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Processing and Health Benefits of Coffee: A Review

Mushtaq Ahmad Beigh, Aaruba Maqbool Sofi, Nazrana Rafique Wani*, Monika Reshi

University of Agricultural Science & Technology of Kashmir, Division of Food Science and Technology, Shalimar Srinagar Kashmir, Jammu and Kashmir India

Abstract

Coffee an important beverage is considered as one of the most consumed beverages worldwide. It has a composition of over 2,000 substances, with a predominance of carbohydrates, lipids, amino acids, melanoidins, and the most important and well-known of all caffeine. Coffee is not only well known commodities in international trade but is also the world's second most popular drink, after water. Coffee is known as the intellectual fuel of the contemporary world and the human brain has been defined as a machine for changing coffee into mathematical theorems. Sine from ancient times coffee is being consumed and throughout its history all sorts of theories have been advanced on its possible effects. Coffee improves short-term memory, increases the level of alertness, and permits better use of the prefrontal cerebral cortex. It also shows antioxidant and antitoxic properties at cellular level, provides protection against degenerative brain diseases like Alzheimer's and Parkinson's. It helps to combat fatigue, improve intellectual performance and stimulate the feel good factor in individuals if consumed in moderate amounts. Caffeine is a xanthine which displays several mechanisms of action on the vascular wall, especially on the endothelial tissue and the vascular smooth muscle cell VSMC. At the same time, it has been found that it acts on the autonomic nervous system and on arterial pressure, with a possible development of tolerance when regularly consumed. Due to the activation or blocking of different types of receptors, such as those of adenosine, IP3, NO, and among others, its effects are produced. Further, its effects seem to be contradictory depending on the cellular structure and the time of exposure over which it acts. Depending upon the caffeine concentration in the VSMC, a mild and transitory vasoconstrictor effect exists. The actual function of caffeine on the vascular wall is vasodilating, acting equally on the VSMC directly or indirectly and also on the endothelial structure. At the endothelial level, nitric oxide is liberated which results in the arterial vasodilation. It has been observed that this effect is caused in the presence or absence of preserved endothelial function. According to the type of stimulus, either at the level of cellular Ca^{2+} concentrations or on competitive effects with specific enzymes it causes the direct or indirect effects on vascular smooth muscle cell. Indirectly, the diffusion of nitric oxide from the endothelial tissue towards the VSMC increases the vasodilator effect.

INTRODUCTION

Coffee is a brewed drink prepared from roasted coffee beans, which are the seeds of berries from the Coffea plant. The Coffea plant is native to subtropical Africa and some islands in southern Asia. It was exported from Africa to countries around the world. Coffee plants are now cultivated in over 70 countries across the globe, primarily in the equatorial regions of the Americas, Southeast Asia, India, and Africa. The two most famously grown are the highly regarded Arabica, and the less sophisticated but stronger and more hardy Robusta. Once ripe, coffee beans are picked, processed, and dried. Green (unroasted) coffee beans are considered

among one of the most traded agricultural commodities in the world. Depending on the desired flavor, the coffee beans are roasted to varying degrees once traded. Roasted beans are ground and brewed produce coffee as a beverage. It has stimulating effect on humans because of its slight acidic nature of its caffeine content. Coffee is one of the most popular drinks in the world. It can be prepared and represented in a variety of ways (e.g., espresso,cappuccino, cafe latte, etc.). People mostly preferred hot coffee, although it can be served as iced coffee also. The majority of recent research proposed that the coffee consumed moderately is benign or mildly beneficial in healthy adults.

Myths about coffee

It's one of the age-old medical flip-flops: First coffee's good for you, then it's not, then it is -- you get the picture.

Today, in 2015, the verdict is thumbs up, with study after study extolling the merits of three to five cups of black coffee a day in reducing risk for everything from melanomato heart disease, multiple sclerosis, type 2 diabetes, Parkinson's disease, liver disease, prostate cancer, Alzheimer's, computer-related back pain and more. To stay completely healthy with your coffee consumption, you'll want to avoid packing it with calorie laden creams, sugars and flavors. And be aware that a cup of coffee in these studies is only 8 ounces; the standard "grande" cup at the coffee shop is double that at 16 ounces.

- 1500's headline: Coffee leads to illegal sex
- 1600's headline: Coffee cures alcoholism but causes impotence
- 1700's headline: Coffee helps you work longer
- 1800's headline: Coffee will make you go blind. Have a cup of hot wheat-bran drink instead
- 1916 headline: Coffee stunts your growth
- 1927 headline: Coffee will give you bad grades, kids
- 1970's and '80's headline: Coffee is as serious as a heart attack
- 2001 headline: Coffee increases risk of urinary tract cancer
- 2007 headline: Coffee decreases risk of liver cancer
- 2010 headline: Coffee and lung disease go together like coffee and smoking
- 2011 headline: Coffee reduces risk of stroke and prostate cancer
- 2012 headline: Coffee lowers risk of heart failure
- 2013 headline: Coffee lowers risk of heart disease and helps you live longer
- 2015 headline: Coffee is practically a health food

