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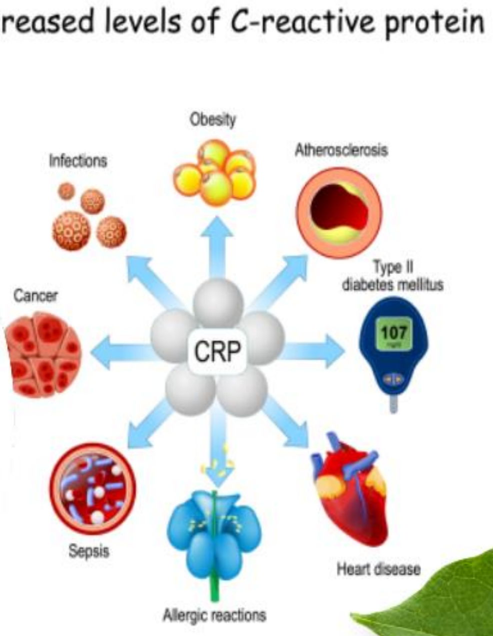

A review on Biosensors for C-reactive protein detection

CRP – When Your Body Speaks, Listen Carefully!

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A review on Biosensors for C-reactive protein detection

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ABSTRACT

C-reactive protein (CRP) is a critical biomarker for inflammation and a wide range of clinical conditions, including cardiovascular diseases, autoimmune disorders, and infections. Conventional laboratory-based methods for CRP detection, such as ELISA and immunoturbidimetry, while reliable, suffer from limitations like lengthy processing times, high costs, and dependence on centralized facilities. Biosensors have emerged as transformative tools for CRP detection, offering rapid, sensitive, and portable solutions. This review explores the advancements in biosensor technologies, including electrochemical, optical, capacitive, magnetic, and wearable platforms. By leveraging innovations such as nanomaterials, molecularly imprinted polymers (MIPs), and IoT integration, these devices address key challenges in scalability, real-time monitoring, and personalized healthcare. Additionally, the review highlights practical applications in cardiovascular disease management, infectious disease diagnostics, and neonatal care. Future directions emphasize sustainable designs, hybrid detection systems, and AI-driven analytics, underscoring the potential of CRP biosensors to revolutionize decentralized healthcare and improve global health outcomes.

Keywords- C-reactive protein, Biosensors, Disease Diagnostics.

1. INTRODUCTION

C-reactive protein (CRP) is a substance produced by the liver in response to inflammation. It is part of the body's immune response and plays a role in protecting tissues during injury or infection. The levels of CRP in the blood rise when there is inflammation in the body, which is why it is used as a marker to detect and monitor various inflammatory conditions.CRP binds to damaged cells or pathogens to help the immune system remove them, promoting healing. A blood test can measure CRP levels, helping doctors assess inflammation [1].

C-reactive protein (CRP) is a pivotal biomarker for assessing inflammation, playing a crucial role in clinical diagnostics and disease monitoring. It is an acute-phase reactant synthesized predominantly by hepatocytes in response to pro-inflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α). CRP's levels in the blood increase dramatically during acute inflammation, infection, or tissue injury, often exceeding 100 mg/L from baseline levels of less than 10 mg/L in healthy individuals. This remarkable sensitivity to physiological changes has made CRP a cornerstone in diagnostic medicine, particularly for conditions such as cardiovascular diseases (CVD), autoimmune disorders, infections, and certain cancers [2].

First identified in 1930 by Tillet and Francis, CRP was named for its ability to precipitate the C-polysaccharide of pneumococcal cell walls. Over the decades, its clinical relevance has expanded beyond its original role in infectious diseases to a broader spectrum of inflammatory and non-inflammatory conditions. Today, CRP is widely recognized not only as a marker of inflammation but also as a prognostic indicator for conditions like myocardial infarction, stroke, and metabolic syndrome. High-sensitivity CRP (hs-CRP) assays have further refined its diagnostic utility, enabling the detection of low-grade inflammation associated with chronic diseases.

Traditional laboratory methods for measuring CRP include enzyme-linked immunosorbent assays (ELISA), immunoturbidimetry, and surface plasmon resonance (SPR). While these methods offer high sensitivity and specificity, they are often limited by their dependence on centralized laboratory infrastructure, skilled personnel, and lengthy processing times. This presents a significant challenge in resource-limited settings or scenarios requiring rapid, point-of-care (POC) diagnostics [3]. For instance, in emergency rooms or remote healthcare setups, the ability to quickly measure CRP levels can be critical for timely decision-making.

