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Coffee, Depression, Alcoholism and Drug Abuse – A Mini-review

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Abstract

Coffee is a natural product that when roasted and brewed delivers thousands of pharmacologically active compounds. Recent studies have revealed that 3 to 4 cups of coffee a day as pleasurable, low cost and convenient way to prevent diverse health problems. Depression, a common mood disorder, is a risk factor for alcoholism and substance abuse. In the last decade, epidemiological studies illuminating preventative effects of coffee have shown an inverse relationship of consumption with the risk of developing diseases affecting the central nervous system. The caffeine in coffee is widely studied and often assumed to be the key pharmacologically active ingredient if not the singular active agent. However other pharmacologically active constituents, primarily chlorogenic acids and related quinides, are demonstrating health benefits. These abundant components are capable of promoting 'in vivo' inhibition of morphine-inducedanti-nociceptive behavior in mice in the same order of magnitude as that reported for naloxone. This review explores the interplay among coffee, depression, alcohol and drug consumption. It explores the preventative effects of coffee and proposes a mechanistic theory to explain the action of coffee constituents on mood disorders such as depression and their consequences as alcoholism and drug abuse.

Introduction

Coffee is one of the most-consumed beverages in the world. Numerous studies have examined its health properties and whether the overall effects are positive or negative has been widely debated. This review focuses on a narrow range of effects, the interplay among coffee, depression, alcohol and drug consumption. Its purpose is to present coffee as more than just caffeine by presenting research on other pharmacologically active compounds.

Coffee and Depression

Depression, a common mood disorder, is the second leading cause of disability in the US and throughout the world. Genetic and environmental factors [1], such as alteration in serotonin transporter (5-HT T) and adverse life events increase the risk of a major depression episode [2]. When left untreated, depressed individuals are at risk of developing a host of medical illnesses ranging from cardiovascular diseases, obesity, diabetes and thyroid disease [3]. Depressed individuals and those with anxiety disorders are more likely to abuse alcohol and drugs.

Stress is a pervasive factor in everyday life and appears to play a major role in the pathophysiology of psychiatric disorders, particularly depression [4,5]. History indicates that mankind seeks substances to induce pleasurable sensations and escape from discomfort related to perceived stress. Drugs of abuse, the legal ones or 'social drugs' (tobacco and alcohol) as well as the illegal ones (cocaine, amphetamines and opiates), are typically used for the euphoric sensation or to reduce stress, depression and anxiety [5,6].

Drug abuse and misuse costs our economy and society greatly as measured in increased health care costs, crime and lost productivity. In 2010 it was estimated that 22.6 million or 8.9% of Americans over the age of 12 were current or former illicit drug users. Around 10 million individual 12 to 20 years of age admitted to being alcohol drinkers, of these, 6.5 million were binge drinkers and 2 million heavy drinkers. Besides the social costs, each year, drug abuse and drug addiction cost employers over 122 billion dollar in lost productivity time and another 15 billion dollars in health insurance costs. These are some of the conclusions that the U.S. Department of Health and Human Services (DHHS), Substance Abuse and Mental Health Services Administration (SAMHSA), Center for Behavioral Health Statistics and Quality published in their 2010 National Survey on Drug Use and Health [7].

The SAMHSA published its plan of action for the period of 2011-2014 [8] and its first priority is the prevention of substance of abuse and mental illness. According to this report, the annual total estimated cost of substance of abuse in US is around $ 510 billion and by 2020, behavioral health disorders will surpass all physical diseases as a major cause of disability worldwide [9].

Recent studies have revealed that 3 to 4 cups of coffee a day to be a pleasurable, low cost and convenient way to prevent various health problems [10-16]. The beneficial effects of coffee, as well as some harmful ones, are commonly attributed to coffee's caffeine content [17-23]. For example, caffeine acts primarily as central nervous system stimulant, improving psychomotor performance, increasing vigilance and reducing fatigue [11];conversely other negative effects on cardiovascular system have been reported [22,24-26]. However, coffee is more thancaffeine. Quinides are found in amounts twice that of caffeine.These substances, formed during the roasting process by dehydration of polyphenols known as Chlorogenic Acids (CGA's)

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have been the object of animal studies and in vitro studies. These substances are thought to be responsible for the antidepressant effect of the decaffeinated coffee as discussed in the following sections [27-33].

