of the most widespread human injuries that is common to all people regardless of their age or geographical background is a broken bone. Accidents, sports, or osteoporosis (a condition that causes bones to be fragile) lead to an annual incidence of millions of people having a fracture (Wu et al., 2021). It is not just a personal tragedy but a huge health crisis facing the whole population, which is costing healthcare systems billions of dollars and causing patients to suffer endlessly and prolonged cures. To make a fracture heal well, there is one principle which is very important, that is the broken part should be held in a perfectly still position. The answer to this issue has been mechanical since centuries. Imagine that it is a precious, fragile item of pottery that needs to be fixed. The conventional method has been to place external casts or, in more serious breaks, internal clamps and scaffolds in the shape of metal plates, screws and pins (Uhthoff et al., 2006). These are the undisputed gold standard in orthopedics that have over a hundred years successfully stabilized countless fractures and restored the functionality of patients using these metallic implants. The Natural Weaknesses of the Gold Standard. But this gold standard is not ideal. It is the very fact that metal is hard, uncompromising and alien to human body that causes a range of serious issues. First, when a rigid metal plate is loaded in place of a bone, the bone will be in effect cushioned against the pressure. This is what is termed

DOI: 10.48175/IJARSCT-33020

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as stress shielding by the body and what this indicates is that the bone is unnecessary and as a result it becomes progressively weak and loses density around the location where the implant is placed (Lewis, 2008). Such a weaker bone can then be susceptible to re-fracture in the event that the metal is removed. Besides, metal implants are foreign permanent objects. They may result in chronic irritation and in certain situations may result in infections which are hard to cure. The most revealing disadvantage is perhaps that these devices, as having been useful, may require a second operation to have them removed. This implies that patients are exposed to more risks, pain, and expenses, which do not add anything that was only a temporary relief (Boker et al., 2019). It is more difficult with complex cases like comminuted fractures whereby the bone breaks into numerous tiny fragments. Surgeons have a tedious and usually incomplete time with screws and plates in attempts to hold these small fragments (Sanchez-Fernandez et al., 2019).

A Revolutionary Vision: The Dream of a Surgical Bone Glue. It is these capacities that have enhanced a compelling dream in scientists and surgeons: what could we do to simply glue the bones together again, rather than clamping them? The idea of a bone glue is a breakthrough. Theoretically, an injectable glue that can fill intricate fracture gaps, bond to wet bone surfaces, achieve instant stability, and then--above all--safely dissolve once the body regrows new bone will eliminate any mark of its existence (Bhagat & Becker, 2017; Farrar, 2012).

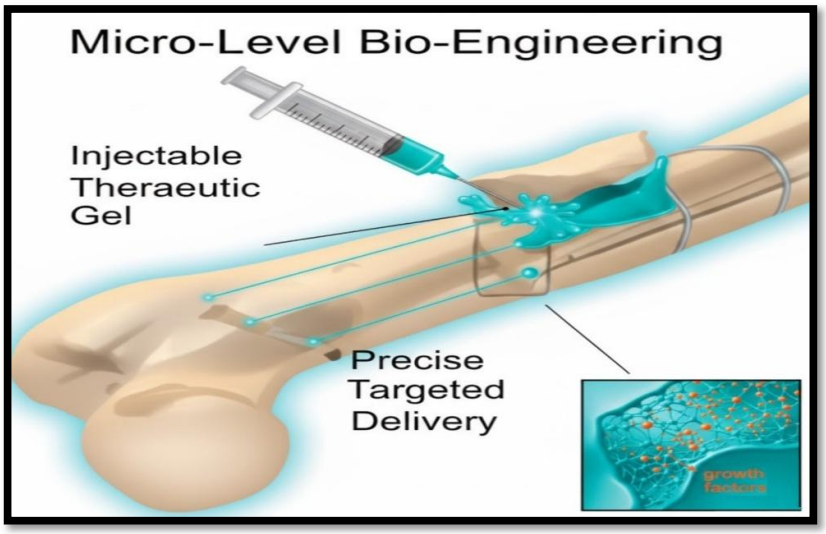

Figure 1. Schematic illustration of an injectable bioengineered bone adhesive enabling precise, localized delivery and in situ curing within fracture gaps.

This was the perfect bone cement that would require an incredibly sophisticated material. It has to be very strong in adhesion to wet tissue and must be strong in internal cohesion to resist tearing itself to pieces when strained. It has to heal quickly in the moist environment of the body but it has not to emit the destructive heat. The rate of its degradation should be exactly the same as bone healing, which takes months. Lastly, the material and all its degradable products should be completely biocompatible (Nam & Mooney, 2021). Stumbling at the Start: The Failure of Early Synthetic Adhesives Stumbling at the Start: The Failure of Early Synthetic Adhesives Stumbling at the Start: The Failure of Early Synthetic Adhesives We have failed in the road to this ideal. First ones just reused pre-existing robust sticking agents. An example is polymethylmethacrylate (PMMA) bone cement which is powerful and has long been used to fix artificial joints. Yet, it is inherently unsatisfactory to use in fracture repair: it is non-biodegradable, it hardens releasing sufficient heat to harm nearby cells, and it is fragile (Arora et al., 2013). Likewise, even cyanoacrylate super glues which are fast to set in wet conditions degrade to products that are toxic to tissue, which leads to inflammation that might greatly hinder healing (Pascual et al., 2016).

