International Journal of Biological Macromolecules 161 (2020) 59–71

Contents lists available at ScienceDirect

International Journal of Biological Macromolecules

journal homepage: http://www.elsevier.com/locate/ijbiomac

Review

Biosensing: The best alternative for conventional methods in detection of Alzheimer's disease biomarkers

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ARTICLE INFO

Article history:
Received 7 May 2020
Received in revised form 26 May 2020
Accepted 28 May 2020
Available online 03 June 2020

Keywords:
Biosensor
Alzheimer
Supermolecule
micRNA
Amyloid-beta (Aβ)
Tau protein
Biotechnology

ABSTRACT

Conceivably the imperative reason for the absence of appropriate treatment for Alzheimer's disease (AD) is the late onset of clinical symptoms followed by late treatment. Specific biomarkers play a vital role in this area. The amyloid-beta peptide, tau protein and micRNA, are the most important biomarker associated in AD. There are many routine methods for identifying these biomarkers which molecular based methods with a high accuracy and sensitivity have been considered. These methods have some limitations such as; false positive and negative results, problem on the interpretation, complexity and time-consuming, high cost instruments and etc. To overcome these limitations, bioassays were developed extensively. There exist a multitude of possible applications for Alzheimer's disease biomarkers by using biosensors. This review mainly focuses on major biomarkers in Alzheimer's disease, routine and old methods in identifying biomarkers of AD and their advantages and limitation, and biosensors to the identification of amyloid beta, tau protein and micRNAs biomarkers. Furthermore, evaluation the strengths and weaknesses of the developed bioassays and introduce leading challenges are considered in this review.

Contents

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https://doi.org/10.1016/j.ijbiomac.2020.05.257
0141-8130/

1. Introduction

Alzheimer's disease (AD) is the imperative progressive neurodegenerative disease that considered by gradual synaptic integrity and loss of cognitive functions. In AD disorder core plaques and neurotic in the cerebral cortex was formed with selective neuronal death [1]. During AD concentration of some components and biomarkers such as beta-amyloid, tau protein and micRNA is altered significantly. Easy to obtain by safe techniques, measureable by simple and low cost methods in primary stage of a disease and distinctive with other diseases biomarker are the most important aspects of ideal biomarkers [2]. Since beta-amyloid can form complexes with some metal ions such as iron, so their existence is very important in pathogenesis [3,4].Several study indicated the relationship between AD progression and the amount of Aβ in body fluids. So, specific and sensitive detection of the level of AB is criticalin AD clinical studies [5]. Tau protein is the second the most important biomarker of AD and belongs to (MAP) as a microtubule associated protein family. This protein expressed in the human central nervous system (CNS) and peripheral nervous system (PNS) as well as neurons, oligodend rocytes, and astrocytes. In axons, tau protein interacts with tubulin and revealed in four forms as well as the Proline-rich domain, N-terminal region, the C-terminal region and finally microtubule-bindingdomain. MicroRNAs (miRNAs) plays crucial role in a broad range of biological processes such as cell transcription and gene expression. The abnormal expressions of miRNAs in plasma are associated to several disorders such as AD and cancers. For the example, great amount ofmiRNA-21 is related with human cancers. Thus, developing novel and modern approaches for the detection of miRNAs are the most important factor in not only in clinical disease diagnosis and gene therapy but also it is remarkable in innovation of new anticancer drugs. Biosensors are analytical devices used to detect a various target by converting and amplifying a bio-molecular recognition event to a measureable signal [6–9] (Table 1).

2. Biological mechanism of Alzheimer's disease

The biological mechanism of Alzheimer's disease is considered by unusual aggregation of Aβ and formation of Tau protein isomers due to hyper phosphorylation [20]. Creation of Tao and beta amyloid protein oligomers play a key role in AD. Formed plaque and oligomers affected brain cells and interact with different membranes and proteins and also, interfere with signaling or some functions. Several study revealed plaque and oligomers of tau and Aβmay be disturbs the usual activities of these proteins in neurotransmission; however the exact mechanisms are unclear [21]. Age-linked disorder of the proteostatic network conceivably cause assembly of aggregating proteins. On the other hand, protein aggregates could disrupt the complex cellular molecular network that tolerates protein folding. Additionally, autophagy is one of the most important regulator of this proteopathic phase. Affected neurons demonstrate tau inclusions that are not discernable from those in AD. Accordingly, abnormalities in autophagy are related to tau pathology [22]. Schematic illustration of AD mechanism presented in Fig. 1 [23].

Table 1
Important biomarkers related in AD.

Biomarker	Pathogenic process	Status in AD	Ref
Aβ1	Amyloid plaque	deposition have been reported	[10]
Truncated amyloid-β isoforms	Amyloidogenesis	Increased	[11,12]
Total-tau	Neuronal injury	Increased	[13,14]
Phosphorylated-tau	Neurofibrillary tangles	Increased	[15]
mi-RNA	expression of miRNA-146a	Increased	[16]
APP isoforms	APP products	Increased	[17]
F2-isoprostane	Increases markedly in plasma	Increased	[18]
CSF cell count	Inflammation	Normal	[19]

3. Conventional methods for detection of AD biomarkers

From the past until now various techniques developed for identification of AD biomarkers. For instance in relation of Aβ, enzyme-linked immunosorbent assay (ELISA), capillary electrophoresis, for recognition of tau protein, ELISA and western blotting, northern blotting, miRNA array technology, real-time reverse transcription polymerase chain reaction (RT-PCR) for monitoring of micRNA [25]. ELISA is one of the most commonly used tests in medical diagnostics. Also, the most important of ELISA is acceptable sensitivity and relatively easy to perform. The most important limitation of the ELISA test is its false positive results, which has made it extremely challenging to use in sensitive diagnoses. Molecular based techniques such as PCR and Real-time PCR have good sensitivity and specificity and the results are reliable [26]. Need for advanced equipment and expert people restricted their application in diagnosis approach [27]. In general, the major limitations of molecular based methods such as time-consuming, high cost, and difficult interpretation of the obtained results make the use of these methods with a great challenge. Conventional methods for detection of AD biomarker and their advantages and disadvantages are introduced in Table 2.

Highlighted from conventional methods in detection of AD biomarkers: **I)** Low sensitivity and high cost are most important disadvantages of routine methods in the biomarkers diagnosis of Alzheimer's disease. **II)** False positive and negative results, especially with regard to ELISA and western blotting, are other disadvantages of routine methods. **III)** The problematic interpretation of the results and the need for skilled and professional people are the limitations of routine methods. **IV)** Routine tests are often difficult and time-consuming; nevertheless, rapid diagnosis is crucial in the treatment of Alzheimer's disease. **V)** Diagnosis in the early stages of the disease using routine techniques is very difficult and largely impossible. One of the important methods for diagnosis of AD disease is biosensing technology. Following section was discussed role of biosensing strategy on the early stage diagnosis of ADs.

4. Medical biosensors

Since the establishment of the innovative oxygen biosensor technology in 1962, bio-sensing tools have extended consideration in recent years in the widely range of science such as medicine and nanotechnology [34,35]. The biosensor technology has shown a potential for presentations in medical diagnostics particularly in microbiology, oncology, pharmacology and several biomarkers association in numerous diseases [36,37]. The bio- sensing devices have been effective in attaining high sensitive in quantifying disease biomarkers both in vitro/vivo environment. The biosensor technology is adept of sensing in the real-time of biomolecules as well as biomarkers [8,38]. Additionally, biosensors can successfully identify the target molecule in low amounts and are powerful tool in detection of disease biomarkers in initial stage to start the early treatment [39]. Accordingly, for detection of AD biomarkers as well as Aβ, tau protein and micRNA several biosensors developed in recent year, which the most important and modern of them were discussed in this part.

