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Advanced sensing technologies of phenolic compounds for pharmaceutical and biomedical analysis

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Highlights

- Recent advances in sensing technologies for detection of phenolic compounds
- Optical detection of phenolic compounds
- Oxidation mechanism of phenolic compounds

- Immobilization methods for biosensors
- Application of sensors for pharmaceutical and biomedical analysis

Abstract

Phenolic compounds are bioactive natural products of considerable interest in pharmaceuticals and biomedicines. Due to their bioactive functions, phenolic compounds have received increasing attention in recent years. Therefore, it is necessary to develop new and advanced analytical methods for determination of phenolic compounds in relation to pharmaceutical and biomedical applications. However, in majority, their detection has been largely conducted by sensitive yet bulky and expensive laboratory instruments, such as gas chromatography-mass spectrometry and liquid chromatography-mass spectrometry. Compared with those laboratory scale instruments, the advanced sensing technologies are extremely attractive due to the advantages of their low cost, time saving, user-friendly, simplified sample pre-treatment, high sensitivity, and excellent selectivity. The aim of this review is to provide critical information on the advanced sensing technologies for detecting phenolic compounds, with emphasis on optical sensors, electrochemical sensors and biosensors. Besides, the present status, critical issues and future trends of the related sensing technologies are outlined.

Keywords: Phenolic compounds; optical sensor; electrochemical sensor; biosensor; pharmaceutical analysis; biomedicine

1. Introduction

Phenolic compounds, ubiquitous in plants, are amongst the most desirable phytochemicals with both well-known functional and health promoting properties [1-3]. Phenolic compounds have been mainly considered as secondary plant metabolites with several thousand compounds identified from plants [4-7]. Without any doubt, the phenolic compounds provide additional values and potential sources in pharmaceuticals and biomedicines, due to their high antioxidant capacity as well as anticancer, antimicrobial, antiviral and anti-inflammatory properties [9-13]. From the past a few decades, the research studies focusing on phenolic compounds for pharmaceutical and biomedical applications have increased considerably, because of their various beneficial effects for human health [14-15]. Furthermore, some essential medicines bearing phenolic groups, such as paracetamol (acetaminophen) and doxycycline, are included in the World Health Organization (WHO) model list and commonly used as antipyretic and analgesic drugs [16]. Besides, some small molecular phenolic compounds (*e.g.* thymol) have been used in biomedicines as antiseptic due to the toxicity [6].

Basically, phenolic compounds contain an aromatic ring bearing one or more hydroxyl groups and their structures could range from that of a simple phenolic molecule to that of a highly polymerized compound [8]. According to their carbon chain, the phenolic compounds can be divided into different classes, mainly including simple phenols, phenolic acids, flavonoids, lignans, biflavonoids, tannins (hydrolysable and condensed), stilbenes and lignans [6, 17]. The pharmaceutical

properties, such as antioxidant activity of phenolic compounds are largely depended on their chemical structures [7]. The number of carbons, basic skeletons and chemical structures of the main phenolic compounds are shown in Table 1.

Due to the well-known health benefits, technological role and marketing of phenolic compounds, there is an increasing demand for highly sensitive and selective analytical methods for the determination of those compounds [18-20]. The chromatographic techniques, including gas chromatography (GC), liquid chromatography (LC) and capillary electrophoresis (CE) are the most common methods for the determination of phenolic compounds, which are capable for identifying and quantifying a wide variety of phenolic compounds from different groups at trace levels with great accuracy [21-24]. Combined with high sensitive and selective mass spectrometry (MS) detection, the chromatographic techniques could provide the simultaneous separation, identification and quantification of different phenolic compounds from plant derived materials, including herbs, fruits, vegetables, wines, beverages, cereals and crops [25-28]. Although accurate and sensitive, chromatographic techniques usually require bulky and expensive instrumentation, labor-intensive sample preparation, and specialized operators.

In the past decades, there has been a trend to develop new sensing technologies to simplify sample preparation, and provide more cost effectiveness, user-friendly and faster analyses [29-30]. In addition to avoid the tedious pre-treatment step, sensors are powerful alternative to conventional analytical techniques, for their particularly high specification, sensitivity, small size, and high sample throughput [31-34]. The

inherent properties of sensors led to convenient quantitation of phenolic substrates in relevant pharmaceutical and biomedical samples [35-39].

According to the principles of interaction with the analytes by either chemicals or biomolecules, the sensors can be classified as chemical sensors, mainly including optical sensors and electrochemical sensors, and biosensors [40-42]. In the following sections, the latest research results and outstanding properties of different sensor systems applied for the detection of phenolic compounds will be discussed. Consequently, several outstanding properties of the sensors, research opportunities and the development potential and prospects will be outlined for pharmaceutical and biomedical analysis.

2. Chemical Sensors

A chemical sensor is a device that convert a chemical or physical property of a specific analyte into a measurable signal, in which magnitude is in relation to the concentration of the analyte [43-44]. Compared with biosensors, chemical sensors are less reported for detecting phenolic compounds, which is mainly due to their low sensitivity and selectivity. To overcome these shortcomings, new materials, especially nanomaterials have been applied to amplify the signal in chemical sensors. Indeed, the emergence of nanotechnology is opening novel fields for fabrication of new sensors based on different nanomaterials, including carbon, metal, quantum dots and transition-metal dichalcogenides in sensing technology [31, 39, 41].

Based on the different transduction principles, chemical sensors can be mainly classified into two main classes: sensors with optical transducers (*i.e.* optical sensors) and sensors with electrical transducers (*i.e.* electrochemical sensors) [40-42, 45]. Nanomaterials have been extensively used for optical and electrochemical sensing and have shown attractive results, due to their unique advantages, such as good optical, electronic, and mechanical properties, much higher specific surface and versatility in surface modification [46-49]. Pelle and Compagnone reviewed the assembly of nanoparticles in functional sensing devices for the detection of phenolic compounds and related antioxidant capacity in food with focus on both optical and electrochemical strategies [31].

