

# Current Trends in Rapid Electroanalytical Screening of Date and Rape Drugs in Beverages

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## Abstract

This review covers the current state of the art about electroanalytical studies focused on drugs used to facilitate sexual assaults. The chemicals that are members of this family and the main target of this review paper are benzodiazepines as a family of molecules, ketamine, gamma-hydroxybutyric acid, fentanyl, and some of the drugs categorized as new psychoactive substances (NPS). Most of the research in this area has been published within the last 10 years. Given the need for on-the-spot date rape drugs detection, we have emphasized sensing scenarios that have been developed and validated using real samples, soft and hard drinks. In the background, we also discuss some of the works focused on body fluids, which could be also applied to the soft and hard drinks analysis. Following a critical discussion of the current state of the art, we present a section outlining future directions along with the highlighted existing knowledge gap.

## 1. Introduction

Date rape drugs (DRD) are a large family of chemical substances that have sedative properties. These molecules can be classified into a few subgroups, this is benzodiazepines (BDZ, e.g. midazolam, temazepam, diazepam, flunitrazepam), ketamine, gamma-hydroxybutyric acid (GHB), fentanyl, and other less popular psychotropic molecules also including emerging recreational drugs. The statistical analysis of drug-facilitated crimes (DFC) is difficult to assess as victims frequently experience amnesia, or choose not to testify, often out of fear of victim blaming. Even though this issue is very

complex, the report of the European Monitoring Centre for Drugs and Drug Addiction provides information that 5% of the rape victims had been drugged (either with illicit substances, alcohol, or both).[1,2] Interesting work published in 2005 provides information about the toxicological analysis performed on rape victims indicating that alcohol, cannabis, cocaine, benzodiazepines, GHB, and ecstasy were involved in the drug-facilitated sexual assault (DFSA).[3] A more detailed analysis was also performed a few years later (2022) by Skov *et al.* which now shows benzodiazepines as the most frequent DRD used worldwide.[4] The same work also indicates that the toxicological profile of the DFSA victims may include common illicit drugs (amphetamine, methamphetamine, cannabinoids, cocaine, 3,4-methylenedioxymethamphetamine), ketamine, GHB, new psychoactive substances (e.g. methylone, dexmedetomidine), as well as the molecules classified as analgesics, antidepressants, and antipsychotics.[4] This information is especially useful during the sensing scenarios development, as a very complex matrix (composed of intrinsic sample composition enriched by different drug mixtures) should be taken into account.

This review paper aims to summarize the current state of the art focused on the electroanalytical detection of DRDs associated with DFC especially DFSA. The benefits and shortcomings of the electroanalytical scenarios are very well described in the scientific literature.[5] The intuitive features of electrochemical sensors are low prices and simple sensing configurations - the final idea is to use this technology in plug-and-play scenarios.[6] We are also convinced that electrochemical sensing is currently being rediscovered due to the commercial availability of very small hardware (potentiostats smaller than the matchbox), software and applications that can provide a binary read-out dedicated to a non-expert user, and finally compatibility with the smartphone technology.[7]

From the forensic point of view, the interest of the scientific community in developing electrochemical sensors is mainly focused on the most popular illicit drugs. We encourage readers to explore the updated review papers (published over the last five years) focused on the electroanalytical detection of cocaine [8,9], fentanyl [10,11], amphetamine and its analogs [12] or illicit drugs as a class of analytes [13]. The analysis of the literature suggests that over the last five years number of reports describing illicit drug detection protocols is blooming (cocaine is the molecule still being in the scientific

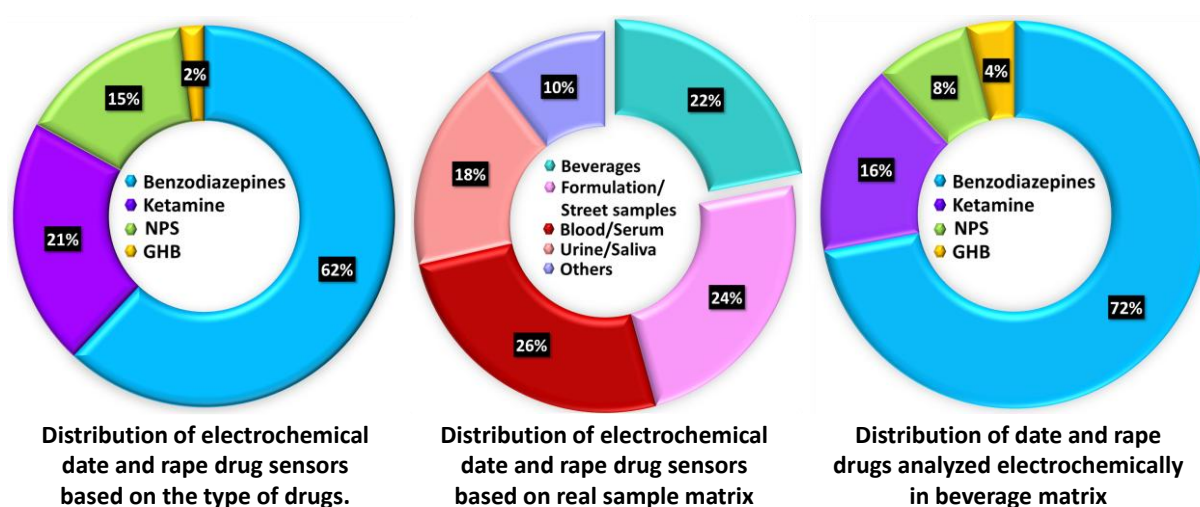
spotlight)[14,15]. Worth noting are the protocols that utilize 3D printing, as this technique brings commonness, reproducibility, and an extremely easy (entire) electrochemical set-up fabrication in R&D laboratories [16,17]. Still, the electroanalytical protocols entirely dedicated to DRD are rare and for many molecules are still missing, not to mention the lack of sensor validation in real samples. With this review paper, we aim to summarize the existing knowledge with a critical evaluation mainly focused on the applicability and functionality of the developed solutions. As seductive drugs are frequently consumed through soft or hard drinks, we underline the reports that are focused on these real samples. We have also identified a few future directions that, along with the conclusions, are expected to address the currently existing knowledge gap.

The key findings for this review can be consisted in a few lines. 1. BDZ are the most used and studied DRD in any medium including beverages. 2. The electrochemical behaviors of various NPS are not well characterized and not studied in beverage medium. 3. Gamma hydroxybutyrate has the least studied DRD in any sensing matrices due to its poor electrochemical behavior and possesses a significant research gap. 4. A few notable reports of wearable, printed lab-on-chip sensors are appealing and promising for practical adoption to screen DRD in beverages. Lastly, 5. The vast diversity in the chemical composition of beverage medium imposes overwhelming analytical complexity towards DRD screening.

## **2. Electroanalytical detection of date and rape drugs.**

For the past 20 years, the development of analytical tools that enable on-site screening of date rape drugs (DRD) that complement conventional analytical methods has been of great research interest.[18] If not all, most of DRD consists of electrochemically active functional group/s that may undergo redox reactions, and hence, be detected with all electroanalytical tools. In the context of this review, we are focused on rapid (minimal/no pre-sampling, and fast testing time) electroanalytical tools proposed to testify DRD in beverage samples with a few exceptions in rapidness of the system citing the significance of the specific report in the evolution of DRD sensors over the past decade. A comprehensive literature survey using the key word combinations of “benzodiazepine, ketamine, gamma ( $\gamma$ )-hydroxybutyrate, morphine, fentanyl, new psychoactive drugs electrochemical sensors, date and rape drug sensors, beverage, juice, alcohol, soft drinks, and hard drinks” in web-of-science, and Scopus over past ten years reveals about 102

electrochemistry-related reports among which BDZ (62%) tops the list as the most studied DRD. Bio samples (blood, serum, urine, and saliva) are the most studied sensing matrix (44% of the reports) followed by pharmaceutical formulations and street samples (24%). Only 22% of the reported electrochemical sensors were targeted to analyse DRD spiked beverages (water, soft, and hard drinks) which is among the most significant real-world samples in resolving and preventing DFC. In this respect, BDZs (72% of the reports) were the most frequently studied drugs, while GHB ends the list. An infographic outlining the distribution of electrochemical sensors reported for various DRD in different samples is presented in Figure 1.



**Figure 1:** A statistical distribution of electrochemical date and rape drug sensors reported in the last decade (NPS-New Psychoactive substances, GHB-Gamma Hydroxybuterate).