The advent of biosensor technology has revolutionized the landscape of CRP detection, addressing many limitations of conventional methods. Biosensors integrate biological recognition elements—such as antibodies, aptamers, or molecularly imprinted polymers—with transducers that convert biochemical interactions into measurable signals. These devices offer numerous advantages, including portability, real-time analysis, lower cost, and the potential for integration with digital health platforms. The miniaturization of biosensors and advancements in materials science, such as the use of nanomaterials, have further enhanced their sensitivity, specificity, and versatility [4].

2. ADVANCEMENTS IN BIOSENSOR TECHNOLOGIES FOR CRP DETECTION

The limitations of conventional methods for CRP detection, such as dependence on centralized laboratories, lengthy processing times, and high costs, have driven significant innovation in biosensor technologies. These advancements aim to deliver rapid, sensitive, and cost-effective solutions suitable for point-of-care (POC) testing and decentralized healthcare. Biosensors integrate biological recognition elements, such as antibodies or aptamers, with transducers that convert biochemical interactions into measurable signals. The major categories of biosensors include electrochemical, optical, capacitive, magnetic, and wearable sensors, each offering unique advantages and applications in CRP detection.

1. Electrochemical Biosensors

Electrochemical biosensors have gained widespread attention due to their simplicity, low cost, and high sensitivity. These sensors measure electrical changes, such as current, voltage, or impedance, resulting from the interaction of CRP with a recognition element immobilized on an electrode [5].

1.1 Impedimetric Sensors

Impedimetric sensors detect changes in the electrical impedance of a system when CRP binds to a functionalized electrode surface. An optimized impedimetric sensor demonstrated a detection limit of 176 pM, showcasing its high sensitivity and reusability. Advances in electrode materials, such as gold nanostructures and carbon-based composites, have further enhanced the performance of these sensors [6].

1.2 Voltammetric and Amperometric Sensors

These sensors measure current changes caused by redox reactions at the electrode surface. By using nanomaterials, such as graphene oxide and gold nanoparticles, researchers have achieved exceptional sensitivity and a broad dynamic range for CRP detection. For instance, a voltammetric biosensor with DNA aptamers as recognition elements achieved a detection limit of 0.1 ng/ml [7].