Coffee and Depression: Experimental Studies

The discovery of opiate receptor-active peptide fragments (exorphins) identified in casein and gluten hydrolysates, and morphine in bovine and human milk led Boublik et al. 1983 [34,35] to screen for similar peptides or alkaloids in other foods. Using rat brain homogenate assay to detect opiate receptor activity they tested instant coffee powders from various manufacturers. They reported that approximately one-fifth of the concentration of a specific quinide contained in a cup of coffee displaced 50% of the binding of the opiate antagonist naloxone. However, at this time, the molecular identity producing this effect could not be determined but was suggested to be of an isomer of feruloylquinide, one of the various quinides originating from chlorogenic acids.

Takeda H et al. 2003 [36] examined the antidepressive and/or anxiolytic effect of caffeic acid, the main component of Chlorogenic Acids (CGA's) [Figure 1] present in roasted coffee, in two different types of stress models in mice. In both models they concluded that caffeic acid acted through indirect modulation of the alpha-1A adrenoreceptor system.

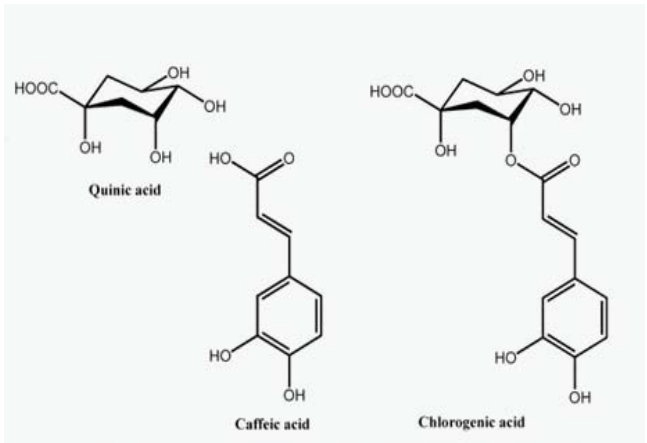

Figure 1: Chlorogenic acid chemical structure

De Paulis T et al. 2002 [37] studied dicinnamoylquinides, another group of compounds derived from CGA's present in roasted coffee. Interestingly, their results showed that these quinides not only bind to the human adenosine transporter, but inhibit the re-uptake of adenosine with potency approximately three times higher than the antagonic effect of caffeine at the human adenosine alpha-2A receptor. This suggests that dicinnamoylquinides present in the coffee could have the potential to raise extracellular levels of adenosine, thereby counteracting the stimulant effect of caffeine.

Later, de Paulis T. in 2004 [38] demonstrated that roasted coffee contains compounds that are pharmacologically active on the human opioid receptor system and identified their structures. The compounds identified, cinnamoyl-1,5-quinides, bind to μ opioid receptors and dose-dependently reverse the anti-nociceptive effects of morphine. This study provides experimental data that confirms the hypothesis from Flores et al (2000) [1,5] that a daily moderate intake of coffee may act as a prophylactic agent by blocking μ opioid receptors. Blocking these receptors decrease the craving for self-reward that could be involved in depression, alcoholism and substance of abuse.

It is commonly understood that the way drugs cause pleasure or reward is by mimicking neurotransmitters that activate the brain reward system – the mesolimbic system [3]. The limbic system is involved with emotion, learning and memory. Positive experiences and the use of alcohol and drugs (cocaine, amphetamines, and nicotine) may lead to rewarding feelings and conditioned behavior by means of reinforcing learning and memory mechanisms. The neuronal circuit implicated in reinforcing behavior that leads to drug addiction appears to be the dopaminergic mesolimbic system (Figure 2) composed of cell bodies in the ventral tegmental area (VTA) with projections to the nucleus accumbens (Nac) through the medial forebrain bundle (MFB). In the VTA, beta-endorphin neurons via μ receptors block the inhibitory action of GABA neurons, increasing the release of dopamine in Nac. This effect is counteracted by dynorphin activation of κ receptors, so that basal dopamine release is determined by the balance between those two opposing opioid systems.

