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Review

A brief review on recent high-performance platforms for electrochemical sensing of azo dye Allura Red (E129): food safety and pharmaceutical applications

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Abstract

Artificial dyes are increasingly widespread, especially in foodstuffs and pharmaceutical products as an industry marketing strategy to attract consumers. Consumption of the synthetic azo dye Allura Red (AR) has potential risks to human health and can cause several adverse health effects such as genotoxicity, carcinogenicity, attention deficit hyperactivity disorder, allergic and asthmatic diseases in children. The limited number of electrochemical sensing platforms for AR successfully applied for safety assessment of foods, beverages, and drug formulations testifies that the food and pharmaceutical matrices present significant analytical challenges and there is still a need to amplify the analytical performances of these systems. The authors intensively reviewed recent papers (mainly since 2019) emphasizing electrode engineering, strategies for electrochemical signal amplification, and analytical applications in food and drug control. A critical discussion on the latest interesting innovations and perspectives of the most promising electrochemical tools for AR electro-analysis is presented. The challenges and limitations in the design of electrochemical sensors for AR analysis are also discussed with a view to providing new directions for future research and development of sustainable sensing devices, paving the way for advancements in this field.

Keywords

Electroanalysis; sensors; synthetic dyes; food analysis; food control; pharmaceutical analysis; drug analysis

Introduction

Colour is one of the most relevant organoleptic attributes of foods and beverages that directly affects modern consumers' acceptance and food product selection [1-3]. Therefore, food colorants (dyes) are one of the most important food additives, widely used in the food processing industry. They are utilized to add colour and improve the visual appeal of various food products

(confectionery, dairy products, ice cream), chewing gums, and beverages (soft drinks, alcoholic beverages). Colouring agents also enhance or sustain the sensory characteristics of the food product, which may be affected or lost during processing because of the degradation of existing natural pigments. Generally, colorants are used to regain these colour losses, to enhance weak colours, to give color to colourless food, and to win back the favor of customers by hiding low quality [4]. These substances do not provide nutrients for the body, they affect the ability of consumers to identify and perceive flavour, thus coloration is a food industry marketing strategy.

Synthetic food colorants, especially azo-dyes, have been used more than natural food colours due to their excellent water solubility, high chemical and photolytic stability, high colouring ability and uniformity, low microbiological contamination, and not at least low cost [5-7]. Allura Red (AR), designated as E129 (C.I. Food Red 17, Colour Index No: 16035; FD&C Red No 40), is a synthetic food dye allowed for the colouring of foodstuffs, pharmaceutical formulations, and cosmetics. AR is a water-soluble monoazo dye, usually supplied as salt - disodium 6-hydroxy-5-[(2-methoxy-5-methyl-4-sulfonatophenyl)diazenyl]naphthalene-2-sulfonate (Figure 1). It is an orange red dye with a red to brownish shade in applications. This additive is a highly versatile food colorant used in decorations and coatings for pastry products, confectionery, candies, jellies, jams, fruit preparations, canned and frozen fruit juices, soft drinks, flavoured yogurts, sauces, flavoured chips, sausages, meat, and seafood. Also, AR is used in a variety of children's medications (prescription drugs and over-the-counter medicines): children's chewable vitamins, pain relievers and cough/cold tablets and syrups. The amounts of AR used in commercial products are proprietary and not labelled.

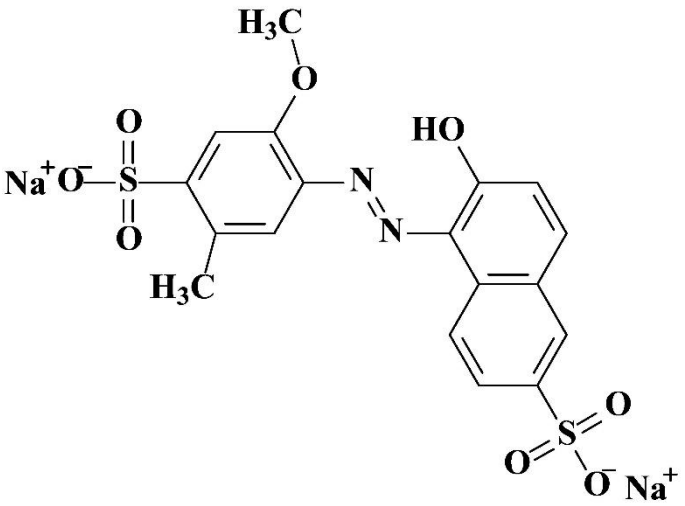

Figure 1. *Chemical structure of Allura Red*

Toxicological aspects and regulatory frameworks

AR was first time introduced in the USA in 1980s and it was synthesized by the classical process of diazotization. Alarmingly, in 2016 94 % of people over 2 years old in the USA consumed AR [8]. AR consumption has been related to occasional behavioural alterations in humans, including attention deficit hyperactivity disorder (ADHD), allergic and asthmatic diseases in children [9].

The main regulatory authorities, European Food Safety Authority (EFSA) in Europe and the US Food and Drug Administration (FDA) in the United States, are responsible for the evaluation and assessment of food products to enhance and promote health safety. EFSA established the maximum permitted level of AR in beverages and foodstuffs from 50 mg/L in non-alcoholic flavored drinks to 500 mg/kg in decorations, coatings, and sauces. Acceptable Daily Intake (ADI) of AR was established

at the level of 7 mg/kg of body weight (mg/kg$_{bw}$) equivalent to 420 mg per day for a 60 kg person [10-12].

According to the European Parliament and Council of the European Union decision, any foodstuffs containing AR must be labelled with the following warning text: ”may have an adverse effect on activity and attention in children” [13]. This statement should be located in a visible place, clearly legible and indelible.

