

# Effects of coffee alkaloids – caffeine, theobromine and theophylline on the human organism

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## Abstract

Alkaloids are alkaline chemical compounds, mainly of plant origin, with a vast array of biological properties, which is why they are widely used as stimulants. Thanks to its taste attributes and content of specific alkaloids – caffeine, theobromine, and theophylline, coffee has become one of the most popular stimulants in the world. It is used not only in many branches of the food industry, but also in pharmaceuticals and cosmetology. It has been shown that the infusion of coffee beans has an advantageous effect on the organism, mainly due to the presence of caffeine. This alkaloid has a beneficial impact on the functions of human systems, supports anti-inflammatory response, and protects against some diseases. The aim of this article is to present alkaloids as natural compounds, with particular emphasis on their presence in the common drink, i.e. coffee. An additional aim was to debunk many common myths about its impact on the circulatory system, elevation of blood pressure, or the risk of coronary-vascular diseases. Furthermore, the importance of coffee in cosmetology as well as its positive aspects regarding antioxidant properties and contribution to skin condition improvement has been emphasised.

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## Introduction

Coffee, an infusion made from ground coffee beans, is one of the most widely consumed beverages in the world. The cause of the great popularity of this brew is its numerous aromatic and flavour qualities and its stimulating effect on the body and mental processes. This is related to the presence of alkaloid substances, mainly methylxanthines, among which caffeine stands out. The consumption of coffee is often associated with negative and even damaging effects on the organism, but studies show that moderate consumption of this drink poses no risk. On the contrary, it brings many benefits by improving the functioning of the system or preventing some diseases [17, 43, 35]. Bioactive components of coffee have also found application in the cosmetics industry as substances improving the condition and appearance of the skin or hair [13, 4].

## Alkaloids

Alkaloids are a very diverse and widespread group of natural organic compounds. They can be synthesised by microorganisms, fungi or animals however, plants are their main and best known source [1]. The production of these compounds within plant tissues is a specific response to the prevailing environmental conditions and stress factors [23]. Alkaloids are basic substances containing nitrogen, usually within a heterocyclic ring. In addition to the nitrogen atom, their molecule also contains carbon, hydrogen and sometimes sulphur, oxygen, or potassium [9]. Chemically, it is a heterogeneous group, which makes it impossible to present a uniform biosynthetic pathway [26]. Despite this, they are formed from common precursors, and the whole process is genetically determined and controlled by specific enzymes [19]. Alkaloids are most commonly found in the solid state, with only a few in the liquid state [36]. Plant secondary metabolites are characterised by a very diverse range of biological effects, starting from stimulant to narcotic and toxic properties [26]: hence, they have found applications as stimulants [5].

## Coffee – chemical composition

Coffee, an infusion made from ground coffee beans (*Coffea* L.), is rich in numerous flavours and aromas, which are obtained by heat treatment of the beans. Roasting causes the sugars naturally contained in the beans to be caramelised. It is this characteristic that is responsible for the global phenomenon of coffee as a universal product, also in economic terms.

The chemical composition of the beverage is very rich in terms of the variety of compounds. It is reported that a coffee brew contains up to 900 substances that are characterised by considerable biological activity. The best known are alkaloids, the most important of which is caffeine, which accounts for up to 2.5% of the brew, depending on the type of coffee and the growing conditions. Other alkaloid compounds include theobromine, theophylline and trigonelline. Coffee also contains phenolic acids, i.e. caffeic acid, quinic acid, or chlorogenic acid, and organic acids (citric, malic) as well as tannins, diterpene alcohols, carbohydrates, proteins, lipids, vitamins (mainly of the B group, i.e. niacin), essential oils and minerals: calcium, potassium, and magnesium [43, 31, 29].