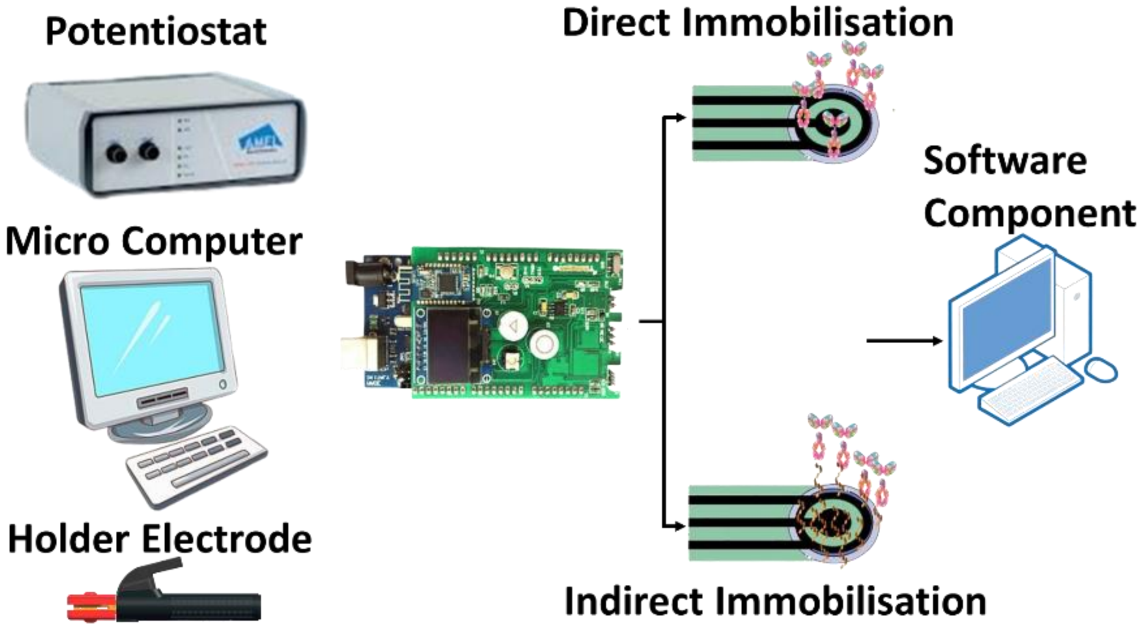

Fig 1. Conceptual design overview of the screen-printed biosensor [3].

1.3 Electrokinetic-Assisted Trapping

Electrokinetic techniques enhance the capture efficiency of CRP molecules by employing Dielectrophoresis and electrothermal effects. This approach reduces detection times to under 90 seconds while maintaining high sensitivity, making it ideal for rapid POC diagnostics [8].

2. Optical Biosensors

Optical biosensors utilize changes in light properties, such as absorbance, fluorescence, or refractive index, to detect CRP. These sensors offer high sensitivity, label-free detection, and the ability to perform real-time analysis [9].

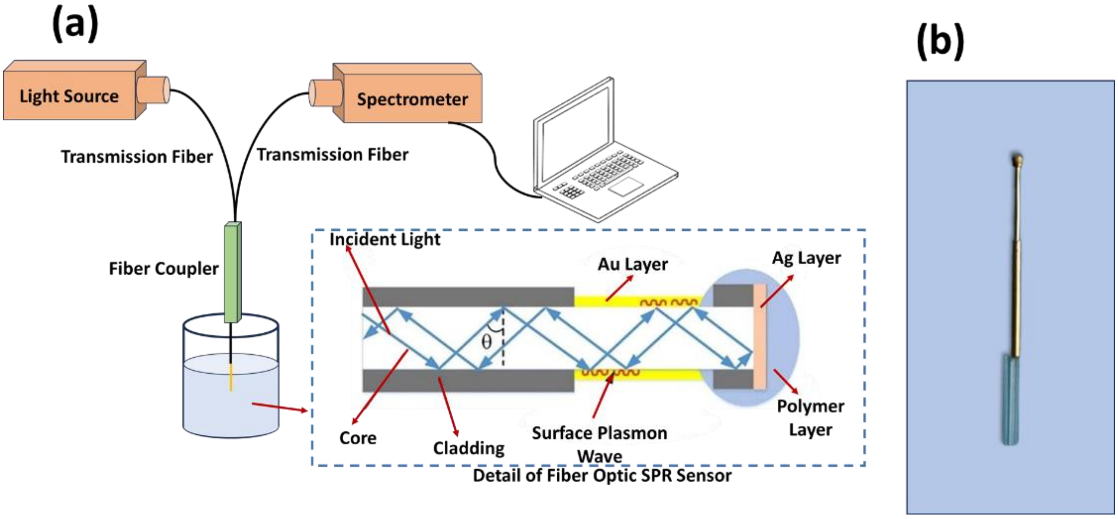

Fig 2. Fiber optic SPR sensing system. (a) Schematic diagram of experimental setup; (b) Image of the fabricated fiber optic SPR sensor [5].

2.1 Localized Surface Plasmon Resonance (LSPR)

LSPR sensors leverage the unique optical properties of plasmonic nanoparticles, such as gold and silver, to achieve ultrasensitive detection. When CRP binds to functionalized nanoparticles, it induces changes in the local refractive index, which are detected as shifts in the plasmon resonance wavelength. These sensors have demonstrated detection limits in the sub-picogram range, making them suitable for early disease diagnostics.

2.2 Photothermal Biosensors

Photothermal sensors measure temperature changes caused by the absorption of light by plasmonic nanoparticles conjugated with CRP-specific antibodies. These sensors provide non-invasive, rapid detection of CRP in biofluids, such as saliva, with a detection limit of 0.1 ng/mL [9].

2.3 Fluorescence-Based Biosensors

Fluorescence biosensors utilize labeled antibodies or aptamers that emit light upon CRP binding. Advances in quantum dot technology have improved the sensitivity and multiplexing capabilities of these sensors, enabling simultaneous detection of multiple biomarkers.