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The Bioinspired Revolution Learning with Nature. A big breakthrough was when scientists resorted to nature to get an inspiration. This is a simple question they put: how do seawater creatures such as mussels get such tenacious sticking to wet, salty and dynamic rock surfaces? The solution was discovered with a distinct set of chemistry around a molecule known as 3, 4-hydroxyphenylalanine (DOPA) (Lee et al., 2007). The catechol group of DOPA gives the mussels a strong combination of bonds forming an adhesive that is incredibly strong and long lasting even in water (Lee et al., 2011). This was a new frontier in chemistry inspired by mussels. To follow this natural approach, researchers started to work on synthetic polymers. As an example, citrate-based polymers were engineered to not just reproduce this adhesive chemistry and also take advantage of citrate, which is a natural metabolite that is important in bone formation (Xie et al., 2015). The results of this bioinspired methodology have resulted in a new generation of injectable adhesives which are robust, biodegradable and have the capability to actively stimulate bone regeneration (Zhang et al., 2021).

A Glimpse of the Future: The "Three-Minute" Breakthrough and the Path Ahead

The discipline is currently developing at a rapid rate. One of the saddest signs of this development is a recent news piece that a group of Chinese researchers created a new kind of bone glue, which could heal a broken bone in three minutes (Xinhua, 2023). Although the whole scientific process is yet to be described, this statement represents the ultimate stage of the research that was conducted over decades. Nevertheless, it does not end at the journey. We should also pay attention to what has been learnt in the past as we adopt these new high-tech synthetics. Certain synthetic polymers may also produce acidic by-products, which would cause local inflammation (Shen et al., 2010). This has been accompanied by a corresponding investigation of safer plant-based options. Scientists are currently exploring natural polymers and integrating medicinal plant extracts with known anti-inflammatory and bone-healing characteristics to develop adhesives that are no longer inert glues, but participate in the healing process (Jalil et al., 2012; Li et al., 2021).

Figure 4. Evolution of fracture fixation strategies from conventional metallic implants to bioinspired, biodegradable smart bone adhesives.

Scope and Purpose of This Review

Thus, this review seeks to document in detail how the fixation of bone fractures has evolved since the initial use of metallic implants to the first use of adhesive-based solutions. We will critically discuss the inefficiency of the conventional approaches and initial synthetic adhesives, outline the bioinspired revolution, and discuss the promising character of the natural, plant-based alternatives. The review will give a clear explanation of the way these new materials

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will reshape orthopedic surgery by placing contemporary advances in this field within the context of this historical and scientific framework.

II. THE LEGACY OF FIXATION: LIMITATIONS OF METAL BASED IMPLANT

2.1. The Dominance of Internal Fixation

Internal fixation with metallic plates, screws, and intramedullary nails has been the main method of treating unstable fractures in over a century (Uhthoff, Poitras, and Backman, 2006). This is referred to as open reduction and internal fixation (ORIF) in which the fracture area is exposed and the bone fragments are realigned back in place and held together by a device. Such implants give the immediate mechanical stability needed to begin the healing process and enables the patients to start their mobilization very early in comparison with the use of cast treatment only. This is a proven methodology that has certainly worked in stabilizing the functions of millions of patients (Jackson and Pacchiana, 2004).

2.2. The Inevitable Trade-offs: Long-Term Complications

Although they have advantages, and are extensively used, metal implants have long-term risks and disadvantages that are inherent and significant and are associated with their nature, as harder, non-degradable foreign substances.

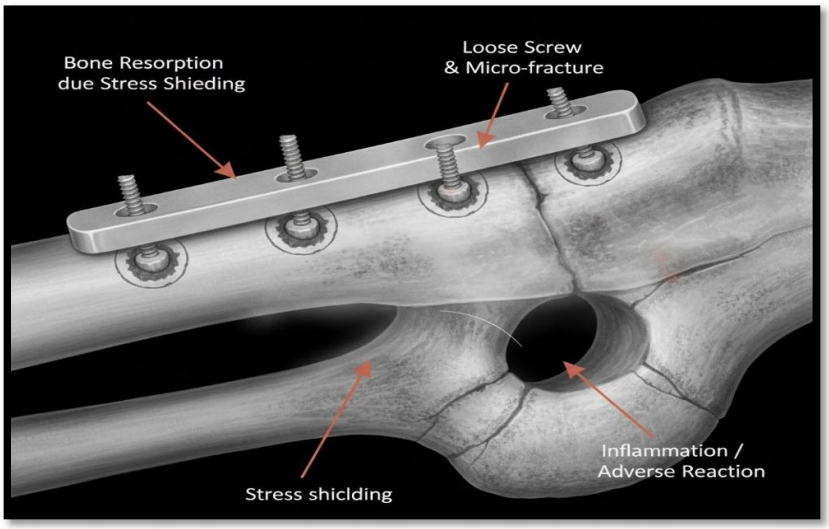

Figure 3. Illustration of complications associated with metallic fixation, including stress shielding, screw loosening, micro-fractures, and inflammatory responses.