5. Biosensor classification

Biosensors have been classified based on numerous views however, the most generally used classification depend on two factors: the biorecognition element and the signal transduction. Signal transduction class comprised four categories as well as electrochemical, optical, thermal sensors, and mass sensors. Also based on the biological recognition element, biosensing tools have been categorized into: immunosensors,

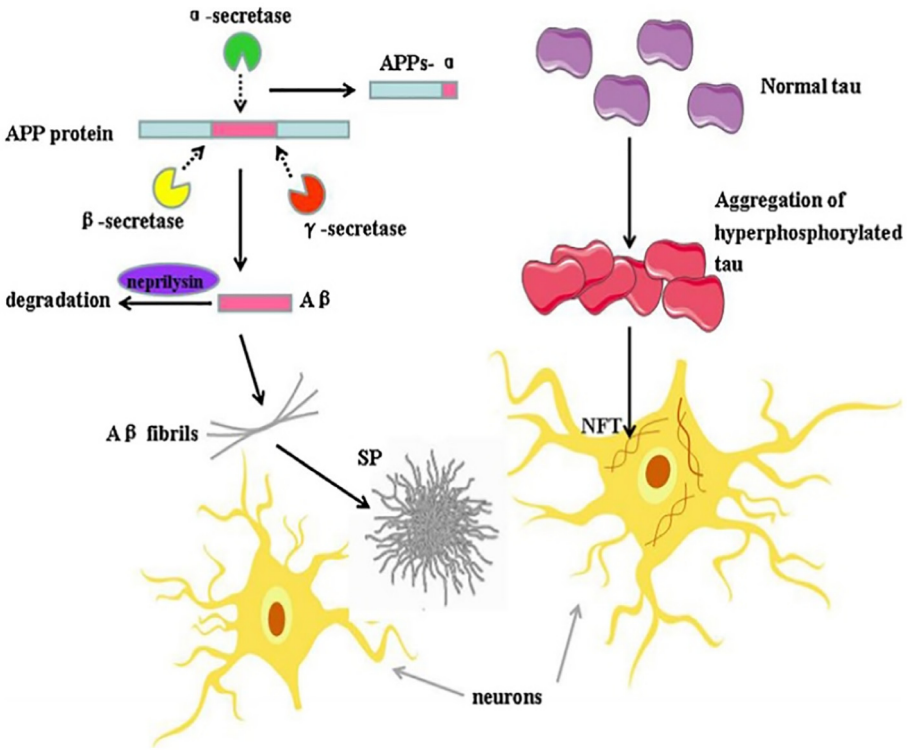

Fig. 1. Biological characteristics of Alzheimer's disease and their formation process [24].

enzymatic, protein/peptide based, gen based biosensors and whole-cell biosensors [40,41].

There exists a multitude of possible applications for Alzheimer's disease biomarkers by using biosensors. This review mainly focuses on major biomarkers in Alzheimer's disease, routine and old methods in identifying biomarkers of AD and their advantages and limitation, and biosensors to the identification of amyloid beta, tau protein and micRNAs biomarkers.

6. Amyloid-beta (Aβ)

Amyloid-beta is the most important compound known to be associated with AD, providing a variety of biosensors for its rapid and specific detection, some of them introduced in this section [42]. Aβ peptide is the remarkable relevant agent of AD and usually produce in low concentration in the healthy people brain. Particularly 42 amino acids (Aβ1–42) type, gathers in the AD brain and prone to accumulation and builds up, various soluble assemblies forms named oligomers [43,44].These forms are differing in morphology, size and conformed as dimers and trimers from with large circular structures. Aβ may be formed as insoluble fibrils and senile plaques, monomeric, oligomeric and fibrillar forms. Several studies shown thatin AD, soluble Aβ oligomers (AβO) forms are the imperative neurotoxic species [45]. Moreover, AβO form binds to neurons, in post-synaptic membrane and not only triggering synaptic dysfunction but also blocking crucial processes which affected memory and learning. Also, the level of AβOs in the brain, mostly "fibrillar" forms, associate with AD and severity strongly than the insoluble fibrillar load [46].

6.1. Biosensor for detection of tau protein

6.1.1. Amyloid-beta (Aβ) immunosensors

Immunosensors are well-defined as the affinity ligand-based biosensor tools where the immunochemical reaction is united to a transducer. The major principle of immunosensors mostly depends on the molecular diagnosis between antibodies and antigens to form a stable composite. Electrochemical and optical, types of immunosensors are the most popular reported. The development of immunoassay technology is a dominant section particularly for the medical and clinical application and this field to be an interesting and exciting area of research

Table 2
Conventional methods in detection of Alzheimer's disease biomarkers.

Target	Method	Advantages	Disadvantages	Ref
Tau and Aβ	ELISA	Simple operation	Low sensitivity, False positives	[28]
	Mass spectrometry	High sensitivity	Need for advanced and expensive equipment, time consuming	[29]
	Western-blot	Acceptable sensitivity	Need for expensive equipment and expert and Time consuming	[30]
micRNA	PCR, qPCR	Acceptable sensitivity	Need for advanced and expensive equipment	[27]
	Chromatography	High sensitivity	Need for advanced, expensive equipment and labor-intensive	[31]
	Microarray	Provide comprehensive data	Requires specific material and equipment, data interpretation is difficult and time consuming	[32]
	Next generation sequencing	Provide comprehensive data	Requires specific material and equipment, skilled bioinformatician and data interpretation is difficult and time consuming	[33]
	Northern blotting	Detects non-amplified microRNAs	Requirement of large amount of starting materials, radioactivity, low sensitive, labor-intensive.	[26]

[47–49]. Hu and co-worker assembled novel immunosensor for sensitive detection of AB. They used colorimetric sandwich immunosensor technique based on twin antibody-modified gold nanoparticles. Result showed a good linearity in a range from 7.5 nM to 350 nM and an ideal detection limit (LOD) of 2.3 nM along with simple structure and operation [25]. Preparation procedure of this immunosensor was shown in Fig. 2.

Also, a Label-Free Electrochemical biosensor was fabricated for sensitive detection of Aβ. This system constructed based on oxidation of tyrosine (Tyr) residue in the peptide on the glassy carbon electrode. Using this method, LOD and linear range were0.7 μg/mL and 1.2 to 8.3 μg/mL, respectively [50]. Similar electrochemical immunosensor was developed on the gold electrode for detection of Aβ1–42. In this work specific formation of antibodies were immobilized on the surface of the gold electrode using a sulfosuccinimidyl and surface binding events were monitored by electrochemical impedance spectroscopy (EIS). Fig. 3 shows schematically construction of this immunosensor. Moreover, the formation of an antigen-antibody complex was measured as a purpose of charge transfer resistance using a $[Fe(CN)_6]^{3-/4-}$ redox probe. Proposed platform showed acceptable LOD which were 50 nM [51].

