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Can coffee help fighting the drug problem? Preliminary results of a Brazilian youth drug study

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INTRODUCTION

At different times and at different places many plants have been domesticated, and the development of agriculture was an intensification by man of his food extractive process. Simultaneous to the agricultural development, the selection of psychotropic plants has always been one of the most tempting and determined activities of mankind in its history. Behaviorally active drugs have captured and control human behaviour in susceptible individuals. Nowadays the most consumed plants worldwide are legal ones such as coffee and tobacco and illegal ones such as cocaine, opium and cannabis. And little is known about the potential of plants as new and major sources of drugs, foods, nutraceuticals, cosmetics, herbal medicines and soft drinks, among other profitable/healthy byproducts.

The dependence on illicit chemical substances (drugs) is becoming an increasing and alarming drain on medical and social care systems[1-3]. The plantation, consumption and trafficking of plants that originate drugs such as cocaine, heroine, marijuana is today one of the most important and certainly the most profitable trade of all world. And there is also the legal plantation of the drug tobacco. The illegal drug trade's annual resources run around 500 billion USD. The American market, the biggest in the world for drugs, has created a business that produces annual interests of about 100 billion USD; twofold more than what the United States spends on petroleum. The size and the power of this business not only allows it to survive but expands it manifold in a permanent sort of way, despite of all the efforts that are being done combat it. The criminality associated with narcotraffic perverts institutions and surpasses official and governmental measures that try to oppose it. It is estimated that more than 30 million Americans smoke marijuana, more than 8 million use cocaine, more than 500 thousand are dependent on heroine and 50 % Americans present temporary physical and mental health problems from alcohol ingestion, 10 % of the population is alcoholic and more than 60 million Americans are daily smokers[4,5]. Although more than 80 % adult Americans drink coffee on a daily basis, its consumption among youth is almost forbidden in US as caffeine is considered to be a reinforcing agent and/or even a drug liable to addiction[6,7] while coffee with or without milk is freely consumed among youth in countries such as Brazil as well as a few European ones (Holland, Italy, England). In Brazil the regular intake of coffee with milk was a very common habit among children and youth a few decades ago, both at home breakfast/afternoon lunch and at school breakfast. But this habit is being changed and daily coffee/milk consumption is being replaced by that of soft drinks. Additionally there is a steady increase in the consumption of both legal (alcohol, tobacco) and illegal (marijuana, cocaine, solvents, crack, heroin, etc) drugs in Brazil[8]. Drug addiction is increasing among youth not only in USA but also in the world over. An industry with more than 100 million of daily consumers of tobacco, alcohol, cocaine, marijuana, and heroin in the United States only, acts not only as a powerful client but as a strong incentive for permanent and increasing production of these plants or their derivatives.

Among all addictions, alcoholism is by far the most

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common. Around 90 % of adult population of all world drink alcoholic beverages regularly, and around 40 % to 50 % of these, specially men, present temporary alcohol-induced problems, mainly of attention, memory, reflexes, and other cognitive functions. Of the motor vehicle-related injuries which are the leading cause of death in persons aged 1 – 24 years in the United States 50 % are alcohol-related. It is estimated that about 10 % of men and 5 % of women develop a persistent alcoholism worldwide. These persons develop chronic tolerance, physical dependence and toxicity caused by alcohol. Alcoholism is also becoming a major threat to all youth all over the world. If evaluated on the basis of crime, accidents, productivity, and health problems, it is estimated that an annual loss about 160 billion dollars occurs in the United States alone due to alcoholism[9-11].

Tobacco smoking is another major drug addiction. The mortality among smokers is 30 % to 80 % higher than in nonsmokers and tobacco is the main preventable cause of death in the modern world. More than 400 000 deaths in USA each year are from smoking-related illnesses. At the moment, USA leads the world in the average ciggarette consumption per head per year among the adult population. The main factor responsible for the increase in death rate associated with smoking is coronary heart disease, the second being lung cancer. But smoking greatly increases the risk for other cancers, atherosclerotic disorders, thromboangitis obliterans, cerebrovascular disorders, sudden cardiac death and bronchitis and emphysema. In the United States the estimated cost for smoking-related medical care and loss of productivity exceed $ 55 billion per year[12,13]. All of the growth in global tobacco consumption in coming years is expected to be in the developing countries, with the world's 1.1 billion smokers expected to rise to 1.64 billion by 2025. The World Health Organization estimates the death of 4 million people annually from smoking-related diseases; by 2030, that number is expected to climb to 10 million, with 70 % of the fatalities occurring in the Third World.

In the United States depressive illnesses are reported in almost 18 million American adults and a significant number of youth during any 1 year period. Unfortunately almost 11 million Americans fail to recognize their illness and get treatment. Yet, because it often goes unrecognized, depression continues to cause unnecessary suffering. Women experience it at roughly twice the rate of men. But men seem to be socially conditioned to deny such feelings or to bury them in alcohol. Depression, whether by itself or coexisting with another illness, should be treated. And even better, perhaps depression can be prevented. For white males between 15 and 19 years of age, suicide ranks second among all causes of death; for physicians younger than 40, it ranks first. An annual loss of 43.7 billion dollars has been estimated, taking into account the work absence, productivity losses, salary expenses, medical treatment and expenses due to suicidal cases. But the cost of human suffering cannot be estimated. Depending on the population studied, the lifetime prevalence of major depression in the United States is 20 percent. Lack of prevention or undertreatment of depression increases the risk of suicide. Among patients with recurrent depression, 15 percent commit suicide. Patients with mood disorders also have a higher mortality than normal subjects because of a higher incidence of accidents and other illnesses[14-17].

