Introductory Chapter: Caffeine, a Major Component of Nectar of the Gods and Favourite Beverage of Kings, Popes, Artists and Revolutionists, a Drug or a Poison?

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Additional information is available at the end of the chapter

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1. Caffeine consumption around the World

Global caffeine consumption is estimated to be around 120,000 tonnes per year, which corresponded to one cup of coffee per day for every human on the planet. Based on the statistics, the top tea-producing countries in the world are: China, India, Kenya, Sri Lanka, Turkey, Indonesia, Vietnam, Japan, Iran and Argentina. Main producers and exporters of coffee are: Brazil, Vietnam, Colombia, Indonesia, Ethiopia, India, Honduras, Uganda, Mexico and Guatemala, **Figure 1**.

Caffeine consumption is the highest in tonnes in the United States (971), followed by Brazil (969), Germany (425), Italy (211) and France (202). About 79% of total consumed caffeine comes from coffee, 15% from tea, only 3% from mate and 4% from cocoa [1]. In general, people in the west drink more coffee, while the eastern world drinks more tea, **Figure 1**. Tea consumption per capita predominates in Turkey, Russia, Iran, Mauritania, Syria and China. In Paraguay, Argentina and Brazil, the consumption of mate is dominant. The rest of the world prefers coffee. Europeans are the world's biggest coffee drinkers. Coffee consumption in Europe varies from around 10 kg per capita per year in the Nordic countries (Finland, Norway) to around 3 kg per capita per year in the United Kingdom and most Eastern Europe countries. Annual consumption over 5 kg per capita per year in Brazil is exceptionally high among over 60 coffee exporters. The largest cocoa consumption is noted in Switzerland, Germany, Ireland, the United Kingdom and Norway. The world's biggest Coca-Cola drinkers are in Mexico, Chile, the United States, Panama and Argentina. Energy drinks containing caffeine like Red Bull, Monster, Suntory, Rockstar have experienced a considerable growth in popularity in the last 25 years, but still represents only 1% of the overall non-alcoholic beverages market. Austria led the global per capita consumption and is followed by Ireland, the United Kingdom, Switzerland, the United States and Australia. Caffeine, in any form, is consumed

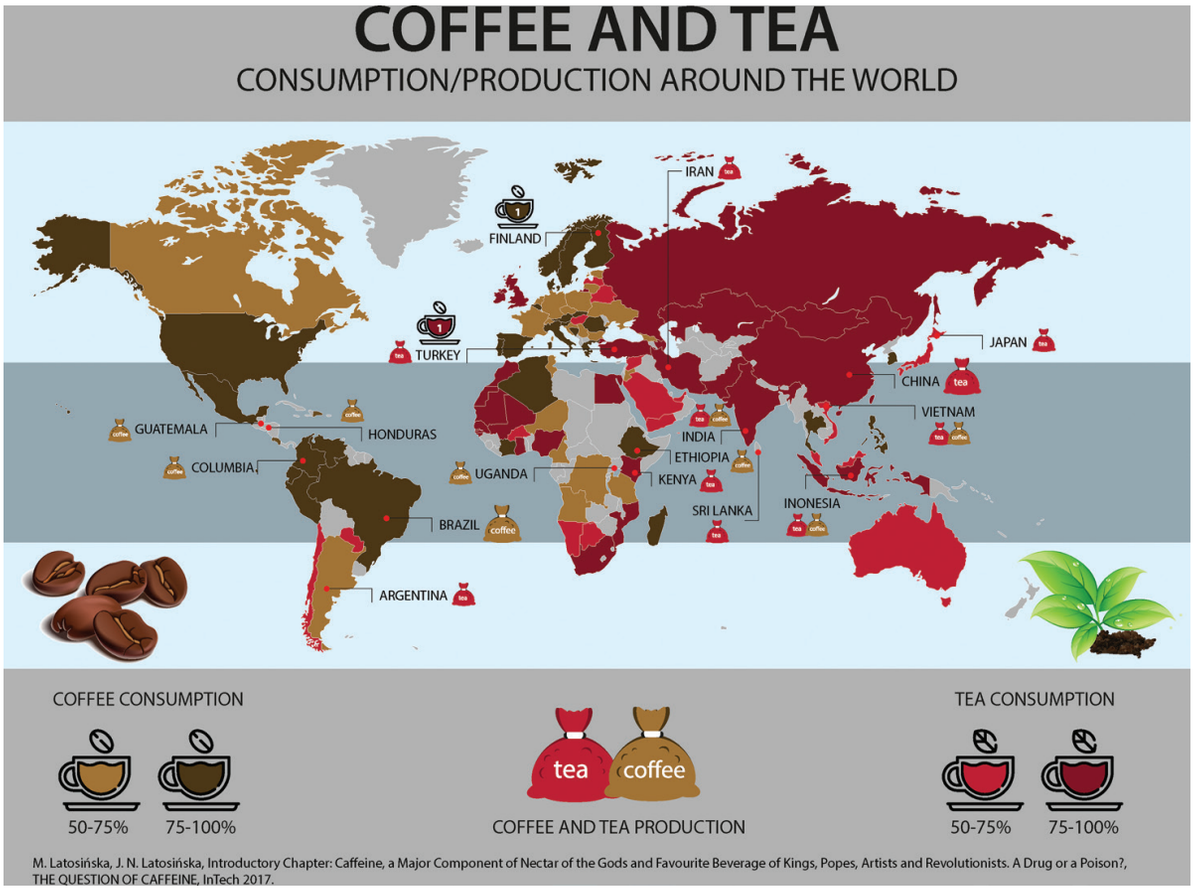

Figure 1. Coffee and tea consumption/production around the world in 2015 (statistical data: Food and Agriculture Organization of the United Nations and Euromonitor).

daily by about 90% of adults, which makes this psychoactive, but legal substance the world's most widely used drug.

