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The concentration and prevalence of ochratoxin A in coffee and coffee-based products: A global systematic review, meta-analysis and meta-regression

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ABSTRACT

The current investigation was aimed to estimate the prevalence and concentration of ochratoxin A (OTA) in different types of coffee and coffee-based products with the aid of a systematic review and meta-analysis. Therefore, the recommended databases including PubMed, Scopus, and Embase from Jan 1983 to Oct 2018 were screened to retrieve the related citations. In this regard, among 1041 explored articles in the identification step, thirty six articles with 3182 samples were included in the meta-analysis and meta-regression. According to findings, the global pooled concentration and prevalence of OTA was calculated as 3.21 μg/kg (95% CI: 3.08–3.34 μg/kg) and 53.0 % (95% CI: 43.0–62.0), respectively. Also, direct correlations between the increases in poverty as well as the amount of annual precipitation and prevalence of OTA was noted, while with decreasing in HDI the prevalence of OTA in coffee significantly was increased. Moreover, the lowest and highest concentrations of OTA in coffee were observed in Taiwan (0.35 μg/kg) and Turkey (79.0 μg/kg), respectively. The outcome of this meta-analysis can be used for the building of risk assessment models aiming to derive data for the development of specific actions to reduce the exposure to this mycotoxin in coffee and coffee-based products.

1. Introduction

The contamination of different food products such as dairy, edible oil, nuts, cereal-based and fruit-based products with mycotoxin always is a matter of concern for both academic and industry (Amirahmadi et al., 2018; Campagnollo et al., 2016; Heshmati et al., 2017, 2019; Khaneghah et al., 2018a; Mousavi Khaneghah et al., 2017, 2018; Nabizadeh et al., 2018; Oteiza et al., 2017; Rahmani et al., 2018a; Rastegar et al., 2017). Among 400 classified mycotoxins, ochratoxin A (OTA) is a secondary metabolite produced by certain fungi species from the genera *Aspergillus* and *Penicillium*, which are found as contaminants of cereals and derivatives, dried fruits, nuts, grapes, wine, milk, cocoa and coffee (Keller and Hohn, 1997; Leitão and Enguita, 2014; Majeed et al., 2018; Oteiza et al., 2017). Chemically, OTA as amino acid phenylalanine with the dihydro-isocoumarin linked by a peptide bond is a low molecular weight compound, having a molar mass of 403.8 g/mol (Benites et al., 2017). The ingestion of this mycotoxin via consumption of contaminated food products can cause some adverse effects such as Balkan endemic nephropathy (BEN) and chronic interstitial nephropathy (CIN), as well as other renal diseases. Moreover, teratogenic, nephrotoxic and mutagenic effects were reported by several

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studies particularly in the case of animal species (Bui-Klimke and Wu, 2015; Ostry et al., 2017; Van der Merwe et al., 1965).

OTA is classified in Group 2B by the International Agency for Research on Cancer, a possible human carcinogen, which has raised great concerns about human exposure to this mycotoxin (Ostry et al., 2017). Therefore, the tolerance limits for OTA in foodstuffs, especially for food products with higher risk of OTA occurrence including coffee beans were established by several countries (ANVISA, 2011, 2017; Copetti et al., 2013). The maximum levels of OTA were established only for roasted and soluble coffee by the European legislation, as 5.0 μg/kg and 10.0 μg/kg, respectively (European Commission, 2006; Duarte et al., 2010). However, The European Food Safety Authority (EFSA) established a provisional tolerable weekly intake (PTWI) for OTA of 120 ng/kg BW/week, based on the 8 mg/kg BW/d LOAEL used in the JECFA evaluation (European Commission, 2006).