## 2.1. Benzodiazepines

Benzodiazepines (BDZ) are a class of psychoactive drugs known for their high sedative nature. BDZs are prescribed to treat a range of medical conditions ranging from anxiety to alcohol withdrawal syndrome.[19] These drugs function as central nervous system depressants by enriching the activity of the benzodiazepine site of the GABA type A receptor (GABAA receptor) towards the gamma-aminobutyric acid (GABA) neurotransmitter. The success of Librium/chlordiazepoxide (the first BDZ drug) in 1960s to treat anxiety, and insomnia triggered the wave of BDZ drug development.[20] Their strong seductive nature and short life span have made them an ideal component in various DFC including DFSA[21]. This property is reflected in the research communities' efforts to

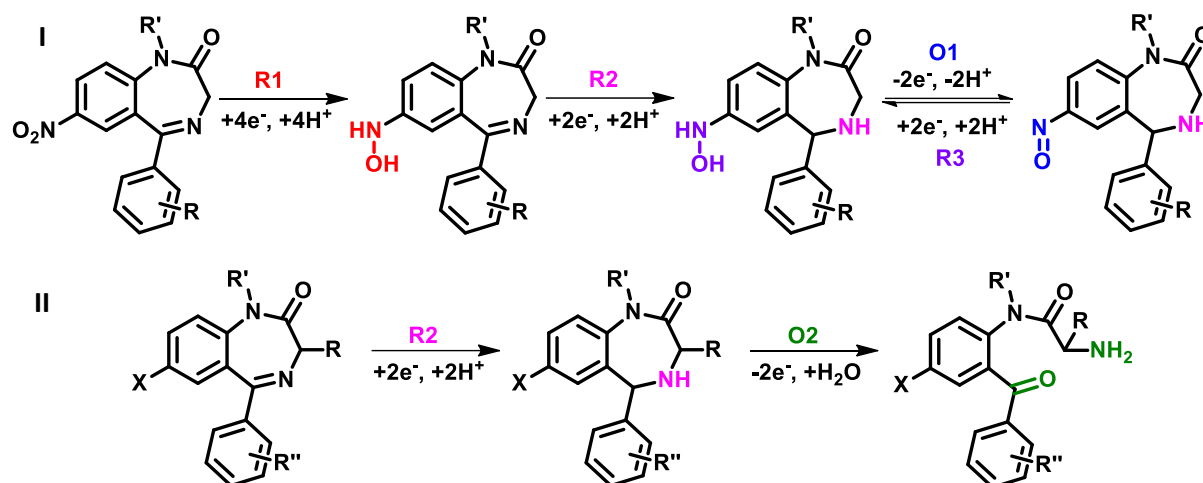
rapidly screen DRD in complex sample matrices and BDZ (as shown in Figure 1) are the most frequently studied analytes during electrochemical sensors development.

The electrochemical behaviour of BDZ drugs is attributed to the azomethine unit in the benzodiazepine skeleton and the presence of other functional groups (such as, amine, nitro, N-oxide, carbonyl, etc.,) distributed among the variants of the BDZ core (for chemical structures see Table 1). Therefore, the most common electroanalytical techniques including voltammetry, polarography, and potentiometry are employed to fabricate electrochemical sensing platforms for the rapid screening of BDZs in various sample matrices. In general, the electroanalytical mechanism of BDZ detection involving redox reactions can be classified based on the presence of functional groups as BDZ-Class I (amine and nitro BDZ) and BDZ-Class II (non-nitro/amine BDZ).[22]

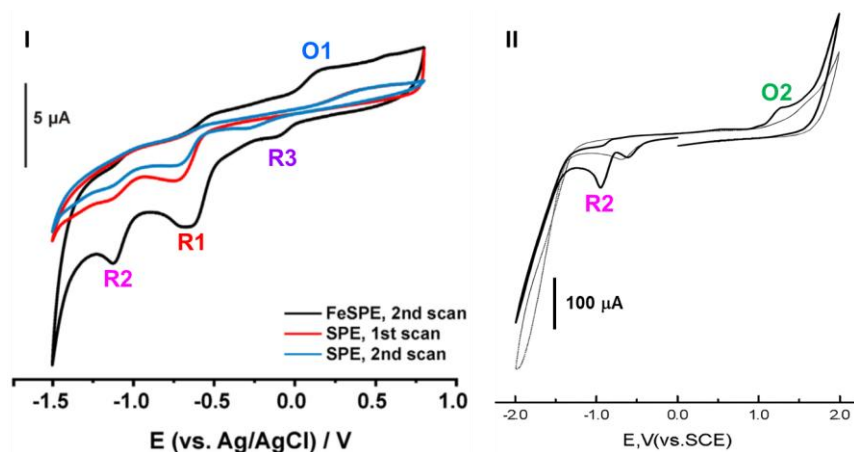
A typical cyclic voltammogram (CV) of Nitro-BDZ drugs (e.g.: Flunitrazepam, Clonazepam, and Nitrazepam) recorded at carbon-based electrodes initially displays two cathodic peaks R1 ( $\sim -0.7$  to  $-0.9$  V vs Ag/AgCl) and R2 ( $\sim -1.1$  to  $-1.3$  V vs Ag/AgCl) followed with an anodic peak O1 ( $\sim 0.4$  V vs Ag/AgCl) which induce the formation of third cathodic peak R3 ( $\sim -0.3$  to  $-0.28$  V vs Ag/AgCl) on the reverse sweep. The overall electrochemical transformation of the process can be described by the equation presented in Figure 2. The cathodic peaks R1 ( $+4e^-/+4H^+$ ) and R2 ( $+2e^-/+2H^+$ ) are attributed to the reduction of nitro, and azomethine groups of Nitro-BDZ into hydroxylamine, and amine groups, respectively. The semi-reversible redox couple of O1 and R3 are the product of hydroxyl amine oxidation (O1,  $-2e^-/-2H^+$ ) into nitroso species and vice versa (R3,  $+2e^-/+2H^+$ ). Thanks to its high correlation and interference-free potentials the semi-reversible redox couple of O1/R3 were widely used for the electroanalytical determination of these nitro-BDZ drugs, while in some cases the peaks R1 and R2 were used depending upon the sensing matrix. Moreover, the redox couple O1/R3 also appears in the amino-BDZ drugs and its metabolites (e.g.: 7-aminoflunitrazepam, 7-aminonitrazepam) and also have been used for electroanalytical purposes[23,24].

The CV of other non-nitro BDZ (e.g.: Diazepam, Midazolam, Alprazolam, and Lorazepam) displays the cathodic peak R2 ( $\sim -1.0$  V vs Ag/AgCl) corresponding to the reduction of azomethine groups into respective secondary amine. A subsequent anodic sweeping displays the reduction (R2) induced anodic peak O2 ( $\sim 1.0$  V vs Ag/AgCl) which originates due to the ( $2e^-/-2H^+$ ) oxidation of secondary amines to open the diazepine ring

of the BDZ skeleton. The CVs and electrochemical reactions of the BDZ derivatives are presented in Figure 2 and scheme 1 [25,26]. Also, a few reports of adsorptive stripping voltammetry and potentiometric sensors describe the electroanalytical detection of BDZ in soft and hard drinks samples.[27–29]



**Scheme 1.** Electrochemical reaction mechanism of **I**. BDZ class I, and **II**. BDZ Class II drugs.



**Figure 2:** I. CVs of flunitrazepam (BDZ Class I) at different electrodes. Adapted from [30] II. CVs recorded in the absence and presence of diazepam (BDZ Class II). Adapted from [22] III. Schematic representation of the fabrication of AGO-Cu/SPCE-based Flunitrazepam sensor applied for fruit juice analyses. Adapted form [31]. IV. (A) Laser-scribing on graphene/polyetherimide, (B) SEM morphology of Laser-scribed graphene, (C) SEM tomography of polyetherimide (D) Chemical structure of diazepam and midazolam (E) Background corrected SWV curves of 2.5-100  $\mu\text{M}$  of diazepam recorded at 0.1M BRB pH 4.0. Adapted form [25]. V. (A) Schematic representation of midazolam sensor sampling at boron doped diamond electrode (BDDE), (B) Electrochemical reduction mechanism of midazolam at BDDE, (C) CVs obtained for 1 mM MID in 0.12 M BRB at pH=2.0. Adapted form [32]. VI. (A) Schematic representation of the fabrication of CoOOH-rGO/SPCE portable electrochemical sensor for clonazepam, (B) Electrochemical reduction mechanism of

clonazepam at CoOOH-rGO/SPCE, (C) DPV analysis of CoOOH-rGO/SPCE for 0.1-350  $\mu\text{M}$  of clonazepam in 0.005 M  $\text{K}_3\text{Fe}(\text{CN})_6^{3-/4-}$  PBS pH 7.4 Adapted from [33].

### 2.1.1. Voltametric sensing of Benzodiazepines

Flunitrazepam (FNZ) is among the most studied BDZ in soft and hard drinks. Its high popularity in DFC including DFSA has led to its withdrawal from the EU market in 2007 [19,20]. Clonazepam (CNZ) and Nitrazepam (NTZ) are two other profound nitro-BDZ drugs. The chemical structure of all three drugs consists of azomethine, carbonyl, and nitro groups that enable the BDZ-Class I electrochemical sensing mechanism.

Electrochemical detection of NTZ and FNZ were reported by Hart *et al.* on a simple screen-printed carbon electrode (SPCE) using CV. Both drugs displayed cathodic (R1, R2, and R3) and anodic (O1) peaks found between -1.5 V, and +0.5 V (repetitive cycling). A simple voltammetric sensor was developed by dropping a small volume of sample (10 - 100  $\mu\text{L}$ ) onto the surface of SPCE, drying step, followed by dissolution in PB supporting electrolyte. NTZ detection was based on O1 peak showing a liner relationship at micromolar range (LOD = 6.3  $\mu\text{M}$ ). The authors proved that NTZ can be detected in Pepsi Max, Vodka Kick Ice Cherry, Absinthe, and brandy with adequate recovery rates [34]. In 2012, Banks *et al.* used screen-printed graphite electrodes (SPGE) to directly detect FNZ in Coca Cola<sup>TM</sup> and the alcopop WKD<sup>TM</sup>. These works has fixed the fundamental obstacle of colorimetric tools toward rapid screening of DRD in colored beverage samples, through a simple ready-to-use electrochemical platform [35]. The challenge remaining to be solved was the fluctuating performance of different SPE. Relatively straightforward modification of SPCE with AGO-Cu provided a detection range of 0.4-140.0  $\mu\text{M}$  for FNZ detection and was applied for spiked fruit juice analysis (Figure 2 III) [31].

