BJPS

Brazilian Journal of
Pharmaceutical Sciences

http://dx.doi.org/10.1590/s2175-97902023e20555

Article

Immunochromatography screening devices for cannabinoids in oral fluid sample

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Cannabis sativaL. is one of the most consumed drugs in the world and recent studies have associated its use with an increase in the number of traffic accidents in different countries. In many countries, like Brazil, simple and reliable methodologies are still needed for the detection of drugs on site, mainly cannabinoids, considering its prevalence of use and oral fluid (OF) has been proved as an appropriate biological matrix for this purpose. Considering that, this work aims to review previous studies on immunochromatographic devices for on-site detection of cannabinoids in OF, discussing their sensitivity, specificity, cut-offs values and confirmatory methods. This data shows the importance of choosing a screening device and it reinforces the need for its implementation in Brazil. The research was conducted on 5 databases and all original articles, published in the last 10 years, were selected. A total of 32 articles were found, providing data for 17 screening devices of distinct brands. Only 2 screening devices showed satisfactory sensitivity and specificity in the evaluated studies (≥80% and ≥90% respectively). However, it should be considered that the screening devices still have some limitations, such as a higher cut-off than those recommended by international guidelines (cut-off > 2 ng/mL), therefore demonstrating the need for more studies in the area and the importance of confirmatory analysis usually fulfilled by LC-MS/MS, GC-MS/MS or GC-MS. Thus, the screening analyzes should not be evaluated by itself, but in association with confirmatory results and observational traits (behavioral changes), for a better understanding of the traffic scenario.

Keywords: Screening devices. Drug test. Traffic accidents. Oral fluid. Cannabinoids. THC.

INTRODUCTION

Traffic accidents (TA) are considered a major public health problem, at the expenses of approximately 3% of the national Gross Domestic Product (GDP) in most countries (WHO, 2020; WHO, 2018). Among the factors that contribute to the statistics are fatigue, speeding and the consumption of alcohol and/or drugs abuse, followed by negligence of safety devices (Leyton *et al*., 2012; WHO, 2018). The legal framework that regulates the use of psychoactive substances (PSs) varies according to the social, legal and economic characteristics of each country, so it is not clear what are the acceptable limits in biological samples from motor vehicle drivers (Herrera-Gómez *et al*., 2018). In Brazil, driving under the influence of alcohol and other PSs is not allowed (Brasil, 2006); however, the legislation does not clarify which are the PSs and does not recommend ways of monitoring them as well as it does not establish acceptable limits – or levels – of PSs in a biological sample (Pechansky *et al*., 2019; Saldanha *et al*., 2014).

Cannabis is the second most consumed drug in the world (Callaghan *et al*., 2013; Perna *et al*., 2016). Cannabinoids are also among the most detected psychoactive substances (PSs) in drivers (Berning, Compton, Wochinger, 2015; Fierro *et al*., 2014; Hartman *et al*., 2015). The cannabinoid Δ^9-tetrahydrocannabinol

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(THC) is the mainly PS present in cannabis samples and is often detected in biological samples from drivers approached in police roadblocks and in drivers involved in TA with minor injuries and/or fatal victims (Lee, Huestis, 2014; Volkow *et al*., 2014). Cannabis exposure affects the ability to drive by promoting changes in perception and in the reaction time, altering the state of attention and compromising the motor skills of individuals (Hartman, Huestis, 2013). Considering the Brazilian traffic scenario and the constant discussion about the legalization and/or decriminalization of cannabis(CEE - FIOCRUZ, 2016; FIOCRUZ, 2013; Moreira *et al*., 2016), it becomes evident the need for simple and reliable methodologies that allow its detection in biological samples of vehicle drivers, as well as the implementation of more specific laws (Pelição *et al*., 2016; Saldanha *et al*., 2014).

Among the biological matrices used for screening analysis of PSs, oral fluid (OF) stands out as a biological sample that has been achieving more space in routine analyzes in Toxicology, specially related to DUID (Driving Under the Influence of Drugs) scenarios. Due to its numerous advantages, OF has shown to be a promising matrix for on-site testing (Gentili *et al*., 2016). OF collection is easy and non-invasive, it can be performed under police supervision, without embarrassment to the driver, and its analysis provides a good correlation with blood, considering the recent use of several classes of PSs (Fiorentin *et al*., 2017; Gentili *et al*., 2016; Logan, Mohr, Talpins, 2014). Furthermore, OF can also be used for subsequent confirmatory analyzes, thus samples for both screening and confirmation can be collected at the same time, increasing the chances of consistent results. However, OF collection can be affected by some factors such as decreased salivary flow and dry mouth, attributed to lack of hydration or drug use (Logan, Mohr, Talpins, 2014).

The most common on-site screening devices chosen by several countries for the detection of cannabis, and other PSs, are usually immunochromatography tests. In general, these assays consist of collection pads attached to porous membrane strips, which are inserted into the donor's mouth. From the swab (pad), the OF migrates by capillarity, mobilizing the reservoir of colored antibodies that flow with the OF along the strip until the lines with the immobilized PSs are reached. In the presence of a positive sample for any PS in the cut-off concentration of the multi-drug device or above it, the binding sites of the respective colored antibody saturate and do not bind to the drug immobilized on the band (Souza *et al*., 2012). However, it is important to note that even with efficient screening devices for on-site use, the need for confirmatory analysis of the suspected drivers OF sample is not ruled out, considering that some devices still demonstrate a lack of specificity (≥ 90%) and of sensitivity (≥ 80%) for Δ^9-THC (Blencowe *et al*., 2011; Musshoff *et al*., 2014; Strano-Rossi *et al*., 2012). International guidelines suggest a cut-off value of 2 ng/mL for confirmatory tests, while they recommend the value of 4 ng/mL for screening tests (Department of Health and Human Services, 2019; Walsh *et al*., 2008).