It is well known that azo dyes in vivo generate a large number of mutagenogen precursors (aromatic amines) with carcinogenicity, teratogenicity and mutagenicity [14-18]. Multiple mechanisms of azo dye toxicity following oral ingestion have been proposed. Previous research has indicated that most toxic effects are probably due to the reduction of the dye catalysed by bacterial azoreductase enzymes in the anaerobic environment of the lower gastrointestinal tract. Cleavage of azo bonds leads to the formation of aromatic amines, which may subsequently be N-hydroxylated or N-acetylated [15].

Rasouli *et al*. presented a study on the binding of bovine serum albumin (BSA) to AR which is essential in order to comprehend the biological effects of this dye [19]. The next year Khayyat *et al.* administered AR orally to rats, 7 (mg/kg$_{bw}$)/day), for 4 weeks [20]. The data show that AR possesses pathological and physiological liver and kidney toxicities. The results obtained by Noorafshan *et al.* indicated that AR can lead to neurotoxicity [21]. A high dose of AR impairs learning and memory and induces damage to rats’ medial prefrontal cortex (mPFC), including loss of the cortex volume, cells, and dendritic tree. Sharma *et al.* concluded that the oral administration of AR in mice (dose of 172.2 (mg/kg$_{bw}$)/day) caused significant variations in haematological, biochemical and antioxidant parameters after 30, 45 and 60 days of treatment, indicating AR toxicity at the given dose level [22]. At the same time, Zhang *et al*. [23].demonstrated that AR inflicts DNA damage, which leads to altered gut microbiota and subsequent inflammation in the distal colon. These findings contribute to the growing body of evidence illustrating AR's adverse impact on colorectal carcinogenesis [23].

In an excellent review article, Hofseth *et al.* [24] summarized the available evidence, suggesting that AR interacts with the mechanisms that control colorectal cancer (inflammation, DNA damage, and microbiome perturbations). AR is a xenobiotic and is metabolized in the gut microbiome, where azoreductases cleave the azo bonds of the dye. The two known metabolites resulting from this cleavage are cresidine-4-sulfonic acid and 1-amino-2-naphthol-6-sulfonic acid. Evidence suggests these metabolites are DNA-reactive and activate the inflammatory machinery.

The more recent alarm concerns the behaviour of AR that is stable in an aqueous solution but can undergo degradation in beverages under the action of sunlight irradiation, to which commercial beverages are often exposed during the steps of transport and storage. The degradation is evidenced by drink decolouration or colour variations in the original sealed bottles already in commerce. The results obtained by Gosetti *et al.* indicate that the identified degradation products are formed from unpredictable side reactions and/or interactions among AR and other ingredients present in the beverage (ascorbic acid, citric acid, sucrose, and aromas) [25]. The presence of aromatic amine or amide functionalities in the chemical structures proposed for the degradation products might suggest potential hazards to consumer health.

Conventional analytical techniques for determination of AR

Several analytical methods have been reported to analyse AR quantitatively [26,27], including high-performance liquid chromatography (HPLC) combined with spectrophotometric (UV-Vis) detector [28,29] or diode array detector [30], solid-phase extraction combined with UV-Vis spectrophoto-

metry[31], liquid chromatography-mass spectrometry (LC-MS) [32], and capillary electrophoresis [33]. Despite these techniques offering high accuracy, they have some shortcomings associated with complex, time-consuming pretreatment of food samples, complicated and expensive equipment, and the need for highly qualified staff. For these reasons, fast and convenient analytical methods that can realize direct and reliable quantitative detection of AR in complex samples are urgently needed for controlling food quality and ensuring the consumers' health safety. The newly developed sensing methods should be easy to integrate with portable devices, thus enabling on-site analysis.

Advanced electroanalytical methods for quantitative detection of AR

Electrochemical methods present an attractive alternative to the above methods due to their high sensitivity, which enables low LOD and LOQ; rapid analytical response, which makes them ideal for flow analysis and alert systems; a practically unlimited variety of electrode materials and configurations; low cost; simple, compact and portable equipment. The simplicity of sample preparation and the high benefit/cost ratio makes electroanalysis economically feasible [34,35].

Electrochemistry offers a wide range of electroanalytical techniques. For the electrochemical measurements, three-electrode cell configuration is required: a working electrode (WE), a counter/ /auxiliary electrode (CE) and a separated reference electrode (RE). This setup is connected to external equipment (potentiostat), often USB-interfaced with a computer/smartphone equipped with the appropriate software. A potentiostat controls the voltage between WE and RE while measuring the current passing between the WE and CE. Analysis of the data recorded reveals various intrinsic electrochemical properties and performance of the sensing electrode [36].

Modern digital technology has allowed instrument designers to commercialize a variety of inexpensive, robust and user-friendly potentiostats. Nowadays, portable electrochemical analysers with disposable electrodes are widely used. An overview of basic detection principles (voltammetry, chronoamperometry, and electrochemical impedance spectroscopy) of the most common used electrochemical sensing techniques is presented in Figure 2. An advantage of voltammetric techniques in relation to amperometry is the possibility of coupling pre-concentration techniques to trace levels, thus obtaining better detection limits.

