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Review

Progress and recent advances in fabrication and utilization of hypoxanthine biosensors for meat and fish quality assessment: A review

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ABSTRACT

This review provides an update on the research conducted on the fabrication and utilization of hypoxanthine (Hx) biosensors published over the past four decades. In particular, the review focuses on progress made in the development and use of Hx biosensors for the assessment of fish and meat quality which has dominated research in this area. The various fish and meat freshness indexes that have been proposed over this period are highlighted. Furthermore, recent developments and future advances in the use of screen-printed electrodes and nanomaterials for achieving improved performances for the reliable determination of Hx in fish and meat are discussed.

Contents

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1. Introduction

1.1. Significance of hypoxanthine

Hypoxanthine (Hx) is a naturally occurring purine derivative with a molecular structure consisting of both benzene and cyclopentane rings, as shown in Fig. 1. It is a minor constituent of its nucleoside, inosine, in transfer RNA. As shown in Fig. 2, it is one of the products of ATP decomposition during fish and meat spoilage. In this process, the oxidation of Hx is catalysed by xanthine oxidase (XOD) to form xanthine (X) and uric acid (UA). It is occasionally found as a constituent of nucleic acids and known to accumulate in fish and beef, as well as in organs, such as heart, kidney and skeletal muscle [1–8]. Thus, the monitoring of Hx concentration in dead fish or animals can provide a useful measure for predicting the time of death. Consequently, the freshness of fish and meat can be readily determined by measuring the Hx concentration. For this reason, the levels of Hx and X are commonly used in the food industry as an index for evaluating meat or fish freshness. Particularly linked to the presence of Hx is the suggestion that it causes a bitter taste which is easy to identify in the degrading fish or meat [9].

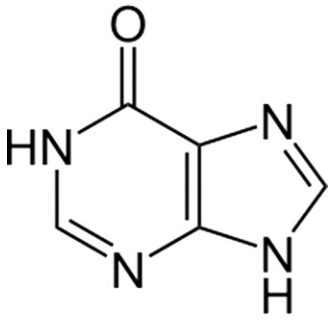

Fig. 1. Molecular structure of hypoxanthine.

Associated with the presence of Hx are various medical and clinical conditions that have also been beneficial in forensic studies. For example, the presence of Hx is known to protect the heart during heart surgery by reducing ischaemic damage [10,11]. Elevated levels of Hx is also an indicator of prolonged

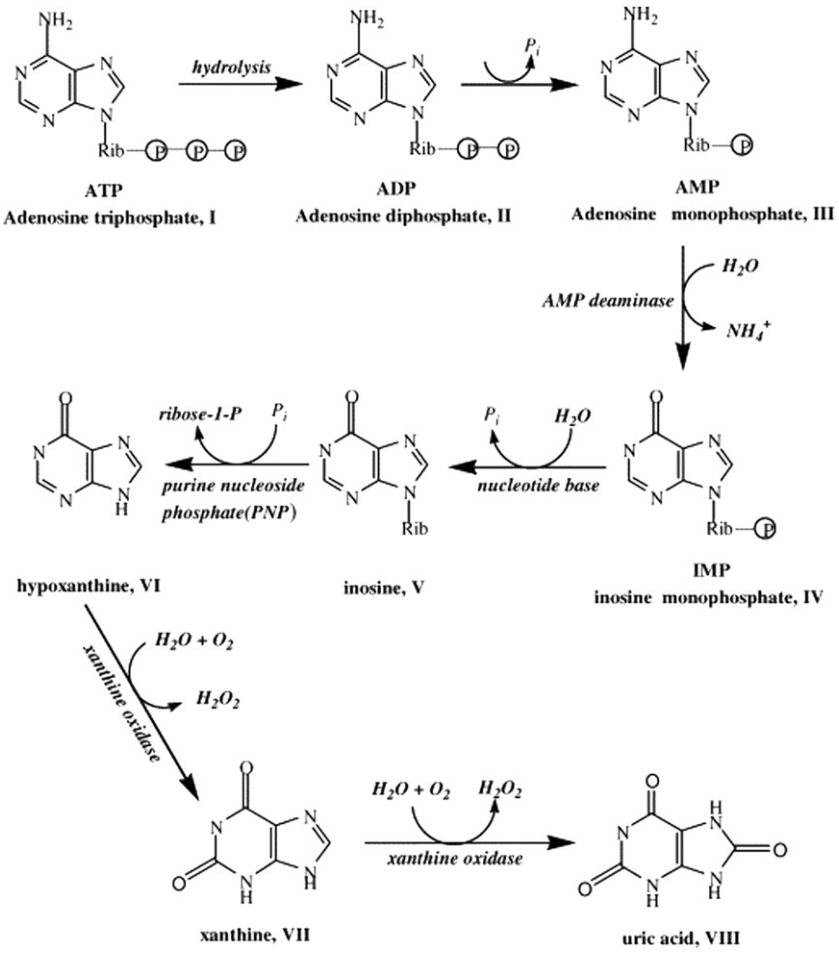

Fig. 2. ATP decomposition during the process of fish or meat spoilage. Reproduced from [210].

(cerebral) hypoxia, used in victims of sudden infant death as a new biochemical method for estimation of post-mortem time [1–3,12–14]. Passos et al. [15], Fang et al. [16] and Munoz et al. [17,18] used Hx concentration to estimate time of human death in post-mortem. The estimation of the time since death known as post-mortem interval (PMI) is very important in the field of forensic science and legal medicine. They determined Hx and K^+ levels since the concentrations of both ions change with PMI. Hx has also been used to determine PMI as a measure of meat freshness [14,19–23] and has been used to predict the remaining days of the validity as sashimi (a raw fish product). It was found that the quality of raw fish and the remaining days of the validity as "sashimi" could be estimated simply and rapidly based on KI value [23–28].