This system is responsible for the control of dopamine levels in

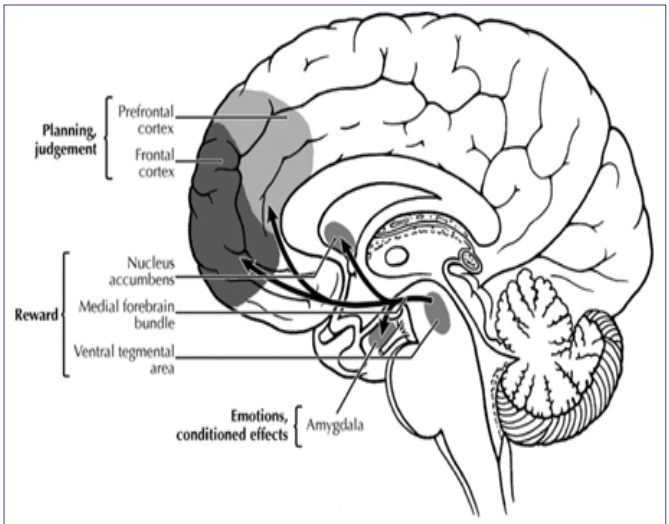

Figure 2: The brain reward system – the mesolimbic system [39]

the nucleus accumbens through secretion of endogenous peptides, which ultimately will lead to the transmission of positive or negative emotional stimulus to the cortex of the brain [3].

Because opiates increase the firing of cells in the VTA and consequently increase in the release of dopamine in Nac (Figure 3), the quinides present in coffee blockthese opiate receptors and thus are blocking the self-reward circuit stimulated by drugs such as alcohol and substances of abuse [5].

Epidemiological Studies

A growing body of work in epidemiology has been published in the last years suggesting preventative effects of daily

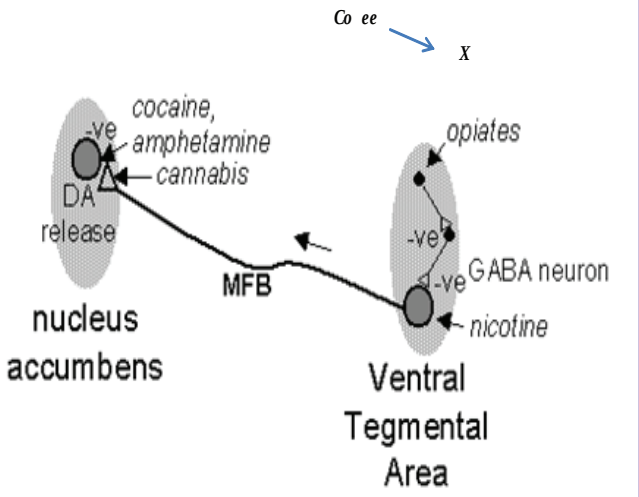

Figure 3: The theoretical mechanistic action of coffee blockade of the brain reward system. The diagram depicts the mammalian rat brain experimentwith sites at which various abusable substances appear to act to enhance brain-reward and thus to induce drug-taking behavior and possibly drug-craving.

(DA= dopamine, MFB=medial forebrain bundle, GABA=gammaamino-butyric acid, -ve=sites where drugs were delivered) [39]"modified

coffeeconsumptionwith an inverse relationship with the risk of developing diseases affecting the central nervous system.A 2010 study with 2,232 middle-aged men in Finland [40], one of the countries with the highest coffee intake per capita (12 kilos/capita/year) [41] , investigated the association between the intake of coffee, tea and caffeine and depression [40]. The population was recruited between 1984 and 1989 and followed until 2006. The primary conclusion was that coffee heavy drinkers (> 4 cups/day) had a decreased risk for depression (relative risk or RR=0.28, 95% CI 0.54, 2.23) when compared with non-drinkers, after adjustment for age and examination years. No association was observed between intake of tea (RR=1.19, 95% CI 0.54 2.23) or caffeine (RR=0.99, 95% CI 0.40 2.45). The lack of association with caffeine intake suggests that other compounds in coffee, such as chlorogenic acids and related compounds (quinides, caffeic acid) may be responsible for anti-depressant effects.

A cross-sectional study examining the association of green tea, coffee and caffeine and depressive symptoms within a population of Japanese workers enrolled 537 men and women aged 20-68 years. A validated dietary questionnaire was used to determine the coffee intake per day as well as lifestyle, mental and physical health. A health examination was performed and blood sample collected to determine C-reactive protein and folate levels to adjust for risk factors to depression. In this study it was found that both higher consumption of green tea, coffee and caffeine were associated with lower prevalence of depressive symptoms [42].