Despite caffeine huge popularity and its countless studies, there is still much confusion, inconsistencies and contradictions in the results, poorly known side effects and unknown applications.

2. Historical aspects

Caffeine-containing species from *Camellia, Coffea, Cola, Ilex, Paullinia, Theobroma* and *Citrus* genus have been known from ancient times, but phytogenic studies indicated that they are not closely related [2]. However, most of them grow in tropical or sub-tropical zones. *Camellia* originates from Asia, *Coffea* and *Cola* from Africa, *Ilex, Paullinia* and *Theobroma* from America, *Citrus* from Australia and Oceania. Tea (*Camellia sinensis* (L.) Kuntze), coffee (*Coffea arabica* (L.), *Coffea canephora var. Robusta*, (Pierre ex A. Froehner), *Coffea liberica* (Bull ex Hiern)), cacao (*Theobroma cacao* (L.)) and citruses (*Poncirus* (L.) Raf., *Fortunella* (Swingle), *Microcitrus* (Swingle)) have been used as medicinal products, stimulating food, dietary supplement or fragrant plants, while cola (*Cola nitida* (*Vent*.) Shott and Endl.)), mate (*Ilex paraguariensis* (A.St.-Hil.)) and guaraná

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(*Paullinia guarana* (Kunth) or *Paullinia cupana* (Kunth), *Paullinia sorbilis*, (Mart)) as ritual plants. Almost each country has got its own legends on finding natural source of caffeine.

According to Cha Jing by Lu Yu, a mythical ruler of prehistoric China Shen Nong (also known as Wugushen or Wuguxiandi), reigning 3000 BC, discovered tea, when a few leaves of the nearby tree *Camellia sinensis* (L.) fell into the boiling water [3]. In the times of the Chinese Shang dynasty, tea was used as a medicinal drink, but later, during the Chinese Tang dynasty, it was popularized in East Asia as a recreational drink [4]. The etymology of the word tea goes back to the Chinese 茶(*tê, chá* and *chai)*, which also indicates the region of its origin. The first unambiguous reference to tea treated as a beverage is dated to 59 BC (Western Han dynasty era) [5]. In 805 AD, the seeds of tea were brought to Japan by the Buddhist saint Saichō (Dengyo Daishi). Soon after that, the cultivation of tea in the five provinces surrounding the capital of the country, Kyoto, was ordered by the enthusiastic 52nd Japan emperor Saga. Exactly who first brought tea to Europe in the seventeenth century remains a mystery, but it is known, that the oriental goods including tea have been imported by the Portuguese since 1517 and by the Dutch since 1610. The seventeenth-century apothecaries added tea to other luxury items like sugar, ginger and spices and sold them next to the medicines. In 1658, Katherine Braganza, Portuguese wife of Charles II Stuart, brought tea to England [6]. It is known that French ruler Louis XIV (the Sun King) drunk tea for health reasons starting from 1665 [7]. By 1675, tea was in general use throughout Holland and started to being sold in grocery stores. To Russia, tea was brought from China as a gift to Russian tsars. For the first time, about 1630—it was a gift to Russian tsar Michael I (Romanov) from a Mongol Khan Sholoi [8] and for the second time, in 1680—it was presented to tsar Alexis I from the Chinese ambassador to Moscow [9]. European tea merchants of eighteenth century recognized only three growing markets: Holland, England and Russia. But the fourth one was the young market in British American colony. The Tea Act, legislative manoeuvre by Lord North, passed by the Parliament of the United Kingdom on 10 May 1773, granted the British East India Company Tea a monopoly on tea sales [10]. On 16 December 1773, the Patriot group 'Sons of Liberty' destroyed a shipment of tea in Boston Harbour. This event that became known as the Boston Tea Party was the signal to American War of Independence [10]. Almost 100 years later, in mid-1800, tea was successfully harvested in South Carolina. Although *Camellia sinensis* (L.) originates from East Asia, the Indian Subcontinent and Southeast Asia, but nowadays, it is cultivated in most tropical and subtropical regions of the world.

The history of coffee has its beginnings in the sixth-century Ethopia [11], however, Ethiopian Galla tribe ground up coffee beans (actually the pit of the berry), mixed them with animal fat and consumed as an energy food, much earlier. The famous legend attributes it to the shepherd of Caldas from Abyssinia, who in 525 AD noticed that the goats that had grazed among the bushes became excited and sleep-deprived. After sampling the fruit from the bushes growing there, he experienced a similar surge of strength. Arab traders brought coffee to Yemen [12]. The oldest written references to coffee ('*bunchum*') were found in Kitab al-Hawi—a comprehensive book on medicine by Abu Bakr Muhammad ibn Zakarijja ar-Razi (the ninth-century Persian polymath, physician, alchemist and philosopher) [13]. By 1414, coffee was known in Mecca and spread to Egypt from Al Mucha (Mocha), the Yemeni port, then to Syria and Istanbul, the capital of the vast Ottoman Turkish Empire [14]. The first

