

Review

Caffeine Consumption through Coffee: Content in the Beverage, Metabolism, Health Benefits and Risks

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Received: 14 February 2019; Accepted: 11 April 2019; Published: 1 June 2019



Abstract: Caffeine (1,3,7-trimethylxanthine) is the most consumed psychoactive substance in the world, acting by means of antagonism to adenosine receptors, mainly A_1 and A_{2A} . Coffee is the main natural source of the alkaloid which is quite soluble and well extracted during the brew's preparation. After consumption, caffeine is almost completely absorbed and extensively metabolized in the liver by phase I (cytochrome P450) enzymes, mainly CYP1A2, which appears to be polymorphically distributed in human populations. Paraxanthine is the major caffeine metabolite in plasma, while methylated xanthines and methyluric acids are the main metabolites excreted in urine. In addition to stimulating the central nervous system, caffeine exerts positive effects in the body, often in association with other substances, contributing to prevention of several chronic diseases. The potential adverse effects of caffeine have also been extensively studied in animal species and in humans. These aspects will be approached in the present review.

Keywords: caffeine; coffee; consumption; metabolism; health benefits; potential adverse effects

1. Introduction

Caffeine consumption is an ancient habit. Different cultures discovered that chewing seeds, barks, or leaves of certain plants containing this substance had the effects of easing fatigue, increasing awareness, and elevating mood [1]. Caffeine (1,3,7-trimethylxanthine) is a heterocyclic organic compound with a purine base called xanthine, consisted of a pyrimidine ring linked to an imidazole ring [2] (Figure 1). Caffeine is known as an alkaloid because it is a secondary plant metabolite derived from purine nucleotides, with a heterocyclic nitrogen atom (definition of true alkaloid) [2,3]. However, because it does not have the incorporation of an amino acid in its biosynthesis [2], some authors call it a pseudo-alkaloid [4].

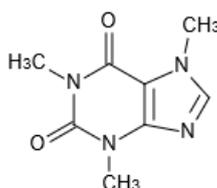


Figure 1. Caffeine chemical structure.

Caffeine is the most abundant methylxanthine in foods [5]. It is present in nearly 100 species in 13 orders of the plant kingdom [6]. Although *Coffea* species are the major sources, it is also abundantly found in *Camelia sinensis*, maté (*Ilex paraguariensis*), coca (*Erythroxylon coca*) and *Coffea* leaves, in cocoa

(*Theobroma cacao*) and guaraná (*Pauliniacupana*) seeds, and in kola (*Cola sp.*) nuts [2,7], in addition to other less significant sources. It is also found in several commercial non-alcoholic beverages, powders, capsules and in association with therapeutic drugs [5].

Although there are reports on the use of coffee at least since the 9th century, caffeine was only understood as a substance and component of food matrices in the middle of the 19th century. The compound was first isolated by the German researcher Ferdinand Runge (1795–1867), under the request of the chemistry and technology professor Johann Wolfgang Döbereiner (1780–1849) and the philosopher Wolfgang von Goethe (1749–1832) [8]. Caffeine was first called “kaffein”, which later became “caffeine” in English and was included in the medical vocabulary in 1823 [9]. In the following years (1827 to 1865), the same compound was isolated from other plants with different names at times [10].

The chemical structure of caffeine was first proposed in 1875 by Ludwig Medicus (1847–1915), who, unusual for that time, deduced it from the already known pure compound [10]. The structures of caffeine and other methylxanthines were validated in 1882 by Hermann Emil Fischer (1852–1919), who published a series of studies on purine synthesis that were cited in his Nobel Prize in Chemistry in 1902. [11,12]. Since then, studies on caffeine have evolved largely, together with its broad consumption worldwide. Today, much is known about the compositional, metabolic and physiological aspects. This review will summarize these aspects, with a focus on contents in different beverages, health benefits and potential adverse effects associated with caffeine consumption through coffee.

2. Chemical Aspects and Analysis of Caffeine

Caffeine is colorless at room temperature, odorless, and bitter [13]. It dissolves well in boiling water, and its solubility is increased by the addition of acids and formation of complexes, such as benzoate, citrate, and salicylate, at high temperatures (1%, *w/v*, at 15 °C and 10% at 60 °C) [14]. Better solubility is achieved in chloroform at room temperature [2]. In aqueous solution, at physiological pH, caffeine is a non-ionized compound. The melting point is 234 to 239 °C and the temperature of sublimation, at atmospheric pressure, is about 178 to 180 °C [2]. Reports on caffeine ultraviolet (UV) absorption region differ slightly in the literature. A reasonable wavelength interval between 250–280 nm can be concluded from reports [2], although wavelengths from 243 to 302 nm have been used for analyses [15]. Maximum absorption (λ max) in aqueous solution occurs at 272/273 nm [4,15,16].

Several analytical methods have been proposed for determination of caffeine in foods. Gravimetry was the first method developed for this analysis in food products [17]. However, it was time-consuming, and the poor cleaning procedure of the extract caused overestimation of the contents [18]. The absorption of electromagnetic radiation in the UV region by caffeine was described in the early 20th century [19]. A low-cost spectrophotometric analytical method based on the absorbance at 272 nm was developed in 1948 [20]. The method was faster, simpler and more accurate than gravimetric methods, but the results could still be overestimated by the presence of matrix interferences, usually associated with food products [18,21].

High-performance liquid chromatography (HPLC) technique was used in caffeine analysis for the first time in the early 1970s [22]. Ion exchange chromatography was also used to separate caffeine from other organic compounds in coffee at that time [23]. The use of HPLC for determination of caffeine was an important qualitative leap in terms of parameters of precision, accuracy, and speed [18], also allowing multi-analysis of methylxanthines. The development of stationary phases containing micro-particles (5 μ m) and the use of the gradient system to separate caffeine from other methylxanthines allowed better resolution in a shorter period of time [18]. However, in coffee matrix, due to the very low amount of other methylxanthines, HPLC and ultra-high-performance liquid chromatography (UPLC) isocratic systems have been often applied for determination and quantification of these compounds, using a reverse-phase column and a mixture of methanol and water as the mobile phase [24–26]. Methods for HPLC analysis evaluating simultaneously caffeine and additional compounds were developed in the 1980s [27]. In some cases, however, when only one methylxanthine is present in

the matrix, UV-Vis spectrophotometric determination in clarified extracts may be preferred due to its low cost, fastness and reasonable accuracy and reproducibility when compared to chromatographic techniques [24]. With the development of UV/diode array detector (DAD), the multi-analysis of methylxanthines improved in terms of precision and accuracy, since each alkaloid was analyzed at its maximum absorption wavelength [28,29]. A UPLC/DAD method using a gradient of formic acid 0.1% and acetonitrile has been recently applied for simultaneous determination of methylxanthines and sugars [30]. Liquid chromatography-mass spectrometry (LC-MS) is one of the preferred techniques for determining caffeine at low levels and/or in very complex matrices. The three advantages of LC-MS over conventional HPLC methods can be represented by three “S”, sensitivity, selectivity and speed. Nonetheless, due to the high cost, LC-MS techniques are not economically justifiable for the analysis of caffeine in major sources of this compound, such as coffee [31].

In recent years, spectroscopy in the infra-red region has been introduced as a promising alternative technique to wet chemical methods [18,32], especially the Fourier transform infra-red spectroscopy (FTIR) [33]. Methods using this technique dissolve the active principles in chloroform, followed by filtration of the solution to remove the excipients [18]. Chemometrics is a valuable mathematical tool that, in combination with different chemical methods, enables the analysis of many variables in a single sample [18]. Principal components analysis (PCA) has been most commonly used among chemometric methods to discriminate samples with different chemical patterns. In the study by Briandet et al. [32], analyses of caffeine were performed by FTIR, followed by PCA, to discriminate *Coffea arabica* and *Coffea canephora* species among lyophilized dry instant coffee blends from Ireland.

More recently, bare carbon electrodes have been proposed as simple and efficient sensors for the quantification of caffeine in commercial beverages, presenting similar values when compared to results from UPLC analyses [30].

3. Contents of Caffeine in Green Coffee Seeds

The caffeine function in coffee plant and seeds seems to be basically related to protection. The “chemical defense theory” proposes that caffeine in young leaves, fruits, and flower buds acts to protect soft tissues from predators, such as insect larvae [34] and beetles [35]. The “allelopathic theory” proposes that caffeine in seed coats is released into the soil to inhibit the germination of other seeds [4,36].

The genetic factor is the key determinant for caffeine content variation in green (raw) coffee seeds, especially between species and, to a lesser extent, varieties [37]. The effect of environment, agricultural practices, including the use of fertilizers, and post-harvest processing on methylxanthines contents seems to be less important than genetic aspects, except in the case of secondary processing, such as decaffeination [38–40]. The range of caffeine contents reported for green *C. arabica* L. vary in the literature between 0.7 and 1.7 g/100 g (dry matter-dm) [15,26,38,41–52], while those for *C. canephora* vary in the range between 1.4 and 3.3 g/100 g (dm) [26,38,41,42,45,49,50,52–56]. However, common values are in a narrower range, between 1.0 and 1.2 g/100 g, dw, for *C. arabica* [15,44,46–51,54], and between 1.7 and 2.1 g/100 g (dm) for *C. canephora* [26,39,43,51,55,56]. In general, *C. canephora* seeds contain 40–70% more caffeine than *C. arabica* species [57,58]. *C. arabica* presents a more homogeneous composition independent of their geographical origin, due to the low genetic diversity characteristic of the species [41], while higher variability is observed in *C. canephora* seeds [55]. The lower caffeine content in *C. arabica* plants makes them more vulnerable to phytopathogens, as well as to biological and mechanical stress, than *C. canephora* plants [59]. Other methylxanthines have been identified in coffee seeds, but their contents are negligible, less than 1% of total methylxanthines [41].

Caffeine forms hydrophobically bound π -molecular complexes with chlorogenic acids, the main phenolic compounds in coffee, especially with 5-caffeoylquinic and 3,5-dicaffeoylquinic acids [60–63], in a 1:1 molecular ratio [64]. According to D’Amelio et al. [62,63], additional complexes may be formed in green coffee, but at lower rates, with caffeoylquinic acid precursors as well as other chlorogenic acid compounds, such as feruloylquinic acids, isomers of dicaffeoylquinic acid, and, during roasting, with

chlorogenic acids lactones [65]. Such complexation in green seeds may be one of the facts responsible for the correlation observed between chlorogenic acids and caffeine contents within the subgenus *Coffea* [65]. These complexes seem to be also formed in the beverage (see Section 4: Contents of caffeine in roasted coffee seeds and brews).

Regarding post-harvest processing, after the fruits harvest, green coffee seeds are obtained by one of the different methods from which the most commonly known are called dry, wet and semi-dry processing [57,66]. Although all methods aim at removing the fruit flesh of coffee cherry, they do it in different ways, and this affects the final contents of some compounds in the seeds [67]. A few studies have compared the caffeine contents in seeds obtained by different post-harvest methods. They included comparisons between wet and dry methods [68], wet and semi-dry methods [48], and dry and semi-dry methods [69]. None of them observed a significant difference in caffeine results from the different methods.

Regarding the degree of maturation, small variation (about 2–10%) in the content of caffeine in seeds have been observed during *C. arabica* fruits development [42,70]. After fruits development, significant changes have been observed among seeds from different maturation stages, with a decrease in contents observed as the fruits ripened and through senescence [44,71].

4. Contents of Caffeine in Regular and Decaffeinated Roasted Coffee Seeds and in Brews

4.1. Caffeine in Roasted and Ground Coffee

The content of caffeine is not significantly altered during coffee roasting due to its thermal stability, but small losses may occur owing to sublimation. In terms of percent composition, an increase in caffeine content may be observed due to the loss of thermolabile compounds [57]. The range of caffeine contents reported for roasted *C. arabica* seeds vary in the literature between 0.7 and 1.6 g/100 g (dm) [4,15,26,29,50,70,72–74], while those for *C. canephora* vary in the range between 1.8 and 2.6 g/100 g (dm) [29,50,54,72].

4.2. Caffeine in Soluble Coffee

Soluble coffee production typically involves treating ground roasted coffee with hot water and high pressure to extract the water-soluble compounds, followed by drying. While in Western countries commercial ground roasted coffee generally consists of *C. arabica* seeds alone or of a blend with a small percentage of *C. canephora* seeds, in some Western countries, a high percentage of *C. canephora* or plain *C. canephora* may be designated for instant coffee production owing to the yield of higher amount of soluble solids in the brew. This explains the higher caffeine contents often observed in reconstituted soluble coffees purchased in some countries, such as Brazil, for example [57]. In *C. canephora* producing countries, such as Indonesia, for example, this species is also abundantly used for commercial ground roasted coffee.

Data from a few studies investigating the contents of caffeine in *C. arabica* and *C. canephora* seeds roasted in small scale laboratory roasters, as well as in commercial ground roasted blends and soluble coffees are presented in Table 1.

Table 1. Summary data from studies investigating the caffeine contents in roasted *Coffea arabica*, and *Coffea canephora* seeds, commercial blends and soluble coffees.

Coffee Species/Cultivar/ Type	Country	N	Range of Caffeine Content (g/100 g)	Mean Caffeine Content (g/100 g)	Reference
<i>Coffea arabica</i>					
cv. Minas	USA	2	0.9–1.2	1.1	[4]
Nr	Ethiopia	4	0.9–1.1	1.0	[15] *
Nr	Hawaii, Colombia, Brazil, Africa	6	0.8–0.9	0.8	[26]
Nr	Brazil, Mexico, Colombia, Guatemala	9	1.2–1.6	1.3	[29]

Table 1. Cont.