2.2.1. Stress Shielding and Wearing out of Bones.

The fact that there is a tremendous difference in stiffness between bone and metal creates a critical flaw. A rigid plate bearing a majority of the mechanical load is effectively protecting the underlying bone of what otherwise it would be subjected to. Based on the law of Wolff, bone will remodel when stressed; when this stress is no longer there, the body can realize that it is not being utilized hence the bone undergoes a process of weakening through resorption (Lewis, 2008). This brings a paradox, an implant, which initially fixes the fracture, may end up producing a weaker bone structure, which may lead to a high rate of re-fracture once the hardware has been removed (Uhthoff et al., 2006).

2.2.2. The Secondary Surgery Burden.

Traditional, non-degradable, implants such as stainless steel or titanium alloy implants do not degrade and tend to stay in the body or they need to be removed in a second operation. This voluntary surgery exposes patients to risks of further anesthesia and pain, recovery time and financial burdens all to fix a device that has been used (Boker et al., 2019). This strife underscores the clinical need to have a provisional fixation material that does not necessitate the second operation.

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2.2.3. Foreign Body Reaction and Risk of Infection.

The fact that a large foreign body is present predisposes the development of complications. The implants may serve as a platform on which bacteria grow resulting in deep-seated infections (osteomyelitis) which are very hard to treat because of the presence of biofilms (Arora, Chan, Gupta, and Diwan, 2013). In addition, there is a possibility of the body developing a chronic foreign body response on the implant that can result in a sustained inflammation, tissue irritation, and in other instances, triggering allergic reactions to the metal ions (Anderson, Rodriguez, and Chang, 2008).

2.2.4. Complex Fracture Scenario Challenges.

Complex fractures, including comminuted fractures where the bone is broken into several small fragments, are the situations in which the limitations of metal hardware are the most evident. These small fragments are difficult to fix with screws and plates because it is a mechanical procedure, which may lead to the sub-optimal reduction and fixation (Sanchez-Fernandez et al., 2019). Moreover, in fragile and brittle osteoporotic bone, screw purchase is compromised, and the chance of an implant failure and fixation loss is high.

Limitation of Metallic Implants	**Description / Clinical Issue**	**Underlying Cause**	**Clinical Consequences**	**Need for Bone Adhesives**
Stress shielding	Implants bear most of the load instead of bone	High elastic modulus of metals (Ti, SS)	Bone resorption, implant loosening	Adhesives distribute load more naturally
Secondary surgery	Implant removal often required	Non-degradable nature	Increased cost, pain, infection risk	Adhesives can be biodegradable
Infection risk	Biofilm formation on metal surfaces	Bacterial adhesion to metals	Osteomyelitis, implant failure	Adhesives can include antimicrobial agents
Poor integration	Limited bonding with bone tissue	Bioinert surfaces	Delayed healing	Bioadhesives promote osteointegration
Imaging interference	Artifacts in CT/MRI	Metal radiopacity	Diagnostic difficulty	Polymer adhesives are imaging-friendly
Mechanical mismatch	Stiffness mismatch with bone	Elastic modulus difference	Micro-fractures	Tunable mechanical properties
Corrosion & ion release	Release of metal ions	Body fluids + wear	Inflammation, toxicity	Adhesives avoid metal ion release
Limited use in complex fractures	Not suitable for irregular surface	Rigid geometry	Surgical difficulty	Injectable adhesives adapt to shape

Table 1: Summary of Key Limitations of Metallic Bone Implants

2.3. Clinical Imperative of a New Solution.

To conclude, although fixation metallic devices are very good in the first-place stability, their retention in the body over time comes with a list of inevitable complications. Stress shielding, the need to perform secondary surgery, risk of infection, and poor performance in complex cases is a major clinical problem of concern (Farrar, 2012). These natural constraints have led to an acute and unmistakable demand to create a novel category of biomaterials capable of stable

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fixation followed by a controlled degradation mechanism, capable of transferring load to the regenerating bone in a seamless and reproducible manner and being devoid of the necessity of removal. The first step towards satisfying this urgent requirement was to consider the easiest way out: the strong synthetic adhesives.

III. THE UNFULFILLED EXPECTATION OF EARLY ADHESIVES THAT WERE SYNTHETIC.

Frequently motivated by the obvious constraints of metal hardware, a bone adhesive search commenced with the simplest solution to the problem of fixing bone, the application of strong, pre-existing synthetic glues. This first wave of optimism was soon dampened however as these first-generation materials manifested a fresh set of critical issues proving that high adhesive strength alone was not enough to achieve clinical success.

3.1. Polymethylmethacrylate (PMMA) The Brittle and Biologically Inert Grout.

Since the 1950s, polymethylmethacrylate (PMMA) bone cement has been a standard component of orthopedic practice, being utilized to fix prosthetic components, artificial hips and knees, to the bone (Arora, Chan, Gupta, and Diwan, 2013). It was an easy sell: it is strong compressively and, during surgery, can be compounded as a soft paste, which solidifies where it is placed. Nevertheless, it mainly acts through mechanical interlocking in which the liquid monomer enters the bone pores and then polymerizes as opposed to creating a chemical bond with the tissue (Lewis, 2008). This non-adhesiveness is only one of a number of serious faults. Polymerization of PMMA is an exothermic process that produces temperatures capable of inducing thermal necrosis (cell death) to the adjacent bone, which could destabilize the early stability and integration of the implant (Dunne and Orr, 2001). Besides, PMMA is brittle by nature and prone to cracking under tensile or shear stress and is not biodegradable. It is a non-biodegradable implant that after implantation becomes permanent inert mass that can be loosened over time and does not allow natural bone regeneration along the site of the defect (Arora et al., 2013).