coffee shop, Kiva Han, was opened in Constantinople in 1475. In the fifteenth century, the Sufis of Yemen routinely used coffee to stay awake during prayers. There was an attempt to ban coffee in 1511 in Mecca, because religious leaders accounted it for stimulation of the radical thinking, but sultan of Cairo overruled the idea and the ban was lifted. By 1630, over one thousand coffee houses were operated in Cairo. In the end of the sixteenth century, coffee spread throughout the middle East. Coffee arrived to Europe by two routes—from the Ottoman Empire, and by sea—from the original coffee port of Mocha. The German botanic Léonard Rauwolf for the first time described coffee in 1576 in *Viertes Kreutterbuech—darein vil schoene und frembde Kreutter* [15]. In the seventeenth century, coffee was known in Europe as 'Arabian wine' or 'Muslim drink' and thus unpopular. Coffee enthusiast pope Clement VIII 'baptized' it around 1600 [14]. The coffee name comes from the original Arabic *quhwah* through Turkish form *kahveh* translated to Italian as *caffè* or *Danish* as *kaffe*. Shortly after the first 'cafes' in Venice, Oxford, London were established. When Turkish siege of Vienna in 1683 was broken, the European victor Johan III Sobieski allowed Jerzy Franciszek Kulczycki, sas coat of arms, to choose as a reward anything from the Turkish camp. Amazingly, Kulczycki opted for 300 bags containing the 'strange seed' (huge coffee supplies). The legend says that Kulczycki opened the first coffee house *Hof zur Blauen Flasche* in Vienna in 1683 [16]. Cafes quickly gained popularity throughout the whole western Europe playing a significant role in shaping social relations. In 1650, Jacobs, a Lebanese Jew, opened the first coffee house in Oxford, England [11]. Shortly thereafter, cafes where people could buy coffee for 1 penny and carry on intellectual conversations, called 'penny universities', began to emerge. Famous *Café Procope* in Paris, a gathering place of many French notables, actors, writers, philosophers and musicians, was opened in 1689 by Francois Procope, a Sicilian who came from Florence [17]. The parts of the furniture of this café were Voltaire, Denis Diderot, Pierre Beaumarchais, Honoré Balzac, Victor Hugo, Paul Verlaine, Jean-Jacques Rousseau, fathers of French revolution: Jean-Paul Marat, Maximilien de Robespierre, Georges Danton and young Napoleon Bonaparte, later France emperor. By 1843, the number of cafes in Paris increased to as many as 3000. The first coffee houses in Germany were opened in Regensburg and Leipzig. Johann Sebastian Bach, Leipziger, the most heavy coffee drinker ever, wrote the Coffee Cantata in its honour. The first and the oldest to date café in Salzburg was *Café Tomaselli* founded in 1700. Frequent cafes guests were Wolfgang Amadeus Mozart, Michael Haydn, Hugo von Hofmannsthal and Max Reinhardt. In Russia, historically, the tradition of coffee-drinking was introduced by Peter the Great, who brought it from his travel to the Netherlands [18] and was fostered by Empress Catherine II the Great [19]. It must be said that in those days not all were coffee lovers. King Frederick II of Prussia even issued a manifesto claiming beer's superiority over coffee and charged a heavy tax on coffee commercialization in 1777 [20]. Coffee reached New Amsterdam (New York) in mid-seventeenth century and then the New World. It immediately obtained a status of one of the most popular drinks. As the demand steadily grew, there was strong competition to cultivate coffee outside of Arabia. The first attempts to plant coffee by the Dutch failed in India, but were successful in Indonesia (Java, Sumatra and Celebes). In 1714, a young coffee plant was given by Gerrit Hooft, the Mayor of Amsterdam, to King Louis XIV of France as a gift [14]. It was carefully planted in the Royal Botanical Garden in Paris. Nine years later, a seedling stolen from this plantation by king's doctor was transported

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to Martinique by Gabriel de Clieu [14]. It was the nucleus of about 18 million trees plantation in Martinique 50 years later. This seedling was also a parent of all the coffee trees throughout the Caribbean, South and Central America. The Brazilian coffee trees also come from France, exactly from French Guiana. Francisco de Mello Palheta was a military responsible for the introduction of coffee cultivation in Brazil [21]. Despite many attempts, he was not able to get coffee plants officially, but in 1720, Marie-Claude de Vicq de Pontgibaud, the wife of the French governor Guiana Claude Guillouet d'Orvilliers, smashed the handful of seeds inside the bouquet of flowers—a farewell gift. Quickly the cultivation of coffee had been introduced in Dutch Guiana (1714), Jamaica (1718) and expanded to the tropical regions of South America. Throughout the nineteenth and the first decades of the twentieth century, Brazil was a monopolist on the coffee market, but later, Colombia, Guatemala and Indonesia started to cultivate coffee. European colonial regimes initiated the coffee cultivation and export in Kenya, Angola, Uganda and Ethiopia, where it all started. During the American Civil War (1861–1865), Union soldiers received from the government in Washington 36 pounds of coffee annually (about 16.3 kg), because without coffee soldiers did not exist. The status of coffee had changed from the scarce elixir into a public beverage.

