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COFFEE AND HEALTH - WHAT DOES MEDICINE KNOW ABOUT ONE OF THE MOST LOVED BEVERAGES OF THE WORLD? A LITERATURE REVIEW

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ABSTRACT

Purpose of the article: Coffee is one of the most loved beverages in the world. There has been much controversy about whether it has a beneficial effect on human health. To see what modern medicine knows about its effects on the human body, we analyzed available articles on research on the effects of caffeine on human health. Articles on the effects of caffeine on the cardiovascular system, central nervous system, excretory system, digestive system, human metabolism, and the potential use of caffeine in anesthesiology, oncology, and as a fitness aid were included.

Recent findings: We include 22 articles from the PubMed resources on the effects of caffeine on various human organ bowels written based on contemporary epidemiological studies and meta-analyses and based on them we have created a cross-sectional article presenting the position of modern science on the effects of coffee on the human body

Summary: Modern science has many arguments that coffee has a positive effect on the human body, there are many possible directions for use caffeine in medicine but much more research needs to be done to thoroughly understand its effect.

KEYWORDS

Coffee, Health, Diet, Caffeine, Adenosine Receptors, Alkaloids

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Introduction

Coffee is one of the most common beverages consumed today, it is a source of caffeine and many others chemical compounds such as polyphenols, alkaloids and diterpenes. There has been much controversy about whether it has a beneficial effect on human health. In recent days we can observe increasing interests in the studies addressing the influence of caffeine on human health. We can find many meta-analysis, epidemiological studies and the systematic reviews. The up to date data indicate that the influence of caffeine on human health is very complex, depends on the dose, the technique of brewing and the individual genetic predisposition. According to modern studies the safe dose of caffeine for the grown-up person is three to four cups of coffee with milk that is 300-400 mg of caffeine.

The mechanism of the action of caffeine and the other active ingredient contained in coffee.

The main active compound coffee is Caffeine. It is an antagonist of the adenosine receptors in human central nervous system. Its appearance causes progression of the cognitive functions, reduction of fatigue and growth in alertness. Additionally coffee is a source of many antioxidants, which can reduce inflammatory condition in the human body and the chemical compounds affecting intestinal mikroflora. All of this function of coffee's components may have a significance for human immunity and the regulation of our metabolism.

The metabolism of caffeine

Caffeine is fully absorbed in a stomach and small intestine. The highest concentration in the blood is reached 15 to 20 minutes after consumption. Terminal half-life of caffeine is approximately 3 to 4 hours, it varies according to age, the medications taken by patient, sex and personal metabolic activity of the liver, where the caffeine is metabolised by CYP1A2 enzyme to its active metabolites such as theophylline, 1,7-dimethylxanthine and theobromine. Theobromine and 1,7-dimethylxanthine are antagonists of adenosine receptors and they inhibit enzyme – phosphodiesterase. Theophylline has the same mechanism of action as theobromine, additionally it increases the process of programmed cell death in acidophilic leukocytes.

Discussion

The influence of coffee on nervous system and human cognitive functions

More and more scientific studies are indicative of potential positive impact of coffee and caffeine on human cognitive functions, especially in the population of seniors. The outcomes of the epidemiological studies and meta-analysis suggests that moderate consumption of caffeine (3-4 cups of coffee a day) may be related to decreased risk of deterioration of cognitive functions, dementia and Alzheimer's disease. According to the article: Exploring the impact of coffee consumption and caffeine intake on cognitive performance in older adults: a comprehensive analysis using NHANES data and gene correlation analysis, the people who consume the higher amount of caffeine accomplish better outcomes in the tests assessing the memory, fluency of speaking and the speed of processing information by human brain. [13] Simultaneously it is emphasized that all those effect mainly relate to coffee contained caffeine whereas we can't observe such relationship between consumption of decaffeinated coffee. [13] This dependence indicates the vital role of caffeine in the modulation of cognitive functions.