3. Capacitive Biosensors

Capacitive biosensors detect changes in dielectric properties or capacitance caused by CRP binding to a sensor surface. These sensors are label-free and capable of real-time monitoring. A microfluidic-integrated capacitive biosensor demonstrated a detection limit of 1 pg/mL, highlighting its potential for rapid and precise diagnostics. Integration with microfluidics also improves sample handling and reaction efficiency [10, 13].

4. Magnetic Biosensors

Magnetic biosensors utilize magnetic particles or field effects to detect CRP. These sensors offer high stability and portability, making them suitable for POC applications [11].

4.1 Giant Magnetoresistance (GMR) Sensors

GMR sensors detect changes in electrical resistance caused by the magnetic field of labeled particles bound to CRP. A flexible GMR biosensor achieved a detection range of 1-10 ng/mL, providing a robust platform for clinical and remote diagnostics.

4.2 Magneto-Impedance Sensors

These sensors leverage changes in magnetic impedance to detect CRP. Their high sensitivity and ease of miniaturization make them attractive for wearable and implantable devices [15].

5. BioMEMS (Biological Microelectromechanical Systems)

BioMEMS, or Biological Microelectromechanical Systems, represent a significant advancement in the integration of biological components with microfabricated devices. These systems are designed to perform specific biological or biomedical functions, such as sensing, diagnostics, and drug delivery, on a microscale. BioMEMS leverage technologies from microelectronics and micromechanics to create compact, efficient, and highly sensitive devices. In the context of biosensors for C-reactive protein (CRP) detection, BioMEMS play a pivotal role in enhancing portability and real-time monitoring. For instance, BioMEMS-based microcantilevers have been developed to detect CRP by measuring cantilever deflection upon biomolecular binding, offering high sensitivity and a broad detection range. Furthermore, their integration with microfluidics allows for automated sample handling, making them ideal for point-of-care diagnostics and applications in resource-limited settings [12, 20].

6. BIOHEMT (Biological High Electron Mobility Transistor)

BIOHEMT, or Biological High Electron Mobility Transistor, is a cutting-edge biosensor technology that combines semiconductor physics with biological recognition capabilities. Built on an AlGaN/GaN heterostructure, BIOHEMT devices utilize the high electron mobility of their transistors to detect biochemical interactions with exceptional sensitivity. These sensors are particularly effective for detecting C-reactive protein (CRP), where the binding of CRP molecules to functionalized surfaces causes measurable changes in the transistor's electrical properties. BIOHEMT systems are valued for their real-time monitoring capabilities, broad detection ranges, and potential for miniaturization. Their high stability in diverse environmental conditions and compatibility with wireless communication modules make them ideal candidates for next-generation wearable biosensors and integration with IoT platforms. Such features position BIOHEMT at the forefront of biosensor innovation, offering a robust solution for personalized healthcare and remote diagnostics [13, 17].

7. Wearable and Flexible Biosensors

Wearable biosensors represent a significant advancement in personalized healthcare. By integrating biosensing elements with flexible substrates, these devices enable continuous, real-time monitoring of CRP levels [14].

7.1 Flexible Electronics

Flexible biosensors use stretchable materials, such as polydimethylsiloxane (PDMS) or polyimide, to conform to the skin or other surfaces. A wearable CRP sensor integrated with a wireless module demonstrated real-time monitoring capabilities, transmitting data to a smartphone application.

7.2 Point-of-Care Wearables

Wearable CRP sensors are being developed for applications in chronic disease management, fitness tracking, and post-surgical recovery. These devices combine biosensing with digital health platforms, enabling proactive and personalized healthcare.

The advancements in biosensor technologies for CRP detection have transformed the field of diagnostics, offering rapid, sensitive, and portable solutions that address the limitations of traditional methods. From electrochemical and optical sensors to magnetic and wearable devices, these innovations have paved the way for decentralized and personalized healthcare. Continued research and development in this domain, particularly in areas such as nanomaterials, data integration, and scalability, will further enhance the impact of biosensors on global health.

