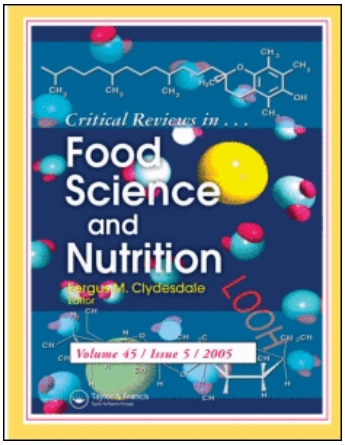

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A Perception on Health Benefits of Coffee

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A Perception on Health Benefits of Coffee

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Coffee, consumed for its refreshing and stimulating effect, belongs to the tribe Coffea *of the subfamily Cinchonoidea of Rubiaceae family. Coffee is a complex chemical mixture composed of several chemicals. It is responsible for a number of bioactivities and a number of compounds accounting for these effects. Few of the significant bioactivities documented are antioxidant activity, anticarcinogenic activity, antimutagenic activity etc. Various compounds responsible for the chemoprotective effects of coffee are mainly polyphenols including chlorogenic acids and their degradation products. Others include caffeine, kahweol, cafestol, and other phenolics. Coffee also shows protective or adverse effects on various systems like the skeletal (bone) system, the reproductive system, the nervous system, the cardiovascular system, the homocysteine levels, the cholesterol levels etc. Harmful effects of coffee are associated with people who are sensitive to stimulants. Overall, with the available information, it can be concluded that the moderate consumption, corresponding to 3 to 4 cups/day with average strength is safer to human health.*

Keywords coffee, biological activities, physiological effects, antioxidant, anticarcinogenic, cardiovascular

INTRODUCTION

Legend scripted that Kaldhi, an Arab goatherd living around 850 A.D., puzzled by his flock's queer antics, tasted the berries of the evergreen bush the goats were feeding on. Experiencing a sense of exhilaration, he proclaimed his discovery to the world (Sivetz and Foote, 1963).

At present, coffee—the dark, aromatic, non-alcoholic brew loved the world over for its stimulating and refreshing taste is a product of the coffee plant. It is the bean extracted from the fruit of the coffee plant that is roasted, ground, and liquored to produce the fascinating brew. Coffee is the most popular beverage consumed by about one-third of the world's population in an amount larger than any other beverage. Arabica accounts for 75% of the worlds coffee production

All coffee plants belong to the tribe Coffea of the subfamily Cinchonoidea of Rubiaceae family. Coffee is one of the two genera of the Coffea tribe, and it has three recognized subgenera. Coffea contains about 85 species and only three of these namely C. arabica, C. canephora (robusta) and C. liberica have been successfully used in commercial cultivation.

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Chemical Composition

The chemical composition of green coffee depends mainly on the variety of the coffee, although slight variations are possible due to agroclimatic conditions, agricultural practices, processing, and storage. The average approximate composition of coffee is given in Table 1.

Processing

To obtain marketable coffee, termed as "Green coffee" the processing techniques are dry method and wet method. The wet method gives coffee a superior cup quality. It includes steps like (i) harvesting, (ii) pulping, (iii) demucilaging, (iv) washing, (v) drying and storage (Scheme 1). For the dry method simple drying is carried out using solar energy or other driers (Scheme 2). Grading, roasting, and grinding comprise the industrial phase of coffee processing (The Wealth of India, 2001).

Roasting and Grinding

Roasting is a process involving the passage of hot air at 200–260°C through the beans. The time required for roasting is 5–10 min in a continuous roaster and more then 20 min in

Table 1 Composition of coffee

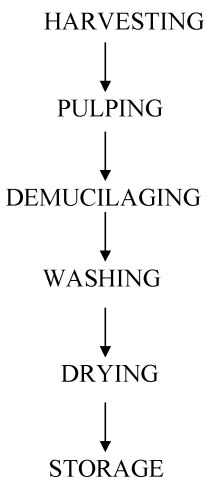
Component	Composition (%)
Reducing sugar	1.0
Sucrose	7.0
Pectin	3.0
Starch	10.0
Pentosan	5.0
Hemi cellulose	15.0
Holocellulose (fiber)	18.0
Lignin	2.0
Oils	13.0
Protein	13.0
Ash	4.0
Chlorogenic acid	7.0
Other acids	1.0
Trigonelline	1.0
Caffeine	1.0

(Ramalakshmi and Raghavan, 1999).

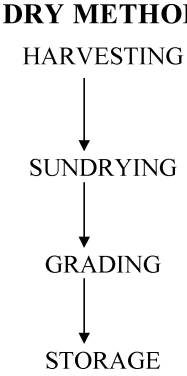
a non-continuous roaster (Carvalho and Chalfoun, 1989). The characteristic aroma is developed during roasting. Grinding is essential to obtain maximum extraction of solubles including aroma and flavor. Various types of grinders are available. The chemical composition of green, roasted, and brewed solids is presented in Fig. 1 (Barter, 2004). ISO specification for roasted and ground coffee is presented in Table 2.

PHYSIOLOGICAL EFFECTS

Coffee is consumed because of its desirable bitter taste and medicinal benefits. The effect of coffee on human physiology varies from person to person and also on the quality and quantity of coffee consumed. Coffee is a complex chemical mixture. It is composed of over 1000 different chemicals. Theoretically, it can be anticipated that according to the doses involved, some may possess biological activities that could be considered potentially adverse to health or, conversely, beneficial. Although coffee has a long history of human food use for over 1000 years, until recently most of the studies on its health effects have focused on potential adverse and toxic effects. Despite a vast amount of research, evidence to support a direct link of coffee with diseases has been limited and inconsistent. However, although not yet proven, recent scientific literature suggests the potential beneficial health effects of coffee and several of its constituents. For example, its positive effects on performance and protection against some types of cancers, liver disease, and radiation–induced tissue damage have been documented.



SCHEME 1



SCHEME 2

Several diseases have been alleged to be caused or exacerbated by coffee consumption (Leviton et al. 1994). Among others, issues have concerned hypertension, cardiovascular disease, cancer, spontaneous abortion, delayed conception, low birth weight, and osteoporosis. Coffee contains a substantial amount of antioxidants and this may explain some of its potential beneficial activities, although several other important advantageous active components have also been identified. The major pharmacologically active compound in coffee is caffeine (methylxanthine), which is known to have effects on a number of functions including the stimulation of the central nervous system (CNS), the stimulation of cardiac muscle, and the relaxation of smooth muscle especially bronchial muscle and to act on the kidney to produce diuresis. The caffeine is metabolically degraded and involves demethylation steps to yield theobromine, theophylline, xanthine, and finally to urea (Fig. 2) (Waler and Suzuki, 1989). Caffeine also produces a slight increase in the basal metabolic rate and increases the capacity for muscular work. Medicinally one of the important components of coffee

Table 2 ISO Specification for roasted and ground coffee

Characteristics	Requirement (% by wt)
Moisture (Max.)	4.0
Total ash	3.0
Acid soluble ash (max)	1.0
Water soluble matter	26–35
Caffeine	1.0
Petroleum ether extract (min)	8.5

(Rao et al., Indian coffee, 1993)

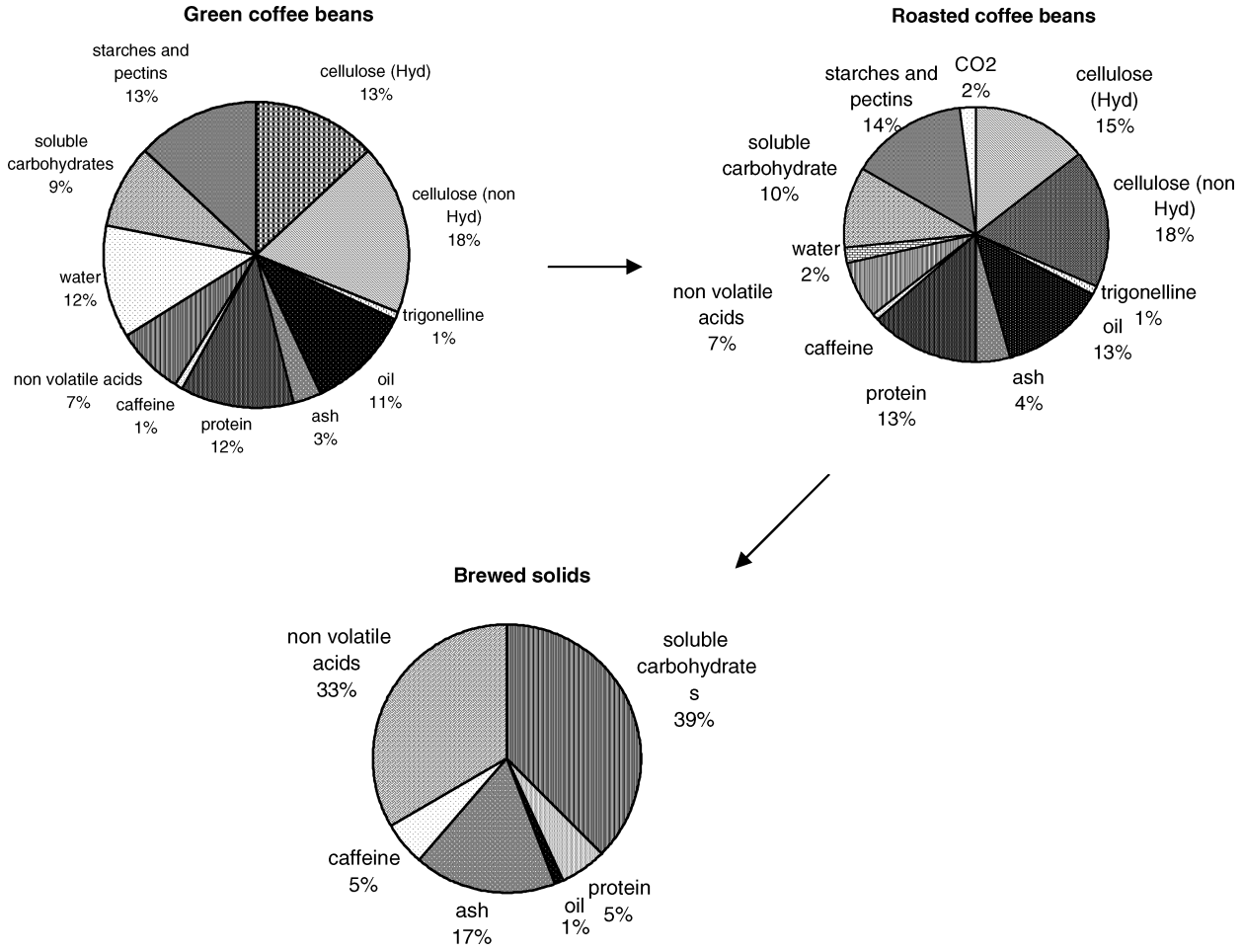


FIGURE 1 Chemical composition of green, roasted, and brewed coffee solids.

is caffeine, but a cups caffeine content depends on how the coffee is prepared. Dark roasted coffee contains less caffeine than coffee made from light and medium roasted beans. The caffeine content of different coffee products are presented in Table 3 (Anon, 2004).

A number of other compounds, such as chlorogenic acid, are also present and are also pharmacologically active. The biological and health effects of coffee have been extensively investigated in various animal and in vitro model systems as well as in humans. Coffee contains substantial amounts of antioxidants and this may explain some of its potentially beneficial activities. Whatever effects are attributed specifically to the consumption of coffee, one must assume that these are associated with compounds in coffee beverage. Immediately this focuses attention upon caffeine, the chlorogenic acids, possibly the sparingly water-soluble diterpenes kahweol and cafestol and miscellaneous products of roasting. The biological and health effects of coffee have been extensively investigated in various animals and *in vitro* model systems as well as in humans. Both potential adverse and beneficial effects of the bioactivities would be discussed. This paper summarizes an overview of various biological activities such as anticarcinogenic, antioxidant, and the antimicrobial activities of coffee.

Table 3 Caffeine content of different coffee products

Coffee product	Caffeine range (mg/100 ml)
Coffee	
Brewed	27–50
Instant	25–35
Decaffeinated, brewed	0.8–1.7
Decaffeinated, instant	0.4–1.7
Espresso	100–165
Cappuccino and Latte	100–165
Moccachino, 1-oz. shot	115–185

Antioxidant Activity

The antioxidants may be of great benefit in improving the quality of life by helping to prevent or postpone the onset of degenerative diseases (Svilaas et al., 2004). Many countries have recommended an increase in consumption of fruits and vegetables, as they are known to reduce the risk of such degenerative diseases. Further, recent research in Norway has shown the role of coffee as a source of antioxidants in the diet. The

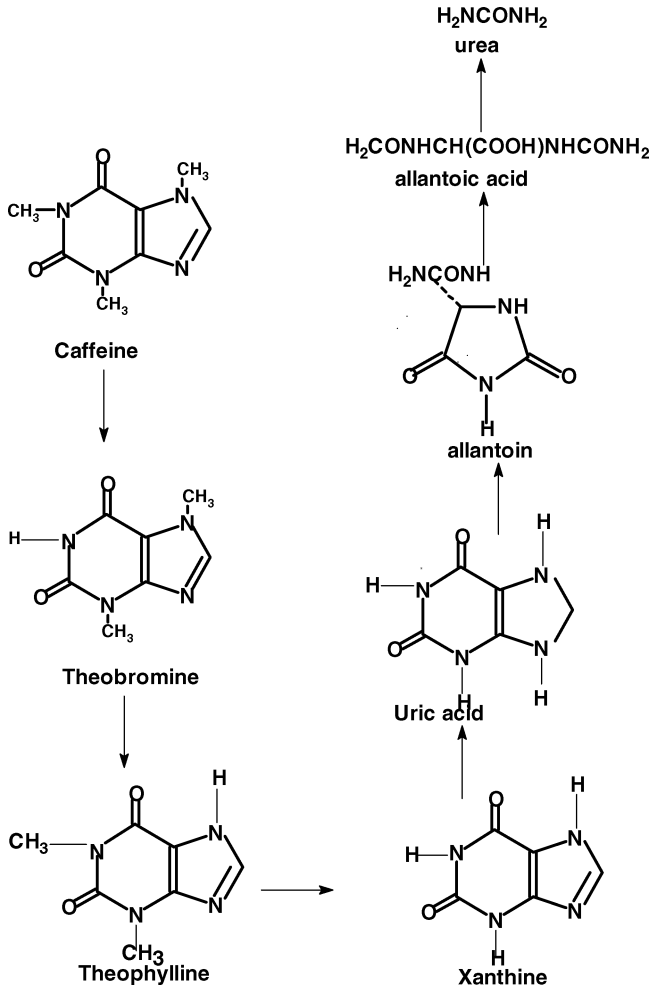


FIGURE 2 Metabolic degradation of caffeine.

total intake of antioxidants from various food groups is given in Table 4.

Beverages prepared from roasted coffee have several hundreds of chemicals, which are both naturally occurring and formed during the roasting process. The chemistry and biological activity of all these substances have not yet been completely revealed. The high worldwide consumption of coffee has stimulated research to study other biological activities of green and especially roasted coffee. Green coffee has shown to possess in vitro antioxidant activity against lipid peroxidation (Kroyer et al., 1989) and antineoplastic activity (Rosenberg, 1990). The roasting process gives rise to changes which confer on coffee its pleasant taste and aroma. It leads to profound changes in the chemical composition and biological activities of coffee, according to the transformation of naturally occurring substances in green coffee as well as the compounds derived from the Millard reaction, namely carbohydrate caramelization and the pyrolysis of organic compounds (Belitz and Grosch, 1999).

Table 4 Antioxidants in various food groups (Svilaas et al., 2004)

	Quantity of antioxidant intake	
Source	(mmol)	%
Coffee	11.1	64
Fruit	1.8	11
Tea	1.4	8
Wine	0.8	5
Cereals	0.8	5
Vegetables	0.4	2
Other foods (fruit juices, edible fat, and cakes)	0.8	5

The antioxidant activity of coffee brews using different methods of preparation was studied by Sanchez et al. 2005. They observed that the antioxidant activity of coffee brews increased significantly when the brews were kept hot (80°C). The cause of this increase may be the formation of Maillard compounds during the heat process.

The antioxidant capacity was evaluated by a chain-breaking activity, which allows the evaluation of the quenching rate of coffee compounds towards a reference radical (DPPH). Higher antioxidant capacity was observed in Colombian conventional roasted coffee blends due to the presence of more robusta coffee beans that contain more chlorogenic acids (Galilea et al., 2006).