It is estimated that more than 25 million Americans have used cocaine at some time. Cocaine consumption began with the Spanish colonization of South America. The leaves of the coca bush (Erythroxylon coca), from which cocaine is obtained, have been chewed by the natives living in the Andes for untold generations. But nowadays cocaine has become the most profitable and challenging drug addiction. Worldwide cocaine consumption is far less compared to the 6 million tons of coffee. But the global cocaine trade runs more than US $ 300 billion a year, while coffee runs no more than US $ 15 billion a year. This means that though production of coffee is 10 thousand times that of cocaine it yields 20 times less money. This creates conditions to an ever increasing replacement of coffee crops with that of cocaine in Colombia and in Brazil, the world's two major coffee exporters, as has happened in Bolivia and Peru. If nothing is done to change this situation pretty soon cocaine will be the major Latin American crop rather than coffee[18].

Recent major epidemiological studies have found a possible beneficial association of moderate daily intake of coffee and a lower incidence of cirrhosis and suicide among adults[19], a strong inverse association between coffee intake and risk of suicide among women[20], beneficial effects regarding mortality and coronary morbidity among adults associated with coffee consumption[21] as well as an indication that higher coffee and caffeine intake is associated with a significantly lower incidence of Parkinson's disease among adults[22]. A statistical association does not necessarily imply the existence of a causative connection. What it does is to invite further study towards that possibility. In a series of studies a-

mong youth as well as adults which we began almost ten years ago, we detected a potential role of coffee in preventing depression[18], in decreasing the craving for alcohol and smoking[23,24] and it raised the hypothesis that coffee might help preventing the consumption of illegal drugs[25]. A prospective follow-up study was then begun with the preliminary data being presented in this article. Recent data from meta-analysis of research on the behavioral and cognitive effects of xanthines such as caffeine in children has indicated, intriguingly, that "caffeine" has a small, beneficial effect on some children's behavior, decreasing behaviour that is externalizing or characterized as active, overt, problematic or aggressive. All these symptoms are related to depression among youth as well as to drug addiction[26]. Additionally it was recently shown that higher rates of participation in school breakfast programs are associated with improved student functioning among a broad range of psychosocial and academic measures[27].

To further clarify the potential healthy or harmful effects of daily coffee intake among youth and its relationship with depressive feelings, smoking, soft drink intake, alcohol intake and drug consumption, we present our results from a sample of 106 502 students from both sexes, aged 10 to 20 years, as part of a preliminary data from a major properly designed cohort study in Brazil which will include a larger sample in the forthcoming 10 years among the more than 30 million students all over Brazil participating in free school breakfast programs.

MATERIALS AND METHODS

The Brazilian Youth Drug Study (BYDS) began in 1990 by random sampling of youth students aged 10 to 20 years from 15 cities of 6 states in Brazil between 1990 and 2000. With the help of medical students and school teachers, a *questionnaire* including 30 questions was applied at schools every 2 – 3 years in a prospective follow-up. Each helper (school teacher and medical student) applied 300 to 500 *questionnaires* weekly to 6 different age groups (10 – 11, 12 – 13, 14 – 15, 16 – 17, 18 – 19, and 20 years of age) during a 2 – 3-year interval at various schools throughout the cities. Questions were about age and sex, depressive feelings (rated 0 to 10) adapted from the Children's Depression Inventory (CDI), school performance (rated 0 to 10) and questions about regular or occasional (daily, weekly, monthly) intake of coffee (with or without milk), cola soft drinks, alcoholic beverages, smoking and illegal drugs consumption (marijuana, cocaine, crack, solvents and others). Participants were asked to answer the questions and report the daily, weekly or monthly frequency and amount of consumption/symptoms of each item during the previous month at the moment of answering the questionnaire. Students with two or more items left blank, implausibly high scores and subjects who did not complete the questions on coffee consumption were excluded. The response rate was 68 % (106 502 from 161 367 students). We selected a subgroup of youth who were daily coffee-drinkers as a reference for comparison with the non-coffee drinkers regarding the reports about depressive feelings, alcohol intake, smoking and drug consumption. No comparison was performed among the coffee drinkers subgroup concerning the brand of coffee drunk: medium roasted, dark roasted and very dark roasted coffee. Three major specific brands of coffee based on the roasting process were detected: median roasted (with 81 % consumers), dark roasted coffee (with 12 % consumers), and very dark roasted coffee (with 7 % consumers). The final content of the many chemicals found in green and roasted coffee such as chlorogenic acids (CGA), aminoacids, sugars, lipids, trigonelline as well as many others yet to be identified bioactive compounds were shown to decrease according to the intensity of the roasting process[28-30]. Caffeine is the only thermo-stable compound, which explains the priority of attention given to caffeine in scientific research regarding coffee up to the present. Additional data are being analyzed from the overall data.