Considering that cannabis is among the main PSs related to TA in Brazil (DeBoni *et al*., 2014; Pelição *et al*., 2016; Saldanha *et al*., 2014), and that there is a need for a screening tool implementation in this country, this article aims to review previous studies regarding immunochromatographic devices for cannabinoids detection, focusing on its main advantages and disadvantages.

MATERIAL AND METHODS

Our research strategy involved a comprehensive systematic review in the following databases: PubMed, Google Scholar, Science Direct, Scopus and Science.gov. The descriptor used for databases was "*cannabis or cannabinoids and oral fluid detection*". The search was conducted in February 2020. Four independent researchers conducted the review, using the following inclusion criteria: a) original studies for immunochromatographic *in loco* devices, for cannabis detection in oral fluid; b) articles published in the last ten years (2010-2020), in order to present a recent panel of studies. Studies that do not include oral fluid as a biological matrix were excluded, as well as different types of screening tests. These studies could either include drivers or not, as long as it evaluated immunochromatographic screening test for cannabinoids in oral fluid.

Figure 1 shows the results for the systematic review. The initial search retrieved 92 non-repeated articles from the total (Google Scholar – 18.000; PubMed – 134; Science Direct – 153; Scopus – 141; Science.gov – 280) and, after a detailed analysis, 32 papers met the inclusion criteria. Other studies that include guidelines and laws were only included in the discussion.

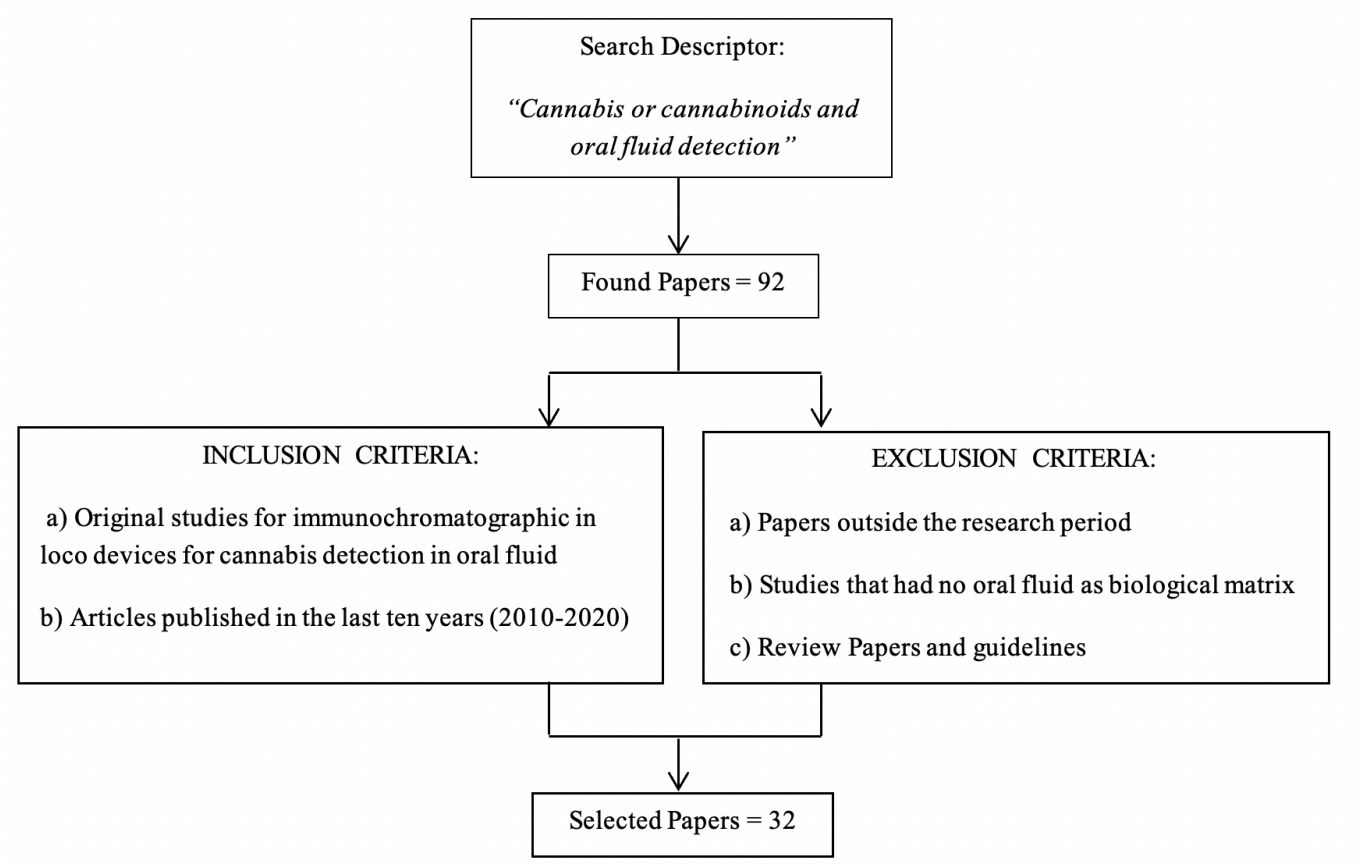

FIGURE 1 - Strategy used in the research of articles for review.