## Caffeine

Caffeine (1,3,7-trimethylxanthine) is a purine alkaloid naturally produced by many plant species. It has a crystalline form with a white colour [12, 9] and is characterised by a bitter taste, lack of odour, and solubility in water despite its hydrophobic character [9, 2]. By means of complex metabolic transformations involving the removal of selected methyl groups, it gives rise to dimethylxanthines, e.g. theophylline, theobromine, and paraxanthine [12]. Caffeine has gained popularity as a stimulant consumed in the form of decoctions from roasted beans of coffee species belonging to the genus *Coffea* [17, 5]. Besides, it can be found in the Theaceae and Sterculiaceae families, leaves of the tea plant *Camellia* sp., cola nuts, or seeds of the cocoa tree *Theobroma cacao* [9]. It is also a component of many pharmaceuticals or sweet and energy drinks [26]. Caffeine is believed to be the

most widespread and at the same time legal psychoactive agent worldwide, the consumption of which is not subject to any regulation [2].

Caffeine is absorbed in the small intestine, reaching its maximum blood content 50-75 minutes after oral intake. The biological half-life of this alkaloid in the body ranges from 4 to about 6 hours. Due to its low hepatic extraction rate, it easily enters the large bloodstream. Moreover, it crosses the placental barrier and the blood-brain barrier, exerting effects on the central nervous system, the cerebral cortex, and striated muscles [41, 38]. The effects of caffeine on the body are determined by specific individual tolerance, physiological state, environmental factors, and frequency of intake [7, 45]. Importantly, the body does not accumulate caffeine [38]. The structural similarity between caffeine and adenosine results in the possibility of combining the alkaloid with central adenosine receptors, where it acts as an antagonist [41]. Thus, it contributes to continuous release of neurotransmitters, e.g. catecholamines (serotonin, dopamine, adrenaline), which manifests itself as fatigue-reducing effects [45, 12]. By competence inhibition, it causes inhibition of the enzymatic activity of phosphodiesterases. The main site of metabolism of this methylxanthine is the liver, and the resulting products are removed from the system via kidneys [38].

## Theophylline

Theophylline (1,3 dimethylxanthine), is a methylxanthine belonging to the group of purine alkaloids present in tea (*Camellia* sp.), and in cocoa or coffee [30]. In the organism, it is absorbed in the gastrointestinal tract and then travels with the blood to tissue compartments. The biological half-life of theophylline after administration is uneven, ranging from 4 to 10 hours. Its biological action is based on inhibition of phosphodiesterase activity, which results in an increase in cAMP content inside cells and further vasodilation of blood vessels and bronchi [26]. Similarly to caffeine, it binds with receptors for adenosine. In addition, it contributes to increased release of interleukin 10, an important anti-inflammatory factor [3]. Due to its action, it has found application in

medicine in the treatment of e.g. respiratory diseases [25], as its presence accelerates cardiac function and increases oxygen consumption [27].

## Theobromine

Theobromine (3,7-methylxanthine) is a purine alkaloid found in black and green tea, cola nuts, coffee and *Theobroma cacao* seeds, where it accounts for 1-4% of the content [25, 37]. Theobromine has the ability to non-selectively bind to adenosine receptors and phosphodiesterases inhibiting these structures, thus causing intracellular changes in the cAMP concentration and protein kinase activity [11]. Likewise other purine alkaloids, theobromine has found application in medicine (in treatment of circulatory insufficiency or bronchial asthma). Besides, it shows strong diuretic effects, which results in increased glomerular filtration and increases blood supply to the renal medulla, causing faster removal of electrolytes [27].

## Effects of coffee and its constituents on the organism

Coffee consumption is burdened with many common myths. For many years, mainly negative information on the effects of coffee on the human body has been spread. This trend has changed in recent years. Currently, the consumption of up to 400 mg of caffeine per day by a healthy adult is considered to be fully safe and even beneficial to health. Only its abuse in the long term (above 500 mg/day) can lead to headaches, digestive problems, or insomnia [50]. It is worth mentioning that the lethal dose of caffeine is about 10 g, which is equivalent to 80 cups of coffee on average [20].