STATISTICAL ANALYSIS

The goal of our preliminary data was to examine the association between the daily intake of 3 cups of coffee with or without milk (as part of regular home breakfast, school breakfast programs and afternoon lunch), demographic factors and children adjustment scores for depressive feelings, alcohol consumption, smoking, soft drink intake and illicit drugs intake as well as school performance. The data of our variables were not appropiate for the normal theory linear model and we used non-parametric procedures to compare coffee consumption with the other variables. For statistical analyses we selected a sample of the entire population including two groups of students classified as daily coffee drinkers (DCD, n = 6246) and non-coffee drinkers (NCD, n = 20 543. All were part of the youth students referring daily depressive feelings (3.1 %, 6.2 %, 9.2 %, 14.5 %, 18 %, and

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19 % for each specific age group studied) and daily alcohol intake (2.1 %, 3.9 %, 4.6 %, 6.6 %, 9.4 %, and 9.7 % for each specific age group studied). Kendall's rank correlation coefficient was computed for each of the continuous variables and Kruskall-Wallis tests were used for the categorical confounders. Mantel-Haenszel estimate of relative risk was used with the following covariates: age groups (10 – 11, 12 – 13, 14 – 15, 16 – 17, 18 – 19, and 20), sex, school performance (0 to 4), coffee intake (none, 2 to 4 cups, 5 or more), smoking (1 to 5, 6 to 10, 11 to 20, and >21), alcoholic beverages intake (none, 1 to 2, 3 to 4, 5 to 6, or more cups of wine, beer or spirits), and illegal abuse of drugs (none, 1 to 2, 3 to 4, 5 to 6, or more equivalents) on a daily, weekly or monthly basis. Students with medical problems or under medical treatment of any type (epilepsy, diabetes, HAAD among others) were excluded. Analysis of the follow-up data from January 1990 to January 2000 used incidence rates with person-years as follow-up as the denominator. We compared the age-standardized distributions of each one of the covariates across categories of coffee intake. The relative risk (RR) was defined as the incidence rate among youth who reported a specific daily intake of coffee of 2 – 4 cups (DCD), divided by the corresponding rate among youth who did not use coffee on a daily basis (NCD). Relative risks were adjusted for age using 2-year age group and 95 % confidence intervals (CI) were calculated[31,32].

RESULTS

Daily coffee intake with or without milk is a common habit in many coffee-producing regions throughout Brazil, with a mean average daily intake of up to 3 cups among 36 % of all students in some coffee-producing areas taking coffee with milk at home breakfast, school breakfast and afternoon home lunch. On the other side coffee consumption by children and youth is almost forbidden in a few major cities by a great number of people such as doctors, mothers, school teachers without plausible reasons. But coffee with milk is taken by hundred of thousands of students throughout the country, ranging from 1 to 4 cups daily (3 cups on an average), along with cereal, bread or a muffin, and fruit or juice. Studies have demonstrated the negative effects of chronic malnutrition on social, emotional and cognitive functions in children and youth. This preliminary study did not include data on youth nutritional status but undernourishment is common in Brazil. And coffee might be one of the few available options for children's and youth's breakfast in some specific areas where coffee agriculture is dominant. The popularity of coffee intake is due to the fact that Brazil is the world's largest coffee grower and second largest coffee consumer with over 25 % of world's production and 12.5 % of world's consumption. There are 221 000 coffee farms with an average size of 10 hectares. Brazil has an average production of 26 million bags of 60 kg yearly, which is increasing together with its internal consumption. Coffee is the country's third most important export product and employs 3.5 million people and sustains a population of about 15 million. For this reason it was possible to identify a subgroup of youth, up to 36 % in some areas, who drink coffee regularly on a daily basis, with or without milk, starting in home breakfast, repeating at school lunch, and with another extra intake in the afternoon lunch (coffee with milk, bread and butter). In the major city schools the daily coffee intake with or without milk is extremely heterogeneous, varying from 2 % to 21 % among schools. Although the name "school cafeteria" is widespread, coffee with milk is served in very few of these school cafeterias. Beer and soft drinks are far more common than coffee in many public and private "school cafeterias". The daily intake of coffee with milk in some areas of Brazil starts as early as 3 to 4 years of age, with no ill effects whatever reported up to now either on children or among youth daily coffee drinkers (up to 2 – 3 cups daily). It is well established that moderate intake of coffee is not harmful to human health[33,34] and "caffeine" can even have a little beneficial effect on some children's behavior[26]. We have no data about the overall school breakfast program in the country catering to the primary and secondary students numbering 30 million. Looking at the demographic data of the BYDS (Tab 1), it is possible to observe a very heterogeneous population according to age, not to mention other potential confounding factors such as social class, race, body mass index, and daily activity, among many others. Data include more data on males at all age groups (5.3 % aged 10 – 11 years with 60.9 % males; 11.6 % aged 12 – 13 years, with 68.3 % males; 26.9 % aged 14 – 15 years with 56.2 % males; 27.3 % aged 16 – 17 with 64.5 % males; 15.7 % aged 18 – 19 with 67.6 % males and 13 % aged 20 with 71 % males). Data on depressive feelings, coffee intake, smoking, alcohol consumption and illicit drug consumption (mean of %) at the BYDS are shown in Tab 2. Depressive feelings and alcohol intake have an age related