Gelsolin is one of the secretory protein and for the first time was described to bind Aβ according to concentration linked manner and can be assayed fixed Aβon the nitrocellulose membrane [52]. For this reason, gelsolin is usable for Aβto both Ab (1–40) and Ab (1–42) identification. According several studies detailed comparison of the Aβ(1–42) and Aβ(1–40) fibril structures demonstrated that they share an axial twofold symmetry and a similar proto-filament structure. Also, the mass-per-length (MPL) data indicate that the proto-filaments of the examined Aβ(1–40) and Aβ(1–42) fibrils have the same number of Aβ molecules per cross-β repeat. In sum, Aβ(1–40) fibril structure, describe as a model for the arrangement of peptides within the Aβ(1–42) fibril [53]. During interestingly study gelsolin-based electrochemical assay was fabricated to detection of Ab(1–42). Proposed structure based on multiwall carbon nanotubes (MWCNTs) and gold nanoparticles (AuNPs) facilitated electron transfer on the film. The created platform showed to have acceptable sensitivity and selectivity and able to assess soluble Ab(1–40/1–42) levels in body fluid as well as the cerebrospinal fluid (CSF) and brain tissues in animal model. Additionally, this technique was useful tool in study of neurodegenerative diseases. In this work linear range was 0.2–40 nM and limit of detection reported as 50 pM [54]. Similar system fabricated for detection of Ab based on amplex red and fluorescein isothiocyanate dextran (FITC-dextran) with acceptable LOD (0.63 nM) and linear range (1–100 μg/mL) [55].

Interestingly an electrochemical biosensor was developed for recognition of soluble Aβ based on the conversion of AgNP colorimetric assay. In this work Aβ oligomer with a peptide as the bioreceptor to reach strongly signals silver nanoparticle (AgNP) used as the redox reporters. The detection limit of the proposed system was found to be 6 pM and linear range reported as 0.01–200 nM. This work was the most important peptide based biosensor for detection of Aβ. Fig. 4. shows preparation of this biosensor [56].

Micro-biosensor using triple barrel carbon fiber microelectrodes was developed as the sensor platform for detection of AB. Tyrosine residue at position 10 in AB structure and act as a target in electrochemistry evaluation. Due to the binding of Ab on the surface of carbon fiber eliminates mutual connection between the three microelectrodes during real-time measurements of Ab1–40 and Ab1–42. Created biosensor able in detection of low amounts of Ab and can generate a quantifiable signal lead to increase sensor performance [57]. According to several studies adsorption of proteins on metal surfaces denaturized and loss of their activity. To overcome this problem AuNPs was used on the surface of gold electrodes consequently this treatment protein retained their bioactivity

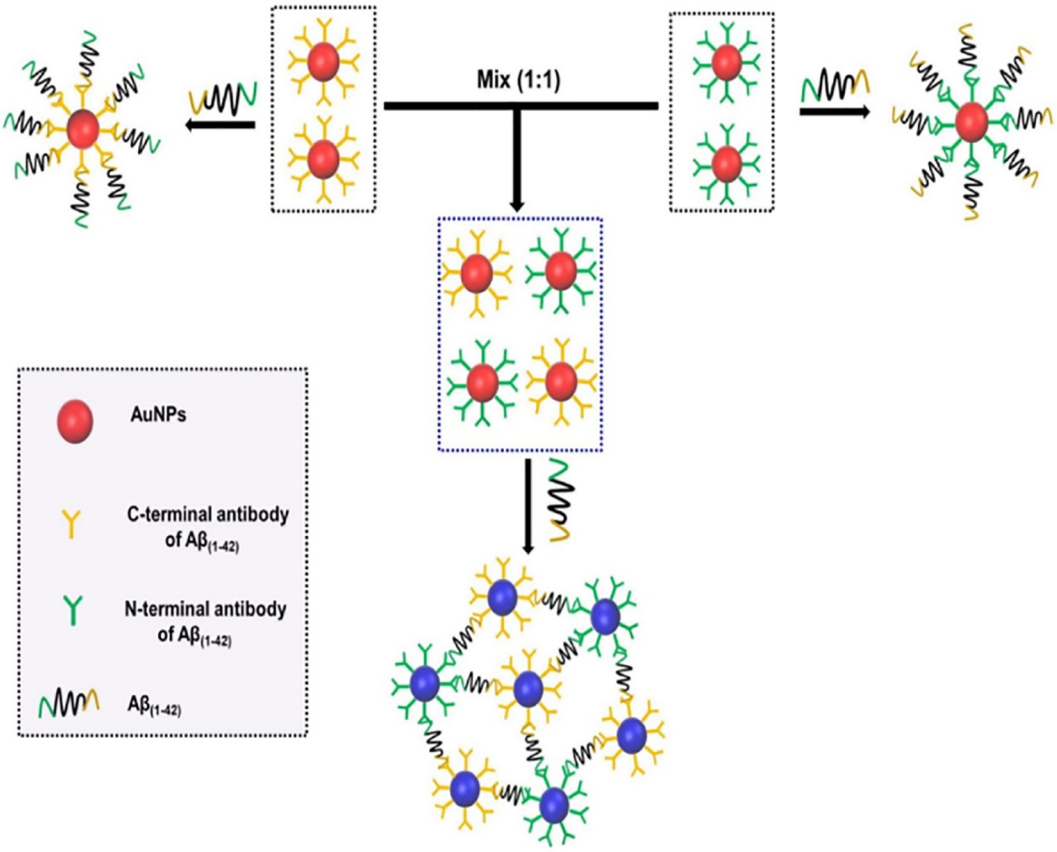

Fig. 2. Illustration of AuNPs@C/N-Ab(1–42) colorimetric sandwich immunosensor for Aβ [25].

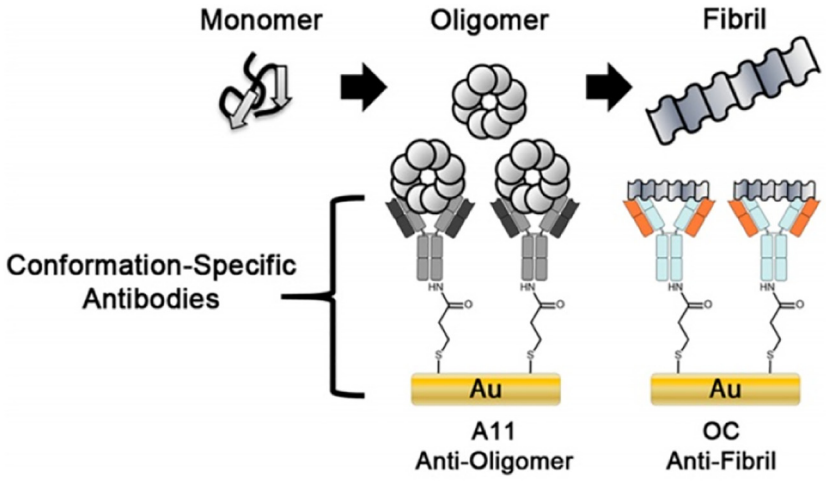

Fig. 3. Covalent immobilization of anti-fibril and anti-oligomer(OC/A11) antibodies on separate gold CD electrodes for the training of immunosensor [51].