These and many more works provide different protocols for BDZs detection which are usually affected by the addition of different types of nanomaterials serving as the carbon-based (most frequently) electrode modification delivered a detection limits of few micromoles. Meanwhile, GCE electrode modified with  $\text{TiO}_2\text{@CuO@N doped rGO}$  and poly(L-cysteine) pushed the LOD down to nanomoles (0.3 nM) for FNZ detection. The real-world applicability of the developed sensor was demonstrated in Tourtel Malt, Coca-Cola drink, and human plasma with recovery rates of 90.0-104.0 % [36]. Later, Prodromidis *et al.* reported a low-cost lab-on-a-screen-printed electrochemical cell (SPC) based on iron-



sparked graphite working electrode modified with glucose oxidase (GOx) and glucose hydrogel droplets (GluHD) for the detection of FNZ. Iron-spark modification of SPE (FeSPE) has increased the current response by 3-fold compared with that of the bare SPE. In addition, the GOx enabled the *in-situ* enzymatic deoxygenation process to improve the analytical resolution by minimizing the background currents limiting nitro group reduction. Altogether this method enabled interference-free voltammetric detection of FNZ in various samples to sub-micromolar levels (LOD- 15 nM) [24]. Especially exciting is the report by Kokkinos *et. al.* who developed a 3D-printed wearable e-finger electrochemical cell to screen multiple DRDs in beverage samples. Under optimized conditions, the wearable e-finger displayed the CVs signature of BDZ-Class I with reduction peaks of 7-nitro, and hydroxylamine groups found for FNZ. The sensing unit was validated on undiluted whiskey, vodka, gin, and beer [37].

Early report of CNZ detection in wine samples was reported by Honeychurch et al. in 2016, through adsorptive stripping voltammetry on a screen-printed carbon electrode. The CNZ displayed typical CVs of BDZ-Class I on SPCE with peak O1 shown linear relationship with CNZ concentration of few micromoles and used to determine CNZ spiked in wine and serum samples [38]. The specific pre-sampling procedures of the study is an obstacle to be addressed for practicality. In sequence, a cobalt oxyhydroxide (CoOOH) nanoflakes self-assembled reduced graphene oxide (rGO) nanocomposite modified SPCE (CoOOH-rGO/SPCE) was also reported for the determination of CNZ in different beverages (Coca Cola, Real Juice, Beer, and Wine) samples with a similar analytical range paired with high sensitivity ( $0.054 \mu\text{A } \mu\text{M}^{-1} \text{ cm}^{-2}$ ), and recovery rates (87–115%)(Figure 2 VI) [33]. While, large interference from uric acid, urea, glucose,  $\text{K}^+$  and  $\text{Na}^+$  ions deters the practical reliability of the CoOOH-rGO/SPCE sensor. Meanwhile, Limbut et al. proposed an electrochemically pre-treated glassy carbon electrode (GCE) probe for high sensitive determination of CNZ spiked in beverage samples through adsorptive cathodic stripping voltammetry(AdCSV). The AdCSV peak currents at EC-GCE was linear against increasing concentration of CNZ between 79 nM to  $4.7 \mu\text{M}$  with a detection limit of 60 nM extending the analytical figures from sub-micromoles to nanomolar concentrations. Moreover, the EC-GCE was used to determine the CNZ in spiked beverage samples with an impressive recovery rate of 98 to 102 % [39].

Diazepam (DIZ), Lorazepam (LRZ), Midazolam (MDZ) and Alprazolam (ALZ) are the most common non-nitro/amino BDZ with closely related chemical structures. LRZ possesses one Cl and OH groups in addition to the single Cl substituent in the DIZ skeleton while the MDZ and ALZ possess imidazole and triazine rings in their backbone. The typical voltammetric features of these drugs follows BDZ-Class II mechanism which primarily focuses on the reduction of azomethine (R2) and oxidation of secondary amine to open the diazepine ring (O2). Differences in the electrochemical properties of these drugs, their redox behaviour affected by different electrode materials, and the effect of the real sample matrix on the resulting electroanalytical output was studied in a few works. Kevin *et al.* in 2013 used simple SPCE along with adsorptive stripping voltammetry to detect DIZ in fortified Red Russian Ice Cherry, vodka-based alcohol pop containing 4% v/v ethanol, and PepsiMax (alcohol-free) [40]. Prakash *et al.*, proposed a graphene oxide/lysine (GO/lys) composite modified GCE for rapid sub-micromolar detection of DIZ in Juice, cola, whisky, and wine without any sample pretreatments with adequate selectivity and rates of recovery [41]. William *et al.* fabricated laser-scribed graphene (LSG) on polyetherimide (PEI) substrate for portable electrochemical detection of diazepam (DIZ) and midazolam (MDZ) in beverage samples using square wave voltammetry (SWV) (Figure 2 IV). The PEI-LSG based DIZ and MDZ sensor has shown a linear range up to 100  $\mu$ M with sub micromolar detection and quantification limits. Further, the PEI-LSG sensor was successful in the screening of DIZ and MDZ in juice, whisky, and sugarcane spirit with recoveries ranging from 97.1% to 117.2% for DIZ and. 92.2% to 114.3% for MDZ[25]. In sequence, Rocha *et al.* used boron-doped diamond electrode (BDDE) for selective MDZ detection in beverage samples (vodka, whiskey, and red wine) (Figure 2 V). The electroanalytical performance of MDZ at BDDE in vodka, whisky, and red wine samples was studied individually and delivered a dynamic range at lower micromoles with sub-micromolar detection limits [32]. Finally, the detection of LRZ in water, urine, and hair samples at trace levels with notable selectivity and recovery [42,43], or FNZ spiked in Coca-cola, Fanta, Sprite, Red Bull, Barbican, and Nestle purelife water [27,44]also exist, and the corresponding electroanalytical parameters (along with other examples) are summarized in **Table 1**.

We have also reported an alternative electroanalytical detection of clozapine (CZ) at electrified liquid-liquid interface (eLLI). The eLLI composed of two immiscible solutions of 10mM NaCl/10mM HCl with 10% EtOH (v/v) placed on top of 5 mM

bis(triphenylphosphoranylidene)ammonium tetrakis(4-chlorophenyl)borate (BTTPA<sup>+</sup>TPBCl<sup>-</sup>) in 1,2-dichloroethane. The detection was based on the transfer of CZ from the aqueous to the organic phase and was studied using ion-transfer voltammetry. Furthermore, the practical feasibility of the system was demonstrated in determining CZ spiked in apple juice, apple juice + vodka, vodka, wine, and beer samples with analytical performance on par with that of chromatographic tools[45]. This have been the first report on the use of eLLI towards electroanalytical detection of BDZ in soft and hard drinks samples that deliver promising results for an alternative approach for the design of electrochemical sensors. Detection of BDZs at the eLLI is an interesting approach that can be extrapolated to detect other molecules of this family based on the ion transfer and not the redox reactions.[46]

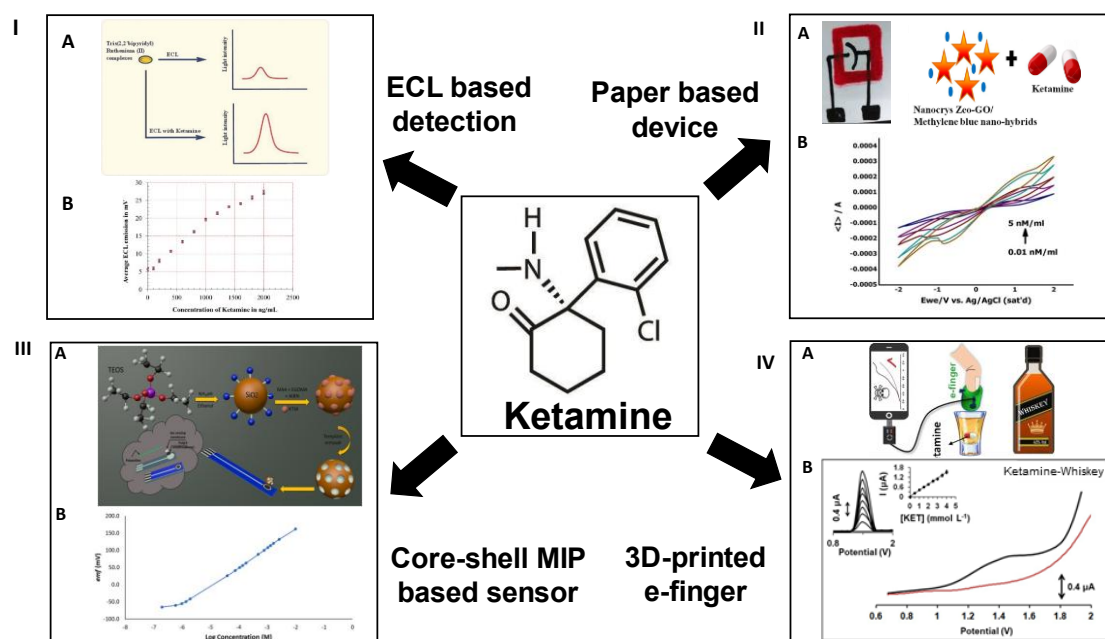
In summary, starting from a decade ago with simple electrode activation protocols to printing custom-made electrochemical cells the electroanalytical tools have been proven to be fully useful in BDZ drug detection in various samples represented by soft and hard drinks. Meanwhile, the design of electrochemical units primarily focused on fabricating comprehensive electrochemical devices (Lab-on-chip, miniaturized/microfluidic electrochemical cells, wearable electrochemical devices) is still to be incorporated, developed, and studied. We believe that thanks to the recent growth in fabrication technologies (mainly 3D printings), and internet-of-things (IOT) on-site periodic detection protocols (based on electrochemistry) for BDZ detection will be soon provided and applied.[16]