Coffee Species/Cultivar/ Type	Country	N	Range of Caffeine Content (g/100 g)	Mean Caffeine Content (g/100 g)	Reference
Nr	Croatia	6	0.8–1.4	1.3	[50]
Nr	Brazil	4	0.7–1.1	0.9	[70]
Nr	Brazil	3	1.2–1.3	1.3	[72]
Nr	Poland	2	1.0–1.1	1.0	[73]
cv. Bourbon, Catuai, Icatu	Brazil	3	1.0–1.3	1.2	[74]
<i>Coffea canephora</i>					
cv. Robusta	India, Honduras, Vietnam, Angola, Caneron	20	2.0–2.6	2.3	[29]
cv. Robusta	Croatia	2	1.8–2.5	2.2	[50]
cv. Robusta	Ivory Coast	1	-	2.0	[54]
-	Brazil	3	2.2–2.3	2.2	[72]
Commercial blends of <i>C. arabica</i> or <i>C. arabica</i> and <i>C. canephora</i> (cv Robusta or cv. Conilon)					
Arabica blends	USA	36	0.8–1.4	1.2	[4]
Blend	Africa	1	-	1.4	[26]
Blends	Brazil	10	0.8–1.4	Nr	[75]
Blends	USA	6	1.0–1.6	1.3	[76]
Nr	Nr	3	1.4–1.9	1.7	[77]
Blends	Brazil	40	0.8–1.6	1.2	[78]
-	Mexico	3	1.5–1.7	1.5	[79]
<i>Soluble coffee</i>					
Nr	Brazil	2	2.0–2.2	2.1	[26]
Nr	Nr	2	4.5–4.8	Nr	[77]
Blends	Brazil	10	1.8–3.1	2.5	[78]
Arabica	Brazil	3	2.8–4.1	3.4	[80]
cv. Conilon	Brazil	3	3.9–5.8	5.0	[80]
Nr	Brazil	9	1.6–3.2	2.5	[81]
Nr	Kenya	2	1.6–3.4	2.7	[82]
Nr	Nr	5	2.2–3.9	2.8	[83]

Note: N: number of samples, Nr: not reported. Analyses performed by liquid chromatography unless specified by * which indicates analysis performed by UV/vis spectrophotometer.

4.3. Caffeine in Coffee Brew

Caffeine content in coffee brew is closely related to its stimulating properties as well as to about 10% or less of its bitterness [39,47]. The final content of caffeine ingested by coffee drinkers depends on all factors that affect the seeds contents, including blend composition, which depends mainly on genetics, the degree of maturation, and the method used to brew the coffee, which may vary considerably according to social and cultural habits of each country [57]. Caffeine is well extracted by the most common hot brewing methods [57]. Percolation and decoction methods tend to extract more than infusion methods which have low extraction power [58], but not only the extraction method is important. The proportion of water to powder, water temperature, size of particle and duration of the brewing process are determinant factors [57,76]. Caffeine seems also to be more easily extracted from dark roasted coffees, and the type of filter may alter the result [84]. Lastly, there is the variability within the preparation method, which may be very low or quite high in the case of commercial establishments with different people preparing the brews. In a study that analyzed caffeine content in 20 different specialty coffees purchased at coffee shops in the United States, the amount of caffeine in brews ranged from 76 to 112 mg/240 mL serving (equivalent to 32 to 47 mg/100 mL) [85]. It was also observed that caffeine content in the same type of coffee purchased in the same store on six separate occasions ranged from 130 to 282 mg/240 mL serving (equivalent to 54 to 118 mg/100 mL) [85]. Data from studies investigating the contents of caffeine in coffee beverages prepared by different methods are presented in Table 2. Average values for the most commonly used methods are presented in Figure 2.

Table 2. Caffeine contents in coffee brews obtained by different extraction methods.

Coffee Species/ Type	Country	N	Amount of Powder (%) to Water/ 100 mL	Water Temperature	Brewing Time	Range of Caffeine Contents (mg/100 mL)	Mean Caffeine Content (mg/100 mL)	Reference
Manual drip								
Arabica	Colombia	2	10	100 °C	2 min	48.1–53.0	50.8	[86]
Arabica	Indonesia	2	10	100 °C	2 min	48.3–57.9	53.1	[86]
Arabica	Kenya	2	10	100 °C	2 min	54.2–57.3	55.8	[86]
Arabica	Costa Rica	2	10	100 °C	2 min	50.7–59.0	57.1	[86]
Arabica	USA	1	7	95 °C	~3 min	-	60.2	[4]
Blend	Brazil	40	10	90 °C	4 min	71.8–44.1	59.9	[85]
Blend	Brazil	7	10	92.3 °C	Nr	39.4–51.8	45.6	[87]
Blend	UK	1	Nr	Nr	Nr	-	55.0	[88]
Blend	USA	26	Nr	Nr	Nr	Nr	51.1	[89]
Nr	USA	1	Nr	Nr	Nr	-	52.0	[90]
Nr	USA	14	Nr	Nr	Nr	30.3–54.8	39.7	[85]
Nr	USA	7	10	100 °C	2 min	Nr	131.0	[91]
Electric dripper								
Arabica	Guatemala	1	6	90 °C	6 min	-	100.8	[92]
Arabica	USA	1	7	95 °C	4 min	-	76.5	[4]
Robusta	Vietnam	1	6	90 °C	6 min	-	200.8	[92]
Robusta	Spain	1	6	90 °C	7 min	-	110.0	[93]
Blend	Brazil	40	10	90 °C	4 min	100.9–138.3	119.6	[85]
Blend	Spain	2	6	90 °C	7 min	22.0–105.0	63.5	[93]
Espresso								
Arabica	USA	1	7	90 °C	28 s	-	72.2	[4]
Arabica	Ethiopia	1	14	92 °C	30 s	-	410.0	[94]
Arabica	Ethiopia	1	18	92 °C	25 s	-	420.0	[94]
Arabica	Guatemala	1	17.5	90 °C	24 s	-	100.7	[92]
Arabica	Ethiopia	1	18	92 °C	25 s	-	420.0	[94]
Arabica	Guatemala	1	17.5	90 °C	24 s	-	100.7	[92]
Arabica	Spain	1	18.7	96 °C	21 s	-	209.0	[95]
Robusta	Vietnam	1	17.5	90 °C	24 s	-	177.3	[92]
Robusta	Spain	1	18.7	96 °C	21 s	-	296.0	[95]
Robusta	Spain	1	17.5	90 °C	30 s	-	375.0	[93]
Blend	Scotland	20	Nr	Nr	Nr	160.4–650.0	378.0	[96]
Blend	Croatia	4	14	95–97 °C	Nr	97.7–190.0	142.0	[97]
Blend	Australia	97	Nr	Nr	Nr	58.0–700.0	247.3	[98]
Blend	Brazil	40	10	90 °C	28 s	159.5–233.2	196.4	[85]
Blend	Spain	2	17.5	90 °C	30 s	63.0–241.0	152.0	[93]
Blend	Spain	1	18.7	96 °C	21 s	-	288.0	[95]
Nr	USA	1	Nr	Nr	Nr	-	123.0	[90]
Nr	USA	6	Nr	Nr	Nr	138.3–290.2	197.1	[92]
Nr	USA	27	Nr	Nr	Nr	-	250.0	[91]
Regular/Nr	Italy	1	Nr	Nr	Nr	-	317.1	[30]
Lungo/Nr	Italy	1	Nr	Nr	Nr	-	171.3	[30]
Ristretto/Nr	Italy	1	Nr	Nr	Nr	-	533.4	[30]
Mocha								
Arabica	USA	1	7	95 °C	10 min	-	92.4	[4]
Arabica	Guatemala	1	8	93 °C	10 min	-	156.4	[92]
Arabica	Ethiopia	1	10	90 °C	Nr	-	128.0	[94]
Robusta	Spain	1	8	93 °C	10 min	-	192.0	[93]
Robusta	Vietnam	1	8	93 °C	10 min	-	226.8	[92]
Blend	Spain	2	8	93 °C	10 min	28.0–159.0	93.5	[93]
Infusion bag								
Arabica	Japan	4	2.5	95 °C	5 min	-	43.2	[4]
French press								
Arabica	Guatemala	1	8	98 °C	5 min	-	118.3	[92]
Arabica	Hawaii	4	10	98 °C	6 min	97.0–104.9	100.5	[99]
Arabica	USA	1	7	90 °C	5 min	-	75.0	[4]
Arabica	Portugal	1	13	100 °C	2.5 min	84.0–106.0	95.0	[99]
Arabica	Ethiopia	1	10	95 °C	5 min	-	52.0	[94]
Robusta	Vietnam	1	8	98 °C	5 min	-	156.4	[92]
Robusta	Spain	1	8	98 °C	5 min	-	136.0	[93]
Blend	Spain	2	8	98 °C	5 min	20.0–112.0	66.0	[93]

Table 2. Cont.

Coffee Species/Type	Country	N	Amount of Powder (%) to Water/100 mL	Water Temperature	Brewing Time	Range of Caffeine Contents (mg/100 mL)	Mean Caffeine Content (mg/100 mL)	Reference
Aero press								
Arabica	Ethiopia	1	6.6	93 °C	1 min	-	78.0	[94]
Cold brewing								
Arabica	USA	1	7	95 °C followed by 10 °C	12 h	-	52.3	[4]
Arabica	USA	1	7	10 °C	12 h	-	51.2	[4]
Arabica	Hawaii	4	10	25 °C	24 h	99.0–123.0	112.0	[99]
Arabica	Ethiopia	1	10	25 °C	6 h	-	125.0	[94]
Turkish coffee								
Arabica	USA	1	7	90 °C	5 min	-	85.3	[4]
Blend	Croatia	3	8	98 °C	5 min	190.0–260.0	233.0	[94]
Boiled coffee								
Arabica	USA	1	7	95 °C	5 min	-	85.0	[4]
Arabica	Brazil	3	10	100 °C	Nr	110.8–122.5	114.7	[100]
Conilon	Brazil	3	10	100 °C	Nr	171.3–192.0	179.8	[100]
Soluble or instant coffee beverage								
-	Brazil	10	2	90 °C	-	257.3–280.7	269.0	[85]
-	Nr	2	1	hot water	-	Nr	212	[21]
-	Nr	2	2.2	hot water	-	Nr	74.5	[101]
-	Nr	2	1	hot water	-	Nr	246.8	[102]
-	UK	Nr	Nr	hot water	-	-	39.0	[93]
-	USA	26	Nr	hot water	-	-	44.0	[97]
-	USA	20	Nr	hot water	-	-	39.0	[90]
Read to drink coffee beverage								
Nr	Japan	4	-	-	-	-	57.1	[4]

Note: N: number of samples. Nr: Not reported.

Figure 2 illustrates the caffeine content variability among brews obtained by different preparation methods as well as the variability within each method. The reasons for such values are already aforementioned. Mostly, in addition to the characteristic power of extraction of the methods, which have been comparatively consistent in literature reports [78,84], the amount of coffee to water and grid also vary traditionally among them. It is important to note that these values are given per 100 mL and, in order to compare the consumption per serving, one has to consider the various existing sizes of cups used for the different types of coffees and cultures. Usually, however, the more concentrated the brew, the smaller the cup is. This explains the large servings of infusions of manually dripped coffees (236.5–591.4 mL/8–20 oz) in the USA, in comparison with 15–30 mL of a ristretto in Italy.

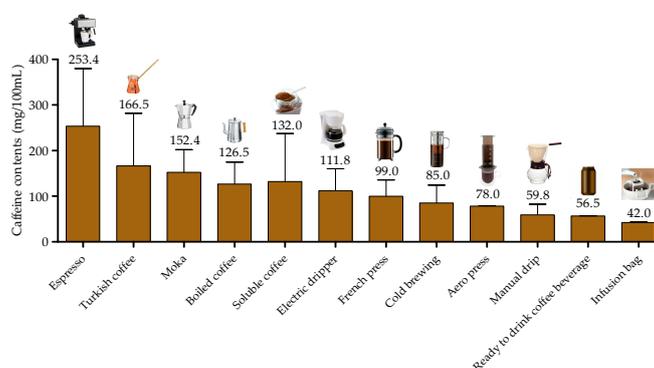


Figure 2. Mean reported caffeine contents (mg/100 mL) in coffee brews obtained from a variety of blends, and by different preparation methods (values extracted from Table 2).

4.4. Caffeine Complexation with Chlorogenic Acids

It has been reported [62,63] that in addition to the free caffeine content presented in Table 2 and Figure 2, there are also some complexes formed between caffeine and other compounds. According to estimates based on results from model complexation with pure compounds and from espresso beverage analysis [62,63], about 20% of total caffeine in the beverage (considering free and bound caffeine) forms a complex with 5-caffeoylquinic acid (the main chlorogenic acid in coffee) and, to a lesser extent, with other major chlorogenic acids and lactones, the latest formed during roasting process. Structurally explaining, it was proposed, using a model in aqueous solution, that in the case of complexation with 5-caffeoylquinic acid, and probably also feruloylquinic acid and lactones, the plane of caffeine molecule would be parallel to the plane of the aromatic ring of the caffeoyl ester group and that the five and six-membered rings of the nitrogen heterocycle would be equally involved in the complex formation. In the case of 3,5-dicaffeoylquinic acid, a sandwich structure (caffeine between two caffeoyl arms) was proposed. For other dicaffeoylquinic acids with lower chances of complexation, other forms of complexations were proposed. In addition to forming complexes with chlorogenic acids, according to the authors, about 10% of caffeine could be bound to other types of substances, such as proteins and, after roasting, to melanoidins. For structures and other information on chlorogenic acids, please see reference [103].