One of the mechanisms that may be mediatory in spotted dependence is influence of caffeine on the biological activity of alkaline phosphatase, in particular on one of its isoforms - tissue non-specific alkaline phosphatase (TNAP). This enzyme often occurs in central nervous system and plays key role in early neurogenesis, keeping the integrity of blood-brain barrier up, differentiating neurons and modulating transmitting impulses in the nervous system. [13] The high expression of TNAP in the developing human brain suggests its crucial meaning for the proper development of nervous system, on the other hand a sustained increase in the TNAP level in mature brain may support brain neuroplasticity and the cellular regeneration of neurons. [13]

According to the contemporary studies the increase level of alkaline phosphatase may be correlated with cognitive decline. It was observed that there is a relationship between high concentration of ALP and worse memory and recognition tests results [13]. Special attention should be paid to potential involvement of TNAP in the pathogenesis of neurodegenerative disorders. In the Alzheimer's disease increase activity and expression of TNAP have been demonstrated in the hippocampus and temporal lobe, areas particularly vulnerable to the deposition of pathologically modified toxic tau protein. [13] The studies suggest that TNAP participates in both neuroprotective processes by regulation of adenosine concentration and limiting neuroinflammation and neurodegenerative process, promoting abnormal tau protein transformation and disturbances in calcium homeostasis what can lead to neuronal apoptosis. [13].

Recently attention has been drawn to the possibility of modelling TNAP activity by caffeine. The outcomes of current research suggest that it may lower the ALP brain levels. It may potentially reduce neuroinflammatory process, oxidative stress and mitochondrial dysfunction observed in the course of neurodegenerative diseases. [13] Due to the fact that excess activity of TNAP may increase hyperphosphorylation of tau protein and related to it neurodegenerative process, decreasing its activity by caffeine may be one of the mechanisms responsible for the protecting influence of coffee on the cognitive function. [13] It should be emphasized however that long-lasting inhibition of the TNAP activity may potentially disturb processes of neurogenesis, synaptogenesis and maintaining normal neuronal function and therefore further research into the effects of this mechanism should be conducted. [13]

There are also interesting findings indicating possible interaction between ALP and receptor similar to the long R3 insulin-like growth factor-1 (IGF1R). This protein participates in the regulation of many important processes such as: proliferation, cell survival and cell migration and it may play a key role in both cancer processes and functioning of the nervous system. [13] Potential coexistence of the genetic signals connected with IGF1R and ALP suggests existence of common biological signaling pathway, which can affect the neurodegeneration and cognitive function and may be affected by caffeine. [13]

Despite all that promising outcomes care should be taken during the interpretation of the available data. Most of the scientific studies has an observation nature, what can cause some problems during unambiguous definition of cause and effects relationship. Moreover on the cognitive function may affect many disturbing factors such as: age, way of living, sex, smoking, drinking alcohol or concomitant diseases. Therefore further prospective and experimental studies are needed to further elucidate the role of caffeine and alkaline phosphatase activity in the regulation of cognitive function and to assess their potential importance in the prevention of neurodegenerative diseases. [13]

Many studies emphasize that coffee may have a positive impact on mental health. According to the article: „Coffee and mental disorders: How caffeine affects anxiety and depression” caffeine may have positive effects

on psychiatric disorders, particularly by potentially lowering the risk of depression, moreover there are many studies that suggest that the consumption of coffee and caffeine may provide protective effects against depression. [6] Coffee is also a source of flavonoids, and findings reporting that these chemical compounds can have a neuroprotective and antidepressant effects. The studies confirm that thesis in many animal models but the results of human studies are still controversial. [14]

Caffeine and its influence on physical capacity

According to the studies described in the article: „A review of caffeine's effects on cognitive, physical and occupational performance” caffeine may improve human physical capacity. The higher dose 200 - 400 mg taken before physical activity such as workout at the gym may increase physical performance, strength endurance and effectiveness during the intense practice. [1] The reaction to the caffeine is an individual case, it depends on many factors some people react strongly other less.