Coffee cultivation can trace its heritage back centuries to the ancient coffee forests on the Ethiopian plateau. Its consumption spread out in the middle of the 15th century in the Sufi shrines of Yemen. In the Horn of Africa and Yemen, coffee was used by the Sufi circles to stay awake for their religious rituals. As these ceremonies were in opposition with the beliefs of the Christian church, thus the secular consumption of coffee was prohibited by the Ethiopian Church until the reign of Emperor Menelik II. During 17th century, for largely political reasons, the beverage was also banned in Ottoman Turkey and was associated with illicit political activities in Europe.Coffee is most popular beverages in disparate cultures around the globe. It is a valued commodity and a central element in the economies of many countries. It is

considered as the world's largest legal agricultural export. Green (unroasted) coffee is one of the most traded agricultural commodities in the world. Coffee cultivation faces some controversies in its production and poses negative impact on the environment. Consequently,these issues causes fair trade coffee and organic coffee to expand. There are over 100 coffee species, among which the two most commonly grown coffee bean types are Coffea Arabica and Coffea Canephora (also known as Coffea Robusta).

Table1. Differences between the two coffee species

	Coffea Arabica	Coffea Robusta
Taste	It tends to have a smoother, sweeter taste, with flavor notes of chocolate and sugar	It has its taste described as burnt tires or rubbery
Caffeine content	1.7%	2.7%
Sugar (%)	6-9 %	3-7%
Lipid (%)	15-17%	10-11.5%
Chlorogenic acid (CGA) content	5.5-8%	7-10%
Cultivation (world's cultivation)	75%	25%

1. STRUCTURE OF COFFEE CHERRY

A Coffee bean is a pip inside the red or purple fruit often referred as a cherry. It is considered as a so-called stone fruit just like ordinary cherries. It's outer skin is called the exocarp. Beneath it is the mesocarp, a thin layer of pulp, followed by a slimy layer called parenchyma. The beans are enveloped in a paper like coating named as endocarp which is referred to as the parchment.The coffee bean consists of a silver skin also called as perisperm or spermoderm, an endosperm and an embryo.

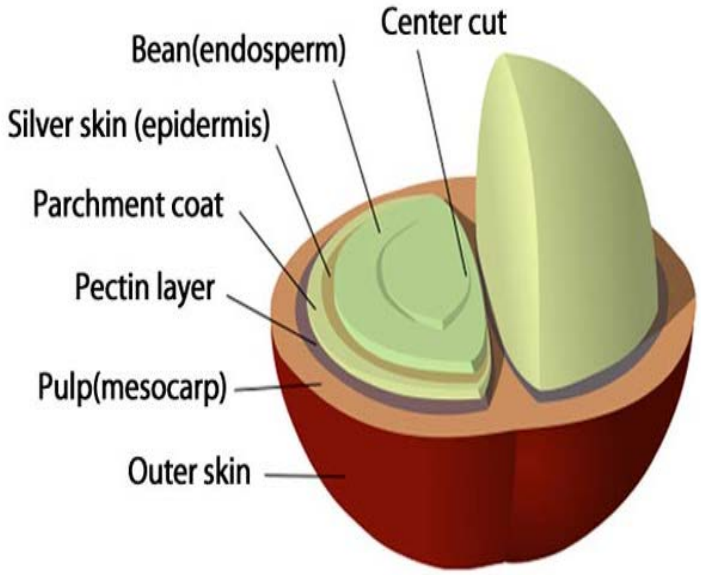

Fig1. Structure of Coffee Cherry

2. COFFEE PROCESSING METHODS

The main steps that are involved in the processing of coffee are:-

a. Wet process

Coffee processed by the wet method is called wet processed or washed coffee. In this method, the coffee cherries are de-pulped before they are dried. Specialised equipment and substantial quantities of water are required in this method.The coffee cherries are placed in large vats to separate the defective beans by immersing them into the water. Defective or unripe fruit will float and the good ripe fruit will sink. To removethe skin of the cherry and some of the pulp, the fruits are pressed by machine in water through a screen. After this process, further a significant amount of the pulp clinging to the bean needs to be removed. This is done either by the classic ferment-and-wash method or with a new procedure called machine-assisted wet processing, aqua-pulping or mechanical de-mucilaging. In the ferment-and-wash method of wet processing, the remaining portion of the pulp is removed by breaking down the cellulose by fermentation of the beans with microbes and then washing them with large amounts of water. Fermentation is done with extra water or, in "Dry Fermentation", i.e. with the own juices of the fruit only. To ensure that the coffee doesn't gain unwanted, sour and off flavors fermentation process has to be carefully observed. Depending on the temperature, thickness of the mucilage layer and concentration of the enzymes, the process of fermentation takes 24 to 36 hours to remove the mucilage. Completion of the fermentation is evaluated by feel, as the parchment layer covering the beans loses its slimy texture and attains a rougher "pebbly" feel. After completion of the fermentation, coffee is thoroughly rinsed with

