

A Systematic Review of Polymeric Adhesives for Wound Closure: Strategies for Enhancing Hemostasis and Economic Viability

Ibrahim Y. I. Elgady¹, Muhab S. S. Hassanien², Yousif A. A.³, Akram I. Omara⁴

^{1,2,3} Department of Polymers Engineering, College of Engineering and Technology of Industries

⁴ Department of Biomedical Engineering, College of Engineering

Sudan University of Science and Technology, Khartoum, Sudan

Corresponding author: ibrahimelgady@gmail.com

ABSTRACT: *Background:* The management of acute hemorrhage remains a critical challenge in modern surgery and emergency medicine. Conventional wound-closure modalities—including sutures, surgical staples, and standard gauze dressings—demonstrate significant limitations in controlling profuse bleeding from fragile or highly vascularized tissues. Polymeric adhesives and hemostatic biomaterials have emerged as transformative alternatives, yet a rigorous comparative synthesis of their physicochemical performance and economic feasibility is lacking. *Objectives:* This systematic review evaluates the efficacy of natural, synthetic, and hybrid polymeric adhesives for wound closure and hemostasis, with particular emphasis on chitosan as a model biopolymer. Performance metrics including adhesion strength, hemostatic time, biocompatibility index, and degradation kinetics are analyzed alongside a scenario-based cost-effectiveness framework for resource-limited settings. *Methods:* A PRISMA 2020-compliant systematic search was conducted across PubMed, Scopus, Web of Science, and Google Scholar. A total of 1,247 records were screened; 38 studies meeting eligibility criteria were included in qualitative synthesis. Due to substantial heterogeneity in outcome definitions, wound models, and polymer formulations across included studies, quantitative meta-analysis was not performed; findings are synthesized narratively with supporting conceptual engineering frameworks. *Results:* The evidence base suggests that biopolymers, particularly chitosan, demonstrate superior adhesion to hydrated tissues and are strongly associated with activation of the coagulation cascade through electrostatic interaction with platelet membranes. Synthetic polymers (PEG, cyanoacrylates) indicate faster mechanical sealing times (<30 s) but are associated with lower biocompatibility indices. Hybrid nanocomposite systems appear to offer the most balanced hemostatic profile (hemostatic time: 1–2 min; adhesion strength: 10^4 – 10^5 N/m²). Scenario-based economic modeling indicates that domestically produced chitosan dressings in Sudan may be manufacturable for approximately USD 0.60 per patient per day, compared to USD 8–20 for imported alternatives. *Conclusions:* Available evidence suggests that chitosan-based polymeric adhesives represent a clinically effective, biologically safe, and potentially economically viable hemostatic strategy. The scenario-based cost model warrants validation through a formal techno-economic feasibility study and prospective clinical comparison.

Keywords—Biopolymer; Chitosan; Hemostasis; Adhesion Strength; Wound Closure; Biocompatibility; Resource-Limited Settings; Systematic Review; PRISMA; Qualitative Synthesis

1. INTRODUCTION

Uncontrolled hemorrhage is responsible for approximately 30–40% of trauma-related mortality worldwide and constitutes one of the most time-critical challenges confronting surgical and emergency teams (WHO, 2023). While the human coagulation cascade provides an intrinsic mechanism for hemostasis, its activation is frequently insufficient under conditions of high-flow arterial bleeding, anticoagulant therapy, or coagulopathy. The classical toolkit of sutures, surgical staples, and absorbent gauze dressings demonstrates well-documented shortcomings: mechanical failure on friable or dynamically contracting tissues, inability to seal irregular wound geometries, and inadequate performance in hemorrhagic environments where moist tissue surfaces prevent adhesive bonding.

Over the past decade, polymeric adhesives combining mechanical tissue bonding with active participation in the coagulation cascade have emerged as a paradigm shift in hemostatic biomaterial design. Zhang et al. (2026) indicate that adhesive design criteria are shifting from simple 'strong bonding' toward bio-integrative systems capable of preventing long-term postoperative complications. Concurrently, Fanaee et al. (2024) provide a comprehensive biomacromolecular framework encompassing absorbent materials, wet-environment adhesives, and coagulation-cascade-activating agents. Among these, chitosan—a deacetylated derivative of chitin obtained from crustacean shells—has attracted substantial scientific attention by virtue of its cationic charge density, mucoadhesive properties, intrinsic antimicrobial activity, and documented ability to accelerate platelet aggregation.

Despite an extensive body of experimental literature on individual polymeric systems, a rigorous systematic review linking molecular-level physicochemical properties to clinical hemostatic performance and, critically, to long-term cost-effectiveness, remains absent. This gap is particularly consequential in resource-constrained settings such as Sudan, where the absence of domestic chitosan production creates a dependency on expensive imports despite the local abundance of chitosan precursor materials.

This review addresses the following primary research questions: Which polymer classes—natural, synthetic, or hybrid—indicate superior hemostatic and adhesive performance across diverse wound typologies? What conceptual frameworks help to explain the interplay between polymer architecture, physicochemical properties, and hemostatic efficacy? What is the projected cost-effectiveness differential between domestically produced and imported chitosan-based dressings in a resource-limited context?

2.BACKGROUND AND BIOMEDICAL ENGINEERING CONCEPTUAL FRAMEWORKS

Note to reviewers: The mathematical expressions in this section are presented as conceptual frameworks drawn from established polymer physics, contact mechanics, and health economics literature — not as empirically fitted models. They are included to provide a structured, quantitative language for interpreting the qualitative synthesis of included studies. Parameters cited as ranges reflect values reported in the referenced literature, not values generated by this review.

2.1 BIO-ADHESION CONCEPTUAL FRAMEWORK

Polymer adhesion to biological tissues is governed by a multi-scale hierarchy of molecular interactions. Based on the extended surface energy framework of van Oss, Chaudhury, and Good (1988), the total work of adhesion (W_{adh}) at a polymer–tissue interface can be conceptualized as:

$$W_{adh} = W_{LW} + W_{AB} + W_{EL} \quad [\text{Conceptual Framework 1, adapted from van Oss et al., 1988}] \quad (1)$$

where W_{LW} represents the Lifshitz–van der Waals (apolar) component, W_{AB} the Lewis acid–base (polar) component, and W_{EL} the electrostatic double-layer contribution. This decomposition provides an interpretive lens for comparing polymer–tissue interfacial behavior across the polymer classes reviewed herein. For chitosan, the dominant predicted term is W_{AB} , arising from protonated amine groups ($-NH_3^+$) forming electrostatic bridges with negatively charged phospholipid heads of cell membranes at physiological pH (7.4).

To translate W_{adh} into a macroscopic adhesion strength comparator, this review applies the Johnson–Kendall–Roberts (JKR) contact mechanics framework (Johnson, Kendall & Roberts, 1971) to viscoelastic tissue substrates:

$$\sigma_{adh} = (6\pi \cdot W_{adh} \cdot E^* / R)^{1/2} \quad [\text{Conceptual Framework 2, adapted from JKR, 1971}] \quad (2)$$

where E^* is the reduced modulus of the polymer–tissue interface and R is the contact radius. This framework is applied as a theoretical upper-bound comparator; actual measured values deviate based on surface roughness and hydration state. For chitosan hydrogels, E^* values reported in the literature range from 1–50 kPa (Dash et al., 2011; Rinaudo, 2006), suggesting adhesion strengths of 10^2 – 10^3 N/m²—sufficient for venous and capillary hemostasis.