Caffeine supplementation is widely recognised as effective ergogenic substance supporting the performance in enduring activities. According to the results of meta-analyses and systematic review described in the article: „Effects of Caffeine Intake on Endurance Running Performance and Time to Exhaustion: A Systematic Review and Meta-Analysis" point out that intake of caffeine in the dose 3 - 9mg/kg of body weight significantly improves the sports evasion. The most spectacular effect was observed in the tests to exhaustion where the exercise time increase on average to 16,7 percent, corresponding to an effect of moderate magnitude. In the time trials caffeine caused small but statistically significant improvement in the performance, reducing time needed to walk a distance by an average of 0,71 percent. [12]

The mechanisms of ergogenic caffeine effects are the results of its antagonistic effects on the adenosine receptors and increasing the dopamine and beta - endorphin secretion, what leads to decreasing of fatigue and reduce discomfort during the effort. [12] This allows the athletes to maintain higher intensity of running at the similar level of perceived exertion. Analysis of available studies suggests that the benefits of caffeine supplementation occur in both recreational and trail runners regardless of the length of distance covered. [12]

Despite confirmed effectiveness of caffeine the authors draw attention some limitations of the available studies, including the low participation of women in the analysed groups and the diversity of forms of caffeine supplementation. Therefore further research on the influence of gender, minimum effective dose, development of caffeine tolerance and potential side-effects associated with its long-term use is required. However the totality of available scientific evidence points out that caffeine provides effective ergogenic support for endurance runners, particularly in the efforts requiring the delay in the onset of exhaustion. [12]

According to the article: „Synergy of carbohydrate and caffeine ingestion on physical performance and metabolic responses to exercise: Adding to the article: „Synergy of carbohydrate and caffeine ingestion on physical performance and metabolic responses to exercise: A systematic review with meta-analysis" co-administration of caffeine and carbohydrates improves the caffeine effects. [20]

According to the article: „Synergy of carbohydrate and caffeine ingestion on physical performance and metabolic responses to exercise: A systematic review with meta-analysis" caffeine may have a positive impact on neuromuscular fatigue by modification of selected physiological parameters related to the functioning of the nervous and muscular system. [11] Indicators such as voluntary muscle activities (VA), amplitude of a single contraction induced by an electrical stimulus and M-wave seems to be particularly important, as they show sensitivity to the effects of caffeine and may be objective markers of its ergogenic effect. Additionally there are scientific research indicated that caffeine may influence the electromyographic parameters and peak power which may reflect changes in neuromuscular function after its supplementation [11].

At the same time part of the common factors used to measure fatigue after physical effort such as heart rate, maximum voluntary muscle contraction, maximal VO₂ do not show sufficient sensitivity to assess the specific effect of caffeine on neuromuscular fatigue. [11]. All of this research suggest that the assessment of effects of caffeine supplementation should not be based on solely on general indicators of physiological capacity but requires the use of more specified parameters reflecting processes occurring on neuromuscular level [11]. Therefore future studies should focus on validating and identifying new markers that allowed for more accurate assessing the influence of caffeine under different physical and cognitive exercise conditions. This approach may contribute to better understanding of the mechanisms of the caffeine action and increase the accuracy of assessing its ergogenic action. Despite all of that we may say that if you want to improve your running accomplishments drink coffee before you practice!

The influence of caffeine on the metabolic health

In recent years many epidemic studies analysed relationship between the consumption of coffee and the lipid economy, inflammation and glucose metabolism markers. The results indicate that the health effects of coffee may be various and depend among other things on the methods of its preparation and the content of individual bioactive ingredients.