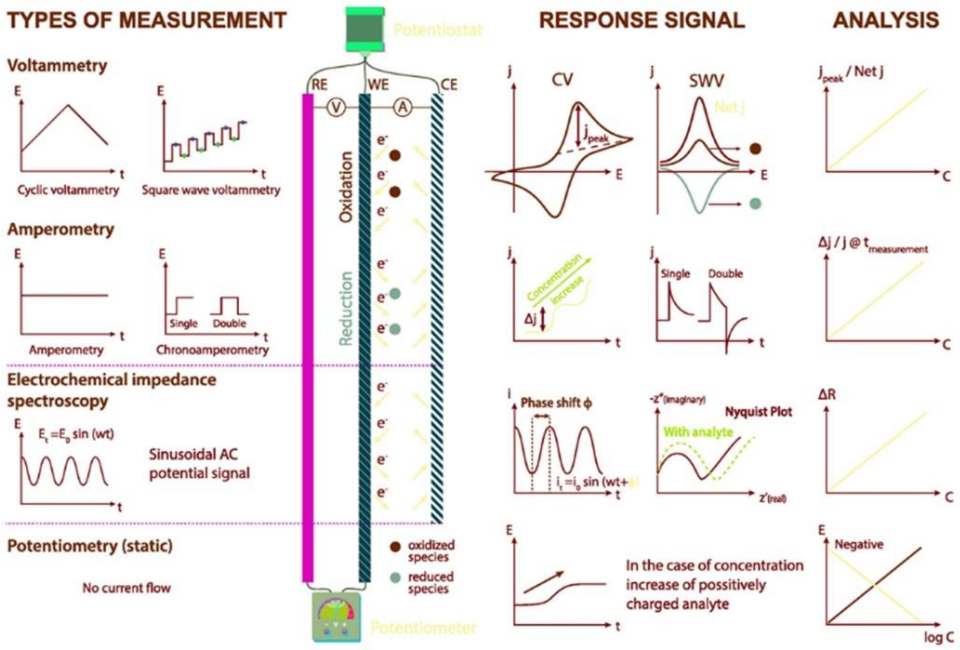

Figure 2. *An overview of electroanalytical methods: voltammetry, amperometry, electrochemical impedance spectroscopy, and potentiometry [37] (CC BY 4.0 Attribution)*

Lipskikh *et al*. presented a review article devoted to the critical comparison of electrochemical sensors and measuring protocols used for voltammetric determination of the most frequently used azo dyes in foodstuffs [38]. AR contains azo group (-N=N-) as the chromophore in the molecular structure (Figure 1), which makes AR amenable to cathodic voltammetric determination based on its electrochemical reduction onto the appropriate electrode. AR also contains electrochemically oxidizable hydroxy group (-OH), which makes possible its quantitative detection using anodic voltammetry. Therefore, according to the principle, the electrochemical sensors for AR determination can be divided into two groups based on either cathodic reduction or anodic oxidation. The next parts of the article provide an overview of how advances in modern electroanalytical technology have contributed to developing reliable and easy-to-handle analytical platforms for AR quantitative detection in food and pharmaceutical samples. A critical discussion on the latest interesting innovations and perspectives of the most promising electrochemical tools for AR electroanalysis is presented.

Electrochemical methods for AR determination based on cathodic reduction

A hanging mercury drop electrode (HMDE) is the most frequently used to detect AR through its reduction [39,40]. In these reports, a well-developed voltammetric peak related to the cathodic reduction of the azo moiety was observed between -0.40 and -0.66 V (*vs*. Ag/AgCl, 3M KCl). Cyclic voltammetric studies indicated that the reduction process was irreversible and primarily controlled by adsorption.

Silver solid amalgam electrodes (AgSAE) represent a suitable non-toxic alternative to the traditional mercury electrodes. These electrodes can be successfully applied in electroanalysis as they possess good mechanical stability, wide potential window, low noise, possibility for regeneration of electrode surface, and miniaturization potential. Detailed study of the electrochemical behaviour of two food azo dyes AR and amaranth (AM) on silver solid amalgam electrode modified by mercury meniscus (m-AgSAE) and on liquid mercury free polished AgSAE (pAgSAE) was presented by Tvorynska *et al*. [41]. The measurements with these amalgam electrodes were compared with HMDE using differential pulse adsorptive stripping voltammetry (DP-AdSV) and direct current adsorptive stripping voltammetry (DC-AdSV) at optimal pH 3.6 in order to develop novel and effective electroanalytical methods for individual determination of these dyes in commercial beverages. Because all other ingredients (sweeteners, regulators of acidity, preservatives, synthetic flavours, and ethanol) are not reducible in the used potential range, the matrix did not interfere (there were no other peaks on the voltammograms), indicating the excellent selectivity of the proposed methods. The limits of detection were found to be 2.1 nM for AM and 3.4 nM for AR on m-AgSAE using DC-AdSV. The electrodes showed good repeatability (relative standard deviation RSD lower than 5.0 %) and were confirmed to be useful tools for azo dye monitoring in a food safety control field. The amalgam electrodes provide a low-cost, non-toxic, fast, portable, and adequate platform for the electrochemical determination of the food additives to control the food quality and detect falsification. Moreover, amalgam electrodes have a longer lifetime (years) than modified electrodes (weeks/months).

On the other hand, glassy carbon [42], and recently on bismuth [43] or antimony [44] film electrodes (FE) were also reported to detect AR by reduction without using mercury electrodes, being more environmentally friendly. Rodríguez *et al.* [44] developed a methodology to determine AR and tartrazine (TZ) in food samples using a sequential injection analysis (SIA) with voltammetric detection (VD) at SbFE. The SbFE could be easily renewed online without affecting the analytical parameters. This feature represents a significant advantage over traditional electrodes since no polishing

procedures are required. The authors demonstrated that the SIA-VD system has good characteristics for routine analysis. The proposed methodology is automated, economical, has a high determination rate, and provides results comparable to those obtained by the reference HPLC method.

Penagos-Llanos *et al.* reported for the first time detection of AR using cobalt (II, III) oxide composite carbon paste electrode (CoOx/CPE) [45]. The authors used transition metal oxides that catalyse the reduction of AR, thereby minimizing the potential magnitude required. The electrochemical sensor is sensitive, stable and selective for analysis of AR in real samples (isotonic drink, soft drink, chili sauce) without pretreatment. Other dyes such as TZ, AM, sunset yellow (SY), ponceaut 4-R (P4R), and sudan (SD) did not show a signal between 0.0 and -0.3 V (*vs.* Ag/AgCl, 3 M KCl), which is the potential range where AR reduction was observed.