[58,59]. Giving this fact to measure the Ab peptide in low amount, microfluidics biosensor engineered based on AuNPs on gold electrode. Proposed system exhibit good linear rang (100 M to 300 M) and acceptable LOD [60]. Due to several advantages include: three-dimensional (3D) porous, has much larger surface area, containing abundant water and changeable its shape and volume according to its conductivity hydrogel electrode used extensively in recent years [61]. An ultrasensitive electrochemical biosensor based on graphene oxide/gold nanoparticles (GNPs) hydrogel electrode was constructed to detection of AβO [61,62]. In this work, thiolated prion protein (PrPC) peptide act as a probe and immobilized on GNPs of the hydrogel electrode and electrochemical impedance spectroscopy was applied for AβO analysis. Reported limit of detection (0.1pM), linear range (0.1 pM to 10pM) and selectivity was satisfactory in engineered system.

Saccharides, are generally expressed on the cell surfaces, is critical in the wide range of biological recognition and extensively used in biosensor technology. In the most cases saccharide-protein interactions are weak, and the original tool is required to apply the collaboration for the sensor apparatus [63]. Commonly, the saccharide–protein interaction improved by glyco-cluster effect of multivalences, and the saccharide gathering by liposome and self-assembled monolayer(SAM) are engaged for the biosensor [64]. Briefly, carbohydrate based immobilized substrates are appropriate for the bioanalysis, and shown the large glyco-cluster effect and are usable in sensitive analytical approaches. AuNPs have been extensively used to improve the sensitivity of the carbohydrate-immobilized substrate due to supreme properties such as high conductibility and larger surface area [65–67]. Accordingly, ultra-sensitive biosensor based on saccharide immobilized AuNPs using carbon electrode was establishing to detection of Ab peptide. The LOD and linear range were0.1–5 μM and 18 nM, respectively [68]. Magnetic microspheres extensively used in various type of biosensor due to their unique properties such as paramagnetic behavior, stability and wide range of size. Accordingly, porous magnetic microspheres (PMM) used as a modern biosensor for detection of Ab. AD biomarker antigen captured and examined by sandwich immunoassay with AuNPs tags and magnetic conjugate suspension was positioned on the

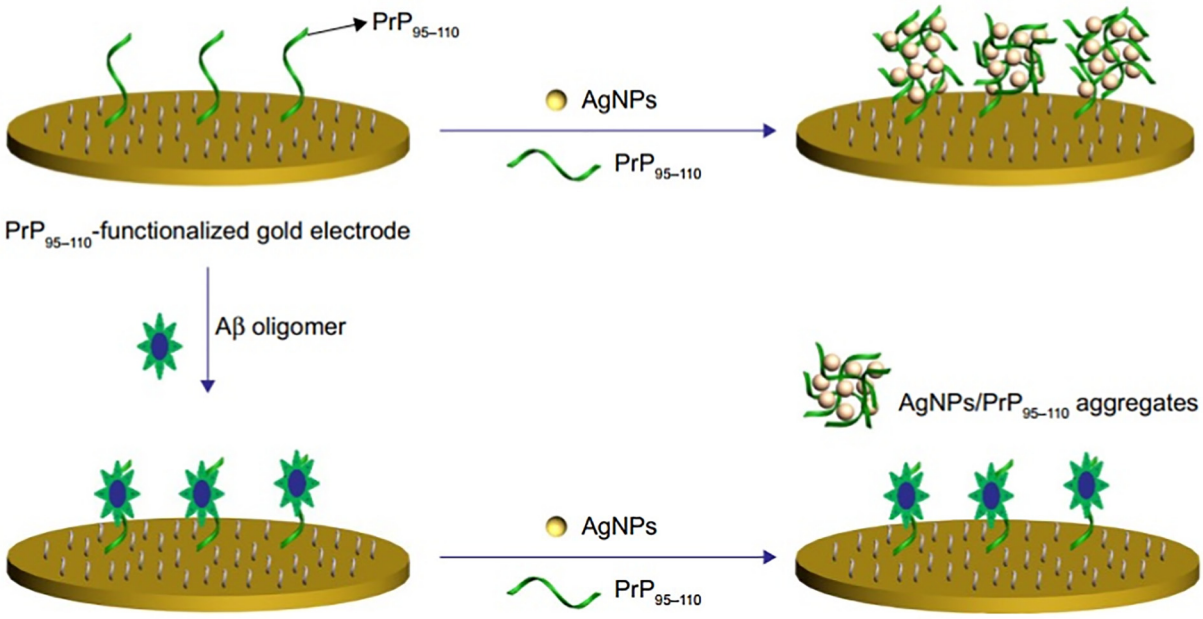

Fig. 4. Illustration for detection of Aβ oligomer with PrP95–110 as the receptor and AgNP aggregates as the redox reporters [56].

surface of screen printed electrodes (SPCE). Briefly, the extra permeability of the PMMs and their large surface area lead to increase the amount of immobilized antibodies and finally improved sensitivity. In this work linear range reported as 0.5–500 ng/mL and LOD was 7.1 ng/mL [69].

A field effect transistor (FET) biosensor is one of the most important type of electrochemical tool that extensively established to detect a widely range of biomaterial such as proteins and infection agent. This type of sensing device intrinsically charges of target proteins and bind to receptors immobilized specifically. In the construction FET biosensor, the SiO_2 gate is placed directly in an aqueous solution and act as a reference electrode [70,71]. FET based biosensors have some advantages, such as low-cost, rapid, being simple, and portable technology. In view of that, FET biosensor engineered for detection of Aβ fibrils. Created system exhibited high potential as a monitoring device in screening for AD disease, since FET biosensors have minimized capability and can be performed for quantity production. 100 pM reported as a limit of detection in this work [72].

Recently, self-assembled monolayers (SAMs) extensively used for electroanalytical chemistry and the basis for biosensors technology. Since they are a simple to modify, control and capability in interface with certain materials that allowing their application in immobilization of some biomolecules such antibodies [73]. Binding of antibody led to retention of SAMs bioactivity [74,75]. Moreover, AuNPs are interesting since of their high conductibility and stability with excellent surface-to-volume ratio. Additionally, the use of AuNPs enhanced sensitivity and selectivity not only by capability in immobilization of an extra amount of antibody but also reserve the bioactivity of the immobilized biomolecules [76]. Recently an ultra-sensitive and rapid SAMs based biosensor developed in simple structure with modified gold electrode for the detection of Aβ (1 42). Created nanoscale electrochemical immunosensor was label-free and showed several advantages such as good stability and selectivity [76].

An innovative label-free impedimetric biosensor based on fragment of the cellular prion protein (PrPC) was established to detection of AβO. In this work, biotinylated PrPC was involved with biotin/NeutrAvidin bridge to polymer functionalized gold screen-printed electrodes. Established system was specific for the ultra-sensitive detection of AβO and have several advantages such as label-free, in detection of natural oligomers [77]. Relatively sensitive quantitative label-free impedimetric immunosensor was developed based on carbon one-use electrochemical printed (DEP) chip for detection of AB [78]. In this study, modifying screen printed carbon ink electrode was applied for expansion of a sensitive label-free impedimetric immunosensor for detection of amyloid Ab peptide. Finding revealed that use of AuNPs in immobilization purpose, to increase stability and surface area for immobilization to obtain a LOD up to 0.57 nM. The planned system also verified cost effective detection simplicity platform, and great reproducibility. In overall point of view EIS technology is a notable technique for monitoring of the antigen-antibody complex that fixed on the surface of electrode [78].