4.5. Caffeine in Decaffeinated Coffee

Coffee decaffeination is performed in the green seeds but given that recommendations for residual content are made for roasted coffee, we chose to present this subject here. The first method for this purpose was developed in Europe, but decaffeinated coffee achieved its first broad market in the United States during the 1950s [104]. Since the early 1970s, the demand for decaffeinated coffee has also gradually increased worldwide. World consumption of this type of coffee is difficult to gauge owing to the lack of separate statistical data for many importing countries. According to the latest Coffee Drinking Study performed by the National Coffee Association (USA), the consumption of decaffeinated coffee in 2009 reached 16% of total coffee consumption [104]. Current information on decaffeinated coffee sales in the US is not available in common coffee market reports. Elsewhere, consumption of decaffeinated coffee has been fairly static over the last two decades and currently accounts for approximately 12% of total worldwide coffee consumption [105], although in many countries new low-caffeine coffee products have been introduced [106].

The decaffeination process can be performed using different methods and extraction vehicles (water, supercritical carbon dioxide, ethyl acetate, methanol chloride) and often leaves residual amounts of caffeine in the seeds [57]. According to various national and international rules and regulations, decaffeination processes should lower the methylxanthine concentration by 97–99.9% in ground roasted coffee and 97% in instant coffee [107–109], with no significant influence on other natural compounds [58]. A more restricted norm is mandatory in the European Community countries, in which decaffeinated coffee must be 99.9% alkaloid-free [58,107].

About 0.3–0.5 mg caffeine/100 g have been reported in decaffeinated ground roasted coffees [76] and 0.7–0.9 mg/100 g in instant decaffeinated coffees [77]. Regarding decaffeinated coffee brews, caffeine values from 0.1 to 2.6 mg/100 mL have been reported for brews made from decaffeinated ground roasted coffees purchased in Brazil and in the United Kingdom [24,88], while in decaffeinated coffee brews purchased in the United States coffee shops caffeine content reached 18 mg/473 mL serving (~3.7 mg/100 mL) [92]. Contents from 0.9 to 1.2 mg/100 mL have been reported for reconstituted instant decaffeinated coffee [21,24,88]. It is noteworthy mentioning that, for a heavy coffee drinker, the ingestion of multiple servings of decaffeinated beverages could result in caffeine doses equivalent to a caffeinated beverage [110].

5. Global Caffeine Consumption Through Coffee

Currently, approximately 80% of the world's population consumes a caffeinated product every day [111], mainly for its stimulating effects, which makes it the most widely consumed psychoactive substance in the world [112–116]. So where does coffee consumption stand in relation to other caffeine sources? Over the last 50 years, world coffee consumption increased at a mean annual growth rate of 1.9%, to almost 9.7 million tons in 2018 [117]. The highest coffee consumption occurs especially in the Americas, Europe and Japan [117]. The European Union is responsible for the largest consumption volume (about 28% of the total world consumption), but breaking up into individual countries, the USA are the first consumer country (about 16% of the total world consumption), followed by Brazil (the largest producer, with 13% of world consumption), European Union countries, and Japan. Philippines, Russia, Ethiopia, Canada and Mexico contribute about 2.8%, 2.5%, 2.4%, 2.3% and 1.5% of total world consumption, respectively [117]. In Canada (6.5 kg/year coffee per capita consumption), as well as in many European countries, such as Denmark (8.7 kg/year), Norway (9.9 kg/year) and Finland (12 kg/year), coffee consumption is very prevalent and accounts for most of the daily caffeine consumption among adults [118].

Considering these data, it is not difficult to accept that coffee is the major contributor to caffeine intake in most countries worldwide. Exceptions occur in specific areas, such as regions of South America [119,120], Ireland and the United Kingdom, China, India and other Asian countries [121], where other beverages, such as maté leaves, natural guaraná beverage, and black/green *Camelia sinensis* teas, are typically consumed.

However, additional sources of caffeine and other methylxanthines, mainly theobromine, are also consumed worldwide and, for this reason, over the past years, there has been a renewed interest in understanding caffeine exposure in populations. The daily caffeine intake and the type of caffeinated product consumed vary considerably around the world, with sex, age segments, cultural habits and household income. The age interval considered for each category also varies among studies and reviews. The cultural habits influence not only the total intake but also the percent contribution of foods to such intake. Differences also occur among geographic regions and between metropolis and countryside, where certain types of products are not available. Other than cultural habits, one reason for the differences in consumption levels is the variable concentrations of caffeine found among home-made beverages [122].

Regardless of the longstanding consumption of caffeine-containing beverages in the diet and acknowledging all the aforementioned aspects, there is a lack of current and comprehensive population-based data on caffeine intake. Most studies on intake still cite information dating back the 1980s and 1990s, when Barone and Roberts [90] highlighted results from earlier population-based surveys or data from the food balance sheets published by the Food and Agriculture Organization (FAO) of the United Nations in 1995 [123], which contains average food consumption estimates in all world countries for all genders and ages. However, the national consumption of caffeine summarized in the food balance sheets depended heavily on official statistics, which were thought to be greatly unreliable at that time [111]. In addition, the estimates did not include soft drinks, although they may be a major source of caffeine for children and adolescents, especially in Western society [90,111,121,124]. As a result, the intake was underestimated. More recently, in a survey performed in 2015 by Mitchell et al. [125], including 37,602 interviews in the United States, adults consumed, on average, 152 mg of caffeine/day and the elderly 207.3 mg of caffeine/day. Less was consumed by adolescents (83 mg/day) and children (30 mg/day). Due to the high consumption of regular soft drinks, they accounted for the main source of caffeine among children and adolescents, while coffee was the main source of caffeine consumption in adults. This was also observed in an earlier study performed by the same authors in 2014 [124]. According to Mitchell et al. [125], the American population, considering all ages, consumes 164.5 mg caffeine/day, with coffee being responsible for 64% of this amount. Considering only adults and the elderly, the coffee contribution was reported to be 63% and 76%, respectively.

Further, in 2015, the Comprehensive European Food Consumption Database organized by the European Food Safety Authority (EFSA) [126] was used for the calculation of caffeine intake from all sources. It contains data from 39 surveys in 22 different European countries for a total of 66,531 participants. In most European surveys covered by EFSA's Food Consumption Database [126], coffee was the predominant source of caffeine for adults and the elderly, contributing, on average (considering all countries), 78% and 84% of total caffeine intake, respectively. Exceptions were Ireland and the United Kingdom, where tea was the main caffeine source. The average caffeine consumption by adults in the UK was reported to be 138 mg/day for adults and 165 mg/day for the elderly, with the coffee contribution of only 34% and 33%, respectively. Nordic countries were among the largest consumers. The reported intakes by adults in Denmark, Finland, and Sweden were 320, 236, and 205 mg/day for adults, and 362, 214, and 222 mg/day for the elderly, respectively, with coffee contributions of 88%, 94% and 85% for adults and 91%, 97% and 89% for the elderly, respectively.

There is no official data on caffeine consumption in Latin American countries [127]. However, it is believed that caffeine intake in countries, such as Brazil and Argentina, are high due to the large popular intake of coffee and maté tea. A similar situation may occur in China due to the high intake of green tea [127]. Recently, in Brazil, caffeine consumption was estimated [128] based on 13,569 interviews by the national consumption survey (Consumer Expenditure Survey, 2008–2009) performed by the Brazilian Institute of Geography and Statistics. The average daily caffeine intake by Brazilians of all genders, age groups, geographic locations, and income classes was, on average, about 130 mg/day, with coffee being responsible for 90% of daily caffeine intake. Considering adults and the elderly, total intakes were, on average, 137 and 146 mg/day respectively, with coffee contributions of 90% and 95%, respectively.

Regarding pregnant or lactating women, studies that evaluated the available data on daily caffeine intake among these groups are very scarce [118]. Using data collected in the United States by Share of Intake Panel for pregnant women, Knight et al. [129] estimated in 2004 the average daily caffeine consumption from beverages in about 58 mg/day. Later, in 2009, using data from interviews, Olmos et al. [130] estimated daily caffeine consumption among Argentinean pregnant women in approximately 200 mg/day.

6. Caffeine Metabolism

The first studies on coffee bioactivity in humans date back centuries ago. Coffee was present in medical journals since the 18th century, and the early physiological explanations already emphasized nervous and vasomotor stimulation [131]. Caffeine is involved in several biological effects in the human body, most of them related to improvements in brain and Central Nervous System (CNS) functions. However, the biological effects associated with caffeine consumption largely depend on its biotransformation in the body [132]. The earliest reported study on caffeine metabolism seems to have been carried out in 1850 by Lehmann, who, following an oral dose, failed to detect traces of caffeine in human urine. This was even before the chemical characterization of the compound by Hermann Emil Fischer (1852–1919) in 1882 [114]. Albanese, in 1895 was the first to report that dogs and rabbits fed large doses of caffeine excreted a monomethylxanthine, showing that ingested methylxanthines were demethylated. A few months later, Rost published data on the excretion of unchanged caffeine and theobromine in a cat, a dog, a rabbit, and a man [114]. The most complete pharmacokinetic studies on caffeine in human subjects as well as various experimental animals started to be performed late in the 1950s [133–137]. Other studies in humans followed including minor methylxanthines, accessing their primary metabolites in plasma [138–141] or in urine [141–143]. Paraxanthine, 1-methylxanthine, and 1-methyluric acid have been the first urinary metabolites of caffeine identified in men and rabbits [133]. Subsequently, theobromine and theophylline were also reported to be urinary metabolites of caffeine in men and dogs [135,144]. Later, improved analytical methodologies confirmed the extensive metabolization of caffeine, identifying secondary metabolites such monomethylxanthines (1-methylxanthine and 7-methylxanthine), and methyluric

acids (1-methyluric acid and 1,7-dimethyluric acid) in both plasma [145–148] and urine [148,149]. However, the most important results obtained in earlier studies have been ratified by recent studies.

6.1. Absorption

The pharmacokinetics of caffeine is relatively well elucidated and has been reported in several studies, including recent ones [114,146,148,149]. Most existing reports on the matter come from studies using pure caffeine in the form of solutions, capsules, and tablets [138,140,150,151]. Among the food matrices evaluated, the most common are coffee, cola, and cocoa products [114,131,140,141,146–148]. The bioavailability of caffeine is similar among dogs, rats, and mice [114,152]. Because no hepatic first-pass effect complicates its pharmacokinetics, caffeine absorption from foods and beverages has been shown to be independent of the administration route, age, sex, health status, and concomitant administration of alcohol, drugs and nicotine exposure [58,114,132].

Following ingestion, caffeine is rapidly and almost completely (up to 99%) absorbed into the bloodstream. About 20% absorption occurs in the stomach, and the remaining 80%, in the small intestine [114,138]. Caffeine can also be quickly absorbed through the oral mucosa [153], as it does not need to pass the stomach and intestine to get into the blood [153–156], and when administered via enema [146]. The pharmacokinetics of a similar dose of caffeine after a single administration of a coffee enema (107.2 ± 2.2 mg) versus coffee consumed orally (96.3 ± 1.3 mg) was compared in healthy male subjects ($n = 11$). The relative bioavailability of caffeine obtained from the coffee enema was about 3.5 times lower than when coffee was consumed orally [132,146].

In different studies, the time to reach the peak plasma concentration (T_{\max}) after oral doses of 72 to 375 mg of caffeine in healthy adult volunteers has most often varied between 15 and 60 min [138,140,142,147,155,156], but, in some circumstances, it has taken 120 min after oral intake, mainly due to delayed gastric emptying [153,157,158]. This involves motility of gastrointestinal tract, individual physiology, and vehicle (the type of food matrix, volume, solid or liquid, capsule, gum) [112,159]. In studies using different food matrices, the absorption of caffeine from soda and chocolate was slightly delayed, relative to coffee [112,140,159], caffeine in a chewing gum format was absorbed faster than in coffee [153] or in capsules [154] and in capsules, the absorption of the same caffeine dose was faster than in coffee [112,140].

After oral consumption of 70–500 mg of caffeine, peak plasma concentration (C_{\max}) varies in reports between 1.1 to 17.3 $\mu\text{g/mL}$ [114,138,140,141,145,147,148,155]. Because caffeine is usually ingested in a daily diet, owing to accumulation, its actual plasma concentration may be more than the value reported in single-dosage studies, which are usually preceded by wash out or clearance period [58,132].

6.2. Metabolism and Distribution

After absorption, caffeine is quickly distributed to most tissues (mean volume distribution of 0.6–1.0 L/kg) and body fluids (i.e., bile, milk, saliva, semen, sweat, and urine) [114], although it is received in the body as a xenobiotic substance. Studies have reported that concentrations of caffeine in saliva are approximately 20–40% lower than in plasma [145,160–163]. The limited plasma protein binding (estimated at 17–30%) combined with the relatively hydrophobic properties of caffeine allow its passage through all biological membranes [14,114] and enables it to easily cross intracellular barriers, including placental (mother-fetus-mother) and blood-brain barriers [114,132]. The distribution pattern usually does not change during a person's entire life, and it can be significantly higher in women when compared to men [164,165]. However, severely obese subjects have exhibited an increased volume of distribution [165,166], although this volume was decreased with weight reduction [114]. The effect was more important in females, and it was suggested that caffeine distribution into the adipose tissue was incomplete, representing 70–80% excess of body weight in obese subjects [164]. Caffeine and its major metabolite paraxanthine can be found in the amniotic fluid throughout gestation [167], and they are distributed to fluids and tissues of the fetus [167]. Caffeine has also been identified in women's milk [133,168].