clean water in tanks or in special washing machines. In machine-assisted wet processing, the bean is isolated from the remainder of the pulp by mechanical scrubbing instead of fermentation. Moreover, it is quiet easier to remove mucilage by machines than removing it by fermentation and washing. Mechanical de-mucilaging can eliminate an important tool that mill operators have of influencing coffee flavor by excluding the fermentation step and prematurely separating fruit and bean. Furthermore, the ecological criticism of the ferment-and-wash method increasingly has become moot, since a combination of low-water equipment plus settling tanks allows conscientious mill operators to carry out fermentation with limited pollution. The wastewater produced during wet processing of coffee can be a pollutant and this wastewater is reprocessed by the ecologically sensitive farms along with the shell and mucilage and used it as compost in soil fertilization programs. The quantity of water used in this process can differ, but ratio of 1:1 is mostly preferred. After the removal of the pulp, the bean is left with two additional layers, the silver skin and the parchment. Before they are stable, the beans are dried upto a water content of about 10%. Coffee beans are dried in the sun or by machine but in most of the cases it is dried under the sun to a moisture content of 12-13% and is brought down to 10% by machine. Drying completely by machine is normally done only where space is at a premium or the humidity is too high for the beans to dry before mildewing. In the sun drying, coffee is most oftenlyspread out in rows on large patios where raking after every six hours is done to promote even drying and prevent the growth of mildew. Some coffee is dried on large raised tables where the turning of coffee is done by hand. The advantage of drying this way allows the better air circulation around the beans promoting more even drying but increases cost and labor significantly. After the drying process (in the sun and/or through machines), the parchment skin or pergamino dried up thoroughly and crumbly, and gets easily removed in the hulling process. Coffee occasionally is sold out and shipped in parchment or in pergamino, however, crunching off the parchment skin is mostly done by a machine called huller before the shipping of the beans.

b. Dry process

This process, also known as unwashed or natural coffee, is thought to be the oldest method of processing coffee. After harvesting, the entire cherry is cleaned up first and then sun dried on tables or in thin layers on patios. Sorting and cleaning of harvested cherries are done to set apart the unripe, overripe and damaged cherries and to remove dirt, soil, twigs and leaves. This process is done by handwinnowing using a large sieve. The undesirable cherries or other material that are not winnowed away can be picked out from the top of the sieve. Separation of the ripe cherries can be done by flotation in washing channelsthat are close to the drying areas. The coffee cherries are sun dried either on large concrete or brick patios or on matting raised to waist height on trestles. After drying of cherries, frequent raking or turning by hand is done to ensure even drying and prevent mildew. Depending upon the weather conditions, it may take up to 4 weeks before the cherries are dried to the optimum moisture content. To speed up the process on larger plantations, machine-drying is sometimes used after the coffee has been pre-dried in the sun for a few days. The drying operation is the most important stage of the process, as it determines the final quality of the green coffee. Over dried coffee will turn brittle and build too many broken beans during hulling (broken beans are considered defective beans). If the coffee

beans are not dried well, it will become too moist and more prone to fungal and bacterial attack that causes rapid deterioration. In special silos dried cherries are stored in bulk until they are sent to the mill where further processes like hulling, sorting, grading and bagging take place. Removal of the outer layers of the dried cherry is done in one step by the hulling machine.About 90% of the Arabica coffee produced in Brazil, most of the coffees produced in Ethiopia, Haiti and Paraguay, as well as for some Arabica's produced in India and Ecuador use dry method. Almost all Robusta's are processed by this method. This method is not applicable in very rainy regions, where the humidity of the atmosphere is too high or where it rains frequently during harvesting.

c. Semi-dry process

Semi-dry process is a hybrid process used in Indonesia and Brazil. This process is also called as "wet-hulled", "semi-washed", "pulped natural". In Indonesia, it is called as "Giling Basah" translated from Indonesian which means "wet grinding". This process reduces the acidity and increasesthe coffee's body. Giling Basah process is mostly practiced by small-scale farmers of regions Sumatra, Sulawesi,Flores and Papua. In this process, the outer skin from the cherries is removed mechanically by the farmers, using pulping machines. The coffee beans, with remaining mucilage, are stored for a day in order to get rid of the mucilage and is washed off. Finally, the parchment coffee is dried partially in the sun upto the moisture content of 30% to 35% before its sale.

d. Milling

In coffee processing, the final steps require the elimination of the last layers of dry skin and enduring fruit residue from the now-dry coffee, and cleaning and sorting it. These steps are usually called as dry milling to differentiate them from the steps that take place before drying, which are collectively called as wet milling.

e. Hulling

In dry milling, the first step is the removal of what is left of the fruit from the bean, which may include the crumbly parchment skin of wet-processed coffee, the parchment skin and dried mucilage of semi-dry-processed coffee, or the entire dry, leathery fruit covering of the dry-processed coffee. In the hulling process, from simple millstones to sophisticated machines are used that gently beat the coffee.

f. Polishing

In this process, removal of left over silver skin that remains on the beans after hulling is done using polishing machine. To improve the appearance of green coffee beans and eliminate a byproduct of roasting called chaff the process of polishing is done. It is described by some to be detrimental to the taste. The chemical makeup of the bean is changedby raising the temperature of the bean through friction

g. Cleaning and sorting

Fine coffee undergoes through an array of machines that are used to sort the coffee in terms of density of the bean and by the size of the bean. It also includes the removal of sticks, rocks, nails, and miscellaneous debris that gets mixed with the coffee during drying. The machines uses the air to blow the beans in order to separate the heaviest and biggest beans fromthe lightest (and likely defective) beans. Furthermore, the beans are shaked by other machines through a series of

sieves and are sorted according to their size. Finally, a gravity separator or density sorter are used to separate the sized beans on a tilted table, so that to set apart the heaviest, densest and best beans to one side of the pulsating table, and the lightest to the other side.