Coffee is considered a very complex matrix (Benites et al., 2017), as contamination of the coffee bean can occur throughout the production chain, besides being directly related to the care and quality of the management of the harvest, storage as well as the type of roasting (Oliveira et al., 2013). In this regard, the coffee beans can be contaminated by microorganisms, during the primary contacts with soil, which can result in the formation of defective, black and sour grains (Taniwaki et al., 2014). In addition to damaging the fruit, some fungi cause grains defects that results in the production of mycotoxin such as OTA (Illy and Viani, 2005; Taniwaki et al., 2003; Toci and Farah, 2008). In this context, the main OTA-producing fungi in the coffee can be mentioned as *A. ochraceus*, *Aspergillus westerdijkiae*, *A. niger* and *Aspergillus carbonarius* (Joosten et al., 2001; Morello et al., 2007; Noonim et al., 2008; Taniwaki et al., 2003). However, coffee can be contaminated with other fungi species, such as *A. steynii*, *A. melleus* and *A. sclerotiorum* (Batista et al., 2003; Leong et al., 2007; Noonim et al., 2008). Once the green coffee beans is contaminated by OTA, it can remain in roasted coffee at levels higher than those allowed by legislation (Oliveira et al., 2018). Moreover, according to Raters and Matissek (2008) and Suárez-Quiroz et al. (2005), the temperature used to roast coffee is not effective for totally destroying OTA in the final product (Raters and Matissek, 2008; Suárez-Quiroz et al., 2005).

In this regard, the occurrence of OTA in coffee and coffee-based products in countries including Brazil, Canada, Dubai, Europe, Japan, and the USA was reported previously (Bui-Klimke and Wu, 2015; FAO, 2001).

Vanesa and Ana (2013) investigated the incidence of OTA in 51 roasted coffee beans and soluble coffee samples collected from Argentina using immunoaffinity columns for sample purification and OTA determination by high-performance liquid chromatography (HPLC) (Vanesa and Ana, 2013). Samples of roasted coffee had mean contamination levels of 1.00 μg/kg and 1.99 μg/kg for soluble coffee, with 54 % and 77 % of contaminated samples, respectively. In another study published by Benites et al. (2017), roasted and ground coffee samples marketed in Portugal were analyzed for OTA levels. The average concentration found in roasted and ground coffee samples was 1.84 and 1.45 μg/kg, respectively. Bessaire et al. (2019) verified the occurrence of 31 mycotoxins in 71 samples of green coffee beans, collected in nine countries (between 2015 and 2016) using the liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS). OTA was detected at a higher level than other mycotoxins, at 12.2 μg/kg. In the study by Nielsen et al. (2015), samples of green coffee, roasted and instant coffee were investigated for OTA levels, using the QuEChERS (fast, easy, cheap, effective, robust and safe) for the extraction, being detected by ultra-high performance (UHP) LC-MS/MS (Nielsen et al., 2015). The results showed that about half the samples of roasted coffee (collected from nine countries) were contaminated with detectable levels of OTA, although only 5 samples were above the EU limit (5 μg/kg) with one sample containing the highest level (21 μg/kg). Of the 25 samples of instant coffee, none had levels of OTA above the tolerance limit of European legislation (10 μg/kg).

Considering the variation of the prevalence data available on OTA in coffee, for the first time, the current study was carried out to conduct a systematic review, meta-analysis and meta-regression regarding the concentration and prevalence of OTA in coffee and coffee-based products in a global scale.

2. Material and methods

2.1. Search strategy

In this study, a systematic review was conducted based on a Cochrane protocol (Higgins and Green, 2011). Search strategies were designed to gather the relevant studies regarding occurrence and concentration of the OTA in coffee and coffee-based products among the international databases including PubMed, Scopus, and Embase which were published between Jan of 1983 to Oct 2018.

The following terms were used in each database: PubMed: ((((mycotoxins [Ti/Ab]) OR ochratoxin [Ti/Ab])) AND coffee [Ti/Ab]) OR "Coffee" [Mesh]; Scopus: ((TI-A-KE (coffee) OR TI-A-KE (food) OR TI-A-KE (roasted AND coffee) OR TI-A-KE (green AND coffee))) AND ((TI-A-KE (mycotoxins) OR TI-A-KE (ochratoxin))) and; EMBASE: 'mycotoxin':ab,ti OR 'ochratoxin':ab,ti And 'coffee':ab,ti. The references of retrieved articles were reviewed to obtain additional articles.