Caffeine is rapidly and extensively metabolized in the liver cells to form dimethyl and monomethylxanthines, dimethyl and monomethyluric acids, and uracil derivatives [114]. Most of the metabolism of caffeine and other methylxanthines is performed by phase I (cytochrome P450 CYP) enzymes, mainly CYP1A2, a major enzyme, among P450 enzymes in the human liver, that accounts for approximately 13% of the total content of this enzyme group. The activity of the CYP1A2 isoform accounts for almost 90% of caffeine metabolism [114,143,169]. The remaining pathways are related to CYP1A1, CYP2E1, CYP2A6, as well as mono-oxygenase and N-acetyltransferase activities [58,132].

Paraxanthine is the major caffeine metabolite in plasma, while methylated xanthines and methyluric acids are the main metabolites excreted in urine [114,148]. The metabolic pathway of caffeine in humans is shown in Figure 3. From the metabolic pathways of caffeine, it is apparent that each metabolite may be derived from more than one precursor [139].

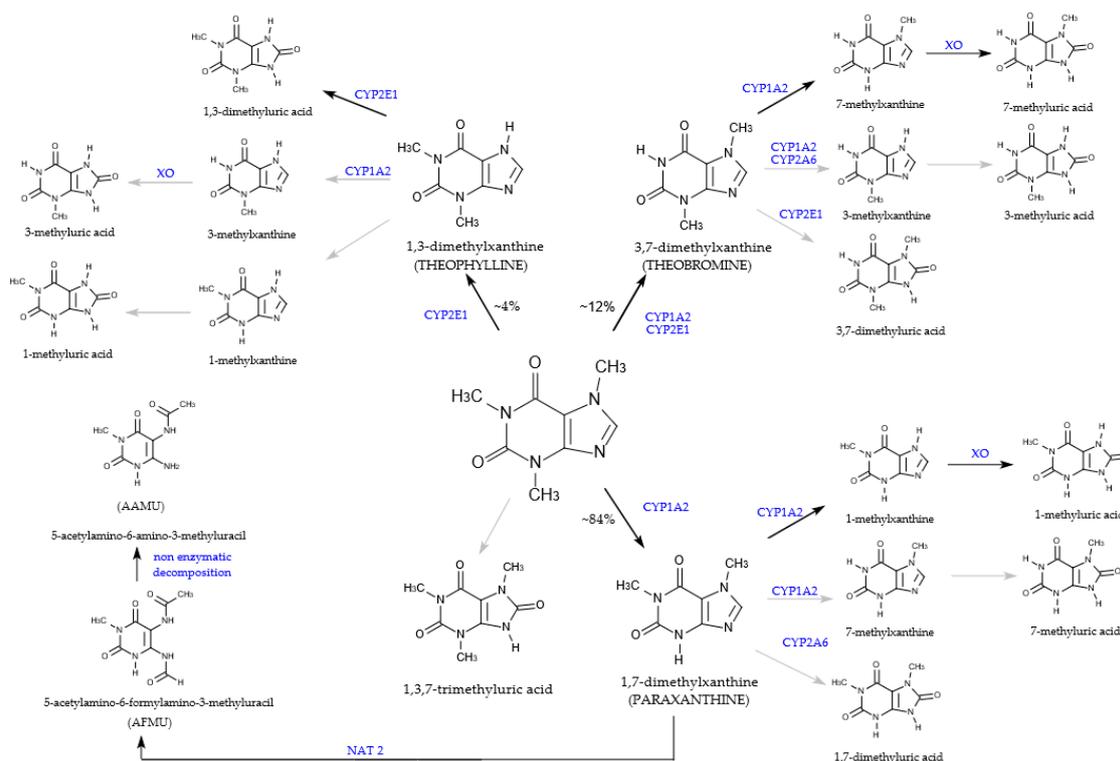


Figure 3. Metabolic pathways of caffeine and metabolites in humans. Grey arrows indicate lower production of the metabolite. Adapted from [132]. XO: xanthine oxidase, NAT 2: N-acetyltransferase 2.

The initial metabolization by CYP1A2, begins with 3-demethylation of caffeine, resulting in the formation of 1,7-dimethylxanthine (paraxanthine), which represents about 84% of primary caffeine metabolites [143,170] (Figure 3). CYP1A2 enzyme may also convert caffeine to theobromine (~12%) [171]. CYP2E1 participates in the metabolism of caffeine accelerating the synthesis of theophylline and theophylline (~4%) by 7- and 1-demethylation [58]. In a lesser extent, caffeine may be converted to 1,3,7-methyluric acid [132]. Paraxanthine, the major primary caffeine metabolite may be demethylated by CYP1A2 to form the main metabolite, 1-methylxanthine (~70%), which may be oxidized to 1-methyluric acid by xanthine oxidase. Secondary metabolites, such as 7-methylxanthine (~20%) may also be oxidized to 7-methyluric acid [58,114], and paraxanthine may also be hydroxylated by CYP2A6 to form 1,7-dimethyluric acid or acetylated by N-acetyltransferase 2, to form 5-acetylamino-6-formylamino-3-methyluracil, an unstable compound that may be non-enzymatically deformylated to form 5-acetylamino-6-amino-3-methyluracil [14,132,172] (Figure 3).

The pharmacological and biochemical properties of caffeine make it a model substrate capable of revealing activity of other drug metabolizing enzymes in animals and humans [173,174]. Caffeine has been extensively used as a probe to assess the metabolic activity and phenotyping of CYP1A2, CYP2A6, N-acetyltransferase 2 and xanthine oxidase enzymes activities, providing valuable information on cancer susceptibility, drug interactions and toxicity in population studies of healthy subjects, given that these are important detoxifying enzymes [175]. For example, the ratio of paraxanthine to caffeine, or the ratio of paraxanthine plus 1,7 dimethyluric acid to caffeine in plasma has been used as an indicator of CYP1A2 activity [58,176,177].

The half-life of caffeine in plasma seems to vary, on average, between 2.5–5 h in adults [14], although larger variations from 2.3 to 12 h have been reported [156], indicating substantial intersubject variability in caffeine elimination time [138]. Caffeine's half-life is altered in the neonatal period. It increases shortly after birth due to lower activity of cytochrome P-450 enzymes and the relative immaturity of some demethylation and acetylation pathways [178]. Caffeine's half-life is about 80 h for the full-term newborn infant and can be over 100 h in premature infants [179]. Infants up to the age of eight to nine months still present a reduced ability to metabolize caffeine, excreting in urine about 85% of the administered caffeine in its unchanged form [180]. Moreover, caffeine's half-life may be influenced by other factors, including sex, smoking habit, use of oral contraceptives, and specific biological moments, such as pregnancy [14,114]. Caffeine's half-life has been reported to be 20–30% shorter in females than in males [178] and 30 to 50% shorter in smokers compared to nonsmokers' adult males [181]. On the other hand, caffeine's half-life is almost doubled in women taking oral contraceptives [182,183] and greatly prolonged (up to 15 h) during the last trimester of pregnancy [184] and in patients with liver diseases [14]. In fact, health status, in general, is another factor that influences caffeine metabolism. The biotransformation is related to the proper function of the liver and kidneys, and the decrease of caffeine plasma clearance is a typical complication of these organ's diseases [132]. Cirrhosis and non-cirrhotic cases of viral hepatitis are the most common liver diseases that may disturb such process [58]. Obesity significantly increases plasma half-life, and decreases elimination rate, without significant effect on the clearance [132].

The consumption of high amounts could lead to saturation in caffeine metabolism [148]. Thus, while linear pharmacokinetics have been observed with caffeine intake between 70 and 100 mg, doses ranging between 250 and 500 mg have resulted in increased plasma concentration, a non-linear kinetic and prolonged half-life [148,154].

Regarding the interindividual variability in caffeine metabolization speed, the activity of CYP enzymes has been reported to vary between individuals up to 50-fold for some metabolic reactions [185]. The large interindividual variability of CYP1A2 activity may be due to factors, such as gender, race, genetic polymorphisms, and environmental influences, such as smoking or exposure to chemicals [186,187]. For example, higher activity of CYP1A2 has been shown in men compared to women [169,177,188–190] and in white compared to black subjects [191]. The enzyme activity is increased by cigarette smoking [192], and by moderate daily coffee consumption (at least three cups of coffee). Some studies have reported that herbal medicines can induce or inhibit human CYP1A2 activity [193–196]. During pregnancy, the excretion of 1-methylxanthine and 1-methyluric acid was decreased in women of between 34–36 gestational weeks that consumed caffeine doses from 123 to 369 mg [197], owing to a decrease in CYP1A2, xanthine oxidase, and acetyltransferase activities [198]. CYP1A2 is also inhibited by oral contraceptives [186].

CYP1A2 appears to be polymorphically distributed in human populations. The CYP1A2*1F polymorphism characterizes the so-called "slow metabolizer" phenotype, which decreases enzyme activity and inducibility and allows caffeine to stay longer bioavailable [192]. Conversely, homozygous individuals (AA) for the allele CYP1A2*1A are rapid caffeine metabolizers. These individuals present lower caffeine plasma levels and shorter exposure to this compound [192]. On the other hand, homozygous individuals (CC genotypes) have been considered as "slow metabolizer" [199,200]. Such polymorphism was observed in 1999 by Sachse et al. [192]. They first sequenced intron 1 of the

CYP1A2 gene in DNA from eight volunteers and observed only one polymorphism represented by an Adenine→Cytosine (A→C) substitution at position 734 (CYP1A2*1F) in the CYP1A2 gene. After this result, a mutation-specific test was developed, and a functional significance of this polymorphism was assessed in 185 healthy Caucasian non-smokers and in 51 smokers by genotyping and phenotyping using caffeine (100 mg/oral doses). The A variant (CYP1A2*1A) was more frequent (46%, $n = 108$) followed by the A/C genotype (44%, $n = 104$), and almost 10% ($n = 24$) corresponded to C variant (CYP1A2*1B). The authors observed a significant difference between the A/A and A/C genotypes in the 5h plasma paraxanthine/caffeine ratios, but not between the A/C and the C/C genotypes and indicated that the A allele is a recessive factor for high inducibility. Differences among CYP1A2 fast and slow metabolizers still require further investigation. The importance given to the phenotype of individuals in relation to CYP1A2 activity using plasma, saliva or urine samples [177] is increasing, since it has been observed that this characteristic may influence the metabolism of individuals and may or not make them susceptible to developing certain diseases. For example, slow caffeine metabolism can enable the occurrence of side effects exposure [200] or make individuals more susceptible to hypertension development [201].

Few studies investigated whether genetic polymorphisms have an effect on coffee and caffeine consumption. Rodenburg et al. [202] studied the effect of CYP1A2*1F polymorphism and smoking on coffee intake in 6,689 subjects in the Netherlands. Smokers drank almost one cup of coffee (0.90 cup/day ~ 110 mL) per day, more than did non-smokers. A meta-analysis [203] of 47,341 individuals of European ancestry, including five studies within the United States, was performed using directly genotyped and 2.5 million single nucleotide polymorphisms (SNP). Two sequence variants were found to be significantly associated with increased coffee consumption: rs2472297-T, located between CYP1A1 and CYP1A2 at 15q24 ($P = 5.2 \times 10^{-14}$) and rs6968865-T, near AHR at 7p21 ($P = 2.4 \times 10^{-19}$). An effect of 0.2 cups a day per allele was observed for both SNP. According to the authors, possibly rs2472297-T and rs6968865-T allow people to consume more coffee because in these carriers clearance of caffeine is more effective as a result of higher CYP1A1 or CYP1A2 enzymatic activities. In agreement with this result, Tantcheva-Poór et al. [204] and Djordjevic et al. [169] observed that heavy coffee consumers have higher CYP1A2 activity than those drinking less coffee, whereas Carrillo and Benitez [205] observed that low CYP1A2 activity we more often found in subjects with toxic symptoms linked to caffeine consumption.

A more recent meta-analysis included 12 studies and looked at the association between habitual coffee intake and CYP1A2 rs762551 polymorphism that splits the population in AA (rapid caffeine metabolizers), AC and CC genotypes (slow caffeine metabolizers). The analysis showed an association between the AA genotype and coffee consumption [OR = 1.13, 95%, CI = 1.03–1.24, $P = 0.06$]. This association was found in men, individuals younger than 59 years, and Caucasians, but not in females, individuals older than 59 years, and Asians [206].

6.3. Excretion

Despite caffeine efficient penetration in tissues and fluids, there is no long-term accumulation of it or its metabolites in the body as seen by whole-animal autoradiography using radiolabeled caffeine [114,207] and in humans [114]. Various experimental and human studies have proved that caffeine is excreted mostly via kidneys. In humans, the total urinary excretion of monomethylxanthines (1-methylxanthine, 3-methylxanthine, and 7-methylxanthine), dimethylurate derivatives (1,3-methyluric acid and 1,7-methyluric acid) and monomethylurates (1-methyluric acid), has been estimated to be equivalent to about 90–95% of the amount of caffeine orally administrated (5–7.5 mg of caffeine/kg body weight–bw), and that less than 5% is recovered as caffeine itself [114,208]. After peaking, plasma concentrations of caffeine decrease more rapidly than those of its metabolite paraxanthine. Therefore, despite important interindividual differences, the concentration of paraxanthine becomes higher than that of caffeine within 8–10 h after administration [114,132]. Caffeine clearance is strongly dependent on renal blood flow and urine passage because this alkaloid and its primary metabolites are extensively reabsorbed (98%) in renal tubule, but the final urine concentration significantly correlates with the

plasma caffeine level, as well as fluid intake [114]. The fecal excretion is not so relevant because it covers only a small percentage (1–5%) of the caffeine ingested [114]. The microbial products identified in human feces are: 1,7-dimethyluric acid (44%), 1-methyluric acid (38%), 1,3-dimethyluric acid (14%) and 1,3,7-trimethyluric acid (6%), and caffeine (2%) [114,209].