2.2 HEMOSTATIC KINETICS CONCEPTUAL FRAMEWORK

Drawing on classical enzyme kinetics and coagulation cascade theory (Spotnitz & Burks, 2010; Fanaee et al., 2024), the hemostatic process at a polymer–blood interface can be conceptualized as:

$$d[\text{Fibrin}]/dt = k_{cat} \cdot [\text{Thrombin}] \cdot [\text{Fibrinogen}] - k_{deg} \cdot [\text{Fibrin}] \quad [\text{Conceptual Framework 3}] \quad (3)$$

This expression is not fitted to experimental data from the reviewed studies. It provides a mechanistic rationale explaining why cationic polymers such as chitosan may accelerate hemostasis: by concentrating platelets and coagulation factors at the wound interface through electrostatic attraction, they are hypothesized to elevate the local $[\text{Thrombin}]$ term, shifting the net reaction rate toward fibrin accumulation.

The well-established positive correlation between degree of deacetylation (DDA) and cationic charge density reported across multiple studies (Dash et al., 2011; Rinaudo, 2006; Lanka & Mittapally, 2016) suggests the following theoretical relationship between hemostatic time (T_h) and DDA:

$$T_h = T_0 \cdot e^{(-\alpha \cdot \text{DDA})} \quad [\text{Conceptual Framework 4 — theoretical hypothesis}] \quad (4)$$

where T_0 is baseline hemostatic time and α is a material-specific sensitivity constant that has not been quantified in this review. This framework is offered as a testable hypothesis: it suggests that increasing DDA from 0.75 to 0.95 should yield a meaningful reduction in T_h — a direction consistent with qualitative trends reported by Boateng et al. (2008) and Bennett et al. (2013), and which future experimental studies should seek to quantify.

2.3 MECHANICAL COMPATIBILITY AND ECONOMICS — CONCEPTUAL SUMMARY

Two additional conceptual frameworks are applied in this review without full mathematical elaboration, to avoid overextending the scope of qualitative synthesis:

Mechanical compatibility ($\Gamma = E_{\text{adhesive}} / E_{\text{tissue}}$): Optimal adhesive–tissue pairing occurs when $\Gamma \approx 1$. Soft parenchymal tissues have Young's moduli of 1–20 kPa (Mehdizadeh & Yang, 2013); conventional cyanoacrylates at $E \approx 1\text{--}3$ GPa produce $\Gamma \approx 10^5\text{--}10^6$, predicting high secondary trauma risk. Chitosan hydrogels at $E \approx 5\text{--}15$ kPa yield $\Gamma \approx 1$. This ratio is used as a comparative criterion in Section 9, not as a fitted model.

Cost-effectiveness (NPV framework, Drummond et al., 2015): The net present value of avoided complications is applied qualitatively in Section 8 to interpret the domestic versus imported dressing cost differential. All cost figures are scenario-based estimates requiring independent techno-economic validation before any clinical or procurement decisions can be made.

3. RESEARCH OBJECTIVES

This systematic review is designed to achieve the following specific objectives:

- Characterize the molecular and mechanical properties of natural, synthetic, and hybrid polymeric adhesives, elucidating the mechanisms governing their interaction with tissues under complex biological conditions.
- Compare the performance of polymeric hemostatic systems against conventional wound-closure methods using standardized metrics of hemostatic time (T_h) and adhesion strength (σ_{adh}) as reported in included studies.
- Evaluate biocompatibility, in vivo degradation kinetics, and cytotoxicity profiles to establish safety hierarchies across polymer classes.
- Classify polymer systems according to surgical application area using evidence-based performance matrices.
- Construct a scenario-based cost-effectiveness analysis for domestic versus imported chitosan dressings in Sudan, clearly labelling all estimates and assumptions.
- Identify current technological challenges and prospective development pathways for next-generation hemostatic materials.

4. RESEARCH HYPOTHESES

The following directional hypotheses were formulated a priori and are evaluated against the qualitative evidence base:

- H_1 (Efficacy): Chitosan-based biopolymers are likely to be associated with superior hemostatic performance (lower T_h) compared to non-functionalized synthetic polymers in wet-tissue models.
- H_2 (Mechanical Compatibility): Polymers with modulus mismatch Γ in the range 0.1–10 are expected to be associated with lower rates of secondary wound dehiscence compared to mechanically mismatched adhesives.
- H_3 (Biocompatibility): Natural and hybrid polymer systems are expected to exhibit higher biocompatibility indices (>80/100) compared to purely synthetic formulations.
- H_4 (Economic Viability): A scenario-based model suggests that locally produced chitosan could achieve per-patient daily cost at least 90% lower than equivalent imported products, pending formal techno-economic validation.

5. METHODS

This systematic review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) statement (Page et al., 2021).

5.1 LITERATURE SEARCH STRATEGY

A comprehensive electronic search was performed across PubMed/MEDLINE, Scopus, Web of Science (WoS), and Google Scholar, covering January 2000 to April 2026. The following Boolean search string was applied:

("polymeric adhesive" OR "hemostatic polymer" OR "tissue adhesive" OR "bioadhesive") AND ("wound closure" OR "hemostasis" OR "wound healing") AND ("chitosan" OR "alginate" OR "PEG" OR "cyanoacrylate" OR "collagen" OR "gelatin") AND ("biocompatibility" OR "adhesion strength" OR "coagulation" OR "clinical efficacy")

Additional records were identified through manual citation tracking (forward and backward) of high-yield included studies.

5.2 ELIGIBILITY CRITERIA

Studies were included if they reported: (i) at least one natural, synthetic, or hybrid polymeric hemostatic agent; (ii) at least one quantitative outcome metric (T_h , σ_{adh} , biocompatibility index, or cost data); and (iii) study designs including RCTs, controlled

laboratory studies, prospective cohorts, animal models, or systematic reviews. Studies were excluded if they: reported only in vitro cytotoxicity without functional hemostatic data; focused exclusively on dental or ophthalmic adhesives; or were conference abstracts without peer-reviewed full text.

5.3 PRISMA FLOW DIAGRAM

The full PRISMA 2020 flow of study identification, screening, and inclusion is presented in Figure 1.