The levels of Hx in body fluids such as human serum [10,29,30], amniotic fluid [31], and urine [32,33] are useful indicators of many clinical conditions, including peri-natal asphyxia, cerebral ischaemia, hyperuricemia and gout. The accurate detection and quantification of Hx in body fluids are critically important in study of the homoeostasis of the XOD system and clinical diagnosis at early stages of related diseases. Hx is an indicator of acute cardiac ischaemia [10] and hypoxia [13]. Cerebral hypoxanthine is important in understanding of neurochemistry in the brain [34] and Hx also helps in the study of communication of neurons in the brain [35]. Both Hx and XOD are known to cause profound natriuresis without affecting renal blood flow autoregulation [36]. Aral et al. [37] found Hx in Kelley–Seegmiller syndrome, which is due to a new variant of the hypoxanthine-guanine phosphoribosyltransferase (I136T) encoding gene (HPRT Marseille) while the analysis of Hx has been used for detection of non-traumatic chest pain [11], foetal and maternal hypoxanthine levels [38,39]. Hx promotes neurite outgrowth and protects colonies of neurons from early cell death. Researchers [40] have also studied the influence of various Hx concentrations on the neurotogeluc development of human foetal brain, neuronal cultures and astrocyte proliferation [36].

The above examples highlight the importance of the determination of Hx to clinical and industrial applications. The aim of this review is to provide an in-depth understanding of the role of Hx levels in biological systems and how various analytical methods have been directed to its reliable determination over a period of over 40 years from 1970 to 2011. Also discussed is the nature of future direction and development in the detection and quantification of Hx, particularly for on-going assessment of fish and meat quality.

2. Analytical methods for determination of hypoxanthine

The methods available for determination of Hx can be classified into two categories, namely, classical and biosensing methods. The attributes of the two types of methods and the associated benefits, limitations and disadvantages are discussed below.

2.1. Classical methods

Classical analytical methods commonly employed for routine determination of Hx are based on spectrophotometric [32,41] and chromatographic [29,42–49] measurements. In general, these techniques require sample pre-treatment that can be time consuming, expensive and may, in some cases, produce undesirable or toxic wastes. Recently, Lin et al. [48] developed a new electrochemical detector for use in HPLC. The electrochemistry of X and Hx at this chemically modified electrode (CME) was investigated by cyclic voltammetry [50]. Other researchers used various chromatographic methods to analyse Hx in meat and fish [10,16,25,49,51–53]. Table 1 provides a summary of the range of classical approaches that have been employed for detection and quantification of X and Hx in meat and fish. These ranged from the use of titrimetric to the use of instrumental methods and further to the more recent use of electronic nose and electronic tongue.

2.2. Biosensor

A biosensor is a device, as shown in Fig. 3, which has a biological sensing element either intimately connected to, or integrated within a transducer that gives an electrical or digital electronic signal [54–56]. More specifically, biosensors are useful for accomplishing rapid, simple, selective and economic detection of various organic and inorganic substances. The aim in fabricating a biosensor is to produce a digital electronic or electrochemical signal, which is proportional to the concentration of a specific chemical or set of chemicals. As evident in Fig. 3, the device usually contains a biological or biologically derived sensing element, such as enzymes, antibodies, micro-organisms or DNA. These bioactive sensing elements are also referred to as "bioreceptors". The biomolecules are usually integrated with or in intimate contact with a physicochemical transducer, such as an electrochemical, optical, thermometric or piezoelectric transducer [55,56].

Table 1
Some classical methods for meat and fish quality evaluation.

Methods	Meat/Fish	Remarks	Refs.
E-Nose	Fish	Depend on aroma, vapour and usually used for fish spoilage analysis	[257–259]
E-Tongue	Meat beef	Depends on taste and usually used for both beef and fish	[260,261]
Biogenic amine	Fish	Used mainly in fish spoilage analysis	[262–265]
Trimethyl amine	Fish	Useful for marine fish	[266]
Sensory	Meat/fish	Sensory schemes for raw and cooked fish were modified according to the trained panelists' perceptions, during ice storage. Freshness K and related values, namely K, Ki, G, P, H, and Fr, were calculated.	[267,268]
Volatile basic nitrogen	Meat	Near infrared spectroscopy is often used	[269]
Volatile amine	Meat	Titration or instrumental methods are often used.	[270]
Microbiological method		Indicative of microbial spoilage in fish	[271,272]
H_2S, C_2SH	Fish and meat	Spoilage at advanced stage. Gas chromatography is often used	[273,274]
Ammonia	Meat (beef)	Indicates advanced spoilage	[273]
Volatile acids	Fish	Good correlation with bacterial spoilage	[191]
Histamine	Fish	Histamine can be analysed by most method because it is thermostable. Its poisoning has been reported in extremely high levels in some salted and dried fermented products in Asia and Europe [274]	[275,276]
Instrumental methods	Fish/meat	Measure spoilage based on electrical properties, pH and visual properties of fish meat	[277–279]

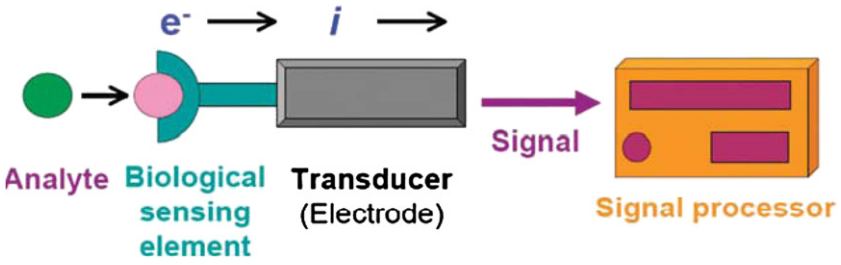

Fig. 3. Schematic diagram of a biosensor with electrochemical transducer. Reproduced from [282].

The role of the bioreceptor is typically to convert or accelerate the conversion of the analyte of interest into another chemical species and/or physical property that can be sensed and then transformed into an electrical signal by the transducer. For example, in this case, the transducer could be an electrode such as a pH or dissolved oxygen probe. In an ideal situation, where the sample matrix is not too complex, the detection of an analyte with this device would be accomplished without pre-treatment or the addition of any reagent. However, the lifetime, stability, reproducibility and calibration requirements of the biosensor are influenced significantly by the chosen bioreceptors. For an enzyme-based biosensor which consists of an immobilized the enzyme catalyzes the reaction between a substrate and a co-reactant to generate a product or products as generally illustrated below:

$$\text{Substrate} + \text{Co-factor} \xrightarrow{\text{enzyme}} \text{Product} \quad (1)$$

Consequently, either the consumption of the substrate or the co-factor or the generation of an electroactive product can be monitored electrochemically. The transduction element of a biosensor must be capable of converting a specific biological reaction (binding or catalytic) into a useable signal. This transducer must also be suitable for the immobilization of the biological component at or close to its surface.