Caffeine, considered to be a psychostimulant, contributes to stimulation of the central nervous system, but the sensations induced by consumption of moderate amounts of the alkaloid are subjective and depend on many individual factors. The positive effects often observed immediately after drinking coffee are related to the presence of this purine alkaloid. These include e.g. increased attention, perceptiveness,

improved psychomotor abilities or increased tolerance to physical exertion [16]. Furthermore, it has been shown that, at a dose of approximately 32 mg, it has a positive effect on improving audiovisual skills [9]. A preclinical stage of research has shown that caffeine can exert an antinociceptive effect on the body by binding to receptors for adenosine and via changes in the enzymatic activity of cyclooxygenases [42]. However, in amounts above 500-600 mg per day, caffeine may have more negative than beneficial side effects; therefore, moderation in coffee consumption is important [15].

Scientists have shown in several studies that caffeine, together with other components of coffee beans, does not have a negative effect on blood pressure, i.e. contrary to the popular opinion, it does not contribute to a sustained pressure rise and hypertension [40]. Analyses of recent data even indicate an inversely proportional relationship between the amount of coffee consumed and the risk of hypertension. Two cups of coffee were found to reduce this risk by 3 %, four cups of coffee by 5 %, and six cups even by 8 % [47]. The protective effect of caffeine on the brain is similar. Based on clinical studies, it has been shown to reduce the likelihood of hypertension-induced strokes [41].

In addition, it has been shown that consumption of caffeine in the form of coffee bean infusion improves conduction of the cardiac stimulus system and increases myocardial tone. In addition, by acting on the vagus nerve, it can reduce the frequency of action of this organ [14, 32].

Studies have shown that people who drank about 6 to 7 cups of coffee brew per day had up to half the risk of developing diabetes compared to people who drank less than 2 cups per day [15]. Researchers have also shown that drinking coffee has a protective effect on the cardiovascular system, and drinking 3 to 4 cups of coffee a day reduces the risk of cardiovascular disease by up to 15% [34].

Polyphenols found in coffee beans may also have positive effects on the cardiovascular system. They have antioxidant properties and thus participate in the reduction and removal of free radicals [9]. Moreover, thanks to their hypotensive character, they contribute to reduction of the blood pressure level. They

also have anti-inflammatory, antibacterial, and anti-fungal effects. In addition to polyphenols, niacin, potassium, and magnesium present in coffee beans have similar effects [50].

The effect of coffee intake on the skeletal system has also been studied. It has been shown that substantial amounts of coffee, i.e. more than 4 cups per day, can lead to disturbances in bone structure, especially during bone growth. Excess caffeine may contribute to osteoporosis and abnormalities in calcium or magnesium absorption. It is reported that the alkaloid taken in large amounts can negatively affect wound healing. The consumption of more than 8 cups of coffee may be associated with an increased risk of injuries or fractures [33, 48]. In contrast, other studies show that reasonable coffee consumption does not contribute to osteoporosis, and that providing the body with up to 400 mg/day of caffeine does not impair calcium metabolism or increase the incidence of bone fractures [46]. Some researchers suggest that the adverse effect of coffee on calcium or magnesium ion metabolism in the organism is related to its diuretic effect, and the amounts of these elements removed from the system are insignificant, and definitely lower than those provided by coffee [21].

Researchers have also investigated the effect of coffee consumption on cancer development. Until recently, there was a view that this beverage contributed to the process of carcinogenesis in the body: however, recent studies show the protective properties of the drink and its compounds, mainly polyphenols, against the development of cancer. The antioxidant capacity, the ability to regulate the cell cycle, and the changes induced in the process of tumour transformation are among the multiple benefits of the substances found in coffee [8]. In addition, caffeine may enhance the cytotoxic activity of some cancer-causing substances and theobromine may enhance the anticancer properties of some antibiotics [31]. Cellular studies on breast cancer have demonstrated a relationship between increased caffeine consumption and reduced proliferation or even reduction in the number of cancer cells [5]. Regular coffee drinking was found to reduce the risk of breast cancer by 5%, and this protective effect may be related to an increase in the concentration of sex hormone-binding

globulin [18, 49]. Positive effects, i.e. minimisation of the risk of carcinogenesis, have also been observed for cancers of the uterine corpus, prostate, oral cavity, colon, or melanoma. [44]. Thus, coffee has been classified by the International Agency for Research on Cancer as non-cancerogenic product for the human body [28].

