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BENEFICIAL AND ADVERSE EFFECTS OF CAFFEINE CONSUMPTION ON HUMAN BODY: A COMPREHENSIVE REVIEW

EFEITOS BENÉFICOS E ADVERSOS DO CONSUMO DE CAFEÍNA NO ORGANISMO HUMANO: UMA REVISÃO GERAL

José Wellington Macêdo Viana
Universidade Federal do Cariri, Pós-Graduando em Microbiologia
wellingtonmacedo1819@gmail.com

Rodolfo Pinheiro Torres
Universidade Federal do Piauí, Professor Bolsista do Programa Língua sem Fronteiras
rodolfotorres23366@gmail.com

Thais Faustino Bezerra
Universidade Regional do Cariri, Pós-Graduanda em Educação Especial e Inclusiva: Ação Docente Especializada
thaisfaustino00@gmail.com

Francisco Wlirian Nobre
Doutorando no Programa de Pós-Graduação em Geografia - PPGG da Universidade Federal da Paraíba
lironobre@yahoo.com.br

Abstract: Caffeine (1,3,7-trimethylxanthine) is a natural alkaloid substance found in different types of plants, in a variety of medications and in dietary supplements, as well as in popular energy drinks, in which the caffeine is added to improve its functional properties on the nervous system. Besides

its stimulating properties, caffeine acts as a potent antioxidant agent associated with the reduction of oxidative stress. On the other hand, studies have shown that the physiological effects of caffeine can be harmful to the human body depending on the frequency of use and the dose of consumption. In this context, the purpose of this review is to summarize and to understand through the analysis of scientific researches, the benefits and risks of caffeine consumption on human body. According to literature, caffeine can be beneficial when it is taken in moderate amount of dosage by healthy adults (<450 mg/day), or harmful to human health when it is consumed in high doses (>450 mg/day). In this case, it contributes to the development of diverse physiological changes, mainly related to the nervous, cardiovascular and renal systems. In addition, it is important to take into account that the adverse effects of caffeine on the body varies according to weight, gender, age, the use of certain kinds of medications and the differences in sensitivity including hypertensive people and diabetic people. Nonetheless, future researches are needed to address further information to these emerging concerns in order to provide a greater empirical support for the caffeine consumption recommendations.

Keywords: Caffeine, Beneficial and Harmful Effects, Dose of Consumption, Frequency of Use.

Resumo: A cafeína (1,3,7-trimetilxantina) é uma substância alcaloide natural encontrada em diferentes tipos de plantas, em uma variedade de medicamentos e em suplementos dietéticos, bem como nas populares bebidas energéticas, nas quais a cafeína é adicionada para melhorar suas propriedades funcionais no sistema nervoso. Além de suas propriedades estimulantes, a cafeína atua como um potente agente antioxidante associado à redução do estresse oxidativo. Por outro lado, estudos têm demonstrado que os efeitos fisiológicos da cafeína podem ser prejudiciais ao organismo humano dependendo da frequência de uso e da dose de consumo. Nesse contexto, o objetivo desta revisão é resumir e compreender, por meio da análise de pesquisas científicas, os benefícios e riscos do consumo de cafeína no organismo humano. De acordo com a literatura, a cafeína pode ser benéfica quando ingerida em doses moderadas (<450 mg/dia) por adultos saudáveis, ou prejudicial à saúde humana quando consumida em altas doses (> 450 mg/dia). Nesse caso, contribui-se para o desenvolvimento de diversas alterações fisiológicas, principalmente relacionadas aos sistemas nervoso, cardiovascular e renal. Além disso, é importante levar em consideração que os efeitos adversos da cafeína no corpo variam de acordo com o peso, sexo, idade, uso de certos tipos de medicamentos e diferenças de sensibilidade, incluindo hipertensos e diabéticos. No entanto, pesquisas futuras são necessárias para abordar

mais informações a essas preocupações emergentes, a fim de fornecer um maior suporte empírico para as recomendações de consumo de cafeína.

Palavras-chave: Cafeína, Efeitos Benéficos e Nocivos, Dose de Consumo. Frequência de uso.

1. INTRODUCTION

Caffeine (1,3,7-trimethylxanthine) is a natural purine alkaloid found in grains, leaves and fruits in more than 60 different types of plants, including coffee (*Coffea* sp.), tea (*Thea sinensis*), kola nuts (*Glue acuminate*), yerba mate (*Ilex paraguariensis*), guarana (*Paullinia cupana*) and cocoa (*Theobroma cacao*) (PORCIÚNCULA *et al*., 2013; MAGUIRE *et al*., 2017; SOCALA *et al*., 2020). Caffeine is also found in a variety of medications and dietary supplements, as well as in popular energy drinks, in which caffeine is added to improve its functional properties, promoting a greater sense of alertness and energy by increasing its stimulating effects on the nervous system (MEJIA; RAMIREZ-MARES, 2014; WIKOFF *et al*., 2017).