The association of coffee, caffeine and risk of suicide has been object of numerous epidemiologic studies. Overall findings suggest a significant inverse association between coffee consumption and depression and/or suicide [10,14-16,43-45]. Kawachi and Lucas from Harvard School of Public Health have extensively studied this interaction and published at least 3 important articles on this topic [44-46]. Kawachi and his group [44] prospectively looked at a cohort of 86,626 nurses (agesranging from 34 to 59 years)fromthe Nurses' Health Study with 10 years of follow up (1980-1990). The study examined the relationship of coffee and caffeine intake to risk of death from suicide assessed by a semi-quantitative food frequency questionnaire. Compared with non-drinkers of coffee, the age-adjusted relative risk of suicide in women who consumed two to three cups per day was 0.34 (95% confidence interval (CI, 0.17 to 0.68) and 0.42 (95% CI, 0.21 to 0.86) in women who consumed four or more cups per day (P for linear trend=.002). These findings remained essentially unchanged after adjusting for a broad range of potential confounding factors. The data suggest a strong inverse association between coffee intake and risk of suicide. A limitation of this study is that the authors were not able to distinguish if major factor was coffee or caffeine intake.

More recently, Lucas M et al. 2011 [46] presented results from a longitudinal study with a total of 50,739 women averaging 63 years old, which were prospectively followed from 1996 through 2006. The purpose of the study was to analyze the relationship between coffee or caffeine consumption and risk of depression. The conclusion was that the risk of depression decreased in a dose-dependent manner with increasing consumption of caffeinated coffee; no association was found between decaffeinated coffee and risk of depression.

Lucas M. and his group in 2013 [45] evaluated the association of coffee and caffeine consumption and suicide risk in three large-scale cohorts: 43,599 men enrolled in the Health Professionals Follow-up Study (HPFS, 1988-2008), 73,820 women in the Nurses' Health Study (NHS, 1992-2008), and 91,005 women in the NHS II (1993-2007). Consumption of coffee, caffeine and decaffeinated coffee was assessed every 4 years by validated food-frequency questionnaires. They found that the estimated mean daily caffeine consumption was 218 mg for NHS, 169 mg for NHS II and 186 mg for HPFS and that the contribution of coffee to total caffeine consumption vary from 71 % (NHS II) to 79% (HPFS) and 80% (NHS). Those findings are in accordance with US Department of Agriculture survey data that says that 90% of the adult population in US consume caffeine, averaging 166-336 mg/day, and that coffee accounts for approximately 81% of the total daily caffeine intake by adults over 36 years of age [47] . The conclusion of this large study was that suicide risk decreased in dose-dependent manner with increasing consumption of coffee. As compared with non-coffee drinkers, the pooled RR multivariate of suicide was 45% lower among individuals who consumed 2-3 cups of coffee per day and 53% lower among individuals who consumed ≥ 4 cups of coffee per day. Considering that the decaffeinated consumption of coffee was low and that suicide risk was no further decreased by the highest level of caffeine intake, suggest that the results for caffeine intake are less convincing than the results for coffee intake.

Coffee, Alcohol and Depression among Students

There is no single factor that determines whether a person will develop alcoholism or a drug addiction. A person's overall risk for addiction is determined by their biological makeup, including genetics, and their exposure to drugs and alcohol. Many self-medicate with alcohol or drugs to combat stress as a way of unwinding. Depression or anxiety disorders are more likely to abuse alcohol or drugs. The evidence that drinking coffee lowered the incidence of depression and risk of suicide led researchers to investigate the relationship of

coffee consumption, alcohol and depression among students. Flores and colleagues [5] published the results of the Brazilian Youth Drug Study (BYDS), a prospective study of 106,502 students ranging in age between 10 and 20 years of age for incidence of depressive feelings, alcohol intake and drug consumption. The purpose of the study was to determine if a relationship existed between daily coffee intake and variables such as depressive symptoms, smoking, or consumption of alcohol, soft drinks and drug consumption. The data was collected through a 30-question standardized questionnaire administered at schools every 2-3 years between 1990 and 2000. Findings indicated that students selected 3 main categories of roasted coffee: medium roasted (81% of students), dark roasted (12%) and very dark roasted (7%). The degree of roast is an important characteristic as it largely determines the content of pharmacologically active compounds present in coffee (CGA's, caffeine, sugars, lipids, etc.). Except for caffeine, which is thermo-stable, all the other compounds are either degraded or decomposed with the increasing degree of roasting (light roast to very dark roast) [29,32,33,48]. The results suggested that those youth who drink coffee, averaging 3 cups/day had a significantly lower chance of having either depressive feelings or craving for alcohol. Therefore, the authors proposed that regular daily coffee intake of ≥3 cups/day could help prevent drug addiction. Basically, the argument is that the opiate antagonistic effect of some CGA's present in coffee, may act as a prophylactic agent blocking opioid receptors and thus decreasing the craving for self-reward that can be involved in the mechanism of depression and/or alcoholism.