Another source of caffeine is cocoa (*Theobroma cacao* (L.)) nuts [22], used by pre-Olmec cultures in Mexico as early as 1900 BC. Olmec, Mayan, Toltec and Aztec civilizations used chocolate as an invigorating drink, stimulating mystical and spiritual qualities [23]. In the New World, chocolate was consumed in the form of a bitter and sharp drink called xocoatl, containing a bit of vanilla, chilli peppers and achiote. Cocoa seeds in pre-Columbian Mesoamerica were luxury goods and used as a means of payment (currency). In 1517, the Spanish conquistador Don Hernán Cortés [23] was treated to xocoatl by the Aztec emperor Montezuma. Eleven years later, he brought xocoatl to Spain, where it became a popular drink on the Spanish royal court. The name of this drink comes from the Nahuatl words *xocoatl* (xoco 'bitter' and atl 'water') and *cacahuatl* (cacao) translated to Spanish as *chocolate*. Spain kept chocolate secret for nearly a century, but when Anne of Austria, the daughter of Spanish king Philip III wed the French king Louis XIII in 1615 [24], chocolate spread across Europe. In 1689, Hans Sloane invented a sweet milky version of this drink, which was originally prepared by local apothecaries until 1897, when the Cadbury brothers acquired the exclusive right to manufacture it [25]. As demand for cocoa increased, its plantations were established in the West Indies (Caribbean Basin), Philippines, Asia and Africa. Due to the technological improvement—cocoa press—invented by the Dutch Casparus van Houten Sr., chocolate-making process was revolutionized [26]. Since then pulverization of cocoa into cocoa powder became a basic step in production of all chocolate products. In 1847, British company J.S. Fry & Sons produced first chocolate bar using cocoa butter, cocoa powder and sugar [27]. Shortly after that bars of chocolate flood the whole Europe. In 1879, in Berne, Switzerland, Rodolphe Lindt invented the conching machine, which gives chocolate a velvety texture and superior taste [26]. A chocolate boom which started in the late 1800s and early 1900s still has not slowed down. During the Second World War, bars of chocolate were the emergency store of each Swiss or US army soldier.

Kola (*Cola acuminata* and *Cola nitida Schott & Endl.)* [28], a tree native to the tropical Africa known from at least the fourteenth century is a natural source of caffeine. The etymology of the

word *kola* derives it from the Latinized form of a West African name of the tree. The kola nuts were chewed in many West African cultures to restore vitality and as appetite suppressant able to alleviate the feeling of hunger [29]. African exports to England and the United States started only in the mid-nineteenth century. The worldwide career of kola began in 1886 when John Pemberton from Atlanta, Georgia, created a recipe of 'Coca-Cola' [30]—an extract based on mixed kola and cocaine, used as a headache and hangover remedy [31].

Another old, but much less popular source of caffeine are the leaves and stalks of three species of holly tree genus *Ilex vomitoria* (Sol. ex Aiton) *(Saint Yaupon*), *Ilex paraguariensis* (A.St.-Hil.) *(Yerba Mate*) and *Ilex guayusa* (Loes.). *Ilex vomitoria* (Sol. ex Aiton) has been used by the North American Indians to brew tea called Asi (black tea) from the archaic era. It contains up to six times more caffeine than strong coffee and provokes vomiting for cleansing the body and soul. In South America (Argentina, Uruguay and Paraguay), a drink called yerba mate was made of *Ilex paraguariensis* (A.St.-Hil.). The Brazilian name is Chimarrão (Erva Mate chimarrão). Yerba Mate name comes from the Spanish *yerba* and *mati*, which in Quechua means *gourd*. Legend tells that when Yarí, the moon and Araí, the pinkish cloud of dusk, came to visit the Earth, a jaguar attacked them. They were rescued by an old Indian, who received in a reward this new kind of plant. People of the indigenous cultures in Argentina, Brazil, Paraguay and Uruguay who have survived periods of drought by drinking yerba mate called it 'Drink of the Gods'. This source of natural caffeine was popularized in Europe as an alternative to Asian tea by Jesuit missionaries who arrived to the Parish basin in the mid-seventeenth century and appreciated the advantages of a beverage made from powdered leaves and shoots. *Ilex guayusa* (Loes.) Amazon tree comes from tropical rainforest of Ecuador but is grown in Peru and Columbia. It is a completely unpopular, but rich source of caffeine, similar to coffee. In contradiction to the other caffeine containing beverages, drink made of its leaves is not only stimulant but also energizing, relaxing, calming and can cause conscious dreams. A great lover of yerba mate is pope Francis, native Argentinean. An exclusive drinking yerba mate kit was a present for pope Francis from the Argentine President Cristina Fernandez de Kirchner during her first audience in Vatican. Che Guevara, Lula da Silva, Jorge Luis Borges, Julio Cortázar, Barack Obama, Hillary Clinton and Madonna are all well-known yerba mate drinkers.

Also guaraná (*Paullinia guarana* (Kunth), *Paullinia cupana* (Kunth) *and Paullinia sorbilis* (Mart)) seeds, named after the Guarani Indian tribes, have been used for centuries by the inhabitants of the Amazon basin to restore lost forces. In the early eighteenth century, guaraná has been discovered and classified by the German botanist C.F. Paulini. Commercial use of guaraná began to spread after 1958, because it became an indispensable ingredient in many brewed beverages produced in Brazil and the United States.