3. COMPARATIVE ANALYSIS OF BIOSENSOR PLATFORMS FOR CRP DETECTION

The rapid advancements in biosensor technologies for C-reactive protein (CRP) detection have given rise to a variety of platforms, each offering distinct advantages and facing unique challenges. This comparative analysis evaluates these platforms based on key performance metrics such as sensitivity, detection limits, speed, portability, cost, and applicability in clinical and point-of-care (POC) settings. The primary biosensor types reviewed here include electrochemical, optical, capacitive, magnetic, and wearable sensors.

Key Performance Metrics

To assess the efficacy of biosensor platforms for CRP detection, several critical parameters must be considered:

- **Detection Limit:** The minimum concentration of CRP that can be reliably detected by the sensor.
- **Sensitivity:** The sensor's ability to detect small changes in CRP concentration.
- **Response Time:** The duration required to produce a measurable signal.
- **Portability:** The ease of deployment in decentralized or POC settings.
- **Cost:** The expense associated with manufacturing, maintaining, and operating the sensor.
- **Ease of Integration:** The potential for incorporation with digital health platforms and Internet of Things (IoT) systems.

Sl. No.	Platform/electrode substance	Method	Limit of detection	Detection range	Response time	References
1	Ca^{2+} Phosphochlorine	Surface plasmon resonance		0.03-5.45mM	170 s	[15]
2	Electrochemical	impedimetric	176 pM	0.5 - 50mM	15 min	[16]
3	CSPE-AuNPs-SAM	LSV,CV, CA		9- 900nM	30 min	[17]
4	Screen printed gold electrode	Chronoamperometry	2.2ng/mL	0.52 - 20 µg/mL		[18]
5	Carbon nanofiber	CV and EIS	90pM	0.42 - 42 nM		[19]
6	C-MIP	EIS	10^{-5}-10^{3} ng/mL	0.41x 10^{-5} ng/mL		[20]
7	Biologically modified Fibre optic probe	Fiber Optic Surface	0.01 µg/mL	0.01–20 µg/mL		[21]

		Plasmon Resonance (SPR)				
8	RNA aptamer based	Non-Faradaic Impedance Spectroscopy (NFIS)	100 pg/mL	100–500 pg/mL		[22]
9	Surface modified	Photothermal	0.1 ng/mL	0.1–100 ng/mL		[23]
10	SPE/AuNPs/GO-COOH	DPV	0.001 ng/mL	0.001–100 ng/mL		[24]
11	Antibody and aptamer	Surface Plasmon Resonance (SPR)	1 µg/mL	1–10 µg/mL		[25]
12	Antibody immobilized surface	Surface Plasmon Resonance (SPR)	1 µg/mL		Real-time detection	[26]
13	Capacitive Biosensor with Microfluidics	Capacititance	1 pg/mL		Real-time detection	[27]
14	Surface modified	Electrochemical Impedance Spectroscopy (EIS)	1 pg/mL		90 seconds	[28]
15	Cobalt-based commercial amorphous ribbon MEMS	Giant Magnetoimpedance (GMI)		1–10 ng/mL	Less than 2 hours	[29]
16	CRP/BSA/Anti-CRP/MPA/Au	Square Wave Voltammetry (SWV)	2.25 fg/mL	5–220 fg/mL		[30]
17	Bio-HEMT/Ref-HEMT/QRE sensor system integrated on an AlGaN/GaN heterostructure	High Electron Mobility Transistor (HEMT)-Based Sensor	0.01 ng/mL	0.01–1000 ng/mL	Real-time detection	[31]
18	Bio functionalised measuring probe	Fiber-Optic Interferometric Sensor	0.01 mg/L	0.01–100 mg/L	Less than 5 minutes	[32]
19	Antibody active site on gold surface	Surface Acoustic Wave (SAW)	0.1 µg/mL	0.1 µg/mL–1 mg/mL		[33]
20	Bio-Microelectromechanical	Deflection of cantilever	1 µg/mL	1–500 µg/mL	30 minutes to 3 hours	[34]