2.2. Inclusion criteria

Inclusion criteria in the our study were: (1) reporting of prevalence of OTA in coffee; (2) published in English language; (3) cross-sectional study; (4) reporting of average and range concentration of OTA; and (5) published between Jan of 1983 to Oct 2018. Case reports, clinical trial study, review articles, books, and experimental studies were excluded.

The software of EndNote X7® (Thomson Reuters, Toronto, Canada) was used to retrieved manage articles.

2.3. Data extraction

The retrieved articles were evaluated and all the required data such as start and end dates of study, country, average, standard deviation and range of concentration of OTA, total sample size, positive sample size, a method of detection, LOD and LOQ of the method were included in the Microsoft Excel software (Microsoft Corporation, WA, US). To perform meta-regression Gross Domestic Product (GDP) ranking, Human Development Index (HDI) ranking and annual average rain in all included countries were obtained from various network databases and then were inserted in excel file.

2.4. Meta-analysis and meta-regression of data

In the current study, random effect model (REM) was used for meta-analysis of data and estimate pooled with 95 % confidence intervals based on the country subgroup (Khaneghah et al., 2018b; Rahmani et al., 2018b) established, while it was estimated among the countries via Freeman Tukey double arcsine transformation analysis (Harris et al., 2008; Keramati et al., 2018; Khaneghah et al., 2018c). Heterogeneity was calculated via *the* I^2 statistics test. The range of the I^2 index was between 0 and 100 %, and if I^2 index $\geq$50 values show that considered heterogeneous (Higgins and Thompson, 2002).

Odds ratio (OR) of OTA in each country was calculated by univariate analysis. Meta-regression was used to determine the effects of GDP, HDI, and rain on the prevalence of OTA in coffee using the method of moment model (Borenstein et al., 2011). Publication bias among the included studies was detected statistically by applying the Egger's and Egger's publication bias test (Egger et al., 1997). As publication bias among studies was considerable (P-value < 0.05), the Meta Trim test was performed to estimate the pooled prevalence of OTA in the coffee to eliminate the publication bias (White, 2009). Analysis of data was performed using STATA 14.0 (2015; STATA 14.0 Statistical Software, College Station, TX, USA). The statistically significant was defined as P-value <0.05.

3. Results

3.1. Study characteristics

In the first step, 1041 articles were obtained among the examined databases. After removal of duplicates (n = 919) and screening based on title and abstract 122 articles were remained for assessing full text. After assessing the eligibility of articles, 36 articles with 3182 samples were included in the meta-analysis and meta-regression (Fig. 1).

Considering the techniques used for detection and quantification, the levels of OTA were determined by HPLC, LC-MS/MS, enzyme-linked immunosorbent assay (ELISA) and UHPLC (Table 1S). Also, the following rank can be proposed for the number of established studies: Brazil (13) > Spain (10) > Philippines (9) > Portugal (8) > South Korea (7) > Malaysia (6) > Italy (5) ~ Taiwan (5) > Argentina (4) ~ Japan (4) > Chile (3) ~ Denmark (3) ~Vietnam (3) > Czech Republic (2) ~ Latvia (2) ~United States (2) > Cyprus (1) ~ Ethiopia (1) ~ France (1) ~ Kuwait (1) ~ Panama (1) ~Switzerland (1) ~Thailand (1) ~ Turkey (1) (Table 1S).

According to Table 1S, regarding the most used methods for the determination of OTA levels in coffee and coffee products, 21 out of 37, 56.8 % were recognized as the HPLC coupled to fluorescence detection (HPLC-FLD) and HPLC coupled to ultra-violet detector (HPLC-UV). Moreover, 21.6 % (8/37) used mass spectrometry based techniques (HPLC-MS, LC-MS/MS, LC/ESI-MS/MS, LC-MS/MS-IT, LC-MS/MS-QqQ, LC-QqQLIT-MS/MS, UHPLC-MS/MS, UHPLC-MS, UPLC-MS/MS); and in 13.5 % (5/37),t ELISA was used as the method for determination of OTA.