Yen et al. (2005) evaluated the antioxidant activity of roasted coffee spent residues in different in vitro model systems. The data obtained, clearly indicated that the coffee spent residues have excellent potential for use as a natural antioxidant source because the antioxidant compounds remained in roasted coffee residues. They have reported that the antioxidant activity of spent coffee residue may be due to the presence of phenoloic compounds such as chlorogenic acid and caffeic acid.

Bio-Active Components Responsible for Antioxidant Activity

Phenolic compounds in coffee are known to have antioxidant activity in which the prevalent one is hydroxy cinnamic acid and the major component of this class is caffeic acid, which occurs in food mainly as esters called chlorogenic acid (CGA) (Rice-evans et al., 1996). Coffee is the major source of CGA in human diet, daily intake by coffee drinkers being 0.5–1.0 g whereas coffee abstainers typically ingest <100 mg/day (Clifford, 1999). Roasting markedly affects the composition (mainly CGA) and antioxidant properties are lost during roasting of coffee beans but the overall antioxidant properties of coffee brews are maintained or even enhanced, due to the formation of compounds possessing antioxidant activity, including Maillard reaction products (Nicoli et al., 1997). Some of the compounds produced during roasting of coffee beans are represented in Fig. 3.

GCA (Green Coffee Antioxidants) is an all-natural green coffee bean extract containing at least 65 percent total polyphenol antioxidants. This extract is a potent antioxidant, also a highly bio-available and cost–effective ingredient for adding increased functionality to nutrition based products. It provides a neutral taste profile, high solubility, and high activity level and so is an ideal ingredient for functional foods and beverages as well as bars, chews, and dietary supplements.

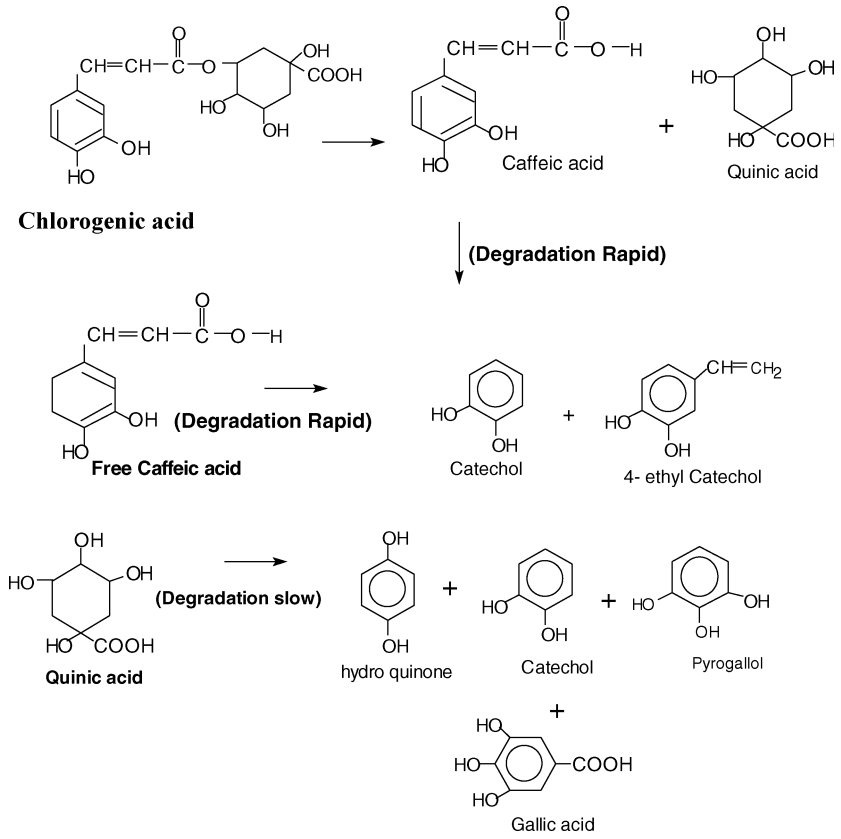


FIGURE 3 Phenolic compounds produced during roasting of coffee beans.

Coffee due to its antioxidant activity is known to show a protective effect on cancer (Benoit et al., 2001) and other cardiovascular diseases. It also protects Low Density Lipoprotein from oxidation. This protective effect is the result of action of several polyphenolic constituents. The physical and chemical properties of individual phenolics, strongly affect their antioxidant activities. In addition, these molecules can have a synergistic or antagonistic effect when present in complex mixtures.

Indeed, the polyphenol composition of the beverage varies in species of coffee and tea (Richelle et al., 2001). In the case of coffee, robusta exhibits a high antioxidant activity than arabica, which could be due to the higher amount of chlorogenic acid. Following light roasting, the antioxidant activities of both coffees decreased markedly but further roasting produced the heterocyclic compounds having the antioxidant activity, and as these polyphenolic rich beverages are often consumed with milk, the effect of milk on different beverages (coffee, cocoa, black tea) were evaluated and coffee was found to have high antioxidant activity.

An understanding of the protective role of dietary antioxidants in vivo requires a better characterization of the polyphenol composition of the antioxidant matrix as well as quantitative data on their absorption, their tissue distribution, their metabolism, and their biological actions (Scalbert, et al., 2000). Indeed, after consumption, polyphenols have to cross the intestinal wall but must also resist further catabolism. The metabolism of polyphenols involves two important organs—the liver, where biotransformation enzymes convert them or their metabolites into conjugated forms such as glucuronides or sulphates, and the colon where microorganisms degrade unabsorbed ones. At present, only little information is available on the absorption of the vast diversity of polyphenols present in these beverages (Richelle et al., 2001). So the antioxidant activity of coffee has to be considered while estimating the daily-ingested dose of polyphenols. Thus, the beneficial effects of coffee may be attributed in part to polyphenols and caffeine serving as antioxidants.

In general the antioxidant ability of caffeine (1,3,7-trimethyl xanthine) was similar to that of the established biological antioxidant glutathione and significantly higher than ascorbic acid (Devasagayam et al., 1996). The pro- and anti-oxidative effects of coffee are also reflected in its mutagenic and antimutagenic activity in the Ames test. Coffee is directly mutagenic on strains TA100 and TA102 due to H_2O_2 formation. However, coffee is also an antioxidant and antimutagen (Stadler et al., 1994). This beverage exerts a strong protective effect against the mutagenicity and cytototoxicity induced by the oxidant *t*-butylhydroperoxide (*t*-BuOOH). Thus, coffee like many antioxidants, exhibits dual effects in vitro which are highly dependent upon parameters such as dose, atmospheric O_2, transition metals, as well as the biological and the chemical end points used for measurement. The mechanism of action of caffeine to scavenge free radicals is shown by the following reaction (Fig. 4).

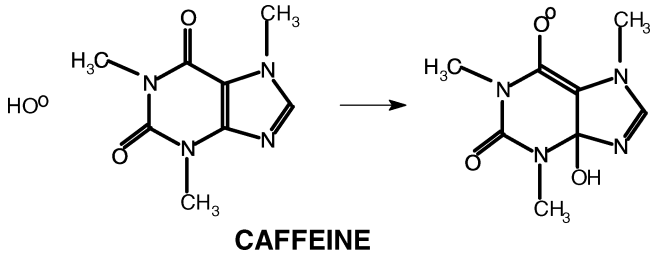


FIGURE 4 Mechanism of scavenging of free radicals by caffeine.

All types of coffee, mainly instant, caffeine-containing, or decaffeinated and various others have similar mutagenic effects on Salmonella typhimurium TA100, TA104, as well as on Escherichia coli WP2 uvrA/pKM101 and K12. Some strains of Salmonella are insensitive to coffee which proves the specificity of coffee action on the genome of certain bacteria (Aeschbacher, 1988).

The mutagenic effect of coffee has also been well established in vivo studies. The effect is observed in cultured mammalian cells, lung cells, and rat fibroblasts, mouse blastocytes, leukemia cell lines, human lymphocytes, fibroblasts, melanoma and hepatoma cell lines, endothelial cells, and keratinocytes. However, the mutagenic effect is dependant on the dose of coffee which is administered to the cells during the study (Aeschbacher, 1988).

The antimutagenic effect of coffee is well documented (Kim and Levin, 1988). The antimutagenic activity varies with the intensity of the coffee exposed rather than the concentration of antimutagenic agents. Caffeine is usually protective when administered before the genotoxic agent in various in vivo tests. However, the mouse bone marrow micronucleus test showed that coffee administered twice orally, 2 and 20 h before DMBA, benzo[a]pyrene or aflatoxin B 1 significantly inhibits their in vivo genotoxicity (Abraham, 1989).

Caffeine has also been investigated for its potential antioxidant activity against oxidative damage to rat liver microsomes. Such damage was induced by three reactive oxygen species of cardinal importance in causing membrane damage in vivo namely hydroxyl radical (OH°), Peroxyl radical (ROO°), and singlet oxygen ($1O_2$). The results showed that caffeine was an effective inhibitor of lipid peroxidation at millimolar concentrations against all the three reactive species (Devasagayam et al., 1996). The extent of inhibition was high against O_2 and low against ROO.°

Apart from phenolic compounds (chlorogenic acids and caffeoyl tryptophan) and organic bases (caffeine and its derived products) that are naturally present in green coffee beans, the melanoidins and phenylindanes are also responsible for the antioxidant activity in coffee brews. Characterestic volatile heterocyclic compounds found in brewed coffee extracts namely pyrroles, furans, thiophenes, and thiazoles, exhibited certain levels of antioxidant activity (Fluckiger et al., 1976). More than 300 heterocyclic compounds including pyrroles, oxazoles, furans, thiazoles, thiophenes, imidazoles, and pyrazines were identified and quantified in brewed coffee (Kenichi et al., 2002).

Anticarcinogenic Activity

A number of epidemiological studies have investigated the relationship between coffee consumption and cancer incidence at various sites. Overall there is no conclusive evidence that coffee drinking represents a significant risk for the development of cancer in humans. Thorough reviews on coffee and cancer had been published by the World Health Organization/International Agency for Research on Cancer (IARC, 1991; Nehling and Debry, 1996). In a large study conducted in Norway (per capita coffee consumption is among the largest in the world) on 43,000 people, no association was reported between coffee drinking and the overall risk of cancer (Stensvold and Jacobsen, 1994).

In contrast, many studies revealed an inverse (protective) association between coffee consumption and the risk of certain cancers (Giovannucci, 1998; Inoue et al., 1998). The epidemiology of colorectal cancer provides the most supportive evidence of a potential coffee–dependent protection. In a recent meta-analysis comprising five cohort and 12 case–control studies, a significant inverse association was found between coffee consumption and colorectal cancer (Giovannucci, 1998).

In a number of animal studies, evidence supporting the potential chemoprotective effect of coffee was provided. In chronic studies conducted in rodents, coffee administered at high levels in the diet resulted in a decreased incidence of spontaneous tumors at different organ sites (Wurzner et al., 1977; Stadler et al., 1990). Some other studies had shown that coffee or coffee constituents protect against the action of well-known carcinogens such as nitrosamines or 1,2 dimethyl hydrazine (Gershbein, 1994). Several other studies had shown that green as well as roasted coffees inhibit the development of 7,12– dimethylbenz(a)anthracene (DMBA)–induced carcinogenesis at various tissue sites in different experimental animal cancer models. (Wattenberg, 1983; Miller et al., 1988, 1993).

Cafestol and Kahweol (C+K)

Caffeine and polyphenols including chlorogenic acids and their degradation products were considered potentially responsible for the chemoprotectiveeffects of coffee (Schilter et al., 2001). In addition, investigations performed in rats, mice, and hamsters led to the identification of a specific lipid fraction as potentially responsible for the chemo preventive effects of coffee on DMBA–induced cancer (Lam et al., 1982; Miller et al., 1991). The major constituents of this fraction were found to be the diterpenes cafestol and kahweol (Fig. 5). Recently attention has been focused on the biological effects of these diterpenes. These

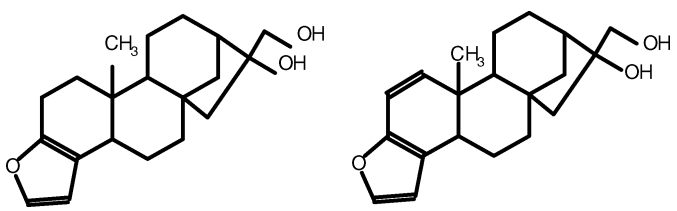


FIGURE 5 Structures of cafestol and kahweol

components, which appear to be relatively specific to coffee, are found in both Arabica and Robusta varieties and comprise up to about 10–15% of the lipid fraction of roasted coffee beans (Ratnayake et al., 1993; Lercker et al., 1995). These specific coffee constituents are very difficult to isolate independently and kahweol is highly unstable when purified. Therefore, the biological properties of these compounds have been studied traditionally using a mixture of both (Cavin et al., 2002).

Chemoprotective Mechanisms

Early studies indicated that cafestol and kahweol induced glutathione S-transferase (GST) activity in mouse liver and small intestine (Lam et al., 1982). Since GST is known to detoxify electrophilic compounds through conjugation with glutathione, these data led to the hypothesis that cafestol and kahweol may possess the properties of blocking agents. It is known that the initiation of tumor formation, which generally consists of a permanent modification of DNA with electrophilic or oxidant metabolites derived from procarcinogen biotransformation, is a target for several dietary anticarcinogenic compounds or blocking agents (Wattenberg, 1985). These act through an inhibition of the formation and or the stimulation of the detoxification of the electrophiles or oxidant intermediates, resulting in decreased DNA damage and in the blocking of initiation. Chemoprotective agents may intervene at one or several steps of the carcinogenic process namely during the initiation, promotion, or progression stages (De Flora and Ramel, 1988; Harris, 1991). Recent reports further confirm that cafestol and kahweol preventive effects may be mediated by both an inhibition of bioactivation and a stimulation of detoxification. Further, it was reported that patients who consumed caffeine-containing beverages such as coffee at the time of their radiotherapy against cervical cancer had significantly decreased incidence of severe late radiation injury (Stelzer et al., 1994).

a) Induction of Detoxifying Enzymes

Following up on the early observations showing an induction of GST activity in mouse liver and small bowel (Lam et al., 1982), the effects of cafestol and kahweol on the expression of various GST subunits were studied in the rat (Schilter et al., 1996; Cavin et al., 1998). Rats were administered C + K in the diet (0, 92, 460, 2300, 6200 ppm) up to 90 days. The most striking effects reported were a strong dose dependent induction of the GST inorganic phosphates subunit Yp and the alpha subunit Yc2 (rGSTA5) in the liver following 28 or 90 days of treatment. The effects were found at the mRNA and protein levels and these were significant ($P < 0.05$) at C + K dietary concentrations of 460 ppm and higher. With respect to GST inorganic phosphates, time course experiments indicated that the C + K mediated induction occurred within a few days. In addition, it was shown that the increased expression was dependent on the continuous presence of C + K in the diet and was reversible following removal of C + K (Schilter et al., 1996). Considerable organ–specific differences were observed regarding the effects of C + K on overall GST activity using CDNB as substrate. In rats fed 0.2% C+ K, increases the activity in the liver and kidneys (two to threefold as compared to controls) were paralleled by a moderate enhancement in the lung, a marginal one in the colon, and no changes in several other organs such as the pancreas, the salivary gland, and the testes (Schilter et al., 1996; Huber et al., 1997; 2000a). The liver and other well-perfused organs may thus contribute to Chemoprotective effects that occur in distant organs as well.

b) Molecular Mechanism of Induction

The cis-acting responsive element (ARE) sequence has been identified on the promoter of several genes involved in detoxification processes (Hayes et al., 1999). It has been suggested that altering the expression of these genes through ARE—mediated transcriptional activation is likely to be a key molecular mechanism explaining how many blocking agents may prevent mutagenesis. bZip Nrf proteins had been found to activate gene induction through this specific enhancer (Venugopal and Jaiswal, 1996). The role of NrF2 transcription factor in the C + K mediated activation of intestinal detoxifying enzymes has been addressed using a mouse line bearing a targeted disruption of the gene encoding factor (McMahon et al., 2001). The results show the key role of this transcription factor in the chemopreventive activity of C + K in the small intestine.

c) Inhibition of Activating Enzyme Expression

Reduction of carcinogen activation was shown to play an important role in the C + K mediated prevention of carcinogen DNA binding besides stimulation of detoxification processes. It was observed that in rats fed diets containing C + K over 28 days, the hepatic expression of the cytochrome P450 (P450) CrP3A2 was significantly decreased at both the mRNA and the protein levels (Cavin et al., 1998). Significant differences as compared to controls were found at dietary C + K concentrations of 2300 ppm and above. The two major P 450s, CYP 2C11, and CYP3A2, responsible for the bioactivation of AFB into AFBD in the rat, was hypothesized that a reduction in the expression of these genes may contribute to the C + K mediated prevention of AFB_1–DNA adduct (Forrester et al., 1990). In a DNA binding assay, the use of microsomes from the liver of C + K treated rats as an activating system resulted in a significant reduction in AFB_1 - DNA adducts formation (Cavin et al., 1998). This effect was dose dependent and maximal at 6200 ppm in the diet (40% reduction). These data support a role for the decrease in phase I enzyme expression in the Chemoprotective effects of C+K against AFB_1 genotoxicity.

d) Inhibition of Enzymatic Activity

A direct inhibition of P450 enzymatic activity without any effects on protein expression is an additional phase I mediated mechanism through which the coffee diterpenes may act. For example C + K has been shown to produce on inhibition of P 4501A1 activity in liver cells which resulted in a reduction of B[a]P activation and DNA binding. Similar inhibitory

effects were found with human P 450 CYP 2B6, a human P450 responsible for AFB_1 bioactivation (Cavin et al. 2001). In addition, it is suggested that the reduction of PhIP–DNA adducts found in C + K treated rats involves an inhibition of the PhIP–activating enzymes P 4501A2 and N-acetyl transferase (NA) (Huber et al., 1998, 2000) C + K was also found to reduce the N-hydroxylation of 4-amino biphenyl in vitro (Hammons et al., 1999).