2.1 Optical Sensor

The optical sensors have been developed as powerful portable analytical devices with high specification, sensitivity, and cost effectiveness for determination of phenolic compounds [50-54]. The principles of optical sensors are based on a measurement of physical quantity in light variations in absorption, reflection of primary light flux, or luminescence (including fluorescence) [50-51, 55]. Optical sensing devices can be further classified by their principles of detection (*e.g.* interferometry, reflectance, chemiluminescence, light scattering and refractive index, and fluorescence spectroscopy). McDonagh *et al.* comprehensively reviewed the developments, basic principles, common sensing platforms and future trends of optical chemical sensors [56]. Rodionov *et al.* reviewed the published works of

optical sensors in 1993–2012 for determining phenolic compounds with different chemical structures [50].

2.1.1 Optical detection

Optical detection methods have been widely used for quantitative phenolic analysis, due to the ubiquity of optical instrumentation in the laboratory [52, 57]. Among them, colorimetric assays have been applied as nonspecific methods for evaluating the levels of phenolic compounds in different samples [52, 58-59].

Typically, a number of colorimetric methods have been developed for the quantification of phenolic compounds [60-63]. Based on different principles, those assays have been used to determine different structural groups present in phenolic compounds [64]. Among them, Folin–Ciocalteu assay has been widely used for determining total phenolic compounds, based on the reduction of phosphor-wolframate-phosphomolybdate complex by phenolic compounds to a blue reaction product [57, 65-66]. The Folin–Ciocalteu assay has been successfully applied for the determination of phenolic compounds in herbs, teas and coffee brews [67-70]. Furthermore, the quantitation of total phenolic compounds can be also achieved by spectrophotometric methods with 4-aminoantipyrine or ferricyanide/Prussian blue [60, 62-63]. Besides, a colorimetric method based on the complexation of the phenolic compounds with aluminum has been applied to determine the total flavonoid contents [71]. The main disadvantage of the colorimetric assays, however

is that they only can estimate the total phenolic content without quantitative measurement of individual compounds.

Ultraviolet–visible (UV-vis) spectrophotometric methods enable to distinguish the different classes of phenolic compounds (e.g. mono-phenols, flavonoids, anthocyanins and hydroxycinnamic acids) with their characteristic UV-vis spectra [72-73]. Aleixandre-Tudo *et al.* published relevant reviews of the main methods used in the characterization and quantification of phenolic compounds by UV-vis spectrophotometric methods [74-75]. Spectrophotometric methods provide very useful qualitative and quantitative information. In fact, spectrophotometry is the main technique used for the quantification of different classes of polyphenols due to its simplicity and low cost. However, spectrophotometric methods alone cannot differentiate various individual phenolic compounds. To overcome this problem, strategies relying upon coupling UV–vis spectrophotometric detection with LC or CE separation allows the analysis of different phenolic compounds simultaneously [76-77].

2.1.2 Optical sensors

Taking advantage of the capacity of optical detections, a variety of optical sensors have been developed for detection of phenolic compounds. For example, the total polyphenol content in green tea beverages were determined by an optical sensor, based on sodium metaperiodate ($NaIO_4$) coupled with 3-methyl-2-benzothiazolinone hydrazone (MBTH) as coloring agent [78].

However, the sensitivity and selectivity of optical sensors are not always sufficient to solve multiple challenges of real applications. Recently, nanomaterials-based approaches have become a valuable strategy to develop novel and improved sensing technologies for the detection of phenolic compounds [31, 46, 49, 52-53]. Vilela *et al.* reviewed the application of nanoparticles as analytical tools for *in vitro* antioxidant-capacity assessment with focus on optical nanoparticle sensing for food and biological samples [79].

To demonstrate that the endogenous polyphenols in real samples are selectively driving the gold-nanoparticle (AuNPs)-formation process, Vilela *et al.* explored representative food samples (*e.g.*, honeys, fruit, wine, tea and soy extracts) with different qualitative and quantitative endogenous polyphenols as natural sources of reducing compounds [80]. The obtained results showed that AuNPs formed from selected food samples provided excellent sigmoidal curves in line with their antioxidant capacity. Although polyphenols are only a minor constituent of honey samples, the red color (indicative of AuNPs) intensified the higher the polyphenol content in honey, as shown in Figure 1A. The overlapped spectra obtained from different honey samples showed a well-defined maximum absorption at $\lambda = 540$ nm (Figure 1B). Furthermore, the transmission electron microscopy (TEM) characterization enabled to confirm that honeys provided gold nanospheres with excellent shape and very well-defined sizes with 13 ± 5 nm diameter.

Besides, CdTe quantum dots (QDs) have been successfully applied to fluorescent assay of total phenolic compounds in common beverages, including green tea, black tea, Pu-Erh tea, lemon balm, peppermint, lime, chamomile and coffee infusions [81]. It was reported that this technique could achieved nearly one order of magnitude more sensitive than the Folin–Ciocalteu assay.

2.2 Electrochemical Sensor

Electrochemical sensors offer unique properties as reliable tools for fast and low cost analysis of phenolic compounds [82-83]. Due to the unique properties, including fast response, easy to use, high sensitivity, low instrumental costs, minimal sample volumes and portability, electrochemical sensors have attracted increasing attention in the field of analytical chemistry [82, 84]. In the literatures, numerous research articles have dedicated to the development and application of electrochemical sensors for pharmaceutical and biomedical analysis [85-86]. In the past decades, considerable progress in electroanalytical chemistry with the development of ultra-microelectrodes, economical and disposable electrodes, molecular devices and smart electrochemical sensors has been achieved. Depending on their working principles, electrochemical sensors could be mainly divided into conductometric, potentiometric and voltammetric/amperometric sensors [87-89]. Dobes *et al.* reviewed electrochemical methods as a tool for determining phenolic compounds in plants [82].