3.2. Prevalence of OTA

The rank of countries regarding the occurrence of OTA in coffee and coffee based products was ordered as Kuwait (100 %) ~ Chile (100 %)~ France (100 %) > Portugal (83.0 %) > Switzerland (73.0 %) > Argentina (72.0 %) > Czech Republic (65.0 %) > Ethiopia (64.0 %) > Taiwan (61.7 %) ~ Malaysia (61.2 %) > Italy (55.0 %) ~ Japan (48.0 %)~ Cyprus (47.6 %) > Denmark (47.2 %) > Brazil (43.0 %) > United States (42.0 %) > Latvia (38.0 %) > Spain (36.0 %) > Panama (19.0 %) > Vietnam (10.0 %) > South Korea (3.0 %) (Table 2S). The global pooled prevalence of OTA in coffee was 53.0 % (95% CI: 43.0–62.0). Also, heterogeneity among studies was considerable (I^2: 94.80, p value < 0.001), Hence random effect mode used for Meta-analysis of data (Table 3S).

3.3. Concentration OTA in coffee

The rank order of countries based on mean concentration OTA in coffee and coffee based products can be summarized as Turkey

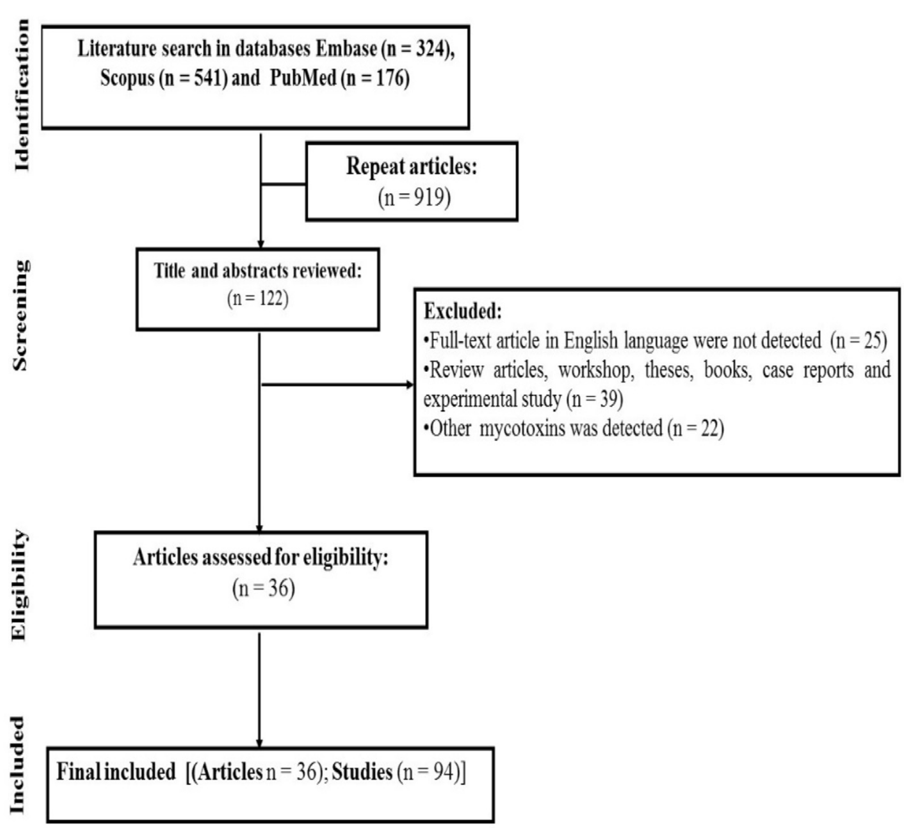

Fig. 1. Flow chart for studies selection process.