Cancer with Relevance to Human Data

Coffee consumption has been linked to cancers (Benoit et al., 2001) in many organs but currently there appears to be little, or no supportive evidence for these contentions. For many years, the attention of the epidemiologists studying coffee was focused on the possible association between coffee drinking and development the of cancer at different sets. Evidence showed less or more links between coffee consumption and cancer. In the following subtitles the association between coffee and different cancers will be discussed.

Cancers of the Gastrointestinal Tract.

a) Cancer of the Pancreas

A number of studies have been carried out to examine the potential link between coffee consumption and risks of pancreatic cancer. Farrow and Davis (1990) examined the risk of pancreatic cancer in relation to medical history and the use of tobacco, alcohol, and coffee. Here the association of coffee with risk of pancreatic cancer was confirmed to be insignificant. The risk of pancreatic cancer was increased in case of use of tobacco and alcohol. A study (La vecchia et al., 1989) conducted on 214 patients in Milan, Italy showed no evidence for pancreatic cancer due to coffee consumption. Most of the studies do not support any association; some have raised the possibility of a weak increase in pancreatic cancer of heavy coffee drinkers (WHO/IARC, 1991). The IARC Working Group (1991) found that "there is inadequate evidence in humans that coffee drinking is carcinogenic in the pancreas." Further studies and more recent analysis of the etiological factors for pancreatic cancer have revealed that the weak effects of coffee, if any, are likely to be related to confounding factors such as smoking and therefore coffee consumption is not considered to represent a significant risk factor for cancer of the pancreas (Nehling and Debry 1996; Silverman et al., 1998; Weiderpass et al., 1998). However, a U-shaped dose response effect was observed through a meta-analysis involving 14 studies published between 1981 and 1993. In another case control study a U-shaped relationship was found between the level of coffee consumption and the rise of pancreatic cancer. The lowest relative risk of pancreatic cancer was found at low consumption levels ranging from one to four cups a day.

b) Oesophageal and Gastric Cancers

Several studies were reported on the relationship between coffee consumption and cancers of the mouth, the pharynx, oesophagus, and the stomach and was concluded that coffee consumption was not causing these cancers (IARC, 1991; Nehling and Debry, 1996). However, protective effects had been suggested (Inoue et al., 1998).

c) Colorectal Cancer

The relationship between coffee consumption and colorectal cancer was inconsistent as per numerous studies conducted in different geographical areas (WHO/IARC, 1991; Nehling and Debry, 1996). Many case control studies have revealed an inverse (protective) association between coffee drinking and the risk of colorectal cancer. Meta analysis of several studies on coffee consumption and colorectal cancer from 1960–1999 revealed the risk of colorectal cancer to be 24% lower among those who drink four or more cups of coffee per day than the non-coffee drinkers (Anon, 2004a).

Rosenberg (1990) reviewed the epidemiological investigations of the relationship of methyl xanthine ingestion to the risk of large bowel cancer and on the basis of the available data it was concluded that there was little reason for concern that coffee consumption increases the risk. The same conclusion was reached at the meeting of the IARC Working Group (1991).

A meta analysis of coffee consumption and risk of colorectal cancer was published (Giovannucci, 1998) which strongly suggests that the risk of colorectal cancer associated with a substantial consumption of coffee (>4 cups a day) is less.

Cancer of the Sexual Organs.

a) Ovarian Cancer

A weak positive association is seen between coffee consumption and ovarian cancer in case control studies. Leviton (1990) reviewed the epidemiological studies of the association of coffee consumption and the risk of ovarian malignancy and concluded that coffee and tea consumption did not increase the risk of ovarian cancer and in most of the studies, the effect was not significant (Nehling and Debry, 1996; IARC, 1991). In its review IARC concluded that the evidence for an association between coffee drinking and ovarian cancer is inadequate although the data indicate a marginal but significant increase in relative risk (IARC, 1991).

b) Prostate Cancer

Studies have shown that there is no association between coffee consumption and prostate cancer (Jain et al., 1998; Hsieh et al., 1999).

c) Breast Cancer

In a prospective study on Norwegian women with a follow up period of 12 years (the age of the women at the time of enquiry was between 35–51 years) 152 incident cases of breast cancer were observed. The coffee consumption (cups per day) was established from the food frequency questionnaire. There was an overall weak negative association between daily coffee intakes and risk of breast cancer. The review of seven case studies by IARC (IARC, 1991) did not reveal any association between breast cancer risk and the consumption of coffee. Other studies further support that coffee intake is not

related to breast cancer (Folsom et al., 1993; Smith et al., 1994; Tavani et al., 1998) in both pre and post–menopausal women.

Cancers of the Urinary Tract.

a) Kidney, Urinary Tract

The etiology of renal cancer is still largely undefined (Nehling and Debry, 1996; Tavani and La Vecchia, 1997). Available information indicates that renal cancer is unlikely to be associated with coffee consumption (IARC, 1991, Nehling and Debry, 1996; Tavani and La Veechia, 1997). A similar conclusion can be drawn for cancer of the urinary tract (IARC, 1991; Nehling and Debry, 1996).

b) Bladder Cancer

The IARC Working Group (1991) on the "Evaluation of Carcinogenic Risks to Humans from Coffee" concluded that there is limited evidence in humans that coffee drinking is carcinogenic in the urinary bladder. Many studies had suggested the possibility that coffee consumption and occurrence of bladder cancer is often a weak association and many others found no correlation (IARC, 1991; Nehling and Debry 1996; Donoto et al., 1997; Probert et al.; 1998). From the different studies carried out it appears that coffee consumption is unlikely to be an important risk factor for bladder cancer in humans.

Altogether, the data on the biological effects of C + K provide a plausible hypothesis to explain some anticarcinogenic effects of coffee observed in human epidemiological studies and in animal experiments.

Mutagenic and Antimutagenic Effects

Numerous studies were carried out to check the mutagenic effects of coffee, using various biological test systems like bacteria, yeast, fungi, mammalian cells, and whole animal (IARC, 1991). Results of these studies showed that high concentrations of coffee had a slightly mutagenic effect on the biological test systems. In bacterial assays coffee is particularly mutagenic to strain sensitive to oxidative mutagens (electrophiles).

Roasted coffee has been found to possess mutagenic activity, probably due to the formation of hydrogen peroxide, as a result of polyphenolic thermal degradation products of chlorogenic and caffeic acid, and was catalyzed by transition metals. At low doses coffee suppresses in vitro mutagenicity of oxidants such as tertiary butyl hydroperoxide and could inhibit lipid peroxidation and malondialdehyde formation (Turesky et al., 1993). The same group also reported that roasted coffee can act as a potent antioxidant and inhibit lipid proxidation in a model system (Stadler et al., 1994).

Spectra of new compounds, having pharmacological potential were produced by the coffee beans on roasting. Some of them were called mutagens (Aeschbacher, 1984; Blair and Shibamoto, 1984; de Kruijif et al., 1987; Starvic et al., 1983). Among the complex system of chemical constituents of coffee, compounds like chlorogenic acid, kahweol palmitate, and cafestol palmitate, and nicotinic acid are known to be beneficial to human health also. Others apparently possess antimutagenic effects.

The role of coffee in modulating the in vivo genotoxicity of some genotoxic chemicals (mitomycin C, cyclophosphamide, procarbazine, and adriamycin) in mice was evaluated and found that coffee (regular, instant, decaffeinated, freeze dried) reduced the in vivo genotoxicity of the first three chemicals, provided it coffee was given 2 hours before the genotoxin (Abraham, 1989).

Coffee and selected ingredients from coffee like chlorogenic acids, and premelanoidins inhibit nitrosourea–induced DNA damage in mice when mice were orally closed with $NaNO_2$ plus N-methyl urea simultaneously received coffee, the formation of nitrosourea in the stomach of mice was prevented (Aeschbacher and Jaccaud, 1990).

A study using instant coffee revealed a dismutagenic effect, when the mixtures of N-methyl-N-nitro-N-nitroguanidine (mutagen) and instant coffee extract was assayed using the Ames test assay with Salmonella typhimurium TA 1535. The antimutagenic effect though not strong was observed (Obana and Nakamura, 1989). On the other hand it was found that roasting of coffee beans to high temperature generated several mutagenic compounds (Kikugawa et al., 1989). A sample of coffee roasted at high temperature (400°C) contained about ten times more mutagens than an unroasted sample (Kato et al., 1989). The structures are still unknown but they appear to be amino-imidazo-azarenes (AIA), which are generally produced by heat treatment in foods. Such compounds were found to be carcinogenic in mice and rats (Sugimura and Wakabayashi, 1990).

Most of the mutagenicity of coffee is abolished by the addition of exogenous detoxification systems such as liver extracts, catalase, or peroxidases, implying that hydrogen peroxide plays a key role in mediating coffee genotoxicity (Nagao et al., 1986). All organisms possess efficient oxidant detoxifying mechanism as well as repair systems. In contrast to the results of the in vitro studies in various biological test systems, in vitro experiments in rodents had not shown any evidence of mutagenicity (Nehling and Debry, 1994).

Instant coffee and its polyphenolics which catalyze H_2O_2 formation and mutagenicity, also exhibit potent antioxidant and antimutagenic activity as evidenced by the protective effect of coffee against t-butylhydroperoxide–challenged cells (Stadler et al., 1994). Other in vitro studies had documented that coffee or polyphenolic rich coffee fractions protect against the mutagenicity of several carcinogenic compounds such as heterocyclic amines (Obana et al., 1986) or nitrosating agents (Stich et al., 1982) as well as counteracting the effects of UV-radiation. Studies conducted in in-vivo test systems confirm the antimutagenic effects of coffee. Like, in case of instant and roasted ground coffee, it was reported to protect mice against the genotoxic actions of various carcinogenic chemicals (Abraham, 1991). On an overall review of the studies of mutagenicity in vivo

and in vitro, the risk of any genetic damage can be ruled out when considering the usual amount of coffee consumed by humans (Nehling and Debry, 1994a; Nehling and Debry, 1996). Thus the possibility of protective, antimutagenic effects has gained experimental support.

Effects on Central Nervous System (CNS)

Coffee is an enjoyable beverage containing the alkaloid caffeine with psychotropic effects. A usual cup of coffee contains about 100 mg of caffeine. Caffeine is a strong stimulating agent of the brain cortex, and the respiratory and circulatory centers. Higher doses of caffeine (Single dose of 1000–1500 mg) may lead to symptoms such as trembling, anxiety, loss of mental concentration, tachycardia, and sleep disorder. Few studies so far have been concerned on the relationship between coffee consumption and the central nervous system. In a study conducted on healthy male subjects a shift in EEG (Electron Encephalograph) power towards the fast side (high frequency, low amplitude) of the total spectrum was observed, and this effect was very similar to that produced by active behavioral attention (Gibbs and Maltby, 1943). Another similar observation was made when 250 mg of caffeine was administered and showed further that the effect was similar to that obtained with other stimulant drugs (Goldstein et al., 1963).

Caffeine at low doses was found to have direct effects on single neuron activity in the reticular formation (Forde and Hirsh, 1976) and using a similar technique, (Chou et al., 1980) it was reported that the arousing effect of caffeine might in part be related to the suppressive effect of the drug on the medical thalamic nuclei system. It was found that caffeine increases the turnover rate of the catecholamines, noradrenalin, and dopamine in the brain (Watanabe et al., 1978). Thus in summary, these experiments present good evidence that caffeine enhances cortical arousal and that this effect is mediated by the ascending activating systems of the brain (Battig, 1985).

Coffee was known to increase alertness as seen with the central nervous system (CNS) and improve performance on vigilance tasks and reduce fatigue (Smith, 1998). Also, it was known to provide a potential preventive influence of caffeine on suicide and depression (Klatsky et al., 1993). A dose dependent study showed that people consuming more than six cups of coffee/day showed a 5 fold lower risk of suicide than non-consumers.

Caffeine–Mechanism of Pharmacological Action

Earlier it was believed that the action of caffeine was related to the inhibition of phosphodiesterase, leading to increased concentrations of cyclic AMP. However, for the inhibition much higher doses of caffeine is required (Mandel, 2002). A more likely mechanism following the intake of low doses of caffeine, involves antagonism of adenosine receptors, which are present in the brain, the blood vessels, the kidneys, the heart, the GI tract, and the respiratory system (Chou and Benowitz, 1994). Other investigators concluded that the stimulatory effect of caffeine was largely due to a blockade of AZA receptors that stimulate GABAergic neurons of inhibitory pathways to the dopaminergic reward system of the striatum. However, this blockade of A1 receptors was considered to also play a role. High affinity A1 receptors inhibit adenylate cycles, whereas low affinity A2 stimulates the activity of that enzyme (Daly, 1993). The functions of adenosine receptors and the role of caffeine have been recently reviewed (Svenningsson et al., 1999).

The behavioral stimulant potencies of caffeine and several metabolites, such as paraxanthine and theophylline, correlate with their affinity for occupation of adenosine receptors (Kaplan et al., 1997). These effects includes mental stimulation, systemic catecholamine release, and sympathetic neural stimulation, leading to an increase in blood pressure and lipolysis with an increase in plasma free fatty acid concentrations (Benowitz et al., 1995; Kalpan et al., 1997).

Parkinson's Disease

In the past 30 years, different studies had shown that regular coffee consumption might reduce the risk of Parkinson's disease (Popoli et al., 1991; Fall et al., 1999; Benedetti et al., 2000). Sufferers develop tremors and have difficulty in moving their arms and legs. One of the characteristics of these patients is a reduced amount of dopamine in certain areas of the brain. Mice, whose brain dopamine content has been depleted, exhibit some symptoms of Parkinson's disease. In a study, caffeine given to these mice prevented the development of Parkinson's symptoms (Popoli et al., 1991).

Six retrospective studies found that people who drank coffee on a regular basis were 50–80% less likely to develop Parkinson's disease than those who did not consume coffee (Hellenbrand et al., 1996). Three of the studies showed a dose response relationship–strong support that the more one consumes coffee, the less likely are the chances to develop Parkinson's disease (Hellenbrand et al., 1996, Fall et al., 1999; Benedetti et al., 2000). Further, in a prospective study covering 30 years, the more coffee consumption lowers the risk of Parkinson's disease when examined at the end (Ross et al., 2000). Consumption of decaffeinated coffee did not lower the risk. In a laboratory study, mice were given a chemical that depletes dopamine in important areas of the brain. Levels of caffeine intake comparable to human consumption successfully reduced the amount of dopamine depleted in the brain as well as the physical symptoms typical of Parkinson's disease in humans (Chen et al., 2001). In this study it was revealed that caffeine's neuroprotective effect in slowing down the progression of Parkinson's disease is due to its ability to block the adenosine A2A receptor.

Effects on Human Behavior

Even a single dose of consumption of caffeine affected acute changes in human behavior and less is known about the effects of regular consumption. In addition to studying the effects of caffeine consumption, the research also considered possible changes in behavior as a function of caffeine withdrawal (Warburton, 1995).

Effects of Caffeine on Mood

Consumption of caffeine leads to increased alertness or reduced fatigue (Warburton, 1995). It is unclear whether the change in behavioral effects is due to caffeine alone or in combination with other compounds in coffee. The beneficial effects of caffeine on alertness are mostly demonstrated when circadian alertness is low, and the mood is measured in the context of doing demanding performance tasks (Liberman, 1992). The other effects are that over doses of caffeine could lead to increased anxiety in some individuals. Caffeine withdrawal increases the negative effect but this may reflect expectancy effects (Smith, 2002).