RESULTS AND DISCUSSION

Among the 32 selected articles, some studies used a device to collect the sample and other device to analyze it, while others use the same for both collection and analysis. The screening devices are multi-drug detection tests; however, only the detection of cannabinoids was approached in this review. All 32 studies evaluated the cannabinoid THC, the major psychoactive cannabis component, for drug detection, but Anzillotti *et al.*,(2014) and Newmeyer *et al.*,(2017) also included more cannabinoids, like cannabidiol (CBD), cannabinol (CBN), 11-Nor-9-carboxy-Δ^9-tetrahydrocannabinol (11-THCOOH), Tetrahydrocannabivarin (THCV) and cannabigerol (CBG). Table I compiles the review results, considering the detected cannabinoids, the analyzed devices, and the confirmatory methods. Also, the cut-offs and the tests parameters, such as specificity and sensibility, are shown.

TABLE I - Equations used to evaluate the parameters examined to evaluate the screening devices

Parameters	Equation
Sensitivity	$ST = \frac{TP}{TP + FN}$
Specificity	$SE = \frac{TN}{TN + FP}$
Efficiency	$Eff = \frac{TP + TN}{TP + TN + FP + FN}$
Positive Predicative Value	$PPV = \frac{ST\ x\ Prev}{ST\ x\ Prev + (1 - ST)(1 - Prev)}$
Negative Predicative Value	$PPN = \frac{SE\ (1 - Prev)}{SE(1 - Prev) + (1 - ST)}$
Prevalence	$Prev = \frac{TP + FN}{NS}$

Sensitivity (ST), Specificity (SE), Efficiency (Eff), True Positive (TP), True Negatives (TN), False Negative (FN), False Positives (FP), Prevalence (prev). Adapted from (Blencowe *et al*., 2010)DRUID 2010.

Sixteen different devices, from distinct manufacturers, were evaluated in these studies. However, some of their brands have different presentations of drug tests. For example, Dräger® brand has four test devices (Drug Test 5000, DCH 5000, DCD 5000, 5000 STK) and DrugWipe® brand have six types of devices (5/5+, 5A, 5, 5+, II Twin, 6S). DrägerDrugTest®5000 is the most used device in the studies – also presenting the lowest cut-off (5 ng/mL) –, followed by DrugWipe®, with a cut-off at 30 ng/mL, and Alere DDS2, with a 25 ng/mL cut-off. For confirmatory methods in OF, Walsh *et al.* (2008) recommends a cut-off of 2 ng/mL for the analysis of cannabinoids, but they do not mention any screening devices(Walsh *et al.*, 2008). Thus, from all studied brands, Dräger DrugTest® 5000 presents the cut-off (5 ng/mL) which is closer to the limit recommended by the current guidelines (2 ng/mL).

Based on the review, the only two screening devices that showed good sensitivity and specificity were Dräger DrugTest®5000 (DDT5000) and Alere™ DDS®2 (DDS2). For Dräger DrugTest®5000, sensitivity and specificity ranged from 76-95% and 71-99.3%, respectively, in the studies. As for Alere™ DDS®2 screening device, the sensitivity varied from 75-100% and the specificity ranged from 80-100%.However, these two devices present a higher cut-off than the recommended the aforementioned guides, and the DDT5000 has the closest value (5 ng/mL), followed by DDS2 (25 ng/mL).

Even after a decade of action for road safety, which it has started in 2011, the American region continues to record approximately 155.000 traffic deaths per year (ONU, 2019a). Brazil had an estimated traffic mortality rate of 19.7 per 100.000 inhabitants, which is higher than the rate in the entire South America continent (15.6) and the average rate in the Southern Cone (18.4) (ONU, 2019b). Although Brazil has managed to reduce the number of deaths in traffic, the country still registers a high number of victims with minor and serious injuries, and this is relative to different factors, including the use of alcohol and/or drugs.

Brazilian Law 11.343/2006 (Brasil, 2006) prohibits drug use, its cultivation and/or distribution, and also differentiates drug use and drug trafficking, with a social approach. Likewise, it defines the severity of the crime and its penalty, but it does not specify a law on driving under drug influence. Brazilian Traffic Code (Brasil, 1997) considers forbidden the use of any PS while driving; however, it does not specify a drug concentration, as it does for alcohol use (≥6 dg/L of ethanol in blood or ≥0.3 mg/L of ethanol in alveolar air), and it does not define ways of monitoring. There is no specific regulation in Brazil for testing devices for drug detection in drivers or a regulated device registered in the national health surveillance agency.

While in other countries drug screening is already performed on roadsides (EMCDDA, 2012), in Brazil there are still no screening tests available for routine monitoring in DUID scenarios, to help prevent TA. Since *Cannabis sativa L*. is the second most consumed drug in Brazil and in the world, along with its relation to TA (Callaghan *et al*., 2013; Perna *et al*., 2016), it should be considered a priority for drug screening, besides alcohol. Thus, recently, the *Cannabis* product cannabidiol (CBD) has been authorized as a controlled substance for therapeutic purposes in Brazil, and any product of *Cannabis* must not exceed the maximum concentration of 30 mg/mL of Δ^9-THC and 30 mg/mL of CBD, considering health recommendations(ANVISA, 2019). Since driving under the influence of cannabis is an expressive risk factors that contribute to TA, the legalization of cannabis, even for medical and very punctual purposes, can be a risk on the road, demonstrating the importance of the understanding how sensitive, specific and accurate are the methods available in the market that make it possible to monitor the driver's impairment.