Besides its stimulating properties, studies have shown that caffeine acts as a potent antioxidant agent since it has been associated with the reduction of oxidative stress due to its ability to neutralize Reactive Oxygen Species (ROS) and to inhibit lipoperoxidation (LPO) in membranes cells, in addition to reduce the production of β-amyloid protein in humans with Alzheimer's disease (KOLAHDOUZAN; HAMADEH, 2017; ENDESFELDER *et al*., 2019; VIEIRA *et al*., 2020). Indeed, researches have revealed that antioxidant substances are associated with a low incidence of degenerative diseases, such as: Alzheimer's, Parkinson's and coronary heart disease by acting to eliminate reactive species and by increasing the endogenous antioxidant defenses (HE *et al*., 2007; CARDINAL *et al*., 2010; MIKIROVA *et al*., 2013).

However, it is important to mention that substances with antioxidant properties can promote adverse effects on the body depending on the dosage and frequency of use (NIKI, 2014; KURUTAS, 2016). It is known that the complete removal of reactive species (oxygen/nitrogen and its derivative products) by supplementation with antioxidants can disrupt cells signaling pathways (VIANA *et al*., 2020), increasing the development of chronic diseases, since reactive species play crucial roles for the maintenance of the normal function of the cells when at cytostatic levels contributing

to viability and basic cellular processes such as cell differentiation and proliferation (RAY *et al*., 2012; MITTLER, 2017). Nevertheless, when at cytotoxic levels, reactive species can trigger the oxidative stress process, which is a damage condition that occurs to the mitochondria, proteins, DNA and lipids, leading to changes in cells functions and finally to cells death (CARAVAN *et al*., 2016; BALDISSERA *et al*., 2019; VIANA *et al*., 2020; ABDELMAGEED *et al*., 2021).

Researches have shown that the physiological effects of caffeine vary depending on the frequency of use and the doses of consumption: caffeine can be beneficial when it is taken in moderate amount of dosage by healthy adults (<450 mg/day), or harmful to human health when it is consumed in high doses (>450 mg/day) (WIKOFF *et al*., 2017; BARCELOS *et al*., 2020). Of note, the amount of caffeine required to produce adverse effects on the body varies according to weight, gender, age, use of a certain type medication and the differences in sensitivity, which includes lifestyle, genetic predisposition to hypertension and diabetes, as well as caffeine consumption habits according to age (CARRILLO; BENITEZ, 2010; TEMPLE *et al*., 2017; AHSAN; BASHIR, 2019).

2. METHODOLOGY

In order to summarize these facts, it was carried out a bibliographic survey in the different databases (*Science Direct, PubMed*, *National Library of Medicine*) for the purpose of understanding in general the benefits and the risks of caffeine consumption on human body. The analysis involves a previous investigative literature study from review and research articles, published in the last two decades, regarding to clinical and experimental trials in the laboratory, which allowed the aggregation of different information about the benefits and the harmful effects of caffeine.

This work is comprised by following the establishments of criteria for inclusion and exclusion of studies/sampling research to the definition of information to be extracted from selected categorization of studies, as well as the evaluation of studies

included in the integrative review followed by the interpretation of the results to the final presentation of the knowledge review/synthesis.

The criteria for inclusion of studies/sampling are consisted of: full text articles available online; in time horizon, classified as original articles; and primary studies published in English that follow the cost-effectiveness analysis method. Duplicate and repeated studies, which were not addressed to the investigated topic, were excluded. The information extracted from selected studies was obtained through the advanced search method by using the titles, abstracts and keywords category, such as "Caffeine", “Benefits of Caffeine for Human Health", "Caffeine Consumption" and "Adverse Effects of Caffeine on the Body”.

3. RESULTS AND DISCUSSION

3.1. Caffeine Consumption and Health

Caffeine is the most consumed psychostimulant worldwide, it is being ingested more often in beverages such as coffee, teas and popular energy drinks (LIU *et al*., 2017; AHSAN; BASHIR, 2019). It is estimated that approximately 80% of the world population consumes caffeinated products every day, and around 90% of adults in North America drink more than 400 million cups of coffee daily (ALMOSAWI *et al*., 2018; DE PAULA; FARAH, 2019). Energy drinks occupy a significant portion of daily caffeine consumption, especially in the United States, given its prevalence and popularity (HECKMAN *et al*., 2010; BRANUM *et al.,* 2014; WIKOFF *et al.,* 2017).