The primary advantage of electroreduction of AR is the avoidance of most interfering species that are commonly troublesome at positive potentials. However, the major drawback of AR sensing in the cathodic region is the necessity to remove carefully dissolved O_2, which complicates and prolongs the assay. Thus, the majority of published AR sensor articles have employed the electrooxidative mode due to the poor LODs and unavoidable O_2 interference via electroreduction.

Electrochemical methods for Allura Red determination based on anodic oxidation

The high oxidation overpotential (higher than 700 mV *vs.* Ag/AgCl, 3 M KCl at most types of electrodes), difficulties in obtaining good reproducibility of the electrode signal in electrochemical oxidation of AR, as well as the problems of electrode bio-fouling, make direct electrochemical measurement of AR in complex food matrices challenge. There are a number of interferences coexisting in real samples; several easily oxidizable electroactive species can generate interference responses over that of the target analyte, leading to difficulty for accurate AR sensing in these complex matrices. In general, the drink samples contained sweeteners (sugar, glucose-fructose syrup, potassium acesulfame, sodium cyclamate), regulators of acidity (citric acid, phosphoric acid), preservatives (for example, sodium benzoate), ascorbic acid, tartaric acid, phenolic compounds, various artificial flavours, metal ions, *etc*. Some matrix components cause electrode passivation. They form an impermeable layer on the electrode surface, hindering the direct contact of the analyte with the electroactive surface. In particular, at suitable anodic potential phenolic compounds form a polymeric film on the electrode surface, thereby decreasing the sensor signal. Furthermore, pH fluctuations also influence the electrode signal. On the other hand, each pharmaceutical matrix has a unique composition, requiring specific electrode adaptations to ensure accuracy and reliability. Thus, the effectiveness of electrochemical sensing platform depends heavily on the composition of the matrix, which plays a crucial role in their design. Despite these challenges, there are promising developments. To overcome these problems, various strategies (nanomaterial doping, chemical functionalization, surface pretreatments, and conducting polymer coatings) have been developed and adopted. Here, we have selected the most representative articles to illustrate the main strategies for developing reliable AR electrochemical sensors.

In order to achieve high sensitivity and selectivity of sensors, modification of the working electrodes using various materials such as graphene [46], graphene oxide [47], carbon nanotubes [48], metal nanoparticles [49], metal oxide nanoparticles [50-59], nanocomposites [60], conductive polymers [49], and ionic liquids [61,62] has been extensively investigated and successfully used to prepare different non-enzymatic sensors. After modification, the electrode shows a special surface effect, high accumulation efficiency, and catalytic activity. These specific properties enhance the electrical conductivity of the working electrode, accelerate the electron transfer in the interface,

reduce the oxidation overpotential of AR, and improve the electrode efficiency. Generally, the material used for the construction of the sensing electrode should meet the following requirements:

- inert towards the supporting electrolyte;
- wide potential window;
- low background currents;
- high signal-to-noise (S/N) ratio;
- high selectivity and sensitivity for trace levels determination;
- high levels of repeatability and accuracy;
- high intra- and inter-electrode reproducibility;
- resistance to passivation of the transducer surface in complex matrices due to accumulation of fouling compounds or products of the electrode reaction;
- easy surface regeneration;
- suitability for miniaturization and portability;
- cost-effectiveness;
- commercialization ability.

Bukharinova *et al*. demonstrated that a carbon fibre electrode, modified with shungite (a natural mineral), provides favourable electrode interface for the electrooxidation of AR [63]. The developed sensor is suitable for detecting the AR with a low limit of detection (0.36 nM), high sensitivity, good selectivity, reproducibility, and repeatability. The findings have shown the effective use of the sensor in analysis of commercial drinks, biologically active food supplements, and pharmaceutical samples (powder for solution preparation). Due to the low cost of manufacturing with modern, scalable technology and small size, the sensing platform is compatible with portable electronics and can be used as a disposable sensor in routine analysis.

A core-shell architecture of Mn_3O_4@C nanocubes has been constructed to fabricate new high-performance microchip sensor for achieving the accurate recognition of AR within only 30 s [51]. The as-prepared sensor could exhibit an ultrawide linear range in the detection of AR in various real sports drinks, together with excellent selectivity. The authors have used a single sensor repetitively once a day for one month to monitor the fluctuations of its sensitivity. After each use, the sensor was cleaned with deionized water and stored at 4 °C. After 30 days of repetitive tests, this sensor retained 28.43 % of the initial sensitivity, indicating its appreciable reusability. The proposed system can be applied in the on-site and portable analysis of foods and drinks.

Individual and simultaneous electrochemical detection of AR and Acid Blue 9 (Brilliant Blue; E133) in food samples was presented by Ravikumar *et al.* [54]. The authors used a GCE modified with double perovskites decorated on halloysite (alumina-silicate clay mineral) nanotubes La_2YCrO_6/HLNTs/GCE. The sensor exhibited robust linearity in the 10 to 120 nM range, with a LOD of 1.26 nM. Using LSV, a sensing electrode was utilized to measure AR and AB in fruit samples (strawberry juice and wine grape juice). The results indicated good recoveries and the potential of this novel sensor system for the quantitative determination of AR and AB in food samples.

Ionic liquids (ILs) are organic salts often composed of big organic cations and small inorganic anions. These salts remain liquid at room temperature and properties such as facile design, high ionic conductivity, wide electrochemical window, and high chemical stability of ILs make them ideal electrolytes to develop a new generation of sensor devices [61-64]. A novel modified electrode based on the immobilization of IL (1-butyl-3-methylimidazolium tetrafluoroborate) and carbon black (CB) nanoparticles within a crosslinked chitosan film over the surface of GCE was developed by Almeida-Silva *et al*. [62]. The proposed sensor presented good precision and no matrix effects as shown by repeatability tests, interference studies and addition/recovery assays. The electroanalytical procedure

was applied in the determination of AR content in commercial soft drink powder samples, and the results were in close agreement with those obtained using a comparative spectrophotometric method at a confidence level of 95 %. The obtained high sensitivity and detectability (at nanomolar levels) are remarkable novelties of this report.