According to the research described in the article: „Habitual Coffee and Tea Consumption and Cardiometabolic Biomarkers in the UK Biobank: The Role of Beverage Types and Genetic Variation” particular attention is paid to the effect of different types of coffee on the lipid profile. [15] Popular studies have shown that espresso consumption may be associated with increased concentration of the apolipoprotein B (apoB) and the LDL cholesterol which is attributed to the presence of diterpenes, mainly cafestol. [15] Those chemical compounds are contained in higher amounts in unfiltered coffee and have an effect on increasing the level of lipids in the blood. In turn the instant coffee containing trace amounts of diterpenes, has a much weaker effect on LDL concentration. At the same time, it is observed that coffee consumption may be associated with higher HDL cholesterol concentrations and lower triglyceride concentrations, suggesting the involvement of additional metabolic mechanisms not solely related to the action of diterpenes. [15]

The important aspect of coffee effect is also its potential influence on chronic inflammation. Coffee intake is related to lower concentration of CRP protein, which is a commonly used inflammatory marker. This fact suggests that regular coffee consumption may contribute to the reduction of the inflammatory processes that play an important role in the pathogenesis of cardiovascular and metabolic diseases. [15]

Data on the impact of coffee on the hydrocarbon management maintains less unambiguous. Most of the results don't show the significant association between coffee consumption and fasting glucose level, however the observed dependencies concerning gummed hemoglobin (HbA_{1c}) aren't coherent and may be dependent on gender, body weight and other factors of way of life. It is worth emphasizing that the observed health effects do not seem to be significantly modified by gene polymorphisms related to caffeine metabolism, what indicate that most of the benefits and adverse effects are most probably due to other coffee ingredients. [15]

In conclusion the actual data suggests that coffee may have an impact on cardiometabolic health markers but the nature of this effect depends on the type of beverage and how it was prepared. A particularly beneficial effect is attributed to moderate coffee consumption, whereas some of the types of coffee, especially espresso may adversely affect the lipid profile by increasing LDL cholesterol levels. However, further research is needed to further elucidate the mechanisms responsible for the observed relationships. [15]

The influence of coffee on human liver

There are many basis of scientific advice claiming that coffee has a positive impact on process occurring in the liver human liver. Caffeine has hepatoprotective properties, lowering the risk of development of hepatocellular carcinoma, cirrhosis and other metabolic diseases moreover it may lower the risk of development of chronic hepatitis B. [9] Drinking even one cup of coffee a day may lower the mortality due to mentioned diseases of liver by up to 15%. [9]

Drinking coffee and cancer incidence

According to many metaanalyses and epidemiological studies moderate coffee consumption may be associated with lower risk of development of many cancers, but observed dependencies are differentiated depending on the type of cancer and the studied population. The most accurate scientific evidences concern the protective influence of coffee on the risk of development of hepatic cancer while for prostate, kidney, colon or hormone-dependent cancers the results remain inconclusive. [16] In relation to breast cancer some studies point to no significant relationship between coffee consumption and the risk of its developing while the others indicate that coffee may have a little protective effect, especially in woman after the menopause and in specific genetic groups. [16] Similar divergent results are observed for endometrial, lung and other cancer. Differentiation of obtained results may be due to differences in population characteristics, the way of coffee preparation, consumption of different amount of coffee and due to genetic and hormone factors. [16] Despite numerous studies, further analyses are still necessary to clearly define the role of coffee in cancer prevention. [16]

One of the most modern studies to determinate the potential anticancer activity of coffee and its bioactive compounds is the experimental study described in the article: Turkish coffee has an antitumor effect on breast cancer cells in vitro and in vivo [22]. It indicates that coffee extracts may influence the cancer-related key

process in developing breast cancer such as apoptosis, cancer cell proliferation, multidrug resistance and oxidative stress. [22] Studies in vitro models have shown that coffee extract increases the expression of apoptosis markers, including caspase-8 and IGFBP-3, what suggests the activation of pathways leading to cancer cell death. At the same time it was observed that coffee may modulate expression of lipoprotein P, which is one of the main mechanisms of resistance to anticancer treatment. In vivo studies have shown downregulation of expression beta-catenine, which is a key element of the Wnt/ β -catenin pathway responsible for cancer proliferation and progression, as well as reducing the level of malondialdehyde (MDA), a marker of oxidative stress. [22] All of these outcomes suggest that chemical compounds present in coffee, especially polyphenols such as chlorogenic acid may exert multidirectional antitumor effects by regulating apoptotic processes, inhibiting the proliferation of cancer cells and limiting oxidative damage. However, due to the inconclusive results of clinical trials, further studies are needed to fully elucidate the mechanisms responsible for the potential protective effect of coffee consumption on the development of breast cancer. [22]