2.2.1 Oxidation mechanism of phenolic compounds

Based on the chemical structure, we could see that phenol can be oxidized to phenoxy radical with a single electron and a proton step, which is thermodynamically unstable and coexists in three isomeric forms. The oxidation of mono-phenols is always irreversible throughout the whole pH range [90-92]. Due to their high sensitivity, voltammetric methods have been successfully used to study the redox behavior of phenolic compounds. The typical cyclic and differential pulse (DP) voltammetric profiles of mono-phenol are shown in Figure 2.

As shown in Figure 2, phenol undergoes oxidation in a single step, peak 1_a, which is always irreversible. While, the two phenol oxidation products, *ortho*-quinone and *para*-quinone are reversibly oxidized in a pH dependent mechanism. The redox behavior of phenol indicated that the voltammetric/amperometric sensors could be possibly used for detecting the phenolic compounds.

The oxidation potentials of different phenolic compounds have been determined by cyclic voltammetry (CV) [92-95]. The oxidation mechanisms of polyphenols are often much more complicated than the simple mono-phenols [96]. But all phenolic compounds have the potential for undergoing redox reactions, which provided valuable insights for electrochemical detections. Besides, CVs also provide valuable information about the quantity of main groups of phenolics, such as catechins, gallates, anthocyanins and monophenolics in complex mixtures [97].

2.2.2 Electrochemical sensors

As mentioned above, the redox behavior of phenolic compounds indicated that the voltammetric/amperometric sensors could be possibly used for detecting the phenolic compounds. So far, voltammetric techniques are the most widely used electrochemical methods for the analysis of phenolic compounds [98-100]. Due to their high sensitivity, voltammetric methods, such as CV, differential pulse voltammetry (DPV), square wave voltammetry (SWV) and adsorptive stripping voltammetry (ASV) have been successfully applied for both qualitative analysis and quantitation of phenolic compounds even at trace amounts [99, 101-103]. As the antioxidant properties of phenolic compounds are related to their ability to donate electrons, the voltammetric methods allow the study of the antioxidant properties, and the detection of polyphenols could be achieved at low potentials [98, 104-105].

Vishnu and Kumar developed a novel electrochemical sensor by introducing an ultra-low cost 6B grade pencil graphite (6B-PGE*) for detection of phenols (meta-cresol and phenol) in insulin formulations [36]. As shown in Figure 3 A-D, 6B-PGE* was prepared by potentiostatic polarization of the pencil graphite (PGE) at an applied potential of 2 V vs. Ag/AgCl for 180 s in pH 7 phosphate buffer solution (PBS). With the novel electrochemical sensor, efficient DPV detection of total phenol content (meta-cresol and phenol) was achieved for three different commercially available insulin injections (Figure 3 E-G). The detected total phenolic content values were closely matching with the respective labeled values of the real samples.

Among the many electrochemical systems that can be applied for analytical purposes, the combination of voltammetric detection with screen-printed electrodes (SPE) can add mass production capabilities, and thus represents one of the most convenient alternatives for analyzing of phenolic compounds [106-108]. Like most electhochemical sensors, disposable screen printed electrochemical sensors typically consist of working electrode, counter electrode, and reference electrode on single platform, which can produce a distinguishable signal under measurement.

It is important to point out that there were some electrochemical methods developed for the determination of phenolic compound in real samples [109-111]. Kang *et al.* developed an electrochemical method for determination of rutin in three Chinese medicine samples with a glassy carbon electrode [109]. Franzoi *et al.* developed a carbon paste electrode modified with poly (vinylpyrrolidone) for the determination of rutin in pharmaceutical formulations [110]. Sochr *et al.* developed an electrochemical method for the determination of adrenaline in human urine with an unmodified boron-doped diamond film electrode [111].

However, it is a strong challenge to simultaneously detect phenolic compounds with similar structures on the unmodified or bare electrodes, because their redox potentials are too close to each other and seriously overlapped in many cases [112-113]. Therefore, it is of great importance to find appropriate and efficient materials to modify the electrode for overcoming this problem.

By far, great efforts have been devoted to developing modified electrodes with functional materials to achieve higher sensitive and selective detection of phenolic compounds. Different functional materials with electrocatalytic properties, such as graphene [114], carbon black [107], nanoporous gold [115], ZnO nanosheets [116], ZnO thin film [117], and reduced graphene oxide-ZnO composite [118] have been applied to modify electrodes, which showed promising results for rapid detection of phenolic compounds. Besides, microfluidic chip strategies coupled with electrochemical detection have been assessed and integrated for complex natural antioxidants determination [119].

3. Biosensors

A main challenge for all chemical sensors, including both optical and electrochemical sensors, is the interference from a complex sample matrix. In recent years, biosensors have attracted a great deal of interest for their application in food and pharmaceutical industry [120-123]. Indeed, biosensors can make ideal sensing systems to efficiently screen and selectively detect phenolic compounds, due to their biological component base, capability to operate in complex matrices, short response time and miniaturized size [32-33, 124]. Therefore, biosensors have proved to be very useful tools for the analysis of phenolic compounds [125-128].

By definition, a biosensor is as an analytical device consisting of at least one biological component (*e.g.*, enzyme, antibody, DNA, cell, artificial membrane and entire animal tissue) and a physical transducer (*e.g.*, optical or electrochemical

device) [129-130]. Many biosensors have been reported for the detection of phenolic compounds based on a number of biological components, including enzymes, microorganisms, antibodies, antigens and nucleic acids [32-33, 124, 131]. Immobilization of biological components to the biosensor may change the optical, electrochemical or structural properties of the layer for measurement of analytes, which can provide a more specific and sensitive measurement [130, 132]. Karim and Fakhruddin summarized the possible biosensors for the detection of phenolic compounds in environmental samples, and presented considerable prospective aspects of this research field [32].

Among different biosensors, enzyme-based biosensors have been most widely applied for the determination of phenolic compounds in the pharmaceutical, biomedical, clinical, environmental and industrial analysis. Basically, enzymes have been considered to be versatile, highly efficient and specific for catalyzing reactions under mild conditions [133]. Some biosensor researches have been carried out on the detection of phenolic compounds based on pure enzymes or crude extracts as enzyme sources, such as laccase [33, 126, 128, 134], tyrosinase [135-140], horseradish peroxidase [141-142] and polyphenol oxidase [143].