A cost-effective, simple and sensitive electrochemical method for the quantitative detection of AR using an anodically pretreated pencil graphite electrode (Ptre/PGE) was presented by Uruc *et al*. [65]. The electrochemical activation process generates various oxygen-containing functional groups (hydroxyl, carbonyl, carboxyl, quinone, *etc*.) on the surface of the graphite and increases its hydrophilicity. These functional groups act as electron transfer mediators in the target reaction of AR oxidation, improving the electrode sensitivity and selectivity. The sensing platform is inexpensive, no additional or hazardous solvents are required, and no modifications are necessary. The degree of electrooxidation can be controlled precisely by adjusting the electrolyte concentration, applied voltage, and time of oxidation treatment. By incorporating the anodization of graphite electrode as a part of the analytical procedure, the authors sufficiently minimized the effects of surface fouling (chemical fouling and biofouling) to achieve accurate and reproducible electrochemical signals. This fast approach of reactivating the electrode surface will keep the electrode catalytically active in repeated long-term measurements in routine analysis. Therefore, we can conclude that the electrochemical activation of graphite is a simple, low-cost, environmentally friendly, easily controllable and reproducible method for electrode processing, and the quantitative measurement of AR shows high sensitivity and considerable reliability.

Zeng *et al.* [46] fabricated flexible self-supported laser-induced graphene (LIG) electrode devices. Benefiting from its superior electrochemical property, these unmodified LIG electrodes exhibited remarkably enhanced electrochemical oxidation activity toward AR.

The advanced electrochemical sensor platforms for the detection of AR and their applications in the food quality and pharmaceutical control fields are listed in Table 1. Experimental results showed that most electrochemical sensors offered a broad linear range and a low detection limit for AR, exhibiting good selectivity, interference resistance and reliability. Additionally, applying these sensors in a wide variety of samples validated their effectiveness and potential for broad applications in food safety and pharmaceutical quality assurance. Compared with other traditional laboratory standard techniques, electrochemical analysis has the advantages of simple operation, fast response time, high efficiency, and environmental protection.

The development and exploration of new nano-sized materials provide more possibilities for constructing novel and specific electroanalytical platforms. A proper selection of nanomaterials employed for their construction can improve selectivity, sensitivity, and response time. Recently, the combination of various functional materials has become a research hotspot. Combining various functional materials produces synergistic effects to obtain an enhanced sensing performance [54-57,60,68]. Here are some disadvantages of the traditional electrode systems based on GCE and CPE, such as recalibration requirements and problematic stability.

Few research teams have reported sensors based on screen-printed electrodes providing low-cost alternatives for in situ AR monitoring in food and pharmaceutical analysis [44,56,60]. Screen printing offers versatility in terms of electrode design and modifications, making the sensing platform affordable and valuable for mobile applications. This technology provides important features, such as the capacity for low-cost mass production and easy procedures of the use. SPEs allow a plurality of tests to be accomplished with small sample volumes without pretreatment or keeping of the electrode.

Table 1. *Electrochemical sensors used for AR sensing in foods, beverages and drugs*

Electrode	Method (Potential, V)	Linear range, µM (LOD, nM)	Real sample	Year	Ref.
m-AgSAE	DC-AdSV (-0.3[a])	0.008 to 0.6 (3.4)	Soft drinks	2019	[41]
SbFE/SPCE	DPV (-0.7[c])	1.0 to 5.0 (300)	Isotonic drink, tomato bouillon cube, flavored cornflour	2015	[44]
CoOx/CPE	SWV (-0.25[b])	- (50)	Chili sauce, isotonic drink, soft drink	2019	[45]
ErGO/GCE	DPV (0.825[b])	0.1 to 0.8 (28)	Soft drinks	2023	[47]
MWCNTs/GCE	DPV (0.75[b])	496 to 4468* (14)	Isotonic sport drink	2019	[48]
PDDA-Gr-Ni/GCE	DPV (0.85[a])	0.05 to 10 (8)	Strawberry juice	2016	[49]
Mn_3O_4@C	DPV (0.95[b])	0.1 to 1748.4 (33)	Sport drink	2022	[51]
La_2YCrO_6/HLNTs/GCE	LSV (0.9[b])	10 to 140 (5.78)	Strawberry juice, wine grape juice	2024	[54]
In^{3+}/NiO/GCE	DPV	0.01 to 700 (4.1)	Soft drinks	2021	[55]
F-nanodiamond @SiO_2@TiO_2/SPE	DPV	0.01 to 0.12 0.12 to 8.65 (1.22)	Soft drink, orange juice	2022	[56]
TiO_2/ErGO/GCE	DPV (0.62[a])	0.3 to 5.0 (50)	Milk drinks	2020	[57]
ZnO/Nafion/GCE	DPV (0.7 V[b])	0.01 to 0.41 (1.0)	Jelly	2023	[58]
$Mo(VI)_{OX}$/CPE	SWV (0.72[b])	0.36 to 6.00 (380)	Gelatin, syrup	2021	[59]
PPy/Co-Ni@rGO/SPCE	SWV (1.2[b])	0.0001-10.00 (0.03)	Energy beverages, water	2024	[60]
IL-CB-CTS-ECH/GCE	SWAdASV (0.9[b])	0.0398 to 0.909 (0.91)	Soft drink powder	2020	[62]
SHU/PCFE	DPV (0.85[b])	0.001 to 0.1 0.1 to 2.0 (0.36)	Carbonated drinks, food supplements, pharmaceutical sample	2023	[63]
Ptre/PGE	DPV (0.71[b])	0.25 to 100 (75)	Cherry juice, energy drink	2021	[65]
CPE/SG/CPCl	SWV (0.95[b])	0.04 to 1.00 (5)	Jelly sweets	2021	[66]
GCE in presence of CPB	SWAdSV (0.95[b])	up to 12 µM (32)	Cherry gelatin, strawberry juice, chili sauce	2018	[67]
IRGO/Au/GCE	SWV (0.73[a])	0.0006 to 0.200 (0.43)	Strawberry jelly, cranberry grain tea, strawberry apple juice, Bacardi breezer	2016	[68]

*µg/L; [a]*vs.* SCE; [b]*vs.* Ag/AgCl, 3 M KCl; [c]*vs.* Ag

However, the SPEs also have some shortcomings; for example, the performance of the SPE film can be variable, from screen-printed electrode to electrode and batch-to-batch variation.