3.2. Cyanoacrylates: Fast Bonding with Poisonous Effects.

Another apparently perfect candidate was presented by cyanoacrylate-based adhesives commonly referred to as super glues. Their capability to polymerize quickly in the presence of moisture which was a common occurrence within the body implied that they would be able to attain an instant fixation (Bhagat & Becker, 2017). In fact, they establish high affinity to different surfaces. But it is this speed that is a two-edged sword. The reaction is fast-setting and produces a lot of heat, like PMMA, which threatens to harm the surrounding tissues thermally (Pascual et al., 2016). Their degradation is however the greatest demerit. The cyanoacrylates are hydrolyzed to give out formaldehyde and cyanoacetate as by-products (Gosain, 2002). These are cytotoxic molecules, which cause a severe inflammatory reaction, tissue necrosis, long-term inflammation and possible nerve damage. Although longer-chain derivatives (such as octyl-cyanoacrylate) were created to delay degradation and minimize the toxicity, the underlying risk is present, with their application to external fixation of the skin being the only approved method and their use as internal fixatives such as bone repair contraindicated (Jain and Wairkar, 2019).

3.3. The Learning: The Failure: A Mismatch with the Biological Environment.

The collapse of PMMA and cyanoacrylates has one common denominator: the basic inability to fit in the dynamic and sensitive biological environment. These materials were not intended to integrate biologically but to be the strength of industry, as given in Table 2. They do not take into consideration the fundamental principles of biodegradability and non-toxic degradation which are as important as initial strength to an effective bone adhesive (Nam & Mooney, 2021). Their failure mode was frequently not only the loss of mechanical integrity, but active damage to the healing process which they were supposed to sustain.

Adhesive Type	Primary Mechanism	Key Advantages	Critical Limitations
PMMA Bone Cement	Mechanical interlocking; No true adhesion.	High compressive strength, radiopacity.	Non-degradable, exothermic reaction (thermal necrosis), brittle, risk of loosening.

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Cyanoacrylates	Rapid anionic polymerization in wet environments.	Very fast setting, strong initial bond strength.	Cytotoxic degradation products (formaldehyde), exothermic reaction, brittle, limited biocompatibility.

Failure of these early synthetic adhesives provided a lesson to the discipline that was very critical. It was clear that a good bone adhesive should not be just any good glue, but should be a biologically conscious substance whose complete lifecycle, including both application and degradation, should be coordinated with physiology of bone repair. It is this discovery that led to a more advanced, bioinspired view of material design.

IV. SPECIFYING THE IDEAL: RECOMMENDATION OF PERFORMANCE REQUIREMENTS OF A NEXT-GENERATION BONE ADHESIVE.

The disappointments of initial synthetic adhesives were a priceless, yet utterly valuable experience: to succeed in the demanding environment of the in vivo setting, a versatile material which corresponds to a predefined range of biological and mechanical requirements is needed. It does not aim to find some adhesive; instead, it is the intention to design a temporary, bioactive interface that actively promotes the healing process. According to decades of the research and clinical experience, the following criteria have become the key standards of a perfect bone adhesive (Sanchez-Fernandez et al., 2019; Nam and Mooney, 2021).

4.1. Strong and Well-rounded Mechanical Characteristics.

Mechanical stability The first action of a bone adhesive is to offer immediate mechanical stability. This requires a delicate balance of two forms of strength: High Adhesion Strength: The adhesive should create a high-adhesion strength bond to the wet, organic-inorganic composite surface of bone tissue. This interfacial strength should be adequate to resist physiological loads (e.g. muscle forces, small impacts) that do not debond. High Cohesion Strength: The inner strength of the adhesive material itself should also be high or it will be lost to Cohesive failure, where the material itself is ripped open internally before the bond to the bone is broken. The adhesive force is preferably to match the mechanical features of natural bone to ensure the absence of a stress-riser site (Bhagat & Becker, 2017).

4.2. Fast and Biocompatible Curing.

The adhesive should also be able to change state to a load-bearing and solid substance within a clinically viable period- usually a few minutes- also starting with an applicable state- such as injectable liquid or paste. Such quick healing is essential in order to reduce the time of surgery. Nevertheless, the curing process should also be biocompatible; it should take place under physiological temperature (37degC) and pH, and should neither produce a lot of heat during polymerization (which may cause thermal necrosis) nor produce toxic by-products (Taboada et al., 2020).

4.3. Time-Regulated and coordinated Biodegradation.

Controlled biodegradability may be considered to be the most important demand of a modern bone adhesive in comparison with its predecessors. The substance should break down at an optimal rate that is just aligned with natural bone healing that can be measured in weeks and months. In case of excessive degradation, the fracture re-displacement and mechanical failure will occur prematurely. In case it is too slow, it can literally hinder the growth of new bone tissue and trigger a chronic inflammatory process (Zhang et al., 2021). The products of degradation should be non-toxic, easily metabolized or excreted by the body.