Besides, microorganisms were also widely used for the construction of biosensors to detect phenolic compounds. The commonly used microorganisms include *Pseudomonas* [144-147], *Escherichia* [148-151], *Arthrobacter* [152-153], *Lactobacillus* [154], *Moraxella* [155], *Rhodococcus* [156] and *Trichosporon* [157].

3.1. Immobilizing Methods

Biosensors can normally work quite well, when the bioreceptor is properly immobilized [32-33, 124]. However, the immobilization of bioreceptors on different carriers is a great challenge in biotechnology. The selection for the immobilization method of bioreceptors, therefore is a critical step for fabrication of biosensors. The main aim of immobilization is to obtain bioreceptors with excellent long-term stability and high activity. The various major criteria should be taken into account for immobilization techniques, mainly including the type of transducer used, the physicochemical properties of the analyte and the operating conditions. Generally, some common methods of immobilization have been found to use as covalent binding, adsorption, cross-linking, encapsulation and entrapment (Figure 4).

Besides, it is also critical to find suitable materials as effective immobilization matrices to design phenolic biosensors with excellent analytical performance. The common matrices used for immobilization mainly included silica gel, chitosan, polyvinyl alcohol, Osmium complex and nafion/sol–gel silicate [32-33, 124]. It has also been reported that the formation of nanomaterial and biomolecule assemblies could provide good biocompatibility and signal enhancement for detection [31, 37, 41, 46, 135, 137, 139, 142]. Similar to chemical sensors, biosensors also could be integrated with different detection techniques, such as optical and electrochemical techniques.

3.2. Optical Biosensors

Optical biosensors normally employ a color reagent, which can interact with the oxidation products and/or free radical of phenols produced by the bioreceptors (*e.g.* enzymes) to form optical detectable products [51, 126, 138]. Therefore, the enzymes are commonly immobilized in combination with a color reagent for an optical detection of phenolic compounds. The matrix for enzyme immobilization for most optical detection should be transparent in the UV and visible regions as well as inert and biocompatible [51]. In particular, the optical biosensors can intermediate with different phenolic compounds to appear spectroscopic/color properties which are detectable with simple portable spectrometer or even distinguished with naked eye.

Setti *et al.* studied the ability of laccase to oxidize methoxyphenols in the presence of 3-methyl-2 benzothiazolinonehydrazone (MBTH) to produce red color azo-dye compounds [158]. Based on this principle, an optical biosensor could be developed for detection of different phenolic compounds, such as catechol, guaiacol, ortho-cresol and meta-cresol [161].

Huang *et al.* designed and fabricated a fiber-optic biosensor based on immobilized laccase catalysis and fluorescence quenching for the determination of adrenaline [160]. The laccase was immobilized on the CuTAPc-Fe3O4 nanoparticles composite to catalyze the oxidation of adrenaline, and the consumption of oxygen was detected with the fluorescent oxygen-sensing membrane. Sanz *et al.* optimized the enzymatic reaction of laccase with phenol by fluorescence and molecular absorption using a laccase-polyacrylamide based optical biosensors [161]. The developed method allowed the effective determination of phenol in environmental samples.

However, it is still challenge to apply the optical biosensors for the determination of phenolic compounds in real biological samples. Therefore, the optical biosensors were coupled to chromatographic separation to screen the phenolic compounds in clinical samples (*i.e.*, plasma and urine) [162-163].

Silva *et al.* developed an optical biosensor for screening of three catecholamines based on a sensitive cladding of laccase [162]. As shown in Figure 5, the optical biosensor was composed of a miniaturized column for catecholamines separation, a biocomponent enzymatic cladding of laccase and an optical fiber with associated electronics. The optical biosensor was successfully applied to the analysis of human urine and plasma.

Ferreira *et al.* also combined the HPLC technique with an optic-fiber coated with an enzyme (laccase) as detection system for quantification of the three catecholamines in plasma and urine samples [163].

3.3. Electrochemical Biosensors

Electrochemical biosensors, especially enzyme-based electrochemical biosensors have been widely developed for the determination of phenolic compounds [31-33, 49, 121, 130, 140]. The electrochemical biosensors normally measure the phenolic compounds the basis of the production of electrons by enzymatic catalysis. Among the enzymes, laccase, tyrosinase, horseradish peroxidase and polyphenol oxidase are groups of enzymes that catalyze the transformation of a large number of phenolic compounds [31-33]. The mechanisms of laccase, tyrosinase and peroxidase in the

electrochemical biosensors are different. For laccase and tyrosinase, the enzymes are re-reduced by phenolic compounds, after they are oxidized by oxygen in electrochemical biosensors [32-33]. The laccase-based electrochemical biosensors can detect phenolic compounds with free para- and meta-position even with a complicated catalytic cycle. While, the tyrosinase biosensors can detect phenolic compounds with at least one free ortho-position [33]. On the other hand, for peroxidase, phenolic compounds are oxidised by enzyme with hydrogen peroxide (H_2O_2) as a co-substrate, and then can be further electrochemically reduced on the surface of the electrode. Horseradish peroxidase based electrochemical biosensors are sensitive to many phenolic compounds, as a great number of phenols can act as electron donors for peroxidase [164].

A comprehensive study on the immobilization of enzymes on electrodes were performed both simple and complex for electrochemical detection of a large number of phenolic compounds [121, 130, 140, 165-166]. Interestingly, da Silva *et al.* immobilized polyphenol oxidase on a support based on β-cyclodextrin [166]. As shown in Figure 6, a biosensor was constructed based on immobilization procedure for detection of phenolic compounds.