However, most of the caffeine consumed daily in the US is imported in the form of coffee and tea in comparison to cocoa, kola nuts and synthetic caffeine, which occupy a smaller portion of these imports since they contain reduced amounts of caffeine (FULGONI *et al*., 2015). In the young population, there is an increase in the caffeine consumed content, predominantly through soft drinks and coffee as children become adolescents (AHLUWALIA *et al*., 2014; TEMPLE *et al*., 2017). In this sense, a study performed by Ahluwalia and Herrick (2015) showed that thereabout 75% of children and adolescents in the USA, from 6 to 19 years of age, consume an average of 38 mg of caffeine per day, in addition to an average

consumption of 25 mg of of caffeine per day in children aged 2 to 12 years old, and 50 mg/day in adolescents aged 12 to 17 years old.

Corroborating this fact, Drewnowski and Rehm (2016) reported that among children and adolescents the highest consumption of caffeine occurs at ages 9 to 13 years, in a consumption of up to 26 mg/day, and at age 14-19 years old, reaching 61 mg of caffeine per day. Similarly, studies have shown that the average caffeine intakes increase from 50 mg/day in childhood (2 to 11 years old) to 180 mg/day in adulthood, due to changes in consumption habits by adults since they adopt a more regular pattern compared to children (FITT *et al*., 2013; AHLUWALIA *et al*., 2014; BRANUM *et al.,* 2014).

Food sources of caffeine change as well. According to Wikoff *et al*., (2017), the adult population intakes caffeine mainly through the consumption of coffee and tea, while children and adolescents intake caffeine through the consumption of soft drinks and chocolates. Coffee is one of the products that generally contains the highest concentrations of caffeine (from 3 to 350/400 mg) compared to tea and some energy drinks, as well as solid foods in general such as chocolate, which contains from 1 to 6 mg of caffeine per serving only (MEJIA; RAMIREZ-MARES, 2014). Indeed, chocolate and other cocoa-based foods have a small contribution of caffeine to the diet, since it offers no significant stimulating effects on the nervous system (TEMPLE *et al*., 2017).

It should be noted that there is a significant variation in the concentration of caffeine within the same category of drinks. For example, it is estimated that a standard cup of coffee (ground coffee) of 240 ml or 8 oz (short for the English unit of measure Ounce for mass or weight) has an average 100 mg of caffeine (HECK; MEJIA, 2007). Of interest, a study conducted by McCusker *et al*., (2013) analyzed the caffeine content in 20 different types of coffee purchased from coffee shops in the United States, reporting that the amount of caffeine in ground coffee can vary from 76 to 112 mg/8 oz. Even greater variations in the amount of caffeine (33 to 400 mg) can be seen in energy drinks in general (MEJIA; RAMIREZ-MARES, 2014).

3.2. Beneficial Effects of Caffeine

In low doses (<200 mg/day), studies reported that caffeine consumption was able to improve mood, alertness and to increase locomotors performance, as well as the sense of attention and the speed in which the information is processed (LIU *et al*., 2017; DE PAULA; FARAH, 2019; ONAOLAPO; ONAOLAPO, 2020). Furthermore, it has been reported that regular caffeine consumption is related to a lower risk of developing neurodegenerative diseases, such as Alzheimer's disease (AD) and Parkinson's disease (PD), because it acts as a neuroantioxidant on nervous system (Table 1) (KI; LI, 2014; KOLAHDOUZAN; HAMADEH, 2017; REN; CHEN, 2020; HONG *et al*., 2020).

In this view, studies conducted on the role of caffeine in the management of these neurological disorders highlighted that this substance has a strong antagonistic effect against the adenosine A2A receptor and a forceful agonistic effect against nuclear-related factor-2 (Nrf-2), regulating the cellular homeostasis at the brain by reducing oxidative stress and regulating the balance of the accumulation of α-synuclein in PD, in addition to reduce the production of β-amyloid protein in humans with AD (RIVERA-OLIVER; DÍAZ-RÍOS, 2014; KOLAHDOUZAN; HAMADEH, 2017; ENDESFELDER *et al*., 2019; IKRAM *et al*., 2020).