Color sorting is the final step in theprocedure of cleaning and sorting, or it is the separation of defective beans from sound beans on the basis of color instead of density or size. In case of sorting and cleaning, color sorting is the hectic and perhaps most important of all the steps. Color sorting for most high-quality coffees is practiced in the simplest possible way that meansby hand. Discolored and other defective beans are separated from the sound beans by the teams of workers. Best coffees are hand-cleaned twice (double picked) or even three times (triple picked). Hand cleaned coffee is usually called asEuropean preparation.Color sorting can also be done by machines. Past sensors are set according to parameters and streams of beans are allowed to fall rapidly one at a time, which identifies defective beans by value (dark to light) or by color. A tiny, decisive puff of compressed air pops each defective bean out of the stream of sound beans the instant the machine detects an anomaly. However, currently these machines are not used extensively in the coffee industry for two reasons. Firstly, due to thehigh capital investment for installation of these delicate machines and the technical support to maintain them is daunting. The second reason is that sorting coffee by hand needs much work for the small rural communities that are assembled around coffee mills. Nonetheless, for regions with relatively high standards of living and high wage demands, computerized color sorters are necessary to coffee industries

h. Grading

In this process coffee is graded by sorting coffee beans on the basis of various measures such as size of the bean, region where the beans were grown and at what altitude it was grown. The theory behind the classification based on bean size is that coffee of the highestaltitude are more dense and larger in size than those produced at lower altitude. Grading also includes how the coffee was prepared and in what manner it was picked and its cup quality, characteristics are also distinguished by senses and can be assessed by professional coffee tasters based on flavor acidity and cup cleanness.Grading of coffee can be characterized by various imperfections also like broken beans, which are defective, presence of pebbles, sticks etc.Origin of the beans like estate, in which region it was grown leads to the production of finest coffees and is especially very important for finest coffees. The farmers or growers of premium estate or cooperative coffees bring into effect a level of quality control that goes well beyond prevailing defined grading measures. Those growers want their coffee dominion the higher price that comes under norms and rules of recognition and consistent quality.

i. Decaffeination

The aim of decaffeination is to extract the caffeine from green coffee beans before roasting. In United States decaffeination is done by the extraction of super critical carbon dioxide (CO_2)extraction. In this process carbon dioxide is maintained at a pressure of about 9000 pounds force per square inch (28mpa) and the temperature between 90 and 100^0C is maintained and moistened green coffee beans are made to come in contact with large quantities of supercritical carbon dioxide which removes about 97% of the caffeine from the beans. By using an activated carbon adsorption systems, caffeine is then recovered from the carbon dioxide. The other method

used in this extraction is solvent extraction, in which oil is used that is extracted from roasted coffee or ethyl acetate as a solvent.

In this process most of the caffeine is extracted from the beans by adding solvent to the moistened green coffee beans. After the beans are removed from the solvent, they are stream stripped to remove any residual solvent. The caffeine is than recovered from the solvent and solvent is reused. Another process which is usually used for decaffeination is Swiss Water Process. On a dry basis decaffeination beans have a residual content of about 0.1%.Decaffeination process is not operated by all facilities and decaffeinated green coffee beans are purchased by many facilities that produce decaffeinated coffee.

j. Storage

Coffee beans can be best stored in jute bags. Jute is a lengthy soft, vegetable fiber that can be spun into stiff, durable threads and are extremely porous exposing the coffee to whatever elements it is surrounded by. Green coffee is mostly transported in jute bags while green coffee can be used for several years, it is susceptible to degradation of quality of the product based on how it is stored. If the coffee is poorly stored it may develop a burlap-like taste known as bagginess which may lead the real and original qualities to fade away. In this regard the specialty coffee market has taken into consideration the best storage of green coffee and utilize enhanced storage methods in order to keep the originality of the product. Sometimes a gas barrier liner to jute bags is used to preserve the quality of green coffee. Less frequently, green coffee is stored in vacuum packaging, which prevents the ability of green coffee to come into contact with oxygen at atmospheric moisture. It is significantly more expensive storage option.

k. Roasting

Roasting coffee changes the physical and chemical properties of green coffee beans into roasted coffee products. Roasting process produces the quality flavor of coffee by causing the green coffee beans to change in taste. Usually all coffee sold to consumers in the entire the world is sold as roasted coffee. In general one of the four degree of roasting are light, medium, medium-dark and dark. Consumers also prefer to buy unroasted coffee to be roasted at home.

Health benefits

Coffee naturally contains a variety of compounds. Over 200 substances are present in coffee. The main constituent of coffee is carbohydrates which make up 38-42% of the roasted coffee beans, caffeine, tannin fixed oil (lipids), and amino acids (proteins).It contains 3-5% fixed oils. The brown color of the beans is due to the presence of melanoidins which make up 23% of the weight. It also contains minerals, aliphatic and chlorogenic acids, trigonelline and volatile aromas. Coffee is the alkaloid most present in green and roasted coffee beans which make up the 1.3 to 2.4% of the beans weight followed by other purinic alkaloids such as theobromine and theophyllineand pyridine such as trigonelline consuming too much coffee leds to various diseases and health alterations. However, due to the lack of actual and continuous information epidemiological studies regarding the relationship have not provided a clean conclusion

regarding the frequency of consumption, the exact composition of the beverage and factors like cigarette smoking, alcohol consumption and sedentarism associated with an unhealthy life style. These factors in combination can cause various health issues or health problems.