Compared to other biological matrices, OF is an advantageous matrix for on-site analysis. Due to the practicality of collection, donor acceptability and the non-invasive collection method (Anizan *et al*., 2015), OF has become increasingly popular in drug testing programs, mainly in the investigation of DUID (Newmeyer *et al*., 2014). Since the collection can be assisted by law enforcement officers without causing embarrassment to the donor, the possibility of adulteration of the matrix is reduced (Lund *et al*., 2011).

The Society of Forensic Toxicologists (SOFT/AAFS), through the guide "Oral Fluid as a Test Specimen for Roadside Studies: Guidelines for Implementing a Data Collection Program" addresses OF as a biological matrix for monitoring DUID cases, as well as the importance of the commitment of all parties in the implementation and the management of a roadside testing program. This guide also reinforces the advantages of using OF over blood, considering it the "gold standard" for alcohol and drugs detection in traffic – for instance, the possibility of sample collection and analysis onsite, without the need of a health professional,like with blood collection, and with the least possible embarrassment to the driver. Furthermore, the guide provides a brief protocol for the Oral Fluid Program, with recommended steps for the suspected drunk and/or drugged driver approach, as well as for on-site analysis, for sample collection and for sample storage, also pointing when to submit the sample for confirmatory analysis (SOFT, 2014).

It is important to point out here that the screening devices (multi-drug devices) for OF analysis are a tool that would help the police to investigate and control DUID cases *in loco* on the roads, allowing the monitoring of the use of psychoactive substances in different traffic scenarios (Gjerde *et al*., 2018). In forensic analyzes focused on the traffic scenario, the use of prohibited substances is considered a crime (HealthNewsReview.org, 2020). In order to fit in this scenario, the chosen screening device must have high sensitivity and specificity, since the main objective is to identify drivers under the effect of PS, contributing in the future to compliance with the traffic safety law (Strano-Rossi *et al*., 2012). The screening device sensitivity is the proportion of true positive OF samples that have been correctly identified (Beirness, Smith, 2017). On the other hand, the screening device specificity is the proportion of true PS negative samples that have been correctly identified (Beirness, Smith, 2017).Both are calculated using the cut-off points adopted by a DRUID study, a fact that reflects the variations observed between studies, and they are calculated according to the equations presented in Table I. In addition, in order to determine the usefulness of a screening device, the true predictive value and the negative predictive value are calculated (Table I) and both are directly dependent on the PS prevalence in the

studied population (Blencowe *et al*., 2010).Thus, the use of a screening device with low sensitivity and/or selectivity can result in an increase of false negative and/or false positive results. In both cases, it leads to wrong tests results and it can have serious legal consequences, considering that the legally controlled substances consumption has a close relationship with crime. False negative results lead to impunity for drivers who pose as a risk in traffic, demonstrating the failure of the evaluation system. As for false positives results, there are risks of condemnation and embarrassment provoked on an innocent driver. Thus, besides sensitivity and specificity, screening devices must be reliable and easy to handle (Strano-Rossi *et al*., 2012), with an easy and fast interpretation of the results, in order to allow that trained police officers can identify the use of psychoactive substances by motor vehicle drivers (Newmeyer *et al.*, 2017).

Current programs that monitor the use of PS in traffic, such as the European Union's (Driving under the Influence of Drugs, Alcohol and Medicines – DRUID), suggest that OF screening devices should be evaluated for their analytical sensitivity, specificity and efficiency and that these values should be higher than 80% (Newmeyer *et al.*, 2017). Other studies established that screening devices must present higher standards (sensitivity ≥ 80%, specificity ≥ 90% and accuracy ≥ 95%), so that it can be considered a satisfactory test (Strano-Rossi *et al.*, 2012). Based on this information, and the data collected in our review, it is possible to verify that only Dräger DrugTest 5000® (DDT5000) and Alere™ DDS®2 (DDS2) devices fits the recommendation for the investigation of cannabis metabolites in OF, presenting sensitivity and specificity greater than 80% in a considerable number of studies (Beirness, Smith, 2017; Gjerde *et al.*, 2018; Newmeyer *et al.*, 2017; Rohrig *et al.*, 2018; Strano-Rossi *et al*., 2012; Swortwood *et al.*, 2017). However, it is important to note that some studies have found low specificity for the DDT5000 device, even though they have found satisfactory sensitivity(Domingo-Salvany *et al*., 2017; Lema-Atán *et al.*, 2019; Logan, Mohr, Talpins, 2014). As for DDS2 device, Veitenheimer and Wagner (2017) have found a 100% of specificity, while the sensitivity was below the recommended values (75%). The Rapid STAT® device showed 71-91% of sensitivity and specificity values ranging from 09-97, thought the studies in this review (Blencowe *et al*., 2011; Musshoff *et al*., 2014; Strano-Rossi *et al.*, 2012; Wille *et al.*, 2010). However Röhrich *et al*.(2010) have found > 80% values for both sensitivity and specificity for this device.