6.2. Surface Plasmon Resonance (SPR) for detection of Aβ

AgNPs are one of the most important nanoparticles in biosensors technology. Due to notable optical properties of the AgNPs was used in the first nono-model application of the LSPR for detection of Aβ. During the first nono-model application of the LSPR, Haes and co-worker developed LSPR based biosensor for detection of AB using AgNPs. Influences of Cr, the nanoparticle adhesion layer, were the most important limitation of this work [79]. In addition, Haesse et al. developed an advanced biosensor for detecting AB based on sandwich-type LSPR. In this work synthetic ADDL and Anti-ADDL accomplished using the LSPR nanosensor technology was used for ultrasensitive detection of ADDL. In this work, linear range was 10 pM to 10 nM with LOD = 10 nM [80]. In this work fibrillar and oligomeric type of Aβ (1–42) were immobilized on to diverse fluidic channels of single chip and the aggregation profiles were accomplished. The designed sensing tool capable in the monitoring of the Aβ aggregation process and the assay reproducibility and accuracy were considerably improved. LOD of this report was 10 μM [81].

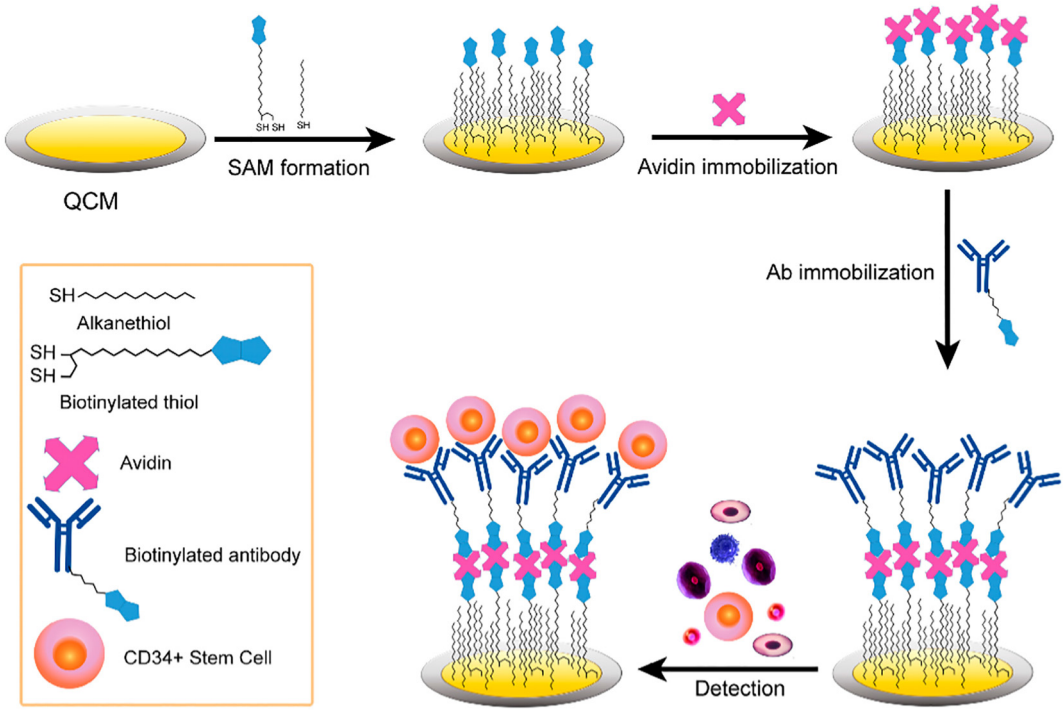

Fig. 5. Schematic of QCM immunosensor for detection of Aβ in stem cell selection and extraction [88].

6.3. Quartz crystal microbalance (QCM) for detection of Aβ

Quartz crystal microbalance is one of the most popular piezoelectric biosensor that able in sensing any alterations in the vibration frequency triggered by an alteration in mass owing to the binding of one target on its surface [58,82,83]. The operation of the quartz crystal with specific targets well as antibody determines what is detected. Resulting use of extremely voltage to the electrodes at both sides of the crystal, applied transducer attitudes shearing fluctuation parallel to the quartz surface. To provide highly stable frequency, transducer thickness is the most important factor (5 to 20 MHz) in oscillation frequency [84,85]. In QCM system transducers are independent on temperature and in experimental conditions used nearby 30 °C and targets are immobilized at one side of the crystal [86]. Interestingly, compared with electrochemical method, there are no particular requirements for the support in relation to conductivity, QCM sensing device has some advantages such as; signal analyzed by the network analyzer, more simple conformation. Moreover, QCM system are capable in recognizing nano-gram changes in mass by frequency counter that detect the oscillation frequency [87].A QCM based biosensor for detection of Aβ in stem cells was presented in Fig. 5 [88].

The Ab concentration is normally monitored by specific enzymes and antibody. Aβ produced in A1–40 and A1–42, is more hydrophobic to cause fibril form that is extra neurotoxic. Amyloid β peptides involve around 43 amino acid sequences, and resulted from the amyloid precursor protein through the cleaving process by β and γ secretases enzymes [89]. The Aβ peptides relate to pathogenesis of AD and display self-gathering behavior and form the amyloid fibrils through a specific aggregation way, relating oligomers. The fibril form is included β-sheet structures and are stable so, considered as the dead end of the aggregation pathway [90,91]. The Aβ oligomers are intermediates form and appear before the fibril state. The oligomers and fibrils are neurotoxicity form and recognized as pathogenicity factors for AD. To understanding the aggregation mechanism and drug improvement for AD people, clarifying the formation mechanism from oligomers into fibrils is unavoidable [92].

Understanding of the formation behavior of the Ab peptide is paramount to clarify the aggregation mechanism, care and identification of AD people [93,94].To study of the aggregation behavior of Ab peptide QCM system was developed in a different temperatures and PHs based on frequency oscillation during aggregation. In this work, 55 MHz wireless electrode-less QCM was applied to biochemical reactions of the A1–42 peptide. A bare immobilized on both the crystal surfaces, and subsequently established by treatment with the antiA1–42 antibody. Then, a solution of A1–42 monomers is inserted to monitor the aggregation of the analyte. Finding indicated that a low-concentration strong hydrophobic bonding occurred respectively [95].Structural alteration of Ab aggregation was explored by QCM biosensor using a 58 MHz quartz crystal. In this study, structural changes from monomer to oligomer and fibril also viscosity properties were investigated by QCM system. Evaluation of viscoelasticity can be providing a major index of fibrillation and valuable for estimating inhibitory medicines in drug expansion [92]. Finally, since of its simplicity, convenience, low cost, and real-time response, QCM method has been important for detection of biomolecules such as disease biomarkers. The QCM immunosensor comprises a quartz crystal with an antigen or antibody immobilized on its surface.

Recently, peptide solutions were injected for nucleation and growth of seeds and immobilization on the sensor chips. Atomic-force microscopy (AFM) and fluorescence technique were applied for assessing configurations of the seeds and aggregation. Additionally, in the case of fibril formation deposition rate, firmed by the frequency reduction, that is about 100monomers/nm2/year. The remarkable deposition behavior was perceived in the deposition of Aβ1–40peptide on Aβ1–42 seeds grown, which is imperative model for Ad [96]. Similar work was planned for detection of fibril Aβ in ultra-fast period. Monitoring of the deposition reaction of Ab1–40 peptides on immobilized seeds grown from Ab1–42, led to formation of oligomers. QCM biosensor allows real-time assessment of the amount of deposited peptides on the surface of seeds and fibril nucleation and elongation [97]. Ultra-frequency wireless QCM biosensor was used for revising heterogeneous deposition behavior of Ab140 peptide on Ab142 nuclei, which were grown under the stirring agitation. The deposition reaction was completed after 40 h, and the determined deposition rate was perceived on the nucleus grown at pH 4.6. On the other hand, ultra-sonication nucleus grown at pH 7.4 formed larger deposition rate. Finding revealed that local structural variation is triggered in the nucleus by ultra-sonication, which adsorbs the Ab peptide more actively than other nuclei. The subsequent deposits clearly show oligomer structure [97].