Many epidemiologic studies have reported the relationship between coffee consumption and the risk of heart disease. On analyzing, the coffee mortality relationship states that there is no direct relationship between coffee consumption and increases in death rate / mortality. On the other hand, the authors explains a nearly inverse relationship between the consuming the coffee and their benefits related to the inflammatory process, endothelial function and risk of developing type 2 diabetes. According to Yukawa, coffee consumed on regular basis proves to reduce the susceptibility of low-density lipoprotein oxidation, a pathway which develops in atherosclerotic plaques thereby, favoring endothelial function. However, it has been observed that in another vein, some coffee components, especially phenolics (chlorogenic acid, ferulic acid), have a great antioxidant capacity , and coffee consumption is associated with a small reduction in mortality in women with hepatic disease and/or cirrhosis and reveals a protective effect on the liver in hepatic cancer. In addition, caffeine increases the urine production with water and patterns of electrolyte secretions very similar to those seen with the thiazides. Underlying mechanisms may depend upon many factors such as dose, chronic exposure, genetic and enzymatic factors, among others. In the study of animals, after being exposed to caffeine, there was an increase in glomerular filtration and kidney blood flow especially in the renal medulla.In a study of the intrarenal mechanisms responsible for the natriuretic effect of caffeine, the renal secretion of sodium rises, and the glomerular filtration rate remains as such, suggesting in reduction of fractional sodium reabsorption, both in the proximal and distal tubule of the nephron, contributes to the natriuretic effect of caffeine. Caffeine the psychoactive substance is consumed most widely in the world. It is not seen only in coffee but also in tea, carbonated beverages or soft drinks, chocolate, and a wide variety of medications, including diuretics, appetite suppressants, analgesics, and decongestants; the majority of which are sold over the counter and do not have a regulatory control. Its estimated that adults over the age of 25 consumes approximately 2.4 mg/kg/day, while children under the age of 12 is estimated to have the consumption of approximately 0.7 mg/kg/day. Furthermore, it has been proved that theobromine and theophylline are alkaloids that are also found naturally in green tea, black coffee, and cacao. However, their direct effect on physiological responses to the ingestion of foods and beverages containing these types of alkaloids, and the role of each, is not yet known.

3. METABOLIC PATHWAY OF CAFFEINE AND ITS METABOLITES

In humans, caffeine is digested into more than 25 metabolites mainly Paraxanthine, Theobromine, and Theophylline .The metabolism of Caffeine produces Paraxanthine as a finished product, which shows 72 to 80% caffeine metabolism. In adults, five main metabolic pathways contribute to caffeine metabolism in which first three consists of demethylization of N-3 to form Paraxanthine, N-1 to form Theophylline (vasodilator, increased cerebral and muscular blood flow), and N-7 to form Theophylline (vascular, bronchiole, muscular, and respiratory relaxant). Most of the caffeine (95%) is metabolized bythe hepatic cytochrome P-450 (CYP) isoenzyme by three demethylizations which on average results an in vivo metabolism percentage of 85% paraxanthine, 10% theobromine, and 5% theophylline. The fourth pathway represents the production of uracil metabolites, and the fifth one is comprised of renal elimination of the left over percentage of caffeine that remains undegraded in the process. Due to

the variations in the metabolism, the large interindividual differences are remarked in plasmatic concentration of caffeine following the administration of an equal dose. There are four factors that are responsible for these variations: genetic polymorphisms, metabolic induction and inhibition of cytochrome P-450, individual (weight, sex), and the presence of hepatic diseases. Caffeine is observed to be rapidlyand completely absorbed from the intestinal tract,building it 100% bioavailable. The time at which maximum plasmatic concentration is acquired (Tmax) is 30–45 minutes fasting and is slowed down with food ingestion. In humans, an average metabolic half -life is 2.5 to 4.5 hours.

4. VASCULAR EFFECTS OF CAFFEINE

A lot of studies on determination of caffeine on cardiovascular system have provided uncertain results. Some have described it consumption having beneficial or neutral effect. But there are also controversies on consumption of caffeine leading to increased cardiovascular risk. Cardiovascular response is different on each individual depending on a number of factors such as the time of consumption, amount ingested, degree of absorption, frequency and also hepatic metabolism. Some of the substances such as theobromine and theophylline (active substances in bronchodilator medication) found in caffeinated beverages have certain effects on variability of these particular physiologic responses. Caffeine is a xanthine that acts in the body's cells through a variety of ways and on a variety of molecular targets. It acts as an adenosine receptor antagonist, phosphodiesterase enzyme inhibitor, calcium liberation channel sensitizer, and GABA receptor antagonist. Further cardiovascular process are related to the lowering of cytoplasmic Ca2+ in vascular smooth muscle cell (VSMC) by cyclic adenosine monophosphate (CAMP) and synthesis of nitric oxide (NO) is favored by the increase of the same in endothelial cell. Other substances present in coffee having similar structure to that of alkaloids provide a significant research tool in the development of treatments for Parkinson’s disease, cancer, asthma, diabetes and Alzheimer diseases. In this study, the main mechanism of action on vascular tissue has been described.