Studies using Cozart® DDS805, Dräger DCH® 5000, Dräger DCD 5000, Envite CSmartClip®THC/Amph, Oral twist, Reader DDS®202S, Drug Wipe® and DrugWipe® II Twin sorting devices do not provide data sensitivities and specificity (Davey *et al*., 2014; Griffiths *et al*., 2017; Matzopoulos *et al*., 2013). The Cozart® DDS 806, OrAlert™, OraLab®6, BIOSENS® Dynamic, OraLab®6, Oratect1 III devices, presented average sensitivity and specificity of 38% and 95% respectively (Blencowe *et al*., 2011). The Saliva Screen® and Ora-Check® screening devices showed 100% specificity (Tang *et al*., 2018). Devices of DrugWipe® brand have (5/5+, 5A, 5, 5+, II Twin, 6S) showed variations between sensitivity and specificity results, when comparing studies (Beirness, Smith 2017; Blencowe *et al*., 2011; Gentili *et al*., 2016; Logan, Mohr, Talpins, 2014; Musshoff *et al*., 2014; Pehrsson *et al*., 2011a; Pehrsson *et al*., 2011b; Strano-Rossi *et al.*, 2012; Tang *et al*., 2018; VanderLinden *et al*., 2015; Wille *et al*., 2010). Dräger DrugTest® and Cozart® DDS 801 devices showed a sensitivity of 87%, however the Cozart® DDS 801 showed improved specificity (Arroyo *et al*., 2014; Musshoff *et al*., 2014). Among the studies that used the DDS® concatene screening device, only the study of Strano-Rossi *et al*., (2012) provided sensitivity and specificity values (38% and 100%, respectively) (Anzillotti *et al*., 2014; Strano-Rossi *et al.*, 2012). For the Varian Oralab®6 device, sensitivity was low (41%), but specificity is adequate (99%) (Goessaert *et al*., 2010). It is desirable that the screening device present a high degree of tracking, in order to present adequate sensitivity and specificity. (Beirness, Smith 2017). Although these values are independent of prevalence, it must be considered that the study population can reflect it, so that the concentrations can be compared between different populations (Blencowe *et al*., 2010). Other important parameters include the positive predictive values (PPV) and the negative predictive value (NPV). These are dependent on the PS prevalence the investigated population (Blencowe *et al*., 2010). Thus, the prevalence

of a certain PS within the study population is derived from the cases proportion in which the PS is detected in the confirmatory samples of all study participants (Blencowe *et al*., 2010). Thus, it is possible to calculate PPV and NPV values through the combination of sensitivity, specificity, and prevalence values (Bayes' theorem) (Blencowe *et al*., 2010).

THC is traditionally known to be a problematic analyte for on-site screening devices (Fierro, González-Luque, Álvarez, 2014). DUID studies have shown low sensitivity of THC screening tests, and it may be associated with their higher cut-offs (Domingo-Salvany *et al.*, 2017). Other factors that can contribute for the device's low sensitivity and its inadequate performance are the possibility of cross-reactivity and poor analyte recovery from the device (Mazina *et al.*, 2015). These factors are particularly difficult to elucidate for cannabinoids (Domingo-Salvany *et al.*, 2017) and it raises concerns about the use of these devices in police routine.

However, although the screening devices have some disadvantages that must be considered, they still are an important tool, and they are currently the method of choice for DUID cases in some countries. As an example, in 2015, the Norwegian Mobile Police Service (NMPS) have started DUID cases monitoring of PS, including cannabis metabolites, using the Dräger DrugTest5000® (DDT5000) screening device for OF (Gjerde *et al.*, 2018). NMPS reported that DDT5000 did not correctly identified DUID offenders, but the screening device was helpful to assist in the identification of possible DUID suspects (Gjerde *et al.*, 2018).

In a study conducted in Italy, trained police officers randomly approached drivers during road patrols, collecting their OFs for screening analysis using two different devices. At the end of the study, they found that only DDT5000 presented acceptable sensitivity for on-site investigation (Strano-Rossi *et al.*, 2012).

In Spain, the Traffic Police is responsible for conducting on-site OF screening tests for alcohol and drugs (Herrera-Gómez *et al.*, 2018). DDS2 and DDT5000 are among the screening devices chosen by the Spanish law(Herrera-Gómez *et al.*, 2018). The device's performance was investigated in a study conducted by Lema-Atán *et al.* (2019) and they have found an appropriated sensitivity considering the devices' cut-offs for cannabis (Lema-Atán *et al.*, 2019). In this study, samples were collected by police officers, investigating the use of psychoactive substances in Spanish drivers, between 2013 and 2015.

In Canada, the government have approved a legislation that would allow the use of screening devices for cannabis on-site investigation in suspected drivers (Canadian Centre on Substance Use and Addiction, 2018). According to this document, the screening device can help the police to decide which actions will be taken for suspected drivers at a risk of causing an accident (Canadian Centre on Substance Use and Addiction, 2018) and allows the traffic officer to decree flagrant and remove drugged drivers from the roads. The Dräger DrugTest® 5000 is one of the devices approved for monitoring DUID cases by the Canadian government, as long as it is used in conjunction with the Dräger DrugTest 5000® STK-CA device. Other approved device includes SoToxa™, as long as used in conjunction with Abbott SoToxa™ test cartridge, and Abbott SoToxa™ OF collection device (Canada, 2019).

In the United States, some studies have been developed in partnership with specialist drug recognition officers (DRE) from the Tulsa Police Department (Oklahoma, US) such as the one developed by Veitenheimer and Wagner (2017).The DDS2 device was used in routine approaches of suspected DUID drivers in 2013. At the end of the study, it was found that the DDS2 screening device is a tool that can provide police a greater confidence in detecting drivers who are under the influence of PS such as cannabis (Veitenheimer, Wagner, 2017).

After on-site analysis, any positive result from a screening test must be confirmed by a validated analytical method (Fiorentin *et al.*, 2017). For confirmatory analysis, it is necessary to collect an additional volume of OF, which is usually performed with a specific collection device. There are also many different manufacturers for those devices, such as Quantisal™, Oral-Eze®, StatSure Saliva Sampler™, and this also require studies to define the better one for cannabinoids recovery, case by case, country by country, scenario by scenario.