Citrus (L.) (all true citrus trees including *Poncirus* (L.), *Fortunella* (Swingle) and *Microcitrus* (Swingle)), the weakest source of caffeine, originates from Australia, New Caledonia, New Guinea [32] and probably Southeast Asia bordered by India, Myanmar and China. The etymology of the word *citrus* derives it from the genus name in modern Latin. Although *Citrus* species leaves and flowers contain caffeine [33], they have been cultivated since ancient times mainly for fruits, in which caffeine is not present. However, citron leaves

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in sugar or honey or Korean honey citron tea (Yuja Cha) made of boiled leaves have also been highly popularized [34]. The fragrances, flavours and oils made of citrus have been known and desirable for many centuries in medicine and perfumery. The oldest traces of citrus in Europe date back to thirteenth-century BC Cyprus. The earliest fragrances (e.g. Eau de *Cologne* 1709 by Farina, Imperial 1850 and Eau de Imperiale 1861 by Guerlain, Jicky 1889 by Coty) contained bergamot, lemon, lime, mandarin and orange blossom oil [35]. Since then the popularity of citrus-spirit type of perfume or eau de toilette has not decreased. Small quantities of caffeine contain some types of honey (e.g. Greek orange honey), because citrus and coffee plants attract bees using caffeine as a part of rewarding system [36, 37].

3. Health considerations

For a long time, it has been a dilemma if coffee and tea are non-toxic and which is better for health—tea or coffee. From among all natural sources of caffeine, only tea started a career as a medicine and became a beverage in the course of time. In the eighteenth century, the Swedish king Gustav III, proposed the twin brothers who were sentenced to death for murder, a death row pardon in exchange for their participation in the scientific experiment [38]. One of the twins had to drink four cups of coffee a day, the other four cups of tea a day. A group of professors from Swedish Kings Academy of Sciences examined them to check the influence of these beverages on their organisms. The twins drank and drank, in the meantime, the king was murdered, the professors died. The first died the tea-drinking brother, while the compulsory coffee fun lived several years longer. But the tea drinker died at the age of 84, which at the time when the average life span was about 40, was considered as unbelievable achievement. What about the final verdict? No doubt by this simple long-lasting experiment, both dietary habits were considered as an important factor positively influencing human health. But the question remained which turned out better for health, tea or coffee, and first of all what factors were responsible for it.

Although all these natural sources of caffeine have been used for a long time as a beverage or drug, the fact that caffeine is the main factor responsible for their effect remained a mystery. Only in 1819, at the personal request of Johann Wolfgang von Goethe, the relatively pure chemical form of caffeine was isolated by Friedrich Ferdinand Runge [11], who called it '*Kaffebase*'. Eight years later, in 1827, M. Oudry obtained '*theine*' from tea [39]. In 1838, Mulder [40] and Jobst [41] showed that theine was actually caffeine. Thus, taking into account caffeine input both tea and coffee should be similarly health-promoting, which would not be a surprising result today, as we know main chemical component. The molecular structure of caffeine (1,3,7-trimethylxanthine; 1,3,7-trimethyl-1*H*-purine-2,6-(3*H*,7*H*)-dione) was described in 1882 by Hermann Emil Fischer, who also made its first complete synthesis, for which he was awarded the 1902 Nobel Prize [42]. He showed that caffeine found in coffee is equivalent to those in tea and cacao. Nowadays, caffeine is still rarely obtained by total chemical synthesis or semi-synthetic processes, which are economically inefficient. Instead, it is extracted from plants often as a by-product in the manufacture of decaffeinated coffee, **Table 1**.

Caffeine source	Origin	Plant	Plant part	Caffeine concentration per milligram (%)	No. of all chemical compounds
Tea	natural	*Camellia sinensis* (L.)	Leaf or shoot	4.8–9.3*	771
Coffee	natural	*Coffea arabica* (L.)	Bean or fruit	0.06–3.2*	154
Cacao	natural	*Theobroma cacao* (L.)	Seed	0.062–1.29*	261
Mate	natural	*Ilex paraguariensis* (A.St.-Hil.)	Leaf	0.2–2.0*	39
Guarana	natural	*Paullinia cupana* (Kunth.)	Seed or fruit	0.9–7.6*	23
Kola	natural	*Cola acuminata* (Schott & Endl.)	Seed	1.5–2.5*	9
Citrus	natural	*Poncirus* (L.), *Fortunella (Swingle), Microcitrus* (Swingle)	Leaf or flower	0–0.008*	495
Caffeine anhydrous	synthetic	-	-	>98.5	1
Dicaffeine malate	synthetic	-	-	65–70	2
Caffeine citrate	synthetic	-	-	45–55	3

*from Dr. Duke's Phytochemical and Ethnobotanical Databases (https://phytochem.nal.usda.gov/).

Table 1. Naturally occurring in plants and synthetic caffeine doses.

When it seemed that everything was known about the structure of caffeine, it turned out that the matter was much more complicated—an untypical polymorphism of caffeine was discovered [43]. An anhydrous caffeine exists in two enatiotropically related polymorphic forms: stable (phase II or β-form) which melts at 508K and metastable (phase I or α-form) melting at 512K [44] and each form displays different physicochemical properties [45].