## **2.2. Ketamine**

Ketamine (KT) is a derivative of chlorophenol with the blocking action on the N-methyl-d-aspartate (NMDA) receptors in neural cells[47]. It is a tasteless, odourless and colourless anaesthetic drug having sedative properties[48]. In low doses, it can demonstrate clinical significance in the treatment of depression [49] and pain-processing neurons related to the spinal cord and brain[50]. KT has become a popular illicit drug[51] (known as e.g. “K-powder”) which may also be used for DFSA[37] . This section will illustrate and describe the electroanalytical protocols for KT detection with the focus given to beverages used as the real matrix.

### **2.2.1. Detection of ketamine in beverages**

Table 1 enlists sensors fabricated for the electrochemical detection of KT in beverages with important parameters including LOD, LDR, and their potential applications in testing alcoholic and non-alcoholic beverages. In this chapter, we will critically discuss only a few examples that were used for KT detection. Lledo-Fernandez *et al.* were the first to report electroanalytical detection of KT using the electrochemiluminescence (ECL) technique employing  $[\text{Ru}(\text{bpy})_3]^{2+}$  as ECL probe. The sensing unit was based on a conventional three-electrode system with GCE serving as the working electrode placed over a miniaturized photomultiplier tube having ECL sensitivity  $\sim 610$  nm. The detection mechanism was typical and relied on the  $[\text{Ru}(\text{bpy})_3]^{2+}$  regeneration by the tertiary amine group from the KT structure. Figure 3(IA) depicts the ECL signal in the presence and absence of KT[52]. A linear detection range from  $0.21 \mu\text{M}$  to  $8.41 \mu\text{M}$  was achieved with a low detection limit of  $0.14 \mu\text{M}$ . This method's utility was verified in discrimination between KT enantiomers and detection in Gordon's Gin & Tonic (alcoholic beverage, Figure 3(IB)) . Narang *et al.* proposed a point-of-care nano-hybrid-based electrochemical microfluidic paper-based analytical device (E $\mu$ PAD) for the detection of KT. Fabrication involved computer-aided design, Whatman no. 1 filter paper (support), and wax-based ink for channel printing (see Figure 3(IIA)). Counter and working electrodes were prepared using conducting carbon ink. Although the WE was modified with graphene oxide (GO) nanoflakes (improving electrode conductivity) and zeolites crystal (Zeo, bringing large surface area) the voltammetric features of the obtained configuration were burdened with significant resistance (see Figure 3(IIB)) which will surely limit the practical applications. Nevertheless, the authors claim that E $\mu$ PAD can be used to detect KT in the presence of the most common interfering agents including glucose, fructose, maltose, AA, hydrocortisone, gentamycine,  $\text{K}^+$ ,  $\text{Na}^+$ ,  $\text{Cu}^{2+}$ ,  $\text{Ni}^{2+}$ ,  $\text{Fe}^{3+}$ . It was also used for the direct detection of KT in alcoholic (e.g. whisky) and non-alcoholic (orange juice) beverages [53].



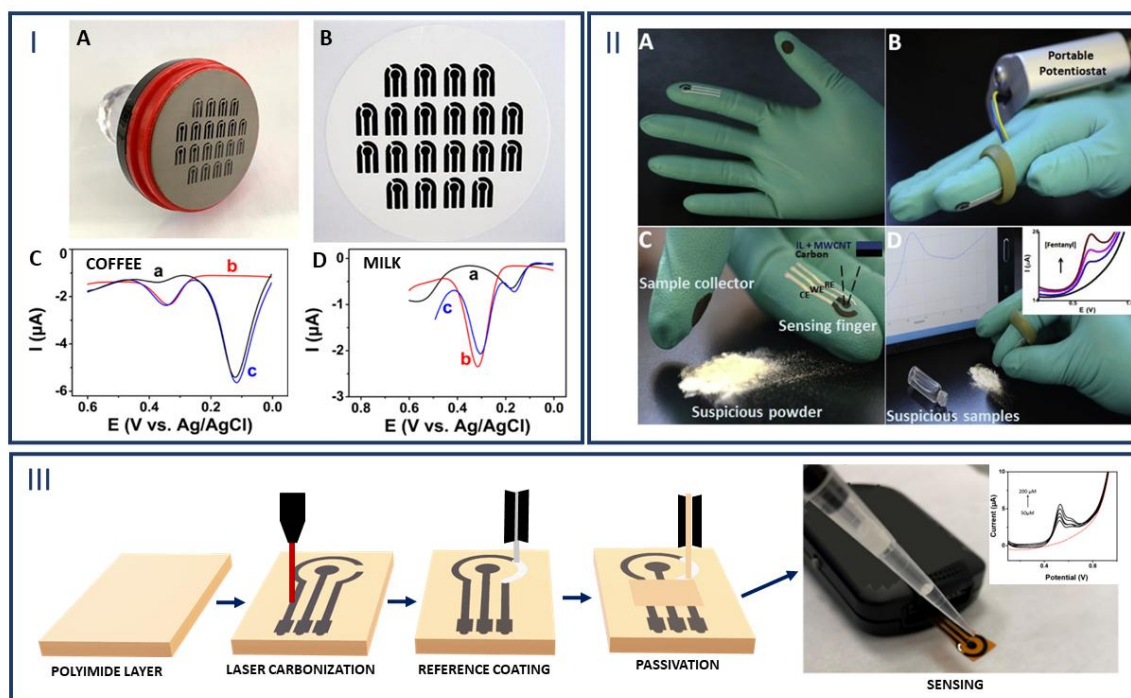
**Figure 3. I.** Electrochemiluminescence (ECL) based electroanalytical detection of Ketamine in alcoholic beverages (A) ECL signal intensity without and without Ketamine, and (B) calibration plot for ketamine recorded in Gordon Gin & amp; Tonic solution. Adapted from [52]. **II.** Microfluidic paper-based analytical device (E $\mu$ PADs) for the Ketamine detection (A) E $\mu$ PAD modified with nanocrystals of zeolites (Zeo) and graphene oxide, and (B) CVs of modified electrode using increasing concentrations (0.01-5  $\mu$ M) of Ketamine. Adapted from [53]. **III.** Core-shell molecularly imprinted polymer (MIP) screen-printed sensor for the Ketamine detection. (A) sensor fabrication steps, and (B) linear relationship between the potential and increasing ketamine concentrations (1.0  $\mu$ M to 10 mM). Adapted from [54]. **IV.** Wearable electrochemical sensor for the Ketamine detection in alcoholic beverages (A) 3D-printed electrochemical-finger based sensing platform, and (B) differential pulse voltammograms (DPV) recorded with the e-finger obtained in untreated and undiluted whiskey before (red line) and after (black line) spiking with 0.5 mM Ketamine. The inset is the baseline corrected DPVs at the e-finger for corresponding calibration plot. Adapted from [37].

Another elegant example of KT detection comes from the work of Soliman *et al.* Here, the SPCE covered with polyaniline was modified with rather a complex assembly of nanomaterials. The ketamine molecularly imprinted polymer (copolymerized methacrylic acid and ethylene glycol dimethacrylate) was placed over silica nanoparticles that were further incorporated into the polyvinylchloride membrane (see Figure 3(IIIA)). The

electroanalytical evaluation of the sensors provided LOD and LOQ equal to 0.93  $\mu\text{M}$  and 1.00  $\mu\text{M}$ , respectively. A selectivity study was done with the common chemical species such as  $\text{Na}^+$ ,  $\text{K}^+$ ,  $\text{Ca}^{2+}$ ,  $\text{Mg}^{2+}$ ,  $\text{Zn}^{2+}$ , and Quetiapine. The authors also proved that their sensing interface can be directly used to detect KT in non-alcoholic beverages (e.g. juices) [54]. We are also happy to underline the work of Poulladofonou *et al.* who fabricated 3D printed wearable electronic finger (e-finger) in a fully “Do-it-Yourself” manner. They have used an accessible and cheap 3D printer, a portable potentiostat that was integrated with the smartphone, and two printing filaments (conductive polylactic acid and acrylonitrile butadiene styrene) to provide a fully functional device for KT detection in alcoholic beverages such as whiskey, vodka, gin, and beer Figure 3(IVA). DPV recorded in the presence of KT using an e-finger depicts an oxidation signal at  $\approx + 1.5$  V that was further used for quantification as shown in the inset of Figure 3(IVB) showing a series of DPVs recorded in spiked and not treated alcoholic samples. Even though the printed device can be considered disposable, the authors proved that it is stable for up to 12 days and can be used for KT detection in the presence of buscopan, ketamidol, and depon [37]. Electroanalytical protocols for the KT detection are mostly focused on body fluids Table S1. Since many working protocols were already developed, their validation in the soft and hard drinks seems to be an intuitive direction.