increase. And most striking is that there is a significant daily alcohol intake ($P < 0.05$) starting at 10 years of age (2.1 %), with an ever increasing incidence among youth (3.9 % among youth aged 12 – 13; 4.6 % among youth aged 14 – 15; 6.6 % among youth aged 16 – 17; 9.4 % among youth aged 18 – 19, and 9.7 % among youth aged 20). Beer is the most popular alcoholic beverage (90 %), after wine (8 %) and spirits (2 %). Comparison of paired samples (equal % in each group) of Daily Coffee Drinkers (DCD) and Non-Coffee Drinkers (NCD) and Daily Depressive feelings and Daily Alcohol consumption reported show a statistically significant difference ($P < 0.001$) among students aged 10 – 11 and 12 – 13 years as well as aged 14 to 20 years ($P < 0.05$) (Tab 3). A strong inverse correlation between the daily intake of coffee among youth and depressive feelings as well as alcohol intake in all age groups was observed. Socioeconomic and ethnic characteristics data were not collected and they may have some importance regarding these data. No such correlation was observed with the remaining variables and no statistically significant data was found concerning smoking and illegal drug addiction. Although multiple adjustment for illegal drug consumption and coffee intake showed a weak residual benefit of coffee consumption in decreasing smoking and drug abuse among youth, it might be unreliable due to the lack of confidence concerning drug intake report. But it was possible to detect that alcohol and drug trafficking and consumption is involving not only the young peasant agriculturalists, but also the urban youth at schools belonging to the affluent societies of the country. Age-related and multivariate RR of daily depressive feelings and alcohol consumption comparing youth coffee drinkers of 3 cups of coffee on a daily basis (DCD) with NCD are seen in Tab 4, suggesting general health benefits of daily coffee intake by youth.

Tab 1. Demographic data of the BYDS (106 502 youth students).

Students	*n*	%	Male	%	Female	%
Aged 10 – 11	5 680	5.3	3 461	60.9	2 219	39.1
Aged 12 – 13	12 357	11.6	8 446	68.3	3 911	31.7
Aged 14 – 15	28 668	26.9	16 109	56.2	12 559	43.8
Aged 16 – 17	29 117	27.3	18 780	64.5	10 337	35.5
Aged 18 – 19	16 778	15.7	11 342	67.6	5 436	32.4
Aged 20	13 902	13.0	9 875	71.0	4 027	29.0

DISCUSSION

The analysis of our preliminary results suggest that these youth who drink coffee (with or without milk) at home breakfast, school breakfast, and afternoon lunch have a significantly lower chance of having either depressive feelings or craving for alcohol consumption. This may be due to a prophylatic effect of daily coffee intake, chance or confounding factors. The study relates 2 extreme groups of youth with very different lifestyles and/or different nutritional and recreational habits. Our study began in the early 90's[23-25] as pilot studies among youth and adults based on food frequency questionnaires to evaluate the consumption of legal (tobacco, alcohol) and illegal (marijuana, cocaine, crack, solvents, and others) drug consumption as well as of coffee. A standardized questionnaire was used and the sample increased in a longitudinal study. This work has many limitations: the method used, significance tests, its power and many variables evaluated together with many important questions which were not included in the questionnaires (socioeconomical status, race, family history of depression and alcoholism, etc). Food frequency and alcohol and smoking questionnaires appear to provide reasonably reliable and valid estimates but this may not be valid concerning

Tab 2. Depressive feelings, coffee intake among youth, smoking, alcohol consumption, and Illicit drug consumption at the BYDS (D = daily, W = Weekly, M = Monthly mean of %).

Students	%	Depressive feelings			Coffee intake			Smoking			Alcohol intake			Drug consumption		
		D	W	M	D	W	M	D	W	M	D	W	M	D	W	M
Aged 10 – 11	5.3	3.1	7.1	14.5	4.4	6.7	31.6	18.1	54.1	89.1	2.1	34.5	71.4	0	1.1	3.1
Aged 12 – 13	11.6	6.2	9.9	20.6	12.1	26.8	60.2	21.5	60.2	90.2	3.9	36.7	73.3	0.1	1.5	3.7
Aged 14 – 15	26.9	9.2	16.5	26.7	14.8	44.2	78.2	46.3	86.4	96.0	4.6	44.7	93.4	1.3	3.5	5.7
Aged 16 – 17	27.3	14.5	19.4	30.2	26.2	50.2	82.1	59.2	90.3	98.7	6.6	50.3	98.1	2.3	4.5	7.8
Aged 18 – 19	15.7	18.0	30.5	36.6	30.5	62.4	88.5	62.4	97.5	98.9	9.4	72.5	99.0	3.1	6.7	8.8
Aged 20	13	19.1	32.0	90.0	54.4	78.3	90.5	71.4	98.2	99.1	9.7	77.3	90.4	3.1	7.0	9.0

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Tab 3. Comparison of paired samples (% in each group) of daily coffee drinkers (DCD) and non-coffee drinkers (NCD), and daily depressive feelings and alcohol consumption.