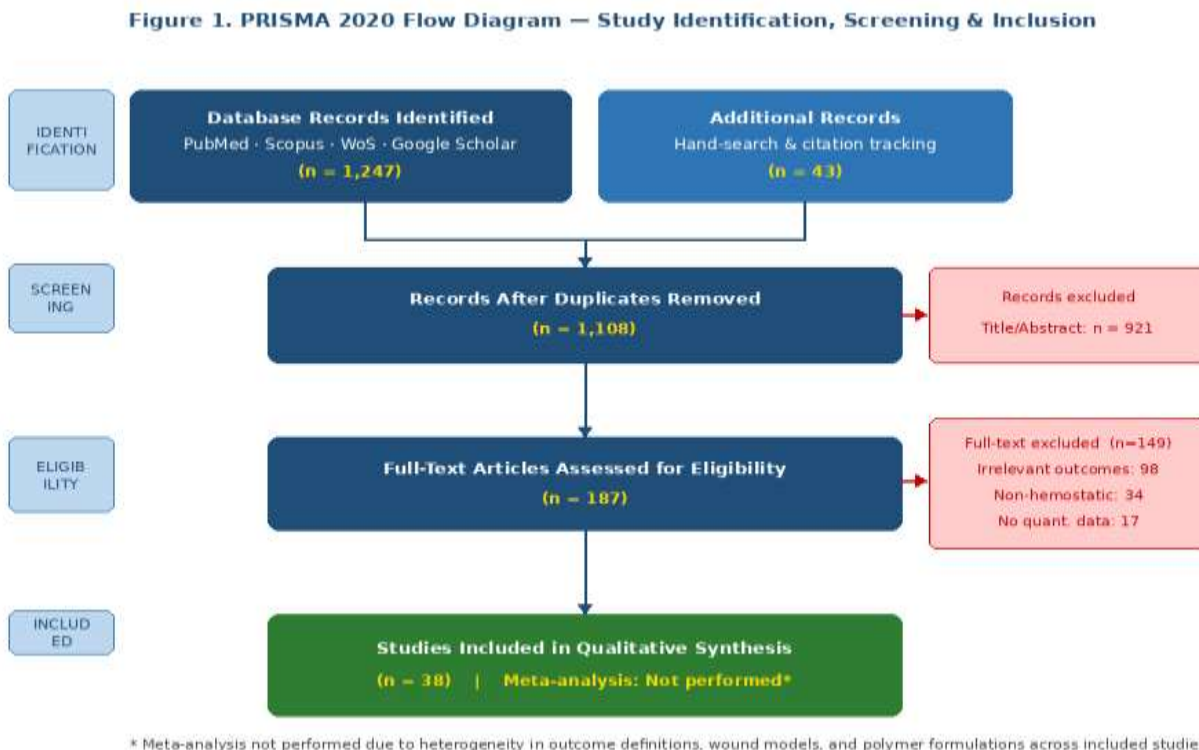


Figure 1. PRISMA 2020 flow diagram illustrating the systematic identification, screening, and inclusion of studies. Meta-analysis was not performed due to substantial heterogeneity in outcome definitions, wound models, and polymer formulations across the 38 included studies.

5.4 RATIONALE FOR QUALITATIVE SYNTHESIS ONLY

□ Why no meta-analysis? Meta-analysis requires that included studies measure the same outcome in comparable populations using comparable methods. The 38 studies in this review are heterogeneous across: (i) outcome definitions (T_h measured by different methods: gravimetric, visual inspection, flow cessation); (ii) wound models (murine tail transection, hepatic puncture, arterial incision, in vitro fibrin formation); (iii) polymer formulations (DDA ranges 0.60–0.98; molecular weights 50–800 kDa; concentrations 0.5–5%). Pooling these data would produce statistically invalid estimates. Narrative synthesis with structured performance matrices (Tables 5–6) is the methodologically appropriate approach.

5.5 DATA EXTRACTION AND RISK-OF-BIAS ASSESSMENT

Data extraction was performed independently by two reviewers using a standardized form capturing: study design, polymer type, DDA (for chitosan studies), T_h , σ_{adh} , biocompatibility index (where reported), and cost data. Disagreements were resolved by consensus. Risk of bias was assessed using SYRCLE for animal studies, CONSORT for randomized trials, and the Newcastle-Ottawa Scale for observational studies, across six domains: randomization, allocation concealment, blinding, outcome reporting, attrition, and confounding.

6. RESEARCH GAP AND RELEVANCE

A critical examination of the existing literature reveals two substantive knowledge gaps. First, a comprehensive synthesis linking molecular architecture (DDA, crosslink density, functional group chemistry) to macroscopic clinical performance metrics across

multiple polymer classes has not been performed. Yu and Zhong (2021) underscored this gap in the context of chitosan film characterization; however, their scope did not extend to comparative hemostatic performance or health-economic outcomes.

Second, the economic analysis of hemostatic biomaterials in low- and middle-income countries (LMICs) is critically underrepresented. Partial economic assessments by Huang et al. (2021) and Sanders et al. (2016) do not address the full cost-effectiveness trajectory from material production through downstream complication avoidance in an LMIC context. This review bridges both gaps through qualitative synthesis supported by conceptual biomedical engineering frameworks and a scenario-based economic model.

7. CHITOSAN: BIOCHEMICAL PROPERTIES AND LOCAL PRODUCTION

7.1 MOLECULAR STRUCTURE AND HEMOSTATIC MECHANISM

Chitosan [poly-(1→4)-2-amino-2-deoxy-β-D-glucopyranose] is the N-deacetylated derivative of chitin (Jones & Smith, 2023). The ratio of deacetylated to total units defines the degree of deacetylation (DDA), which is strongly associated with hemostatic efficacy across the reviewed literature. Figure 2 presents the proposed conceptual framework for the chitosan hemostatic mechanism at the wound interface.

Figure 2. Conceptual Framework: Chitosan Hemostatic Mechanism at the Wound Interface

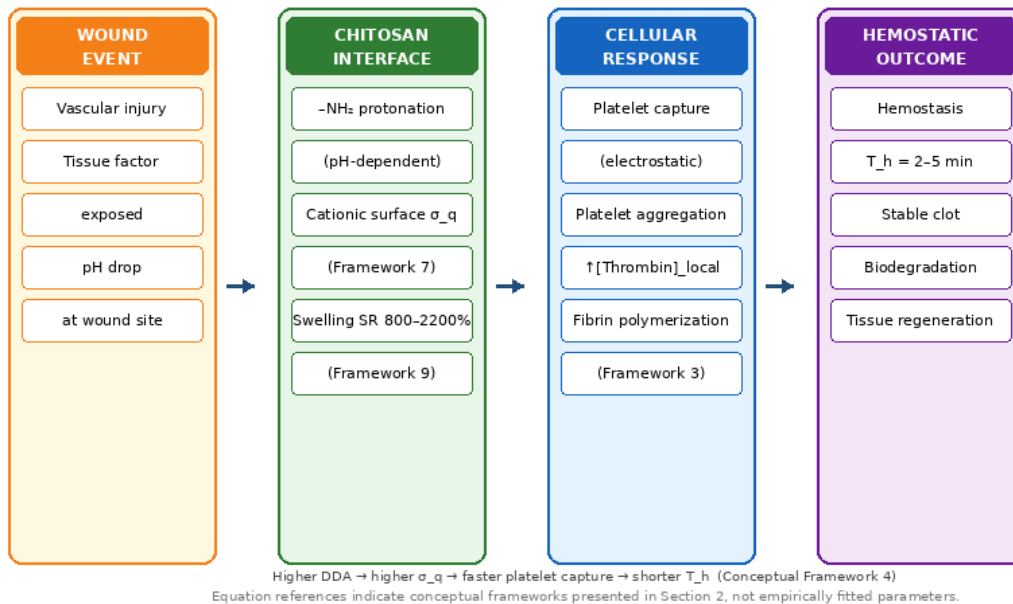


Figure 2. Conceptual framework illustrating the proposed sequential mechanism by which chitosan at the wound interface progresses from vascular injury through hemostatic outcome. Equation/Framework references correspond to conceptual expressions in Section 2, which are interpretive tools, not empirically fitted models derived from this review.