All of the biosensors for detection of Aβ summarized in Table 3A and Table 3B).

Highlighted from Table 3(A and B); As illustrated in the table, a variety of biosensors are designed to detection of Aβ, the most important of which are immunosensors. Selection of appropriate nanomaterials plays a decisive role in biosensor quality. According to Table 2, AuNPs dramatically increase biosensor sensitivity. The type of electrode is

Table 3A
Biosensors for detection of Aβ.

Technique	Type of Aβ	NPs	Electrode	Linear range	LOD	Ref
Colorimetric sandwich immunosensor	Aβ	AuNPs	–	7.5 nM to 350 nM	2.3 nM	[25]
Label-free electrochemical	Peptides (Aâ-40, Aâ-42)	–	GCE	1.2 to 8.3%	0.7 μg/mL	[50]
Electrochemical Immunosensors	Aβ1–42	–	Au	–	50 nM	[51]
Gelsolin-based electrochemical assay	b-Amyloid(1–40/1–42)	MWCNTs/ AuNPs	SPCEs	0.2–40 nm	50 pm	[54]
Electrochemical biosensor	Soluble beta-amyloid	AgNPs	Au	0.01–200 nM	6 pM	[56]
Immunosensors	Ab1–40 and Ab1–42	–	Carbon fiber microelectrodes	20–50 nM and 20–140 nM	–	[57]
Microfluidic biosensor/CV	A(1–42)	AgNPs	Au	100 M to 300 M	–	[60]
Impedimetricimmunosensor	AβO	AgNPs/Hydrogel	Au	0.1 pM to 10	0.1 pM	[62]
Electrochemical	Aβ(1–40)	–	Au	0.1–5 μM	18 nM	[98]
Electrochemical quantification	Aβ(1–40)	–	Au	0.1–5 μM	18 nM	[68]
Magnetic microspheres electrochemical	Aβ	AuNP	SPCEs	0.5–500 ng/mL	7.1 ng mL1	[69]
Field effect transistor (FET) biosensor	Aβ42	–	Metal electrode	–	100-pM	[72]
Silicon microarray/Immuno assay	Aβ 1–42	–	Silicon chips	0 to 100 ng/mL	5 ng/mL	[99]
label-free electrical impedimetric	AβO	–	Au	480 pM to 12 nM	240 pM	[100]
Field effect transistor (FET) biosensor	Aβ	Au	CE	10^{12}−10^{-9} g/mL	1013 g/mL	[101]
Label-free impedimetric	Aβ	Au	SPE	2.04 mM to 2.65 nM	0.57 nM	[78]
LSPR*	ADDL**	AgNPs	–	10^{-15} -10^{-6} M	1.7 × 103	[79]
Sandwich-type LSPR	ADDL	AgNPs	–	10 pM to 10 nM	10 nM	[80]
SPR	Aggregative	–	–	–	–	[81]

*LSPR: Localized surface Plasmon resonance. **ADDL: Amyloid-derived diffusible ligand.

Table 3B
QCM biosensors for detection of fibril amyloid.

	Thickness	Resonance frequency	Long time	LOD/Linear range	Ref
Fibril	3 mm	55 MHz	–	67 pM and 67 nM	[95]
	28 μm	58 MHz	21 h	10 μM	[92]
Amyloid	–	55 MHz	40 h	–	[96]
	28.5 mm	58 MHz	Ultra-fast	–	[97]
	–	55 MHz	40 h	–	[97]

one of the most important factors in the engineering of biosensors and the results show that due to the high electrical conductivity of gold and carbon such electrodes have a crucial role in increasing the sensitivity of the biosensors. However, in the meantime, carbon electrodes can be the focus of attention due to their low cost and effortlessly availability. Given that one of the prominent features of beta-amyloid is polymerization and formation of mass structure, the development of QCM biosensors would be valuable.

7. Tau protein

Tau protein plays key roles in AD and the hallmark pathologies observable in the brains of demented people [28]. Additionally, Aβ is a basic component of extracellular amyloid plaques and tau of intracellular neurofibrillary masses. Several study revealed that Ab accumulate intracellular and tau protein when released extracellular effects on acetylcholine muscarinic receptors and can be neurotoxic [28]. In the human brain six isoforms of tau protein were expressed and play remarkable role in promoting of microtubule stabilization and polymerization. Phosphorylation at several sites led to hinder insteady the microtubules, contributing to paired helical filaments formation and mass neurofibrillary. The gathering of abnormal tau is known to precisely predict disease severity [102]. For the first time in 1993, ELISA technique was applied for quantification of tau in CSF [103]. This technique was based on the mid-domain combined with a polyclonal anti-tau antiserum in the sandwich format and the mixture of a monoclonal anti-tau antibody [103]. Subsequently, sandwich ELISA method was published after 2 years based on monoclonal antibodies, as the "Innotest"/"Innogenetics" assay [104]. This assay identifying all tau isoforms nevertheless of phosphorylation state as a "total" tau (T-tau) assay [104,105].

7.1. Biosensor for detection of tau protein

The protein-based electrochemical sensing device was established for detection of the tau protein by identifying of mis-folding proteins. This technique screens tau-taumis-folding structure and binding while the primary step of tau oligomerization. EIS was applied to detect binding occurrence between immobilized tau and solution tau protein and performing as a recognition element. Formation of tau-tau-Au complex not only increased selectivity and linear range significantly but also was recognized to an improved charge permeability of tau-tau-Au surface to a redox probe. Tau-tau binding induced conformational and electrostatic change and allowed for a rapid sample analysis [106]. This biosensor was applicable in screening of the onset of neurodegeneration and aggregation inhibitors. Linear range was observed from 0.2 to 1.0 μM.

SPR biosensor based on sandwich assay developed for detection of Ab-Tu protein. After interaction of tau protein and Ab, an antibody against tau was located on the surface of sensor and covalently attached to a triggered mixed self-assembled monolayer (SAM). Subsequently, complex of Ab-Tau protein was passed across immobilized antibody against tau. Finally, antibody against Ab was passed over the attached compound and specifically bound to Ab existing in the captured complex . Developed biosensor using sandwich assay was seems to be able to detect Ab–Tau complexes arising in cerebrospinal fluid, as potential biomarkers of AD [107].

Table 4, summarize analytical performance of some biosensor for detection of tau protein.

Highlighted from tau protein biosensors (Table.4): **I)** Proteins are one of the most prominent targets in biosensor research and development, in which a wide variety of biosensors, including gen based biosensors and immunosensors, are of great importance. **II)** The human tau gene comprises more than 15 exons, with six isoforms by ranging in length from 350 to 441amino acids [109]; therefore, a wide range of biosensors can be developed, while very few have been industrialized to date. **III)** Compared to amyloid peptides, tau proteins are soluble in water, most stable, and have hydrophilic and unfolded construction [110].These features should be considered in the development of tau protein biosensors. **IV)** Despite the unique properties of the tau protein, few biosensors have been developed, and the improvement of various biosensors, especially QCM and SPR based biosensors, seems necessary.