Caffeine and Performance Efficiency

A number of different central nervous system mechanisms were identified by which caffeine could change performance. Earlier reviews suggested variable or slight effects. There appeared to be no direct effects of caffeine on sensory functions. A number of studies showed that caffeine improved simple and choice retention time. Sustained attention had also been shown to be improved by caffeine. Effects of caffeine on memory had not been demonstrated. Simulations of real-life tasks (driving) had shown beneficial effects of caffeine. Caffeine has been shown to remove impairments produced by decreases in arousal. Complex interactions between caffeine, personality, and the time of day had been reported. Some studies had shown that caffeine impairs fine motor control. A cost-benefit analysis suggested that doses of caffeine similar to those consumed by the majority of the population increase alertness and the ability to sustain attention. Adverse effects occur when excessive doses are consumed or when caffeine is given to certain individuals (Smith, 2002).

Effects of Caffeine on Sleep

It is quite clear that high doses of caffeine in the late evening will increase the time taken for some individuals to go to sleep. The effects of smaller doses vary from individual to individual and even when sleep is affected there is no clear evidence that the effects are of a sufficient magnitude to influence health and well being. Indeed, people are usually very good at controlling their caffeine intake, which means that there is not any strong evidence relating level of caffeine consumption to sleep problems.

Reproductive and Developmental Potentials

Several reports attempted to determine whether women who consume caffeine-containing beverages had any adverse effect in their reproductive system or during the developmental stage of the foetus. The results of the studies were conflicting. Since caffeine was shown to be teratogenic in animal models, safety concerns were raised regarding coffee drinking during pregnancy (Cook et al., 1996). It is well documented that caffeine metabolism is slower in pregnant women, resulting in longer and possibly higher exposures. Consequently a number of studies were carried out to study the potential effects of caffeine on various reproductive and developmental outcome.

Effect on Fertility

The effect of caffeine on fertility is dose dependent as per the limited numbers of reports available. i.e., the time to become pregnant increased in rodents suggesting a possible effect of coffee (Benoit et al., 2001). The reports on humans gave inconsistent and controversial results. A study on women in Denmark reported that a delayed time of conception was found in smokers consuming high doses (>8cups) of coffee (Olsen et al., 1991). High levels of caffeine (>300 mg/day) consumption resulted in delayed conception even in non-smokers (Staton and Gray, 1995).

Based on the data reports caffeine could be considered as a weak risk factor that probably reduces fecundity by a certain fraction, but without being a sufficient cause of infertility. Delayed conception is relatively common and many factors, including exercise, stress, nutrition, lifestyle, and social influences may be involved. The question of the mechanism involved in the potential effects of coffee or caffeine is not answered. In conclusion there is no solid evidence linking moderate coffee consumption and adverse effects on fertility parameters.

Spontaneous Abortion

Here again the results of the studies are conflicting. It is documented that nausea is associated with a decrease in spontaneous abortion (Stein and Susser, 1991) Therefore it was postulated that a pregnancy with a higher probability of a viable outcome might increase nausea and in consequence decrease caffeine ingestion. Another survey found a modest increased risk of clinically recognized spontaneous abortion when caffeine intake exceeds 300 mg/day (Dlugosz et al., 1996). Also the association between material serum paraxanthine, the primary caffeine metabolite and the risk of spontaneous abortion was associated with 6 cups/day. The intake of caffeinated or decaffeinated coffee showed no effect on spontaneous abortion (Fenster et al., 1997).

Low Birth Weight, Growth Retardation, and Pre-maturity

Low birth weight (<2500 g) of infants may be the result of a shortened gestational period (prematurity) or the

consequence of intrauterine growth retardation. Many medical, social, and lifestyle factors are known to influence birth weight, some of them are correlated with coffee consumption. A significant trend towards lower birth weight was found with increasing consumption of coffee and teas, however, these effects became non-significant after correlating with smoking (Brooke et al., 1989)

The use of treatment of idiopathic aponea in premature infants using caffeine or theophylline showed that the two drugs were equally effective (Fuglsang et al., 1989). The authors reported preference to use caffeine because of the wider therapeutic range and the ease of administration. Thereby no evidence was reported on potential long-term adverse consequences resulting from coffee-or caffeine-induced low birth weight.

A beneficial use of caffeine in pre-term infants was reported (Walther et al., 1990). The cardiovascular effects of caffeine were evaluated in 20 clinically stable pre-term infants. Compared with controls, caffeine significantly increased left ventricular output and stroke volume. Although theophylline is more frequently used to treat breathing problems, caffeine, which is less toxic, is generally used.

NeuroDevelopment Effects

Caffeine is a stimulant because of its neuropharmacological properties. The potential effect of caffeine on neurodevelopment had been widely investigated both in humans and animal models. Limited information is available regarding the potential influence of caffeine intake by pregnant women on the function of the newborn nervous system. Studies showed that prenatal caffeine exposure did not influence neurobehavioural outcomes and the suckling reflex in the first 2 days of life (Barr and Streissguth, 1991) and no effects on cognitive and motor development could be observed at 8 months of age (Streissguth et al., 1980, Barr et al., 1984). In addition, no effects on intelligence quotient at 4–7 years or on motor ability at 4 years and on vigilance at 7 years were found (Barr and Streissguth, 1991).

Congenital Malformations

Borlee et al. (1978) suggested that drinking more than eight cups of coffee a day during pregnancy was weakly associated with an increased frequency of congential malformations.

In a later report, three cases of extrodactyly in children born from mothers consuming high amounts of coffee (8–25 cups/day) (Jacobson et al., 1981) unless an increased incidence of such a malformation is observed and confirmed in other controlled, large-scale epidemiological studies, this report may not be appropriately interpreted.

The rate of different types of congenital malformation including chromosomal abnormalities was found to be about twice as high in the coffee drinkers than in non-drinkers (Furuhashi et al., 1985) suggesting that coffee may have teratogenic and mutagenic effects. This outcome is surprising since most of the well-documented teratogens are known to produce a specific pattern of teratogenicity and not a wide variety of different malformations.

Several epidemiological surveys examined the association between caffeine ingestion and congenital malformations. Most of the reports do not support any link between caffeine intake and teratogenicity (Nehling and Debry, 1994 b, Brent, 1998). Overall there is no evidence to implicate moderate coffee/caffeine consumption in the etiology of human congenital malformations.

Effect on Homocysteine

Consumption of unfiltered or filtered coffee raises total homocysteine concentration in healthy volunteers. The responsible compound, however, is unknown (Verhoef et al., 2002). A high plasma total homocysteine concentration is associated with increased risk of cardiovascular disease. Elevated serum concentrations of total homocysteine have been correlated with an increased risk of atherosclerotic cardiovascular disease. The mechanism involved is still unclear. Experimental evidence has indicated that homocysteine may promote vascular damage through oxidative stress (Meleady and Graham, 1999), suggesting a potential link between heavy coffee consumption and total plasma homocysteine (Nygard et al., 1998; Oshaug et al., 1998; Stolzenberg–Soloman et al., 1999) and reported a direct and dose dependent association between coffee consumption and blood homocysteine. The subjects generally had nine or more cups of coffee a day. No effect was found with decaffeinated coffee. In contrast, no association was found between coffee consumption or caffeine intake and the total blood homocysteine in a sample of the atherosclerotic risk in community study (Nieto and Comstock, 1997). In another study it was observed that the consumption of 1 L of strong unfiltered boiled coffee everyday for 2 weeks was associated with a 10% increase in mean plasma total homocysteine concentration (Grubben et al., 2000). However, this extreme coffee intake may affect diet composition and other factors, which may influence plasma homocysteine (Vollset et al., 2000).

Elevated plasma homocysteine levels were correlated with coffee intake mainly in people with low to intermediate homocysteinemia (Nygard et al., 1997). Therefore the link between the coffee–dependent increase in homocysteine and overall cardiovascular risk within the general population may not be straightforward to establish.

Daily intake of one liter of unfiltered French press coffee for two weeks increased homocysteine levels by 10% after a washout period of 8 weeks. The researchers claim that the 10% rise seen in plasma homocysteine by drinking 6 cups of unfiltered coffee a day could increase cardiovascular risk by 10% if homocysteine is an independent casual factor (Vollset et al., 2000).

There is clear evidence that high homocysteine levels are linked to poor nutrition, in particular, deficient levels of folate and vitamins B6 and B12 (Selhub, 1997; Lindenbaum, 1994). An adverse effect on homocysteine levels from coffee consumption was observed and the lead scientist stated, "The largest variation

in plasma total homocysteine was observed in subjects with low intakes of dietary folate, mostly determined by fruit and vegetable intake" (Grubben et al., 2000). Another work in 1999 demonstrated that people with sound diets showed no effect on their plasma homocysteine levels from all forms of coffee consumption. (Stolzenberg -Solomon et al., 1999).

Verhoef et al. (2002) reported that caffeine treatment had a much weaker acute effect on homocysteine concentration, wherein 48 subjects aged 16–65 years underwent 3 treatments (6 capsules providing 870 mg of caffeine/day) each lasting 2 weeks. The effects of caffeine were stronger in women than in men, but the effects of coffee did not differ significantly between men and women. It is concluded that caffeine is partly responsible for the homocysteine-raising. Coffee but not caffeine, affects homocysteine metabolism within hours of intake, although the effect is still substantial after an overnight fast. In summary, a slight increase in blood homocysteine in heavy coffee drinkers had been shown in several studies. The direct implication of coffee and the health significance of such an effect, have still to be demonstrated (Benoit et al., 2001).

Effects on Bone System

The effect of coffee on bone health and calcium metabolism was studied (Sakamoto et al., 2001). The potential role of caffeine, mainly through coffee consumption as a contributing factor of bone loss in humans has received a lot of attention. In recent years numerous studies have reported on caffeine consumption as a possible risk for osteoporosis.

Osteoporosis is a chronic degenerative bone disease that affects mainly, but not exclusively, post menopausal women, and the demineralization of bones leads to fractures. It has a common etiology that includes genetic, physiological, and environmental contributors. Among the factors, estrogen deficiency, smoking, heavy alcohol consumption, lack of exercise, obesity, and inadequate nutrition are believed to play significant roles in the development of this disease (Benoit et al., 2001).

Calcium Metabolism

Debry (1994) showed that caffeine increases calcium excretion in experimental animals. The urinary loss of calcium has been advocated as a significant factor affecting osteoporosis (Nordlin and Morris, 1989). The effect of caffeine on calcium intake economy in premenopausal women was reported by Heaney and Recker (1982). Other reports indicated that caffeine induces a significant acute calcium diuersis (Massey and Wise, 1984; Debry 1994; Heaney, 1998). However, subsequent investigation suggested that the increase in calcium excretion was followed by reduction in excretion, resulting in a net negative effect on calcium balance lower than previously thought (Kynast–Gales and Massey, 1994).

The effect of caffeine on calcium metabolism was addressed in a double blind, randomized placebo-controlled, cross-over metabolic study. The administration of 400 mg of caffeine over 19 days did not produce any effect on a total 24 hours calcium loss (Heaney and Recker, 1982; Barger–Lux and Heaney, 1995). However, a small negative balance effect was detected due to a slight difference in the calcium absorption efficiency. Massey et al. (1994) confirmed that caffeine only produced observable effects on calcium. Overall, the magnitude of the caffeine effect on calcium balance is low and it has been estimated that it could offset simply by the addition of one or two tablespoons of milk to a cup of coffee (Barger-Lux and Heaney, 1995). It is currently thought that at standard recommended calcium intake, caffeine is unlikely to have harmful effects on calcium bone economy. In the most recent United States Recommended Daily Allowances (USRDA), it was stated that the available evidence does not warrant a specific calcium intake recommendation for people with different caffeine intake.

Osteoporosis

Contradictory results have been obtained on the potential link between caffeine consumption and the risk of osteoporosis (Debry, 1994; Heaney, 1998). Caffeine, which increases urinary calcium excretion, is a risk factor for osteoporosis. Since a frequent result of osteoporosis is hip fracture, experiments were carried out to examine the effect of coffee drinking on the incidence of hip fractures (Kiel et al., 1990). A study conducted on 3170 individuals showed that hip fractures occurred in 135 subjects during 12 years of follow up. These relative risks were not elevated for 1.5–2 cups of coffee or 3–4 cups of tea per day. Consumption of more than 2.5 cups of coffee per day significantly increased the risk of fracture. However, other than coffee consumption, other factors may also be responsible like smoking, consuming high calorie foods, etc.

Some epidemiological studies have also suggested that caffeine may slightly increase the risk of fracture or may decrease bone density, but the majority of reports available failed to find any effects of caffeine (Debry, 1994; Heaney, 1998). A review of 23 observational studies indicated that 5 showed a negative effect of caffeine on bone health and 16 showed no effect, also two showed a partial effect (Heaney, 1998). A negative effect was proposed for women whose dietary intake of calcium is below the recommendations (Barrett-Connor et al., 1994; Harris and Dawson-Hughs, 1994).

The potential link between caffeine and bone health was evaluated on women who are still in the period of bone gain. Caffeine did not affect the rate of gain in spinal bones in women of 30 years age or less (Packard and Recker, 1996). Lloyd et al. (1998) revealed that caffeine at levels presently consumed by American teenage women was not correlated with total mineral bone gain or hipbone density at age 18.

Cardiovascular System

Numerous reports are available to describe the effect of coffee on the cardiovascular system. The circulatory effect of substances like theophylline, caffeine is complex and mediated in

part through antagonistic actions. The main actions appear to be the direct effects on the heart and the vascular tissues and the indirect effects through increased release of catecholamines and possibly the rennin angiotensin system (Robertson et al., 1978; Burghardt et al., 1982).

Studies had focused on the potential link between coffee consumption and cardiovascular studies in humans and have recognized end points of it such as myocardial infarction and arrhythmias. Other reports being investigated on the possible effects of coffee on known cardiovascular risk factors are hypertension, elevated blood cholesterol, and more recently, increased homocysteine levels.

Conflicting results were obtained from epidemiological studies on coffee and coronary heart disease and suggested that this conflict could be due to other factors including bio-chemical constituents other than caffeine (Rosmarin, 1989). It was reported that coffee might induce cardiac arrhythmias, including potentially lethal ventricular ectopy in certain individuals. However, the chronic ingestion of coffee does not induce hypertension, but only a small, short-lived increase in blood pressure as reported. He suggested that coffee is a safe beverage in moderate amounts in healthy persons (Stavric, 1992).

Stensvold et al., (1989) reported the relative risk of coronary deaths with coffee consumption. The results showed that in men the difference between the daily consumption of 9 or more and from 1 to 4 cups of filter coffee corresponded to a relative risk of 0.94. This was based on a cross–sectional study of more than 29,000 participants in which coffee drinking was correlated with serum cholesterol levels and blood pressure.

The association between the number of cups of coffee consumed per day and deaths from heart disease was examined while taking other major coronary risk factors into account (Tverdal et al., 1990). The duration of the study was 6.4 years. Total serum cholesterol, high-density lipoprotein cholesterol, blood pressure, height, and weight were measured. Self-reported information of smoking, physical activity and coffee drinking was recorded. But the method of brewing coffee was not recorded. A total of 168 men and 16 women died of coronary heart disease. Mean cholesterol concentration increased in the coffee consumption group. The relation, risk for men who consumed less than one cup to those who consumed nine or more cups of coffee per day was estimated to be 2.2. For women the corresponding data was 5.1. This study suggests that high coffee consumption is related to death from coronary heart disease, over and above its effect of raising cholesterol concentration (Stavric, 1992).

The effect of coffee or caffeine intake on other risk factors for cardiovascular diseases, such as oxidizability of LDL particles, vascular proliferation, or thrombosis is little known. However, prospective cohert studies from the United States and Western Europe mostly failed to find a link between coffee intake and cardiovascular disease (Myers et al., 1992; Greenland, 1993; Kawachi et al., 1994).

Effects on the Heart

Caffeine increases both the force and the rate of contraction in isolated mammalian preparations (de Gubareff and Sleator, 1965). It has been reported that for caffeine the duration of the action potentials increased isolated atria at low frequencies of stimulation, resembling catecholamine action, whereas at high frequencies of stimulation the rise in the action potentials was faster and the duration shorter, resembling the action of calcium (Gualtierotti, 1955a, 1955b, Shibata and Hollander, 1967). High consumption of boiled coffee (decanted without filtering), a brew particular to Scandinavian countries, is related to coronary heart disease (Tverdal et al., 1990). In Scandinavia, a substantial percentage of the decline in serum cholesterol over the years has been attributed to the switch from boiled to filtered coffee, leading to a reduction in cardiovascular disease (Tverdal et al., 1990; Johansson et al., 1996).