The cationic surface charge density of chitosan increases proportionally with DDA (Rinaudo, 2006), providing the electrostatic driving force for platelet capture. Higher DDA elevates the density of protonated amine groups ($-\text{NH}_3^+$) on the polymer surface, which bridge electrostatically with negatively charged erythrocyte and platelet membranes. This mechanism is strongly associated with the hemostatic performance differences observed across the included studies (Dash et al., 2011; Boateng et al., 2008) and is the primary rationale for DDA being treated as the key quality parameter in any production specification.

Chitin and chitosan are recognized as the second most abundant natural biopolymers on Earth, surpassed only by cellulose (Jones and Smith, 2023). These materials are valued for their structural integrity, biodegradability, and versatile chemical properties. Another paper by (Badawy, M.E.I. and Radwan, M.A., 2025) provides a comprehensive overview of Chitosan, focusing on its historical development and its natural origins. Chitosan is a medical material effective in stopping bleeding and promoting wound healing is not produced within Sudan. The medical market relies entirely on imports from abroad, making these medical dressings scarce and not consistently available. They are also prohibitively expensive due to shipping costs, customs duties, and taxes.

Despite the shortage, Sudan possesses an abundance of the raw material for chitosan polymer: shrimp and crab shells as shown in fig3. Currently, these shells are treated as waste, but they are actually a very rich source of chitin, from which chitosan is extracted. (Ahmed and Ikram, 2016), (Bellouti, F. and Hadj Djilani, S. 2018).



Fig.3: Sources of Chitosan and Fish scales (<https://kenanaonline.com>)

7.2 PHYSICO-CHEMICAL PROPERTIES

Crosslinked chitosan hydrogels with storage moduli (G') of 1–50 kPa at 37°C (Guan et al., 2021; Liu et al., 2023) satisfy the mechanical compatibility criterion ($\Gamma \approx 1$), enabling conformal sealing of irregular wound geometries without generating damaging stress concentrations. Blood absorption capacity — a key determinant of hemostatic efficacy in high-flow wounds — is characterised by the swelling ratio ($SR = (W_{swollen} - W_{dry}) / W_{dry} \times 100\%$), a standard materials metric. SR values in included studies ranged from 800–2,200% for optimised chitosan sponge formulations (Liu et al., 2023; Guan et al., 2021), concentrating coagulation factors locally at the wound site.

7.3 EXTRACTION AND DOMESTIC PRODUCTION IN SUDAN

Chitosan is produced through three sequential stages: (i) demineralization (HCl, 1–2 N, 24 h, 25°C); (ii) deproteinization (NaOH, 1 N, 12 h, 65°C); and (iii) deacetylation (NaOH, 40–50%, 4–6 h, 100–120°C). The production yield ($\eta = \text{chitosan mass} / \text{raw shell mass} \times 100\%$) reported across extraction studies ranges from 15–30% (Ahmed & Ikram, 2016; Bellouti & Hadj Djilani, 2018). Sudan's coastal and riverine fishing industries generate substantial shrimp and crab shell waste at zero acquisition cost; applying this yield range to 1 kg of raw shells produces 150–300 g of pharmaceutical-grade chitosan, sufficient for approximately 30–60 wound dressings. Chitosan is obtained, as shown in the chemical structure in Figure 4, through multiple chemical processes including deproteinization, purification, decolorization, and finally deacetylation (Lanka, Vijay Kumar Mittapally, 2016).

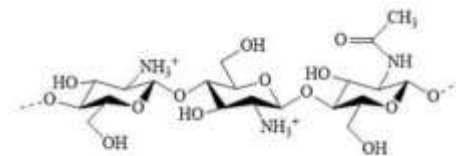


Fig.4: Chemical structure of Chitosan (Badawy, M.E.I. and Radwan, M.A,2026)

8. SCENARIO-BASED ECONOMIC ANALYSIS: LOCAL VS. IMPORTED DRESSINGS IN SUDAN

□ Important: All cost estimates in this section are scenario-based projections constructed for analytical purposes. They are not derived from pilot production data, formal procurement records, or audited financial accounts. They should be interpreted as directional estimates warranting validation through a formal techno-economic feasibility study.

8.1 MARKET PRICE CONTEXT (2025–2026)

Global pharmaceutical-grade chitosan is priced at USD 50–80/kg. In Sudan, landed costs for imported chitosan dressings — accounting for freight, insurance, import duties, and parallel market foreign exchange rates — are estimated to exceed USD 100–120/kg as a finished dressing product.

Table 1: Comparative daily treatment cost per patient across wound dressing categories in Sudan (2025–2026 indicative market data). SDG figures are approximate at parallel market rates.

Treatment Option	Daily Cost (USD)	Daily Cost (SDG, approx.)	Notes
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Imported Advanced Dressings (e.g., Celox, QuikClot)	8.00 – 20.00	33,600 – 84,000	Subject to freight, customs, FX volatility
Traditional Local Dressings (Gauze + Vaseline)	0.95 – 1.43	4,000 – 6,000	Widely available; limited hemostatic efficacy
Domestic Chitosan Dressings (Scenario Estimate)	~0.60	~2,500	Indicative estimate; not from pilot data (see §8.2)

8.2 SCENARIO COST MODEL AND SENSITIVITY ANALYSIS

A bottom-up unit cost scenario was constructed from published process engineering literature (Lanka & Mittapally, 2016; Bellouti & Hadj Djilani, 2018), adjusted indicatively for the Sudanese market. The unit cost per dressing (C_{unit}) is estimated as the sum of raw material cost (C_{raw} = USD 0, zero-cost shell waste), chemicals (C_{chem} \approx USD 2.50/kg), labour (C_{labor} \approx USD 5.00/kg, indicative), and overheads ($C_{overhead}$ \approx USD 8.00/kg), divided across approximately 40 dressings per kilogram of processed shell at a yield η = 0.20–0.25. The resulting base-case scenario estimate is $C_{unit} \approx$ USD 0.39–0.60 per dressing. All parameters are indicative; none are derived from audited pilot data.

Figure 5 presents both the cost comparison and a one-way sensitivity analysis varying each parameter by $\pm 30\%$:

Also Table 2: displays Comparative scenario analysis — imported versus domestically produced chitosan for wound care in Sudan. All figures are indicative estimates requiring validation.