Moderate doses of caffeine (around 200-300 mg/day) may have a considerable role in weight loss by acting on the metabolism rate since its metabolites can trigger inhibition of critical enzymes on the systemic metabolism and, in turn, to modulate lipid and glucose metabolisms (CANO-MARQUINA *et al*., 2013; BARCELOS *et al*., 2020). It was also demonstrated that caffeine acts in the prevention of certain types of cancer, including endometrial, prostate, rectal and liver cancer, when it is ingested by healthy humans in moderate doses through complex cellular signaling mechanisms (Table 1) (GAPSTUR *et al*., 2017; AHSAN; BASHIR, 2019; INOUE; TSUGANE, 2019; ISMAIL *et al*., 2021).

In this context, meta-analysis of cohort, observational and prospective studies highlighted in a review work carried out by Poole *et al*., (2017) showed a lower incidence of several types of cancer for low doses to moderate doses of caffeine content in coffee, reporting that caffeine consumption was associated with a weak risk of developing prostate cancer and oral cancer (WANG *et al*., 2016), endometrial cancer (ZHOU *et al*., 2015), leukemia (YU *et al*., 2011), melanoma (YEW *et al*.,

2016), non-melanoma skin cancer (CAINI *et al*., 2017) and liver cancer (BRAVI *et al*., 2016), with significant linear dose-response relations indicating benefits for health.

Of relevance, a meta-analysis study has showed that a high consumption versus a low consumption of decaffeinated coffee was associated with a lower risk of lung cancer (TANG *et al*., 2016), evidencing that we need to focus on other bioactive compounds besides the caffeine. However, in people who smoke, the risk of developing lung cancer must be associated with the excessive consumption of caffeine due to the vicious habit of drinking coffee before smoking (XIE *et al*., 2016; GALARRAGA *et al*., 2016).

Researches have examined the effects of low to moderate caffeine doses (5-13 mg/kg body mass) on exercise and sport situation. At low doses (<3 mg/kg body mass, ~200 mg), caffeine can improve the locomotors performance during exercises, the enhancing of vigilance, alertness, mood and the cognitive processes (SPRIET, 2014). Of importance, motivation and caffeine consumption habits can influence the cognition response and the general performances during and after exercises (SHABIR *et al*., 2018), as well as during the sex and age on caffeine ergogenicity, therefore, causing modifying effects of genotype (PICKERING; GRGIC, 2019).

According to Burke (2008), the beneficial performance of caffeine can be seen with moderate amounts (~3 mg.kg-1 body mass), but these benefits are likely to occur across a range of sports, including endurance events, stop-and-go events, and sports involving sustained high-intensity activity, for example swimming, rowing, and middle and distance running races. On the other hand, as reported by Gues *et al*., (2021), high doses of caffeine (e.g. 9 mg/kg) are associated with a high incidence of side-effects and they do not seem to be required in order to elicit an ergogenic effect in a wide range of aerobic and anaerobic sport-specific actions.

Studies in the toxic-pharmacological area have shown that caffeine is able to reduce the levels of reactive species and pro-inflammatory molecules, such as Tumor Necrosis Factor (TNF) and interleukins (IL), which acting on cells signaling pathways that trigger inflammatory processes (AMER *et al*., 2017; WILLSON, 2018; BARCELOS *et al*., 2020; IKRAM *et al*., 2020). Moreover, caffeine can act as an antioxidant molecule, being capable of reducing the levels of lipoperoxidation (LPO) in cell lipid membranes that may cause, in a last instance, consequent damage to DNA, proteins and mitochondria, resulting from the oxidative stress process (Table 1)

(PERGOLIZZI *et al*., 2018; VIEIRA *et al*., 2020), a condition characterized by a shift in the balance of the endogenous antioxidant defense mechanisms due to the high production of Reactive Oxygen Species (ROS) (VRAILAS-MORTIMER *et al*., 2012; DA SILVA *et al*., 2018; VIANA *et al*., 2020; ABDELMAGEED *et al*., 2021).

Additionally, caffeine is able to act as a regulatory factor in the cell cycle that modulates the DNA repair system, and as an immunomodulatory substance that interacts with specific receptors as well as cytokines, thereby modulating the immune system through mediation of its effects on T lymphocytes, B lymphocytes, natural killer of cells and macrophages (CUI *et al*., 2020). Interestingly, Lipton *et al*., (2017) reported the role of caffeine also as an analgesic adjuvant in the acute treatment of primary headache with over-the-counter drugs, and in the migraine condition. It was found that the combination of caffeine in doses of ≥100 mg and analgesic medications, including acetaminophen, acetylsalicylic acid and ibuprofen have showed a significant improvement in the treatment of patients with tension-type headache and migraine.