The distinct advantage of using enzymes as the biocomponents in biosensor development is the ability to achieve greater analyte specificity. The high specificity reduces the need for pretreatment of samples so that direct analysis may be carried out regardless of the sample matrix or complexity [54]. Ideally, enzymes with absolute specificity would be preferable for analytical use [125]. Examples of these include cholesterol oxidase [126], glucose oxidase, sulphite oxidase, urease, XOD, [105,106], PNP [122] and urate oxidase.

Several researchers have reported the successful fabrication of biosensors for the determination of various substances, such as glucose [57–96], urea [97–100], L and D amino acids [101], sulphite [102,103], DNA [56,104], Hx [105,106], cholesterol [107–119] and phosphate [120–122]. Of these, the development of biosensors based on electrochemical detection has attracted most interest in recent years. Most of these sensors are based on a redox enzyme such as glucose oxidase, where an electron is transferred from the substrate through an electron mediator or directly to the transducer (e.g. amperometric detector). An electrochemical method provides a quick and quantitative site assessment that can be performed by non-expert. They are portable, easily miniaturized and their operation is simple. Electrochemical biosensors combine the sensitivity of electroanalytical methods with the inherent bioselectivity of the biological component. The biological component in the sensor recognizes its analyte resulting in a catalytic or binding event that ultimately produces an electrical signal monitored by a transducer that is proportional to analyte concentration. Some of these sensor devices have reached the commercial stage and are routinely used in clinical, environmental, industrial, and agricultural applications.

The use of biosensors has, in general, eliminated the need for sample preparation and these devices are easily adapted to automatic clinical laboratory and industrial use. Biosensors for personal blood glucose monitoring have been in the market since the beginning of this century. Most biosensors use electrochemical detector for the transducer because of the low cost, ease of use, portability, and simplicity of construction. For these reasons, biosensors are increasingly being introduced as alternative approaches to many analytical methods, such as spectrophotometry [32,41] and chromatography [29,42–49,123], due to their simplicity of operation, as well as the ability to achieve rapid analysis at a low cost [124]. Furthermore, electrochemical biosensors provide high sensitivity and selectivity which enables the achievement of low detection limits, wide linear concentration ranges, good stability and reproducibility. In particular, a main advantage of electrochemical biosensor is that the analytical signal is electrical in nature and this greatly reduces the complexity of the required transduction and controlling electronics.

The different types of electrochemical detection modes that are employed in these biosensors are discussed below.

2.2.1. *Amperometric biosensor*

An enzyme electrode usually consists of a layer of immobilized enzymes attached to an electrode material, such as gold, platinum, silver, copper or carbon. The enzyme is chosen to catalyse a reaction which generates a product or consumes a co-reactant and can be monitored electrochemically [56]. In amperometric biosensor, a constant potential is applied and the redox current generated is measured. The current response provides a measure of the analyte concentration.

The electrode reaction involved in most biosensing devices is often the reduction of oxygen or the oxidation of hydrogen peroxide. This is, illustrated in Fig. 4, as well as in the equations below:

$$O_2 + 2H_2O + 2e^- \rightarrow H_2O_2 + 2OH^- \quad (2)$$

$$H_2O_2 \rightarrow 2H^+ + 2e + O_2 \quad (3)$$

Evidently, oxygen takes part in these reactions as a reactant, while hydrogen peroxide is a product of the reaction. These electrode reactions usually take place at the surface of an electrode (or other transducer), as illustrated in Fig. 4. The reactant or the product of the enzymatic reaction is often detected amperometrically.

2.2.2. *Potentiometric biosensor*

Potentiometric sensors are based on measuring the potential of an electrochemical cell while drawing negligible or no current. Common examples are the glass pH electrode and ion selective electrodes for ions such as K^+, Ca^{2+}, Na^+, and Cl^-.

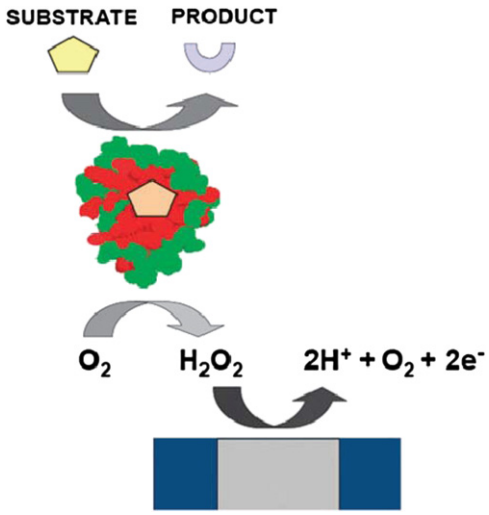

Fig. 4. Oxygen-dependent first-generation biosensor with amperometric detection. Reproduced from [282].

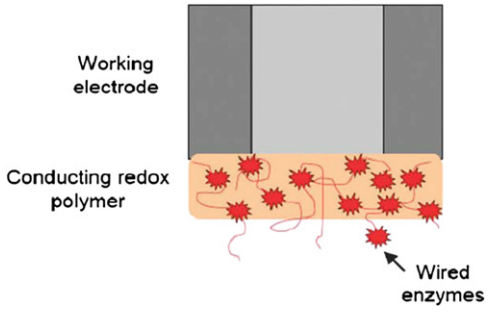

Fig. 5. Biosensor containing enzymes wired to the electrode through a conducting polymer [282].

A potentiometric biosensor consists of a layer of immobilized enzymes on an electrode and the measurement of potentials at the working electrode is made with respect to a reference electrode. The rate of potential change, rather than steady state potential values, is often used as the analytical signal for quantification of the substrate. Some of the reported potentiometric biosensors include the use of glucose oxidase immobilized in polypyrrole (PPy) for potentiometric detection of glucose [90,127]. Urease immobilized in an electrodeposited PPy layer was used for potentiometric detection of urea [102]. A creatinine enzyme electrode was made by co-immobilization of creatinase, and sarcosine oxidase in a PPy matrix [128]. Govender [129] fabricated a potentiometric biosensor to analyse cholesterol in blood samples based on immobilization of cholesterol oxidase in PPy. Menzel et al. [130,131] have also described a potentiometric enzyme electrode for phosphate determination which involved co-immobilization of PNP and XOD. Adeloju and Lawal [121,132–134] also described potentiometric enzyme electrode for hypoxanthine determination which involved immobilization of XOD into PPy film.