Some authors consider the existence of phase III [46], while the others a mixture of two phases I and II [47]. The phenomenon of polymorphism further complicates the co-existence of structural and dynamical disorder. A number of experimental techniques (e.g. X-ray [47–49], synchrotron X-ray diffraction [50] mid-infrared (MIR), near-infrared (NIR) Raman spectroscopies [51, 52], dielectric measurements [46], NMR-NQR spectroscopy [53, 54]) have been applied to clarify the matter but still new doubts arise. Screening of polymorphs is of importance due to the differences in solubility, long-term stability, dissolution rate and bioavailability. Many novel beverages like soda or energy drinks [55] as well as drugs contain pure caffeine, thus there is considerable public health interest in its effects on humans.

Because caffeine is the most widely used stimulant, its metabolism and effect on the human body have been intensively studied. Caffeine is known to stimulate the central nervous system (affects sleep, arousal, cognition, learning and memory), as well as muscular, respiratory and circular systems [56–59]. But it is supposed that a broad spectrum of caffeine effects is a result of action of its metabolites. Caffeine demethylation yields to about 4–5.4% of theophylline, 10.8–12% of theobromine and 81.5–84% of paraxanthine [60]. While caffeine, theophylline and

theobromine naturally occur in about 80 green plants species, paraxanthine does not, because it is not accumulated in plants due to the very slow N1-methylation of 7-methylxanthine [61, 62]. But, paraxanthine discovered in human urine by Solmon [61] results from demethylation of caffeine at the 3-position through the catalytic action of polymorphic cytochrome P450 subtypes 1A2 (90%) and 1A1, 2E1, 3A4 and 2D6 (10%) [63, 64]. It was discovered that caffeine and its metabolites belong to the pharmacological group of adenosine A-receptor (A_1, A_{2A}, A_{2B} and A_3) antagonists [65]. The A_1 and A_2 receptors bind caffeine at low doses and the A_{2B} receptor at high doses. The A_3 is caffeine insensitive. Caffeine and its metabolites theophylline and theobromine act primarily as non-selective antagonists at A_1 and A_{2A} receptors in both human central nervous system and heart. Surprisingly, only paraxanthine acts similarly to caffeine [66], theobromine acts as vasodilator, diuretic and heart stimulant [67], theophylline relaxes smooth muscles of the bronchi and is effective in chronic obstructive pulmonary disease and asthma [68]. Theobromine is a weaker antagonist of adenosine receptors and therefore has a lesser impact on central nervous system, but stronger on heart. Most caffeine activity has been attributed to this antagonism and raised attention to it as potential parent compound in designing dual-target-directed drugs that simultaneously inhibit monoamine oxidase B (MAO-B) and antagonize adenosine A_{2A} receptors ($AA_{2A}R$) in the brain [69]. But caffeine also acts by the inhibition of non-adenosine receptor $GABA_A$, an ionotropic receptor, responsible for most of the physiological activities of GABA in the central nervous system [70], while paraxanthine by the inhibition of cyclic guanosine monophosphate (cGMP), which is a key-factor for anti-inflammatory and psychostimulant effects [71].

It is known that caffeine has the ability to reduce the physical, cellular and molecular damage caused by spinal cord injury (SCI), stroke or neurodegenerative chronic diseases of Parkinson [72–74] and Alzheimer's [75–78]. But it has been reported that paraxanthine, rather than caffeine itself, reduces the risk of developing Parkinson's disease [79, 80] and contrary to caffeine it is strongly protective against neurodegeneration and loss of synaptic function [71]. Besides, caffeine exhibits inhibitory activity against diabetes II, gallstones and cirrhosis of the liver [81]. It acts as diuretic [82, 83] and stimulate tear secretion [84] which makes it helpful in the dry eye syndrome treatment [85]. Antioxidant properties of caffeine and scavenging abilities of reactive oxygen species (ROS) are associated with its ability to reduce the risk of liver, kidney, basal, colorectal and endometrial cancers [86–90]. Only recently caffeine-based gold compound has been discovered as a potential anti-cancer drug selective for ovarian cancer [91]. Caffeine mitigates the adverse mutagenic effect of ultraviolet radiation [92–95] or anti-cancer drugs [96–98]. It is difficult to study pure caffeine effect on health because it is consumed with many different additional chemical compounds (tea up to 771, coffee up 154, cacao up to 261, mate up to 39, guarana up to 23, kola up to 9 and citrus up to 495), **Table 1**. The problem is further complicated by the presence of metabolites of caffeine in their composition.

Such a broad spectrum of its action has stimulated a significant interest in studies of caffeine at much more sophisticated level, which should explain the differences in the individual reactions to caffeine. How we react to caffeine varies between individuals because it is largely dependent on individual genome. The earliest studies on the possible link between genes and coffee consumption date back to the 1960s [99]. Although a number of further twin experiments provided some evidence for the heritability factor in response to caffeine [100], the genetic contribution to caffeine consumption strongly depends on sex and decreases with

age. Thus, true importance of individual genetic variability has been testified in larger diverse populations and focused on caffeine rich diet-disease studies at molecular level [101, 102]. According to them, five genes *CYP1A2, AHR, ADORA2A, COMT* and *PDSS2* are known to be related to the caffeine sensitivity. Gene '*CYP1A2*' releases the liver CYP1A2 enzyme, which breaks down caffeine [103, 104]. 'COMT' controls the breakdown of catecholamines, 'AHR' controls the state on/off of CYP1A2 [105, 106], 'PDSS2' regulates the production of CYP1A2 [80] and 'ADORA2A' is responsible for the variation of A2A to which caffeine binds and controls caffeine sensitivity [107].