4.4. Good Biocompatibility and Bioactivity.

The adhesive and its degradation products should be non-cytotoxic, non-immunogenic as well as non-inflammatory. In addition to passive compatibility, an optimal adhesive would be bioactive, i.e., one that would promote a positive healing environment. It may include either the proliferation and stimulation of bone forming cells (osteoblasts) or even the release of ions (calcium, phosphate, silicate), which trigger bone regeneration (Bai et al., 2020).

4.5. Practical Handling and Sterilization

Lastly, the content should be clinical to use. It must be able to be sterilized conveniently without losing its workability. Its handling properties, including its viscosity and working time, should be appropriate to be used in a complex surgical

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setting, which may need injectability using syringes to access isolated fracture locations without needing to expose the area (Boker et al., 2019)

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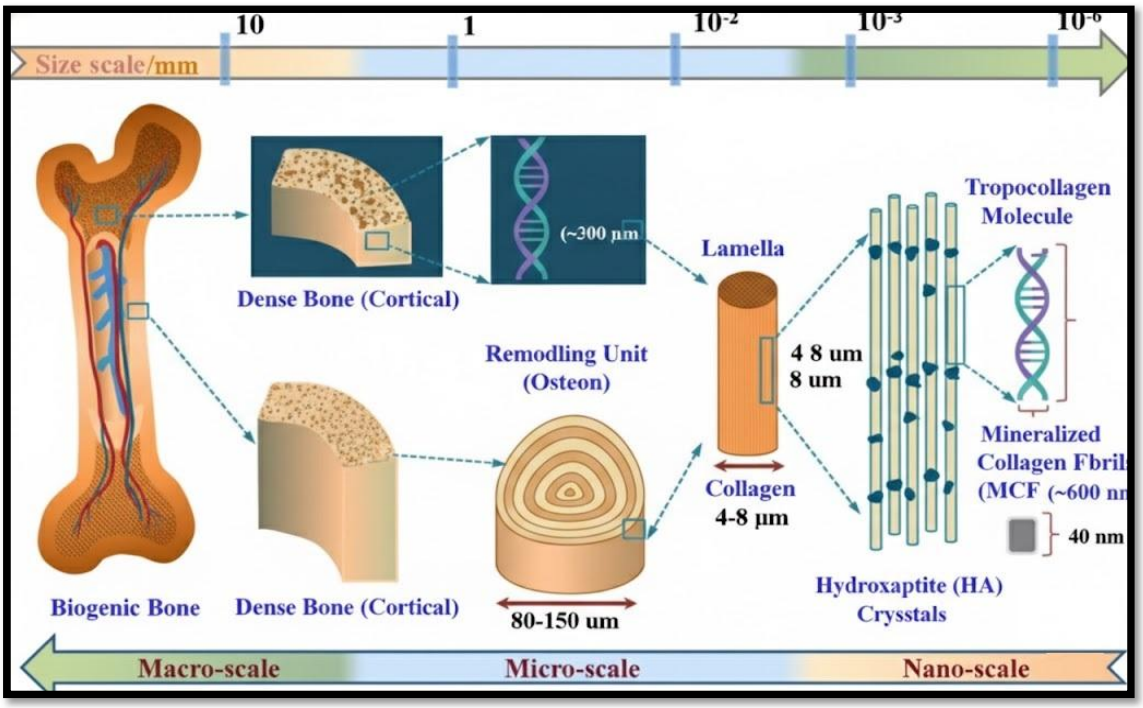

Figure 2. Hierarchical organization of bone from macro- to nano-scale, highlighting osteons, collagen fibrils, and hydroxyapatite crystals that govern adhesive interactions.

Requirement	Key Characteristics	Rationale
Mechanical Performance	High wet adhesion strength; Cohesive strength matching bone.	Provides immediate stability under physiological loads.
Curing Profile	Rapid setting (minutes) at body temperature; low exothermic heat.	Minimizes surgery time and prevents thermal tissue damage.
Biodegradation	Rate synchronized with bone healing; non-toxic degradation products.	Allows gradual load transfer to new bone; avoids secondary surgery.
Biocompatibility/Bioactivity	Non-cytotoxic, non-inflammatory; ideally osteoconductive/inductive.	Ensures safety and actively promotes the healing process.
Clinical Handling	Sterilizable, injectable, with adequate working time.	Facilitates practical use in a surgical setting.

Table 3: The "Gold Standard" Requirements for an Ideal Bone Adhesive

These are the five pillars that are used as the check-list against which all new technologies of bone adhesives are evaluated. They are the paradigm of transforming simple glues to advanced temporary regenerative scaffolds. The framework of rigorousness preconditions the comprehension of the reason why the further evolution of bioinspired strategies has become so influential. Learning to be like nature: The Bioinspired Revolution.

V. LEARNING TO BE LIKE NATURE: THE BIOINSPIRED REVOLUTION.

With the strict demands of an optimal bone adhesive, nature became more and more the source of design inspiration. Rather than attempting to use harsh synthetic chemistry, this new method attempted to model materials and processes as

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millions of years of evolution had modified them to operate in wet, dynamic, and biologically active environments. There are two most promising strategies to come out of this bioinspired revolution: mussel-inspired adhesion, and citrate-based biomaterials.