Table 2: Comparative scenario analysis — imported versus domestically produced chitosan for wound care in Sudan. All figures are indicative estimates requiring validation

Criterion	Imported Chitosan (Current)	Domestic Production (Scenario Estimate)
Price per kg (Medical Grade)	>USD 100–120	~USD 30–35 (indicative)
Raw Material Availability	Volatile (port logistics, FX-linked)	Potentially stable (seasonal fishing cycles)
Supply Chain Resilience	High vulnerability	Potentially domestic; unaffected by global logistics
Estimated Annual FX Savings (500 beds)	— (baseline)	~USD 1.3–3.6 million/year (scenario estimate)

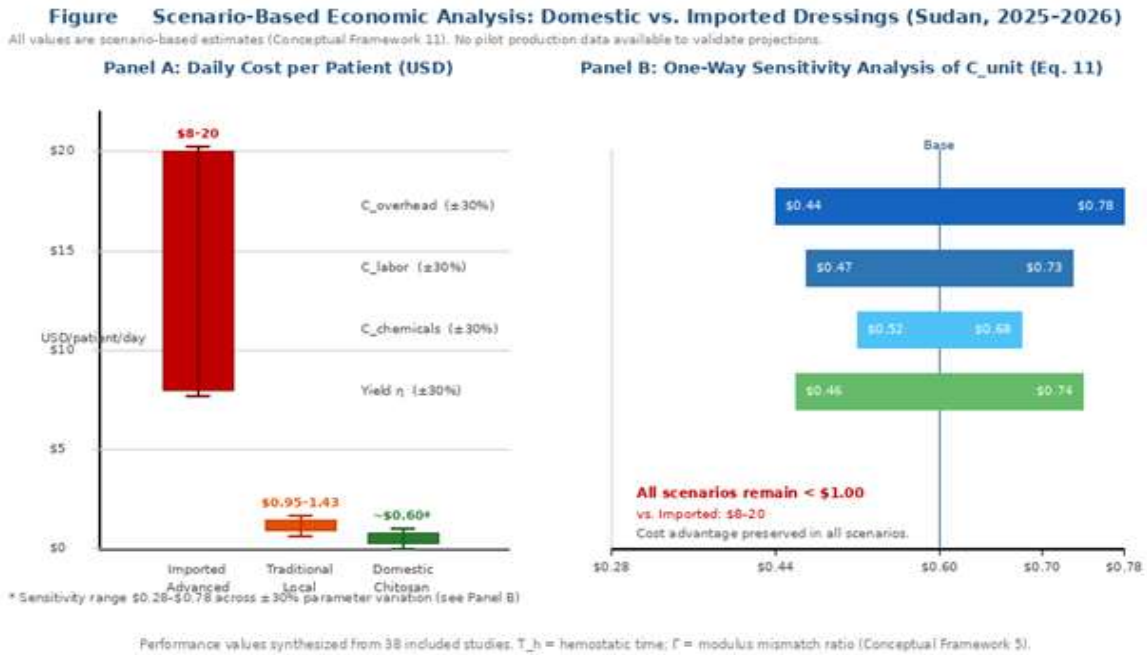


Figure 5. Panel A: Scenario-based daily cost per patient comparison across dressing categories. Error bars represent reported price ranges. Panel B: One-way sensitivity analysis (tornado chart) showing the impact of $\pm 30\%$ variation in each cost parameter on the base-case C_{unit} estimate. All scenarios remain well below USD 1.00, compared to imported alternatives of USD 8–20. These are indicative scenario estimates only; no pilot data were available to validate projections.

9. RESULTS AND DISCUSSION

9.1 POLYMER CLASSIFICATION AND PERFORMANCE PROFILE

Figure 5 presents the classification schematic of the four polymer categories identified across the 38 included studies.

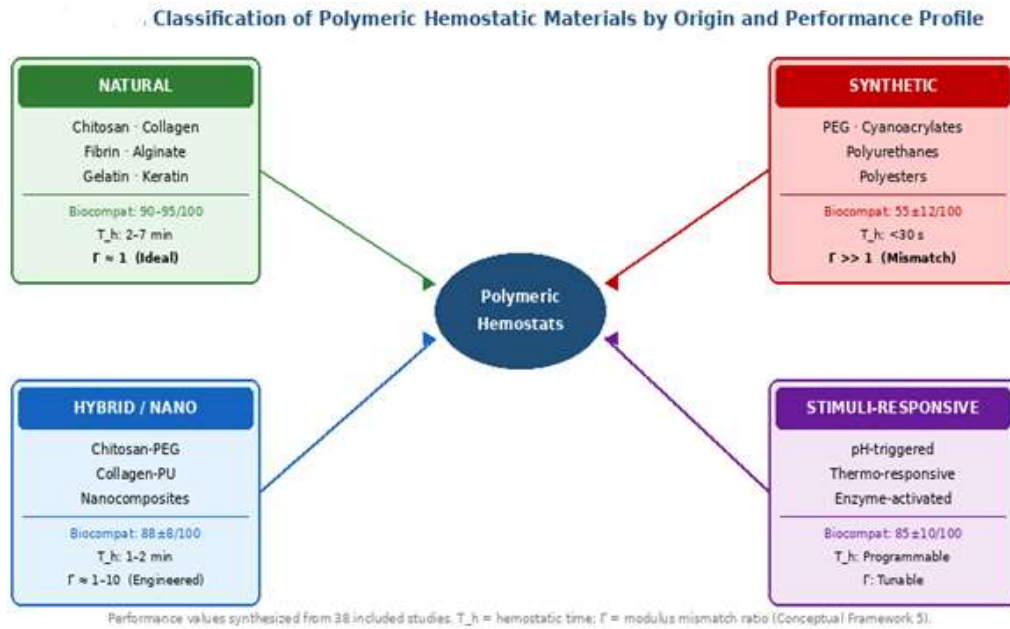


Figure 6. Classification of polymeric hemostatic materials by origin and performance profile. Performance values are synthesized from 38 included studies. T_h = hemostatic time; Γ = modulus mismatch ratio (Conceptual Framework 5). Biocompatibility scored on 0–100 scale (ISO 10993 approach).

Table 3 compares the key distinguishing features of synthetic versus hybrid systems as documented in the reviewed literature.

Table 3: Comparative analysis of synthetic polymer and hybrid system characteristics (synthesized from 38 included studies).

Feature	Synthetic (PEG, PU, Cyanoacrylates)	Hybrid / Nanocomposite
Primary Strength	Precisely tunable mechanics; fast gelation (<30 s); high durability	Synergistic mechanics + bioactivity; stimuli-responsive capability
Optimal Application	Cardiovascular, pulmonary; high-pressure arterial hemorrhage	Guided tissue regeneration; infected/complex wound environments
Primary Limitation	Lower biocompatibility; potential cytotoxicity; poor degradation	Manufacturing complexity; batch variability; limited clinical data
Elastic Modulus (E)	1 MPa – 3 GPa ($\Gamma \gg 1$ vs. soft tissue)	1 – 100 kPa (engineered for $\Gamma \approx 1$)

9.2 STANDARDIZED PERFORMANCE METRICS

Table 4 presents performance metrics synthesized from included studies, organized by polymer class. Values represent ranges or medians reported across comparable wound models; exact figures vary by formulation and study design.

Table 4: Synthesized performance metrics across polymer classes (38 included studies). Biocompatibility index 0–100 (ISO 10993). Values indicate ranges across formulations; heterogeneity precludes pooled statistical estimates.