### 2.3. New Psychoactive Substances

New Psychoactive Substances (NPS) are drugs that are frequently referred to as *legal highs* or *legal drugs*. NPSs encompass a broad list of chemical structures, including synthetic cannabinoids, fentanyl analogs, synthetic cathinones, tryptamines, and others. These substances often elicit psychoactive effects akin to well-known illicit drugs such as cannabis, ecstasy, and LSD. Many of the NPSs are used directly as DRD or are added to the illicit drug formulations. Regarding the use of electrochemical techniques for detecting NPSs, there is a limited number of literature reports, indicating significant potential for expansion in this area. Those available have been thoroughly analyzed and are incorporated into Tables 1 and S1. Among these publications, only one focuses on detecting morphine in beverages (milk and coffee)[55]. The remaining studies center around determining substances in model samples[56], artificial or spiked human body fluids (such as serum[57], urine[58], and plasma[59]), synthetic urine[60], street samples[61], pharmaceutical formulations[59,62], and blotting papers[63].



**Fig. 4** I. shows the platforms for the determination of morphine using (A) a patterned flash foam stamp and (B) SWCNTs three-electrode arrays on a PVDF membrane; (C) DPV plots for the detection of morphine in coffee (D) and morphine in skimmed milk samples by the SWCNTs-based sensor: a. food samples without morphine; b. morphine in the PBS buffer; c. morphine in food samples. Adopted from[55] II. Lab-on-a-Glove concept for on-site detection of fentanyl; (A) A glove equipped with an ionic liquid/MWCNT modified measuring finger and sample collector; (B) Gloved sensor with a portable electroanalyzer (C) Image showing suspicious sample collection in powder phase. (D) Joining of thumb (collector) and sensing finger after swiping a powder sample; inset shows the voltammograms of direct fentanyl detection. Adopted from[56] III. Schematic representation of the fabrication of LCE sensor for fentanyl determination. Adopted from [57].

While the focus of this work is on the electrochemical analysis of psychoactive substances in beverages, this chapter will also discuss the electroanalysis of NPSs which are considered DRDs. In 2022, Yang *et al.* devised a straightforward filtration method for the scalable production of disposable single-walled carbon nanotubes (SWCNTs)-based antifouling electrochemical sensors for detecting morphine in unprocessed coffee and milk[55]. The sensor manufacturing process involved multiple steps. Initially, electrode templates were printed on kraft paper using a standard office printer. Subsequently, the template was secured in a glass clamp alongside a fresh stamp made of photosensitive

foam and exposed to UV light in a flash stamping machine. The resulting stencil, with distinct patterns (see Figure 4 IA), underwent treatment with a polydimethylsiloxane (PDMS) prepolymer solution to imprint the patterns under pressure onto a polyvinylidene fluoride (PVDF) membrane covered with the SWCNTs (Figure 4 IB). From the entire matrix, a specific set of electrodes was cut, and sealed with PVC tape, and the reference electrode was coated with Ag/AgCl conductive paste, rendering it ready for morphine detection. A linear relationship was determined over a concentration range of 0.7 to 350  $\mu$ M and a detection limit was 0.22  $\mu$ M. In addition, the stability and reproducibility of the developed sensors were investigated, and an extensive analysis of the influence of a total of 21 potentially interfering substances and ions was carried out and showed no significant effect on the morphine-derived signal. Electrochemical experiments utilizing the newly developed sensors were carried out on both instant coffee and skimmed milk samples. Figure 4 IC, shows resulting voltammetric curves, with (a) representing the coffee sample without morphine addition, displaying a distinct strong oxidation peak at 0.13 V. Curve (b) corresponds to the PBS solution with the addition of morphine, revealing an oxidation peak at 0.33 V, while curve (c) was recorded post morphine addition to the coffee solution. Similarly, the graph in Figure 4 ID, illustrating results from electrochemical tests conducted in skimmed milk. Although the proposed protocol was successful the presence of proteins and fats necessitates the development of additional antifouling interfaces.

Very interesting is the work by Barfidokht *et al.*, [56] which addresses the rapid detection of fentanyl *in situ* with the transducing element placed on the tip of glove. The sensors was based on the flexible screen-printed carbon electrodes modified with multi-walled carbon nanotubes (MWCNT) and a room-temperature ionic liquid (IL, 4-(3-butyl-1-imidazolium)-1-butanefulfonate (Figure 4 IIA and C). The glove sensor facilitates the direct oxidation of fentanyl in both liquid (in 0.1 M PBS, pH 7.4) and powder (conducting agarose hydrogel that covers the sensing finger was used as an electrolyte) forms, achieving a detection limit of 10  $\mu$ M through the square wave voltammetry technique (SWV) (Figure 4 IID). By combining sampling on the thumb and detection on the index fingers, this integration facilitates swift screening of fentanyl, even in the presence of various cutting agents (acetaminophen, caffeine, and glucose). We are sure that this approach could find applications in soft and hard drinks analysis, especially since the



"Lab-on-a-Glove" sensor can be paired with the portable electrochemical analyzer (EmStat3 Blue) (Figure 4 IIB).

In the context of fentanyl sensing, Mishra *et al.*[57] introduced a new approach utilizing laser-induced nanoporous carbon (LCE) structures directly applied to commercially available polyimide sheets. The set-up involving a polyimide sheet, Ag/AgCl paste, and silicone used as insulation is shown in Figure 4 III. Before fentanyl determination, it was essential to clean the surfaces of the LCE electrodes with ethanol and deionized water, followed by drying with pure nitrogen. These sensors facilitated fentanyl determination through SWV, exhibiting a detection limit of 1  $\mu\text{M}$ . The measurable signal from fentanyl appeared at a potential of +0.526 V, within the clinically relevant working range of 20-200  $\mu\text{M}$ , demonstrating consistent performance in both PBS and serum samples. None of the tested potentially interfering substances (theophylline, acetaminophen, ascorbic acid, uric acid, and caffeine) significantly influenced the analyte signal.

Electroanalysis is a useful tool in the context of NPSs. Due to the relatively small number of scientific articles focused on these molecules, we can see a lot of place for improvement, especially in the detection of these substances in beverages. An asset worth highlighting is the effectiveness of the determination of psychoactive substances despite the presence of potential cutting substances. None of the review work indicated the problems related to the interfering species.

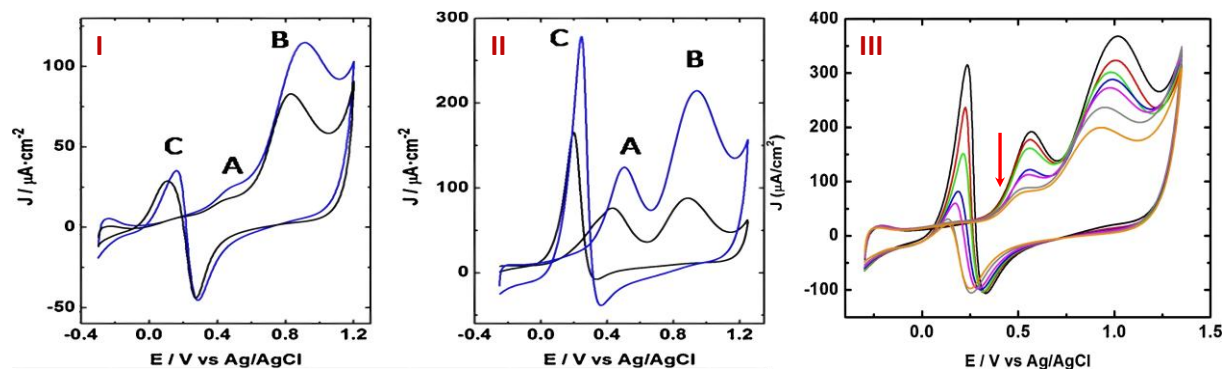
#### **2.4. Gamma( $\gamma$ )-hydroxy butyrate**