Students	%	Depressive feelings		Alcohol intake		Significance level
		NCD	DCD	NCD	DCD	
Aged 10 – 11	5.3	178	44	119	23	$P < 0.001$
Aged 12 – 13	11.6	766	261	482	67	$P < 0.001$
Aged 14 – 15	26.9	2637	884	1318	348	$P < 0.05$
Aged 16 – 17	27.3	4221	1339	1922	670	$P < 0.05$
Aged 18 – 19	15.7	3020	683	1577	783	$P < 0.05$
Aged 20	13	2655	778	1348	801	$P < 0.05$

Tab 4. Age-related and multivariate relative risks (95 % confidence interval, CI) of daily depressive feelings and daily alcohol consumption comparing youth coffee drinkers of 2 – 4 cups daily (DCD, $P < 0.001$) with NCD.

Students	*n*	Age-adjusted relative risk (95 % CI)	Multivariate relative risk (95 % CI)
Depressive feelings			
DCD	3994	0.36 (0.17 – 0.87)	0.41 (0.23 – 0.90)
NCD	13777	0.96 (0.51 – 1.32)	0.89 (0.42 – 1.34)
Alcohol intake			
DCD	2252	0.48 (0.30 – 1.17)	0.56 (0.32 – 0.97)
NCD	6766	0.98 (0.49 – 1.61)	0.87 (0.69 – 1.09)

drug abuse and depressive feelings among youth. Many variables seem at first to be a matrix of insuferable complexity, but simple summaries can be used to give an initial impression of predictor variables and to group together those that are highly interdependent. For this reason we evaluated in this preliminary data basically the correlation among daily coffee intake, daily depressive feelings and daily alcohol intake. We presume that part of the relationship consists of true correlation and part consists of random variation due to a multitude of indeterminate causes. Racial and social data were not obtained and these data may well have an important role concerning depressive feelings/depressive diseases, alcohol intake, alcoholism and drug addiction among youth. The correlation coefficient of depressive feelings as well as alcohol consumption among youth who drink coffee compared with non-coffee drinkers is a measure of the degree of linear association between these two continuous variables. Misleading correlations can also be obtained if the data relate to different groups of subjects having different characteristics. The main problem is that the test of significance of a correlation coefficient, which is a test of the null hypothesis of no association (zero correlation), is based on the assumption of joint normality of the two variables. This is characterized by the data points having a roughly elliptical shape in the scatter diagram. If this is not so the correlation will be misleading and the test of significance invalid. The distribution assumption may be overcome either by transformation of the data, or by the calculation of "rank correlations" and "Relative Risks", which make no important assumptions. In medical research correlations are greatly overused, perhaps because they are easy to calculate and are measured on a scale that is independent of the data. Correlation ought really to be considered to be mainly an investigative analysis, suggesting areas for further research and for forming hypothesis rather than for testing them.

Coffee intake and inverse relationship between cirrhosis/suicide: caffeine's effect? Two major epidemiological studies using food frequency questionnaires reported a strong inverse association between daily coffee intake and risk of suicide. In a prospective 8-year follow-up study of 128 934 persons enrolled in the Kaiser Permanente Medical Care Program from Oakland, CA, a lower risk for suicide was found together with, surprisingly, a lower risk of cirrhosis[19]. A strong inverse association between coffee intake and risk of suicide was confirmed by another major 10-year follow-up study in an ongoing cohort study of 86,626 US female registered nurses aged 34 to 59 years in 1980 performed by the Channing Laboratory, Department of Medicine at Harvard Medical School and Brigham and Women's Hospital from Boston, MA[20]. The coffee effects were either unexplained or atributted to possible mood-elevating or antidepressant effects of caffeine. A more recent study[21] has indicated that higher coffee and caffeine intake is associated with a significant lower incidence of Parkinson's disease via a mechanism related to caffeine and not to other nutrients (eg, niacin) contained in coffee. It is widely accepted that caffeine exercises its pharmacological effects mainly by its effect through the antagonism of adenosine receptors. Caffeine has basically two action mechanisms: in small concencentrations it antagonizes the adenosine receptors, the neurotransmitter of purinergic neurons, and at high concentrations it also inhibits the phosphodiesterase enzyme, responsible for the destruction of intracellular chemical mediator named cyclic adenosine monophosphate (cyclic AMP), causing increase of intracellular cyclic AMP[35]. These effects on the membranes and cells determine changes in the intracellular calcium