For confirmation and quantification of cannabinoids in OF, the most commonly applied analytical tools are

gas chromatography coupled to mass spectrometry (GC/MS or GC-MS/MS) and liquid chromatography coupled to mass spectrometry (LC-MS/MS) (Table I). THC, as the major psychoactive cannabinoid, is also the chosen metabolite for confirmatory testing in OF, as it is for screening tests (Molnar *et al.*, 2014), along with CBD and CBN. When detecting these cannabinoids in OF, it can be generally assumed that there was the recent consumption of cannabis (Vindenes *et al.*, 2011). This information is also relevant, considering that the Brazilian Traffic Code (CTB) regulates the driving under drug influence, while an old drug consumption does not constitute a traffic crime (Baggio, 2017). When develop a confirmatory method for THC in OF, one should consider THC capacity of adherence to plastic (Anzillotti *et al.*, 2014; Molnar, Lewis, Fu, 2013), leading to its poor recovery from collection devices and affecting the recommended cut-off (2 ng/mL) (Walsh *et al.*, 2008). Considering this, special devices with elution/stabilization buffers are generally used to collect OF (Anizan *et al.*, 2015) which should favor the elution of THC with minimal dilution.

Another important factor for clinical and for forensic purposes is the investigation of the analyte stability in the OF, considering its importance in the interpretation of concentrations (Lee *et al.*, 2012) and to guarantee accurate and reliable results (Scheidweiler *et al.*, 2017). Thus, the collection devices and the storage conditions of the sample are variables to be considered. Studies of the stability of cannabinoids in real OF collected by different collection devices are described in the literature. Lee*et al.*(2012) have found that THC and other cannabinoids (THCCOOH, CBD and CBN) are stable for 4 weeks when stored at 4°C, in the Quantisal™ device. StatSure Saliva Sampler™ and Oral-Eze® devices also have presented stability for THC, THCCOOH, CBD and CBN in OF, under the same conditions of time and temperature. StatSure™ device also have been able to maintain samples stability within 24 weeks, if stored at -20°C (Anizan *et al.*, 2015). The stability of minority cannabinoids in real OF was investigated by Scheidweiler *et al.*(2017). THC, THCV, 11-OH-THC, CBD and CBG had satisfactory stability when kept under refrigeration at 4°C during the period of 8 weeks, extracted from OF stored in Quantisal™ devices (Scheidweiler *et al.*, 2017). Therefore, the stability of cannabinoids depends on the collection device, as well as the time and conditions of the storage of the sample, and this aspect is also something to be considered.

In Brazil, the Ministry of Justice and Security organized a work team composed of members of the National Drug Policy Secretariat (SENAD), the Federal Highway Police (PRF) and the National Public Security Secretariat (SENASP), with the purpose of assisting in the implementation of the use of screening devices to monitor other PS in addition to alcohol (MJSP, 2020). In order to be successful in the implementation of screening devices for PS monitoring in traffic, it is extremely important to have solid evidence-based information, considering local contexts (Scherer, 2017). In addition, special attention should be paid to costs for both the implementation of screening devices and the processing of confirmatory analyzes. For example, non-volatile analytes that that require LC-MS/MS analysis present a higher cost when compared to GC/MS analysis (Huestis *et al.*, 2011; SENAD, 2014). Particularly in Brazil, only a few forensic laboratories have a LC-MS/MS instrument available for sample processing (SENAD, 2014).

In conclusion, this systematic review selected 32 articles for analysis of immunochromatographic devices and the analysis of cannabinoids in OF onsite. From all evaluated devices, only two have shown appropriated sensitivity and selectivity, as recommended by international guides. Some limitations that must be considered and improved, such as the devices cut-offs and the possibility of cross reactions, could lead to false positives results. Considering the legal and the emotional impact that false positive results can cause in the lives of drivers who are not under the influence of PS and the potential risk that false negative drivers represent for traffic, the improvement of screening devices by manufacturers is essential. Thus, confirmatory analyzes by GC/MS, GC-MS/MS and/or LC-MS/MS are also needed. However, drug screening tests results can assist the law enforcement in determining the offense of *flagrante delicto,* preventing possible traffic accidents. Besides the limitations, the implementation of screening tests for cannabinoids on the roadside still can be very helpful to reduce traffic accidents in Brazil, as it has been seen in some developed countries worldwide.

TABLE II - Identification of cannabinoids in OF on the surveillance of traffic accidents