Several mechanisms may explain the stimulant effects of caffeine and other xanthines on the heart muscle tissue. An increase in plasma adrenaline and noradrenaline by about 100 and 50% respectively was observed, when caffeine (250 mg) was supplemented (Robertson et al., 1978). Another hypothesis suggests that the xanthines inhibit phosphodiesterase, leading to increased levels of cyclic AMP, which in turn is followed by increased glycogenolysis and a rise in glucose – 6 – phosphate levels (Ellis, 1956; 1959; Belford and Feinleib, 1962). But, caffeine was found to be less potent than other xanthines and that even maximal doses of caffeine were found to inhibit phosphodiesterase by only a few percent (Beavo et al., 1970). The potency of caffeine to release calcium from the cistern of the sarcoplasmic reticulum suggests another mechanism of action. The effect had been demonstrated for caffeine with low therapeutic doses in skeletal muscle preparations (Katz et al., 1977), and similar effects in skeletal and cardiac muscle tissue have also been shown (Blinks et al., 1972).

Effects on Blood Vessels

Therapeutic doses of caffeine produced a decline in peripheral resistance, which is generally found modest, independent of arterial blood pressure, and temporary (Ogilvie et al., 1977). Because of its modest effect it is less used in the treatment of peripheral vascular disease. Certain studies had shown that the xanthines have particularly been observed to increase coronary blood flow. This increase, however, hardly contributes to an increase in the oxygen supply to the cardiac muscle or may be an indirect consequence of the simultaneous increases in heart work. In contrast to the debating action of xanthines, including that of caffeine on peripheral blood vessels, these substances are known to increase cerebrovascular resistances (Moyer et al., 1952). This effect is believed to be the clinically observed relief for migraine and other types of headaches caused by cerebrovascular distinction.

Effects on Medullary Centers

Caffeine is considered to be more active in stimulating the medullary respiratory vasomotor and vagal centers than theophylline and theobromine, which is more potent in its effects like cardiac functions, coronary dilation, smooth muscle relaxation, and diuresis. These effects were also found to be modest and the stimulation of the respiratory functions may become apparent only in cases where these centers are depressed by drugs like barbiturates, opioids etc. Electrophysiological studies had shown increases in firing rates of neurones in the brain stem reticular formation of the rat after administration of 1–2 mg/kg caffeine (Foote et al., 1978).

Myocardial Infarction

In a meta–analysis involving a total of 1,43,030 people, it was concluded that there is no association between coffee consumption and coronary heart diseases (Myers, 1992). The relationship between coffee consumption and myocardial infarction has been assessed in many prospective surveys. Most of the studies did not show any correlation between moderate coffee drinking and myocardial infarction, while the absence of any link to heavy coffee consumption is less clear (Debry, 1994). In another study a higher risk of myocardial infarction was seen in women who consumed more than five cups of coffee a day (Palmer et al., 1995). In a recent case control study neither caffeinated nor decaffeinated coffee was associated with the risk of myocardial infarction, even for those drinking more than four cups a day (Sesso et al., 1999).

There is no clear cut evidence showing any correlation between coffee consumption and myocardial infarction for moderate coffee drinkers, but the risk at the same time cannot be ruled out for high coffee consumers.

Arrhythmias

Experimental, epidemiological, and clinical reports explain the defects of coffee on the heart rate. Caffeine has been the focus of many reports, being a pharmacologically active compound, on arrhythmias. The results suggest that moderate amounts of coffee or caffeine do not affect cardiac rhythm.

In a review on arrhythmias it was judged that caffeine ingestion at levels equivalent to five or six cups of coffee a day does not affect the severity or frequency of cardiac arrhythmias in healthy subjects or patients with coronary heart disease or persons with known ventricular ectopy (Myers, 1991). A similar result was also found in an epidemiological report on more than 125,000 people, which did not find any influence of coffee consumption on death attributed to cardiac arrhythmias (Klatsky et al., 1993).

The information on the relationship between arrhythmias and coffee consumption was further confirmed saying that moderate caffeine is unlikely to affect the heart rate in both normal people and patients with heart disease (Newby et al., 1996; Arciero et al., 1998; Daniels et al., 1998, Myers, 1998).

Blood Pressure

Surveys on animal models and humans show that caffeine can interfere with purinergic receptors and can therefore antagonize the vasodilating effect of adenosine. The pharmacological effect increases peripheral vascular resistance and may therefore induce hypertension. A caffeine dependent stimulation of the sympathetic nervous system activity resulting in neither increased plasma nor epinephrine had also been proposed as a possible trigger for high blood pressure (Debry, 1994). Several studies have been carried out, involving acute caffeine dosing in the presence or absence of stress, or chronic exposure to caffeine.

The potential link between coffee consumption and blood pressure in the general population has been addressed in several epidemiological studies. The results are variable and inconsistent (Green et al., 1996; Myers, 1988, 1998) and these suffer from methodological limitations. Few reports had shown no association, a positive association, and inverse relationships with systolic and diastolic blood pressure (Green et al., 1996). One study found a curvilinear association with abstainers and high users (more than nine cups) showing no difference in blood pressure, but with those taking one to four cups per day showing a slight rise (Stensvold et al., 1989).

a) Acute Dosing

Effects of acute dosing are either a small or a transient rise within the first few hours following the dosing. Increase in blood pressure was seen in people where caffeine was restricted for variable periods of time before dosing. Abstinence from caffeine, for periods as short as 24 hours, may lead to a partial loss of tolerance to caffeine (Benoit, 2001). Physical and mental stress is known to increase blood pressure. In a review, it was concluded that, overall, stress plus acute dosing of caffeine cause small increases in blood pressure in caffeine naïve individuals (Green et al., 1996).

b) Chronic Exposure

The studies on repeated/chronic exposure to caffeine are in agreement with that of acute dosing (Green et al., 1996; Myers, 1988, 1998). Many of them did not find any effects on blood pressure while some reported a small increase. When increase was found the magnitude of the effect was very little than that found in acute dosing (Myers, 1998). In a recent meta–analysis of 11 controlled clinical trials in which the effects of long-term coffee drinking on blood pressure was assessed, a small increase of 2.4 and 1.2 mm Hg were found respectively, for systolic and diastolic pressure (Jee et al., 1999). Compared to other factors known to affect blood pressure on a daily basis, the clinical significance of the increases, if any, resulting from caffeine ingestion was considered to be minimal (Green et al., 1996; Myers; 1998).

c) Potential Effects on Hypertensive People

Studies show that there is no effect of caffeine on ambulatory blood pressure. For example two weeks of caffeine use versus placebo were compared in hypertensive patients who were treated. No effect on blood pressure was observed.

Similarly in untreated patients with borderline hypertension, caffeine use over two weeks had no effect on ambulatory blood pressure (Mac Donald et al., 1991).

Effects on Cholesterol, Triglycerides, and Lipoprotein

It is increasingly acknowledged that foods contain non-nutritional constituents, which may possess biological activities compatible with beneficial health effects. The full assessment of such food components requires a thorough investigation of both efficacy and safety. The coffee specific diterpenes Cafestol and Kahweol (C+K) can be considered as interesting examples of such biologically active food components.

Cholesterol

It is well documented that cafestol potently raises cholesterol in humans (Weusten et al., 1994; Ugert et al., 1997). In a meta–analysis of 11 experiments with cafestol rich preparations each 10 mg of cafestol consumed per day (equivalent to 2–3 cups of coffee brewed without the use of a paper filter) raises serum cholesterol by 0.15 mmol/L (Urgert and Katan, 1997). Coffee beans of commercial blends will inevitably contain the cholesterol raising compound cafestol. Filtered coffee does not contain kahweol or cafestol, as the diterpenes are retained by paper filters (Van et al., 1991). Diterpene levels are low in instant coffee also (Urgert et al., 1995b); an experiment explained that "boiled" coffee indeed raised cholesterol, whereas in a parallel group, filtered coffee had no effect (Aro et al., 1987). The brewing method thus made the crucial difference (Table 5).

High consumption of boiled coffee (decanted without filtering), a brew particular to Scandinavian countries, had been clearly associated with elevated levels of serum cholesterol (Urgert and Katan, 1997). In Scandinavia, a substantial percentage of the decline in serum cholesterol over the years has been attributed to the switch from boiled to filtered coffee (Tuomilehto and Pietinen, 1991). Subsequent epidemiological and controlled clinical studies have further confirmed that the hypercholesterolemic effect of coffee was dependent on the method of preparation of the coffee brew.

The coffee brews with moderate amount of diterpenes in it like Mocha and Espresso coffee appear harmless with consumption of few cups per day. The ones which are rich in diterpenes, a recommendation to limit their use in favor of filtered or instant coffee seems justified in patients with a high cholesterol level or an increased coronary risk (Urgert and Katan, 1997).

Cholesterol Raising Factor. Several reports attempted to find the factor in boiled coffee that raised the cholesterol level. Ingestion of 1.3 g of boiled coffee per day by 10 volunteers increased the serum cholesterol by 23% (Zock et al., 1990). Experiments found that boiled coffee had 1–2g of lipid/liter, whereas filtered coffee hardly had any (Van et al., 1991). This showed that the cholesterol-raising factor was a lipid. Another experiment showed that ingestion of 148 mg of purified diterpene alcohol per day raised cholesterol by 32% and similar raises were observed with purified diterpene esters. (Heckers et al., 1994; Weusten et al. 1994; Urgert et al., 1997). Cafestol alone and the mixture of cafestol and kahweol (63 mg) was given to 10 volunteers and cholesterol levels were monitored. Cafestol raised the cholesterol by 17% whereas the mixtures of 60 mg of cafestol plus 51 mg of kahweol per day increased the cholesterol by a further 2% only (Urgert et al., 1997). Thus the content of cafestol was the main factor contributing to the rise in cholesterol than kahweol.

In a trial of eleven humans given supplements of known diterpene content, the serum total cholesterol was found to be raised by 0.13 mmol / liter (5.0 mg / dl) with each 10 mg of cafestol and by 0.02 m mol / liter (0.9 mg / dl) with each 10 mg of kahweol consumed per day for four weeks. This indicates that cafestol raises the cholesterol level more than kahweol. The effect was linear up to 100 mg of cafestol/day (the amount present in 15–30 cups of boiled coffee). About 80% of the increase in total cholesterol was accounted for by LDL cholesterol and the rest was due to rise in very low-density lipoproteins. HDL (High density lipoproteins) may fall slightly when cafestol and kahweol are ingested (Urgert et al 1997; Weusten et al., 1994; Zock et al., 1990).

The mechanism by which coffee diterpenes affect lipid metabolism is by far unknown. But a study shows the involvement of the LDL receptor, which is synthesized / generated on all membranes and is responsible for the removal of LDL cholesterol from the blood stream. Cafestol decreased uptakes of LDL cholesterol into human fibroblasts (Halvorsen et al., 1994) and hepatoma cells (Halverson, 1996) but raised it in an intestinal cell line (Ranheim et al., 1995). More studies are required to clarify this discrepancy.

Triglycerides

A marked increase in serum triglyceride was found when volunteers were supplemented with boiled coffee. Again cafestol was the major factor responsible for the increase. Cafestol alone raised triglycerides by 86% while kahweol increased the response by only 7% (Urgert et al., 1997). However most of the rise in triglycerides may subside with chronic intake of coffee diterpenes.

Lipoprotein

Lipoprotein, which consists of an LDL particle attached to apolipoprotein is a risk of cardiovascular diseases (Dahlen, 1994). Most of the rises in total LDL cholesterol caused by coffee diterpenes persist with chronic intake, whereas most of the rise in triglycerides subside coffee diterpenes which reduces the serum lipoprotein in the first months of intake only (Urgert et al., 1997).

Table 5 Effect of coffee diterpenes* on serum cholesterol

Coffee type	C or k[@]	C[#]	K[#]	C [$]	K[$]	C (Mean)	K (Mean)	Serum cholesterol (mmol/liter)
Paper filtered	0.1	0.1	0.1	<0.1	<0.1	0.1	0.1	<0.01
Instant	0.1	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Percolator	—	0.3	0.3	—	—	0.3	0.3	0.02
Mocha	—	1.1	1.4	2.3	2.3	1.7	1.9	0.13
Espresso	3.6	1.5	1.8	1.0	1.0	2.0	2.1	0.15
Cafeteria	1.6	3.5	4.4	—	—	2.6	3.0	0.20
Turkish	3.4	3.9	3.9	5.3	5.4	4.2	4.2	0.32
Boiled	8.4	3.0	3.9	7.2	7.2	6.2	6.5	0.47

[+] Qunatity - mg/cup; Intake - five cups per day.
[@] Ratnayake et al., 1993; [#]Urgert et al. 1995; [$]Gross et al., 1997.

Other Effects

Risk of Liver Disease

The intake of coffee diterpenes (Van Rooji, 1995; Weusten 1994) or unfiltered coffee (Urgert, 1996; Wensten, 1994) raised the serum activity of alanine amino transferase in volunteers. A rise of liver enzyme activity in serum may indicate injury to hepatocytes. This is not due to cholestasis, as coffee diterpenes reduce rather than raise the serum activity of γ- gutamyl transferase and alkaline phosphatase (Urgert et al., 1995a). It is unlikely that a perturbation of liver cell function explains the effects of coffee diterpenes on blood lipids, because both cafestol and kahweol raise amino transferases, but kahweol had little effect on blood lipids (Urgert, 1997).

Clinically relevant damage to liver cells in healthy subjects drinking unfiltered coffee appears unlikely and the risk of liver disease cannot be ruled out as patients with elevated alanine aminotransferase levels would be preferred to reduce their coffee consumption to not more than a few cups of boiled Turkish or cafetiere coffee (containing high diterpene content) per day.

Risk of Asthma

Coffee prevented the clinical manifestation of bronchial asthma. When a double-blind study was done on 10 asthmatic patients who were given 7 mg/Kg body weight of caffeine before 2 hrs of exercise, it prevented exercise induced broncho constriction (Kivity et al., 1990). After a dose of 3.5 mg caffeine /Kg. there was a trend towards improvement.

Effect on Immune System

Studies showed that consumption of coffee modified the immune system. The findings suggest that taking 5 cups/day of instant coffee for 5 weeks brought up this effect (Melamed et al., 1990). The abstinence from coffee, suppressed the lymphocyte response to mitogen stimulation, but increased the proportion of suppressor T-cells and natural killer cells.

Ergogenic Effect

In addition to steroid and hormones, caffeine has also become a compound of interest because some athletes who have used caffeine as an ergogenic aid and reported that it apparently enhanced performance in endurance sports (Jurisic and Randic, 1990). Few studies also showed that subjects exercised significantly longer, performed more physical work, or experienced longer neuromuscular reflex response time when they consumed caffeine (Jacobson and Edwards, 1990)

Thermogenic Effect

In humans, caffeine was known to stimulate thermogenesis by an unknown mechanism and its effect on body weight has not been studied. A study found that a cup of coffee (4 mg caffeine/kg body weight) consumed with a meal produced a significantly greater thermic response than that with a cup of decaffeinated coffee, and this difference can be almost totally accounted for by the thermogenic effect of the caffeine (Acheson et al., 1980). It appears that only a few different doses of caffeine have been studied and other constituents of coffee, other than caffeine, may influence lipid metabolism.

Hepatoprotective Effect

Coffee was found to antagonize the promoting effects of hepatitis B and C infection on cirrhosis development, suggesting a protective effect of coffee on non-alcoholic cirrhosis (Benoit et al., 2001). Also, coffee consumption has repeatedly found in clinical and epidemiological studies to reduce the levels of serum γ-glutamyl-1-transferase a marker of hepatobiliary diseases (Tanaka et al., 1998), hence a protective effect on liver.

Antimicrobial Esffect

Antimicrobial effect may be due to the mutagenic effect of coffee on the microbes (Alan and Jane, 1994). Roasted coffee was shown to possess antibacterial activity against both gram-positive and gram-negative bacteria including *Streptococcus mutans*, which is considered to be a causative agent for dental caries in humans.

Diabetes Mellitus (Type 2)

Coffee is a rich source of caffeine, which acutely reduces insulin sensitivity but also possesses as potentially beneficial effects. The association between coffee consumption and the risk of clinical Type 2 diabetes was investigated in a population-based cohort of men and women aged 30–60 years. Individuals who drank more than 7 cups of coffee/day were 0.50 times (95% confidence interval 0.35–0.72) as likely to develop type 2 diabetes. It is concluded that high coffee consumption is associated with a substantial reduction of risk of type 2 diabetes (Dam et al., 2002).