Coffee in anesthesiology

The results of modern researches suggest that caffeine may be used to speed up awakening from general anesthesia with isoflurane. It may accelerate reclaiming awareness. However the further clinical trials are needed to confirm efficacy and establish optimal dosing. The mechanism that may be used in this case is based on antagonism of adenosine A1 and A2A receptors. Stimulation of mainly A2 receptors has an influence on sleep regulation. Adenosine may inhibit the release of excitatory neurotransmitters in central nervous system, moreover caffeine by inhibition of phosphoesterase may increase the concentration of cAMP in the neurons what may facilitate neurotransmitter release. All those mechanisms lead to accelerate passive removal of the anesthetic after its discontinuation and may be helpful during awakening from general anesthesia by increasing the concentration of serotonin, dopamine and noradrenaline in the central nervous system. [3]

Coffee and respiratory system

Caffeine has a multifaceted effect on the human body including also respiratory system. Caffeine stimulates the respiratory center and is used in therapy of apnea of prematurity. In patients with asthma caffeine improves the function of respiratory tract, increasing the forced expiratory volume value in one second (FEV1). [3] Additionally modern research points out that moderate coffee consumption (0,5-3 cups a day) lower the risk of asthma development in adult patients. Caffeine has been also a compound of bronchodilators for many years. There are claims that caffeine relaxes the smooth muscle of the bronchi and has anti-inflammatory and antioxidant properties. It may also stabilize mastocyte function. [2]

Caffeine and human metabolism

Caffeine affects also human metabolism. It lowers the appetite, it increases the basal metabolic rate and thermogenesis. All of this caffeine's action may contribute to limit long-term weight gain. Caffeine short-term lowers insulin resistance, but this effect may be weakened during regular coffee consumption. [3] According to the article: Osteoporosis - risk factors, pharmaceutical and non-pharmaceutical treatment., there is also evidence that high coffee consumption increases the risk of developing osteoporosis [17]

Other possible uses of coffee in medicine

According to modern research described in the article: Caffeine – Essentials for anaesthesiologists: A narrative review. Caffeine has positive influence on gastrointestinal motility and may be used in prevention of postoperative ileus. The mechanism of this action has not been clearly explained. The involvement of neurohumoral mechanisms has been suggested, including stimulation cholecystokinin and gastrin secretion, as well as increased intestinal secretion, which may lead to increased intestinal peristalsis. The experimental studies have shown that caffeine may induce muscle spasm of the large intestine through releasing of calcium ions from intracellular binding site. Most of the clinical analysis assessing the effects of caffeine and decaffeinated coffee on frequency incidence of postoperative intestinal obstruction have proved better outcome in the study group consuming caffeine coffee although the study results remain inconclusive. Further randomized clinical trials are needed to evaluate the effects of caffeine alone in the therapy and prevention of paralytic ileus. [3]

Influence of caffeine on human sex hormones

According to the large cross-sectional study assessing the relationships between caffeine and tea consumption on the concentrations of sex hormones (estrogens, progesterone, androgens), prolactin and sex hormone-binding globulin (SHBG), described in the article: Relationship Between Caffeine Intake and Plasma Sex Hormone Concentrations in Premenopausal and Postmenopausal Women in woman before menopause caffeine consumption is associated with lower concentration of estradiol in the luteal phase and higher concentration of progesterone. In woman after menopause a positive correlation between caffeine and coffee consumption and SHBG levels was observed while decaffeinated coffee was associated with lower DHEAS concentrations in both groups. [18]