7. Health Benefits of Caffeine Consumption

The most well-known acute effects of caffeine consumption are stimulation of brain function and improvement in mood, and physical performance [57]. However, along the past few years, several epidemiological studies have associated moderate coffee consumption with the reduction in the relative risk of development of chronic degenerative diseases and death [210–219], and caffeine is one of the compounds responsible for many of these benefits. They include reduction in the risk of Parkinson's and Alzheimer's diseases as well as hepatoprotective effects. The mechanisms involve antioxidant and anti-inflammatory activities, among others. The main caffeine benefits will be commented below.

7.1. Caffeine, Mood, and Behavior

Once caffeine is absorbed, it exerts a variety of pharmacological actions at diverse central and peripheral sites [220,221]. These effects are predominantly related to its antagonistic activity at adenosine receptors [222], which are widely distributed throughout the body, allowing the substance's wide range of effects. Of the four adenosine receptors (A_1 , A_{2A} , A_{2B} , and A_3), caffeine acts mainly as an antagonist to adenosine A_1 and A_{2A} receptors, that are expressed in the CNS [112,223]. In humans, A_1 and A_{2A} have been shown to be activated in normal plasma caffeine concentrations (10–50 μM), while the other two receptors (A_{2B} and A_3) are only stimulated at higher concentrations [223]. Thus, when caffeine intake is able to cause an extracellular concentration of 10–50 μM , it selectively blocks adenosine receptors and competitively inhibits the action of adenosine [224]. Consequently, caffeine increases the responses from dopaminergic receptors [225] and the release of various neurotransmitters, such as norepinephrine, dopamine, and serotonin [226], stimulating psychomotor properties and improving behavioral functions, such as mood and wellbeing [227], sense of energy [228], and effects related to alertness, mental focus/attention [229,230], memory, speed at which information is processed [115,230], awareness, and reaction time [227,229,231]. According to EFSA [126], who reviewed all existing evidence of caffeine on mental performance, generally, a dose of 75 mg is needed to obtain these effects, although very large differences in individual responses to caffeine are observed as stated above. There is a consensus that in most people, at low (~50–250 mg) to moderate doses (~250–400 mg) [123,231] or 1–5 mg caffeine/body weight/day for a 70-kg person [223] positive changes occur in mood and human behavior, such as enhanced energy, well-being, sociability, willingness and motivation to work, improved self-confidence and cognitive function, including enhanced alertness and mental focus, vigilance, learning and memory [123,232]. This is generally true for both caffeine-deprived and caffeine-tolerant individuals [223].

7.2. Caffeine and Exercise Performance

Caffeine exerts a positive effect on endurance and exercise capacity owing to the aforementioned neural mechanisms that trigger a chain of physiological reactions, which makes it an ergogenic resource [233]. Exercise performance is shown to be significantly improved by oral caffeine administration or by the consumption of dietary sources, either by avoiding fatigue, improving substrates supply or by enhancing oxygen uptake [221,234]. Ergogenic effects of caffeine are similar in both non-habitual and habitual caffeine consumers [235] and have been observed after administration of doses between 3 and 6 mg/kg of body weight [233,236]. Considering a 70 kg individual and a supplemented dose of 3 mg/kg of caffeine, the intake could be estimated in 210 mg [237]. Caffeine also increases coordination [238] and reduces the perception of pain and fatigue [222]. Because caffeine increases metabolic rate, energy expenditure, lipid oxidation and presents lipolytic and

thermogenic activities, all favorable components for weight management, coffee has been used for weight loss [239,240].

Historically, in 1984 the International Olympic Committee had caffeine on the list of banned substances for urinary concentrations greater than 15 µg/mL (equivalent to 5–6 mg of caffeine/kg bw), being considered a doping infraction [241]. In 2003, the World Anti-Doping Agency (WADA) included caffeine in the list of stimulants banned from sports competitions, with a maximum allowed urinary concentration of 12 µg/mL [242]. However, it was observed that both the commonly consumed doses and the supplementation doses indicated to promote ergogenic effect (3 to 6 mg/kg bw) resulted in urinary concentrations far below the limit proposed by WADA. Because of the difficulty to differentiate the low levels of habitual caffeine ingestion from the intentional use of caffeine to improve athletic performance, WADA removed caffeine from the list of prohibited substances in 2004 and added it to its monitoring program [243], which includes substances that are not prohibited in sport, but which WADA examines in order to detect patterns of misuse [237].

7.3. Caffeine and Antioxidant and Antiinflammatory Activities

Some of the beneficial health effects reported for caffeine have been associated with antioxidant properties [244–250] although not all studies have found such activity at physiological micromolar concentrations [251]. Caffeine has been reported to be an efficient scavenger of hydroxyl radicals generated by the Fenton reaction [239], evaluated by electron spin resonance spin trapping, and it has also been reported to inhibit lipid peroxidation of rat liver microsomes at millimolar concentration by reducing the production of TBARS (thiobarbituric acid reactive substances) and lipid hydroperoxides [252]. Caffeine metabolites, especially 1-methylxanthine, 1-methyluric acid [251], and 1-methylurate [253] have also exhibited effective in vitro antioxidant activity, in the case of 1-methylxanthine, equivalent to ascorbic acid activity. Caffeine intake has also been responsible for an increase in glutathione levels in rats [250]. Corroborating in vitro results, the average plasma iron-reducing capacity of human subjects was higher after regular coffee consumption than after decaffeinated coffee consumption [254], suggesting that whole coffee is more efficient than decaffeinated coffee in respect to its antioxidant capacity. This was later confirmed by other studies [255,256].

Since inflammation is correlated with and influenced by various cytokines and chemokines, reduction of these markers should decrease the degree of overall inflammation [257]. The anti-inflammatory action of caffeine is thought to be related to phosphodiesterase inhibition and/or with adenosine receptor antagonism mechanisms [244,258]. Caffeine anti-inflammatory potential has also been linked to modifications in cell signaling molecules production [259]. In many studies, caffeine potentiated the release of anti-inflammatory cytokines, including interleukin 10 (IL-10) [260,261]. Additionally, caffeine mediates immune-suppression of pro-inflammatory cytokines release, including tumor necrosis factor alpha (TNF-α), interleukin 2 (IL-2) and interferon-gamma (IFN-γ), which have a central role in autoimmune disease initiation and propagation [262,263].

7.4. Caffeine and Antimicrobial Activity

Regarding caffeine's antimicrobial activity, there are a few in vitro studies showing that caffeine contributes to the antibacterial effect of coffee against *Streptococcus mutans*, the main cariogenic bacteria [264], as well as intestinal pathogenic bacteria's [265,266]. Additionally, a study showed the effectiveness of caffeine in inactivating and inhibiting significantly the growth of *Escherichia coli* O157:H7 in brain heart infusion broth, indicating that caffeine has potential as an antimicrobial agent for the treatment of *E. coli* O157:H7 infection and could be investigated further as an eventual food additive to increase bio-safety of consumable food products [267].

7.5. Caffeine and Neurodegenerative Diseases

The effect of caffeine on neurodegenerative diseases has gathered considerable attention in the last years [244]. Several studies have reported that regular coffee/caffeine intake is related to lower risk

of neurodegenerative diseases development, especially Parkinson's and Alzheimer's [245,268–272], and prevention of memory decline during aging [273,274]. A few findings from selected studies and meta-analyses are presented here.

Parkinson's disease is characterized by selective degeneration of dopaminergic neurons in the midbrain with a clinical presentation of motor and non-motor symptoms and by the prominent alpha-synuclein-containing proteinaceous inclusions, called Lewy bodies [275,276]. Coffee consumption appears to reduce the risk of Parkinson's disease or to delay its onset [238], by attenuating dopaminergic neurodegeneration [277]. In a meta-analysis of 26 studies from the USA, Europe, and Asia, a 25% lower risk of Parkinson's disease was found in coffee drinkers as compared to non-coffee drinkers [237,271]. The overall risk has been reported to fall at least by 24–32% per 300 mg (three cups of 100 mg) increase in caffeine intake [271]. Higher risk reduction (up to 80%) have been suggested for the intake of more than four cups of caffeinated coffee daily [231]. This inverse relationship was confirmed by similar findings in two larger ethnically diverse cohorts involving 47,351 men and 88,565 women. In both studies, the consumption of caffeinated (but not decaffeinated) coffee was associated with reduced risk of developing Parkinson's disease [277,278].

Differences between genders [278] regarding the association of caffeine intake and the risk of Parkinson's disease have been reported: while for men a strong inverse association was found, for women, this association was non-linear (“U-shaped”), with the lowest risk occurring at moderate intake (one to three cups/day). The authors further investigated this difference in two large cohorts in the USA [279,280] and found an interaction among the use of postmenopausal hormones, caffeine intake, and risk of Parkinson's disease. In one of the cohorts, the risk was increased among women who were in hormonal replacement therapy [279]. In the second cohort, the risk was increased among hormone users who were heavy coffee drinkers (more than six cups/day) [280]. The reason for the interference of estrogens on the protective effect of coffee was not clear [279,280]. Additional studies involving caffeine protection against Parkinson's disease development are presented in Table 3.

Alzheimer's disease is the most frequent cause of dementia, leading to a progressive cognitive decline [237]. Definitive diagnosis of Alzheimer's disease is based on the presence of senile plaques and neurofibrillary tangles that are identified in post-mortem brain specimens [281]. The formation of Alzheimer's disease-specific lesions is attributed to the pathological accumulation of either toxic extracellular amyloid beta peptide in the brain [282], or intraneuronal hyperphosphorylated Tau protein [283]. Constituents of the lesions are prone to promote synaptic deficits leading to memory impairments [284]. Currently, there is no medication against Alzheimer's disease once it is installed [285], but there are a few ways of preventing it, among them the consumption of foods rich in polyphenols and caffeine [281]. A meta-analysis has reported an inverse association between regular coffee consumption and the development of Alzheimer's disease, with a 27% risk reduction observed in the highest category of coffee consumption compared with the lowest [286]. The mechanism for caffeine protection is believed to be related to an anti-inflammatory effect on the A1 and A2 receptors as well as to the reduction in the deposits of toxic beta-amyloid peptide in the brain [287]. Alzheimer's disease mouse model study confirmed these findings, reporting that heavy coffee intake (the human equivalent of 500 mg caffeine or five coffee cups/day) was able to protect against and could treat Alzheimer's disease [287].

Exceptionally, in a study evaluating Japanese-American men, the authors did not find a significant association between caffeine intake and the risk of dementia [288]. However, they interestingly reported that, at autopsy, patients in the highest quartile of caffeine intake (>277.5 mg/day—all caffeine sources) were less likely to have any of the neuropathological lesions, such as Alzheimer's disease-related lesions, ischemic microvascular lesions, cortical Lewy bodies, hippocampal sclerosis or generalized atrophy [288]. Additional studies on the protective effect of caffeine against Alzheimer's disease are presented in Table 3.

7.6. Caffeine and Liver Diseases

In the past three decades, caffeine has been related to a lower incidence of chronic liver diseases, such as cirrhosis and hepatocellular carcinoma [289–291]. Additionally, in several studies, regular coffee consumption has been significantly associated with reduced hepatic fibrosis related or not with non-alcoholic fatty liver disease [292] and with chronic hepatitis C [293]. In 2016, The International Agency on Research on Cancer (IARC) evaluated several studies [294] and concluded that higher coffee consumption was associated with lower blood concentrations of biomarkers of liver damage, including alanine aminotransferase and γ -glutamyl transferase [295]. Moreover, in prospective studies, coffee consumption was associated with a lower risk of liver cirrhosis [296]. Two important meta-analyses that combined data from cohort and case-control studies, adjusting the results for potential confounders (age, sex, alcohol intake, smoking, and history of liver diseases), confirmed the inverse association between coffee consumption and liver cancer [297,298].

Caffeine, together with other bioactive compounds, such as chlorogenic acids and trigonelline, has been reported to be responsible for coffee's hepatoprotective effect. The mechanisms underlying the potential benefits of caffeine have not yet been fully determined. However, some plausible explanations have been suggested [291]. In patients with chronic hepatitis C, a suggested possible mechanism would be the alteration in liver signaling and inflammatory pathways [291]. In a rat model, caffeine suppressed connective tissue growth factor expression by interfering with a profibrogenic cytokine, transforming growth factor beta (TGF- β) signaling through the Smad pathway [299]. Smad comprises a family of structurally similar proteins that are the main signal transducers for receptors of TGF- β , which are critically important for regulating cell development and growth. Caffeine also has a direct inhibitory effect on hepatic stellate cells by downregulating focal adhesion kinase and actin synthesis and also induces hepatic stellate cells apoptosis [300]. Additional studies on the protective effect of caffeine on the liver are presented in Table 3.

Table 3. Complementary studies on the protective effect of caffeine against neurodegenerative and hepatic diseases.