3. Hypoxanthine biosensors

3.1. Fabrication of hypoxanthine biosensor

The electropolymerization of pyrrole offers one of the unique and beneficial approaches for direct and indirect immobilization of enzymes and other bioactive substances in or onto conducting polypyrrole (PPy) films. Direct immobilization by this approach involves entrapment of bioactive substances into the polymer during electrochemical polymerization, as illustrated in Fig. 5. In contrast, the indirect immobilization involves chemical attachment, usually by covalent bonding or cross-linking of the bioactive substance onto a pre-formed PPy film.

Both of these approaches have gained considerable interest in the fabrication of conducting polymer biosensors [136]. Recent studies by Adeloju et al. [121,122,134,137,138] have demonstrated that the electrochemical immobilization of enzymes, such as urease, sulphite oxidase, PNP, XOD and formate dehydrogenase, into conducting polypyrrole can be employed for the fabrication of biosensor for urea, sulphite, phosphate and formate determination, respectively. Gosh et al. [139] also immobilized PNP and XOD onto electropolymerized polypyrrole. For fabrication of phosphate biosensor, Adeloju and Lawal also used this method of immobilization of PNP and XOD for detection of phosphate [121,132–134,140] and Hx [105,106]. An important advantage of this electropolymerization strategy is the ability to enable both the enzyme catalysis and analyte sensing to be performed on a single conducting polymer film. These have been used in various detection modes to detect hypoxanthine in various samples. The reported studies in the various detection modes are described below.

3.2. Amperometric hypoxanthine biosensor

The development of Hx biosensor started in early 1983 when Watanabe [141] designed a Hx biosensor based on the immobilization of XOD onto a cellulose triacetate membrane coupled to an oxygen probe for Hx detection by measurement of oxygen consumption. They also measured nucleotide concentrations for evaluation of fish freshness [142–147].

The mechanism of amperometric Hx biosensor is based on the direct oxidation of H_2O_2 formed from the enzyme reaction, as given in Eq. (4) [12,13,105,106,145,148–151] or on O_2 consumption [2]. However, the direct detection of H_2O_2 is usually accomplished by application of anodic potentials (greater than +0.6 V vs. SCE). In contrast, O_2 is usually reduced by application of cathodic potentials (less than 0.5 V vs. SCE).

$$2HX + O_2 \xrightarrow{(XOD)} X + H_2O_2 \quad (4)$$

The determination of Hx based on both oxygen consumption or on generated hydrogen peroxide (H_2O_2) at positive potentials (600–650 mV) has been successfully used in a number of studies [152–154].

3.2.1. Immobilization of XOD

Several Hx amperometric biosensors have been reported based on the use of various immobilization strategies. In many Hx biosensors, XOD is immobilized in membranes [167–171] and in Nafion to improve the selectivity of the electrodes [35,44,159–161,163,172–179]. Sol–gel technique was alternatively used for the immobilization of XOD on a graphite–ceramic for Hx biosensor with or without benzyl viologen as a mediator [180]. Nui and Lee [164,183] also immobilized XOD in a silica–graphite matrix by sol–gel techniques.

In a very interesting demonstration of the use of Nafion for immobilization of XOD, Mao et al. [178] fabricated and characterized a miniaturized amperometric Hx biosensor for monitoring Hx in myocardial cell culture media. The choice of Nafion for XOD immobilization is based on its film hydrophobicity, enzyme-favoured environment, and electrostatic interaction with XOD. In this case, the XOD was immobilized on carbon fibre microelectrodes (CFMEs) by using a composite film of Nafion and electropolymerized

phenol (PPh). The enzyme was dispersed in the film by immersing the Nafion-coated CFMEs in XOD solution for 5 h. PPh film was subsequently electropolymerized as an overlay on Nafion and XOD-modified CFMEs. Hx was measured with the sensor by the oxidation of enzymatic reaction products, hydrogen peroxide (H_2O_2), and uric acid (UA) at +0.60 V (vs. Ag/AgCl). The use of Nafion and PPh films for XOD immobilization led to enhanced specificity, sensitivity, and achievable linear concentration range. A dynamic linear range of 5.0 μmol L^{-1}–1.8 mmol L^{-1}, a detection limit of 1.5 μmol L^{-1} ($S/N=3$) and a sensitivity of 3.144 nA/mmol L^{-1} were achieved with the Hx biosensor. In addition, the measurement was virtually interference-free from easily oxidizable species such as UA, ascorbic acid, physiological levels of neurotransmitters, and their principal metabolites. The biosensor was used to monitor Hx accumulation in myocardial cell culture media, in which the level of extracellular Hx was found to increase with ischaemic tolerance. Lanqun et al. [225] also fabricated a miniaturized amperometric biosensor with immobilized XOD and used the device successfully to determine Hx in cell culture media. Zhang et al. [158] also fabricated a Hx biosensor by using an electrode treated with 6 μL of an acetone solution containing 70 mmol L^{-1} tetrathiafulvalene (TTF) and 0.1% of Nafion.

XOD has been immobilized on a carbon fibre microelectrode coated with Nafion and poly(phenol) [155]. Hu and Liu [176] used a Nafion-paraquat modified glassy-carbon electrode to develop a Hx biosensor. The biosensor works by detecting oxygen consumption during the XOD catalysed enzymatic reaction. The biosensor achieved a linear concentration range of 1–200 μmol L^{-1} and can be reused for more than 100 times without significant deterioration in performance. Hu and Liu [161] also developed an amperometric biosensor for the determination of fish freshness by immobilizing 5′-nucleosidase (NT), NP and XOD enzymes on a Nafion-paraquat chemically modified glassy-carbon working electrode. Luong and Talipamala [187] developed a Hx biosensor with immobilized deflavo enzyme which showed high operational and storage stabilities with a detection limit of about 0.1 μmol L^{-1} for Hx. No significant sensitivity loss was observed with the biosensor after 150 repeated analyses during a 7.5-h operation.