5. MECHANISMS OF ACTION OF CAFFEINE AT THE ENDOTHELIAL LEVEL

The most extensive tissue in humans is endothelium which forms both anatomic and functional barrier covering arterial walls, highly selective and permeable via a continuous, uninterrupted and pliable surface. A broad spectrum of vasoactive substance is being synthesized and released by it resulting in the interfering with VSMC tone modulation by interacting with vasoconstrictor (angiotensin, rennin, ET-1, etc) and vasodilator substances (PgI2, NO, bradykinin, endothelium derived hyperpolarizing factor, etc.). The NO production is stimulated when caffeine directly acts on the endothelial cell. The effect was assessed when NO pathway was blocked with NG-nitro-L-arginine, methylene blue and oxyheamoglobin. Nitric oxide (NO) is produced by the enzyme nitric oxide synthase (eNOS) from L-arginine and oxygen. Calmodulin (CaM) must be bound to the enzyme for its production and it gets bound only in the presence of Ca2+ that is obtained from cytoplasmic content. The ryanodine receptor activity is stimulated in the endothelial endoplamic reticulum by the caffeine, adenine nucleotides and concentration of Ca2+. Once the Ca2+ is released by caffeine, its concentration gets increased in the cytoplasm (iCa2+) and forms a complex with CaM favoring the activation of eNOS. This mechanism is consistent with the basic characteristics of calcium-induced calcium release (CICR) wherein a small amount of Ca2+ is required in the cytoplasm: not sufficient to activate eNOS, but adequate enough to encourage the release of additional Ca2+ from reticulum, thereby increasing iCa2+. It has been seen that caffeine reduces the threshold for activating the CICR, that means the mechanism gets stimulated practically at rest Ca2+ levels. The entrance mechanism for Ca2+ in

VSMC responsible for the sustained cellular activation are mediated by both voltage operated Ca2+ channels as well as specific receptors.

Thus to summarize the caffeine effect on vascular endothelium is a greater expression of NO, having an autocrine effect, acts on same endothelial cell with an aim to increase Ca2+, potentiating the response and finally coming out of endothelial cell so as to diffuse rapidly to VSMC in a paracrine fashion. Various arguments among authors produce greater vasodilation by acting on endothelium rather than on VSMC.

6. CAFFEINE MECHANISMS OF ACTION ON SMOOTH MUSCLE CELLS

Caffeine's direct or indirect effect on the VSMC may have vascular modes of action.

6.1. Direct Effects

A minimal initial contraction and major vasodilator is generate when caffeine acts on the VSMC. Various mechanisms that demonstrate these effects is explained as:

6.1.1. Caffeine and the Ryanodine Channels

The CICR mechanism is generated through ryanodine channels when caffeins acts on VSMC that results in increase in iCa2+ and slight transitory contraction. The response is independent of both the amount of extracellular Ca2+ and presence of Ca2+ to blockers. The entrance of the extracellular Ca2+ to the cell begins via a slow/ L type channels and the non-selective cation channel in the cell membrane only when intrareticular Ca2+ is used. Caffeine activates the non-selective cation channel directly so as to increase iCa2+. The increase in iCa2+ extends the contraction started by CICR. The experiment carried in laboratory with caffeine in hum arteries animal models showed no contraction therefore leading to believe that is almost a minor vasoconstrictor effect.

6.1.2. *Caffeine and cAMP*

The vitro experiments performed with caffeine demonstrate that a vasodilator effect is seen in spite VSMC iCa2+ increase. Caffeine has been found to be a non-selective competitive inhibitor of phosphodiesterase enzymes. The enzymes have capacity to degrade the phosphodiesterase bond in ceratin compounds such as cyclic guanosine monophosphate (vGMP) and cAMP. One of the important enzyme AMP phosphodiesterase that degrades cAMP is inhibited by caffeine causing its local accumulation. The activity of antiphosphodiesterase is concentration dependent and inhibits enzyme 5% to 80% at concentrations of 1× M. Moreover, it also depends on time and generates a huge accumulation of cAMP the longer the incubation time. The increase in the phosphorylation of the kinase enzyme of myosin light chain (MLC) in cells contractile apparatus (i.e., actin-myosin) is a result of cAMP accumulation. This is the state where enzyme is little sensitive to Ca2+ and hence the activity diminishes. MLC phosphorylation is reduced when the enzyme is inhibited, and the actin-myosin interaction is inhibited resulting in an increase in intracellular Ca2+ concentration without contraction, described as loss of “sensitivity” to Ca2+. The activity of MLC- phosphatase and relaxation dominates with the decrease in MLC-phosphorylation.

The kinase enzyme of myosin light chain in smooth muscle yet so far is the enzyme activating the MLC through phosphorylation to a particular domain. In smooth muscle the intracellular concentration of Ca2+ is increased by agonist stimulation, causing it to bind with the calmodulin,

which activates the kinase enzyme when bound to Ca2+ in the myosin light chain, hence activates the form interacting with actin to cause contraction.
However, latest studies reveal that this mechanism is not the only controller of actin-myosin interaction. Study conducted by Rembold et al. suggests that upon adding 20mM of caffeine to pre-contracted arteries an increase in iCa2+ was observed without any significant increase in tone , which could not be explained purely by the increase in phosphorylation of MLC kinase. They also found that Ca2+ had a heterogeneous distribution and finally concluded that caffeine increases the iCa2+ concentration in regions that are distant from contractile apparatus, thereby results in no contraction. It is apparent that this effect of caffeine is arbitrated by cAMP as cAMP increases “non-contractile” Ca2+. Though the effect of caffeine described cannot be endorsed to the increase in cAMP. Ozaki et al. in 1990 carried an experiment on pre-contracted arteries to which caffeine or forskolin (also inceases cAMP) was added. Caffeine inhibits the contraction of VSMC to a good extend than forskolin when Camp is prepared in two preparations at similar levels.