(79.0 μg/kg) > Philippines (52.7 μg/kg) > France (38.9 μg/kg) > Panama (21.3 μg/kg) > South Korea (5.62 μg/kg) > Spain (4.52 μg/kg) > Cyprus (3.90 μg/kg) > Malaysia (3.48 μg/kg) > Vietnam (2.86 μg/kg) > Denmark (2.82 μg/kg) > Kuwait (2.56 μg/kg) > Brazil (1.81 μg/kg) > Portugal (1.71 μg/kg) > Ethiopia (1.53 μg/kg) > Argentina (1.39 μg/kg) > Switzerland (1.30 μg/kg) > Italy (1.21 μg/kg) > Chile (1.10 μg/kg) > Thailand (0.89 μg/kg) > Czech Republic (0.84 μg/kg) > Japan (0.48 μg/kg) > Taiwan (0.35 μg/kg) (Table 4S). Also, the global pooled mean concentration of OTA in coffee was 3.21 μg/kg (95% CI: 3.08–3.34 μg/kg) (Table 4S).

3.4. Odds ratio of the OTA in coffee

The rank order of countries based on Odds ratio of the OTA in coffee and coffee based products was Kuwait (35.220) > France (35.220) > Chile (35.250) > Turkey (35.150) > Portugal (26.130) > Switzerland (25.440) > Argentina (25.360) > Czech Republic (22.750) > Ethiopia (22.310) > Taiwan (21.350) > Malaysia (21.350) > Italy (18.920) > Japan (16.800) > Cyprus (16.450) > Denmark (16.450) > United States (15.140) > Philippines (14.850) > Spain (13.170) > Latvia (13.040) > Brazil (11.070) > Panama (6.950) > Vietnam (3.530) (Table 5S).

3.5. Meta-regression of data

Meta-regression regarding the effect of GDP ranking shows that with decreasing GDP ranking, the prevalence of OTA in coffee and coffee-based products significantly increased (C = 0.0062; P-value = 0.01) (Fig. 2A). Meta-regression regarding the effect of HDI shows that with increasing HDI ranking, the prevalence of OTA in coffee and coffee-based products decreased (C = −0.00028; P-value = 0.79) (Fig. 2B). Meta-regression regarding the effect of average annual rain demonstrated that with increasing rain the prevalence OTA in coffee and coffee-based products increased (C = 0.0005; P-value = 0.21) (Fig. 2C). According to publication bias test, A significant publication bias among studies was noted (C = 2.38; P-value = 0.001) (Fig. 3). Therefore, for removing the effect of publication bias on the pooled prevalence of OTA, meta-trim analysis was performed. The meta-trim analysis revolved that the pooled prevalence of OTA was 48.0 % (95% CI: 40.0–55.0) (Fig. 4).

4. Discussion

4.1. Prevalence of OTA in coffee and coffee products

The prevalence of OTA in coffee and coffee products in different countries during (1983–2018) was shown in Table 1S. Currently, the market offers to consumers a wide variety of coffee-based products such as green coffee, roasted coffee beans, instant

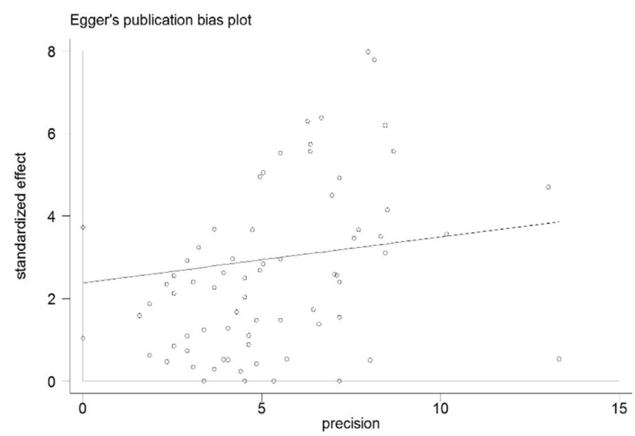

Fig. 3. Publication bias analysis by Egger's test.