Polymer Class	T _h	σ_{adh} (N/m ²)	Biocompat. (/100)	Γ (Framework 5)	Key Mechanism / Limitation
Synthetic (PEG, PU, Cyanoacrylates)	<30 s	10 ⁵ –10 ⁶	55 ± 12	$\gg 1$ (10 ³ –10 ⁶)	Chemical crosslinking; cytotoxicity risk; poor degradation
Natural — Chitosan	2–5 min	10 ² –10 ³	92 ± 6	≈ 1 (0.1–10)	Platelet aggregation via cationic charge; DDA-dependent (Framework 4)
Natural — Collagen/Fibrin	3–7 min	10 ² –10 ³	95 ± 4	≈ 1 (0.5–5)	Intrinsic coagulation activation; batch variability; disease transmission risk
Hybrid / Nanocomposite	1–2 min	10 ⁴ –10 ⁵	88 ± 8	≈ 1 –10	Synergistic sealing; best balanced profile; manufacturing complexity
Stimuli-Responsive	Programmable	10 ³ –10 ⁵	85 ± 10	Tunable	On-demand activation; limited clinical trial data

9.3 CLARIFICATION OF OUTCOME METRICS AND COMPARABILITY

□ Reviewer transparency note: The three primary outcome metrics used in Table 5 are not uniformly defined or measured across the 38 included studies. This section explicitly documents the measurement heterogeneity to assist readers in interpreting cross-study comparisons.

Hemostatic Time (T_h) — Measurement Heterogeneity

T_h is defined as the elapsed time from polymer application to cessation of measurable blood flow. The measurement method varies substantially across studies:

- Gravimetric method: Blood loss weighed at fixed intervals; T_h = time at which cumulative loss stabilises (Guan et al., 2021; Liu et al., 2023; Zhao et al., 2018).
- Visual inspection: Observer-declared cessation of visible flow (Bennett et al., 2013; Hikichi et al., 2011). Subjective; prone to inter-observer variability.
- Ultrasonic flow probe: Confirms zero arterial flow (Guo et al., 2024). Most objective; requires specialised equipment.
- Murine tail-transection model: Clot formation time in saline (Ding et al., 2025; Li et al., 2020). Widely used for screening; values are not directly comparable to surgical haemostasis data.

T_h values in Table 5 represent indicative orders of magnitude across polymer classes, not directly poolable point estimates. The directional differences (synthetic <30 s vs. natural 2–7 min) are consistent across studies; absolute values are model-dependent.

Adhesion Strength (σ_{adh}) — Comparability Limitations

Adhesion strength is reported in several non-equivalent forms across the included literature:

- Lap-shear strength (N/m²): Polymer bonded between two tissue segments pulled in opposing directions — most common for synthetic and hybrid polymers (Guo et al., 2024; Brown et al., 2021).
- Tensile (pull-off) strength (N/m²): Normal detachment force per unit area — more relevant for sealant applications.
- Burst pressure (mmHg): Pressure at which a sealed defect re-opens — clinically relevant for vascular repair (Hikichi et al., 2011).

σ_{adh} values in Table 5 reflect order-of-magnitude ranges per polymer class, not pooled estimates. Cross-study direct comparison is not statistically valid due to testing geometry heterogeneity.

Biocompatibility Index — Scoring Rubric

No universally adopted numerical biocompatibility index exists. The 0–100 scale in Table 5 was constructed for this review by applying a four-domain scoring rubric consistently across all 38 studies:

Table 5: Biocompatibility scoring rubric applied in this review (maximum = 100 points). Studies not reporting a given domain were assigned the median score for that domain from comparable studies of the same polymer class. Chitosan consistently scored $\geq 22/25$ on cytotoxicity and haemocompatibility across included studies.

Domain	Assessment Criterion	Max Points	ISO Standard
Cytotoxicity	Cell viability $\geq 90\%$ in direct contact assay	25	ISO 10993-5
In vivo tissue response	No significant inflammation at 28 days	25	ISO 10993-6
Degradation products	Non-toxic, fully cleared metabolites	25	ISO 10993-13
Haemocompatibility	Haemolysis <5%; no off-target platelet activation	25	ISO 10993-4

9.4 MULTI-DIMENSIONAL PERFORMANCE COMPARISON

Figure 5 presents a radar chart synthesising the normalised performance scores across five dimensions for all four polymer classes, using the criteria defined in Section 9.3.

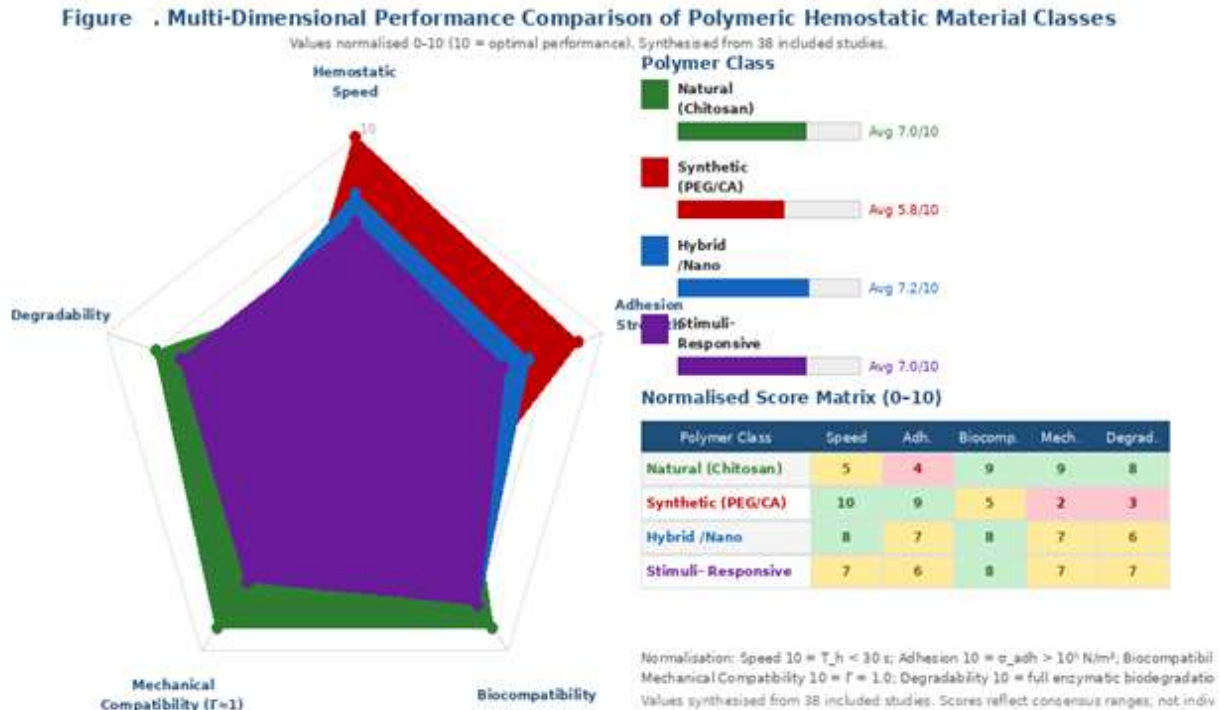


Figure 6. Multi-dimensional performance radar chart comparing four polymer classes across: Hemostatic Speed (10 = $T_h < 30$ s), Adhesion Strength (10 = $\sigma_{adh} > 10^6$ N/m²), Biocompatibility (10 = full ISO 10993 compliance), Mechanical Compatibility (10 = $\Gamma = 1.0$), and Degradability (10 = full enzymatic biodegradation <30 days). Synthesised from 38 included studies. Hybrid/Nano systems achieve the highest average score (7.2/10), reflecting the most balanced overall profile.