8. miRNA

Several study have presented that some of human diseases are linked with miRNAs dysregulation, and expressions and related with the pathogenesis of greatest human genetically disorders [111]. Small non-coding RNAs (miRNAs) are nucleotides in 18–25 length and by mRNA dissociation or inhibiting translational efficiency regulate genes [112]. Finding revealed that some of miRNA such as mir-137 are related in AD and in primary stage significant changes has been shown in its level may deliver primary marks for diagnostics of AD patients [113]. To evaluation of miRNA, several techniques such as microarrays, northern blot and qPCR have been developed [114]. Although the molecular based method such as PCR and real-time PCR has acceptable sensitivity and specificity but they are expensive, need for advanced equipment and expert, long operation time and sophisticated techniques [115,116]. Recently, to eliminate these troubles modern technique such as biosensors developed extensively.

8.1. Biosensors for detection of micRNA

Using nanomaterial in construction of bio-sensing systems reduces the device size, and improves advantageous to biosensors and leading to operative progresses in sensitivity and selectivity of them [117,118]. From 2007 until now electrochemical nano-biosensors for miRNA identification has been developed broadly [119]. For example, a probe was immobilized on a 3D tetrahedral scaffold, and hybridization chain reaction (HCR) improved signals and detection sensitivity. After hybridization of target with the tetrahedral probes, biotin-modified sequences (H1 and H2) were used to increase the hybridization signal by adding amplified chain on each target. Finally, the avidin-modified HRP was attached on the HCR products that can produce an electrocatalytic signal [120]. Fig. 6 shows schematic structure of this biosensor. In this work linear range reported 1.0, 0.10 μM and limit of detection was 0.10 μM.

Recently UV–vis based biosensor developed extensively for detection of several target such as pathogenic bacteria and various biomarkers [121]. Accordingly, ultra-sensitive biosensor based on gold

Table 4
Tau protein biosensors.

Technique	Material	Electrode	Linear range	LOD	Ref
EIS[a]	SAM[b]	Au	–	0.03 pM	[28]
EIS	AuNPs	Au	0.2 to 1.0 μM	0.15 nM	[106]
SPR	–	–	50 to 1000 nM	5 nM	[107]
EIS	CdS NPs[c]	SPCE	10 and 100 nM	0.15 nM	[108]

[a] EIS: Electrochemical impedance spectroscopy.
[b] SAM: Self-assembled monolayer.
[c] CdS NPs: Cadmium sulfide nanoparticles.

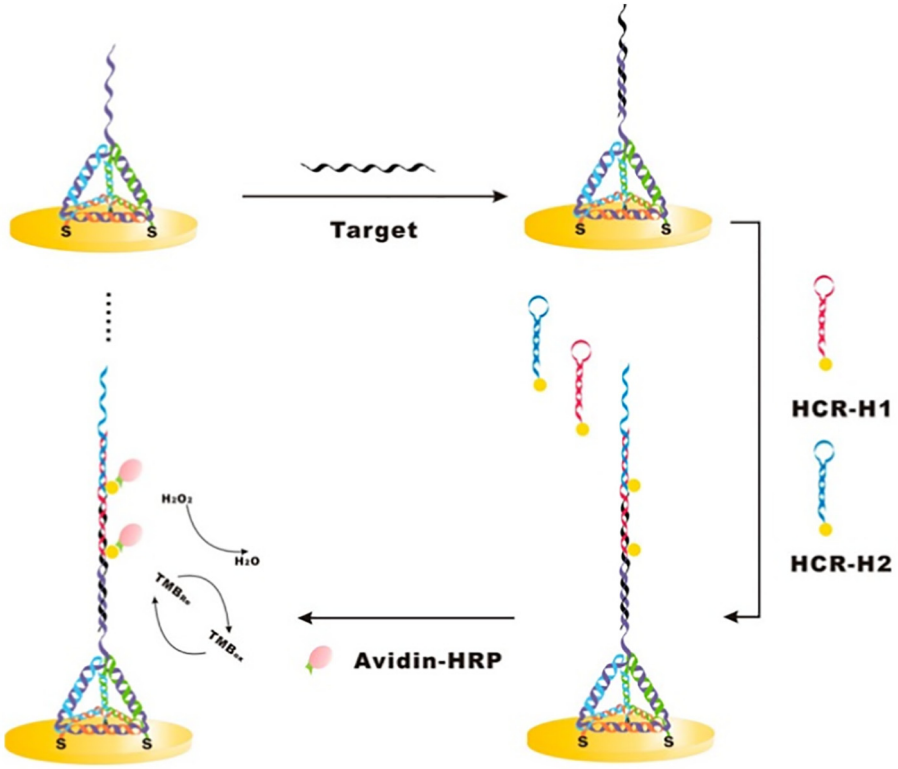

Fig. 6. Schematic illustration of electrochemical DNA detection [120].

nanoparticle was developed for detection of mir137 as a paramount biomarker of AD. In this work AuNPs and DNA-linked AuNPs were identified by UV–vis spectrophotometry device performed based on combines AuNP colorimetric with DNA hybridization chain reaction (HCR) amplification and no require the for enzyme and intricate technique. Using this biodevice, miRNA 137 was determined in 0.25 nM (LOD) which linear range was 0.25 nM–5 nM [122].

Interestingly, impedimetric based on graphene oxide biosensor established for detection of microRNA-34a.Modified pencil graphite electrodes (PGEs) were applied for electrochemical identification of microRNA-34a.The GO modified onto the surface of one-use PGE by passive adsorption and its electrochemical behavior was measured by cyclic voltammetry (CV). In this work, LOD and dynamic range were1.9 mg/mL and 0 to 10 μg/mL, respectively [123]. Also, biosensing device based on hybridization chain reaction (HCR) was developed for detection of miRNA-21. In this work HCR was occurred between hairpin probes (H1/ H2) and target miRNA-21 subsequently. Then, AuNPs adsorb on the surface of dsDNA polymers based on the electrostatic adsorption. Due to increases in gravity they precipitated on the surface of biosensor. Therefore, more HCR products formed along with the increase of miRNA, which directly induced the precipitation of AuNPs. Finally, miRNA-21 detected easily based on detecting the concentration of AuNPs in supernatant by using the simple UV–vis spectrum technique [124]. Fig. 7 shows all of the preparation and detection procedure of this biosensor. Using this biosensor miRNA 21 was detectable in low concentrations (LOD = 6.8 pM).

Also, an electrochemically-reduced graphene oxide (RGO) based on gold nanowires biosensor developed for detection of mic137 as a validated biomarker of AD. In this study to modify the surface of a screen-printed carbon electrode (SPCE) rGO with gold nanowires (AuNWs) was used and doxorubicin (Dox) applied as an intercalated label. Finding has been shown widely linear range (5.0 to 750.0 fM) and acceptable LOD (1.7 fM). Additionally, planned display an excellent selectivity to discriminate between target oligos vs. non-specific oligossuch as miR-21 and miR-155 [125].

Importantly, a label free electrochemical biosensor based on carbon nanofibers modified screen printed electrodes was developed for detection of miRNA-34a as confirmed biomarker of AD. Due to excellent properties of carbon nanofibers (CNFs) as a fiber-structured in nano-sized carbon materials, with brilliant thermal and mechanical feature used extensively in bio-sensing field. Accordingly application of CNFs on the structure of biosensor improved significantly the sensitivity and selectivity of the planned biosensor although simple and low cost construction [126]. Linear range and limit of detection were reported 25 to 100 μg/mL and 10.98 μg/mL, respectively. For complete of our discussion, Table 5 was summarized all biosensors for detection of micRNAs related on detection of AD.