6.1.3. Other Direct Mechanisms

It has been found that caffeine inhibits the inositol triphosphate (IP3) compound that stimulates secretion of Ca2+ from the sarcoplasmic reticulum and is vital for the contraction. The addition of ATP results in the inhibitory effect of IP3 pathway by caffeine. It has been found that xanthenes can interact competitively with ATP binding site on IP3 receptor as xanthenes contain adenine ring that is identical to the ATP. Moreover, caffeine inhibits the entrance of Ca2+ by acting directly on voltage dependent channels of Ca2+ in plasmatic membrane which is independent of its antiphosphodiesterase action. Ozaki et al. also revealed that caffeine acts directly on MLC kinase and actin-myosin interaction, hence slight inhibition in phosphorylation and contraction. As per Sandow et al. the vascular cellular calcium modulation (control of vascular tone, flow and blood pressure) is regulated by specific signaling microdominions in vascular smooth muscle cells that are spatially positioned in Ca2+ channels and receptors and interacting functionally.

6.2. Indirect Effects

The indirect of caffeine can be seen via NO on the VSMC , synthesized in endothelial cell by the eNOS that diffuses rapidly to VSMC. The NO binds to the heme group of enzyme guanylate cyclase once it enters the VSMC and hence activates it. This catalyzes the conversion of GTP to cGMP, which boosts the activity of cGMP-dependent protein kinases (PKCs), especially the I type.Through phosphatase, the PKI induces the dephosphorylation of the MLC, resulting in vasodilation. PKCs and cGMP also inhibit IP3 and decrease cytoplasmic Ca2+. Caffeine, in turn, inhibits 35 cGMP phosphodiesterase competitively, causing even greater cGMP buildup.

7. Other Mechanisms of Action

7.1. Action through Adenosine Receptors

Different adenosine receptors are labeled as A1, A2a, A2b, and A3 respectively. Caffeine proves to be the inhibitor of A1, A2a and A2b receptors. It blocks the receptors demonstrated by Sattin and Rall in their experiment in 1970 but the effect can be reversed if more ATP were added to preparations. The main metabolite of caffeine“paraxanthine”is powerful blocker of these receptors compared to caffeine. The mode of action of adenosine depends on both the type of

receptor it stimulates and type of the tissue or cell in which it is found. Adenosine's local vascular effects are essentially vasodilation of the various beds. This impact is mostly mediated by A2a receptors, which are abundant in vascular tissue. Caffeine increases the plasmatic concentration that in turn results in increase in its systemic effects by competitively blocking the andesine receptors. Adenosine stimulates the chemoreceptor at a systemic level throughout the circulation resulting in a generalized increase in sympathetic tone with an enhancement in catecholamine circulation, rennin secretion and peripheral vascular resistance. Several studies have found a 6 to 7.5 mmHg increase in systolic arterial pressure and a 2.6 to 4 mmHg increase in diastolic arterial pressure 60 minutes after taking 300 mg of coffee (equivalent to drinking a triple espresso). Despite the fact that caffeine has an indirect vasoconstrictor action, it is of utmost importance to note that the prolonged caffeine use creates a tolerance to its adenosine receptor-dependent effects.

An “up regulation” (increase in number and sensitivity of the receptors) of receptors is induced when chronic blocking of adenosine receptors take place, demonstrated by the low-moderate consumption of caffeine. In 1999 meta-analysis was carried out that described an increase in systolic and diastolic arterial pressure (2.4 mmHg and 1.2 mmHg) with chronic consumption of coffee (on an average 5 cups a day), significantly lesser value than the one obtained from studies on subjects who were not consumers of caffeine. The "abstinence syndrome," as described by Griffiths in 1988, is characterized by headache, exhaustion, flushing, and anxiety as a result of this "up-regulation." Once the consumption of caffeine is stopped abruptly in a regular consumer, a huge number of adenosine receptors available potentiate the vasodilation produced by adenosine causing symptoms. Since low doses (m) are required for studies that indicate their influence on Ca2+ and phosphodiesterase (mM), which are concentrations that are not obtained in vivo, it has been claimed that the primary cardiovascular effects of caffeine occur at the adenosine receptors. However, the in-vitro studies conducted by us were carried out with micro molar (m) concentrations of caffeine and it showed significant effect of vasodilator (approx. 75%) at human consumption concentrations. Because in vitro studies do not assess the systemic response to caffeine, it is unclear which of the modes of action predominates in vivo, given the numerous factors that influence its metabolism and effects.