Electrodes modified with conducting polymers [105,106], or with Os-poly (vinylpyridine)-peroxidase have been used for fabrication of Hx biosensor. Arai et al. [198] immobilized XOD in a conductive redox polymer, poly(mercapto-p-benzoquinone) by electropolymerization of mercaptohydroquinone in the presence of the enzyme. An Au-electroplated glassy carbon electrode coated with the resulting polymer film functioned well for amperometric detection of Hx, where the polymer chain served as a conductive molecular chain between the active sites in the enzyme and the substrate electrode.

Another study [146] used both XOD and PNP, co-immobilized on a membrane previously used for measurement of both Hx and HxR. The biosensor responded to both Hx and HxR in the presence of phosphate, but responded only to Hx in the absence of phosphate. A linear correlation was observed between current reduction and the Hx and HxR concentrations from 0.5 to 2.0 mmol L^{-1}. A biosensor which consists of nucleosidase, PNP and XOD could also measure inosine monophosphate (IMP). Measurements in fish such as sea bass, mackerel, yellow fish, etc. showed a good correlation when compared with the conventional enzymatic assay [146].

Shen et al. [199] fabricated a Hx amperometric biosensor by immobilizing XOD on a silk membrane on a platinum disc electrode. The biosensor was highly sensitive to Hx levels in fish and therefore could be used to assess fish freshness.

Hanendez et al. [19] fabricated a Hx biosensor by employing XOD in soluble or immobilized form, in combination with an oxygen electrode and optimized the biosensor to determine the Hx content in pork meat at different post-mortem times as a measure of meat freshness. The amperometric signal obtained was related to the oxygen consumed during oxidation of Hx in the soluble or immobilized enzyme. In both cases a linear relationship between the signal and the Hx was obtained from 8 to 26 μmol L^{-1}. Also, Yano et al. [185] used Hx biosensor for evaluation of meat spoilage and the progress of aging.

In a somewhat different approach, Gonzalez et al. [186] developed a Hx amperometric biosensor by adsorbing XOD on a carbon paste electrode (CPE) and physically entrapping the enzyme in a semipermeable membrane. In this study, uric acid produced during the enzymatic reaction was oxidized electrochemically at +0.4 V vs. Ag/AgCl to give a steady-state current which is directly related to the bulk concentration of Hx. Kirgoz et al. [181] and Mao et al. [155,190] also used glassy carbon electrode for determination of Hx.

3.2.2. Multienzyme Hx biosensors

The use of multiple enzymes has also been considered for fabrication of more sensitive and selective Hx biosensor. Cayuaela et al. [188] fabricated a bienzymic amperometric graphite–Teflon composite biosensor for the determination of Hx in fish samples. XOD and peroxidase, together with ferrocene as a mediator, were incorporated into the electrode matrix. A detection limit of 9.0 μmol L^{-1} was achieved and successfully applied to the determination of Hx in sardine muscle tissue.

A multienzyme biosensor has also been successfully developed for simultaneous determination of adenosine monophosphate (AMP), Hx, Ino and IMP [143,145]. These substances were determined on the basis of the reactions given in Fig. 2. The required enzymes were covalently bound to a membrane prepared from cellulose triacetate, 1, 8-diamino-4-amino methyloctane and glutaraldehyde. Sensors for Hx, HxR, and IMP were prepared by attaching membrane of XOD, XOD–NP, XOD–NP–NT and XOD–NP–NT–AD, respectively, to four oxygen electrodes. Each sensor was based on the principle that the output current of the oxygen electrode decreased due to oxygen consumption, when Hx is oxidized to uric acid by XOD. The multielectrode system has been successfully used for quality evaluation of various fish species [143,145].

3.2.3. Bilayer Hx biosensors

The use of bilayers has also been exploited for fabrication of Hx biosensors. Qiong et al. [171] and Cheng et al. [224] fabricated bilayer coated-wire electrodes which incorporated XOD for estimation of fish freshness. The modified electrode was constructed with two membranes, a silk fibroin membrane with immobilized enzyme and a cellulose acetate membrane for elimination of interference from high molecular weight compounds such as proteins. The biosensor is based on detecting hydrogen peroxide released from the enzymatic reaction. It shows high sensitivity and long-time stability for fish samples. The minimum concentration of Hx that could be detected was 0.1 μM. Due to the protection of the cellulose acetate membrane the electrode was stable for 6 weeks or 400 assays of fish tissue samples. The results were in good agreement with those of traditional assays for determination of the freshness of some river fishes.

Yano et al. [185,221] set up a chronoamperometric method for Hx and Putrescine (Put) determination in meat in which the potential was stepped from 300 mV to 600 mV. A linear relationship was obtained between 5 and 60 nmol L^{-1} for Put and 0.05 and 1.0 μmol L^{-1} for Hx. The coefficient of variation was 0.75% for 20 nmol L^{-1} Put solution and 2.2% for a meat sample using the putrescine sensor, 1.09% for 0.25 μmol L^{-1} Hx solution, 2.6% for a meat sample using the xanthine sensor. Yano et al. [220] also

used xanthine sensor to analyse X and Hx in meat, while Calvahero and Barajta [216] used active graphite and carbon fibre surfaces produced by different mechanical/electrochemical methods of surface activation to investigate the amperometric determinations of X and Hx under physiologically relevant conditions.

3.2.4. Improvement of performance with mediators

Mediators have been employed in some instances to improve the performance of Hx biosensor as indicated in Table 2. These substances are useful in promoting direct electron transfer between the enzyme and the electrode [124]. Some of the mediators that have been immobilized during fabrication of Hx biosensors include Prussian blue [34], hexacyanoferrate(II) [156] hydroxymethyl ferrocene (HMeFe) [157], ferrocene [106], potassiumferrocyanide [105], bromocresol purple [50], tetrathiafulvalene [158], methyl viologen [159–163], benzyl viologen [164], hexacyanoferrate(III) [165] and the conducting organic salt TTF–TCNQ [158,166]. Wang and co-workers [181] developed a Hx biosensor based on the use of glassy carbon paste electrode (GCPE), XOD and bromocresol purple as a mediator to obtain much better electrochemical reactivity towards hydrogen peroxide than with XOD immobilized in carbon paste electrode (CPE) without a mediator.