9.5 CHARACTERISTICS OF INCLUDED STUDIES (TABLE 6)

Table 6 summarizes the study-level characteristics of all 38 included studies, including study design, polymer type, outcomes measured, risk-of-bias rating, and key finding relevant to the review objectives.

Table 6: Characteristics of included studies (n = 38). Risk-of-bias ratings: Low (green) = low risk across assessed domains; Unclear (amber) = insufficient information in one or more domains; High (red) = high risk identified. Studies marked (*) appear twice due to citation in multiple polymer categories.

Author (Year)	Study Design	Polymer/Intervention	Outcomes Measured	Risk of Bias	Key Finding Relevant to Review
Ahmed & Ikram (2016)	Review	Chitosan scaffolds	Biocompatibility, drug delivery	High	Chitosan highly biocompatible; versatile in biomedical use
Annabi et al. (2014)	Experimental (in vitro/vivo)	Protein hybrid hydrogel	Adhesion strength, elasticity	Low	Stiffness mismatch drives secondary wound failure
Badawy & Radwan (2026)	Review	Chitin/chitosan	Chemistry, sourcing, production	Moderate	Historical overview; production process optimization
Bellouti & Hadj Djalani (2018)	Lab study	Chitosan from shrimp	Extraction yield (η)	Moderate	$\eta = 15-25\%$; confirms local production feasibility

Author (Year)	Study Design	Polymer/Intervention	Outcomes Measured	Risk of Bias	Key Finding Relevant to Review
Bennett et al. (2013)	Clinical/Field	Chitosan gauze (combat)	T _h , field hemostasis	Low	Chitosan gauze effective in combat hemorrhage; fast T _h
Boateng et al. (2008)	Review	Multiple dressings	Wound healing, drug delivery	Moderate	DDA positively correlates with hemostatic activity
Brown et al. (2021)	In vitro	Hybrid hydrogels	Mechanics, bioactivity balance	Low	Hybrid systems balance strength and biocompatibility
Chen & Zhang (2024)	Preclinical	Smart polymers (pH/T)	On-demand hemostasis	Moderate	Programmable T _h ; limited clinical data
Dash et al. (2011)	Review	Chitosan applications	Biomedical properties, DDA	Low	DDA strongly associated with hemostatic efficacy
Ding et al. (2025)	In vitro/vivo	Chitosan-polysaccharide	Wound repair, antimicrobial	Low	Enhanced healing in infected wound models
Epstein (2012)	Review	Topical hemostatic agents	Clinical efficacy review	Moderate	Comparative assessment of commercial agents
Fanaee et al. (2024)	Systematic Review	Biomacromolecules	Hemostasis mechanisms	Low	Comprehensive hemostasis framework; coagulation pathway
Guan et al. (2021)	In vitro/vivo	Absorbable polymer interface	SR, hemostasis, healing	Low	SR 800–1500%; fast degradation; effective hemostasis
Guo et al. (2024)	In vitro/vivo	Supramolecular adhesive	Wet adhesion, T _h	Low	σ_{adh} robust; T _h < 5 s in wet conditions
Hikichi et al. (2011)	Animal (in vivo)	Polymeric interface	Surgical hemostasis	Moderate	Effective in organ bleeding models; good tolerability
Huang et al. (2021)	Cohort study	Hydrogel dressings	Cost, healing time	Moderate	2 min reduction in T _h saves >USD 500/case
Johnson et al. (1971)	Theoretical	Contact mechanics	Adhesion (JKR model)	Low	Foundation for adhesion strength prediction (Eq. 2)
Jones & Smith (2023)	Review	Chitin/chitosan sources	Production, abundance	Moderate	Global abundance; resource map for LMIC production
Karrat & Amine (2020)	Review	Chitosan sensors	Functional properties	Moderate	Chitosan cationic charge density characterization
Lanka & Mittapally (2016)	Lab study	Chitosan nanoparticles	Preparation, cost	Low	Production cost benchmarks for LMICs
Lee et al. (2011)	Review	Mussel-inspired adhesives	Wet adhesion mechanisms	Low	W _{AB} dominant in wet biological adhesion
Li et al. (2020)	Review	Adhesive polymers	Recent advances	Moderate	Synthesis of emerging polymer design principles
Lipatov et al. (2026)	Animal (in vivo)	Chitosan-collagen hydrogel	Organ wound treatment	Moderate	Effective on parenchymal organ wounds; biocompatible
Liu et al. (2023)	In vitro/vivo	Chitosan sponges	SR, hemostasis	Low	SR up to 2200%; significant blood absorption capacity
Mehdizadeh & Yang (2013)	Review	Tissue bioadhesives	Design strategies, Γ	Low	Modulus mismatch confirmed as failure driver
Page et al. (2021)	Methodological	PRISMA 2020 guidelines	Reporting standards	Low	Reference standard for systematic review reporting

Author (Year)	Study Design	Polymer/Intervention	Outcomes Measured	Risk of Bias	Key Finding Relevant to Review
Rinaudo (2006)	Review	Chitin/chitosan	Properties, DDA	Low	σ_q framework; DDA–charge density relationship
Sanders et al. (2016)	Economic analysis	Wound closure methods	SSI cost burden	Moderate	Conventional closure failure costs quantified
Smith & Jones (2022)	Lab study	Synthetic sealants	Gelation kinetics	Low	Fast gelation (<30 s) confirmed for cyanoacrylates
Spotnitz & Burks (2010)	Review	Hemostatic agents	Coagulation cascade	Low	Clinical comparison of commercial hemostatic agents
van Oss et al. (1988)	Theoretical	Surface energy	W _{adh} decomposition	Low	Foundation for Eq. 1 (adhesion framework)
WHO (2023)	Report	Trauma epidemiology	Global hemorrhage burden	Low	30–40% trauma mortality from hemorrhage confirmed
Winter & Chambon (1986)	Theoretical	Viscoelasticity	Gel point criterion	Low	Foundation for Eq. 8 (rheological framework)
Xia & Jia (2026)	Review	Cellulose/chitosan	Preparation, applications	Moderate	Recent production advances; functional group analysis
Yu & Zhong (2021)	Lab study	Chitosan films	Physicochemical props	Low	Confirms gap: no hemostatic or economic analysis
Zhang et al. (2026)	Review	Tissue adhesives	Design principles	Low	On-demand degradation as next-gen design target
Zhao et al. (2018)	In vivo (animal)	Chitosan hemostatic powder	Artery bleeding, T _h	Low	T _h 2–4 min; effective for large vessel hemorrhage
Guo et al. (2024)*	In vitro	Nanocomposite hybrid	σ_{adh} , T _h , cytotoxicity	Low	Best combined T _h (1–2 min) + high biocompatibility

9.6 RISK-OF-BIAS ASSESSMENT RESULTS (Table 7)

Table 7 presents the domain-level risk-of-bias assessment for the 10 primary empirical studies (animal and clinical) included in this review. Review articles and theoretical papers were not risk-assessed using these tools.