Sub.	*NS and PCS*	*Country and Time Period*	*Collec. on Site and Type of Vehicle*	*Triage Device*	*Cut-off (ng/mL)*	*Sens. and Spe. (%)*	*PPV and NPV (%)*	*AT and QL (ng/mL)*	*Reference*
THC	10.064 8294	Spain Dec. 2013 to Feb.2015	Roadside -	Dräger DrugTest® 5000	25	95.3 71	86.4 88.6	LC–MS/MS[1] 1	(Lema-Atán *et al*., 2019)
THC	369 159	Norway Nov. 2015 to Mar. 2016	- -	Dräger DrugTest® 5000	5	82.9 88.7	- -	UHPLC–MS-MS[3] GC/MS[2] 0.94	(Gjerde *et al*., 2018)
THC	179.645 62.876	Spain Year 2011 to 2016	Roadside -	Dräger DrugTest® 5000 DrugWipe® Alere™ DDS®2	5 - 25	- -	- -	CT -	(Herrera-Gómez *et al*., 2018)
THC	100 18	United States -	Roadside -	Alere™ DDS®2	25	≥80 ≥80	≥80 ≥80	LC-MS/MS 1.4	(Rohrig *et al*., 2018)
THC	547 515 549 39	Hong Kong -	Hospital -	Ora-Check® DrugWipe® 6S Saliva Screen®	50 20 50	0 100 22 100 0 100	100 94 - 93 - 93	LC-MS 0.5	(Tang *et al*., 2018)
THC	646 323	Canada -	- -	Alere™ DDS®2 Dräger DrugTest®5000 Drug Wipe 6S®	25 5 10	86.9 95.5	- -	LC-MS/MS or GC/MS 0.25	(Beirness, and Smith, 2017)
THC	2744 206	Spain Year 2015	Roadside Police control Checkpoints Motor vehicles, excluding bicycles and vehicles over 3,500 kg	Dräger DrugTest® 5000	25	90 77	- -	UHPLC-MS/MS 0.4	(Domingo-Salvany *et al*., 2017)

TABLE II - Identification of cannabinoids in OF on the surveillance of traffic accidents

Sub.	*NS and PCS*	*Country and Time Period*	*Collec. on Site and Type of Vehicle*	*Triage Device*	*Cut-off (ng/mL)*	*Sens. and Spe. (%)*	*PPV and NPV (%)*	*AT and QL (ng/mL)*	*Reference*
THC	953 114	Queensland, Australia Year 2010 to 2016	Waterways of Queensland, AUS Boats and/or watervessels	DrugWipe® II Twin Cozart® DDS805 Dräger DCH® 5000/ Dräger DrugTest® 5000 STK	-	- -	- -	LC-MS/MS -	(Griffiths *et al*., 2017)
THC	124 27	Miami, Florida, United States -	Music festival -	Alere™ DDS®2	25	100 100	100 96.7	LC-MS/MS 1	(Krotulski *et al*., 2017)
THC THCCOOH, 11-OH-THC, THCV, CBD, and CBG	16 - 16	- -	Institutional Review Board -	Dräger DrugTest® 5000 Alere™ DDS®2	5 25	89.3 94.7	- -	LC-MS/MS 0.2 15	(Newmeyer *et al*., 2017)
THC	25 8	United States Summer of 2013	Roadside -	Alere™ DDS®2	25	75 100	100 75	LC-MS/MS 4	(Veitenheimer, Wagner 2017)
THC	20 - 20	- -	Dräger DrugTest® 5000 Alere™ DDS®2	5 25	≥80 99.3	- -	LC-MS/MS 0.2	(Swortwood *et al*., 2017)
THC	83 18	Rome, Italy Jan. to Mar. 2015	Five principaldiscos, pubs, andmusicbars of Rome metropolitan area -	DrugWipe® 5A	10	29 88	- -	HS-SPME-GC/MS[7] 0.18 ng/pad	(Gentili *et al*., 2016)
THC	3.900 2.600	Belgium Apr. 2008 to Mar. 2013	Roadside -	Drug Wipe-5+®	10	- -	- -	GC/MS or UPLC-MS/MS -	(VanderLinden *et al*., 2015)
THC CBD CBN	70 42	- -	- -	ConcatenoDDS Dräger DCD® 5000	-	- -	- -	UPLC-MS SPME-GC/MS -	(Anzillotti *et al*., 2014)
THC	2.180 1371	Spain 2009 to 2010	Roadside -	Cozart® DDS 801	31	87 86	94 73	GC/MS 10	(Arroyo *et al*., 2014)

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THC	90	Miami United States	Traffic stop	Dräger Drug Test® 5000	5	58.3	93.3	GC/MS -	(Logan, Mohr, and Talpins, 2014)
	15+10	-	-	DrugWipe 5®-Panel		98.5	86.8		
					2	43.5	66.7		
	91					100	82.7		
	15+13								
THC	2.129	Queensland, Australia	Roadside	Drug Wipe®	5	-	-	-	(Davey, Armstrong, and Martin, 2014)
	634	Dec. 2007 to Jun. 2012	-	II Twin		-	-	-	
	480			Cozart® DDS805 Cozart® DDS Reader DDS®202S					
	32								
THC	2.63	Spain Jul. 2008 to Aug. 2009	Roadside	Dräger DrugTest® 5000	27	76.3	81.25	LC-MS/MS 1	(Fierro, González-Luque, and Álvarez, 2014)
	253		-			94	50.68		
						76.5			
						80			
THC	20	-	-	Dräger DrugTest®5000	-	-	-	LC-MS/MS 1	(Lendoiro *et al*., 2014)
	20	-	-			-	-		
THC	10	-	Roadside	DrugWipe® II Twin	-	-	-	LC-MS/MS 1	(Molnar *et al*., 2014)
	10	-	-	Cozart® DDS		-	-		
					31	-			
						-			
THC	1.212	North Rhine-Westphalia, Germany Jan. to Nov. 2010	Roadside	Dräger DrugTest®	5	87	92.6	-	(Musshoff *et al*., 2014)
	91		-			47	32.7	-	
				Rapid STAT®					
	12				5	91	92.6		
	236					9	25		
				Drug Wipe 5/5+®					
					30	71	70		
						49	28		