Coffee purine alkaloids also affect the functioning of other systems in the human body. Theophylline is mainly characterised by significant anti-asthmatic and anti-inflammatory activity, acting as a suppressor of the immune response. In addition, it has a relaxing effect on muscles, causing vasodilation of blood vessels or bronchi and an increase in serum glucocorticoids. The biological activity of theobromine is based on anti-inflammatory and diuretic effects [31, 26]. The consumption of coffee bean infusions may also have positive effects on the body's metabolism and lipid metabolism. It has been evidenced that consumption of such extracts can cause reduction of adipose tissue by enhancing lipolysis and limiting lipogenesis, which is associated with inhibition of the activity of enzymatic proteins involved in the different stages of this process [17].

## Use of coffee in cosmetics

Due to its exceptional antioxidant activity, caffeine is a plant secondary metabolite commonly used in cosmetics. It is mainly used to improve the condition and appearance of the skin, e.g. to even skin tone or reduce wrinkles [13]. It has been shown that caffeine can have a protective effect on skin tissue in the case of oxidative stress and mechanically contribute to removal of reactive oxygen species via autophagy. In addition, it modulates the enzymatic activity of proteins involved in the neutralisation of ROS (reactive oxygen species), contributing to the protection of skin cells against the damaging effects of ultraviolet radiation [35].

One of the many skin disorders quite common in humans is cellulite, i.e. degenerative changes in connective tissue connected with abnormal distribution and storage of subcutaneous fatty tissue. Due to its lipolytic properties and ability to penetrate the skin

barrier, caffeine is used in anti-cellulite cosmetics [4, 24]. The function of this methylxanthine consists in phosphodiesterase inhibition resulting in intensification of lipolysis and, consequently, limiting fat accumulation within adipocytes. Moreover, caffeine stimulates the production of catecholamines and intensifies their action, resulting in improved skin condition and appearance [24]. The use of this alkaloid for elimination of cellulite changes is also related to its ability to stimulate microcirculation and circulation in capillaries, resulting in better oxygenation of the tissue [10].

Caffeine has also gained popularity as a substance preventing hair loss. It has the ability to inhibit the activity of enzymes involved in the conversion of testosterone to DHT, i.e. a compound responsible for hair loss. Moreover, it decreases the tension of hair follicle smooth muscles and increases the circulation in the capillaries of the scalp, which facilitates the transport of nutrients [4]. Based on *in vitro* studies, it has been shown that caffeine can induce hair follicle growth, increase hair length, and stimulate proliferation of hair matrix keratinocytes [39].

Coffee and its extracts are also an ingredient in scrubs. These preparations improve the overall appearance of the skin by cleansing it and improving its colour. The outer layer of the epidermis is abraded. Such treatments prepare the skin for the application of other types of cosmetics whose active substances can penetrate the skin layers more easily [13].

Caffeine is also used in mesotherapy treatments and numerous SPA procedures. Moreover, it has found application in cosmetics for swollen skin under the eyes. It also helps to reduce bruises and improve blood microcirculation in this delicate and sensitive area of the face [6].

## Summary

The aim of this study was to provide an overview of current knowledge on alkaloids, with particular emphasis on caffeine as a substance present in coffee brews, and to dispel common myths regarding its consumption. It was emphasised that caffeine and other compounds present in coffee do not raise blood

pressure: on the contrary, an inverse relationship between the risk of hypertension or coronary heart disease and coffee consumption has been demonstrated. The effects of this beverage on the central nervous and cardiovascular systems are presented. The relationship between coffee consumption and the risk of type 2 diabetes and selected cancers was analysed, and no long-term interrelationship was observed. The study showed that coffee components have antioxidant properties and inhibit the process of tumour transformation. Moreover, the influence of coffee intake on the osteoarticular system and development of osteoporosis was demonstrated. It was also noted that coffee bean alkaloids are involved in the processes of lipolysis and stimulation of metabolism. The antioxidant properties of coffee alkaloids and their beneficial role when both consumed and used in cosmetology as anti-cellulite compounds improving blood circulation or preventing hair loss were emphasised.

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