7.1.1.Caffeine in Relation to Migraine Type Headaches

Migraines are irregular and episodic which is why there is no specific explanation for why a migraine occurs at any given time. In general it is supposed that exposure to certain environmental factors combined with individual internal factors causes migraine episodes. There are reports that certain dietary, physical, hormonal, emotional, and environmental factors trigger or cause migraine episodes. Those most frequently reported include stress, alcohol, foods, excess or lack of sleep, and weather conditions.Headaches (migraine) may be related to caffeine consumption due to its removal from the usual diet, causing an abstinence syndrome: an alteration in the normal functioning of the nervous system. The mechanism by which this occurs is a blocking of the adenosine receptors; when there is an excessive release of adenosine there is a response in which the release of neurotransmitter molecules, such as serotonin, noradrenaline, acetylcholine, and dopamine, is inhibited, causing an imbalance that can be seen in the symptoms associated with migraines. There is no clear conclusion that migraines can be caused by caffeine. Adenosine has opposite effects depending on its site of action; centrally, in the brain and spinal cord, adenosine acts as an analgesic, but peripherally it can cause pain. Adenosine dilates blood vessels in the head and neck. The concentration of adenosine in the head and neck

increases approximately 68% above normal concentrations during migraine episodes, causing vasodilation and pain. The nervous system compensates the interference of caffeine by releasing more adenosine, increasing the number of adenosine receptors in the neuron surface, increasing the affinity of these receptors and decreasing the rate at which adenosine molecules are removed. All these changes tend to increase the activation of adenosine receptors, to compensate the receptors occupied by caffeine.Caffeine is also a common ingredient in many medications used for treating migraines, due to the fact that it makes analgesics work more efficiently, causes a faster absorption, and allows for a reduced dosage which decreases possible side effects of certain analgesics.

7.2. Action through the Activation of the Autonomic Nervous System

As we have already discussed that adenosine receptors are blocked by the caffeine stimulating a reflex activation of sympathetic system in conscious patients. As per the study conducted by Corti et al. the sympathetic system gets activated in regular coffee consumers but no significant increase in the peripheral vascular resistance is escorted, where as in non-habitual consumers coffee stimulates sympathetic system and also increases arterial pressure. This study showed that coffee consumption(regular and decaf coffee) produces an increased sympathetic tone after ingestion. Though most of the studies show that caffeine results in the increase in arterial pressure but there is possibility that various other substances in coffee contribute to the increase in sympathetic tone and arterial pressure. Moreover, it is essential to differentiate results of various studies conducted on the effect of caffeine on arterial pressure showing variations as per population groups (age, hypertensives and stress factors). In accordance with this analysis, the precise conclusion based on this data is that tolerance generated with regular caffeine consumption reduces the effect of caffeine on arterial pressure near about 30 minutes after administration, with increased peak in the range of 1 to 2 hours and a persistence of about 4 hours.

Caffeine boosts the plasmatic levels of stress hormones like adrenaline and noradrenaline, as well as cortisol. Both the sympathetic-adrenal medullary system and the adrenocorticoid components of the neuroendocrine response to stress are engaged, in accordance with these humoral effects. It has been suggested that the ingestion of caffeine causes increase in sympathetic nervous activity and slight change in blood pressure, heart rate and body temperature. Studies have also shown the pharmacologic effects of caffeine are associated to sympathetic nervous system. High doses may result in tachycardia, rise in plasmatic activity of rennin, thermogenic and lipolytic effects and also significant rise in plasmatic adrenaline concentrations. This effect on sympathetic activity has a wide range of outcomes and is still disputed and poorly understood.

7.3. Action through the Renin-Angiotensin-Aldosterone Axis (RAA)

There are three major effects of caffeine on the RAA axis. Firstly, it will block the inhibitory effect of adenosine on juxtaglomerular cells present in kidney resulting in the increase in renin secretion. Besides, it increases cAMP concentration- a precursor of renin due to its antiphosphodiesterase activity and also there is secreation of renin by sympathetic system activation. The increase in secretion of renin causes vasoconstriction and rise in peripheral vascular resistance.

Caffeine has this impact only in conditions where renin levels are high (e.g., cirrosis, congestive heart failure), not in normal physiologic states. As a result, coffee has no effect on renin production in healthy people.

Conclusions

Coffee is one of the most consumed beverages worldwide and has a composition of over 2,000 substances, with a predominance of carbohydrates, lipids, amino acids, melanoidins, and the most important and renowned of all caffeine. Caffeine is a xanthine that demonstrates numerous mechanisms of action on vascular wall particularly on the VSMC and endothelial tissue. It affects the autonomic nervous system and blood pressure, and regular use may lead to tolerance. The different effects that are produced are actually the result of activation or blockage of various receptors like adenosine, NO and IP3. Moreover, its effects appear to be conflicting depending on cellular structure and exposure time over which it acts. Depending on the caffeine concentration in VSMC a slight and transitory vasoconstrictor effect exits. The major and most important effect of caffeine on the vascular wall is vasodilation that affects both the VSMC directly and indirectly, as well as the endothelial structure. NO is liberated at endothelial level and results in production of arterial vasodilation. It has been shown that this effect is caused in the presence or absence of preserved endothelial function.As for the effects on the vascular smooth muscle cell, caffeine causes direct and indirect effects according to the type of stimulus, either at the level of cellular $Ca2+$ concentrations or on competitive effects with specific enzymes. Indirectly, the diffusion of nitric oxide from the endothelial tissue towards the VSMC increases the vasodilator effect.In spite of being a widely consumed substance worldwide, its vascular effect, and cardiovascular effect in general, continues to be controversial. From studies it is clear that the effects of coffee consumption vary as per population, specific metabolite and pathological factors. Therefore, it becomes important to carry on the search for better information related to the mechanism and effects of caffeine so as to determine the impact of mechanism as risk factors or if said mechanisms can be considered protective at a cardiovascular level.

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