SUMMARY

Coffee has been enjoyed as a drink by millions of people worldwide for over at least one thousand years. Coffee contains a complex mixture of chemical compounds. Substances that dissolved in water to form the beverage during brewing are classified as nonvolatile components (viz., caffeine, trigonelline, chlorogenic acid, phenolic acids, amino acids, carbohydrates, and minerals). Volatile aroma components include organic acids, aldehydes, ketones, esters, amines, and mercaptans. Some components, particularly those related to the aroma, are produced during roasting of the green beans.

Although coffee contains a wide variety of substances, it is generally accepted that caffeine is responsible for many of its physiological effects. Caffeine influences the central nervous system in a number of ways, mainly it enhances alertness, concentration, and mental and physical performance. A cup (150 ml) of instant coffee contains about 60 mg caffeine, filter coffee contains about 85 mg, and a decaffeinated beverage contains only 3 mg of caffeine.

Coffee develops stimulating effects on the central nervous the system, the heart, and blood circulation, which are mainly caused by caffeine. Extensive epidemiological studies conclude that there is no correlation between coffee consumption and certain risk factors such as hypertension, heart infarction, diabetes, gout, or cancer diseases. Furthermore, there was no evidence that coffee or its caffeine content is able to induce genetic alterations or even malformations.

Coffee beans are one of the richest dietary sources of chlorogenic acid for many consumers. It has been reported that a cup (150 ml) of arabica coffee contains between 50–150 mg of chlorogenic acid whereas a cup of robusta coffee contains between 50–270 mg. The amount of chlorogenic acid or caffeic acid available to act as an antioxidant in vivo will depend on absorption from the gut. It has recently been demonstrated that humans absorb about 33% of ingested chlorogenic acid and about 95% of ingested caffeic acid, when chlorogenic and caffeic acids were ingested at 2.8 mmol and 2.8 mmol caffeic acid respectively on separate days (Olthof et al., 2001).

High consumption of boiled coffee (decanted without filtering), a brew particular to Scandinavian countries, may cause mild elevation of plasma cholesterol concentration in some people due to the presence of cafestol and kaweol. But instant and filter coffee have no such effects. The coffee brews with moderate amount of diterpenes like Mocha and Espresso coffee which appear to be harmless with consumption of 3–4 cups per day.

There is no evidence that coffee increases the risk of heart disease. Moderate consumption of coffee does not increase cardiac arrhythmias. In some sensitive individuals, ingestion of coffee after a period of abstinence may cause a temporary rise in blood pressure but there is no persistent hypertensive effect in the long term. There is no proof that coffee increases the risk of cancer of the female breast, ovary, pancreas, or kidney. It is now accepted that cigarette smoking primarily causes the small increased risk of bladder cancer sometimes associated with coffee drinking. The reports indicate that coffee protects against colon cancer, male breast cancer, and gallstone disease.

Reports suggest that coffee does not promote indigestion in the majority of people, although it is known to increase heartburn and this effect is not large enough to justify advising people with gastro-oesophageal reflux disease to abstain from drinking coffee. There is no evidence that coffee increases the risk of developing peptic ulcer disease. Research studies advocate that modest consumption of coffee has no effects on pregnancy as well as on infants.

Coffee has been linked to an increasing number of potential health benefits, including protection from Parkinson's disease. Furthermore, few studies suggest that it might also protect against liver cancer and type 2 diabetes. The relationship between coffee consumption and diabetes is an area of active investigation but no clear picture has emerged so far. Available evidence suggests that coffee might also protect against liver cirrhosis.

Harmful effects of coffee are associated with people who are sensitive to stimulants. Beyond this there is no evidence that coffee intake is connected with adverse health effects. Therefore the moderate consumption of 3–4 cups of instant or roasted coffee per day, assuming an average caffeine concentration of 60-85mg per cup, is good for human health (Benoit et al., 2001).

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REFERENCES

Abraham, S. K. (1991). Inhibitory effect of coffee on the genotoxicity of carcinogens in mice. *Mutat. Res.* **262**:109–111.

Abraham, S. K. (1989). Inhibition of in vivo genotoxicity by caffeine. *Food Chem Toxicol*. **27**:787–792.

Acheson, K. J., Zahorskia-Markiewicz, B., Pittet, P., Anantharaman, K., and Jequier, E. (1980). Caffeine and coffee : their influence on metabolic rate and substrate utilization in normal wt. and obese individuals. *Am. J. Clin. Nutr.*, **33**:989–997.

Aeschbacher, H. U. and Jaccaud, E. (1990). Inhibition by coffee of nitrosourea-mediated DNA damage in mice. *Food Chem Toxicol*. **28**:633–637.

Aeschbacher, H. U. (1988). Mutagenicity of coffee, In *Coffee, Vol. 3: Physiology,* by Clarke, R. J. and Macrae, R. (Eds.), Elsevier Applied Science, London, 195–213.

Aeschbacher, H. U. (1984). Mutagenesis of coffee. *Trends pharmacol.Sci.* **5**:1–2.

Alan, H. V. and Jane, P. S. (1994). Coffee. *Beverages.* **2**:191–236.

Anon. (2004). Questions about coffee and health, *Indian coffee*, **68**:31–34.

Anon. (2004a). Coffee and Health, *Indian Coffee*. **68**:5.

Arciero, P. J.,Gardner, A. W., Benowitz, N. I., and Pochlman , E. T. (1998). Relationship of blood pressure ,heart rate and behavioural mood state to nor epinephrine kinetics in younger and older men following caffeine ingestion. *Eur. J. Clin. Nutr.* **41**:334–337.

Aro, A., Tuomilehto, J., Kostianen, E., Uusitalo, V. and Pietinen, P. (1987). Boiled coffee increases serum low density lipoprotein concentration. *Metabolism*, **36**:1027–1030.

Barger-Lux, M. J. and Heaney, R. P. (1995). Caffiene and the calcium economy revisited. *Osteoporosis Int.*, **5**:97–102.

Barone, J. J. and Roberts, H. R. (1996). Caffiene consumption. *Food Chem Toxicol*., **34**:119–129.

Barr, H. M. and Streissguth, A. P. (1991). Caffiene use during pregnancy and child outcome: a 7-year prospective study. *Neurotoxicol. Teratol.*, **13**:441–448.

Barr, H. M., Streissguth, A. P., Martin, D. C. and Herman, C. S. (1984). Infant size at eight months of age: Relationship to maternal use of alcohol, nicotine and caffeine during pregnancy. *Pediatrics*, **74**:336–341.

Barrett-Connor, E., Chang, J. C. and Edelstein, S. L. (1994). Coffee associated osteoporosis offset by daily milk consumption . *J. A. M. A.* **271**:280–283.

Barter, R. (2004). A short introduction to the theory and practice of profile roasting, *Indian Coffee.* **68**:34–37.

Battig. (1985). The physiological effects of coffee consumption, In *Coffee: Botany Biochemistry and Production of beans and beverages*. The AVI publishing Company, INC, Westport, Connecticut. Ed.5. 394–439.

Beavo, J. A., Roger, N. l., Crafford, O. B., Hardmann, J. G., Sutherland. E. W. and Newman, E. V. (1970). Effects of xanthine derivatives on lipolysis and on adenosine3, 5-monophosphate phosphodiesterase activities. *Mol. Pharmacol.* **6**:597–603.

Belford, J. and Feinleib, M. R. (1962). The increase in glucose -6- phosphate content of the heart after the administration of isotropic catecholamines, calcium and aminophylline. *Biochem. Pharmacol.* 11: 987–994.

Belitz, H. D. and Grosch, W. (1999). Coffee, tea, cocoa. In Food Chemistry; Springer-Verlag: Berlin, 874–883.

Benedetti, M. O., Bower J. H., Maraganore, D. M., Mc Donnell, S. K., Peterson, B. J., Ahlskog, J. E., Schaid, D. J. and Rocca, W. A. (2000). Smoking alcohol and coffee consumption preceding Parkinson's disease: a case control study. *Neurology.* **55**:1350–1358.

Benoit, S., Christophe, C., Angelika, T. and Anne, C. (2001). Health effects and safety considerations, In *Coffee recent developments,* Agricultural Series By Clarke, R. J., and Vitzthum, O. G. (Eds.), 165–183.

Benowitz, N. C., Jacob, P., Mayan, H. and Denero, C. (1995). Sympathethomimetric effects of paraxanthine and caffeine in humans. *Clin. Pharmacol.Ther.* **58**:684–691.

Blair, C. A. and Shibamoto,T. (1984). Ames mutagenicity tests of overheated brewed coffee. *Food Chem Toxicol*. **22**:971–975.

Blinks, J. R., Olson, C. B., Jewell, B. R. and Braveny, P. (1972). Influence of caffeine and other methylxanthines on mechanical properties of isolated mammalian heart muscle. Evidence for a dual mechanism of action. *Circ. Res.* **30**:367–392.

Borlee, L., Lechat, M. F., Bouckert, A., and Mission, C. (1978). Le café, facteur de risqué pendant la grossesse? *Louvain Med*., **97**:279–284.

Brent, R. L. (1998). A Systematic Evaluation of the Reproductive Risks of Caffiene. International Life Sciences Institute (ILSI) North America Publishers, Washington, D.C.

Brooke, O. G., Anderson, H. R., Bland, J. M., Peacock, J. L. and Stewart, C. M. (1989). Effects on the birth weight of smoking, alcohol, caffeine, socioeconomic factors, and psychosocial stress. *Brit. Med.J.* **298**:795–801.

Burghardt, W., Geist, D., Grun, M., Staib, A.H. and Wernze, H. (1982). Does caffeine influence the sympathadrenal system, rennin-angiotensin-aldosterone-system and blood pressure? Serono symposium, *Endocrinology of Hypertension*. **50**:415–421.

Carvalho, V. D. de and Chalfoun, S. M. (1989). *Indian Coffee*, **53**:5.

Cavin, C., Holzhauser, D., Constable, A., Hugget, A. C. and Schilter, B. (1998). The coffee - specific diterpenes cafestol and kahweol protect against aflatoxin B1- induced genotoxicity through a dual mechanism. *Carcinogenesis*. **19**:1369–1375.

Cavin, C., Mace, K., Offord , E. A. and Schilter, B. (2001). Protective effects of coffee diterpenes against aflatoxin B1-indued genotoxicity: Mechanisms in rat and human cells. *Food Chem Toxicol*. **39**:549–556.

Cavin, C., Holzhaeuser, Scharf, G., Constable, A., Huber, W. W., Schilter, B. (2002). Cafestol and kahweol, two coffee specific diterpenes with anticarcinogenic activity. *Food Chem Toxicol*. **40**:1155–1163.

Chen, J. F., XuK, Petzer, J. P., Staal, R., Xu, Y. H., Beilstein, M. , Sonsalla, P. K., Castagnoli, K., Castagnoli Jr, N., and Schwarzschild, M. A. (2001). Neuroprotection by caffeine and A2A adenosine receptor inactivation in a model of Parkinson's disease. *J. Neurosci.* **21**:143.

Chou, D. T., Forde, J. H. and Hirsh, K. R. (1980). Unit activity in medical thalamus: comparative effects of caffeine and amphetamine. *J. Pharmacol. Exp. Ther.* **213**:580–585.

Chou, T. M. and Benowitz, N. L. (1994). Caffeine and coffee: effects on health and cardiovascular disease. *Comp. Biochem.Phys C*.,s **109c**:173–189.

Clifford, M. N. (1999). Chlorogenic acids and other cinnamates- nature, occurrence and dietary burden. *J. Sci. Food Agric.* **79**:362–372.

Cook, D. G., Peacock, J. L., Feyerabend, C., Carey, I. M., Jarvis, M. J., Anderson, H. R. and Bland, J. M. (1996). Relation of caffeine intake and blood caffeine concentrations during pregnancy to fetal growth: prospective population based study *BMJ* **313**:1358–1362.

Dahlen, G.H. Lipoprotein in cardiovascular disease. *Athereosclerosis.* (1994). **108**:111–126.

Daly, J. W. (1993). Mechanism of action of caffeine In: Garattini,S. (Ed) *Caffeine, Coffee and Health* Raven Press, New York. **97**–150.

Dam, R. M. and Feskens, E. J. M. (2002). Coffee consumption and risk of type2 diabetes mellitus. *Lancet* **360**:1477–1478.

Daniels, J. W., Mole, P. A., Shaffrath, J. D. and Stebbins, C. L. (1998). Effects of caffeine on blood pressure, heart rate, and forearm blood flow during dynamic leg exercise. *J. Appl. Physiol.* **85**:154–159.

De Flora, S. and Ramel, C. (1988). Mechanism of inhibitors of mutagenesis and carcinogenesis.Classifiation and overview. *Mutat. Res.* **202**:285–306.

De Kruijf, N., Schouten, T. and Vanderst, G. M. (1987). Rapid determination of benzo(a) pyrene in roasted coffee and coffee brew by HPLC with fluroscence detector. *J. Agr. Food Chem*. **35**:545–549.

Debry, G. (1994). Coffee and Health Gerard, Edition John Libbey, Eurotext, Paris, France.

Devasagayam, T. P., Kamat, J. P., Mohan, H. and Kesavan, P. C. (1996). Caffeine as an antioxidant: Inhibition of lipid peroxidation induced by reactive O_2 species. *B.B.A*. **1282**:63–70.

Dlugosz, L., Belanger, K., Hellenbrand, K., Holford, T. R., Leaderer, B. and Bracken, M. B. (1996). Maternal caffeine consumption and spontaneous abortion: a prospective cohort study. *Epidemiology*. **7**:250–255.

Donato, F., Boffetta, P., Fazioli, R., Aulenti, V., Gelatti, U. and Porru, S. (1997). Bladder cancer, tobacco smoking, coffee and alcohol drinking in Brescia, Northern Italy. *Eur. J. Epidemiol*. **13**:795–800.

Ellis, S. (1959). Relation of the biochemical effects of epinephrine to its muscular effects. *Pharmacol.rev.* **11**:469–479.

Ellis, S. (1956). The metabolic effects of epinephrine and related amines. *Pharmacol. Rev*. **8**:485–565.

Fall, P. A., Frederikson, M., Axelson, O. and Granerus, A. K. (1999). Nutritional and occupational factors influencing the risk of Parkinson's disease: A case control study in South Eastern Sweden. *Movement Disord.*, **14**:28–37.

Farrow, D. C. and Davis, S. (1990). Risk of pancreatic cancer in relation to medical history and the use of tobacco, alcohol and coffee. *Int. J. Cancer.* **45**:816–820.

Fenster, L., Hubbard, A. E. and Swan, S. H., Swan, Shanna H., Windham, G. C., Waller, K., Hiatt, R. A. and Benowitz, N. (1997). Caffeinated beverages, decaffeinated coffee, and spontaneous abortion. *Epidemiology*. **8**:515–523.

Fluckiger, R. and Winterhalter, K. H. (1976). In vitro synthesis of hemoglobin A_{ic} *Febs Lett*. **71**:356–360.

Folsom, A. R., McKenzie,D. R., Disgard, K. M., Kushi, L. H. and Sellers , T. A. (1993). No association between caffeine intake and post-menopausal cancer incidence in the Iowa women's health study. *Am. J. Epidemiol*. **138**:380–383.

Foot, W. E., Holmes, P., Pritchard, A., Hatcher, C., and Mordes, J. (1978). Neurophysiological and pharmacodynamic studies on caffeine and on interactions between caffeine and nicotinic acid in the rat. *Neuropharmacology.* **17**:7–12.

Forde, J. H. and Hirsh, K. R. (1976). Caffeine effect on reticular formation neurons in the deceberate cat. *NeuroScience Abstracts*. **2**:867.

Forrester, L. M., Neal, G. H., Judath, D. J., Glancey , M. J. and Wolf, C. R. (1990). Evidence for involvement of multiple forms of cytochrome P-450 in aflatoxin B1 metabolism in human liver. *P. Natl. Acad. Sci. U.S.A*. **87**:8306–8310.

Fuglsang, G., Nielsen, K., Kjaer Nielsen, L., Sennels, F. and Jacobsen, P., Thelle, T. (1989). The effect of caffeine compared with theophylline in the treatment of idiopathic apnea in premature infants. *Acta Paediatr. Scanndinavia*. **78**:786–788.

Furuhashi, N., Sato, S., Suzukhi, M., Hiruta, M., Tanaka, T. and Takahashi, T. (1985). Effects of caffeine ingestion during pregnancy. *Gynecol. Obstet. Inves*. **19**:187–191.

Galilea, L. I., Andueza, S., Leonarda, I., Pe a, M. P., and Cid, C. (2006). Influence of torrefacto roast on antioxidant and prooxidant activity of coffee. *Food Chemistry,* 94:75–80.