	Systems (MEMS) Microcantilever					

Comparison of Biosensor Platforms

Biosensor Type	Detection Limit	Advantages	Challenges	Biosensor Type
Electrochemical Sensors	0.176 pM to 100 ng/mL	Low cost, high sensitivity, portable	Dependence on electrode materials, limited multiplexing	**Electrochemical Sensors**
Optical Sensors	Sub-picogram levels	High sensitivity, label-free detection	Complex fabrication, high instrumentation cost	**Optical Sensors**
Capacitive Sensors	1 pg/mL	Real-time, label-free, mass-producible	Signal drift in complex matrices	**Capacitive Sensors**
Magnetic Sensors	1-10 ng/mL	High stability, portable	Requires external magnetic fields	**Magnetic Sensors**
Wearable Sensors	Real-time monitoring	Continuous, non-invasive, patient-centric	Integration with IoT and scalability	**Wearable Sensors**

Detailed Analysis

1- Electrochemical Biosensors

Electrochemical biosensors are widely regarded for their cost-effectiveness, portability, and ease of miniaturization. These sensors rely on electrical signals generated by the interaction of CRP molecules with immobilized recognition elements on the electrode surface.

- **Strengths:** Exceptional sensitivity, rapid response time, and the ability to integrate with portable devices.
- **Weaknesses:** The performance is highly dependent on the quality and functionalization of electrode materials. Furthermore, challenges in multiplexing limit their application for simultaneous biomarker detection.

2- Optical Biosensors

Optical sensors, including localized surface plasmon resonance (LSPR) and photothermal biosensors, offer unparalleled sensitivity and real-time detection capabilities. These sensors rely on changes in light properties upon CRP binding.

- **Strengths:** Sub-picogram detection limits and the ability to study biomolecular interactions in real-time.
- **Weaknesses:** The fabrication process for optical sensors can be complex and costly, requiring precise nanostructures and specialized instrumentation.

3- Capacitive Biosensors

Capacitive biosensors detect changes in dielectric properties caused by CRP binding. These label-free sensors are well-suited for real-time monitoring.

- **Strengths:** High reproducibility and compatibility with microfluidic systems, enabling efficient sample handling.
- **Weaknesses:** Signal drift and interference from complex biological matrices remain significant challenges.

4- Magnetic Biosensors

Magnetic biosensors utilize magnetic nanoparticles or magnetoresistance principles to detect CRP.

- **Strengths:** High stability and portability, making them ideal for POC applications.
- **Weaknesses:** External magnetic fields and particle functionalization can complicate device design and increase costs.

5- Wearable and Flexible Sensors

Wearable biosensors represent a breakthrough in continuous monitoring, allowing real-time tracking of CRP levels in non-invasive ways. These sensors integrate with flexible substrates for enhanced user comfort.

- **Strengths:** Continuous, non-invasive monitoring and compatibility with digital health platforms.
- **Weaknesses:** Challenges include data integration with IoT platforms, scalability, and ensuring robustness for prolonged use.

The choice of biosensor platform depends on the specific requirements of the diagnostic application, such as sensitivity, cost, and portability. Electrochemical sensors offer an affordable and portable solution, while optical sensors are unmatched in sensitivity and real-time capabilities. Capacitive and magnetic biosensors provide robust alternatives for specific use cases, whereas wearable sensors are paving the way for personalized healthcare. Future efforts should focus on hybrid platforms that combine the strengths of multiple sensor types, alongside advancements in materials science, signal processing, and IoT integration to address existing limitations.

CONCLUSION

The advancements in biosensor technologies have revolutionized the detection and monitoring of C-reactive protein (CRP), a vital biomarker for inflammation, cardiovascular risk assessment, and a wide range of pathological conditions. By addressing the limitations of conventional methods, biosensors offer rapid, sensitive, and cost-effective solutions that align with the growing demand for decentralized and personalized healthcare.

Electrochemical, optical, capacitive, magnetic, and wearable biosensors have each demonstrated unique strengths, from ultrasensitive detection to real-time, non-invasive monitoring. These innovations have expanded the applications of CRP biosensors across diverse medical fields, including cardiovascular disease management, infectious disease diagnostics, neonatal and pediatric care, and chronic disease monitoring. Moreover, their integration with digital health platforms and Internet of Things (IoT) systems has further enhanced their potential for remote healthcare and telemedicine.

Despite their transformative potential, several challenges remain. Issues such as matrix interference, fabrication variability, and high production costs hinder the widespread adoption of CRP biosensors. Additionally, regulatory hurdles and the need for robust data integration systems pose barriers to commercialization and clinical use. Addressing these challenges through interdisciplinary collaboration and continued research will be essential for scaling biosensor technologies to meet global healthcare needs.