It has been reported recently a lot of novel electrochemical biosensors that combined the advantages of enzymatic sensors (amplification through electrocatalytic redox cycling) with electrochemical detection of phenolic compounds [31-33, 167-170]. Leite *et al.* developed a laccase–peroxidase bi-enzymatic biosensor for voltammetric detection of various catecholamines [168].

Rawal *et al.* fabricated a polyphenol biosensor by covalently immobilizing laccase onto electrochemically deposited silver nanoparticles (AgNPs)/carboxylated multiwalled carbon nanotubes (cMWCNT)/polyaniline (PANI) layer on the surface of gold (Au) electrode. Zhao *et al.* fabricated three kinds of electrochemical biosensors by immobilizing different morphologies of nanostructured silica–phytic acid (SiO_2–PA) and laccase onto the glassy carbon electrode surface [169]. The electrochemical biosensor with the best electrochemical performances was applied for the determination of dopamine concentration in pharmaceutical injection samples and rabbit blood serums [170].

Many electrochemical biosensors have been reported for the detection of phenolic compounds in pharmaceutical and biomedical applications [165, 168, 170-183]. However, most of the applications are only focused on the pharmaceutical formulations or synthetic samples without complex sample matrices. Khoobi *et al.* used multivariate curve resolution by alternating least-squares for electrochemical biosensors to determine dopamine in the presence of unexpected interference [111]. The proposed method has been used for the reliable analysis of dopamine in real human blood serum samples.

4. Conclusions

As current analytical strategies such as spectrometric and chromatography methods for detecting and monitoring phenolic compounds are tedious, very time-consuming, not portable and need relatively large amount of sample they are not suitable for

rapid on-site applications. Compared with those conventional analytical strategies, chemical sensors and biosensors are attractive due to the advantages of simple operation, time saving, low cost, free of complicated sample pre-treatment, high sensitivity and excellent selectivity. Therefore, these advanced sensing techniques have attracted enormous interests for analysis of phenolic compounds in pharmaceutical and biomedical samples.

The new materials, such as nanomaterials offered a lot of promising prospects for fabricating new sensors with improved sensitivity and selectivity. It is worth to mention that colorimetric assays have been applied as nonspecific methods for evaluating the levels of phenolic compounds in different samples. Based on the similar detection principles, optical sensors have been developed for detecting the total phenol compounds. Based on the redox behavior of phenolics, the electrochemical sensors have been developed for detection of phenolic compounds. Due to the redox behavior of phenolic compounds, voltammetric or amperometric methods are commonly used in electrochemical analyzing of phenolic compounds.

Compared with biosensors, chemical sensors are less reported for detecting phenolic compounds. Nevertheless, the development of chemical sensors without using the bioreceptors is also important for phenolic detection. As compared to chemical sensors, biosensors usually offer lower stability at room temperature and as a consequence not appropriate for field application.

In biosensors, a bioreceptor is typically immobilized at the surface of biosensors. Development of suitable immobilization techniques remain challenges for the construction of useful biosensing devices. Among the different sensors, electrochemical biosensors have been most widely studied and extensively applied for detection of phenolic compounds in pharmaceutical and biomedical samples.

However, it is still very challenging for sensors to simultaneously detect phenolic compounds with similar structures, as their absorbance wavelengths and/or redox potentials are too close to each other and largely overlapped in most cases. Chromatographic separation and microfluidic chip strategies coupled with sensing detection hold a promising solution for this issue.

Despite a great number of investigations, the application of sensors to real pharmaceutical and biomedical samples still remain limited with few examples available. Nevertheless, the current reported works have obtained very good results using short time analysis and low sample consumption which highlight the clear potential of the sensors as convenient quantitative method of phenolic substrates. It is expected that the fabricated sensing devices could be useful in the development of pharmaceutical and biomedical analysis.

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Figure captions

Figure 1 (A) Formation and characterization of AuNPs using endogenous polyphenols from honey samples: AuNP colloidal solutions formed by 10 different honeys (1–10), blank solution (control C) and mixture glucose: fructose 60:40 w/w (control S). (B) AuNP spectra formed by honeys 1, 3, 5, 8 and 10 and TEM characterization of AuNPs (inset). {Reprinted with permission from [80]}.

Figure 2. (A). Cyclic voltammograms (CVs) with baseline subtracted in pH 7.0 0.1 M phosphate buffer 30 µM phenol: (—) first scan and (···) second scan, v = 50 mV s^{-1}. (B). DP voltammograms of (—) supporting electrolyte pH 7.0 0.2 M phosphate buffer and 25 µM phenol: (—) first and (—) second scan, and DP voltammograms baseline-corrected, (···) first and (···) second scan. {Reprinted with permission from [90]}.

Figure 3 (A) Photograph of a 6B-pencil graphite (PGE); (B) scheme of a 6B-PGE prepared using parafilm by wrapping on the cylindrical surface portion of the pencil graphite; (C) a 2 V-180 s/pH 7 PBS preanodized 6B-PGE (6B-PGE*); (D) selective phenol oxidation reaction scheme on 6B-PGE* at 0.55 V vs. Ag/AgCl in pH 7 PBS; and (E-G) Typical DPV responses of 6B-PGE* for the detection of total phenolic content (meta-cresol and phenol) in three different real pharmaceutical insulin samples (A–C) by a standard addition approach. {Reprinted with permission from [36]}.

Figure 4. Common methods of immobilization used in biosensors: (A) covalent binding; (B) adsorption; (C) cross-linking; (D) encapsulation; and, (E) entrapment. {Reprinted with permission from [33]}.

Figure 5 (a) Schematic configuration of the whole optical biosensor detection system (AT – analytical tube; GT – glass tube; IC – injection cell; L – laser; OC – optical coupler; OF – optical fiber; P – photodetector; PC – laptop for data acquisition and processing; PS/DVB F – styrene/divinylbenzene fiber) and (b) schematics of the enzymatic reaction occurring at the OF surface coated with laccase. {Reprinted with permission from [162]}.