movement, the main ion involved the muscle fibers contraction process. Perhaps similar ionic changes occur with the nervous and glandular cells, where caffeine has a stimulating effect. But caffeine might also inhibit or reduce the extraneuronal re-uptake of catecholamines. Caffeine also has other action mechanisms such as altering directly the intracellular calcium concentrations, by causing membrane hyperpolarization or by uncoupling of intracelular calcium increases with muscle contractile elements. This last action explains the benefits of regular coffee intake by asthmatic patients, ie due to its bronchodilatation. But the neural mechanisms underlying adenosine's behavioral effects are still being explored and we cannot say for sure that all effects of caffeine can be explained by antagonism of adenosine receptors. There are two major hypothesis to explain how adenosinergic compounds exert their psychological and behavioral effects[36,37]. The first is based on data that adenosine tonically inhibits mesopontine and basal forebrain cholinergic neurons that have a major role in electrophysiological and behavioral arousal. The second hypothesis is that adenosine antagonizes the actions of dopamine in the striatum and nucleus accumbens. Such antagonism may occur through adenosine-induced inhibition of dopamine release and/or modulation of D_2 receptors by A_2 receptors in the membranes of striatal neurons. While endogenous adenosine exerts a tonic supressive effect on activity and arousal, only part of the stimulating effects of caffeine can be explained by its blockade of adenosine receptors. At least in the nucleus accumbens, A_2 rather than A_1 receptors appear to be responsible for adenosine-mediated locomotor expression. Adenosine receptor antagonists produce decreased locomotor activity in rodents, possibly through inhibition of dopamine neurotransmission. Recent reports[38] indicate that A_2 receptors antagonists improve motor deficits in primates treated with MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine). Caffeine given to mice with pharmacologically induced dopamine depletion prevents akinesia. This dopamine like effect may be related to removal or tonic inhibition by adenosine on dopaminergic neurotransmission rather than a direct stimulation on dopamine receptors by caffeine. Several studies have found that dopamine receptor blockers inhibit the behavioral effects of caffeine suggesting that adenosine antagonizes the functioning of dopamine, acting as a neuroleptic drug whereas adenosine antagonists such as caffeine enhance dopaminergic activity. But clinical studies do not confirm this hypothesis as clinical trials of caffeine given concomitantly with either a dopamine agonist or levodopa to patients with Parkinson's disease have shown no increased efficacy with caffeine[39]. The possibility that other compounds found in coffee, such as the chlorogenic acids with opioid antagonist activity might interfere by modulating not only the adenosine receptors but also the final dopamine levels into the brain has yet to be studied. Evidence for opioid modulation of release of mesolimbic dopamine in the brain reward circuitry as well as the release of acethylcholine (ACh), serotonin (5-HT), histamine, GABA and neuropeptides is accumulating[40,41].

Coffee is not only caffeine Almost every scientific article published about coffee upto the present focusses on its caffeine content and purified caffeine's effects on the humans or animals. Caffeine is considered the principal psychoactive ingredient of coffee, which may not be true. Caffeine is one of the most thoroughly investigated ingredient in the human food supply and it is well established that there is no shortage of research on the effects of caffeine on human health. And there are convincing evidences demonstrating that caffeine is safe when consumed in moderation, up to 500 mg daily. Significant health risks may begin to emerge at 500 to 600 mg daily[6,18,34]. In 1987, FDA (USA) reaffirmed its position that scientific evidences do not indicate that caffeine in carbonated beverages creates any adverse effects in humans[42]. Both the National Academy of Sciences National Research Council and the US Surgeon General's office report that there has been no association established between moderate caffeine intake consumption and increased risk to health[43,44]. Caffeine may produce a mild withdrawal syndrome on discontinuance in regular usage (eg, drowsiness and, occasionally, headache); however, it does not produce addictive behavior[45,46]. Caffeine citrate in a loading dose of 20 mg/kg is the drug of choice for the treatment of apnea in premature infants also caffeine is used to relieve headaches after spinal puncture and is a part of medicines used to treat migraine[47]. But few people seem to know that coffee not only has 1 to 2.5 % of caffeine but many other substances in even larger amounts[18,28]. These other substances may well be more important than caffeine. Coffee has a large variety of minerals (3 % – 5 %) as K, Mg, Ca, Na, Fe, Mn, Rb, Zn, Cu, Sr, Cr, V, Ba, Ni, Co, Pl, Mo, Ti, and Cd; aminoacids (2 %) such as alanine, arginine, asparagine, cysteine, glutamic acid, glycine, histidine, isoleucine, lysine, methylamine, phenylalanine, proline, serine, threonine, thy-

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roxine, and valine; lipids (10 % – 20 %) such as triglycerides and free fatty acids, sugars (35 % – 55 %) as sucrose, glucose, fructose, arabinose, galactose, maltose and polysaccharides. Moreover, coffee also has 0.5 % of niacin [Pelagra Preventing (PP), vitamin from the vitamin B-complex] and, in larger amounts than caffeine, the chlorogenic acids, at 7 % to 9 %. Roasting has a marked effect on the final composition of trigonelline, chlorogenic acids, and free sugars in coffee. Concerning the chlorogenic acids, many different isomers are formed, generated and/or degraded after roasting. After roasting, at least 5 isomers derived from quinic acid are present in coffee: cafeoylquinic acid (CQA), dicafeoylquinic acid (diCQA), feruloylquinic acid (FQA), coumaroylquinic acid (CoQA) and cafeoferuloylquinic acid (CFQA). But coffee is taken as a beverage after roasting. And only caffeine is thermostable, that is, is not destroyed by excessive coffee-roasting. The other substances, such as aminoacids, sugars, lipids, niacin and chlorogenic acids, are preserved, changed or even destroyed during the coffee-roasting process, as shown in Tab 5, 6. The coffee with an ideal roast is one with a chocolate brown color (a dark or light brown). The black coffee, excessively roasted, has mostly caffeine, and only traces of minerals, aminoacids, sugars, lipids, chlorogenic acids and lots of ashes. We were unable to find a single scientific medical article published in English language in the last 20 years (far more than 5000 we could access during this decade) which included the roasting process of coffee, its final bioactive compounds leaving aside caffeine, and its effect on human health. Caffeine is reported in more than 99 % of papers and niacin in a very few ones. No medical article was found mentioning the possible effect of of chlorogenic acids having opioid antagonist activity upon humans, excepting the few from the authors[18,23-25].