$\gamma$ -hydroxybutyrate (GHB) is an endogenous neurotransmitter mainly present in the mammalian brain. GHB is one of the most notorious DRD with quick and strong if not the quickest and strongest sedative effect through its rapid inhibition of the central nervous system [64]. The symptoms of GHB intoxication include but are not limited to amnesia, disinhibition, dizziness, memory loss, and muscle suppression and relaxation. GHB is a colorless and odourless substance completely soluble in water and alcohols making it untraceable once mixed in common drinking water or beverages. Once ingested GHB is quickly eliminated from the body with a truly short plasma half-life period of 30-50 minutes. Moreover, only  $\sim 1$ -5 % of the GHB dose can be recovered from the urine samples within 3-10 hr from its ingestion. For instance, to instigate sedative effects a drink volume of  $\sim 150$  mL must be spiked with about (and only)  $10 \text{ mg}\cdot\text{mL}^{-1}$  of GHB ( $\sim 100 \text{ mM}$ ) and the

possibility of finding a maximum dose of GBH in the urine samples of the victim for next 3-10hr is collectively equal to only  $\sim 5$  mM. This explains the analytical complexity of GHB detection [65]. To this date, complex analytical methods are used for the analysis of GHB in blood and urine samples of the victims in forensic testing. However, these are overly complex and require skilled professionals and specific technological equipment. Most importantly all these methods are developed for GHB detection post-ingestion and not to prevent GHB-induced DFC. At this trend, there are not many forensic tools available to detect GHB in suspicious samples to prevent DFC including DFSA in real-time. Furthermore, unlike other DRD discussed earlier, GHB is not electrochemically active (i.e., non-redox active) under normal conditions at carbon (and many others) electrodes and hence its electrochemical detection is seldom. The electrochemical works that do exist are focused on the electrochemical mechanistic and not analytical aspects [66–68]. So far, only one report on electroanalytical GHB sensor development was released by Rodriguez *et al.* in 2018 [69]. They have studied the electrooxidation of GHB and ethanol on a glassy carbon/platinum nanoparticles/polyvinyl alcohol (GC/PtNPs/PVA) modified electrode in a weakly acidic medium through CV and chronoamperometry. The results of CVs investigation revealed that GHB significantly suppressed the oxidation peak currents of ethanol (once added to the mixture) as both alcoholic groups of GHB and EtOH compete for the active sites of Pt according to a Langmuir-type expression. This observation supports the idea, that GHB dominates the electrocatalytic activity of Pt over other commonly active species like alcohol due to the presence of carboxylic acid group and leading to the fall of current densities of ethanol oxidation (Figure 5 III). This depression in the current density attributed to ethanol oxidation in the presence of GHB was used for the determination of GHB in the concentration range of 1 and 75 mM. The authors have evaluated the practical feasibility of the GC/PtNPs/PVA in alcoholic drinks (vodka, lemonade + vodka, gin, rum, tequila, and whisky) spiked with GHB and obtained recovery (80 -120 %) and precision for intra (RSD= 0.99 - 5.99%; n=9) and inter-assay (RSD=1.29 - 6.49%; n=3 days) meeting the standards of the presumptive analysis.

The limited reports on the electroanalytical detection of GHB (not limited to hard/soft drinks, as in any sample matrices) indicate great potential and need for research in this direction. Unlike other DRDs discussed earlier, the endogenous nature of GHB made its ingestion indistinguishable during forensic analysis of biosamples retrieved from DFC victims including DFSA. Therefore, analytical tools that can be used to detect GHB in food

and drinks on-site are crucial. At present, colorimetric sensors emerging as a promising tool for on-site screening of GHB are not suitable for colored beverages. As such, platforms that enable rapid on-site screening of GHB in food and drinks require major research focus to prevent GHB-associated DFC.



**Figure 5:** CVs of **I.** GHB, **II.** EtOH, and **III.** GHB in whisky samples. Reproduced from [69].

### 3. Other significant reports.

Some specific design principles and significant analytical performance towards electroanalytical DRD sensing falling beyond the applied classification are worth special attention.

For instance, differential pulse adsorptive cathodic stripping voltammetry (PDAdCSV) of BDZ on hanging mercury drop electrode (HMDE) has shown a great potential towards BDZ (ALZ [28], CNZ, and DIZ [29]) detection in water samples. The technique delivered impressive analytical parameters such as high sensitivity, wide dynamic range, low LOD, LOQ, and high recoveries. Despite all its analytical merits the technique was not popularized due to its inherent downsides such as larger size, complicated electronics and mechanics for precise drop generation, and the use of toxic mercury [70]. These irreparable shortfalls of HMDE eventually halt its opportunities to be an alternative electroanalytical platform for DRD sensing.

Similarly, Karolien *et al.* reported a readily available disposable SPE modified with sodium dodecyl sulfate (SDS) for electrochemical detection of multiple DRD (cocaine, heroin, MDMA, Cl-PVP, and KT) in oral fluids. The simple SDS modification significantly magnifies the analytical signals by 3 to 6 folds, and delivers high accuracy (RSD 1.8 - 5.3 %)[71]. This work presented the use of a surfactant-mediated solution as potent modifier for the electrocatalytic detection of DRD over renowned nanocomposites. A few significant

reports of electrochemical DRD sensors studied non-beverage matrices are surveyed and presented as Table S1 in the supporting information.

#### 4. Challenges and Future perspectives

This article summarizes recent progress in the development of electrochemical sensors to detect DRD in soft and hard drink samples. The core challenges identified for the given topic cover: 1. Analytical complexity of the real samples. 2. Complex testing procedures and site of investigation. 3. Sensing units and components that should be cheap, portable, disposable, miniaturized, and display high precision and reliability. 4. Electroanalysis of GHB, morphine, and new psychoactive substances in hard and soft drinks samples.

The electroanalytical complexity of DRD in beverage samples is obvious citing the chemical composition of various drink samples including but not limited to sugars, flavoring agents, amino acids, vitamins, proteins, alkaloids, food colors, alcohol, etc. Much of these co-existing species are electroactive and pose interfering electrochemical signals, and/or cause electrode fouling that promptly reduces electrocatalytic behaviour of the sensor towards target DRD. Resolving these obstacles leads us to challenge 2 which mandates complex pre-sampling procedures. Even though there are reports on the simple use of SPCE and activated GCE towards DRD sensing without any sample pretreatments these reports are not very successful and are compromised by chemical interference or surface fouling. On the other hand, the complex sampling procedures are not suitable for on-site screening of DRD in beverage samples supplied in public gatherings, partying, bars, etc. which are the common spots of DRD spiking. Resolving these issues needs an innovative design of electrochemical systems that minimize sample volume, sampling steps, and the sample preparation time. The ultimate goal is to offer a design that can be used in a plug-and-play manner. Initial reports on the wearable e-finger multidrug sensor (FNZ, KT, and SCO), the wearable glove-based sensor for detecting fentanyl, or other disposable and miniaturized drop volume sensors printed/scribed on various substrates (for BDZ, KT, fentanyl) discussed in this article seems to be seminal in this respect.

To our surprise the knowledge gap on the electroanalytical behavior of GHB, morphine, fentanyl and other NPS in beverage samples is obvious and requires further effect. This lack of information is due to the combination of all three obstacles discussed earlier as these substances possess significant analytical complexity thanks to their chemical and

electrochemical behavior. Therefore, there is an immense need and scope for the design of novel electroanalytical platforms that resolve the obstacles in analytical principles, operational methods, and fabrication techniques to enable the rapid determination of these substances in various samples associated with DRD. Finally, the massive profiling of the beverage's electroanalytical response on a variety of transducing elements would provide a large amount of data that could be used for the presumptive detection of DRD, as the simple electrochemical profile of the real sample in the presence and in the absence of the drug could be treated as the analytical information. A comprehensive summary on the existing electroanalytical methodologies, its analytical milestones, limitations, and possible remedies directing at future perspectives in rapid on-site detection of DRD in beverages are listed and presented as Table 2.

## 5. Conclusions

This review presents recent progress in the design and development of electroanalytical platforms towards rapid on-site screening of date-rape-drugs (DRD) in beverage samples. This field attracted the attention of scientists only in the last decade. We have found that bio samples, pharmaceutical formulations, and formulated street samples are the most studied real-samples covering about 68% of all published reports. Around 22% of the works evaluated the utility of the electroanalytical sensing solutions for DRD detection in spiked beverages. Benzodiazepines top the list of the most studied DRD when it comes to the overall number of reports and beverage analyses. Successively, this review staged a critical analysis of the design fabrication and analytical performance of existing electroanalytical DRD sensors. We guide the reader through the common protocols employing screen-printed electrodes to advanced solutions that are based on the lab-on-chip, glove, and e-finger technology. Many published reports offer ready-to-use protocols with high sensitivity, analytical reliability, and reproducibility. The exponential growth in the development of DRD sensors over the past decade is not distributed equally as we underlined a serious lack of research attention toward the design of electroanalytical platforms that have the potential to study new psychoactive substances and gamma-hydroxy butyrate in beverage samples. In essence, this review illustrates periodical progress in the current state-of-art electrochemical sensors reported for rapid screening of DRD in beverage samples but also highlights the existence of a knowledge gap in certain areas to build a course for future advancements in the field.

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583 (descriptions about fentanyl).

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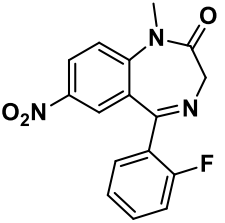
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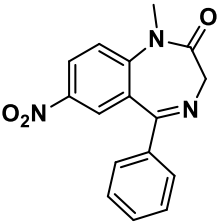
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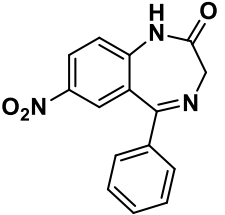
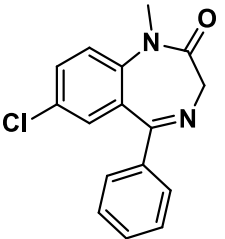
864 **Table 1:** Analytical performances of the reported electrochemical date and rape sensors studied at beverage matrix.