Figure 6. (A) Immobilization procedure using β-cyclodextrin modified support, (B) composition of the proposed biosensor and (C) polyphenol oxidase -catalyzed oxidation of rutin with its subsequent electrochemical reduction on the biosensor surface. {Reprinted with permission from [166]}.

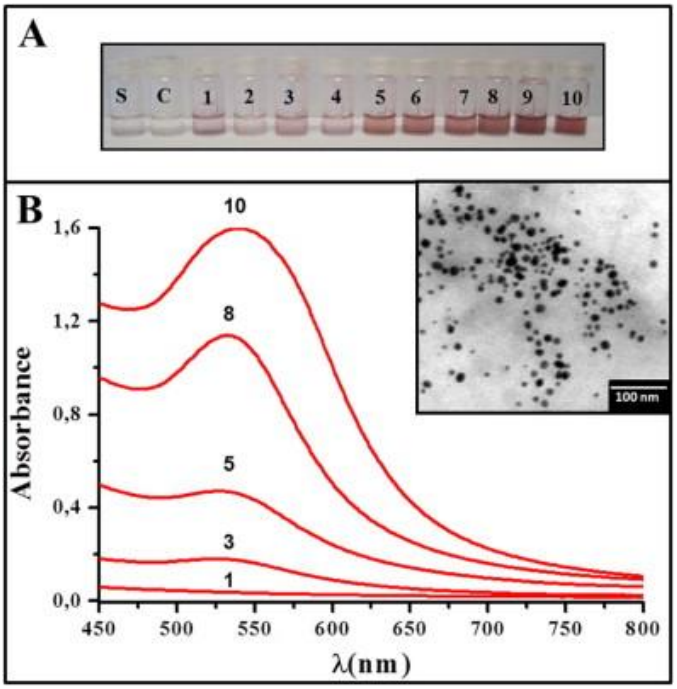


Figure 1

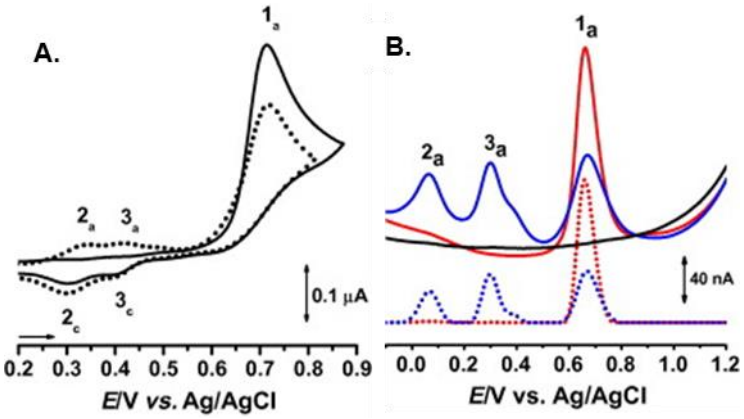


Figure 2

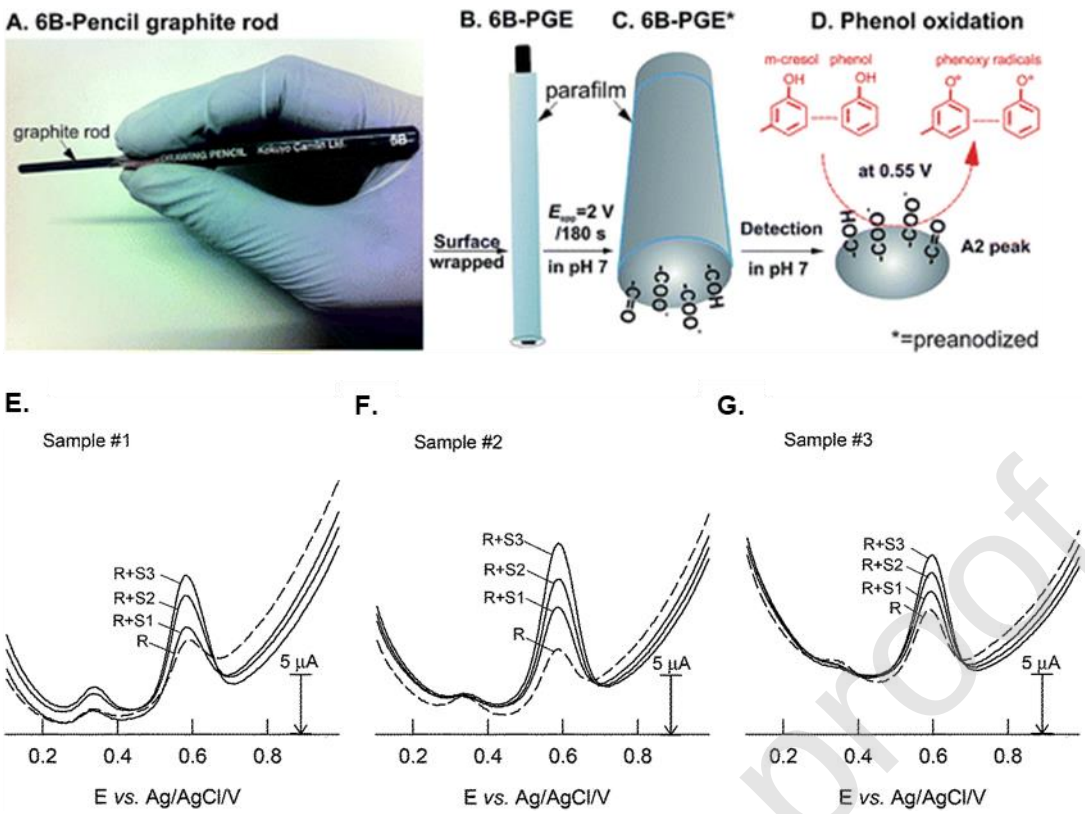


Figure 3

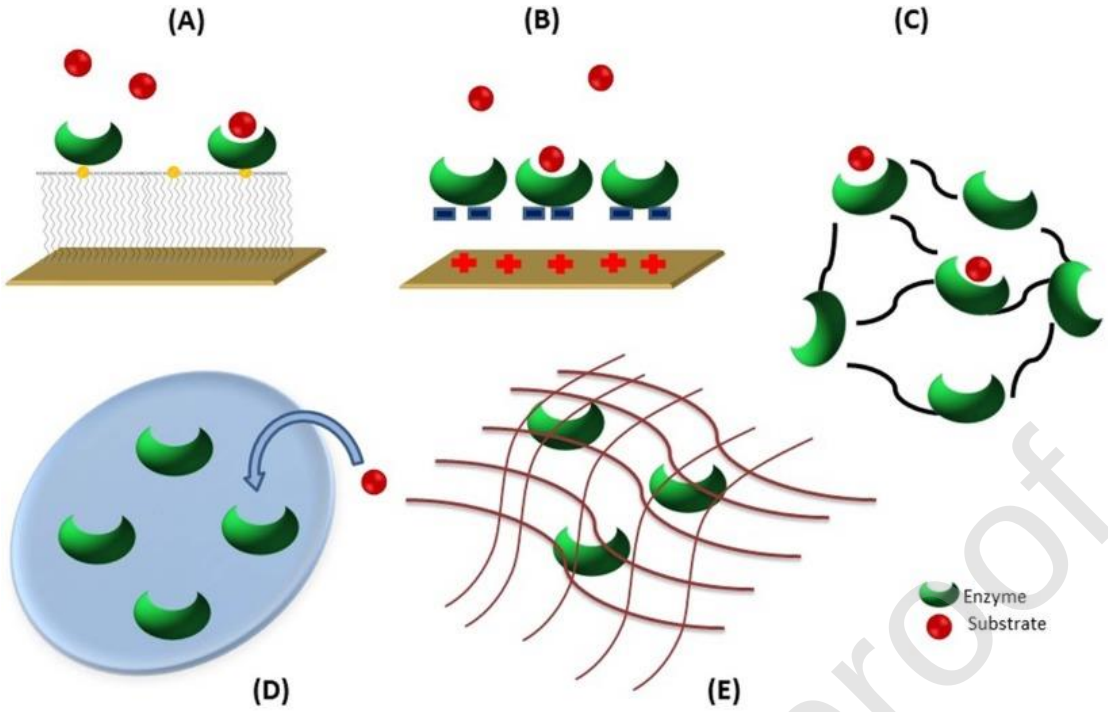


Figure 4

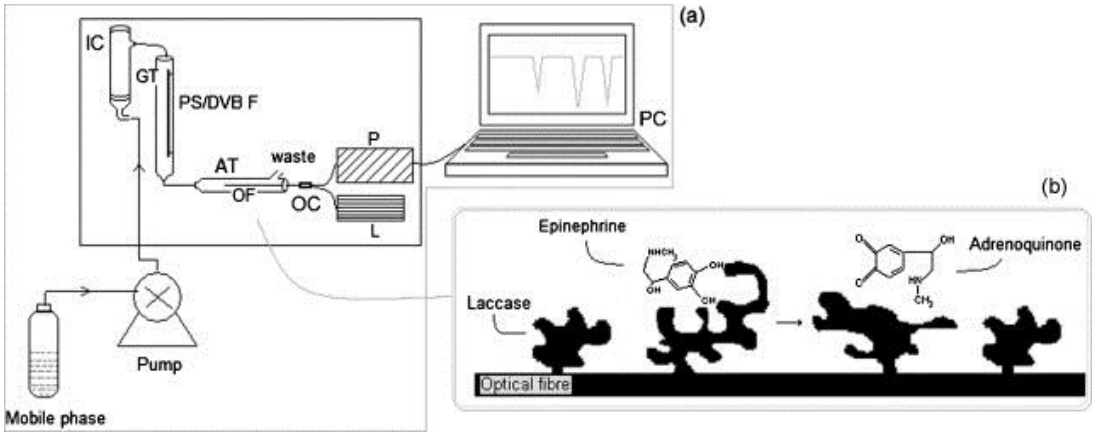


Figure 5

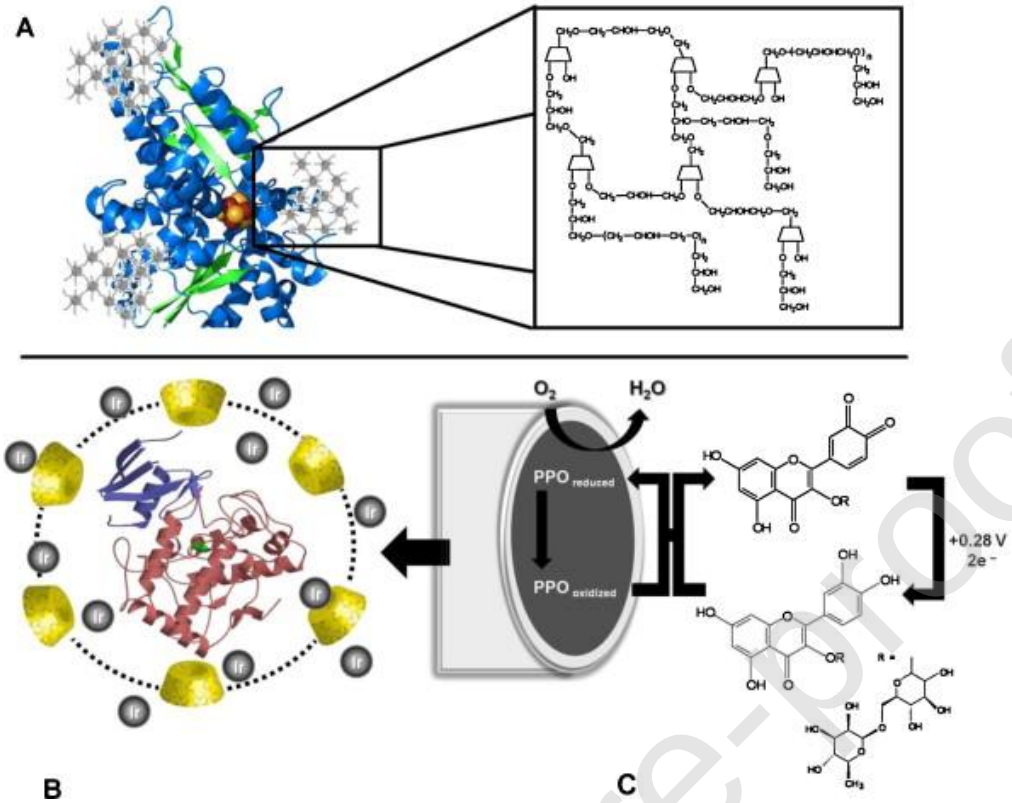
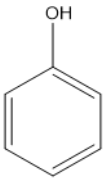
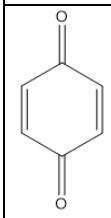