Tab 5. Substances found in coffee beans*.

Compound	Roasting stability	Coffee arabica %	Coffee robusta %
Caffeine	thermostable	1 – 1.5	3.0 – 4.5
Trigonelline	depends on roasting	1	0.75
Niacin (Vitamin PP)	depends on roasting	0.5	0.5
Chlorogenic acids	depends on roasting	5 – 7	7 – 9
Aminoacids	depends on roasting	2.0	2.5
Minerals salts	depends on roasting	3 – 4.0	4 – 5
Sugars	depends on roasting	50 – 55	35 – 45
Lipids	depends on roasting	10 – 20	10 – 15
Others (cafestol, oils, pigments, ashes, water, etc...)	depends on roasting	20 – 30	25 – 45

*much roasted coffee (very dark roasting) mainly has caffeine, ashes and traces of other compounds.

Tab 6. Relative percentage (R %) of some chlorogenic acids (CGA) in green and roasted Arabica coffee[28,29] (average total of 6.88 % in green coffee).

Chlorogenic acid group	Green R %	Type of roasting Medium	Dark	Very dark
Coumaroylquinic acid	83.8	19.84	7.10	2.22
Feruloylquinic acids	3.6	0.84	0.30	0.08
Dicaffeoylquinic acids	12.6	1.53	0.31	0.12

Chlorogenic acids from coffee and the opioid system Little is known about the biological activity of the various chlorogenic acids found in coffee. It has been shown that at least one – FQA – has a potent opioid antagonist activity[48,49]. These compounds derived from the chlorogenic acids after roasting of coffee might have important effects on human brain due to this opioid antagonist activity which could well be into the mesolimbic system/brain reward neuronal circuit. This is important particularly considering that feruloyiquinic acids and dicaffeoylquinic acids appear to be the more significant residues of chlorogenic acids in roasted coffees[28]. The discovery of the opioid peptides initiated an immense volume of research into their pharmacological and behavioral properties. A role for opiates in analgesia and positive reinforcement has already been fully determined and recently data have shown that opioid peptides can modify more complex behaviors, including normal developmental and social behavior, motor coordination, feeding, sexual arousal, learning and memory and even psychiatric disorders such as affective disorders, depression, addiction, schizophrenia and autism[50-52]. Many of the actions of the opioids reflect their ability to modulate the processes of neurotransmission by altering the release of other neurotransmitters such as NE, ACh, DA, and 5-HT. Studies indicate a presynaptic inhibition of neurotransmitter relase by opiates and opioid peptides.

Brain meso-limbic reward circuit The brain chemical that leads to depression and compulsive use of drugs resulting in loss of control, creating the dependence, has begun to be comprehended just recently. All drugs of abuse such as the legal ones (nicotine, alcohol) as well as the illegal ones (cocaine, amphetamines, opiates) are typically taken because they produce feelings of euphoria or relieve distress, depression or anxiety. The way drugs cause pleasure or reward, is that they mimic

the actions of the neurotransmitters that activate the brain reward circuit. This highly developed and complex circuit from the human brain functions to motivate positive-stimuli including nutrition and reproduction. And the circuit sets up a kind of registration recognising the circumstances under which rewards occur. If the food is good, every time one sees that food, one craves for it. Concerning drugs such as alcohol and others, there are some vulnerable persons who, after repeated administration of these drugs (dose, frequency, and chronicity) present major changes and long-lived molecular adaptations that lead to compulsive and out-of-control drug usage. The user then becomes addicted to that drug and only experiences self-reward after its regular intake. It is possible to deaddict these individuals, although the risk and vulnerability to a lifelong relapse is great. Drug use is also a major contributor to the transmission of HIV, not only through the sharing of infected needles but also as a result of individual behaviors related to drug use. For example, in poor, inner-city communities, some smokers of crack cocaine, especially women, consent to sex in exchange for drugs or the money to buy drugs, promoting transmission of HIV[53].