In conclusion, CRP biosensors represent a critical leap forward in the quest for efficient, accessible, and personalized healthcare. By overcoming existing challenges and embracing future advancements, these technologies have the potential to redefine how inflammation and related conditions are diagnosed and managed, ultimately improving patient outcomes and reducing healthcare disparities worldwide.

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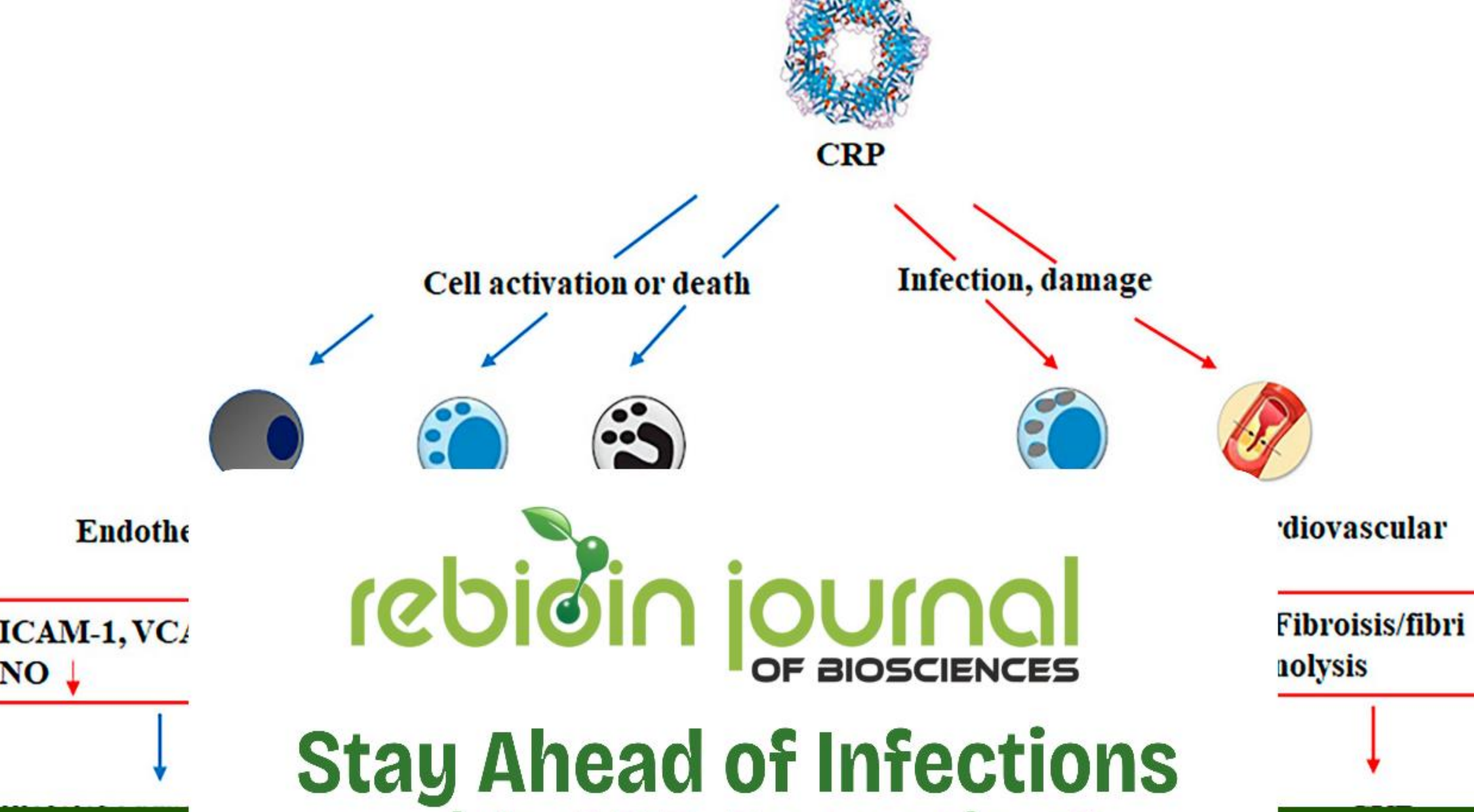

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