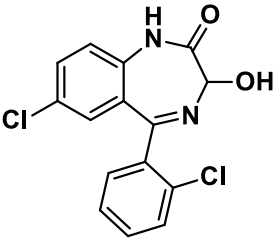
Date and Rape Drug	Technique	Signal Transducer	Detection Condition	LDR	LOD	Tested Interferons	Tested Real samples	Ref.	Comments
<b>Flunitrazepam/ Rohypnol</b> 	DPV	GOx/GluHD-FeSPCE	Reduction $E_p = -0.58$ V 0.1 M PBS pH 7.0	0.05 – 10 $\mu$ M	0.015 $\mu$ M	Dissolved oxygen	Pepsi cola, Gin, Vodka, Whisky, Tequila, Rum	[30]	A First-of-kind enzymatic transducer based SPCE is proposed.
	DPV	Wearable printed electrochemical finger (e-finger)	Reduction $aE_p = -0.93$ V 0.1 M PB pH 7.4	6.3 – 51 $\mu$ M	0.2 – 0.3 $\mu$ M	Buscopan, Ketamidol, Depon	Whiskey, Gin Vodka, Beer.	[37]	(i) 3D-printed wearable device for on-the-spot self-checking and onsite forensic investigation.
	DPV	TiO <sub>2</sub> @CuO-N-rGO/poly (L-Cys)/GCE	Oxidation $E_p = +0.65$ V	1 nM – 50 $\mu$ M	0.3 nM	Sodium, iron, chloride, sulfate,	Tourtel Malt, Pepsi Cola	[36]	S: 0.288 $\mu$ A $\mu$ M <sup>-1</sup>

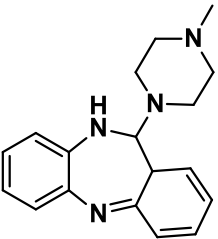


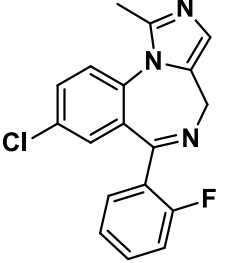
			0.04 M BRB pH 3.0			nitrate, citric acid, sucrose, fructose, dopamine, and uric acid			
	DPV	AGO-Cu/SPCE	Oxidation $E_p = +0.25$ V 0.04 M BRB pH 7.0	0.4–140 $\mu$ M	0.13 $\mu$ M	$\text{Na}^+$ , $\text{Cl}^-$ , $\text{Mg}^{2+}$ , $\text{Ca}^{2+}$ , $\text{NO}_3^-$ , $\text{PO}_4^{3-}$ , $\text{NH}_4^+$ , $\text{Fe}^{2+}$ and $\text{CO}_3^{2-}$	Fruit juice	[31]	S: 0.405 $\mu\text{A } \mu\text{M}^{-1}$
	CV	SPCE	Reduction $E_p = -0.85$ V 4 M KCl	7.9 – 79.8 $\mu$ M	1.8 – 14.6 $\mu$ M	GHB, Ketamine, and Scopolamine.	Whiskey, Vodka, and Gin.	[44]	LOQ: 1.7- 3.5 S: 0.142 $\mu\text{A } \mu\text{M}^{-1}$
<b>Clonazepam</b> 	DPV	CoOOH-rGO /GCE	Reduction $E_p = +0.11$ V 0.005 M $\text{K}_3\text{Fe}(\text{CN})_6^{3-/4-}$ PBS pH 7.4	0.1–350 $\mu$ M	38 nM	L-cysteine, uric acid, urea, glucose, ascorbic acid,	Juice, cola, beer, wine	[33]	S: 0.054 $\mu\text{A } \mu\text{M}^{-1}$

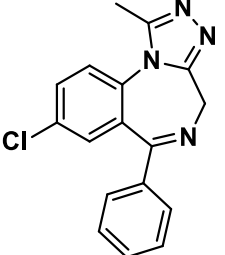
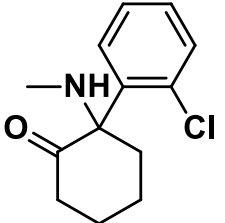
						Na <sup>+</sup> , K <sup>+</sup> , and SO <sub>4</sub> <sup>2-</sup>			
	ASV	C10903P14 ink/SPCE	Oxidation  E <sub>p</sub> = -1.5V, 60s  10% EtOH in 0.1 M PB  pH 7.0	6.5 – 25.5 μM	6.2 μM	Not studied	Wine	[38]	S: 6.9 nA μM <sup>-1</sup>
	AdCSV	EP-GCE	Reduction  E <sub>p</sub> = -0.56 V  0.1 M PB  pH 7.0	79.8 nM – 4.7 μM	60 nM	Not studied	Full Moon, Smirnoff and drinking water	[39]	LOQ: 0.199 μM S: 10.04 μA μM <sup>-1</sup>
	PDA CSV	HMDE	Reduction  E <sub>p</sub> = -0.41 V  0.1M PB  pH 8.0	2.0 – 47.88 nM	0.6 nM	Not studied	Natural water		S: 0.045 nA nM <sup>-1</sup>

<b>Nitrazepam</b> 	AdSV	SPCE	Oxidation $E_p = -0.1$ V 10% EtOH in 0.1M PB pH 7.0	50.1 - 600 $\mu$ M	6.3 $\mu$ M	Aspirin, gamma-butyrolactone, and Paracetamol	Pepsi Max, Vodka Kick Ice Cherry, Absinthe, brandy.	[34]	S: 15.2 nA $\mu$ M <sup>-1</sup>
<b>Diazepam</b> 	DPV	GO/lysine/GCE	Reduction $E_p = -0.86$ V 0.1M PB pH 7.0	0.17–50 mM	0.046 mM	Glucose, Uric acid, and Nitrazepam.	Juice, cola, whisky, wine	[41]	LOQ:156 nM S: 0.209 $\mu$ A $\mu$ M <sup>-1</sup>
	ASV-DPV	SPCE	Oxidation $E_p = +1.0$ V 10% EtOH in 0.1 M PB pH 6.0	24.9 – 1000 mM	6.3 mM	Aspartame Ascorbic acid, Citric acid, and Paracetamol.	PepsiMax, Vodka Cherry alcopop	[40]	S: 7.4 nA $\mu$ M <sup>-1</sup>

	SWV	PEI-LSG	Reduction $E_p = -1.15$ V 0.1M BRB pH 4.0	2.5 – 25 – 100 $\mu$ M	0.66 $\mu$ M	Glucose, Ascorbic acid, Citric acid, 20% Ethanol (v/v), MDMA, and Midazolam	Juice, whisky, Cachaça	[25]	LOQ: 2.18 $\mu$ M  S: 0.20 $\mu$ A $\mu$ M <sup>-1</sup>
	PDAdCSV	HMDE	Reduction $E_p = -0.87$ V 0.1M PB pH 6.0	0.94 – 70 nM	0.28 nM	Not studied	Natural water	[29]	S: 0.013 nA nM <sup>-1</sup>
<b>Lorazepam</b>  	DPV	MMWCNTs/PGE/HF	Oxidation $E_p = +0.3$ V 0.1M PB pH 6.0	0.032 – 64 $\mu$ M	0.003 $\mu$ M	Ascorbic acid, glucose, urea, and uric acid.	Water, Urine, Hair	[42]	LOQ: 0.06 $\mu$ M  S: 1.7 $\mu$ A nM <sup>-1</sup>

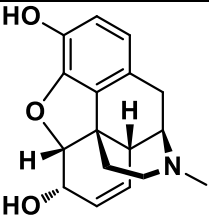
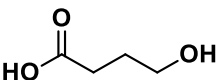
	SWV	NiO/SWCNTs/CPE	Oxidation $E_p = \sim +0.94$ V 0.1M PB pH 7.0	0.1–280 $\mu$ M	50 nM	Not studied	Drinking water	[43]	S: $0.371 \mu\text{A } \mu\text{M}^{-1}$
<b><i>Clozapine</i></b> 	ITV	eLLI	Ion transfer $E_p = \sim +0.475$ V 10mM NaCl 10mM HCl 5mM BTPPATPBCl	15 – 150 $\mu$ M	1 $\mu$ M	Not studied	apple juice, vodka, vodka + apple juice, wine, and beer	[45]	First report on the use of eLLI to screen BDZ in beverage samples.
<b><i>Midazolam</i></b>	SWV	PEI-LSG	Reduction $E_p = -1.05$ V 0.1M BRB pH 4.0	2.5 – 25 – 100 $\mu$ M	0.61 $\mu$ M	Glucose, Ascorbic acid, Citric acid, 20% Ethanol (v/v),	Juice, whisky, Cachaça.	[25]	LOQ: 2.01 $\mu$ M S: $0.094 \mu\text{A } \mu\text{M}^{-1}$