3.3. Potentiometric, conductimetric, and voltammetric hypoxanthine biosensors

Other electrochemical techniques that have been used for the development of Hx biosensors include potentiometry, conductimetry and voltammetry. To date, very few attempts have been made on fabrication of potentiometric Hx biosensors. Lawal and Adeloju [106,153] fabricated a potentiometric hypoxanthine biosensor by entrapment of XOD into galvanostatically grown PPy-XOD films. They achieved a detection limit of 5 μmol L^{-1} and a linear concentration range of 5–25 μmol L^{-1}. The PPy-XOD biosensor was also successfully applied to the determination of Hx in a range of fish samples, such as Blue Grenadier, Lake Entrance flat head, Nile perch and Sword fish.

Conductometric biosensors based on detection of changes in the electrical conductivity of the sample solution or the electrode medium have also been employed. These types of biosensor include those which employ enzymes whose charged products result in ionic strength changes, and thus increased conductivity. Zhang et al. [184] has successfully used a polypyrrole-based XOD biosensor for conductometric detection of Hx. Zang et al. [226] also used bio-impedance measurement to investigate the bio-impedance characteristics of freshwater fish silver carp during storage. It was reported that the impedance and phase decreased with post-mortem time, the accuracy of using impedance and phase angle index to determine fish freshness is 88.89% and 81.49%, respectively.

Wang and Tong [50] recently fabricated a novel electrochemical sensor based on the use of an electroactive-polymerized film of bromocresol purple (BCP) grown on GCE for simultaneous determination of uric acid (UA), X and Hx. The electrochemical behaviours of UA, X and Hx at the modified electrode were studied by cyclic voltammetry and they found that this biosensor exhibited excellent electrocatalytic activity towards the oxidation of the three analyses. The anodic peaks of the three species were well defined and, thus, enabled simultaneous voltammetric measurement of UA, X and Hx by differential pulse voltammetry. Under the optimum conditions, linear concentration ranges were obtained for UA, X and Hx from 0 5 to 120, 0.1 to 100 and 0.2 to 80 μmol L^{-1}, respectively. Also the detection limits achieved for these three compounds were 0.02, 0.006 and 0.12 μmol L^{-1}, respectively. The method was successfully applied to simultaneous determination of UA. X and Hx in human serum with satisfactory results [227,228]. Yan et al. [229] also used CV to analyse Hx with a rotating ring-disc electrode based on the electrochemical oxidation of Hx catalysed by $[Ru(bpy)3]^{/2+}$. Excellent electrocatalytic activities were obtained for Hx oxidation and the electrocatalytic currents increased linearly with increasing Hx concentrations from 0.2 to 1.2 mmol L^{-1}. Oliveira-Brett et al. [230] used voltammetric and impedance methods at glassy carbon electrodes to investigate the oxidation mechanism and adsorption of inosine 5′-monophosphate and Hx in solutions of different pH. For both compounds, the pH dependence of differential pulse voltammetry showed that the same number of electrons and protons are involved in the rate-determining step of the electrochemical reaction. The impedance measurements corroborated the voltammettic results and enabled the study of the adsorption of Hx on glassy carbon. Other studies [231–233] have also used voltammetry for determination of Hx concentrations. Hu et al. [217] also developed a method for Hx detection based on the monitoring of oxygen consumption

Table 2
Analytical performances of some hypoxanthine biosensors.

Hx biosensor	Transuder	Mediator	Fish/meat	Shelf life (days)	Detection limit (μM)	Linear range (μM)	Refs.
XOD–CPE	O_2Electrode	–	Fish	50	2.5	2.5–3.7	[280]
XOD–OE	O_2Electrode	–	Meat	> 30	–	8.68–26.05	[19]
XOD–PPy–PtE	Potentiometry	Fc	Fish	7days	1	1–5	[106]
XOD–PPy–PtE	Amperometry	Potassium ferric cyanide	Fish	3	10	10–20	[105]
MWCNT–DCP	Amperometric	–	Fish	10	0.2	0.5–200	[192]
XOD–TTF–TCNQ–PtE	Amperometric	TCNQ	Fish	75	200	Up to 6000	[158,166]
Nafion-XOD/NP–PtE	Amperometric	–	Meat	20		Up to 200	[172]
XOD/FeTPPNP/GC	O_2Electrode	–	Fish		1000	Up to 3400	[182]
XOD–GCE XOD–		–	Fish/meat	10	0.53	0.02–80	[181]
XOD–/CPE	Amperometric	HMFc	Fish	> 30 days	6	Up to 70	[281]
Nafion/XOD/PPh/CFMEp	Amperometric	–	Fish	14 days	0.8	1–400	[178]
Nafion GOD/XOD–GCE	Amperometric	–	Fish/meat	20 days	0.2	1–500	[156]
XOD–GCPE	Amperometric	–	Fish		5.3	20–80	[181]
Nafion-XOD/PPh/CFME	Amperometric	–	Fish		1.5	5–1800	[178]
XOD–PtE	Amperometric	–	Fish		0.1	0.05–100	[199]
XOD–PtE	Amperometric	–	Fish		0.5	1–20	[170]
XOD–SPE	Amperometric		Fish		8.9	Up to 50	[210]
Os-gel–HRP/XOD/GCEs)	Amperometric	osmium	Fish/meat		0.2	0.5 to 80	[155]
XODPtE	Amperometric	–	Meat		0.05	0–05–1	[185]

during the enzymatic reaction. They used CV to evaluate the electrocatalytic reduction of oxygen and the response of the sensor was linear in the range of 1 μmol L^{-1}–0.4 mmol L^{-1} Hx and the minimum detectable level was 0.8 μmol L^{-1}. The sensor was successfully applied to the determination of Hx in fish and was effective for eliminating interferences from coexisting substances in the samples.

In another study, Xai et al. [234] used mesoporous TiO_2-modified CPE for voltammetric determination of Hx in human blood serum and meat samples.

4. Other sensing methods for hypoxanthine

Besides electrochemical methods of detection of Hx, a number of other analytical methods have been considered for its determination. These include optical, luminescence, and chemiluminescence methods. In particular, near infrared spectroscopy, fluorescence, luminescence, chemiluminescence, spectrophotometric and UV methods, as well as chemical sensor arrays known as electronic nose (E-nose) have attracted some interests for detection and quantification of Hx. Farkas and Dalmadi [235] have shown by using near infrared spectroscopy that spectrofluorometic measurements have potential for estimation of fish and meat freshness. Horváth et al. [236] also used near infrared spectroscopy to determine Hx and spoilage in fish and meat. Weeranantanaphan et al. [41] and Saker et al. [237] used spectrophotometric flow-injection analysis for Hx determination based on the detection of superoxide anion. Mei et al. [238] used high performance liquid chromatography with diode array detector for simultaneous determination of Hx, X and UA, together with adenosine and inosine.