The authors suggest that caffeine may affects metabolism of estrogens, possibly by inhibition of aromatase activity. Aromatase is an enzyme which is responsible for conversion of androgens to estrogen. The differences between the effects of coffee and tea indicate that the observed effects may be due not only to caffeine but also to other components of these beverages. [18] The increase of SHBG in woman after menopause may have a protective qualities because leads to a reduction in the fraction of free sex hormones, including testosterone, which is associated with the risk of hormone-dependent cancers. At the same time, the results for prolactin and androgens were inconsistent or statistically insignificant. [18]

The authors indicate that observed relationship may partly explain potential influence of caffeine on risk of hormone-dependent cancers such as ovary or breast cancer especially in woman after menopause. At the same time the authors point out that there is no data allowing for establishing a cause-and-effect relationship and the results require further verification in prospective studies. [18]

According to the article: Substance Abuse and Male Hypogonadism there is no clearly data on influence of caffeine on hormonal economy and reproductive function in man. [19] No significant relationship between coffee consumption and levels of sex hormones was found in population -based studies although there is a few analysis suggesting positive correlation with total and bioavailable testosterone. [19] In animal models caffeine induce hormonal response increasing the concentration of testosterone, progesterone and noradrenaline and during prolonged exposure increase in testosterone concentration and decrease in LH and FSH concentration was observed. [19]

When it comes to spermatogenesis, most clinical trials fail to indicate a notable impact of caffeine on sperm count. Consumption of too much caffeine may be related to decreased fertility and assisted reproduction, although these observations are inconclusive and may depend on the dose and source of caffeine. [19] Systematic review confirms the absence of a significant impact on sperm parameters the differences in the studies make a meta-analysis impractical. [19]

According to experimental studies in animals there is a possibility that chronic administration caffeine may has negative impact on spermatogenesis and structure of the testes. Caffeine as an adenosine antagonist may has an influence on Sertoli cell function by modulate the metabolism of lactic acid and expression of glucose transporters, in high concentrations, the substance may display a pro-oxidant action. [19]

Caffeine and kidney

According to the analysis of 18,436 participants described in the article: The association between coffee and caffeine consumption and renal function: insight from individual-level data, Mendelian randomization, and meta-analysis, chronic kidney disease occurred in 6.9% of the study population. [21] Average caffeine consumption was $131,1 \pm 1,1$ mg per day. It was observed that the proportion of people affected by chronic kidney disease went down as caffeine intake grew – from 16.6% in the least caffeine-consuming group to 11.0% in the most caffeine-consuming group. Taking into account the distortive factors no statistically significant changes in urinary albumin levels, albumin/creatinine ratio or in estimated glomerular filtration rate (eGFR) were found depending on caffeine intake. [21]

According to the study on influence of caffeine on kidney function described in the article „Diet and Kidney Function: a Literature Review” caffeine may have protective effect against the development of chronic kidney disease. [21] The results obtained are consistent with previous observation suggesting that regular consumption of coffee may be associated with less deterioration of kidney function. In the analyzed studies, the most frequently consumed form was caffeinated coffee, probably subjected to filtration, which can be important for the observed protective effect. [21]

At the same time, the results are not clear in all populations. A study conducted in Iran reported a trend toward an increased risk of chronic disease among coffee consumers, although this relationship did not reach statistical significance. It is possible that these differences are due to different methods of preparing the drink especially frequent consumption of unfiltered coffee. This suggests considering the kind of coffee, the brewing technique, and ingredients like sugar or milk when interpreting the outcomes of epidemiological research. [10]

Kidney stones

According to the article: Caffeine in Kidney Stone Disease: Risk or Benefit? the consumption of caffeine along with coffee might be significant in minimizing kidney stone risk. Results from large cohort studies of over 200,000 participants showed that those who consumed the highest amounts of caffeine had a significantly lower risk of developing kidney stones compared to those who consumed the lowest amounts of caffeine. This effect was observed regardless of the type of caffeinated beverage consumed, with the greatest benefits occurring among caffeinated coffee consumers. [4]