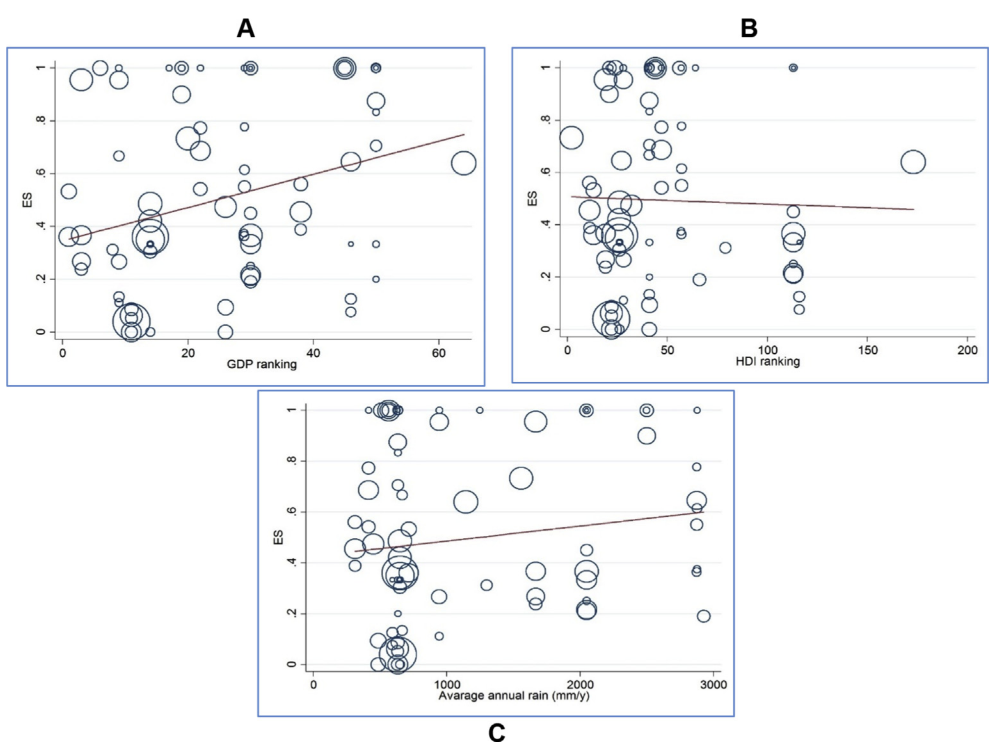

Fig. 2. Meta-regression regarding the effect of GDP ranking (A) of HDI ranking (B) and average annual rain (C) on prevalence ochratoxin A (OTA) in coffee and coffee-based.