Farthing et al. [11] used a chemiluminescence method based on enzymatic conversions of inosine to Hx followed by Hx to X to UA, and subsequently generated superoxide anion radicals (by-product) which reacts with Pholasin®, a sensitive photoprotein used for chemiluminescence detection, to produce measurable blue-green light. The method did not require plasma clean-up steps prior to analysis and complete analysis of total Hx levels took approximately 3.7 min. In another study, Hayashi et al. [239,240] used chemiluminescence flow injection for Hx analysis in fish, while Hlavay et al. [241] used fibre optic and chemiluminescence for Hx measurement. In the latter, XOD and horseradish peroxidase (HRP) were immobilized on different pre-activated membranes which were mounted on to a fibre-optic bundle tip. The H_2O_2 produced from the XOD-catalysed reaction of Hx was measured by chemiluminescence using luminol and peroxidase. Yaguida et al. [242] also determined Hx and X based on a chemiluminescence reaction, while Li et al. [243] used fibre optic and chemiluminescence for Hx measurement.

Chen et al. [244] developed an electrochemiluminescent (ECL) enzyme biosensor for detection of Hx based on immobilization of XOD on the heated indium-tin-oxide (ITO) electrode and the ECL of 6-(4-methoxyphenyl)-2-methylimidazo[1,2–a]pyrazin-3(7H)-one (MCLA). Electrochemiluminecence was also used by Lin et al. [245] and Zhang et al. [246]. Zhang et al. [246] used poly (diallyldimethylammonium chloride)-functionalized carbon nanospheres (PFCNSs) to load CdS quantum dots (QDs) and developed a high sensitive ECL biosensing method for detection of hypoxanthaine. The ECL biosensor showed a fast response to Hx with a linear concentration range from 2.5 nmol L^{-1} to 14 μmol L^{-1}. The limit of detection was 5 nmol L^{-1} at a signal-to-noise ratio of 3.

Potentiometric ion selective electrode is one of the earliest methods used for detection of Hx. This method has the particular advantage of being highly portable, and inexpensive to produce. However, it is not sensitive or selective enough for detection of Hx at concentrations below 1 μmol L^{-1}[15]. Barat et al. [14] recently evaluated the correlation of potentiometric measurements, obtained with gold and silver electrodes, with physicochemical, microbiological and biochemical analyses of sea bream stored under refrigeration. Their results showed a strong correlation between the potentiometric measurements and the determined changes in fish, and an important correlation with the K1 index, dependent on the nucleoside degradation, which is used as a good indicator of post-mortem time and freshness.

5. Fish and meat freshness index

Most Hx biosensors used different indexes [200] for the determination of fish or meat freshness index, such as Ko value suggested by Fujita et al. [201] to be: the ratio of non-phosphorylated ATP metabolites, including xanthine, to the total ATP breakdown products:

$$[((\text{Ino}+\text{Hx}+\text{X})/(\text{ATP}+\text{ADP}+\text{AMP}+\text{IMP}+\text{adenosine}+\text{Ino}+\text{Hx}+\text{X})) \times 100)]$$

On the other hand, Okuma and Watanabe [202] and Watanabe et al. [203] suggested *K*-value, which is: the ratio of non-phosphorylated ATP metabolites to the total ATP breakdown products:

$$[((\text{Ino}+\text{Hx})/(\text{ATP}+\text{ADP}+\text{AMP}+\text{IMP}+\text{Ino}+\text{Hx})) \times 100)]$$

Other researchers also utilized *K* values for their determination of freshness in fish and meat [170,202,204–207]. This was subsequently simplified to K_1 value [161,168,170,203,208–210], which is the ratio of ionsine and hypoxantine to total inosine and hypoxantine.

$$[((\text{Ino}+\text{Hx})/(\text{IMP}+\text{Ino}+\text{Hx})) \times 100)]$$

Hx ratio or *H* value [(Hx/(IMP+Ino+Hx)] was later used by Ghosh and others [26,205,211,212] and K_2 values [((Hx/(Ino+Hx))] × 100) by Nanjyo and Yao [213]. These multienzymatic system, were found to be complex and several researchers have thus proposed the determination of just Hx as freshness index in meat and fish. Many amperometric biosensors have been designed by various researchers based on the enzyme reaction catalysed by the XOD in the determination of Hx in fish [105,143,148,160,166,171,176,180,199,209,210,214–219]. Reported Hx determination in beef includes that of Yano et al. [208,220,221], Numata et al. [151] and Basu et al. [222], while Hx determination in poultry includes that of Fujita et al. [201], Agui et al. [152] and In-Seon et al. [211].

Augustini et al. [204] reported that a study on *K*-value change at low temperature storage had been carried out down to a temperature of −40 °C. However, this reaction rate could not be determined if the temperature were lowered below the storage temperature normally used especially for tuna meat (−60 °C).

Karube et al. [223] developed an enzyme sensor system consisting of a 5′-nucleotidase membrane and a nucleoside phosphorylase-xanthine oxidase membrane attached to an oxygen electrode [223]. A small anion-exchange resin column was connected to the enzyme sensor for separation of nucleotides in order to measure each nucleotide concentration. Good correlation was obtained between *K*-values determined by the biosensor and conventional methods.

Luong and Male [212] developed another Hx biosensor to measure the Hx concentration ratio Hx/(Hx+IMP+HxR). The system consisted of a detection chamber equipped with an amperometric electrode using immobilized xanthine oxidase for measurement of Hx. The sensor detected both hydrogen peroxide and uric acid released during the oxidation of Hx. Immobilized nucleosidase was used for conversion of IMP to HxR.

After injection of soluble nucleoside phosphorylase and phosphate, the resulting HxR was introduced for determination of the Hx ratio. The system, which had the flexibility for measuring the *K*-value, was successfully used to measure the quality of several fish varieties [212].

6. Emerging developments and future direction

Two key new emerging areas of developments in the fabrication and utilization of Hx biosensors in the past two decades have been in the construction of screen printed Hx biosensors and in the use of various nanomaterials to improve sensitivity of these devices. Each of these aspects is discussed below.