Simultaneous electrochemical quantification of AR and other foodstuff dyes

Researchers have applied new approaches in order to develop integrated electrochemical devices for multi-component detection [69-77]. Multiplexed analysis reduces the required sample volumes, as well as the time and the total cost of analysis. A sensor system that can simultaneously monitor AR and other food synthetic dye/dyes levels in a single miniaturized and user-friendly device will provide a more complete picture of exposure to these compounds.

An effective strategy to detect analytes with similar redox potentials is to modify the working electrode to change the redox reaction kinetics. Buharinova *et al*. [73] designed a sensitive electrochemical sensor for the simultaneous detection of AR and TZ in foodstuffs based on a carbon veil modified with graphene nanoplates and phytosynthesized cobalt oxide Co_3O_4 nanoparticles. The used composite nanomodifier contributes to an increase and better separation of the oxidation

currents of these azo dyes in their simultaneous presence. The analytical range for both dyes is 0.1 to 15 µM. The sensor has been successfully used in the analysis of fruit jellies and beverages. The commented work offers a strategy for developing a multiplexed sensor with promising potential to achieve rapid, simple and effective analysis of food samples.

For the first time, Deroco *et al*. reported a novel electroanalytical method for the simultaneous quantification of the dyes AR and indigo carmine (IC) by coupling flow injection analysis and multiple pulse amperometry (MPA) with a cathodically pretreated boron-doped diamond electrode [74]. This technique enables high accuracy and selectivity due to the possibility of constant application of specific potential pulses to prevent contamination and to cause activation of the electrode surface. These advantages of MPA can be added to those of FIA systems, thereby minimizing the risk of solution contamination and interference. The proposed method permits up to 153 determinations per hour with good precision, and it was successfully applied in the quantification of these dyes in samples of commercial candies. The obtained contents were similar (at a 95% confidence level) to those from a comparative HPLC method.

A novel electrochemical sensor IL/$NiFe_2O_4$-rGO/CPE was introduced for the determination of AR, TZ and SY in a ternary mixture [75]. To demonstrate the ability of the designed system for potential application in real sample analysis, the sensor was applied to determine AR, TZ and SY in orange juice powder and personal care product (hair shampoo) using the standard addition method and values were compared to HPLC results. The RSDs were all below 5 % confirming that the fabricated sensor displays a high analytical performance with acceptable results. Unfortunately, the authors have not presented data on reusability and long-term stability (days, weeks) of the electrode material.

Well-separated oxidation peaks and enhanced peak currents of AR, TZ and Ponceau 4R were observed at modified IL-GO-MWCNT/GCE [76]. Detection limits at the nanomolar range have been obtained. The fabricated sensors were further applied to detect the three dyes in alcoholic beverages (fruit wine samples) using the SWV method.

Rivera-Hernández *et al*. [77] used a bare carbon paste electrode (BCPE) to detect AR and TZ analytes via DPV. Well-resolved oxidation current peaks were formed at 0.61 and 0.84 V *vs*. Ag/AgCl, respectively. The 230 mV potential difference between both peaks enables the quantification of these dyes even if both are present in the same sample. It is important to mention that UV-vis spectrophotometry cannot be used to simultaneously quantify AR and TZ due to the dyes absorbance overlap. A real sample carbonated orange flavored beverage (Mirinda®), the label of which only stated the presence of both dyes without specifying the amount, was used to analyze. From the analytic parameters estimated, it can be concluded that the designed electrode offers adequate reproducibility, repeatability, and an outstanding operational lifetime (95 % of the initial signal after 10 months). The authors reported that before carrying out electrochemical quantification, the electroactive surface of the BCPE was mechanically polished. This simple procedure cannot be used with modified CPEs, which seriously limits their operational lifetime due to fouling of surfaces. Therefore, the commented work presents the quantification of AR and TZ using an unmodified CPE and displays relevant advantages compared with other modified electrodes: simple technical construction, easily renewable working surface, excellent reproducibility and lower fabrication costs. In many respects, this work demonstrates that simplicity can be a good thing in electrode design for electroanalytical sensing devices.

Advantages of electrochemical sensors over traditional analytical methods for AR

Rovina *et al.* [26] critically summarized traditional analytical methods (spectrophotometry, capillary electrophoresis, mass spectrometry, HPLC, LC-MS, and LC-MS/MS) for determination of AR in food and beverage products. In this high-quality review paper, the authors have provided comprehensive coverage of different strategies used for the pretreatment, elimination of interferences, and extraction. A comparative examination clearly shows that most of these methods are unsuited for rapid and point-of-use because of complex analytical protocols and the long duration of the analytical procedure. The conventional analytical approaches require complicated pre-concentration, time-consuming steps, high-cost instruments, and skilled personnel, which hinder real-time and rapid analysis of AR.