Subjects' Origin	Sample	Study Type	Conclusions	Reference
Neurodegenerative diseases				
Finland	$n = 6.710$	Large prospective study (follow-up for 22 years)	Results support the hypothesis that coffee consumption reduces the risk of Parkinson's disease.	[301]
Greece	$n = 26.173$	Population-based prospective cohort (follow-up for 3–5 years)	Results support the hypothesis that coffee consumption reduces the risk of Parkinson's disease.	[302]
Denmark	$n = 1.876$	Large case-control study	Moderate coffee intake (3.1–5 cups/day) was associated with a lower odds ratio for Parkinson's disease.	[303]
Mostly from USA, Europe, and Asia	-	Dose-response meta-analysis	Non-linear relationship between coffee intake and the risk of Parkinson's disease was found, with maximum protection effect at approximately 3 cups/day and no improvement after that.	[304]
Canada	$n = 6.434$	Prospective analysis of risk factors (follow-up for 5 years)	Daily coffee consumption decreased the risk of Alzheimer's disease by 31% during the follow-up.	[305]
Finland	$n = 1.409$	Population-based cohort study (follow-up for 21 years)	Coffee drinkers at midlife had a lower risk of dementia and Alzheimer's disease later in life compared to those who drank no or little coffee, with lower risk (65% decreased) in those who drank 3–5 cups per day.	[269]
Mostly from USA, Europe, and Asia	-	Systematic review	Findings indicate that moderate coffee/caffeine intake decreases the risk of cognitive impairment/decline and dementia/Alzheimer's disease later in life.	[306]

Table 3. Cont.

Subjects' Origin	Sample	Study Type	Conclusions	Reference
Liver diseases				
Mostly from USA, Europe, and Asia	-	Systematic review and dose-response meta-analysis	Regular intake of three cups of caffeinated and decaffeinated coffees was associated with reductions of 27% and 14% in the risk of hepatocellular carcinoma, respectively.	[307]
USA, France and Brazil	-	Systematic review and meta-analysis	Decreased risk of advanced liver fibrosis and liver inflammation among hepatitis C virus-infected patients who consumed caffeine on a regular basis.	[308]
USA	<i>n</i> = 5.944	Population-based cohort study	Dose-effect relationship between coffee and caffeine consumption and decrease in aminotransferase (ALT) levels, reducing the prevalence of above-normal ALT value by 50% for two cups/day, and by 66% for three cups/day.	[309]
Italy	<i>n</i> = 732	Population-based study	Coffee caffeine may inhibit the onset of alcoholic and nonalcoholic liver cirrhosis.	[310]

8. Potential Adverse Effects of Caffeine Consumption

8.1. Caffeine Acute and Chronic Toxicity

Based on scientific evidence, moderate caffeine consumption is currently considered by EFSA [126], Food and Drug Administration (FDA) [311] and the Scientific Committee on Food within the European Commission (SCF) [312], among other health authorities, to be a safe habit. However, caffeine acute toxicity effects related to excessive intake may occur and are well characterized. The first studies on the toxicity of caffeine were performed in the 19th century, initially with animals [313], and soon after, with humans [314]. In 1850, Lehmann [314] reported several adverse symptoms after acute oral administration of 2 to 10 g of caffeine. Such intoxication results in 'caffeinism', which refers to a syndrome characterized by a range of adverse reactions, for instance, restlessness, nervousness, anxiety, irritability, agitation, muscle tremor, insomnia, headache, diuresis, tachycardia, arrhythmia, pulse irregularity and increased frequency, elevated respiration and gastrointestinal disturbances (e.g., nausea, vomiting, diarrhea) [315]. Besides tachycardia and diuresis, caffeine toxicity in children has also been implicated in severe emesis, photophobia, palpitations, muscle twitching, convulsions, and unconsciousness, especially at doses around 80 mg/kg of body weight [14].

Regarding lethality, caffeine death-related reports in humans are unusual, implying rather significant concentrations which are not provided by regular coffee drinking. Only a few cases have been reported in the literature [316]. Concerning the exact dose, as previously mentioned, the metabolism and physiological effects of caffeine vary greatly, depending on several factors. For slow metabolizers, the lethal dose will be lower than for fast metabolizers. Foods or medications taken simultaneously will affect caffeine metabolism and, therefore, also the lethal acute dose [316]. Other complications would be age and previously existing cardiovascular diseases or other types of diseases. According to Frerichs [317], severe symptoms might be induced in humans about 15 min after oral administration of 25 g of the drug, which is an extremely high amount. Currently, studies using potentially lethal doses (LD) are not performed in humans, and the perception of LD is only based on extrapolation of animal studies or case reports. Tarka and Cornish [318] determined the LD50 (the amount given acutely which causes death of 50% of the animals) for caffeine in rats and extrapolated the results to humans. According to them, the LD 50 for caffeine in humans would be about 192 mg/kg of body weight. For Cappelletti et al. [245] the LD of caffeine should be about 10 g/day, which according to the authors could be comparable to drinking 100 cups of instant coffee. Arnaud [14] also estimated in 10 g the acute LD of caffeine which they extrapolated to 150–200 mg/kg bw in agreement with Tarka and Cornish [318], but death has been reported after ingestion of 6.5 g of caffeine [14], which

is in agreement with a report from Kerrigan and Lindsey [319] suggesting lethal doses to be typically in excess of 5 g, although according to the authors, there has been several cases in which adults and teenagers consumed between 5–10 g and survived. The survival of a patient who supposedly ingested 24 g of caffeine has also been reported [315,320].

In general, high chronic exposure to caffeine (more than 400–600 mg/day) has also been associated with a range of dysfunctions involving the gastrointestinal, liver and renal systems, besides musculature [315,320], unstable bladder, mainly developed in women [321]. In more extreme cases, symptoms may include myopathy, hypokalemia, muscular weakness, nausea, vomit, diarrhea, and weight loss [322].

Following, the most commonly reported potential negative effects of acute and chronic caffeine consumption on the human body are discussed, especially the effects on CNS and behavior, cardiovascular system, glucose metabolism, bone and calcium balance, reproductive and development effects and carcinogenesis. Caffeine withdrawal syndrome will also be approached.

8.2. Potential Adverse Effects of Caffeine on Mood, Behavior, and Sleep

The effects of caffeine on mood in adults have been extensively studied and the most common negative effects reported after caffeine intake are related to its stimulating effects due to the aforementioned responses in dopaminergic D₁ and D₂ receptors [225] and release of neurotransmitters, such as norepinephrine, dopamine, and serotonin [112]. Although ingestion at low to moderate doses tends to elicit the pleasant sensations previously described in this review, higher doses consumed either on a single occasion or within short periods of time can produce or exacerbate jitteriness, insomnia (especially in those who are caffeine-abstinent) [112], nervousness and anxiety, especially in those with preexisting psychiatric anxiety disorders, but also in healthy adults, particularly when they are non-habitual caffeine consumers [232]. The dose range considered to cause anxiety and mood change varies considerably among authors and official guidelines, from 400 to 2000 mg caffeine/day [14,232,323–325]. In slow metabolizers, such negative effects can be felt at much lower doses compared to fast metabolizers, as low as 50 mg or less. After repeated intake, however, tolerance to general effects of caffeine is usually observed. The mechanism to increase tolerance is not well understood and is highly variable among the population, but it has been attributed to upregulation of adenosine receptors [112]. However, in adults, tolerance to such anxiogenic effect develops with frequent caffeine consumption, even in genetically susceptible individuals [326]. The inter-individual variability in the anxiogenic response to caffeine intake has been suggested to be caused by a single nucleotide polymorphism in the gene coding for the adenosine A_{2A} receptor (ADORA_{2A}) [326,327]. In any case, such high doses are consumed only by a small segment of caffeine consumers, and individuals experiencing the anxiogenic effects of caffeine as well as slow metabolizers who are sensitive to its effects in general are likely to avoid the use of the substance [315]. Thus, the self-limiting nature of caffeine intake reduces caffeine potential to produce anxiety in adults [326,327].

Regarding sleep, in adults, single doses equivalent to about 100 mg of caffeine or more (1.5 mg/kg bw/day in a 70 kg adult) have increased sleep latency, in a dose-dependent manner and reduced sleep duration when consumed close to bedtime [328]. This may be accompanied by impairment of sleep quality, characterized by an increased number of spontaneous awakenings and body movements. Doses lower than 100 mg do not appear to have such an effect on sleep in most people [14,329]. Chronic high consumers of caffeine, however, are less likely to report sleep disturbances than individuals consuming caffeine more occasionally, also suggesting the development of tolerance to the effects of caffeine on this parameter [330].

There seem to be only a few human intervention studies, meta-analysis and controlled trials investigating the effects of caffeine on psychological, behavioral, cognitive functions and sleep of children and adolescents [331–342]. In an earlier study by Rapoport et al. [333], daily caffeine consumption was investigated for two weeks in relation to self-reported anxiety, parents/teachers' ratings of children's behavior and side effects in pre-pubertal children. Data from 19 children were

analyzed depending on whether they were “low” (up to 50 mg/day) or “high” (more than 300 mg/day) caffeine consumers. The results provided evidence that “high” habitual caffeine consumers (and their parents) tended to report more side effects during the caffeine withdrawal period, compared to “low” caffeine consumers, suggesting the development of tolerance and withdrawal symptoms in “high” habitual consumers. Moreover, in “high” habitual caffeine consumers, despite the significant improvements in tasks related to vigilance and significant increases in locomotor activity, symptoms as “nervous/jittery” were also reported, although not classified as anxiety [126,333]. Considering the existing literature data on the subject up to 2015, according to EFSA [126], regular consumption of caffeine (up to about 3 mg/kg bw/day, approximately 60–120 mg of caffeine/day) does not appear to induce behavioral changes in children and adolescents.

8.3. Potential Adverse Effects of Caffeine on Cardiovascular System

Investigations regarding the effects of caffeine consumption on the cardiovascular system generally focus on evaluating the heart functioning as the onset of morbi-mortality covering the main risk factors. For this, it is especially important to distinguish acute from long-term cardiovascular effects of caffeine [126,172]. Single 200–250 mg doses of pure caffeine acutely increased plasma renin activity, catecholamine concentrations, and blood pressure, and were able to induce cardiac arrhythmias (mostly atrial) in healthy subjects [343,344].

Possible mechanisms for the acute cardiovascular effects of caffeine include antagonistic action on adenosine receptors, activation of the sympathetic nervous system (release of catecholamines from adrenal medulla), stimulation of adrenal cortex (release of corticosteroids), renal effects (diuresis, natriuresis, activation of the renin-angiotensin-aldosterone system), and inhibition of phosphodiesterase’s (increase in cyclic nucleotides), although the contribution of each of these mechanisms to the acute cardiovascular effects of caffeine is unclear [126,201], and may depend on the source of caffeine, the dose administered, and on plasma concentrations prior to caffeine administration [126].

According to epidemiological data, the coffee effect on blood pressure differs with CYP1A2 genotype [345]. While in fast caffeine metabolizers (CYP1A2*1A) the effect of caffeine on blood pressure seems to be insignificant, in slow metabolizers (CYP1A2*1F) the hypertensive effect seems to prevail [345]. However, it has been observed that in fast metabolizers, caffeinated cola consumption, but not coffee, has been associated with hypertension, which may be due to the lack of polyphenols in the cola beverages [345]. Watanabe et al. [346] examined the blood pressure-lowering effect of chlorogenic acids (the main polyphenols in coffee) in patients with mild hypertension through a placebo-controlled, randomized clinical trial. Subjects ($n = 28$) were randomized to receive treatment with chlorogenic acids (140 mg/day) from green coffee extract or placebo daily for 12 weeks. In the chlorogenic acids group, but not in the placebo group, blood pressure (systolic and diastolic) decreased significantly during the ingestion period, demonstrating the hypotensive action of coffee phenolic compounds, a mechanism that seems to involve nitric oxide-mediated vasodilation [347].

Comparing the hypertensive effect with frequency of caffeine consumption, acute increases in systolic and diastolic blood pressures, as well as in pulse pressure have been reported after single doses of caffeine ranging from 80 to 250 mg, in coffee abstainers and in habitual caffeine consumers, after 12 to 48 h withdrawal [126,348–350]. Although the hypertensive effect of caffeine was observed in many repeated-dose studies, it was not as consistent as in the acute-dose studies [344]. Tolerance usually develops within a couple of days, and it is accompanied by a reduced release of adrenaline, noradrenaline, and rennin, compared with the non-tolerant state. Although fast tolerance development has been observed in habitual coffee drinkers (within one to three days), the hypertensive response is regained after relatively brief periods of abstinence (12 h) and depends on how much caffeine is consumed, the schedule of consumption, and on the half-life and elimination of caffeine from the body [351,352].

Caffeine intake has also been associated with the occurrence of arrhythmias in humans. It produces a direct stimulation of myocardial tissue, leading to increased heart rate and force of contraction [14]. Cardiovascular disease has been assessed by a range of outcome variables, including death from myocardial infarction or Coronary Heart Disease (CHD), non-fatal myocardial infarction or coronary event, angina pectoris and/or hospitalization for CHD. Prospective epidemiological studies and case-control studies were more likely to show an increased risk in cardiovascular disease onset only when five or more cups of coffee were consumed per day (≥ 500 mg caffeine/day) [353–357]. However, as with blood pressure, in patients with a history of cardiovascular disease, slow caffeine metabolizers (CYP1A2*1F), were associated with increased risk of myocardial infarction when coffee consumption was increased [199]. Additional studies on the effect of caffeine on blood pressure and cardiovascular diseases are presented in Table 4.