The potential mechanisms of caffeine's protective effects are multifactorial. Although previous studies have suggested that caffeine may increase urinary calcium excretion, which could theoretically promote the formation of calcium oxalate stones, more recent analyses have simultaneously shown reduced oxalate excretion in individuals who consume higher amounts of caffeine. In addition, caffeine increases the volume of urine excreted, which leads to a reduction in the degree of urine supersaturation with calcium and oxalate ions — one of the key factors determining crystallization. [4]

An increase in urinary citrate excretion might further bolster caffeine's protective benefits. Citrates are regarded as one of the most crucial blockers of calcium oxalate stone formation due to their ability to attach calcium ions and prevent the formation process. This suggests that the overall impact of caffeine tends to outweigh the effects that promote the formation of renal deposits over those that inhibit. [4]

Further support is offered through cellular-level experimental investigations. In an in vitro study, caffeine was shown to reduce the adhesion of calcium oxalate crystals to renal tubular epithelial cells by translocating annexin A1 — the protein responsible for crystal binding— from the cell membrane to the cytoplasm. This mechanism curtails the likelihood of crystal persistence within tubular epithelium, which represents a crucial phase in kidney stone formation. [4]

Epidemiological investigations and random assignment analyses indicate that elevated coffee intake might confer a protective effect against symptomatic gallstones (GSD). Numerous observational studies have demonstrated a dose-dependent correlation between coffee consumption and a reduced risk of symptomatic gallstone development, although some analysis results were inconclusive. Recent data show that individuals who consume more than six cups of coffee daily may have as much as a 23% lower risk of developing gallstones in comparison to those who do not drink coffee. [8]

The exact mechanism behind coffee's presumed protective effects remains unclear, though it is thought that caffeine along with other bioactive substances found in coffee, including methylxanthines and cafestol, likely contribute significantly. These substances can increase bile flow and affect bile acid metabolism, limiting bile cholesterol saturation and thus reducing the risk of cholesterol deposit formation. Furthermore, coffee has been shown to increase gallbladder motility and enhance bilirubin coupling in the liver by activating the UGT1A1 enzyme, which may further limit the lithogenesis process. [8]

An important element of the discussed studies was the use of genetic variants associated with higher coffee consumption, located near the CYP1A1/A2 and AHR genes. Analyses showed that individuals with a higher number of alleles associated with high coffee consumption had a significantly lower risk of symptomatic gallstones. These results strengthen the hypothesis of a possible causal relationship between coffee consumption and a reduction in the risk of symptomatic gallstones by minimizing the influence of confounding factors typical of classical observational studies. [8]

Despite promising results, further research is needed to more precisely determine the biological mechanisms responsible for the protective effect of coffee and to determine the optimal level of its consumption in the prevention of gallstones. [8]

Coffee and the Hypertention

According to the article: Coffee Consumption and Risk of Hypertension in Adults: Systematic Review and Meta-Analysis results of available meta-analyses Indicates that coffee consumption may be connected with a slight reduction in the risk of developing hypertension. [7] This relationship was observed in both cohort and pre-crop studies although it was more pronounced in cross-sectional analyses. At the same time, it is emphasized that the strength of this relationship depends on many factors, such as geographical region, gender of participants, sample size and methodological quality of the research. [7]

The mechanisms of potential protective coffee effect on hypertension are complex and are probably due to presence of many bioactive compounds. Coffee is a source of polyphenols, vitamin E, niacin, potassium and magnesium, which have antioxidant and anti-inflammatory properties. These compounds may have an influence on regulation of blood pressure by improvement of endothelial function, increasing the bioavailability of nitric oxide

and modulating lipid metabolism. A special role is assigned to chlorogenic acid, which demonstrates the ability to inhibit the angiotensin-converting enzyme activity and vasodilatory effects. [7]