Due to its anti-inflammatory effects, caffeine can also exert potent effects as a clinical preventive medicine for other types of injuries, such as, bronchopulmonary dysplasia as demonstrated by Zhao *et al*., (2019). They found that caffeine inhibits NLRP3 inflammasome activation by suppressing MAPK/NF-κB signaling and A2aR-associated ROS production in LPS-induced THP-1 macrophages by decreasing the development of bronchopulmonary dysplasia.

Table 1 - Main beneficial effects of caffeine on human body.

Health claims	Action of caffeine intake	Dose and frequency of use[1]	References
Neuroprotection	Improves the mood and the alertness system, increases the locomotors performance		Eskelinen and Kivipelto (2010) Postuma *et al*., (2012) Mandel (2012) Kolahdouzan and Hamadeh (2017)
	Lower risk of developing neurodegenerative diseases,		

	such as, Alzheimer and Parkinson	<200 mg/day	Liu *et al*., (2017) Onaolapo and Onaolapo (2020) Ikram *et al*., (2020)
Metabolic action	Weight loss (acting on the metabolism rate)	~200-300 mg/day	Cano-Marquina *et al*., (2013) Pan *et al*., (2016) Barcelos *et al*., (2020) Mansour *et al*., (2020)
Anticancer action	Prevention of certain types of cancer (oral, colorectal, endometrial, prostate and liver cancer; melanoma, non-melanoma skin cancer and liver cancer)	~150-300 mg/day	Vitaglione *et al*., (2012) Sinha *et al*., (2012) Zhou *et al*., (2015) Schmit et al., (2016) Yew et al., (2016) Wang *et al*., (2016) Temple *et al*., (2017) Caini *et al*., (2017) Gapstur *et al*., (2017) Ahsan and Bashir (2019)
Antioxidant and anti-inflammatory action	Reduced levels of oxidative stress, pro-inflammatory enzymes (TNF and IL) and lipoperoxidation (LPO) in cell membranes	~200-300 mg/day	Horrigan *et al*., (2004) Agudelo-Ochoa *et al*., (2016) Martini *et al*., (2016) Amer *et a*l., (2017) Lipton *et al*., (2017) Barcelos *et al*., (2020) Vieira *et al*., (2020)
	Improves the locomotors performance, vigilance, the		Burke (2008) Spriet (2014)

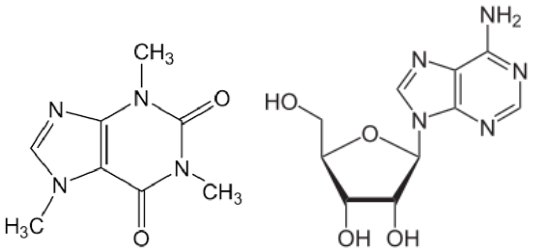
Exercises and sport situations	alertness, the mood and the cognitive processes	<200mg/day	Shabir *et al*., (2018) Wickham and Spriet (2018) Grgic *et al*., (2019) Pickering and Grgic (2019) Guest *et al*., (2021)

1 – Average numbers based on the variation in the amount of caffeine ingested by healthy adults reported in different cited studies.

3.3. Adverse Effects of Caffeine

On the other hand, excessive doses of caffeine contribute to the development of diverse physiological changes, mainly related to the nervous, cardiovascular and hepatic systems (WATSON *et al*., 2016; GÖKCEN; ŞANLIER, 2017; RODDA *et al*., 2020). In the nervous system, the caffeine can cause changes in the brain neurotransmitter levels by triggering behavioral and neurochemical changes associated with antagonism of inhibitory presynaptic adenosine receptors, as well as alteration in the number of these receptors, releasing an uptake and turnover of neurotransmitters (BARCELOS *et al*., 2020).

Adenosine is a molecule involved in numerous biochemical pathways, mainly in the transfer of energy in the form of adenosine triphosphate (ATP) and cell signaling, in addition to being a neuromodulator that can promote sleepiness, affecting the memory and the learning process (GOMES *et al*., 2011). There are several types of cognate receptors in which adenosine can act, notably A1, A2a, A2b and A3, which are proteins coupled to G protein (RIBEIRO; SEBASTIÃO, 2010; TEMPLE *et al*., 2017). Caffeine can cause sleeping disturbance because it has the potential to occupy the sites of the adenosine receptors, in special A1 and A2a, since both caffeine and adenosine have a similar molecular structure with a kind of comparable double bond ring (FISONE *et al*., 2014) (Figure 1).