						MDMA, and Diazepam			
	SWV	ePADs	Reduction $E_p = -0.82$ V 0.1M PBS pH 3.5	7.6 – 460.4 $\mu$ M	6.1 $\mu$ M	Citrate, lactose, Citric acid, PEG 6000	Water, Beer, liquor, vodka.	[26]	A reusable microelectrode array fabrication is demonstrated
	DPV	BDDE	Oxidation $E_p = +1.7$ V 0.1M BRB pH 4.0	4 – 25 $\mu$ M 1 – 10 $\mu$ M 1 – 15 $\mu$ M	0.46 $\mu$ M 0.43 $\mu$ M 0.33 $\mu$ M	Clonazepam Flunitrazepam, and Diazepam	Vodka, Whiskey, Red wine.	[32]	S: 0.038 $\mu$ A $\mu$ M <sup>-1</sup> S: 0.116 $\mu$ A $\mu$ M <sup>-1</sup> S: 0.065 $\mu$ A $\mu$ M <sup>-1</sup>
<b>Alprazolam</b>	PDAdCSV	HMDE	Reduction $E_p = -0.95$ V 0.1M PB pH 7.0	1.6 – 323.8 nM	0.22 nM	Humic acids, Cu <sup>2+</sup> , Zn <sup>2+</sup> , Fe <sup>3+</sup> lorazepam, clonazepam, and diazepam.	Water	[28]	LOQ: 1.3 nM S: 0.017 nA nM <sup>-1</sup>

									
<b>Ketamine</b> 	CV	nanocrystal Zeo-GO E $\mu$ PAD	Oxidation $E_p = +1.5$ V 50 mM SPB, pH 7.0	0.001 – 5 $\mu$ M	1 nM	glucose, fructose, maltose, AA, hydrocortisone, gentamycine, $K^+$ , $Na^+$ , $Cu^{2+}$ , $Ni^{2+}$ , $Fe^{3+}$	Whiskey, Orange juice, Urine	[53]	This work report paper based microfluidic device for the detection of Ketamine.
	DPV	Wearable 3D- printed electrochemical finger (e-finger)	Oxidation $E_p \approx +1.53$ V 0.2 mol·L <sup>-1</sup> H <sub>2</sub> SO <sub>4</sub>	0.5 – 4 mM	0.18 mM	Buscopan, Ketamidol, Depon	whiskey, vodka, gin, beer	[37]	(i) 3D-printed wearable device for on-the-spot self-checking and onsite forensic investigation.

	Potentiometry	Carbon-SPE/PANI/ ISM(MIP)	Double junction Ag/AgCl, 10mM PB pH 4.0	1.0 $\mu\text{M}$ - 10 mM	0.929 $\mu\text{M}$	Na <sup>+</sup> , K <sup>+</sup> , Ca <sup>2+</sup> , Mg <sup>2+</sup> , Zn <sup>2+</sup> , Quetiapine	non- alcoholic beverages (juices), plasma, urine	[54]	Sensor follows IUPAC guidelines, Nernstian slope: 54.7 mV/decade LOQ: 1.0 $\mu\text{M}$
	ECL	GCE	Oxidation  E <sub>p</sub> = +1.1 V  1 mM acetate buffer, pH 4	0.21 - 8.41 $\mu\text{M}$	0.14 $\mu\text{M}$	ketamine	alcoholic beverage (Gordon's Gin & Tonic)	[52]	ECL has been used for the first time for the electroanalytical detection of Ketamine.
<b>Morphine</b>	DPV	SWCNTs/GCE	Oxidation  E <sub>p</sub> = +0.35 V  10 M PBS pH 7.4	0.7 - 350 $\mu\text{M}$	0.22 $\mu\text{M}$	ascorbic acid, dopamine, aspirin, acetaminophen, tetracycline, phenylalanine, valine, citric	Milk, coffee	[55]	This is the only report that studied Morphine spiked in beverage samples.



						acid, salicylic acid, niacin NaNO <sub>3</sub> , glucose, fructose, xylose, ribose, galactose, Cl <sup>-</sup> , CO <sub>3</sub> <sup>2-</sup> , SO <sub>4</sub> <sup>2-</sup> , Ca <sup>2+</sup> , Mg <sup>2+</sup>			
<b>GHB</b> 	CV+ CA	PtNPs-PVA/GC	Oxidation E <sub>p</sub> = +0.90 V 0.1M PA pH 4.0	1 – 75 mM	0.872 mM	Ethanol	lemonade, lemonade+ Vodka, Vodka, Whisky, Rum, Tequila, Gin	[69]	This is the only electroanalytical report that studied GHB spiked in alcoholic beverages.

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866 LDR- Liner detection range, LOD-Limit of detection, LOQ- Limit of quantification, S-Sensitivity, GCE-Glassy carbon electrode, EPGCE-  
867 Electrochemically pretreated glassy carbon electrode, SPCE/SPE- Screen printed carbon electrode, SPGE- Screen printed graphite electrode  
868 GC-Carbon sheet, CPE-Carbon Paste electrode, CoOOH-rGO: Cobalt oxyhydroxide nanoflakes/reduced graphene oxide, PEI-LSG: Laser-  
869 scribing graphene/polyetherimide, ePADs- Electrochemical paper-based analytical device, CFVE- carbon fibre veil electrode, LC-DED:

870 liquid chromatography dual electrode detection, PVA-Polyvinyl alcohol, PtNPs-Platinum nanoparticles, SWCNTs-Single walled Carbon  
871 nanotubes, MWCNTs- Multi walled Carbon nanotubes, NiO-Nickel Oxide, GHB- gamma-hydroxybutyric acid, GOx/GluHD-FeSPCE- glucose  
872 oxidase (GOx)/ glucose hydrogel droplets (GluHD)/ Iron-spark Screen printed carbon electrode (FeSPCE), AdSV/ASV- Adsorption Stripping  
873 Voltammetry, DPV- Differential pulse voltammetry, HDV- Hydrodynamic voltammetry, SWV- Square Wave Voltammetry, CA-  
874 Chronoamperometry, PDAdsCSV - Differential pulse adsorptive cathodic stripping voltammetry, HMDE : hanging mercury drop electrode,  
875 BDDE: boron-doped diamond electrode, MDMA: 3,4-Methylenedioxymethamphetamine, nanocrystal Zeo-GO E $\mu$ PAD: nanocrystals of  
876 zeolites (Zeo) and graphene oxide (GO) nanoflakes integrated electrochemical micro fluidic paper-based analytical device (E $\mu$ PAD),  
877 MIM/GCE- molecular imprinted membrane modified glassy carbon electrode, ECL: electrochemiluminescence, PANI- polyaniline.  
878 BTPPATBPCl- 1,1,1-triphenyl-N-(triphenylphosphoranylidene)phosphoraniminium tetrakis(4-chlorophenyl)borate; E<sub>p</sub>: Electrode  
879 potential against standard Ag/AgCl electrode in Sat. KCl or 3M KCl. <sup>a</sup>E<sub>p</sub>: Electrode potential against carbon black reference electrode <sup>b</sup>E<sub>p</sub>:  
880 Electrode potential against Ag ink pseudo reference electrode.

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888 **Table 2:** Electroanalytical solutions reported for rapid detection of DRD in beverages: milestones, limitations, and future perspectives.

DRD	Existing electroanalytical probes	Methodological milestone	Key electroanalytical limitations.	Future direction
<i>Benzodiazepines</i>	Bare and modified SPCE, GCE, BDDE, and 3D printed electrodes.	The wearable e-Finger[37] and LSG-PEI[25] based multi drug sensors are a promising to provide a comprehensive electroanalytical solutions for BDZ sensing.	<ol style="list-style-type: none"> <li>1. Electrochemical interference of coexisting species from sample matrix.</li> <li>2. Surface passivation.</li> <li>3. Electrode fouling.</li> </ol>	<ol style="list-style-type: none"> <li>1. Efficient modifiers to minimize surface passivation, electrode fouling, and chemical interference.</li> <li>2. A comprehensive electrochemical profile of sensing media has to be developed.</li> </ol>
<i>Ketamine</i>	Printed and modified carbon electrodes, GCE and ECL probes.	Paper based EμPAD[53] and wearable e-Finger[37] are the promising tools for comprehensive	<ol style="list-style-type: none"> <li>1. The electroanalytical signals of KT at EμPAD are not refined to meet the standards for on-site screening of KT in beverage samples.</li> </ol>	<ol style="list-style-type: none"> <li>1. The fabrication methodologies and electrode modification strategies has to be improved to obtain refined electroanalytical signal for KT to improve the analytical</li> </ol>

		detection of ketamine in beverage samples.		reliability of the future sensing solutions.
<b><i>New psychoactive substances</i></b>	Printed and modified carbon electrodes.	Flash printed carbon electrode to detect morphine[55] in milk and Lab-on-glove to screen fentanyl[56] in street samples are promising analytical tools for NPS screening.	1. Undefined toxicological and electrochemical behaviour of various NPS.	1. A comprehensive electrochemical study on the electrochemical behaviour of various NPS has to be studied documented to be used for analytical references.
<b><i>Gamma hydroxy butyrate</i></b>	Modified GCE	GC/PtNPs/PVA is the sole report of GHB[69] detection in alcoholic medium.	1. Poor electrochemical behaviour of GHB. 2. Limited resources on electrochemical behaviour of GHB in various mediums.	1. The research to explore the electrochemical behaviour of GHB at modified/ fabricated electrodes has to be amplified to maximize the sensitivity of GHB redox reactions. 2. The electrochemical profile of

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				GHB at various sensing mediums (including non-alcoholic) has to be studied.
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