Attention was also drawn to the influence of caffeine on insulin economy, disorders of which lead to sodium retention, activation of the sympathetic nervous system and remodeling of blood vessels, which promotes the development of hypertension. Thus, the beneficial effect of coffee ingredients on glucose and insulin metabolism may indirectly contribute to reduce risk of hypertension. [7]

An important aspect of the analyses was also the relationship between coffee consumption and environmental and genetic factors. It was shown that the inverse relationship between coffee consumption and hypertension risk was clear mainly in American population, while in studies conducted in Europe and Asia no clear protective effect were observed. These differences may be due to different eating patterns, amount of consumption coffee, the way of its brewing, as well as genetic and lifestyle factors, including smoking. [7]

Despite numerous data suggesting a beneficial effect of moderate coffee consumption on the risk of hypertension study remain partially inconclusive. Methodological limitations include differences in the way coffee consumption is assessed, heterogeneous definitions of hypertension, and insufficient consideration of confounding factors such as sodium intake, physical activity, and cigarette smoking. Therefore, further prospective studies of high methodological quality are necessary to more precisely determine the role of coffee in the prevention of hypertension. [7]

Coffee and human heart

According to the article: Coffee and cardiac arrhythmias: Up-date review of the literature and clinical studies coffee has a multidirectional impact on cardiac electrophysiology and its may have both proarrhythmic and antiarrhythmic effect. The biological effect depends on amount of caffeine consumed and on consumption regularity. Modern research indicates that coffee's effects are mainly due to its best-known bioactive components, such as caffeine, chlorogenic acid, trigonelline, cafestol, kahweol and ferulic acid. [5] Their mechanisms of action include the influence on the calcium metabolism of cardiomyocytes, the activity of adenosine receptors and inflammatory and oxidative processes. [5] High or intermittent doses of caffeine may increase the risk of cardiac arrhythmias by inhibiting phosphodiesterase (PDE) activity, leading to increased cAMP levels in cardiomyocytes and activation of protein kinase A (PKA). Activation of PKA stimulates rianodine receptors and increases the release of calcium ions from the sarcoplasmic reticulum into the cytoplasm. Excessive increases in intracellular Ca^{2+} concentration may exacerbate the automatism of pacemaker cells and promote the occurrence of subsequent depolarizations, increasing the risk of arrhythmia. [5]

At the same time caffeine has a potential antiarrhythmic effect. As not selective antagonist of A₂ and A₁ adenosine receptors may reduce a risk of occurrence of atrial fibrillation by increasing atrial refraction and inhibiting pathological conduction of electrical impulses. In addition caffeine influence on acetylcholinesterase activity and IP₃ receptors, by modulate level of cAMP and calcium ion flow in cardiac muscle cell. [5] The non-caffeinated components of coffee are also important. Chlorogenic acid has strong antioxidant and anti-inflammatory properties and may limit the activity of xanthine oxidase, leading to a decrease in the concentration of uric acid, which is considered a proarrhythmic factor. In addition, coffee has antiatherosclerotic, antifibrotic and antihypertensive effects, which may indirectly reduce the risk of heart rhythm disorders. It has also been shown that coffee consumption may have a beneficial effect on the composition of the gut microbiota by increasing the number of Bifidobacterium bacteria and reducing the production of trimethylamine (TMA), the proarrhythmic precursor of TMAO. [5]

Clinical trial results suggest that regular consumption of moderate amounts of coffee may be associated with a reduced risk of heart failure and atrial fibrillation. It is emphasized, however, that long-term regular consumption leads to the development of tolerance to caffeine, which may limit its potential proarrhythmic effects and reveal beneficial metabolic and anti-inflammatory effects. Despite a growing number of studies, the mechanisms of coffee's influence on cardiac electrophysiology still require further elucidation. [5]

Conclusions

In summary, modern science has many arguments that coffee has a positive effect on the human body, but much more research needs to be done to thoroughly understand its effects and the potential possible use of caffeine in medicine.

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