1,3,7-trimethylxanthine **Adenosine**

Figure 1 - Similarities between the chemical structures of 1,3,7-trimethylxanthine (caffeine) and adenosine.
Source: Fisone et al., (2014).

Studies have reported that caffeine can cause a state of dysfunctional excitation in the nervous system, leading to sleeping disturbances, in amounts above 450 mg of caffeine/day (Table 2) (WATSON *et al*., 2016; ONAOLAPO; ONAOLAPO, 2020). In children, clinical trial studies highlighted in a review work conducted by Wikoff *et al*., (2017) have shown that the excess of caffeine alters normal sleeping patterns, affecting the healthy development of children as they grow up. Hence, it must be established that they should consume lower amounts of caffeine or equal to 2.5 mg/kg body weight/day.

Moreover, researches have also reported that high doses of caffeine (>500 mg/day) can cause high levels of tension, nervousness, irritability, nausea, palpitations and restlessness in healthy humans (Table 2) (LIU *et al*., 2017; WILLSON, 2018). In this sense, high doses of caffeine can lead to an anxiety disorder making individuals with pre-existing anxiety disorder more susceptible to the effects of moderate doses of caffeine (200-300 mg/day) than individuals who do not have any depression symptoms (WANG *et al*., 2016; DE PAULA; FARAH, 2019).

The effects of caffeine regarding cardiovascular disorders show that the consumption of low to moderate amount of caffeine per day is associated with a reduced risk of cardiovascular disease (WENG *et al*., 2020; SOCALA *et al*., 2020), but an acute caffeine intake (>500 mg/day) can stimulates a modest increase in blood pressure triggering supraventricular tachycardia perhaps due to the increased of intracellular calcium concentrations, norepinephrine releasing and sensitization of

dopamine receptors (CANNON *et al*., 2011; CHRYSANT, 2017; TURNBULL *et al*., 2017). In addition, arrhythmia, atrial fibrillation and coronary disease also have been detected in healthy and hypertensive individuals or with historic of cardiovascular problems (Table 2) (HARTLEY *et al*., 2000; O'KEEFE *et al*., 2013; BODAR *et al*., 2019). Other factors that can influence the development of these cardiovascular disorders as well as their aggravation by the excessive consumption of caffeine are obesity, diabetes, high blood pressure, tobacco smoking and alcohol (JOHN, 2020).

Different studies have reported the negative association of caffeine consumption through coffee with metabolic, gastrointestinal, and liver disorders (AWAAD *et al*., 2011; ARNAUD, 2011; MEREDITH *et al*., 2013; KENNEDY *et al*., 2016; HODGE *et al*., 2017; MANSOUR *et al*., 2020). Most of these disorders were reported in the enzymatic systems responsible for the metabolism of caffeine in the body, in particular the cytochrome P450 oxidase system, mainly by the enzyme CYP1A2 present in the liver and other tissues, including the brain (Table 2). Several cytochrome P450 (CYP) isoforms are implicated in caffeine demethylation and hydroxylation (CYP1A2, CYP1A1, CYP2E1 and CYP3A), but the liver enzyme CYP1A2 is in charge of the clearance of caffeine in the human body (SOCALA *et al*., 2020). Otherwise, the pharmacokinetics process of caffeine is not affected by the hepatic first-pass effect, and its elimination is regarded as a first-order process described by a one-compartment open model system within the intake range of 2–10 mg/kg (NEWTON *et al*., 1981; BLANCHARD; SAWERS, 1983).

Table 2 - Main adverse effects of caffeine on human body.

System	Adverse effects	Dose and frequency of use[1]	References
Nervous system	Dysfunctional excitement, sleeping disorders, nervousness and irritability; High neurostimulant effects; Headache and difficulty concentrating; Contributes to risk of developing neurodegenerative diseases	>450 mg/g/day	Nawrot *et al*., (2003) Ferré (2008) Costa *et al*., (2010) Watson *et al*., (2016) Temple *et al*., (2017)

			Wikoff *et al*., (2017) Kolahdouzan and Hamadeh (2017)
Cardiovascular system	Increase in blood pressure causing hypertension and increase in heart rate; arrhythmia, atrial fibrillation and coronary heart disease	>500 mg/g/day	Pelchovitz and Goldberger (2011) Mesas *et al*., (2011) Cano-Marquina *et al*., (2013) Cheng *et al*., (2014) Grosso *et al*., (2016) Chrysant (2017) Turnbull *et al*., (2017) Willson (2018) Bodar *et al*., (2019) De Paula and Farah (2019)
Hepatic system	Cytotoxicity and an increased of the detoxification load; a considerable clearance reducing, and prolonged half-life elimination	>400 mg/g/day	Arnaud (2011) Perera *et al*., (2013) Cheng *et al*., (2014)
Gastrointestinal system	Nausea, vomiting, abdominal pain and diarrhea.	> 450 mg/g/day	Devies *et al*., (2012) Doherty and Smith (2014) Willson (2018)

1- Average values based on the variation in the amount of caffeine ingested by healthy adults reported in the different studies cited.