8.4. Potential Adverse Effects of Caffeine on Glucose Metabolism and Insulin Resistance

Coffee consumption has been associated with reduced risk of type 2 diabetes [358–364]. However, a key issue that remains to be resolved is whether the consumption of caffeinated and decaffeinated coffees is similarly associated with the reduced risk of type 2 diabetes [365,366]. Shearer et al. [365] observed that glucose infusion rates and measures of whole-body metabolic clearance were greater in rats that received decaffeinated coffee (2 g/100 mL) than in placebo or caffeine (20 mg/100 mL) added to decaffeinated coffee (2 g/100 mL), indicating increased whole-body insulin sensitivity in decaffeinated coffee. It was concluded that caffeine can antagonize the beneficial effects of decaffeinated coffee. Most evidence, in fact, indicates that caffeine alone promotes adverse effects on glucose metabolism [366–368] and reduces insulin sensitivity [364,369]. The intake of about 500 mg/day by usual coffee drinkers was associated with higher average daytime glucose concentrations and exaggerated post-prandial glucose responses in diabetic patients [366]. In healthy individuals, the ingestion of caffeinated coffee with either a high or a low glycemic index meal significantly impaired acute blood glucose management and insulin sensitivity compared with decaffeinated coffee [367]. These effects could be partially explained by the direct inhibition of glucose uptake in adipocytes and skeletal muscle through antagonism of adenosine receptors [370] or possibly as a result of elevated plasma epinephrine [371].

On the other hand, both caffeinated and decaffeinated coffee consumption enhanced insulin sensitivity in a cross-sectional study [372] and in epidemiological studies [373–376], suggesting beneficial effects of both drinks on glucose homeostasis. Other studies have found that when controlling for total coffee intake, caffeine intake was not associated with diabetes risk [363,364], showing that the consumption of both decaffeinated and caffeinated coffees is significantly associated with a lower risk of developing type 2 diabetes [358,359,366,373,374]. As with blood pressure, although most data from short- and long-term studies indicate that caffeine intake promotes adverse effects on glucose metabolism [377–379], evidence points out that coffee components other than caffeine, especially chlorogenic acids and trigonelline [102,365,380], exert several positive effects on glucose homeostasis, balancing caffeine effects [364,378–382].

In conclusion, although regular consumption of both decaffeinated and regular coffees is proved to reduce the risk of diabetes, decaffeinated beverages seem to be more beneficial for glycemic control than caffeinated ones, although most epidemiological studies have failed to discriminate the effects of these two types of coffee on the protective effect of coffee against type 2 diabetes. Additional studies on this topic are presented in Table 4.

8.5. Potential Adverse Effects of Caffeine on Calcium Balance

This is one of the most discussed potential adverse effects of caffeine intake. Caffeine potential to adversely influence calcium excretion and bone metabolism was investigated by epidemiological studies which evaluated the relationship between caffeine intake and the risk of fracture and fall [383–387], bone mineral density (BMD) and osteoporosis [388–393], and the effect on calcium homeostasis [394,395]. On the potential risk factor for bone fracture and fall, most studies reported a lack of association between

caffeine intake and increased risk of fracture considering consumption below 400 mg/day [383–387]. However, in a cross-sectional study, caffeine intake was associated with an increased incidence of low trauma fractures [396]. When the consumption was estimated in more than 544 mg caffeine/day, consumers had a higher risk of hip fracture than those who ‘almost never’ consumed coffee. Hallström et al. [397] also reported that a daily intake of ≥ 330 mg caffeine might be associated with a modestly increased risk of osteoporotic fractures (relative risk (RR): 1.20, CI: 1.07–1.35), especially in women with low calcium intake. However, when stratified by calcium intake, the increased risk was only significant when calcium intake was low (less than 700 mg/day). No trend in increased risk of osteoporotic fractures was observed with higher caffeine intake in participants with high calcium intake.

Caffeine consumption of 175 mg/day has been positively associated with increased 24-h urinary calcium excretion [398]. Heaney and Rafferty [394] also reported that acute consumption of caffeinated beverages (60–92 mg caffeine) produced small increases in calcium excretion, which, according to the authors, could be offset by small increases in calcium intake (15–30 mL of milk). Based on a study group of women who habitually consumed low-calcium, Ribeiro-Alves et al. [395] reported that exposure to 285 mg caffeine resulted in increased calcium excretion. However, in another study by Barger-Lux et al. [399], when a greater amount of caffeine was ingested by healthy premenopausal women for a prolonged time (400 mg/person/day for 19 days), no effect on calcium absorption, endogenous fecal calcium or urinary calcium excretion was found, despite the observation of bone remodeling. Interpretation of caffeine’s effects on bone metabolism is complex since caffeine intake is usually associated with other risk factors for osteoporosis, such as lower calcium intake [393,400] and advanced ages [401,402]. Considering all available data, and evaluating the same population of postmenopausal women studied by Barger-Lux et al. [399], a model was elaborated: coffee intake higher than 1000 mL/day (760 mg caffeine/day) could induce excess calcium loss, while intakes of 150–300 mL coffee/day (112–224 mg caffeine/day) would have little impact on calcium balance [403].

The effect of coffee consumption on BMD in elderly men and women, with regards to the CYP1A2 genotype, was recently evaluated by Hallström et al. [397]. A decrease in BMD of the proximal femur was observed in men consuming four or more cups of coffee daily. It was also found that, in high coffee consumers, fast caffeine metabolizers had lower BMD values than slow metabolizers. Considering that in a higher CYP1A2 activity condition caffeine is more rapidly metabolized and the concentrations of its metabolites in plasma increase in relation to the parent compound, it was suggested that the deleterious effects of coffee consumption on bone might be due to caffeine metabolites, especially paraxanthine [391]. This metabolite has been found to be a potent suppressor of transforming growth factor beta (TGF- β) in vitro [404], which stimulates bone formation [405]. Moreover, deactivation of the adenosine receptors, which are expressed in bone cells, can result in reduced bone formation [406]. Since paraxanthine acts through the same mechanism as caffeine, that is the competitive antagonism interaction with A₁ and A₂ adenosine receptors [405], it could also act on such signaling pathway to reduce bone formation. Therefore, paraxanthine seems to be the main contributor to the coffee effect on BMD reduction, being the rapid metabolizers of caffeine at higher risk for bone loss induced by coffee than slow metabolizers [391].

Considering all previously published data, Nawrot et al. [232] concluded in a review published in 2003 that caffeine intake lower than 400 mg/day does not have significant effects on bone status or calcium balance in individuals ingesting at least 800 mg calcium/day. No other recommendations were made thereafter. Additional studies on this topic are presented in Table 4.

8.6. Potential Adverse Effects of Caffeine on Fertility and Reproductive and Developmental Effects

The effects of caffeine consumption have been reviewed in terms of reproduction or fertility [407–410] and in terms of pregnancy outcomes, including spontaneous abortion, birth weight, gestational length, and congenital malformations [410]. Consistent relationships between caffeine intake and subfecundity have not been observed to date. However, bringing together existing data available up to 2003, Nawrot et al. [232] suggested that the consumption of caffeine at doses greater

than 300 mg/day might reduce fecundability in fertile women. In respect to male fertility, Dlugosz and Bracken [407] suggested that doses higher than 400 mg/day might decrease sperm motility and/or increase the percentage of dead spermatozoa, but not sufficiently to affect the male fertility in an adverse manner.

Once pregnant, women who regularly consume caffeine may be at risk of miscarriage, but current evidence of spontaneous abortion remains insufficient to allow conclusions regarding the potential role of caffeine [411]. The existing data do not support convincing results that caffeine consumption increases the risk of any perinatal adversity [412]. Nevertheless, based on several studies evaluating the association of caffeine intake and risk of perinatal adversities, Nawrot et al. [232] advised that women who are pregnant or are planning to become pregnant should limit the consumption of caffeine to less than 300 mg/day, which is historically a common amount consumed by this group with no adversities [413].

The potential adverse impact of caffeine consumption during pregnancy on fetal growth has also been a concern for many years. Caffeine increases the levels of cyclic adenosine monophosphate through inhibition of phosphodiesterase's, which might interfere with fetal cell growth and development [414]. It is known that caffeine ingested by the mother is rapidly absorbed from the gastrointestinal tract and readily crosses the placenta, being distributed to all fetal tissues, including the CNS. Once present in the fetus organism, caffeine has increased half-life due to the immaturity of the enzyme complex involved in its metabolism. Therefore, if a pregnant woman does not limit her caffeine intake, the fetus and neonate may be exposed to substantial amounts of caffeine and metabolites and may suffer the consequences of potentiated adverse effects [14]. According to Rosenberg et al. [415], no association was found between drinking caffeine-containing beverages at levels up to 400 mg caffeine/day and five types of malformation (inguinal hernia, oral clefts, cardiac defects, pyloric stenosis, neural tube defects) in a case-control study. These results were ratified by Olsen et al. [416]. Although published results are not yet entirely consistent, evidence suggests that caffeine intake at doses higher than 300 mg/day may cause adverse effects on some fetus developmental parameters, such as fetal intrauterine growth retardation or decrease in birth weight [407,417]. Being cautious, based on two prospective cohort studies that investigated positive association between caffeine intake during pregnancy and risk of adverse birth weight-related outcomes [418,419], EFSA [126] concluded that caffeine intake from all sources up to 200 mg/day by pregnant women in the general population does not raise safety concerns for the fetus. The association between caffeine intake and other adverse pregnancy-related outcomes was less consistent [419]. Additional studies on this subject are presented in Table 4.

8.7. Potential Carcinogenicity of Caffeine

In 1983, a safety assessment on caffeine consumption was performed by the SCF within the European Commission [312]. Comparatively high doses of caffeine had shown weak teratogenic effects in experimental animals and mutagenic effects *in vitro*, but not *in vivo*, and it was concluded that there was no evidence for concern over carcinogenic, teratogenic, or mutagenic effects of caffeine in man at the actual levels of intake (between 2.0 and 4.5 mg/kg of body weight/day) and that human epidemiological studies provided no evidence for any association between coffee consumption and congenital defects [312]. In 1987, caffeine underwent another extensive review in which the FDA declared its safety for all consumers, including children. In 1991, several studies suggesting the potential carcinogenic effects of coffee, specifically regarding bladder [420–422] have led IARC [423] to classify coffee as possibly carcinogenic to humans, based on limited evidence of association with cancer of the urinary bladder from case-control studies, and inadequate evidence of carcinogenicity in experimental animals. However, IARC [423] concluded that there was no evidence for concern over carcinogenic, teratogenic, or mutagenic effects of caffeine in man at the observed levels of intake (between 2.0 and 4.5 mg/kg/day) and that human epidemiological studies provided no evidence for any association between coffee consumption and congenital defects. Most evidence indeed supports a lack of substantial relation between caffeine intake, as measured by coffee consumption, and various

types of cancer, including gastric cancer [424], renal cancer [425], breast cancer [426,427] and colorectal cancer [428]. In 2016, IARC [294] re-evaluated studies investigating the association between coffee consumption and cancer. For this re-evaluation, a much larger database of prospective cohort and population-based case-control studies that controlled adequately potential confounders, including tobacco and alcohol consumption, was available. For bladder cancer, there was no consistent evidence of association with coffee drinking. In several studies, relative risks were increased in men but were null or decreased in women, consistent with residual confusion caused by smoking or occupational exposures among men. IARC concluded that positive associations between coffee and bladder cancer reported in some studies could have been due to inadequate control for tobacco smoking, which can be strongly associated with heavy coffee drinking, and, as a result of the re-evaluation, IARC changed coffee classification to no carcinogenicity to humans [294]. In the same evaluation, for endometrial cancer, the five largest cohort studies showed mostly inverse associations with coffee drinking. These inverse associations were also observed in cohort and case-control studies of liver cancer in Asia, Europe, and North America, in several types of studies, which lead IARC in 2016 to acknowledge the protective effect of coffee [294], and suggest that an increase in consumption of one cup of coffee/day (and consequently, an increase in caffeine intake of about 50–150 mg/day) was associated with reduced risk of kidney, breast, buccal and pharyngeal, colorectal, endometrial, esophageal, leukemic, pancreatic, and prostate cancers [429–431] and, therefore, regular caffeine intake does not seem to be associated with increased risk of cancer when considering whole coffee consumption. Additional studies on this topic are presented in Table 4.

8.8. Caffeine Withdrawal Syndrome

It has been widely experienced that the sudden cessation of regular caffeine ingestion produces specific interrelated symptoms [432,433], which are named caffeine withdrawal syndrome as stated by the Diagnostic and Statistical Manual of Mental Disorders of the American Psychiatric Association (APA) [434]. Characteristic symptoms of caffeine-withdrawal include headache, drowsiness, lethargy, fatigue, work difficulty (decreased motivation for work and impaired concentration), decreased wellbeing (including decreased self-confidence and increased irritability), fall in blood pressure and rise in cerebral blood flow [432,433,435]. These are opposite sensations to those obtained after caffeine consumption. Withdrawal symptoms generally begin about 12 to 24 h after cessation of caffeine consumption and reach a peak after 20 to 48 h. However, in some individuals, these symptoms can appear within only 3 to 6 h and can last for a week [316]. Thus, even a short abstinence equivalent to missing the morning cup of coffee can lead to significant unpleasant effects [436,437]. The syndrome is probably specifically due to the discontinuation of caffeine intake because it persists in spite of analgesic consumption [112] and is reversed by caffeine ingestion [438]. The fact is that daily consumption of caffeine can result in physical dependence and the removal of caffeine causes withdrawal symptoms, irrespective of the pattern of intake across the day [435] and of small (129 mg: one to two cups of coffee) or large (2548 mg: 20–30 cups of coffee) amounts of caffeine ingested [432,437,438]. Caffeine withdrawal syndrome can be avoided if caffeine ingestion decreases slowly.

Slow caffeine metabolizers are less likely to experience sedation on withdrawal or onset of anxiety on resumption. This is in accordance with the general principle that slow reduction minimizes withdrawal symptoms [439]. Moreover, slow metabolizers are likely to drink less coffee and less frequently, which also decreases withdrawal syndrome probability.