5.1. The Secret of the Mussel: Wet Sticky.

One of the most important breakthroughs was made by researching marine mussels which produce a protein-based glue enabling them to cling to rocks tenaciously even with pounding waves. This strong adhesive is the secret of a particular amino acid known as 3, 4-dihydroxyphenylalanine (DOPA) (Lee, Dellatore, Miller, and Messersmith, 2007). The main functional group of DOPA is the catechol, and it allows adhesion to be achieved via an effective, multifunctional manner:

Strong Coordination Bonds: The catechol group is able to make strong complexes with metal ions (e.g. calcium, iron) contained in the mineral component of the bone (hydroxyapatite).

Covalent Bonding: When catechol is oxidized it may be converted into quinone which is easily reacting with amine and thiol groups on the bone tissue surface to form strong covalent bonds.

Hydrogen Bonding and Hydrophobic Interactions: There are also many weaker interactions that are cumulative and the catechol group is involved (Lee, Messersmith, Israelachvili, and Waite, 2011).

This versatile mussel-inspired chemistry represents a template towards forming synthetic polymers that are capable of forming a powerful adhesion in the wet hostile environment of a fracture site. As an illustration, using this concept, Bai et al. (2020) made a mineral-organic adhesive (SF@TA@HA) in which tannic acid (a polyphenolic material filled with catechol groups) bridged silk fibroin and hydroxyapatite nanoparticles to form a tough, highly adhesive, and OG material.

5.2. Biomaterials of Citrate: Metabolic Advantage.

Another biomimetic approach builds upon molecules that the body already has in place in its metabolism. Citrate is an important intermediate of the Krebs cycle and occurs in high concentrations naturally in the bone, where it forms complexes with calcium ions of hydroxyapatite which is an important part of bone mineralization and bone stability (Xie et al., 2015). This natural bone affinity is used in citrate-based biomaterials. By including citrate within polymer backbones (e.g., poly (octamethylene citrate)) scientists have developed a line of injectable adhesives, which solidify in place.

The materials have a number of benefits:

Intrinsic Osteocompatibility: Citrate is a natural metabolite that is the degradation product of them and can potentially be used by cells to aid in energy generation and bone formation.

High Adhesion: The carboxylic acid moieties in citrate offer many platforms of interaction with the bone surface either by ions or covalent bonds.

Design Flexibility: The polymer synthesis can be adjusted to finely control the mechanical properties of the material and its degradation rates (Yang et al., 2020).

One such example is the injectable citrate-based mussel-inspired bioadhesive (iCMBA), a citrate-based bioadhesive with catechol chemistry that results in strong adhesion and considerable stimulation of the formation of new bone in animal models (Xie et al., 2015).

5.3. Integrating Strategies to improve performance.

These bioinspired ideas are most frequently combined with material science using the most sophisticated adhesives. An example of such biodegradable organic-inorganic composites is the use of bioactive ceramics to create organic-inorganic composite such as nano-hydroxyapatite or bioactive Glass into a biodegradable polymer matrix (e.g., polyurethane, polyester). This technology emulates a natural composite framework of the bone resulting in materials of enhanced mechanical strength, osteoconductivity, and adhesion (Kirillova, Kelly, von Windheim, and Gall, 2018; Tang et al., 2021).

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Strategy	Bioinspired Source	Key Mechanism	Advantages
Mussel-Inspired (Catechol)	Marine mussel adhesive proteins.	Catechol groups form coordination, covalent, and hydrogen bonds.	Excellent wet adhesion, versatility, can be grafted onto various polymers.
Citrate-Based	Human bone metabolism (Krebs cycle).	Citrate chelates with bone mineral (calcium ions).	Innate biocompatibility, osteoconductivity, tunable properties.
Organic-Inorganic Composites	Natural bone structure.	Reinforcing ceramic particles within a polymer network.	Enhanced mechanical strength, bioactivity, and bone-bonding ability.

Table 4: Key Bioinspired Strategies for Bone Adhesives

This bioinspired approach represents a fundamental shift from simply gluing bones together to creating intelligent materials that participate actively in the healing process. By learning from nature's solutions, researchers have developed adhesives that meet the critical requirements of strength, compatibility, and biodegradability, moving the field closer to a viable clinical alternative to metal hardware.

VI. BEYOND SYNTHESIS: THE GREEN WAY OF NATURAL/PLANT-BASED ALTERNATIVES.

Although bioinspired synthetic adhesives may be a significant step in the right direction, the search of the optimal bone glue has brought researchers to another parallel approach, in the strength of the building blocks that nature has to offer. This strategy aims at employing natural polymers and the extracts of medicinal plants to produce adhesives not only effective but also naturally biocompatible and bioactive and possibly safer than the entirely synthetic ones.