Although coffee intake has been supposed to be a risk factor for heart disease, it was not related to genes. The enzyme catechol-O-methyl transferase (COMT) is known to break down catecholamines, which in high concentrations can induce a heart attack. Due to variability of the '*COMT*' gene, the COMT enzyme has a number of variants. For example, the COMT rs4680 variant is accompanied with low level of COMT enzyme. But in the presence of caffeine, the release of catecholamines strongly increases and thus a risk of a heart attack also increases [108]. The gene *'CYP1A2'* releases the key enzyme that breaks down caffeine. Two variations of this gene (*CYP1A2*1A*—high activity and *CYP1A2*1F*—low activity, differing in nucleotide and marked by A->C substitution at position 734) help metabolize caffeine: one faster and the other one slower [103, 104, 109]. Because every person has two copies of this gene inherited from each parent, a particular combination is responsible for the speed of one's own metabolism (fast in the case of fast + fast, and slow in the case of fast + slow/slow + slow combinations) [103, 104, 110]. Fast metabolism is of course beneficial as it is related to much (22%) lower risk of heart attack and higher fertility. But CYP1A2 is also a key enzyme in the activation of carcinogenic heterocyclic aromatic compounds [101]. Thus, caffeine consumption has been associated with ovarian cancer risk, which strongly depends on the variations in *CYP1A2* genotype (high-inducibility A/A and low C). A similar study has shown that caffeine consumption protects only women with a BRCA1 mutation against breast cancer [102]. A genome-wide association study on two populations in Italy and the Netherland allowed identification of a *PDSS2* gene that regulates the production of proteins metabolizing caffeine in the human body. The higher levels of this gene result in a slower caffeine metabolism and necessity to drink less amounts of coffee [80]. It has been found that a common variation in *ADORAA2A* is also associated with caffeine sensitivity. Two copies of C allele of *ADORA2A* induce sleep disturbances caused by intake of caffeine [107, 105] while two copies of the T allele of *ADORA2A* result in an increase of anxiety level after caffeine [104]. These observations are helpful in explanation of the habitual coffee consumption [110] as well as in the understanding of differences in the individual reaction to caffeine. Although not all caffeine consumers suffer caffeine withdrawal symptoms, but it is so common that in 2013, it was added by the American Psychiatric Association to the Diagnostic and Statistical Manual of Mental Disorders. A particular combination of the variants of five genes mentioned above may significantly increase or decrease a risk of disease or poor tolerance. Thus, the intake of caffeine can have both positive and negative health effects. The International Agency for Research on Cancer only recently, in 2016, revised its classification from 1991 and moved coffee from Group 2b ('Possibly carcinogenic to humans') to Group 3 ('Not classifiable as to carcinogenicity'). This category is used for compounds for which the statistical evidence of carcinogenicity is inadequate in humans or limited in experimental animals. But that does not mean that its safety is not deceptive. It just indicates explicitly that our knowledge is still incomplete.

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One more aspect related to the individual caffeine sensitivity should be mentioned—the difficulties in estimation of caffeine lethal dose (LD50), which is about 150–200 mg/kg [111, 112] i.e. 80–100 cups of coffee. When we compare a case of death after ingestion of 6.5 g/person and a case of survival after ingestion of 24 g/person [113, 114], the range of tolerance/intolerance makes an impression and is a warning. Too much caffeine in a few cans of energy drink had killed a 19-year-old Austrian football player, 33-year-old Brooklyn construction's worker or three Swedish teenagers. The statistical data of victims of caffeine overdosing collected by National Poison Data System in the United States indicate that 67% of all 6309 cases of poisoning affect children and adolescents under 20. How much caffeine was in the caps of coffee which Honoré de Balzac, true coffee lover, drank in 60 coffee cups per/day? Caffeine content in popular drinks is collected in **Table 2**. The US Food and Drug Administration,

	Caffeine drink	Size in oz (ml)	Caffeine (mg)
Coffee	Brewed	8 (237)	95–165
	Brewed, decaffeinated	8 (237)	2–5
	Espresso	1 (30)	47–64
	Espresso, decaffeinated	1 (30)	0
	Instant	8 (237)	63
	Instant, decaffeinated	8 (237)	2
	Latte or mocha	8 (237)	63–126
Tea	Brewed black	8 (237)	25–48
	Brewed black, decaffeinated	8 (237)	2–5
	Brewed green	8 (237)	25–29
	Instant	8 (237)	40
	Ready-to-drink, bottled	8 (237)	5–40
	Green tea	8 (237)	25
	White tea	8 (237)	28
	Yerba mate	8 (237)	85
	Guayusa	8 (237)	66
Soda	Coca Cola	8 (237)	24–46
	Pepsi Cola	8 (237)	25
Energy drinks	Energy drink	8 (237)	27–164
	Energy shot	1 (30)	40–100
Shots	Liquid caffeine	1 (30)	500
	NoDoz	1.89 (56)	115
Chemicals	Pure anhydrous caffeine	1 teaspoon (5 g)	4706

Table 2. Caffeine content in popular drinks.

FDA, recently issued warnings due to risk to consumers for overdosing caffeinated products containing pure powdered caffeine. A single teaspoon of pure anhydrous caffeine (5 g) is roughly equivalent to the amount in 28 cups of brewed coffee or in 6 energy shots, **Table 2**.