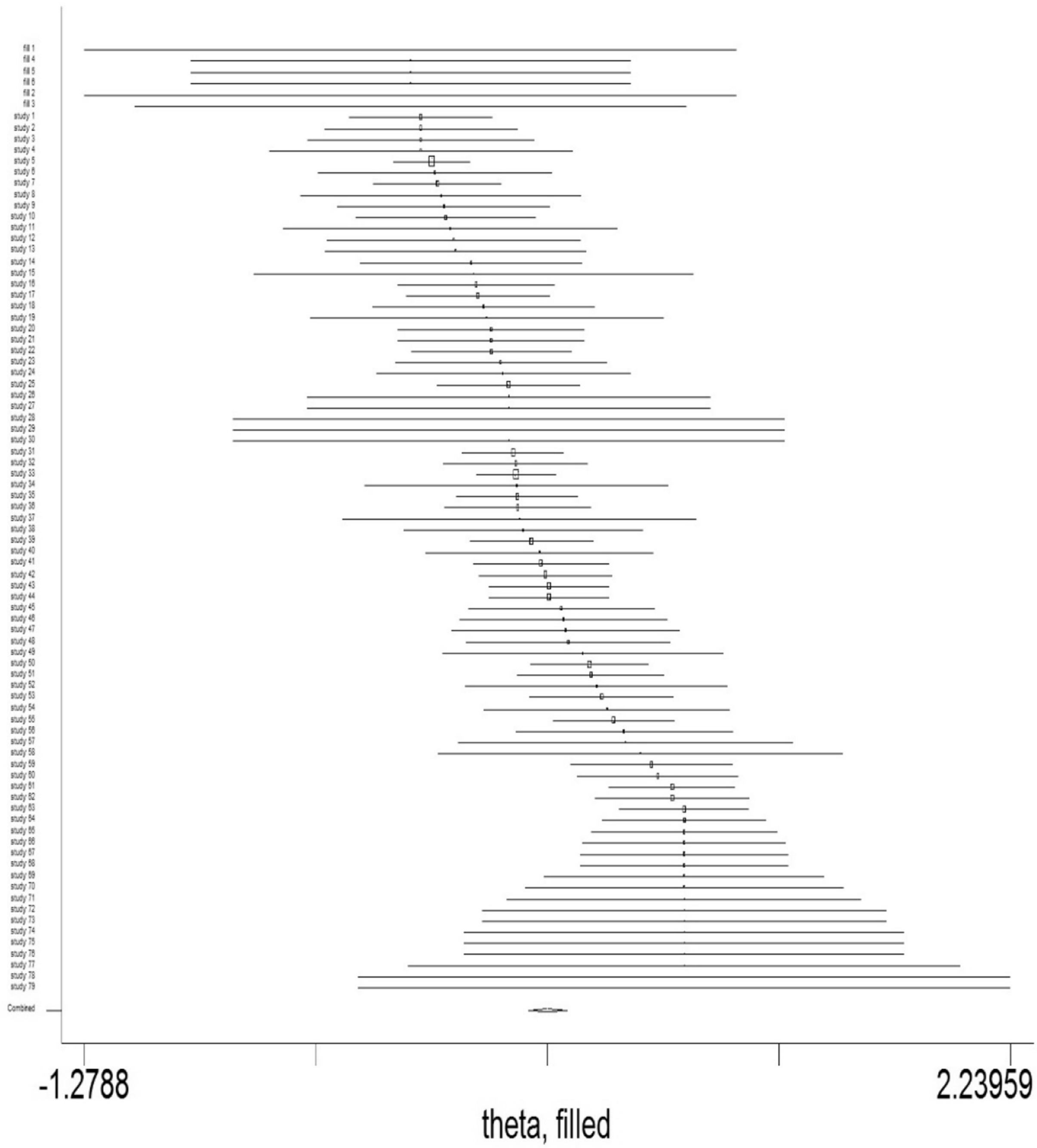

Fig. 4. Meta-Trim Analysis plot to determine pooled prevalence ochratoxin A.

coffee, coffee beverage, ground roasted coffee, beverages, plain soluble coffee, mixtures of cereals with coffee, among others, which were analyzed among studies investigated regarding OTA levels.

Consumers are increasingly looking for practical and tasty products. Soluble coffee is an example of a quick and practical product since the powder dissolves instantly in hot water (Casal et al., 2014). Unfortunately, soluble coffee, despite its practicality, may pose risks due to OTA contamination. According to Table 1S, in a study in South Korea, OTA was present in 50.0 % of the instant coffee samples, with a mean concentration of 25.5 μg/kg (Lindenmeier et al., 2011). OTA was also present in soluble coffee, with an average concentration of 5.71 μg/kg in Malaysia (Lee et al., 2012a).

In the Philippines, 33.0 % of the green coffee samples were contaminated with OTA, with an average concentration of 257 μg/kg and a variation of 3.71–514 μg/kg (Barcelo and Barcelo, 2018). Also, other studies conducted in the Philippines with samples of ripe coffee samples and dried coffee samples, about 26.0 % of the samples were contaminated, with mean levels of 51.2 μg/kg and 97.3 μg/kg, respectively (Culliao and Barcelo, 2015). Green coffee grains and their extracts are known as natural and inexpensive ingredients with the potential to induce weight loss, as it has high concentrations of caffeine and chlorogenic acids (Tanaka et al., 2009; Vaclavik et al., 2013). Currently, no OTA limits are available on legislation for green coffee and its dietary supplements. However, regulatory limits for OTA in green coffee will be established by the EU in the future (European Commission, 2006; Vaclavik et al., 2013).

According to Rehmat et al. (2019), coffee consumption has increased considerably in recent decades, with more than 19 million tons of coffee expected to be consumed by 2019 (Paterson et al., 2014). Coffee drinks have a high demand worldwide, occupying the place of the second largest food product marketed (Rehmat et al., 2019). In Portugal, 87.5 % of coffee beverages samples presented mean OTA levels of 5.90 μg/kg (Casal et al., 2014). Samples of processed coffee presented a mean OTA concentration of 21.3 μg/kg, in a study carried out in Panama (Franco et al., 2014).