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Sub.	*NS and PCS*	*Country and Time Period*	*Collec. on Site and Type of Vehicle*	*Triage Device*	*Cut-off (ng/mL)*	*Sens. and Spe. (%)*	*PPV and NPV (%)*	*AT and QL (ng/mL)*	*Reference*
THC	244	South Africa Feb. to Sept. 2008	Roadside	Oral twist EnviteCSmartClip®THC/ Amph Drug Wipe®	100	-	-	-	(Matzopoulos, Lasarow, and Bowman, 2013)
	4		-		15	-	-	-	
					30				
THC	38	California, United States Summer of 2012	Roadside	Alere Mobile Test System DDS®2	25	-	-	GC/MS or LC- MS/ MS -	(Moore, Kelley-Baker, and Lacey, 2013)
	5 (2)		-			-	-		
THC	500	Italy Nov. 2010 to Jul. 2011	Roadside	Concateno DDS®	31	37.80	100	UHPLC–MS/MS	(Strano-Rossi *et al*., 2012)
	-		-	Dräger DrugTest® 5000		100	94.1	1	
	500				5	92.3	80		
	-			Drugwipe 5+®		96.7	98.9		
					15	46.6	84.4		
	500			Rapid STAT®		98.9	93.4		
	-				30	72	78		
	500					97	96		
	-								
THC	66	-	-	Dräger DrugTest® 5000	5	75.9	-	GC/MS	(Desrosiers *et al*., 2012)
	-	-	-			100	-	0.5	
THC	136	-	-	Drug Wipe® 5+	30	63	71	GC/MS	(Pehrsson *et al*., 2011b)
	-	-	-	Rapid STAT®		94	91	1	
					15	85	64		
	132					88	96		
	-								
THC	1807	Finland Jul. 2007 to Dec. 2008	-	Drug Test® 5/5+	30	43	46	GC/MS 1	(Pehrsson *et al*., 2011a)
	-		-			87	86		

TABLE II - Identification of cannabinoids in OF on the surveillance of traffic accidents

Sub.	*NS and PCS*	*Country and Time Period*	*Collec. on Site and Type of Vehicle*	*Triage Device*	*Cut-off (ng/mL)*	*Sens. and Spe. (%)*	*PPV and NPV (%)*	*AT and QL (ng/mL)*	*Reference*
THC	118	Belgium, Finland and Netherlands October 2007 to Dec. 2009	-	BIOSENS®Dynamic Cozart® DDS 806	Undetermined	Average sensitivity: 38%	-	UPLC–MS/MS, GC/EI/MS[4] or GC/NICI/MS[5]	(Blencowe *et al.*, 2011)
	-		-	DrugWipe® 5+	31				
	138			Dräger DrugTest® 5000		Average specificity: 95%			
	-			OraLab®6	30		-	1	
	136			OrAlert™	5				
	-			Oratect1 III					
	223			Rapid STAT®	50				
	-				100				
	250				40				
	-								
	125				15				
	-								
	58								
	-								
	349								
	-								
THC	250	-	DRUID Project	Varian Oralab®6	50	41	10	LC-MS/MS	(Goessaert *et al.*, 2010)
	-	-	-			99	99	1	
THC	134	Rheinland-Pfalz, Germany Apr. to Nov. 2008	Roadside	Rapid Stat™	15	85	87	GC/MS	(Röhrich *et al.*, 2010)
	-		-			87	97	1.8	

TABLE II - Identification of cannabinoids in OF on the surveillance of traffic accidents

Sub.	*NS and PCS*	*Country and Time Period*	*Collec. on Site and Type of Vehicle*	*Triage Device*	*Cut-off (ng/mL)*	*Sens. and Spe. (%)*	*PPV and NPV (%)*	*AT and QL (ng/mL)*	*Reference*
THC	58	Belgium	Roadside	Drugwipe-5®	30	71	--	GC/MS	(Wille *et al.*, 2010)
	11	-	-	Rapid STAT®	15	55		1	
	46					71			
	-			DrugTest® 5000	5	50			
	48					93			
	-					71			

Captions: Substance (Sub); Number of Samples (NS); Positive Cannabinoids Samples (PCS); Sensitivity (Sens.); Specificity (Spe.); Collect (Collec); Analytical Technique (AT); Quantification Limit (QL). January (Jan); February (Feb); March (Marc); April (apr); June (Jun); July (Jul); August (Aug); September (sept); November (Nov); December (Dec). –Liquid Chromatography Tandem Mass Spectrometry; Liquidchromatography TandemMass Spectrometry(LC-MS/MS); Gas Chromatography Mass Spectrometry (GC/MS); Ultraperformance Liquid Chromatography Tandem Mass Spectrometry (UPLC–MS/MS) or Ultra-High- Liquid Chromatography Tandem Mass Spectrometry (UHPLC–MS/MS); Gas Chromatography Electron Impact Mass Spectrometry (GC/EI/MS); Gas Chromatography negative-ion chemical ionization Mass Spectrometry (GC/NICI/MS); Headspace Solid-Phase Microextraction Gas Chromatography Mass Spectrometry (HS-SPME-GC/MS); Chromatographic Techniques (CT); Uninformed (-).

ACKNOWLEDGMENTS

The authors are thankful to the Graduate Program of Pharmaceutical Sciences, from the Federal University of Rio Grande do Sul (PPGCF-UFRGS), *Coordenação de Aperfeiçoamento de Pessoal de Nível Superior* (CAPES), *Conselho Nacional de Desenvolvimento Científico e Tecnológico* (CNPq) and *Fundação de Amparo à Pesquisa do Estado do RS* (FAPERGS).

CONFLICT OF INTEREST

The authors have no conflict of interest.

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Received for publication on 13rd July 2020
Accepted for publication on 12nd January 2021