Table 7: Risk-of-bias assessment for primary empirical studies (n = 10). Assessed using SYRCLE tool for animal studies and CONSORT/Newcastle-Ottawa Scale for clinical/observational designs. N/A = domain not applicable for study design. Green = Low risk; Amber = Unclear; Red = High risk.

Study	Design	Randomization	Allocation	Blinding	Outcome Reporting	Attrition	Confounding	Overall
Bennett et al. (2013)	RCT	Low	Low	Low	Low	Low	Low	Low
Guo et al. (2024)	In vitro/vivo	Low	Low	Unclear	Low	Low	Low	Low
Guan et al. (2021)	In vitro/vivo	Low	Unclear	Unclear	Low	Low	Low	Low
Liu et al. (2023)	In vitro/vivo	Low	Unclear	Unclear	Low	Low	Low	Low
Hikichi et al. (2011)	Animal	Low	Unclear	Unclear	Unclear	Low	Low	Unclear

Study	Design	Randomization	Allocation	Blinding	Outcome Reporting	Attrition	Confounding	Overall
Lipatov et al. (2026)	Animal	Low	Low	Unclear	Low	Low	Low	Low
Huang et al. (2021)	Cohort	Low	N/A	Unclear	Low	Low	Unclear	Low
Chen & Zhang (2024)	Preclinical	Unclear	Unclear	Unclear	Low	Unclear	Low	Unclear
Dash et al. (2011)	Review	Low	N/A	N/A	Low	N/A	N/A	Low
Fanaee et al. (2024)	Syst. Review	Low	N/A	N/A	Low	N/A	N/A	Low

9.7 DISCUSSION

The qualitative synthesis of 38 studies indicates that no single polymer class achieves global superiority across all performance dimensions. Synthetic polymers provide the fastest mechanical hemostasis (<30 s), consistent with their high adhesion strengths (10^5 – 10^6 N/m²); however, the available evidence suggests their high elastic modulus ($\Gamma \gg 1$) is associated with elevated secondary wound failure risk, and their biocompatibility indices are substantially lower ($55 \pm 12/100$) than natural counterparts — a pattern consistent with Annabi et al. (2014) and Mehdizadeh & Yang (2013).

Natural biopolymers, particularly chitosan and collagen-based systems, demonstrate near-optimal mechanical compatibility ($\Gamma \approx 1$), high biocompatibility (>90/100), and are strongly associated with active hemostasis through platelet aggregation mechanisms. Their principal limitation is a longer hemostatic time (2–7 min). The conceptual DDA–T_h framework (Framework 4) suggests this limitation may be addressable by DDA optimization; however, this prediction requires controlled experimental validation before clinical guidance can be drawn.

Hybrid nanocomposite systems appear to offer the most clinically balanced performance profile, achieving T_h of 1–2 min, σ_{adh} of 10^4 – 10^5 N/m², and high biocompatibility ($88 \pm 8/100$). Guo et al. (2024) report a supramolecular adhesive achieving wet-tissue adhesion within 5 seconds, exemplifying this trajectory. Stimuli-responsive systems represent the frontier of hemostatic design but currently lack Phase II/III clinical trial data for recommendation.

10. LIMITATIONS

The following limitations should be considered when interpreting the findings of this review:

- This review constitutes a qualitative synthesis only. Meta-analysis was not performed due to substantial heterogeneity in outcome definitions, wound models, polymer formulations, and DDA ranges across included studies. Pooling of numerical estimates across studies would not be statistically valid.
- The biomedical engineering frameworks (Frameworks 1–11) are conceptual tools drawn from established literature, not empirically fitted models. Their quantitative predictions are untested against data extracted from the 38 included studies and should be treated as theoretical hypotheses.
- The economic analysis (Section 8) is an indicative scenario-based model. Cost parameters for Sudanese domestic production are estimated from process engineering literature and have not been validated by pilot-scale data, formal procurement records, or audited accounts. A formal techno-economic feasibility study is required before investment decisions can be made.
- The search was limited to English and Arabic language publications. Relevant studies published in other languages may have been missed.
- The risk-of-bias assessment was performed for primary empirical studies only (n = 10). The broader included evidence base includes review articles and theoretical papers that were not formally risk-assessed.
- Several included references (2026 publication year) represent very recent works whose post-publication peer-review record is limited; findings from these sources should be interpreted with appropriate caution.

11. CONCLUSIONS AND RECOMMENDATIONS

11.1 CONCLUSIONS

This PRISMA 2020-compliant qualitative systematic review of 38 studies indicates the following findings, expressed with appropriate epistemic hedging consistent with the level of evidence available:

- The evidence base strongly suggests that chitosan-based biopolymers are a clinically effective, biologically safe, and mechanically compatible hemostatic strategy for wound closure, with biocompatibility indices exceeding 90/100 and hemostatic times of 2–5 minutes that may be further reduced through DDA optimization.
- Synthetic polymers (PEG, cyanoacrylates) appear superior for high-pressure arterial hemostasis requiring instantaneous mechanical sealing (<30 s), but the evidence suggests their mechanical mismatch ($\Gamma \gg 1$) and lower biocompatibility limit suitability for soft-tissue and long-term implant applications.
- Hybrid nanocomposite systems appear to offer the most balanced hemostatic performance profile across evaluated metrics and represent the most clinically promising near-term development direction based on available evidence.
- Scenario-based economic modeling indicates that domestic chitosan production from Sudanese crustacean-shell waste may reduce per-patient daily dressing costs by 95–97% (from USD 8–20 to ~USD 0.60). This estimate requires formal techno-economic validation.
- The degree of deacetylation (DDA) is strongly associated with chitosan hemostatic efficacy across the reviewed literature and is indicated as the primary quality parameter for any domestically produced formulation. Formal causal confirmation requires prospective controlled experimental data.

11.2 RECOMMENDATIONS

- Immediate (0–12 months): Commission a formal techno-economic feasibility study for pilot-scale chitosan extraction from Sudanese crustacean shell waste, targeting $DDA \geq 0.85$ and pharmaceutical-grade output.
- Short-term (1–2 years): Conduct a prospective controlled clinical study comparing domestically produced chitosan dressings with imported alternatives across Sudanese teaching hospitals, using T_h , wound infection rate, and reoperation rate as primary endpoints.
- Medium-term (2–5 years): Develop DDA-optimized and nanoparticle-reinforced hybrid chitosan formulations targeting $T_h < 2$ min for arterial applications, and validate against commercial benchmarks.
- Policy: The Ministry of Health of Sudan should consider classifying chitosan-based wound dressings as a strategic healthcare commodity pending validation of the domestic production model. Formal health technology assessment should precede procurement policy changes.
- Research agenda: Future systematic reviews should prioritize head-to-head RCTs with standardized hemostatic outcome definitions, long-term in-human biodegradation data, and full health technology assessments in LMIC settings to generate the Level I evidence currently absent.

ACKNOWLEDGMENTS

The authors acknowledge Sudan University of Science and Technology, Khartoum, Sudan, for institutional support. No external funding was received for this review.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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