In pregnancy, studies have investigated the relationship between the association of high-doses of caffeine intakes (>500 mg/day) by pregnant women and the underlying complications of fetal development, indicating an increasing in the incidence of spontaneous abortion, fetal growth restriction, mental retardation and congenital malformations, as well as low birthweight babies (CARE STUDY GROUP,

2008; MORGAN *et al*., 2013; WIKOFF *et al*., 2017; GASKINS *et al*., 2018). In this context, James (2020) exanimated the evidence of the association between maternal caffeine consumption and the negative pregnancy outcomes through a narrative review study, which summarized that the maternal caffeine consumption is reliably associated with major negative pregnancy outcomes, in which caffeine consumption from moderate to high levels increased the risk of fetal complications for all pregnancy women, associating with stillbirth, low birth weight babies and/or small for gestational age.

Given the effects that caffeine may have on brain development, it is recommended that pregnant women reduce the caffeine consumption during pregnancy in amounts less than or equal to 300 mg of caffeine/day (equivalent to 5 mg/kg of weight body/day for a 70 kg person, about two or three small cups of coffee per day) (HECKMAN *et al*., 2010; MEREDITH *et al*., 2013; MEJIA; RAMIREZ-MARES, 2014; CARO; FAST, 2020). Accordingly, it is important that women receive sound evidence-based advice about potential caffeine-related harm (JAMES, 2020).

Moreover, the association between the increasing of caffeine consumption, particularly from coffee, and the relative risk of developing type 2 diabetes mellitus were also investigated in several studies (AGARDH *et al*., 2004; BIDEL *et al*., 2008; DING *et al*., 2014; JIANG *et al*., 2014; CHRYSANT, 2017; SOCALA *et al*., 2020). The risk of developing this metabolic syndrome is notably associated with the high amounts of caffeine consumption in long terms, especially in predisposed individuals (SHANG *et al*., 2016). Nonetheless, the risk is generally not very high at low caffeine concentrations (170 to 200 mg/day), it even enhances the physiological functioning of pancreatic beta cells and it also improves the glucose tolerance (SANTOS; LIMA, 2016; AHSAN; BASHIR, 2019; SAID *et al*., 2020).

However, it is important to take into consideration other bioactive compounds present in coffee, such as trigonelline, cafeic and chlorogenic acids, which can alter the effect of glucose absorption by the liver and the insulin sensitivity in pre-diabetics patients (HECKMAN *et al*., 2010; CANO-MARQUINA *et al*., 2013; MIRMIRAN *et al*., 2018). Consumption of decaffeinated coffee also seemed to have similar associations of comparable magnitude when it is intake in higher doses by susceptible individuals (DING *et al*., 2014; POOLE *et al*., 2017) (Figure 2).