6.1. Disadvantages of Total Synthetic Pathways.

In spite of the achievements of the synthetic methods, such as mussel-inspired polymers, there are still certain concerns concerning the synthetic methods. Some biodegradable polyesters, including poly(lactic-co-glycolic acid) (PLGA) break down through hydrolysis to form acidic by-products (lactic and glycolic acid). This has the potential to form a localized acidic microenvironment which can cause unwanted inflammatory reactions and recovery (Shen, Hu, Yang, Bei, and Wang, 2010). Moreover, the synthesis of these polymers is complicated and the risk of remaining toxic monomers requires a lot of purification and safety experiments. These constraints have given a second lifeline to natural materials that are evolved to be in harmony with the workings of the biological system.

6.2. Natural Polymers as the Structure.

One of the opportunities is to resort to natural polymers as the primary scaffold of bone adhesives. Such materials are usually based on renewable materials and have high inherent biocompatibility.

Chitosan: Chitosan is the polysaccharide derived in the shells of crustaceans, characterized by biodegradability, hemostatic (blood-clotting) effects and the weak antibacterial effect. Its amino groups could be chemically functionalized to add adhesive catechol groups or cross-linked to provide hydrogels (Rasheed & Ashok, 2020).

Alginate: This is a brown seaweed derivative that can create gels softly when in contact with calcium ions which is why it is ideal in trapping cells or growth factors. Although its adhesion is initially low, it can be enhanced by chemically, e.g. oxidation to produce aldehyde groups, which allow the formation of stronger bonding (Forooshani and Lee, 2017).

Fibrin: Fibrin glue is a naturally occurring substance which is already utilized clinically as a hemostatic agent. Its mechanical strength is however too weak to fix bones. Studies are also geared towards strengthening fibrin using other natural or synthetic material so that it may be used in load bearing applications (Shah & Meislin, 2013).

6.3. Active Biological Agents, Medicinal Plants.

The most innovative thing of this green way is the introduction of certain phytochemicals- bioactive compounds of medicinal plants. Such compounds have the potential of converting a passive adhesive into an active therapeutic device.

Anti-Inflammatory and Antioxidant Effects: There are numerous plant compounds such as flavonoids and polyphenols that are produced by plants as protective measurements. These compounds may be used to control the inflammatory

IJARSCT
International Journal of Advanced Research in Science, Communication and Technology
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
ISSN: 2581-9429 Volume 6, Issue 7, April 2026 Impact Factor: 8.2

phase of the healing process when they are incorporated into adhesives. Incidentally, icariin (Epimedium herb), curcumin (turmeric), are known to possess strong anti-inflammatory and antioxidant effects that can build a more conducive microenvironment to support bone regeneration (Jalil, Shuid, & Muhammad, 2012).

Direct Osteogenic Activity: there are a number of phytochemicals that have been shown to be active in stimulating bone formation. Naringin (citrus fruits) and berberine (Berberis plants) were observed to stimulate activity of osteoblasts (bone-forming cells) and inhibit osteoclasts (bone-resorbing cells) and thus speed up the healing process (Li, Wang, and Li, 2021). The inclusion of these into an adhesive matrix delivers to the fracture site in a localized and sustained manner.

Antimicrobial Properties: An important complication of orthopedic surgery is infections. Neem or tea tree oil are plant extracts that have a broad-spectrum antimicrobial effect. Their background in bone adhesives can give a proactive mechanism against infection, which is a great benefit compared to passive materials (Kumar, Teli, and Jha, 2019).

Feature	**Synthetic (e.g., PLGA, PEG-based)**	**Natural/Plant-Based (e.g., Chitosan + Phytochemicals)**
Biocompatibility	Good, but can vary; risk of acidic degradation.	Excellent; inherently recognized by the body.
Bioactivity	Can be engineered (e.g., with RGD peptides).	Intrinsic; many natural compounds are osteoinductive/anti-inflammatory.
Degradation Products	Synthetic molecules (e.g., lactic acid).	Natural metabolites (sugars, amino acids, safe phytochemicals).
Manufacturing	Controlled but can be complex and costly.	Often simpler, derived from renewable sources.
Antimicrobial Potential	Requires addition of synthetic antibiotics.	Intrinsic to many plant extracts.

Table 5: Comparison of Synthetic and Natural/Plant-Based Adhesive Strategies

6.4. A Sustainable and holistic Future.

Biomaterial design: - The investigation of natural and vegetal alternatives is a change to a more holistic and sustainable philosophy in biomaterial design. Through materials that the human body has co-evolved with, scientists seek to create bone adhesives not only functionally mechanical in nature, but biologically compelling, actively instructing the body to repair itself efficiently and effectively without eliciting negative responses to it. It would be in line with the objectives of green chemistry and personalized medicine, and a good direction of the orthopedic material of the next century.

VII. CLINICAL TRANSLATION AND UNRESOLVED PROBLEMS.

The tremendous development of laboratory research on the adhesives to bone is only a beginning of a long road of clinical implementation. Despite the obvious potential shown by substances like the aforementioned and so-called, three-minute bone glue, there are many hurdles that have to be overcome prior to the innovative solution becoming a part of the orthopedic surgeon arsenal. The process between the bedside and the bench is full of strict validation procedures, production and control measures.