In contrast, electrochemical sensors are advanced techniques for quantifying AR. Electrochemical sensing approach is very attractive for many reasons: remarkable accuracy, operational simplicity, relatively low cost, and easy miniaturization. In comparison with other analytical procedures, the proposed electrochemical platforms decreased the real time for the determination because no pretreatment steps were required. In most of the published methodologies, the procedure requires only appropriate sample dilution followed by immediate analysis. This is another significant advantage of electroanalytical approach - suitability to the analysis of very diluted samples is a simple strategy to avoid matrix effects in food analysis. Moreover, the electrochemical signal is not affected by the turbidity of the sample. This is an extra advantage in the food control field, where food/beverage samples often exhibit a certain turbidity level.

Due to the ability to integrate electrodes in microchips easily, electrochemical sensors can be miniaturized into compact, versatile, and powerful hand-held tools without compromising analytical behavior. Such analytical systems, with special advantages of portability and low cost, can be used for applications outside the laboratory environment to overcome the drawbacks of conventional analytical procedures [78]. A miniaturized analyzer can be connected to a smartphone for powering, processing, data analysis and visualization. The integration of complex electrochemical sensing capabilities with digital signal processing and wireless connectivity facilitates their use by individuals without specialized training [79]. Thus, the coupling of exclusive principles of electroanalysis with the enormous possibilities of nano-sized materials has led to portable, easy-to-use sensing systems accessible to a broader range of stakeholders - producers, regulators, and consumers. Recent advances in nanotechnology, surface modification, microfabrication, and signal processing have paved the way for the design of reliable devices for real-time monitoring.

Generally, strategies based on electrochemical sensing are promising candidates for AR determination. Electrochemical sensors for AR demonstrate irreplaceable advantages in food applications, including high selectivity and sensitivity for trace levels determination, extremely low LODs and LOQs, low sample volumes (microliters) requirement and minimum pretreatment, fast response time (few seconds), high benefit/cost ratio, simple and low-cost equipment, ultra-low power consumption, suitability for miniaturization and portability, on-site detection, wireless network, and multiplexing capabilities.

Approaches for improving the electrochemical determination of AR

Some shortcomings, such as non-specific adsorption and electrode biofouling, unsatisfactory long-term stability, and problematic device-to-device reproducibility, make the proposed sensor platforms difficult to apply commercially. A brief summary of the advantages and limitations of electrochemical sensors for AR determination in food and pharmaceutical samples is presented in Figure 3.

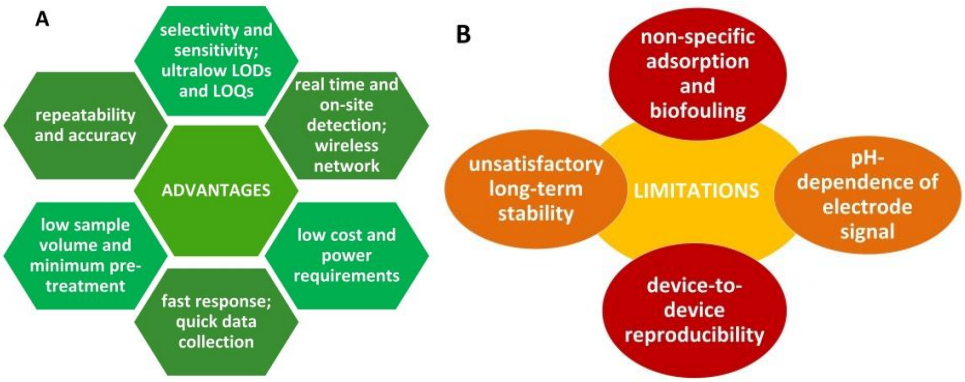

Figure 3. *A - Advantages and B - imitations of electrochemical sensors for AR determination*

Clearly, challenges still exist for AR electroanalytical approaches. Electrochemical determination can be affected by the electrode surface fouling (or poisoning) phenomenon caused by matrix components or the oxidative product of AR. The non-specific physisorption of reaction products or biological macromolecules (proteins, lipids, carbohydrates, *etc*.) on the electrode surface is insulated and blocks further oxidation of AR, affecting the robustness of measurements (higher background signal, low sensitivity, and low accuracy).

Furthermore, most electrode preparation procedures are unsuitable for the rapid large-scale production of cost-effective sensors. Generally, in the articles, researchers give a brief description of the fabrication process and raw materials used for electrode preparation, but they don't provide a detailed manufacturing workflow that is specific to industrial production.

The systematic review shows that drop-casting methods were widely used to fabricate the modified electrodes. However, this approach could be characterized by some drawbacks, such as low homogeneity, stability, and reproducibility of the resulting modified surfaces. The reasons for this can be summarized as:

(i) the phenomenon labelled as “coffee ring effect” can alter the distribution of the nanoparticles drop-casted on the electrode surface: capillary forces (the result of solvent evaporation) push the modifier to the edges of the underlying electrode, thus the periphery of the ring was seen to be concentrated with the solute particles in contrast to the center of the stain [80];
(ii) the agglomeration of particles leads to a decrease in the fraction of electroactive nanoparticles;
(iii) the modifier is physically adsorbed onto the electrode surface and may be gradually stripped off in long-term measurements. All these processes negatively affect the sensing performance of the electrodes modified by drop-casting layers.

Numerous studies proved electrodeposition as an attractive direct method for the preparation of nanostructures with well-defined morphologies. Electrodeposition is a simple, rapid and efficient process for depositing materials from the electrolyte onto electrode surfaces that does not require expensive equipment or special experimental conditions (high temperature or pressure, use of hazardous reagents). The main advantage of electrochemical techniques is the possibility of strict control over the material formation process and its structure. Such precise particle size control is achieved by adjusting applied potential or current density and electrolysis time. This feature leads to high reproducibility of the modification procedure. Additionally, the electrodeposited nanomaterials do not need to be stabilized as required if the same materials are synthesized in solution by chemical methods. Therefore, the electrochemical depositions are more environmentally friendly.