6.1. Screen printed electrode (SPE)

Screen-printed electrodes (SPEs) patterned with working, reference, and auxiliary electrodes have gained popularity in electrochemical biosensors due to their low cost, ease and speed of mass production using thick film technology. The adaptation of electrochemical methods of detection to biosensors has increased the interest in transferring the technology to screen-printed strips to improve ease of use and permit wider accessibility. SPE is ideal for electrochemical detection [247–253] and its modification enables simple mass-production of low-cost and miniaturized sensing units with good sensitivity and repeatability [254].

Carsol et al. [210] used carbon-based screen-printed electrodes to which XOD was immobilized either directly on the surface or in a reactor with aminopropylsilane in a FIA assembly. The use of the reactor gave better reproducibility and lifetime. The screen-printed biosensor enabled optimum detection of Hx, HxR and Inosine monophosphate (IMP). Calibration curves for IMP, HxR and Hx are linear up to 50 $\mu mol\ L^{-1}$ with a detection limit of 1 $\mu mol\ L^{-1}$ for 50 μl injection. One assay is completed within 30 s. The reproducibility achieved for 20 $\mu mol\ L^{-1}$ of Hx was 2% CV.

Zen et al. [255] used pre-anodized nontronite-coated screen-printed carbon electrodes (NSPEs*) to simultaneously determine purine bases of Hx and uric acid (UA). The NSPE* was successfully used for the simultaneous determination of Hx, X, and UA in blood plasma and urine samples. It was also used for estimation of fish freshness by monitoring the Hx content with very good reproducibility.

Teng et al. [256] fabricated a new type of disposable XOD amperometric biosensor with SPE. The screen-printed three-electrode system, consisting of carbon-working, carbon-counter and Ag/AgCl reference electrodes, were all manually printed on the polyethylene terephthalate substrate by a conventional screen-printing process. Prussian blue was used as a mediator to catalyse the electrochemical reduction of hydrogen peroxide produced from the enzymatic reaction, and also to keep the favourable potential around 0 V. X and Hx were successfully measured, achieving sensitivities of 13.83 mA/mol L^{-1} and 25.56 mA/mol L^{-1}, respectively, and a linear concentration ranges between 0.10 and 4.98 $\mu mol\ L^{-1}$ for X and 0.50 and 3.98 $\mu mol\ L^{-1}$for Hx.

Kotizan et al. [177] used SPE modified with ruthenium dioxide to determine hydrogen peroxide concentration by using flow injection analysis (FIA). Glucose oxidase (GOx) or XOD were immobilized onto the electrode surface through formation of Nafion films, enabling biosensing of glucose or Hx.

6.2. Nanobiosensor for hypoxanthine

The use of nanomaterials has attracted a great deal of interest in recent years for fabrication of biosensors with improved analytical performances, ruggedness and mechanical stability. These improvements are often attributed to the unique chemical and physical properties of the nanomaterials. In this respect, a very practical approach for direct incorporation of nanomaterials into biosensors based on the use of either small or irregularly shaped electrodes, microelectrodes and microarray electrode is by use of electropolymerization [135]. Li [182] has recently fabricated a Hx biosensor based on immobilized XOD on iron (III) meso-tetraphenylporphyrin nanoparticles modified GCPE. He achieved a detection limit of 1.0 $\mu mol\ L^{-1}$ and a linear concentration range of 0.01–0.34 $mmol\ L^{-1}$. Furthermore, Li [182] successfully applied the nanobiosensor for the determination of Hx in rat brain. More recently, Zhang et al. [184] fabricated a nanocomposite electrode from graphene and constructed a hypoxanthine biosensor by combining the nanocomposite electrode with the enzymatic reaction of XOD. The biosensor exhibited a wide linear range from 30×10^{-8} $nmol\ L^{-1}$ to 28×10^{-5} $\mu mol\ L^{-1}$. The detection limit of 10 $nmol\ L^{-1}$ (signal-to-noise ratio of 3) achieved with this nanobiosensor was one order of magnitude lower than that previously reported. Also, the assay results of Hx obtained in fish samples were in a good agreement with the reference values.

Agui et al. [152] also developed a Hx nanobiosensor, based on a CPE modified with electrodeposited gold nanoparticles (AuNPs), together with immobilization of XOD for the amperometric determination of Hx The usefulness of the biosensor for the analysis of real samples was demonstrated by determining Hx in sardines and chicken meat. In another study, Chubukcu et al. [189] also used AuNPs with glassy carbon paste to fabricate Hx nanobiosensor and determined Hx in canned tuna. The sensor has a detection limit of 0.5×10^{-7} $\mu mol\ L^{-1}$ and linear concentration range of 0.5 to 10 $\mu mol\ L^{-1}$. More recently, Kumar and Shamugan [191] used glassy carbon electrode with multiwall carbon nanotube to fabricate a Hx nanobiosensor. Achieved detection limits for UA, X and Hx were 141 $nmol\ L^{-1}$, 134 $nmol\ L^{-1}$ and 2.87 $\mu mol\ L^{-1}$, respectively. The use of carbon nanotubes for fabricating Hx nanobiosensors have also been reported in other studies [192–197].

7. Conclusions and future directions

This review has highlighted the progress made in the fabrication of various biosensors over the past four decades for reliable detection of Hx. Considerable efforts continued to be directed towards further optimization of the various methodologies to achieve much lower detection limit and improved reliability. Concerns about interference from other substances such as ascorbic acid continue to be an issue. Thus, there is a pressing need for new methods or strategies for the elimination of interferences and rapid analysis that will be amenable to automation. Screen printed electrode is, at present, beginning to meet the drive to automate and to miniaturize analytical system with a view to make them cheap to produce and amenable to automation and mass production. However, at present, the high LOD achieved with SPE for Hx limits their suitability for ultratrace (≤ 30 nM) analysis. Nevertheless, the current gap is likely to be bridged in the future through increased use of nanomaterials such as graphene, carbon nanotubes, metallic nanoparticles, nanowires and nanorods for fabrication of more robust and more sensitive Hx biosensors. This is also likely to increase interest in combining the nanomaterials with screen-printed electrodes to enable improved sensitivity, ease of use and promote wider access of the Hx biosensors. Another potential area of future development is in the use of nanomaterials, such as nanowires and nanrods for fabricating novel array biosensors with capability for multi-component detection.

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