Another study utilizing a modified questionnaire from BYDS and in collaboration with Brazilian researchers was executed as a pilot trial at South University, GA, Savannah campus involving 1,126 students [49]. The objective of this follow-up study with an American student populationwas to evaluate the relationship between reported consumption of coffee and alcoholic beverages with the development of signs and symptoms of apathy and depression. Unlike the BYDS, the survey was only a single snap shot in time but like the larger study, data on roast preference was captured. The data suggested a strong inverse association between regular to moderate (3-4 cups/day) coffee intake and depressive feelings and to alcohol intake when compared to non-coffee drinkers. This study provided support for the results seen in the BYDS study in Brazil for the first time in USA.

Coffee consumption, suicide risk and total and cause-specific mortality

The Nurse's Health Study began in 1976 enrolling 121,700 US married female registered nurses between the ages of 30 and 55. Participants responded to an initial questionnaire and then again every 2 years a follow up questionnaire to ascertain incident diseases and update lifestyle characteristics. The study ended on June 1996. The data collected was used to examine, between other factors, the association of self-perceived stress, use of diazepam and death from suicide. The lifestyle evaluation also included smoking status, and coffee and alcohol consumption. Diazepam use was significantly predictive of suicide; but high coffee consumption (≥ 2 cups/day) was weakly associated with work stress and diazepam use [43].

The Nurse's Health Study, involving 50,739 women averaging 63 years of age and free of depressive symptoms at the baseline (1996) were prospectively followed through 2006. In this 10 year span a total of 2,607 incident cases of clinical depression were documented. It was found an inverse, age-adjusted, dose-response relationship between caffeinated coffee and depression risk (p for trend=.03) [46].

The association between coffee and caffeine consumption and suicide risk in three-large scale cohorts in US was object of another study [45]. In this study a validated food-frequency questionnaire was assessed every 4 years and a biennial questionnaire on lifestyle from 1980 through 2003. Among the 208,424 participants 277 deaths from suicide were documented. The results showed that suicide risk decreased in a dose-dependent manner with increasing consumption of coffee (RR of suicide, compared with non-drinkers, was 45% lower for consumption of 2-3 cups/day and 53% lower for those who consumed ≥4 cups/day). However, the study had limited ability to distinguish between caffeine and other coffee constituents, and results for decaffeinated coffee should be interpreted with caution since the sample of population drinking decaffeinated coffee was small. The results suggest an association between greater consumption of coffee and lowered risk of suicide.

Recently, a series of large cohort studies targeting the association of coffee consumption and all-cause mortality and total mortality have been conducted [50-52]. The Health Professionals Follow-up Study and Nurses' Health Study, totaling 41,736 men and 86,214 women were prospectively followed from 1980 through 2004. The objective was to evaluate association between coffee consumption and mortality from cardiovascular disease (CVD) and cancer, provided that there was no history of those diseases at the baseline. They found an inverse association relative to moderately reduced risk for CVD that was independent of caffeine intake and no statistically significantly association with risk for cancer death [51]. On the contrary, a large-scale cohort study in Japan, the JACC Study, totaling 97,753 men and women were followed for 16 years. The purpose of the JACC was to assess coffee consumption and all-cause or cancer mortality. They concluded that there are beneficial effects of coffee on all-cause mortality among men and women. Furthermore, the results showed that coffee consumption may not be associated with an increased risk of total cancer mortality, particularly in women [52].