Gershbein, L. L. (1994). Action of dietary trypsin, pressed coffee oil, silmarin and iron salt on 1, 2-dimethylhydrazine tumorigenesis by gavage. *Anticancer Res*., **14**:1113–1116.

Gibbs, F. A. and Maltby, G. A. (1943). Effects on the electrical activity of the cortex of certain depressant and stimulant drugs–barbiturates, morphine, caffeine, Benzedrine and adrenaline. *J. Pharmcol. Exp. Ther.* **78**:1–10.

Giovannucci, E. (1998) Meta-analysis of coffee-consumption and Risk of colorectal cancer. *Am. J. Epidemiol*. **147**: 1043–1052.

Goldstein, L. and Murphree, H. B., Pfeiffer. (1963). Quantitative electroencephalography in men as a measure of CNS stimulation. *Ann. NY. Acad. Sci.* **107**:1045–1056.

Green,P. J., Kirby, R. and Suls, J . (1996). The effects of caffeine on blood pressure and heart rate: a review. *Ann.Behav. Med*. **18**:201–216.

Greenland, S. (1993). A meta analysis of coffee. myocardial infarction and coronary death . *Epidemology*. **4**:366–374.

Gross, G., Jaccaud, E. and Hugget, A. C. (1997). Analysis of the content of the diterpenes cafestol and kahweol in coffee brews. *Food Chem. Toxicol.* **35**:547–554.

Grubben, M. J., Boers, G. H. and Blom, H. J. (2001). Unfiltered coffee increases plasma homocysteine concentration in healthy volunteers: a randomized trial. *Am. J. Clin. Nutr.* **71**:480–484.

Gualtierotti, T. (1955a). Contribution of spinal centres to the action of caffeine on frog's spinal reflexes. *J.Physiol.* **128**:326–332.

Gualtierotti, T. (1955b). Variations in the frog 's spinal reflexes caused by the action on the brain of large doses of caffeine. *J.Physiol.* **128**:320–325.

Gubareff, T., de and, Sleator, W., Jr. (1965). Effects of caffeine on mammalian atrial muscle, and its interactions with adenosine and calcium. *J. Pharmacol. Exp. Ther.* **148**:202–214.

Halvorsen, B. (1996). Metabolism of low-density lipoprotein. Relation of certain nutrients, drugs and proteoglycans. *Ph.D Thesis Univ. Oslo, Norway*.

Halvorsen, B., Nenster, M. S., Christiensen, E. N., Huggett, A. C. and Drevon, C. A. (1994). Effects of cafestol on cholesterol metabolism in human skin fibroblasts. *Circulation* **90**:1–75.

Hammons, G. J., Fletcher, J. V., Stepps, K. R., Smith, E. A., Balentine, D. A. Harbowy, M. E., and Kadlubar, E. F. (1999). Effects of chemoprotective agents on the metabolic activation of the carcinogenic arylamines PhIP and 4-aminobiphenyl in human and rat liver microsomes. *Nutr. Cancer*. **33**:46–52.

Harris, C. C. (1991). Chemical and Physical carcinogenesis: advances and perspectives for the 1990s. *Cancer Res.* **51**:5023–5044.

Harris, S. S. and Dawson-Hughes, B. (1994). Caffeine and bone loss in healthy postmenopausal women. *Am. J. Clin. Nutr*. **60**:573–578.

Hayes, J. D., Ellis, E. M., Neal, G. E., Harrison, D. J. and Manson, M. M. (1999). Cellular response to cancer chemopreventive agents: contribution of the antioxidant responsive element to the adaptive response to oxidative and chemical stress. In: Downes, P. Wolf, R. and Lane, D. P. (Eds), Cellular Responses to Stress. *Biochemical Society Symposium*. *Portland Press, London* **64**:141–168.

Heaney, R. P. (1998). Effects of caffeine on bone and calcium economy. International Life Sciences institute (ILSI) North America Publishers, Washington, D.C.

Heaney, R. P. and Recker, R. R. (1982). Effects of nitrogen, phosphorous and caffeine on calcium balance in women. *J. Lab. Clin.Med*. **99**:46–55.

Heckers, H., Gobel, U. and Kleppel, U. (1994). End of the coffee mystery:diterpene alcohols raise serum low density lipoprotein cholesterol and triglyceride levels. *J. Intern. Med*. **235**:192–193.

Hellenbrand, W., Boeing, H., Robra, B. P., Seidler, A., Vielegge, P. Nischen, P., Joerg, J., Oertel, W. H., Schneider, E. and Ulm, G. (1996). Diet and Parkinson's disease 11: A possible role for the past intake of specific nutrients. Results from a self-administered food frequency questionnaire in a case-control study. *Neurology*. **47**:644–650.

Hsieh, C. C., Thanos, A., Mitropoulos, D., Deliveliotis, C., Mantzoros, C. S. and Trichopoulos, D. (1999). Risk factors for prostrate cancer: a case- control study in Greece. *Int. J. Cancer* **80**:699–703.

Huber, W. W., McDaniel, L. P., Kaderlik, K. R., Teitel, H., Lang, N. P. and Kadlubar, F. F. (1997). Chemoprotection against the formation of colon DNA adducts from the food-borne carcinogen 2-amino, 1-methyl–6-phenylinidazo[4,5}pyridine (PhIP) in the rat. *Mutat.Res.* **376**:115–122.

Huber, W. W., Teiel, H., King, R. S., Mc Daniel, L. P., Wiese, R., Harris, G. J., Mulder, F.F., Kadlubar, F. F. and Schultte-Hermann, R. (2000). Modifiation of the enzymes N-acetytransferase and glutathione-S-transferase as a potential chemoprotetive mechanism of the coffee components Kahweol and kafestol in the rat. *N-S Arch.Pharmacol.* **357**:134.

Huber, W. W., Prustomersky, S., Lang, H., Grasl-Kraupp, B., Wurzer, G., Scharf, G., Turesky, R. J. and Schulte-Hermann, R . (2000a). Chemoprotection by the coffee components kahweol and cafestol :potential mechanistic role of individual enzymes and organs. *N-S Arch.Pharmacol.* **361**:174.

IARC Working Group (1991). IARC Monographs on the Evaluation of the Carcinogenic Risks to Humans. Coffee, Tea, Mate, Methylxanthines and Methylglyoxal. *International Agency for Research on Cancer, Lyon*. 51.

Inoue, M., Tajima, K. and Hirose, K. (1998). Tea and coffee consumption and the risk of digestive tract cancers: data from a comparative case-referent study in Japan. *Cancer Causes and Control*. **9**:209–216.

Jacobson, B. H. and Edwards, S. W. (1990). Effects of ingested doses of caffeine on neuromuscular reflex response time in man. *Int. J. Sports Med.* **11**:194–197.

Jacobson, M. F., Goldman, A. S. and Syme, R. H. (1981). Coffee and birth defects. *Lancet*. **1**:1415–1416.

Jain, M. G., Hishop, G. T., Howe, G., Burch, J. D. and Ghadirian, P. (1998). Alcohol and other beverage use and prostrate cancer risk among Canadian men. *Int. J Cancer*. **78**:707–711.

Jee, S. H., He, J., Whelton, P. K., Suh, I. and Klag, M. G. (1999). The effects of chronic coffee drinking on blood pressure: a meta-analysis of controlled clinical trials. *Hypertension*. **33**:647–652.

Johansson, L., Drevon, C. A. and Bjornebor, G. E. A. (1996). The Norwegian diet during the last hundred years in relation to coronary heart disease. *Eur. J. Clin. Nutr.* **50**:277–283.

Jurisic, B. and Rendic, S. (1990). HPLC method for the determination of methylxanthines:application to the control of caffeine misuse in sport *Farmaceutski Glasnik*. **46**:61–71.

Kaplan G. B., Green Blatt, D. J., Ehrenberg, B. L., Goddard, J. E., Cotreau, M. M., Harmatz, J. S. and Shader, R. I. (1997). Dose dependent pharmacokinetics and pscychomotor effects of caffeine in humans. *J.Clin.Pharmacol.* **37**:693–703.

Kato, T., Takahashi, S. and Kikugawa K. (1989). Generation of heterocyclic amine-like mutagens during the roasting of coffee beans. *Eisei Kagaku*. **35**:370–376.

Katz, A. M., Repke, D. I. and Hasselbach, W. (1977). Dependence of ionophore and external and internal calcium ion concentrations. *J. Biol.Chem.* **252**:1938–1949.

Kawachi, I., Colditz, G. A. and Stone, C. B. (1994). Does coffee drinking increases the risk of coronary heart disease? Results from a meta analysis. *Br. Heart J*., **72**:269–275.

Kenichi Y., Kwang-Geun L. Hirotomo O. and Takayuki S. (2002). Antioxidant activity of heterocyclic compounds found in coffee volatiles produced by maillard reaction. *J. Agric. Food Chem*. **50**:5480–5484.

Kiel D. P., Felson, D. T., Hannan , M. T., Anderson J. J. and Wilson P. W. F. (1990). Caffeine and the risk of hip fracture: The Framingham Study. *Am. J. Epidemiol.* **132**:675–684.

Kikugawa, K., Kato, T. and Takashashi, S. (1989). Possible presence of 2-amino-3,4-dimethylimidazo [4,5-f]quinoline and other heterocyclic amine-like mutagens in roasted coffee beans . *J. Agric. Food Chem*. **37**:881–886.

Kim, J., and Levin, R. E. (1988). Mechanism of caffeine repression of mitomycin C induced reversion in Salmonella typhimurium strain TA94, *Microbios*, **53**:181–190.

Kivity, S., Ben Ahron, Y., Man, A. and Topilsky, M. (1990). The effect of caffeine on exercise –induced broncho constriction. *Chest*. **97**:1083–1085.

Klatsky, A. L., Amstrong M. A., and Friedman, G. D. (1993). Coffee, Tea and mortality. *Am. J. Epidemiol*. **3**:375–381.

Kroyer, G. T., Kretschmer, L. and Wasuettl, J. (1989). Antioxidant properties of tea and coffee extracts. *Agric. Food Chem. Consum. Proc. Eur. Conf. Food Chem. Vth*. **2**:433–437.

Kynast-Gales, S. A., and Massey, L. K. (1994). Effect of caffeine on circadian excretion of urinary calcium and magnesium. *J. Am. Coll. Nutr*. **13**:467–472.

La Vecchia, C., Ferraroni, M., Negri, E., D'Avanzo, B., Decarli, A., Live, F. and Franceschi, S. (1989). Coffee consumption and digestive tract cancers. *Cancer Res.* **49**:1049–1051.

Lam, L. K. T., Sparnins, V. L. and Wattenberg, L. W. (1982). Isolation and identification of kahweol and cafestol palmitate as active constituents of green coffee beans that enhance glutathione-S-transferase activity in the mouse. *Cancer Res.* **42**:1193–1198.

Lercker, G., Frega, N., Bocci, F. and Rodriguez-Estrada, M. T. (1995). High resolution gas chromatographic determination of diterpenic alcohols and sterols in coffee lipids. *Chromatographia*. **41**:29–33.

Leviton A. (1990). Methylxanthine consumption and the risk of ovarian malignancy. *Cancer Lett.* **51**:91–101.

Leviton, A., Pagano, M., Allred, E. N., and El lozy, M. (1994). Why those who drink the most coffee appear to be at increased risk of disease. A modest proposal. *Ecol. Food Nutr*. **31**:285–293.

Liberman, H. R. (1992) Caffeine In: Smith, A. P., Jones, D. M.(Eds). *Handbook of Human Performance 2, Academic Press, London*. 49–72.

Lindenbaum. J. (1994). Prevalence of cobalamin deficiency in the Framingham elderly population. *Am. J. Clin. Nutr.* **60**:2–11.

Lloyd, T., Rollings, N. J., Kieselhorst, K., Eggli, D. F., and Mauger, E. (1998). Dietary caffeine intake not correlated with adolescent bone gain. *J. Am. Coll. Nutr*. **17**:454–457.

MacDonald, T. M., Sharpe, K. and Fowler, G. et al . (1991). Caffeine restriction: effect on mild hypertension. *Brit. Med. J*. **303**:1235–1238.

Mandel, H. G. (2002). Update on caffeine: consumption, disposition and action. *Food Chem. Toxicol.* **40**:1231–1234.

Massey, L. K., and Wise, K. J. (1984). The effect of dietary caffeine on urinary excretion of calcium, magnesium, sodium and potassium in healthy young females. *Nutr. Res*. **4**:43–50.

Massey, L. K., Bergman, E. A., Wise, K. J., and Sherrad, D. J. (1994). Interactions between dietary caffeine and calcium on calcium and bone metabolism in older women. *J. Am. Coll. Nutr*. **13**:592–596.

Mc Mahon, M., Itoh, K., Yamamoto, M., Chnas, S. A., Henderson, C. J., Mlellan, L. I., Wolf , C. R., Cavin, C. and Hayes, J. D. (2001). The cap 'n' collar basic leuine zipper transcription factor Nrf2 controls not only the basal expression of intestinal detoxifiation and glutathione biosynthetic enzymes but also their induction by cancer chemopreventive agents. *Cancer Res.* **61**:3299–3307.

Melamed, I., Kark, J. D. and Spirer, Z. (1990). Coffee and the immune system. *Int.J. Immunopharmaco*. **12**:129–134.

Meleady, R. and Graham, I. (1999). Plasma homocysteine as a cardiovascular risk factor: Casual, consequential, or of no consequence. *Nutr. Rev*. **57**:299–305.

Miller, E. G., Formby, W. A., Rivera-Hidalgo, F., Wright, J. M., Hirsbrunner, P., and Sunahara, G. I. (1988). Kahweol and cafestol : inhibitoion of hamster buccal pouch carinogenesis by green coffee beans. *Oral Surgery* **65**:745–749.

Miller, E. G., McWhorter, K., Rivera-Hidalgo, F., Wright, J. M., Hirsbrunner, P. and Sunahara, G. I. (1991). Kahweol and cafestol: inhibitiors of hamster buccal pouch carcinogenesis. *Nutr. Cancer*. **15**:41–46.

Miller, E. G., Gonzales-Sanders, A. P., Couvillon, A. M., Binnie, W. H., Sunahara, G. I. and Bertholet, R. (1993). Inhibition of oral carcinogenesis by roasted beans and roasted coffee beans fractions. In: Association Scientific international du café, 15th ASIC International Colloquium on coffee. ASIC, Paris, France .

Moyer, J. H., Tashnek, A. B., Miller, S. I., Synder, H. and Bowman, R. O. (1952). The effect of theophylline with ethylenediamine (aminophylline) and caffeine on cerebral hemodyanmics and cerebrospinal fluid pressure in patients with hypertensive headaches. *Am. J. Med. Sci.* **224**:377–385.

Myers, M. G. (1991). Caffeine and cardiac arrhythmias. *Ann. Intern. Med*. **114**:147–150.

Myers, M. G. (1998). Cardiovascular effect of caffeine. *International Life Sciences Institute (ILSI). North America Publishers, Washington D. C*.

Myers, M. G. (1988). Effect of caffeine on blood pressure. *Arch. Intern. Med*. **148**:1189–1196.

Myers, M. G. and Basinki, A. (1992). Coffee and coronary heart disease. *Arch. Intern. Med.* **152**:1767–1772.

Nagao, M., Fujita, Y., Wakabayashi, K., Nukaya, H., Kosuge, T., and Sugimura, T. (1986). Mutagens in coffee and other beverages. *Environ. Health Persp.* **67**:89–91.

Nehling, A. and Debry, G. (1996). Coffee and cancer: A review of human and animal data. *World Rev. Nutr. Diet*. **79**:185–221.

Nehling, A. and Debry, G. (1994). Potential genotoxic, mutagenic and antimutagenic effects of coffee: A review, *Mutation Research,* **317**:145–162

Nehling, A., and Debry, G. (1994). Potential teratogenic and neurodevelopmental consequences of coffee and caffeine exposure: a review on human and animal data. *Neurotoxicol. Teratol*. **16**:531–543.

Newby, D. E., Neilson, J. M., Jarvies, D. R., and Boon, N. A. (1996). Caffeine restriction has no role in the management of patients with symptomatic idiopathic ventricular premature beats. *Heart.* **76**:355–357.

Nicoli, M. C., Anese, M., Parpinel, M. T., Franceschi, S. L. and Lerici, C. R. (1997). Loss and formation of antioxidants during food processing and storage. *Cancer Lett.* **114**:71–74.

Nieto, F. J. and Comstock, G. W. (1997). Coffee consumption and homocysteine: results from the artherosclerosis risk in the communities study. *Am. J. Clin. Nutr.* **66**:1475–1476.