Similarly to humans, the individual sensitivity and additionally breed/division diversity have also been observed in animals. A poor ability to metabolize caffeine which makes it toxic to dogs, cats [115–118] and birds [119, 120] is quite well documented in domestic animals. The toxic doses are so small that single chocolate bar can kill our beloved pet. But 'Creme Puff' cat, the 'oldest cat ever', listed in the *Guinness Book of World Records* for living 38 years, was served coffee with cream every day by its owner [121]. Caffeine is also known to be harmful to wild organisms like molluscs [122], insects [123] and spiders [124], thus making a part of the natural defence of plants against herbivores, larvae of mealworms, mosquitoes [123], tobacco hornworms, snugs and snails [122]. However, there are awesome exceptions like coffee berry borer, which can reduce a crop yield by 80% and survive the dose equal to 500 shots of espresso/person [125].

4. Final remarks

Caffeine is a chemical component of the oldest known food plants (about 5000 years), the most widely consumed (not counting water) and the most extensively studied (1,468 books, 39,551 journal articles, 2,211 dissertations) component of diet. The seeds or seedlings of plants containing caffeine were stolen, smuggled, hated and desired, accused of demonic or radical influence—banned and baptized. The wars for plantations/colonies were fought and fortunes gained and lost. Caffeine drinks were used in religious asceticism and creative amok, behind closed doors of the cafes were written operas, manifestos and revolutions started. After all coffee seeds were used as a currency and reward, tea and chocolate were sipped by emperors, kings and tsars, coffee was loved by artists, writers, musicians, philosophers, students, popes, revolutionists and belt down by soldiers, mate is preferred by actual pope, a few presidents, writers and celebrities, and energy-drinks containing pure caffeine are nowadays trendy and desired by teens and adolescents. Caffeine under the pretence of tea or coffee changed social manners and war results—coffee has been considered the '*soldiers drink*' since Napoleon. Energy drinks like Coca-Cola, Pepsi, Dr. Enuf, Power Horse or Red Bull containing large amount of pure caffeine fight physical fatigue, increase vigilance and reaction speed and allow people to function almost without sleep, but sometimes they are deadly.

Day by day we are coming into contact with caffeine—in drinks (coffee, tea, soft-drinks as Coca-Cola, soda, chocolate, energy drinks), drugs (above 50 different drugs contain *Coffeinum, Coffeinum Natrium benzoicum, Coffeinum Natrium salicylicum, Coffeinum citricum, Phenazonum Coffeinum citricum*), cosmetics and personal care products, bath (e.g. giant caffeine spa in Japan), even fuels (e.g. 'car-puccino'). We deliver it to inside and outside of our bodies in large amounts but as a matter of fact, we still do not know much about it, because it jealously protects its secrets. The ubiquity of caffeine in both natural and synthetic forms has been a cause of a lot of concerns among researchers and public health defenders.

Researchers have shown that caffeine increases memory [126], improves reaction time and logical reasoning, helps in periods of sleep restriction related to job and reduces drivers or pilots errors [127] and reduces risk of suicide [128] and depression [129]. It may protect against Parkinson's and Alzheimer's diseases [130]. Caffeine increases stamina during exercise [131], relieves post-workout muscle pain (cut the pain) [132] and may prevent weight gain [133]. Caffeine is beneficial in age-related chronic inflammation [134], which leads to high blood pressure, hardening of the arteries and heart diseases. It may protect against eyelid spasm [135], cataracts [136] and retinal degeneration [137], leading to blindness, against different kinds of cancer including skin cancer [138] and may prevent tinnitus (ringing in the ears) [139]. Caffeine is shown to be useful in asthma [140], lowering blood pressure [141], detoxication of the liver and the colon [142], reduction of fatty liver in non-alcoholic-related diseases [143], reduction of the liver fibrosis risk in hepatitis C [144], reduction of kidney stones risk and gout prevention [145]. It increases quality of semen in men [146] and acts as hair stimulant used in balding of men and women [147].

But due to the differences in individual sensitivity, caffeine can be easily overdosed, which may results in death—more than four cups of coffee are linked to premature death. Caffeine consumption may raise blood pressure [148], increase a risk of heart attacks among young adults [149] and gout attacks in the case of scarce caffeine overdosing [150]. It can reduce fertility [151], increase the risk of miscarriage [152], worsen the menopausal symptoms [153] and it may be a cause of breast tissue cysts in women [154]. Increased anxiety [155], depression [156], insomnia [157] and prolonged sleep deprivation problems, migraine headaches [158] are common side effects of its use. Adverse effects like incontinence [159], indigestion [160] forceful heart contractions, allergies, risk of bone fractures [161], impairment of hearing loss recovery [162], inhibition of the collagen production in the skin [163], even obesity and diabetes [164] are also on the list of potential negative effects. Recently, a large population study in the United States showed that an increase in caffeine consummation results in decrease in telomere length, which signifies accelerated ageing [165].

Many above observations, results, conclusions are mutually contradictory, which proves that despite of many years of scientific research, there are still unrevealed mysteries concerning caffeine chemical structure, physicochemical properties, its impact on living organisms, etc. Caffeine's role in producing beneficial and harmful effects is still poorly understood and definitely requires more extensive investigation.

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