And not least, in modern analytical practice, there is a great demand for multiplexed quantification with a low technical threshold. Multiplexed detection of azo dyes is essential in various fields, from food safety and pharmaceutical control to environmental monitoring. In this regard, a database

containing inputs and outputs should be used to build regression models to resolve the overlapping peaks problem and to reduce measurement deviation. With the ability of machine learning models to learn from new data, it is also possible to continuously improve the accuracy, making the sensing equipment better with time and usage. That's why we expect artificial intelligence (AI) algorithms to be introduced to power electroanalytical methods in the foreseeable future. The outlook for AI-assisted electrochemical detection is promising as the AI-powered multimodal analytical device based on a single sensing material will be highly efficient and low-cost.

Approaches for improving the electrochemical determination of AR are summarized in Table 2. The highlighted options will be helpful in opening new ideas in the field of sensor fabrication for more effective, practical, and affordable electrochemical detection of AR.

Table 2. *Approaches for improving the electrochemical determination of AR*

Problems and challenges	Problem solving options
Biofouling and chemical fouling of catalytically-active electrode surface	(i) Use of antifouling layers and permselective membranes in order to provide a physical barrier between fouling agents and electrode surface. (ii) Development of new catalytically-active materials resistant toward passivation. (iii) Incorporating the electrochemical activation of electrode surface at regular intervals as a part of the analysis procedure. The use of cathodic/anodic potential or a train of pulses should reduce adsorption of fouling agents or remove already attached substances. Additionally, this method of reactivating electrode surface will keep the catalyst active in a long-term experiments and repeated measurements.
Fabrication challenges	(i) Development of advanced manufacturing techniques and automated procedures that lowering the overall production costs and facilitating manufacturability. (ii) Integration of nanocomposite materials into microchips. (iii) 3D-printing provides an economical and robust alternative to current strategies. Great flexibility in the sensor's design in terms of size and geometry, high batch-to-batch precision and uniformity are some of advantages of this technology. 3D-printing reduces waste generation and it has enormous potential for robust and large-scale fabrication in a mechanized/automatized process, that have paved the way for novel electrode designs and architectures.
Need of integrated devices for multi-component electrochemical detection	A sensor that can simultaneously monitor the levels of AR and other azo dyes into a portable format will have great potential in the applications of food and pharmaceutical safety. Development of multi-channel electrochemical platform in a single miniaturized and user-friendly device will offer the promise of practical applications. Recent achievements in microfabrication, multiplexing, electronics integration, and machine learning can help realize the potential of these sensing platforms.

Future directions for regulatory policies

According to the available literature and clinical studies, new toxicity concerns have arisen in AR due to its ability to bind to human serum albumin. This dye requires continuous monitoring as some *in vivo* studies indicate detrimental effects even at ADI doses. Based on the results of the latest studies on the toxicity of AR, regulatory agencies should reconsider the safety concerns of this synthetic dye and make ADI revisions. Additionally, it should be noted that there are studies proving that children may consume more colored foods and drinks than expected by the regulatory

authorities. Subsequently, there is a need for studies to evaluate the intake of mixtures of colorants to re-evaluate exposure in children. It is recommended that regulatory authorities require independent toxicity studies that evaluate the intake of mixtures of colorants.

Regarding artificial dyes in the food, pharmaceutical, and cosmetics industries, consumers are demanding improved information about the health risks. An international database would provide clearer knowledge of dye use and potential risks. Although the regulations might differ across countries, ADI values and toxicological specifications for all legal dyes should be the same worldwide. Designating internationally harmonized analytical methods for official control would also reduce the population's health risks. In this context, we expect the integration of electrochemical sensor technologies into existing analytical frameworks in the foreseeable future.

Conclusion remarks

This article covers the current state of reliable electrochemical platforms for AR sensing in foodstuffs and pharmaceutical formulations. The review shows that metal oxide nanoparticles and carbon-based nanomaterials are most commonly used as electrode modifiers. Furthermore, there is also a tendency to use sensing systems based on novel functional materials, such as nanocomposites, conductive polymers, ILs, and their combinations. The results demonstrate that most modified electrodes possessed acceptable reproducibility and stability for analytical applications. The received data testify that the electrochemical techniques offer outstanding benefits and provide a feasible path toward the next generation of sustainable and high-performance sensing devices. There is great potential for a smooth integration between electrochemical sensors and machine learning, making them important tools in analytical chemistry. Machine learning can boost the precision of the analytical data, offering an accessible and pragmatic option that ensures reliable results. Thus, the use of artificial intelligence will become increasingly common in the field of sensor development. We are confident that the convergence of nanoscience, nanotechnology, electroanalytical techniques and machine learning will allow the development of precise integrated electrochemical sensors for express food safety and pharmaceutical control.

Abbreviations

ADI acceptable daily intake
AM amaranth
AR allura red
BAFS biologically active food supplements
CPB cetylpyridinium bromide
CPE carbon paste electrode
CPCl cetylpyridinium chloride
EGPE expanded graphite paste electrode
ErGO electro-reduced graphene oxide
GCE glassy carbon electrode
ILs Ionic liquids
IRGO water-dispersible reduced graphene oxide based on IL of 1-allyl-3-methylimidazolium chloride
HMDE hanging mercury drop electrode
HPLC high-performance liquid chromatography
LC-MS liquid chromatography-mass spectrometry
LC-MS/MS liquid chromatography with tandem mass spectrometry
LSV linear sweep voltammetry
PCFE planar carbon fiber electrodes
PDDA poly(diallyldimethylammonium chloride)
PGE pencil graphite electrode
P4R Ponceaut 4-R
RSD relative standard deviation
SCE saturated calomel electrode
SD sudan
SG silica gel
SHU shungite
SPCE screen printed carbon electrode
SWAdASV square-wave adsorptive anodic stripping voltammetry
SWSV square-wave stripping voltammetry
SY sunset yellow
TZ tartrazine.

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