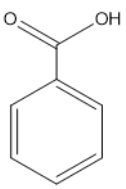
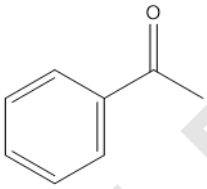
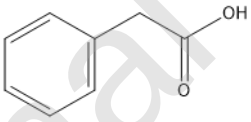
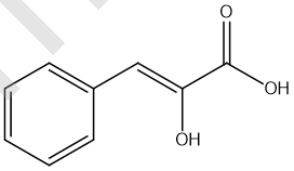
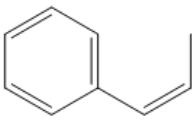
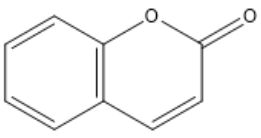
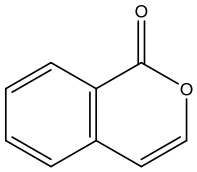
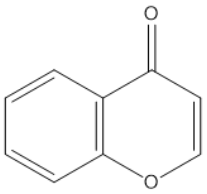
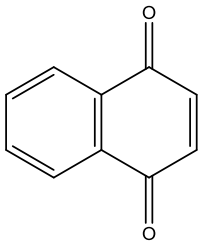
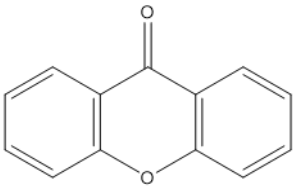
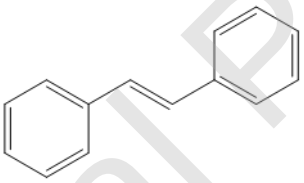
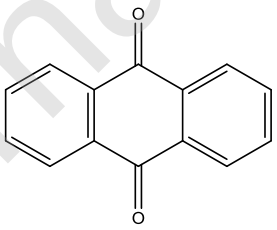
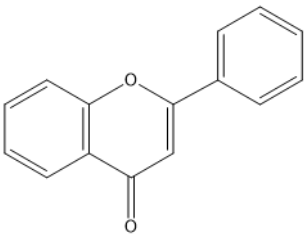
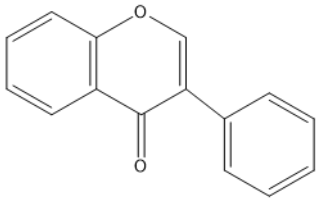
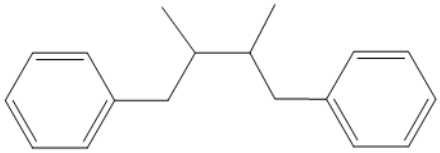
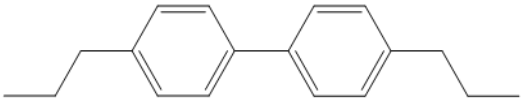
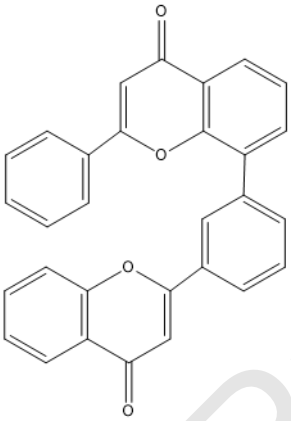