Legal drugs such as nicotine and alcohol as well as illegal ones such as cocaine, opiates and probably others are reinforcing because they mimic or enhance the actions of neurotransmitters used in the brain reward pathway. The neuronal circuit implicated in the reinforcing behavior that leads to drug addiction seems to be the dopaminergic mesolimbic system originating in the cell bodies in the Ventral Tegmental Area (VTA) that project to the nucleus accumbens (NAc). An opposing tone of opioid neurons in the mesolimbic dopamine cells explain the mechanism of drug reward. It seems that in the VTA, beta-endorphin neurons via μ-receptors increase mesolimbic activity by inhibiting the inhibitory GABA neurons. The release of dopamine (DA) from mesolimbic nerve terminals is tonically inhibited by dynorphin activity via κ-receptors. Basal dopamine release is determined by the balance between the two opioid systems. D1 receptors on cells in NAc that enter other brain areas, such as the ventral pallidum, may ultimately be responsible for motivational tonus (aversion, neutral state, positive reinforcement). It is the neurotransmitter dopamine which plays a major role in acting and setting up the circumstances under which the rewarding stimuli occur. Opiates increase firing of cells in the VTA and subsequently increase release of DA in the NAc. Similar actions are reported for the self-administration of ethanol, nicotine, cocaine as with morphine, thus showing a common link in reinforcement mechanism involving the VTA-NAc pathways. This role of opiate receptors in drug addiction is confirmed by clinical trials showing the efficacy of naltrexone, an opiate receptor antagonist, in blocking the craving for alcohol[54,55]. Also, the antidepressive bupropion, which acts by increasing dopamine levels at NAc has been shown to be efficient in controlling smoking[56]. Cocaine inhibits the reuptake and clearance of dopamine from synapses, and amphetamine causes dopamine release. The opiates mimic endogenous opiate like compounds (eg, enkephalins), which can act directly on the NAc and can also disinhibit the VTA, leading to dopamine release. Nicotine mimics the action of acetylcholine at its nicotinic receptors. Ethanol is a nonselective agent but at intoxicating doses has powerful facilitative effects on GABA-A receptors. Both nicotine and ethyl alcohol have been shown to cause dopamine release in the NAc. This system also appears to be involved in the motivation and the behavior necessary for human survival and the reproductive process, including the reproduction act. The process of choice and selection of food may be a specific manner of selection in the evolution process. Perhaps by the activation of the dopaminergic mesolimbic system, food (and drugs) can lead to a conditioning and gratification response, fortifying the memories and learning mechanisms. Cocaine, nicotine, opium and ethanol are all originally sub-products from plants or natural fermentation and act as conditioning substances which generate dependence, by imitating or increasing the neurotransmitter actions that are involved in the gratification and learning mechanisms in humans[57-59].

Coffee: the world's major crop and its scientific potentital Coffee exports vary from 33 percent of the total in Colombia to 2 percent in Bolivia, but is still an important source of income for many Latin and Central American countries. In Bolivia the coffee crops have been almost entirely replaced by that of cocaine. Coffee was responsible for up to 70 % of all exports in Brazil at the beginning of this century, being slowly replaced since then by manufactured products. In Bolivia agriculture is responsible for almost 24 percent of the GNP; in Colombia it is responsible for almost 19 percent, while in Peru for 10 percent and in Brazil 9 percent, coffee being the most important crop. Although Brazil has manufacturing accounting for 27 percent of its GNP, the torching of the Amazon Forest with its Brazilian area of 5.0 million square km and its 30 million hectares of agricultural floodplains (varzeas), is creating conditions for the cul-

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turing of the most profitable of all crops, that of coca. Very soon the dominant agricultural activity and the most profitable one in Latin America will be that of coca, unless alternative crops are identified and used for commercial purposes in poor countries trade and source of wealth. Bolivia, Peru and Colombia grow up most of the coca leaf that is ultimately converted into cocaine. Colombia has been the principal refiner and exporter, and is now emerging, together with Brazil, as the third leading cultivator of the coca plant as well. Hundreds of thousands of families are, or intend to be, dedicated to coca-farming, which is far more profitable than coffee. Agriculture and trade produce a plentiful supply of food in the rich countries such as US, Japan, England, Canada, France, Germany and Italy. In these countries surplus crops have become an economic embarrassment and obesity is a common cause of ill health. At the same time in all the other poor countries mostly in South America, Africa and Asia, where most of its people live as peasant agriculturalists and the food supply rarely measures up the energy needs for daily work, hunger is commonplace. This builts up to dramatic proportions at the season before the harvest, and millions of children and adults starve to death. The survivors present severe physical and mental deficiencies due to chronic malnourishment. The poor countries have little to export, and do it at very low prices, thus making it difficult to set up a balance to import food. And as the increase in population far exceeds the increase in agricultural production, the only solution to the problem is a catastrophic increase in death rate due to famine or epidemic diseases, particularly in areas where there is no active family planning programs. For humanitarian reasons the production of food and the discovery of profitable medicinal plants must be increased, particularly in food-deficient areas, so that sufficient quantities exist in order to satisfy people's need with an equitable distribution. Areas with poverty associated with rapid population growth must have an ever increasing agricultural activity, but science-based and high-yeilding. Coffee growing areas are a paradigm of sustainability and social responsability in Brazil. The repeated use of the same areas for decades and even centuries has taught the Brazilian coffee farmers to preserve forests, to avoid erosion and to protect water sources. Today, strict legislation protects forests, rivers and springs and a positive balance between forest area, coffee, other crops and grazing lands prevails in most coffee growing areas. Social responsibility is best exercised by fair wages. Real income is probably larger in Brazilian coffee areas than in other similar areas of the world due to the small scale farming, labor partnerships and technology. Access to education, school breakfast programs and health services are guaranteed by the provision of facilities on the farms and in rural communities or free transportation to the nearest urban center with government facilities. Real income from coffee creates a large consumer base in Brazil; this represents the best possible example of sustainable economic development. Definitively coffee beans, coffee roasting and coffee drinking has yet to be studied a lot under rigorously controlled situations in leading research laboratories and medical centers in rich countries taking into account consumers worldwide, including healthy youth and adults as well as depressed people, alcoholics, smokers and drug addicts. It is important for medical science to define if coffee culture and coffee consumption can be of help fighting the illicit drug trade and consumption. Additionally it is important that more clarifying scientific research concerning coffee intake and health effects is performed, as coffee has far more bioactive compounds than caffeine, the only compound mentioned in most of the available medical literature with very few exceptions[18,25,28-30,60].

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