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7.1. The Path to the Bedside

To translate a promising adhesive in laboratory to operating room involves going through a complicated pathway. The initial challenge is large scale production with Good Manufacturing Practice (GMP) conditions. A gram-scale synthesis needs to be reliably and consistently replicated in a kilogram-scale research laboratory, and purity, sterility, and lack of pyrogens must be ensured (Taboada et al., 2020). Moreover, the adhesive system should be arranged to be conveniently used in the clinical practice. This involves the design of easy-to-use delivery systems (e.g., two-component adhesives that are delivered using dual-barrel syringes) and the compatibility of the working time and setting time with the work of surgery (Bingol et al., 2023).

7.2. Biological and Mechanical Hurdles that are not solved.

Nonetheless, despite the solution of manufacturability, there are a number of biological and mechanical problems:

Long-Term Degradation and Immune Response: Although animal tests in short-term (e.g., 12-week) tend to exhibit good biocompatibility, longer-term behaviour of these materials and their degradation products is also an important issue. Even biodegradable synthetic polymers can result in chronic inflammation or foreign body reaction in the event that the rate of tissue healing is not perfectly matched with the rate at which the polymer degrades (Grossterlindi et. al., 2006; Hulsart-Billstrom et. al., 2020). There is the possibility of the material causing an immune response in months or years and this has to be considered carefully.

Challenging clinical situation performance: Laboratory adhesion tests are commonly carried out on healthy bone surfaces which are clean. The clinical setting in the real world is much more difficult. Blood, marrow and soft tissue presence could also severely affect adhesion. A sufficiently good bone adhesive should also exhibit high performance in such dirty, bloody surgical areas without being washed away or not bonding (Sanchez-Fernandez et al., 2019).

Infection Prevention: Fracture sites are prone to getting an infection. Although there are adhesives that include antibiotics or silver nanoparticles, the effectiveness of these treatments in the long term and the possibility of developing antibiotic resistance is a concern. The perfect glue would either possess antimicrobial properties, or a smart release system, which only would be activated when bacteria are present (Yang et al., 2023).

Evidence of Superiority: To be approved by the regulators and widely adopted new bone adhesives need not only be proven safe, but also provide evidence of clinical superiority or, at minimum, non-inferiority to the existing gold standard of fixation of bone, metal. This necessitates big, multi-centre, randomised control trials with long-term follow up to demonstrate that they result in improved functional outcomes, quicker recovery, or reduced complications (Fedak et al., 2011).

7.3. Hurdles of regulatory and Standardization.

A biodegradable bone adhesive has a very regulated regulatory route. Such agencies as the U.S. Food and Drug Administration (FDA) insist on voluminous data packages that prove mechanical performance, degradation, and, most significantly, safety and efficacy in the form of pre-clinical and clinical testing (Boker et al., 2019). The absence of standardized testing is one of the greatest barriers. Models are applied differently by different research groups (e.g. different types of bones of different animals, different rates and conditions of testing), and it is hard to compare the findings of studies and come to some universal standards of performance (Taboada et al., 2020).

Challenge Category	Specific Hurdles	Potential Solutions / Current Efforts
Manufacturing & Practicality	Scaling up GMP production; user-friendly delivery systems.	Development of automated synthesis; pre-packaged sterile delivery kits.
Biological Safety	Long-term immune response; unpredictable degradation kinetics.	More sophisticated animal models (e.g., osteoporotic); long-term follow-up studies.

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Challenge Category	Specific Hurdles	Potential Solutions / Current Efforts
Clinical Performance	Adhesion in bloody fields; prevention of infection.	Incorporating hemostatic agents; designing inherently antimicrobial polymers.
Regulatory & Standardization	Lack of standardized testing; proving superiority over metal implants.	Developing ASTM/ISO standards for testing; designing robust clinical trials.

VIII. CONCLUSION

The metallic implants like plates and screws are still the gold standard in fracture fixation; still, their clinical practica has been characterized by inevitable drawbacks, which include stress shielding, implant loosening, risk of infections, mechanical mismatch, and the common need of secondary removal operations. These disadvantages have led to the outcome of trying to identify other fixation approaches which can offer adequate stability and encourage natural bone regeneration. The initial synthetic bone glues such as PMMA and cyanoacrylates proved that good adhesion is not sufficient to fix a fracture. Their inability to degrade biologically, exothermic curing, cytotoxic degradation products and the poor biological integration reduced their clinical applicability. These failures underlined the necessity to develop adhesives which are both mechanically strong, biologically, as well as those with controlled degradation. The latest developments in the bioinspired materials have brought a big step in the sphere of bone adhesion. Catechol chemistry Mussel-like catechols, citrate-based biomaterials and organic-inorganic composites have enabled the production of injectable, biodegradable adhesives with high wet bonding, increased osteointegration, and biodegradation kinetics similar to that of bone healing. also the natural and plant-based biomaterials have become the new promising alternatives since they have intrinsic biocompatibility, antimicrobial activity and osteogenic potential and thus they promote fixation and biological repair. Although this shows a promising development, it has a lot of challenges such as long-term safety, performance under complicated fracture conditions, scalable manufacturing, and permission by the regulatory authorities. Massive clinical trials are necessary to prove the effectiveness and high quality of bone adhesives compared to traditional fixation techniques. In general, bioinspired and biodegradable bone adhesives are an exciting move in a new approach of minimally invasive, biologically active fracture management, which may change the future orthopedic approach to treatment.

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Volume 6, Issue 7, April 2026
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