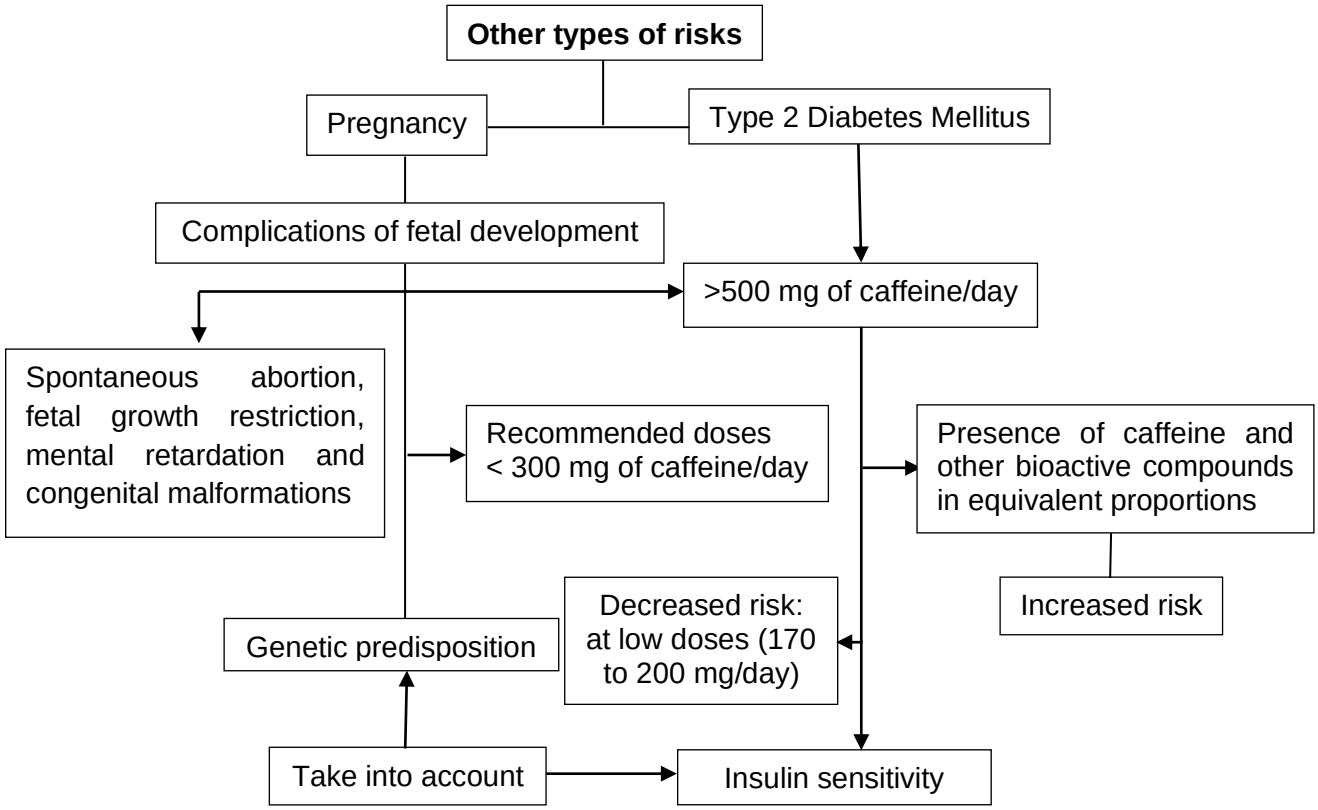


Figure 2 - Flowchart correlating the association among pregnancy, type 2 diabetes mellitus and caffeine consumption.

Finally, we must analyze those individuals who want to stop consuming caffeine, because it is necessary to do this progressively, since the sudden cessation of regular caffeine consumption produces symptoms, such as headache, drowsiness, lethargy, fatigue, labor difficulties, a decreasing in the well-being state, a drop in blood pressure and an increasing in the blood flow in the brain that are associated with the Caffeine Withdrawal Syndrome (CWS) (LADER *et al*., 1996; GÖKCEN; ŞANLIER, 2017; RODDA *et al*., 2020). The intensity and persistence of these symptoms vary according to the degree of sensitivity to caffeine and among other factors previously listed. As CWS occurs due to the sudden interruption of caffeine intake by individuals who usually consume it daily through products containing caffeine, the symptoms can be avoided if this intake is gradually decreased (PHILLIPS-BUTE; LANE, 1998; DE PAULA; FARAH, 2019). Despite the withdrawal symptoms previously described, the caffeine is not listed in the category of substances that can cause addiction (DE PAULA; FARAH, 2019).

4. CONCLUSIONS

In sum, the literature reviewed in this study suggests that depending on the frequency and the dosage of caffeine consumption, it can cause a beneficial effect or an adverse physiological effect on the human body. When it is ingested in moderate amounts (<450 mg of caffeine per day) by healthy adults, caffeine can act as an antioxidant, anti-inflammatory and as a regulator for certain important metabolic pathways. However, when it is consumed in high doses (>450 mg of caffeine per day), caffeine can be harmful to the human health by contributing to the development of diverse physiological changes, mainly related to the nervous, cardiovascular, renal and hepatic systems.

It is worth mentioning that the amount of caffeine required to produce adverse effects on the body also varies according to some factors such as: weight, gender, age, the use of certain types of medications and the difference in sensitivity. Those factors also include people at risk group, for instance, hypertensive people, diabetics or people with disorders in the nervous system. Nevertheless, further researches are needed in order to add more information to these emerging concerns, and to provide a greater empirical support for the recommendations related to the caffeine absorption, distribution, metabolism and consumption.

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