Nygard, O., Refsum, H. and Ueland, P. M., et. al. (1997). Coffee consumption and plasma total homocysteine the hordaland homocysteine study. *Am. J. Clin. Nutr*. **65**:136–143.

Nygard, O. (1998). Major life style determinants of plasma total homocysteine study. *Am. J. Clin. Nutr*. **67**:263–270.

Nygard, O., Vollset, S. E., Refsum, H. and Ueland, P. M. (1997). Reply to F. J. Nieto *Am. J. Clin. Nutr*. **66**:1476–1477.

Obana, H. and Nakamura, S. (1989). Possible antimutagenic effect of an instant coffee. *Chemistry Express*. **4**:581–584.

Obana, H., Nakamura, S., and Tenaka, T. (1986). Suppressive effects of coffee on the SOS responses induced by UV and chemical mutagens. *Mutat. Res*. **175**:47–50.

Ogilvie, R. I., Fernandez, P. G. and Winsberg, F. (1977). Cardiovascular response to increasing theophylline concentrations. *Eur. J. Clin. Pharmacol.* **12**:409–414.

Olsen, J., Overvad, K., and Frische, G. (1991). Coffee consumption, birthweight and reproductive failures. *Epidemiology*. **2**:370–374.

Olthof, M. R., Hollman, P. C. H. and Katan, M. B. (2001). Chlorogenic acid and caffeic acid Are absorbed in humans *Journal of Nutrition.* **131**:66–71.

Oshaug, A., Buge, K. H. and Refsum, H. Diet , (1998). an independent determinant for plasma total homocysteine . A crosssectional study of Norwegian workerson platform in the North Sea. *Eur. J. Clin. Nutr.* **52**:7–11.

Packard, P. T. and Recker, R. R. (1996). Caffeine does not affect the rate of gain in spine bone in young women. *Osteoporosis Int*. **6**:149–152.

Palmer, J. R., Rosenberg, L., Sowmya, R., and Shapiro, S. (1995). Coffee consumption and myocardial infarction in women. *Am. J. Epidemiol*. **141**:724–731.

Popoli, P., Caporali, M. G. and Scotti de C. A. (1991). Akinesia due to catecholamine depletion in mice is prevented by caffeine. Further evidence for an involvement of adenosinergic system in the control of motility. *J. Pharm. Pharmacol.* **43**:280–281.

Probert, J. L., Persad, R. A., Greenwood, R. P., Gillatt, D. A. and Smith, P. J. B. (1998). Epidemiology of transitional cell carcinoma of the bladder: profile of an urban population in the south-west of England. *BJU International*. **82**:660–666.

Ramalakshmi, K. and Raghavan, B. (1999). Caffeine in coffee:Its removal why and how? *CRC Crit. Rev. Food Sci.* **39**:441–456.

Ranheim, T., Halvorsen B., Nenster , M. S., Christansen, E. N., Hugett A. C. and Drevon, C. A. (1995). Effect of a coffee lipid (cafestol) on regulation of lipid metabolism in CaCo-2 cells. *J. Lipid Res*. **36**:2079–2089.

Rao P. G. P., Ramalakshmi, K., Abraham K. O. and Shankaranarayana. M. L. (1993). Chemical analysis of coffee powder. *Indian Coffee*. **57**:3.

Ratnayake, W. M. N., Hollywood, R., O'Grady E. and Starvic, B. (1993). Lipid content and composition of coffee brews prepared by different methods. *Food Chem. Toxicol.* **31**:263–269.

Rice-Evans, C. A., Miller, N. J. and Paganga, G. (1996). Structure antioxidant activity relationships of flavonoids and phenolic acids. *Free Radical Bio. Med.* **20**:953–956.

Richelle, M., Tavazzi, I. and Offord, E. (2001). Comparison of the antioxidant activity of commonly consumed polyphenolic beverages (coffee, cocoa, tea) prepared per cup serving. *J. Agric. Food Chem.* **49**:3438–3442.

Robertson, D. Frohlich, J. C., Carr, R. K., Watson, J. T., Hollifuld, J. W., Shanol, D. G. and Dates, J. A. (1978). Effects of caffeine on plasma renin activity, catecholamines and blood pressure. *New Engl. J. Med.* **298**:181–186.

Rosenberg L. (1990). Coffee and tea consumption in relation to the risk of large bowel cancer: a review of epidemiological studies. *Cancer Lett.* **52**:163–171.

Rosmarin, P. C. (1989). Coffee and coronary heart disease: a review. *Prog. Cardiovasc. Dis.* **32**:239–245.

Ross, G. W., Abbott, R. D., Petrovitch, H., Morens, D. M. and Grandinetti, A., Tang, K. H., et al. (2000). Association of coffee and caffeine intake with the risk of Parkinson's disease. *J. Am. Med. Assoc.* **283**:2674–2679.

Sakamoto, W., Nishihira, J., Fujie, K., Iizuka, T., Handa, H., Ozaki, M. and. Yukawa, S. (2001). Effect of coffee consumption on bone metabolism. *Bone,* **28**:332–336.

Sanchez-Gonaza, I., Jimenez-Escrig, F. and Saura-Calixto, F. (2005). In vitro antioxidant activity of coffees brewed using different procedures (Italian, espresso and filter). *Food Chem.* **90**:133–139.

Scalbert, A. and Williamson, G. (2000). Dietary intake and bioavailability of polyphenols. *J. Nutr*. **130**:2073s–2085s.

Schilter, B., Perrin, L., Cavin, C. and Hugget, A. C. (1996). Placental glutathione S- Transferase (GST-P) induction as a potential mechanism for the anti-carcinogenic effect of the coffee-specific components cafestol and kahweol. *Carcinogenesis* **17**:2377–2384.

Schilter, B., Holzhaeuser, D. and Cavin, C. (2001). Health benefits of coffee. Proceedings of the 19th International Scientific Colloqium on Coffee. Trieste: 14–18.

Selhub, J. (1997). The Homocysteine/B Vitamin Story. ILSI Annual Meeting, Miami Beach, Florida.

Sesso, H. D., Gaziano, J. M., Buring, J. E., and Hennekens, C. H. (1999). Coffee and tea and the risk of myocardial infarction. *Am. J. Epidemiol*. **149**:162–167.

Shibata, S. and Hollander, P. B. (1967). Effects of caffeine on the contractability and membrane potentials of rat atrium. *Experientia*. 23:559.

Silverman, D. T., Swanson, C. A. and Gridley, G., et al. (1998). Dietary and nutritional factors and pancreatic cancer: a case-control study based on direct interviews. *J. Natl. Cancer I*. **90**:1710–1719.

Sivetz, M. and Foote, H. E., (1963). Coffee Processing Technolgy, Vol. I, The AVI Pub. Co.Inc., Westport, Connecticut.

Smith, A. (2002). Effects of caffeine on human behavior. *Food Chem. Toxicol.* **40**:1243–1255.

Smith, S. J., Deacon, J. M. and Chilvers, C. E. D. (1994). Alcohol, smoking, passive smoking and caffeine in relation to breast cancer in young women. *Brit. J. Cancer* **70**:112–119.

Stadler, R., Bexter, A., Wurzner, H. P. and Luginbuhl, H. (1990). A carcinogenicity study of instant coffee in Swiss mice. *Food Chem. Toxicol*. **28**:829–837.

Stadler, R. H., Turesky, R. J., Muller, O., Markovic, J. and Leong-Morgenthaler, P. M. (1994). The inhibitory effects of coffee on radical-mediated oxidation and mutagenicity. *Mutat. Res*. **308**:177–190.

Starvic, B., Stolz, D. R. and Klassen, R. (1983). Toxicants in food with special emphasis on mutagens in beverages, fruits and vegetables. *Toxicon. Suppl*. **3**:409–412.

Staton, C. K.and Gray, R. H. (1995). Effects of caffeine consumption on delayed conception. *Am. J. Epidemiol*. **142**:1322–1329.

Stavric, B. (1992). An Update on Research with Coffee/Caffeine. *Food Chem. Toxicol*. **30**:533–555.

Stein, K. and Susser, M. (1991). Miscarriage, caffeine and the epiphenomena of pregnancy: the causal model. *Epidemiology* **2**:163–167.

Stelzer, K. J., Koh, W. J., Kurtz, H., Greer, B. E., and Griuffin, T. W. (1994). Caffiene consumption is associated with decreased severe late toxicity after radiation to the pelvis. *Int. J. Radiat. Oncol.* **30**:411–417.

Stensvold, I., Tverdal , A., and Foss, O. P. (1989). The effect of coffee on lipids and blood pressure. Results from a Norwegian study, men and women, 40–42 years. *J. Clin. Epidemiol.* **42**:877–884.

Stensvold, J., and Jacobsen, B. J. (1994). Coffee and cancer: a prospective study of 43000 Norwegian men and women. *Cancer Cause. Control* **5**:401–408.

Stich, H. F., Risin, M. P. and Bryson, L. (1982). Inhibition of mutagenicity of a model nitrosation reaction by naturally occurring phenolics, coffee and tea. *Mutat. Res.* **259**:307–324.

Stolzenberg-Solomon R., Miller, E. R., Maguire, M. G., Selhub, J. and Appel, L. J. (1999). Association of dietary protein intake and coffee consumption with serum homocysteine concentrations in an older population. *Am. J. Clin. Nutr.* **69**:467–475.

Streissguth, A. P., Barr, H. M., Martin, D. C., and Herman, C. S. (1980). Effects of maternal alcohol, nicotine, and caffeine use during pregnancy on infant mental and motor development at eight months alcoholism. *Clin. Exp. Res*. **4**:152–164.

Sugimura, T., and Wakabayashi, K. (1990). Mutagens and carcinogens in food. In Mutagens and Carcinogens in the Diet .Edited by M.W Pariza, H. U., Aeschbacher, Felton J. S., and Sato, S. Wiley-Liss, Inc., New York. 1–18.

Svenningsson, P., Le Moine, C., Fisone, G. and Fredholm, B. B. (1999). Distribution, biochemistry and function of striatal adenosineA_{2A} receptors. *Prog. Neurobiol.* **59**:355–396.

Svilaas, A. Sakhi, A. K., Anderson, L. F., Svilaas, T., Strom, E. C., Jacobs, D. R., Ose, L. and Blomhoff, R. (2004). Intakes of Antioxidants in coffee, wine and vegetables and coorelated with plasma carotenoids in humans. *Journal of Nutrition*, **134**:562–567.

Tanaka, K., Tokunaga, S. and Kono, S. et al. (1998). Coffee consumption and decreased serum gamma-glutamyl transferase activities among male alcohol drinkers. *Int. J. Epidemiol*. **27**:438–443.

Tavani, A. and La Vecchia, C. (1997). Epidemiology of renal-cell carcinoma. *Nephrol*. **10**:93–106.

Tavani, A., Pregnolato, A., La Vecchia, C., Favero, A., and Franceschi, S. (1998). Coffee consumption and the risk of breast cancer. *Eur. J. Cancer Prev*. **7**:77–82.

The Wealth of India, first supplement series, Council of Scientific and Industrial Research, New Delhi (2001). 2: Cl-Cy, 120–148 and references cited there in.

Turesky, R. J., Stadler, R. H. and Leong-Moer Ganthaler (1993). P. M., ASIC. 15th Colloque, Montpellier, ASIC: Paris. 426–431.

Tverdal, A., Stensvold I., Solvol, K.,Foss , O. P., Lund-Larsen, P., and Bjartveit, K. (1990). Coffee consumption and death from coronary heart disease in middle aged Norwegian men and women. *Brit. Med. J.* **300**:566–569.

Ugert, R., Esseol, N., Vander Weg ,G., Kosmeiger-Schuil, T. G. and Katan, M. B. (1997). Separate effects of the coffee diterpenes cafestol and kahweol on serum lipids and liver transaminases. *Am. J. Clin. Nutr*. **65**:519–524.

Urgert, R., and Katan, M. B. (1997). The cholesterol-raising factor from coffee beans. *Annu. Rev. Nutr.* **17**:305–324.

Urgert, R., Mey boom, S., Kuilman, M., Rex Winkel, H. and Vissers, M. N., et al. (1996). Comparision of effect of cafetiere and filtered coffee on serum levels of liver aminotransferases and lipids: a six month randomnised controlled trial. *Brit. Med. J.* **313**:1362–1366.

Urgert, R., Schulz, A. G. M. and Katan, M. B. (1995a).Effect of cafestol and kahweol from coffee grounds on serum lipids and serum liver enzymes in humans. *Am.J. Clin. Nutr.* **61**:149–154.

Urgert, R., Vander Weg G., Kosmeiger-Schuil, T. G., Vande Bovenkamp, P. and Hovenier, R. (1995b). Levels of the cholesterol elevating diterpenes cafestol and kahweol in various coffee brews. *J. Agr. Food Chem.* **43**:2167–2172.

Van D., M., Katan, M. B., Van Viet, T., Demacker, P. N. M. and Stalenhoef, A. (1991). Cholesterol-raising factor from boiled coffee does not pass a paper filter *Arterioscler. Thromb. Vasc.Biol.* **11**:586–593.

Van Rooji J., Vander Stegen G. H., Schoemaker, R. C., Kroon, C., Burggraaf, J., Hollaar, L., Vroon, T. F., Smelt, A. H. and Cohen, A. F. (1995). A placebo controlled parallel study of the effect of two types of coffee oil on serum lipids and transaminases :identification of chemical substances involved in the cholesterol raising effect of coffee. *Am. J. Clin. Nutr.* **61**:1277–1283.

Venugopal, R. and Jaiswal, A. K. (1996). Nrf1 and Nrf2 positively (and) c-fos and Fra 1 negatively regulate the human antioxidant response element-mediated expression of NAD (P) H: quinine oxidasereductase$_1$ gene. *Pro. Natl. Acad. Sci. USA.* **93**:14960–14965.

Verhoef, P., Pasman, W. J., Vliet , T. V., Urgert, R. and Katan, M. B. (2002). Contribution of caffeine to the homocysteine-raising effect of coffee: a randomized controlled trial in humans. *Am. J. Clin. Nutr.* **76**:1244–1248.

Vollset, S. E., Nygård,O., Refsum, H. and Ueland, P. M. (2000). Coffee and homocysteine: An editorial. *Am. J. Clin. Nutr*. **71**:403–404.

Waler, G. R. and Suzuki, T. (1989). Caffeine metabolism by *coffea arabica* L. fruit. ASIC Thirteenth International Colloquium on Coffee. 351–361.

Walther, F., H., Erickson, R. and Sims, M. E. (1990). Cardiovascular effects of caffeine therapy in preterm infants. *Am. J. Dis. Child.* **144**:1164–1166.

Warburton, D. M. (1995). Effect of caffeine on cognition and mood without caffeine abstinence. *Psychopharmacology*. **119**:66–70.

Watanabe, H., Watanabe, K., Hagino, K. and Ikeda, H. (1978). Effects of dopaminergic stimulating agents caffeine and antipsychotic drugs and rotational behavior in mice with unilateral striatal 6-hydroxydopamine lesions. Yakugaku zasshi. **98**:1613–1618.

Wattenberg, L. W. (1985). Chemoprevention of cancer. *Cancer Res.* **45**:1–8.

Wattenberg, L. W. (1983). Inhibition of neoplasia by minor dietary constituents. *Cancer Res.* **43**:2448–2453.

Weiderpass, E., Partanen. T., Kaaks, R., Vainio, H., Porta, M., Kauppinen, T., Ojajarvi, A., Boffetta, P. and Malats, N. (1998). Occurrence trends and environmental etiology of pancreatic cancer. *Scand. J. Work Env. Hea*. **24**:165–174.

Weusten–vander Wouw, M. P. M. E., Katan, M. B., Viani, R., Huggett, A.C. Liardon, R., Lund-Larsen, P. G., Thelle, D. S., Ahola, I., Aro, A. Meyboom, S. and Beynen, A. C. (1994). Identity of the coffee raising factor from boiled coffee and its effects on liver function enzymes. *J. Lipid Res*. **35**:721–733.

Wurzner, H. P. Lindstrom, E. Vuataz, L. and Luginbuhl, H. (1977). A 2 year feeding study of instant coffees in rats. II Incidence and types of neoplasms. *Food and Cosmetics Toxicology* , **15**:289–296.

Yen, W., Wang, B., Chang L., and Duh, P. (2005). Antioxidant properties of coffee residues. *J. Agric. Food Chem.* **53**:2658–2663.

Zock, P. L., Katan, M. B., Merkus, M. P., Van Dusseldorp, M. and Harryvan, J. L. (1990). Effect of a lipid-rich fraction from boiled coffee on serum cholesterol. *Lancet* **335**:1235–1237.