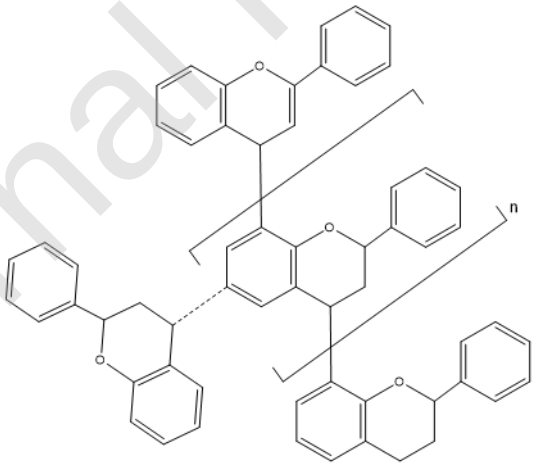


Figure 6

Table 1. Different classes of phenolic compounds based on their carbon chain [6, 17]

No. of Carbon	Basic Skeleton	Basic Chemical Structure	Class
6	C_6		simple phenols
			benzoquinones
7	C_6 - C_1		phenolic acids
8	C_6- C_2		acetophenones
			phenylacetive acids
9	C_6-C_3		hydroxycinnamic acids
			phenylpropenes
			coumarins

			isocoumarins
			chromones
10	C_6-C_4		naphthoquinones
13	C_6-C_1-C_6		xanthones
14	C_6-C_2-C_6		stilbenes
			anthraquinones
15	C_6-C_3-C_6		flavonoids

			isoflavonoids
18	$(C_6\text{-}C_3)_2$		lignans
			neolignans
30	$(C_6\text{-}C_3\text{-}C_6)_2$		biflavonoids
n	$(C_6\text{-}C_3\text{-}C_6)_n$		flavonals (condensed tannins)