In general, according to Table 1S, green coffee presented the highest levels of contamination, with concentrations ranging from 0.30 to 257 μg/kg. The other coffee products presented had significant concentrations, although not as high as those of green coffee. The coffee product that contained a considerable level of OTA was dried coffee, with 97.3 μg/kg of mycotoxin.

The data in Table 2S present the results regarding the prevalence of mycotoxins in coffee and coffee products in several countries. In the table, the countries were divided into subgroups, for better visualization of the data.

Among the countries that presented studies related to OTA contamination in coffee and its derivatives are Japan, Brazil, Philippines, Portugal, Taiwan, Cyprus, Spain, Kuwait, Panama, Chile, Ethiopia, Italy, Malaysia, Czech Republic, Denmark, France, United States, Argentina, Latvia, South Korea, Switzerland, Turkey and Vietnam. The products analyzed for OTA levels included green coffee, roasted coffee beans, instant coffee, coffee beverage, ripe coffee, dried coffee, ground roasted coffee, plain soluble coffee, mixtures of cereals, freshly brewed coffee, canned coffee, coffee, natural roasted coffee, torrefacto roasted coffee, pre-portioned milk, coffee beverage, among others. The rank order of countries based on the prevalence of OTA in coffee is explained in item 3.2.

In the current study, the results of Meta-regression analysis showed that the prevalence of OTA in coffee and coffee-based products significantly increased with an increase in poverty, as indicated by lower GDP and HDI values in the different countries evaluated (Fig. 2A, B). This is in agreement with the fact that agriculture practices and preventive strategies in the food chain especially of cereals are highly influenced by economical parameters like GDP and HDI (Drăgoi et al., 2018; FSEG, 2018; Milani, 2013). Thus, poor harvesting and storage conditions of grains and failures or mild control measures adopted in cereal foods processing in some developing countries (Tola and Kebede, 2016) could greatly contribute to increase the growth of fungi and consequently, the mycotoxins prevalence in foods like coffee. Also, meta-regression shows that higher rainfall can increase the prevalence of OTA in coffee (Fig. 2C). Since a high relative humidity of the ambient air is expected to occur in regions with higher annual rainfall (Chowdhury et al., 2018), there is a positive relationship between rain precipitation and the growth of toxigenic fungi in foods (Doohan et al., 2003; Milani, 2013), as a consequence of the increased water activity in the grain exposed to high relative humidity (Northolt and Bullerman, 1982). Palacios-Cabrera et al. (2004) observed higher OTA production by *Aspergillus ochraceus* at 25 °C with water activity values of 0.84–0.86, when compared with values between 0.78 and 0.80. Therefore, it is plausible that the higher prevalence of OTA in coffee in countries with higher rainfall can be related to higher high humidity in the air and higher chance for fungal growth.

5. Conclusion

In the current study, the prevalence and concentration of OTA in coffee and coffee-based products were meta-analyzed based on defined subgroups such as country and type of coffee products. Also, Meta-regression between the prevalence of OTA in coffee with GDP, HDI and rainfall were conducted. The highest prevalence and OR values of OTA were noted in the investigated coffee samples in the Kuwait ~ Chile, and France while the lowest prevalence corresponded values were attributed to coffee samples investigated in Panama, Vietnam, and South Korea. The highest concentrations of OTA in coffee were found in Turkey, Philippines, and France; and the lowest concentrations were observed in Czech Republic, Japan and Taiwan. Meta-regression shows that with increasing poverty and decreasing HDI, the prevalence of OTA in coffee increased significantly. Also, with increases in annual rain, the prevalence of OTA in coffee significantly increased. Considering the significant effects of GDP, HDI and rainfall on the occurrence of OTA in coffee, it is recommended that they should be considered in food health management plans. The outcome of this meta-analysis can be used for the building of risk assessment models aiming to derive data for the development of specific actions to reduce the exposure to this mycotoxin through the consumption of the coffee and coffee based products.

Conflicts of interest

There is no conflict of Interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.funbio.2019.05.012.

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