Highlighted from Table 5;several studies showed that electrochemical genosensors are the most important biosensing tools in various fields of medical science as well as microbiology and infectious disease, pharmacology and diagnosis of wide range of diseases biomarkers. The most important feature of genosensors is the use of specific genes in their structure that greatly increases their sensitivity. The use of appropriate nanomaterials such as gold nanoparticles due to their electrical properties improves the quality of genosensors. The type of electrodes used in the structure of the genosensor as well as the techniques used is largely effective in improving their performance [128,129].

9. Conclusion

Findings have shown that rapid and sensitively detection of biomarkers particularly in early stages play a key role in the retrieval and treatment of Alzheimer's disease. Considering the disadvantages of routine methods such as high cost, hard operation and time consuming, low sensitivity and false positive results expansion of biosensor as a powerfully and analytical devices seems necessary and unavoidably. The following topics are important in relation to development of AD biomarkers and their prospects in future research: **1-** Biomarkers of AD are present and detectable in the blood and plasma environment, genome levels and cerebrospinal fluid so a wide range of optical,

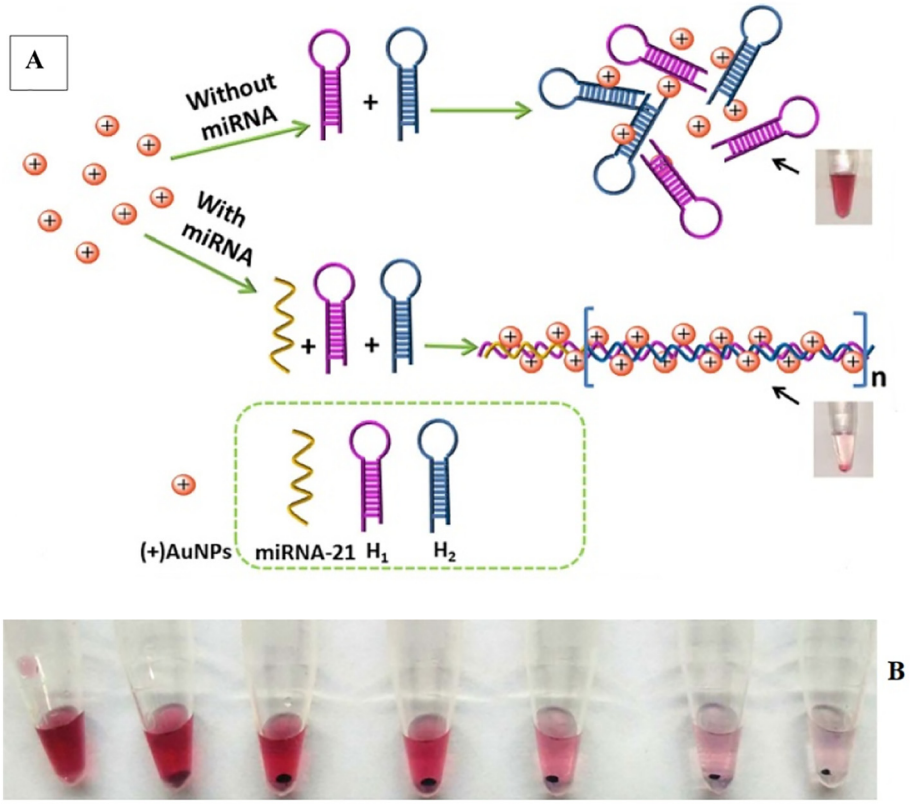

Fig. 7. A) Illustration of miRNA-21 detection based on the precipitation of DNA-AuNPs nanostructure. B) AuNPs subsequently the incubation of them using hairpin sequences (H1 or H2) mixture in the existence of altered concentration of target miRNA-21) [124].

electrochemical and mechanical biosensors such as SPR and QCM can be developed to identify them. **2-** Due to the different forms of Aβ protein and its polymerization process, mechanical biosensors such as QCM and colorimetric biosensors seem to be more important and attractive however, the colorimetric biosensors have a very simple and inexpensive structure. **3-** Given the existence of diverse gene isoforms associated with the tau protein, the development of gene based sensors should be considered. **4-** Despite the exceptional features of the tau protein just a few biosensors have been developed to date, and given its great importance in the diagnosis of Alzheimer's disease, more focus should be put on the improvement of tau biosensors. **5-** Although microarray and next generation are very important and sensitive tests, they are highly expensive and require advanced devices and skilled people, so biosensors can be a golden alternative to these techniques in detection of micRNAs. **6-** Miss folding and formation of mass construction are intrinsic characteristics of protein biomarkers that should be considered in biosensor expansion. **7-** Aβ and tau-protein are biomarkers with long half -life and high stability, while microRNAs are unstable biomarkers, so provision should be made for their biosensors. **8-** High sensitivity and specificity are prominent features of ideal biosensors. The results of various studies demonstrated that the type of used nanomaterials in biosensor structure plays a vital role in providing suitable biosensor. For example, it has been shown that the use of gold nanoparticles in biosensor structure significantly increases the sensitivity and specificity of the system. **9-** The most important object about gene based biosensors is the use of specific genes in their preparation, so according to the results of various studies, genosensors are the best option for identifying both DNA and RNA nucleic acids.

Briefly, due to the unique features of biosensors such as high sensitivity and specificity, fast diagnostic process and simple, low-cost structure, in the near future, biosensors will have a greater contribution in detection of AD biomarkers. Additionally, different types of biosensors, the gen based and colorimetric biosensors should be considered and developed in particular.

Table 5
Recent biosensor for detection of micRNA.

Target	Technique	Electrode	Linear rang	LOD	Sequence	Ref
microRNA	Electrochemical	Au	0.10–1 μM	10 μM	BiotinTCAAACACCATTGTCACACTCCAGCAATTTGGAGTGTGACA ATGGT	[120]
miR-137	Spectrophotometry	Au	0.25–5 nm	0.029 nm	5′-TTATTGCTTAAGAA TACGCGTAG-3′	[122]
miRNA-34a	Impedimetric	PGEs[a]	0 to 10 μg/mL	1.9 mg/mL	5-NH2- (CH2)6 - ACA ACC AGC TAA GAC ACT GCC A-3	[123]
miRNA-21	Spectrophotometry	–	20 pM to 10 nM	6.8 pM	5-UAGCUUAUCAGACUGAUGUUGA-3	[124]
miRNA-122	Spectrophotometry	–	–	5 nM	5-UGGAGUGUGACAAUG GUGUU UG-3	[127]
miR-137	Electrochemical impedance spectroscopy (EIS)	SPCE	5.0 to 750.0 fM	1.7 fM	5 TTATTGCTTAAGAATACGCGTAG-3	[125]
miRNA-34a	Electrochemical impedance spectroscopy (EIS)	SPEs	25 to 100 μg/mL	10.98 μg/mL	probe-1: 5′ NH2-ACA ACC AGC TAA GAC ACT GCC A-3 probe-2: 5′ NH2-ACA ACC AIC TAA IAC ACT ICC A-3′	[126]

[a] PGEs: Pencil graphite electrode.

Acknowledgments

This study was supported by Tabriz University of Medical Sciences, Tabriz, Iran.

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