Freedman and col [50] from Division of Cancer Epidemiology and Genetics (NCI/NIH/HHS) published results from a study with 229,119 men and 173,141 women in the National Institutes of Health-AARP Diet and Health Study. These subjects were between 50-71 years at baseline. They examined the relationship between coffee drinking with subsequent total and cause-specific mortality. The results showed that coffee appeared to be inversely associated with most major causes of death, in both, men and women, including heart disease, respiratory disease, stroke, injuries and accidents, diabetes and infections. In contrast, they found no significant association between coffee consumption and death in women and a borderline positive association in man, as opposed to the Japanese study referred previously. Importantly, they concluded that the study provide reassurance with respect to the concern that coffee drinking might adversely affect health.

Coffee: Caffeinated or Decaffeinated

Caffeinated beverage ingestion is associated with increases in

mood and attention [30], and particularly with increased arousal and reduced sedation [12,23,53-59]. In an in vivo study [59] the responses of different levels of caffeine in tea and coffee to acute physiological reactions and mood with healthy non-smokers volunteers, were carried. Coffee and tea levels of caffeine were manipulated to achieve equivalent measures of caffeine per cup. The study was divided into two arms. In one arm the caffeine intake was increased by administering two different strengths (1 or 2 cups of coffee or tea). In the second arm, caffeine was varied by the caffeine content in a tea-based beverage utilizing decaffeinated tea was the base. They found that when the strength of the beverage was perceived (arm1) no evidence for a dose-response effect was evident, all treatment produced similar effects. On the contrary, in arm 2, where the caffeine manipulation was blind to the subjects, a dose-dependency effect on short-term autonomic responses was observed. However, the effect on the mood was atypical, with the lowest and highest doses of caffeine demonstrating the greatest improvement in mood. An interesting conclusion was that there is a role for sensory factors such as perception of the strength as bitterness intensity and aroma. These positive effects on the mood have been reported in other studies even in low doses of caffeine [15,53,55-57].

In another in vivo study in Australia [30], thirty nine healthy older volunteers were enrolled in a randomized, double-blind, crossover trial. The objective was to ascertain if a coffee enriched with chlorogenic acid modulates brain function. Decaffeinated coffee was compared with regular amount of chlorogenic acid and placebo. Caffeinated coffee showed a robust positive effect on higher-level mood and attention processes. However, decaffeinated coffee high in chlorogenic acid (enriched) also improved mood and behavioral responses. They concluded that non-caffeine compounds in coffee, such as chlorogenic acids, may be capable of exerting acute behavioral effects.

It is clear from the studies discussed on coffee consumption that caffeine cannot conclusively be excluded as a possible cause for the effects of coffee consumption on human health. Most of the studies acknowledged that the overall health effects are easy to attribute tothe most studied component, caffeine. This is exacerbated by traditional study designs that rarely found differences in effects or studied the effects between caffeinated and decaffeinated coffee. However, limitations of studies include: lack of data on the amount of caffeine and chlorogenic acids present in the coffee regularly consumed by study participants, not including a comparable number of decaffeinated coffee drinkers and not differentiating between decaffeinated from caffeinated-coffee drinkers. Finally, all the studies reviewed unanimously stated that further investigations are needed in order to confirm their findings.

Conclusion

Coffee is a natural product that when roasted and brewed delivers thousands of pharmacologically active compounds. One component, caffeine, dis proportionally receives more attention and is the primary reason health care professionals recommend restricting coffee intake. However, researchers are turning their attention to other pharmacologically active constituents present in coffee, such as chlorogenic acids and related quinides.These components are more abundant than caffeine and are capable of promoting 'in vivo' inhibition of morphine-induced anti-nociceptive behavior in mice in the same order of magnitude as that reported for naloxone. Thisopioid antagonistic effect, similar to the prescription drug naloxone, is suggested to act at the mesolimbic system, thereby blocking craving for drugs of abuse such as alcohol and opiates. There are very few animal and in vitro studies on basic pharmacology of coffee polyphenols and even less on human in vivo studies. There is a need of development of appropriate biomarkers for coffee consumption in order to bridge the animal studies and the mounting epidemiological data already available. It is our research group's objective to identify those biomarkers through initial determination of bioavailability of polyphenols (CGA's) in healthy volunteers after drinking a standardized brewed coffee formula. In depth studies on the clinical pharmacology of coffee constituents particularly the chlorogenic acids and their quinides, are needed to better understand the potential preventative effects of coffee on mood disorders such as depression and their consequences as alcoholism and drug abuse.

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