Withdrawal symptoms have also been reported in newborns whose mothers were heavy coffee drinkers during pregnancy. These infants displayed irritability, high emotivity, and even vomiting. Symptoms begin at birth and spontaneously disappear after a few days [440]. Caffeine withdrawal may also occur in children who largely consume soft drinks [441].

Despite the described withdrawal symptoms, according to the Diagnostic and Statistical Manual of Mental Disorders, (by APA) [434] caffeine is not present in the category of substances classified as causing “substance dependence”, since the substance does not cause the severity of withdrawal or

harmful drug-seeking behaviors as street drugs or alcohol and these symptoms are easily and reliably reversed by ingestion of caffeine.

Table 4. Complementary studies on the potential adverse effects of caffeine on health.

Sample	Type of Study	Coffee/Caffeine Doses	Conclusions	Reference
Anxiety				
Healthy subjects (<i>n</i> = 13)	Clinical study	9 mg of caffeine/kg body weight (bw)	High caffeine doses (> 400 mg/day) significantly increased some anxiety aspects.	[442]
Subjects with panic disorders (<i>n</i> = 28), performance social anxiety disorder (<i>n</i> = 19), and healthy subjects (<i>n</i> = 26)	Clinical study	480 mg of caffeine	Patients with panic disorders and performance social anxiety disorders had a higher number of induced panic attacks, some specific anxiety symptoms, and a more severe anxiety response than healthy volunteers.	[443]
Cardiovascular system				
Normotensive subjects	Critical review and meta-analysis	Single doses 200–250 mg of caffeine	Increase in systolic blood pressure by 3–14 mm Hg and diastolic blood pressure by 4–13 mm Hg. Induced average increases of 8.1 mm Hg in systolic and 5.7 mm Hg diastolic blood pressure, observed within the first 60 min after intake and persisting for 180 min, on average.	[345]
Hypertensive subjects	Systematic review and meta-analysis	Single doses 200–300 mg of caffeine	No effect on heart rate associated with consumption as compared to those who consumed < 410 mg/day.	[444]
Hypertensive subjects	Systematic review and meta-analysis	Doses ≥ 410 mg of caffeine/day for at least 7 days		[445]
Glucose metabolism and insulin resistance				
Healthy subjects	Systematic review and meta-analysis	3–6 mg of caffeine/kg bw	Acute caffeine ingestion reduces insulin sensitivity. Caffeine intake increased blood glucose concentrations by 16–28% of the area under the curve (AUC) and insulin concentrations by 19–48% of the AUC.	[446]
People with type II diabetes	Systematic review of randomized controlled trials	~200–500 mg of caffeine		[447]
Bone and calcium balance				
Healthy postmenopausal women (<i>n</i> = 205)	Randomized clinical trial	280–420 mg of caffeine/day	Daily consumption of 280–420 mg caffeine/day may accelerates bone loss from the spine and total body in women with calcium intakes below the recommended dietary allowance of 800 mg.	[448]
Healthy women (<i>n</i> = 61,433)	Longitudinal population-based	≥ 560 mg of caffeine/day	Not associated with higher rate of fractures and bone mineral density	[385]
Healthy women	Systematic review and meta-analysis	2–8 cups of coffee/day	The fracture risk was 14% higher in women and 24% lower in men with the highest level of coffee consumption.	[387]
Fertility and reproductive and developmental effects				
Healthy women	Systematic review and dose-response meta-analysis	≥600 mg of caffeine/day	Coffee/caffeine consumption is associated with a significantly increased risk of spontaneous abortion.	[449]
Healthy pregnant women	Systematic review	up to 300 mg of caffeine/day	Lack of birth defects following consumption of caffeine in healthy pregnant women.	[354]
Carcinogenesis				
Healthy subjects	Dose-response meta-analysis	1–3 cups of coffee/day	Caffeinated but not decaffeinated coffee consumption was negatively associated with basal cell carcinoma risk.	[450]
Healthy subjects	Meta-analysis	5 cups of coffee/day	Caffeinated but not decaffeinated coffee consumption might have chemo-preventive effects against malignant melanoma risk, coffee.	[451]

9. Maximum Caffeine Intake Recommendations

Because of the high caffeine consumption worldwide, continuous research on potential health effects and on safety aspects has been performed. However, there is currently no recognized reference standard for caffeine consumption, such as an acceptable daily intake (ADI) [452]. A number of assessments have been made around the world, and exposure limits have been adopted for different population groups. Some of the most important ones are presented in Table 5.

Individuals that do not consume caffeine daily are at greater risk of negative physiological effects than the habitual consumers [127]. In the same way, for those who are highly sensitive to the stimulating effects of caffeine, it is hard to determine the safety limit for its consumption [453]. Some slow metabolizers called popularly “ultra-sensitive”, can be over-stimulated by the delay in caffeine metabolism and clearance in the body. Moreover, individual differences in responses to caffeine may occur not only at the metabolic (pharmacokinetic) level but also at the drug-receptor (pharmacodynamic) level and they can contribute to the quality and magnitude of direct physiological effects and as a consequence to caffeine consumption. Additional factors are age, use of other drugs and circadian factors [122]. The biological mechanisms of these possible sources of variation involve interactions at multiple sites with the enzymes that break down caffeine in the liver, as well as receptors in the brain that are affected by caffeine [454]. For these reasons, the exact amount of caffeine necessary to produce adverse effects varies from person to person depending on their sensitivity to caffeine [453] and therefore caffeinated beverages should be consumed by these individuals with caution, until a person understands how it interacts with his/her particular genetic structure and health profile [455]. If willing to consume caffeine, ultra-sensitive consumers should try small amounts until they find the amount appropriate or acceptable for them, offering the wellbeing sensation without causing side-effects. For these people, decaffeinated coffee, which still contains residual amounts of caffeine, may be more appropriate.

Commenting on adolescents and children, a study from The University Children’s Hospital in Zurich showed that caffeine can interfere with children and teenagers’ (aged 10–16 years, $n = 32$) sleep, possibly hindering proper brain development, and, therefore, limiting caffeine intake was recommended [456]. Moreover, recently, EFSA recommended no consumption of caffeine for children under 12 months [126] and this involves no consumption of all caffeine-containing drinks and foods, such as chocolate drinks, maté, *Camelia sinensis* teas, and soft drinks, which are often offered by parents.

Attention deficit hyperactivity disorder (ADHD) is one of the most common children’s mental health conditions. It involves symptoms of inattention or impulsivity and hyperactivity that lead to behavioral impairments [457]. Many studies have investigated the possible role of caffeine in ADHD. In an animal model study using rats, caffeine restored the function of dopamine as a neurotransmitter in the brain [457]. It is also known that being a vasoconstrictor, caffeine can mimic ADHD medications, such as amphetamine, that also constricts blood vessels and increase concentration [458,459]. Notwithstanding the fact that caffeine appears to be beneficial for some children (and also adults) with ADHD, lack of adverse effects is not guaranteed. Overconsumption should be avoided in children, especially on a regular basis and over a long period of time. It is noteworthy mentioning that in some Latin American producing countries, such as Brazil and Colombia, for example, people start drinking coffee with milk early in childhood. In Brazil, a project to stimulate the children’s coffee and milk consumption was launched in 2007 and continues to exist to date [460]. Such a small quantity (20 mL coffee per 200 mL cup) is supposed to be safe and has helped increase attention and learning capacity of children and teenagers in these countries. While limiting caffeine to teenagers to a great extent would be ideal, due to cultural habits and to the increasing demands placed on this age group regarding school, sports, and even work in some places, caffeine consumption is becoming more common among them. According to the American Academy of Pediatrics [461], for all the above reasons and because of possible unknown medical conditions, developing teens should consume no more than 100 mg of caffeine daily.

Table 5. Caffeine intake safety limit for different age groups recommended by studies and regulatory agencies around the world.

Agency or Study	Safe Limit of Caffeine Consumption (mg/day or mg/kg Body Weight – bw/day)	Equivalent to (Approximately)
Adults		
USA: Nawrot et al. [232] Canada: Health Canada [462] South Korea: Korean Food and Drug Administration [463] Belgium: Belgium Superior Health Council [325] Europe: European Food Safety Authority [126]	400 mg/day	1 cup of 100 mL espresso coffee + 2 cups of 100 mL manual dripped coffee or 6 cups of 100 mL manual dripped coffee or 3 cups of 100 mL French press coffee + 1 cup 100 mL cold brewing coffee
Europe: European Food Safety Authority [126]	Single doses of up to 200 mg	3 cups of 100 mL manual dripped coffee or 1 cup of 100 mL soluble coffee + 1 cup 100 mL cold brewing coffee or 2 cups of 100 mL aero press coffee + 1 cup of 100 mL infusion coffee bag
Reproductive-aged women		
International Life Science Institute (ILSI) [464]	Less than 5 to 6 mg/kg bw/day	(amounts estimated for a 70 kg bw woman) 1 cup of 100 mL espresso coffee + 1 cup of 100 mL French press coffee or 2 cups of 100 mL mocha coffee
Pregnant and lactating woman		
USA: Nawrot et al. [232] New Zealand: New Zealand Ministry of Health [452] South Korea: Korean Food and Drug Administration [463] Belgium: Belgium Superior Health Council [325]	300 mg/day	1 cup of 100 mL espresso coffee + 1 cup of 100 mL dripped coffee or 2 cups of 100 mL mocha coffee or 2 cups of 100 mL electric dripper coffee + 1 cup 100 mL ready to drink coffee beverage
United Kingdom: UK Food Standard Agency [465] Europe: European Food Safety Authority [126]	200 mg/day	3 cups of 100 mL manual dripped coffee or 1 cup of 100 mL soluble coffee + 1 cup 100 mL cold brewing coffee or 2 cups of 100 mL aero press coffee + 1 cup of 100 mL infusion coffee bag
Children		
USA: Nawrot et al. [232] Canada: Health Canada [462] South Korea: Korean Food and Drug Administration [463] Belgium: Belgium Superior Health Council [325]	< 2.5 mg/kg bw/day	(amounts estimated for a child a 5-8-year-old, with 22 kg bw) 1 cup of 100 mL manual dripped coffee or 1 cup of 100 mL ready to drink coffee beverage
UK: Knight et al. [466] New Zealand: New Zealand Ministry of Health [452]	45 mg/day (up to 4 years) 95 mg/day (aged 5-12 years)	1 cup of 50 mL cold brewing coffee or 1 cup of 75 mL of manual dripped coffee 1 cup of 100 mL manual dripped coffee + 1 cup of 50 mL ready to drink coffee beverage (amounts estimated for a 5-8-year-old child, with 22 kg bw)
Europe: European Food Safety Authority [126]	< 3.0 mg/kg bw/day	1 cup of 100 mL manual dripped coffee or 1 cup of 100 mL ready to drink coffee beverage

10. Concluding Remarks

In the present review, reports on the contents of caffeine in coffee seeds, commercial ground roasted coffees, instant coffees, and brews were summarized with focus on the variability of caffeine content in brews due to cultural habits, which are reflected in the blend composition, extraction

methods, and proportion of powder/water used for brews preparation. Lower amounts of caffeine in coffee can be obtained by decaffeination processes and low-caffeine cultivars.

Caffeine intake varies significantly considering different types of beverages commonly consumed in the various cultures and population groups around the world. Coffee typically contains more caffeine than most other beverages and is widely and frequently consumed. Thus, it contributes significantly to overall caffeine consumption in populations, particularly in adults and the elderly. Considering the widespread caffeine consumption around the world, some assessments have been made in order to establish the maximum safe consumption limit for different population groups. In this case, the inclusion of caffeine on product labels may prevent its unsafe consumption.

A number of studies have demonstrated that caffeine is rapidly absorbed and extensively metabolized mainly in the liver by CYP1A2, which is polymorphically distributed in human populations, causing a considerable difference in clearance time and sensitivity of caffeine's acute effect in the body and this is likely to be an issue that warrants further investigation, regarding health outcomes. Regarding the complexation between caffeine and chlorogenic acids, the bioaccessibility and health effects of these complexes are unknown. Considering that plain caffeine and caffeine from coffee were reported to exert similar stimulating effects [127], it is more probable that caffeine is not unbound during digestion and that these complexes are not absorbed. If absorbed, it is probable that they do not bind adenosine receptors. If not absorbed, it is possible that such complexes could exert an antioxidative effect in the digestive system, as it occurs when chlorogenic acids are bound to melanoidins. This subject deserves a thorough investigation.

Caffeine has been the subject of extensive research for its long history of use and elevated consumption worldwide both in natural foods and in medicines. The combined physiological and psychological impacts of caffeine intake depend mainly on the individual genotype and on the pattern and the degree of exposure to the substance. It must also be noted that most mechanistic explanations on caffeine's effects have been derived from acute administration to fasting subjects submitted to a period of caffeine abstinence in order to ensure low plasma caffeine concentrations. It is thus difficult to extrapolate the results to the usual pattern of caffeine consumption, given that most people consume it at different intervals throughout the day and over periods of years. Controversies regarding caffeine's benefits and risks still exist, but reliable evidence is becoming available supporting its health promoting potential when moderate amounts are consumed.

Funding: This research received no external funding other than the scholarships cited below.

Acknowledgments: The authors would like to acknowledge the scholarships provided by the National Council for Scientific and Technological Development (CNPq, Brazil reg.# 309091/2016-0) and the Rio de Janeiro State Research Support Foundation (FAPERJ: E-02/2017# 234092).

Conflicts of Interest: The authors declare no conflicts of interest.

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