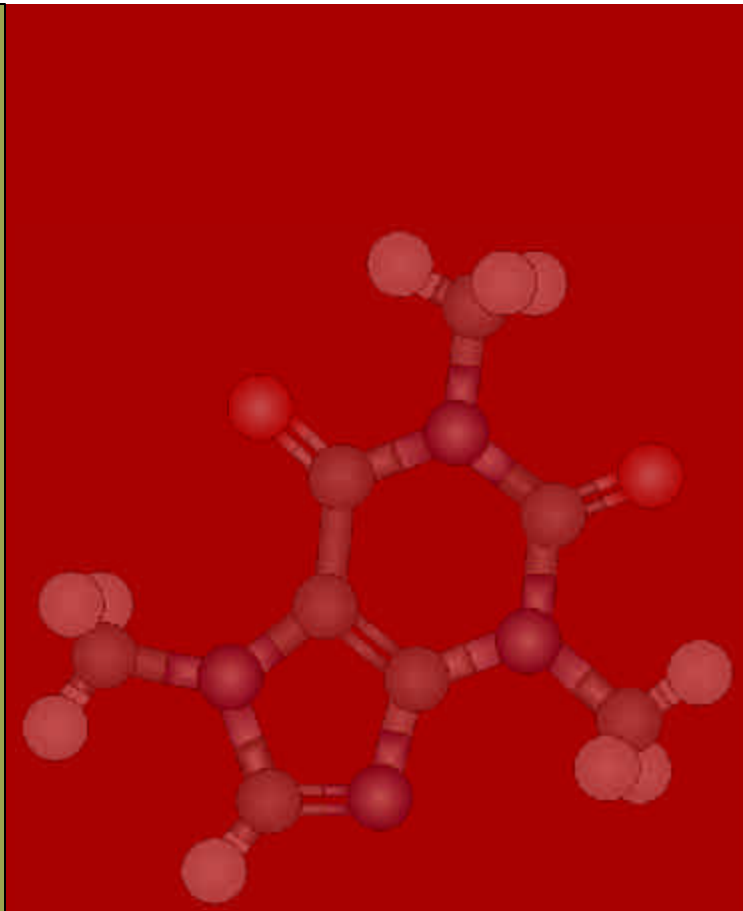
About the ICO

Established as an intergovernmental organization in 1963 to serve the international coffee community, the ICO is the focus for international cooperation on coffee matters, coordinating activities with other international agencies and bringing together producing and consuming Governments and private sector representatives to exchange views and address policy issues. In October 2001, the latest International Coffee Agreement entered into force, with new objectives including promoting quality, promoting coffee consumption and encouraging the development of a sustainable coffee economy. The ICO provides the following services: up-to-date information and statistics; innovative projects to benefit the world coffee economy; economic studies; and promotion of coffee consumption in emerging markets.

Opening of the Seminar on Coffee and Health
40th Anniversary meeting of the ICO
Cartagena, Colombia, 15 september 2003

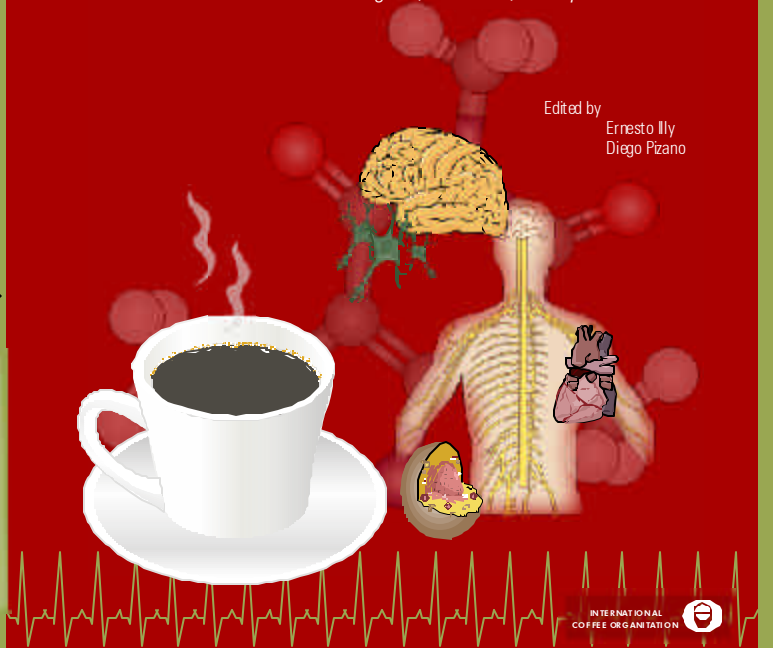


COFFEE AND HEALTH

New Research Findings

Proceedings of the International Seminar on Coffee and Health
40th Anniversary meeting of the ICO
Cartagena, Colombia, 15 september 2003

Edited by
Ernesto Illy
Diego Pizano



Coffee is the world's second most popular drink, after water. Over a billion people around the globe drink it on a daily basis. The beverage has been described as the intellectual fuel of the contemporary world. To celebrate the first 40 years of the International Coffee Organization, an international seminar on coffee and health was organized in Cartagena, Colombia (September 15, 2003). This book presents the proceedings of this important seminar.

Over the past decade research into the health aspects of coffee drinking has gone from negative to positive. In this book leading researchers explain recent findings, which show coffee can help control or prevent various diseases. Consumers can enjoy the pleasure of a good cup and at the same time benefit from the medicinal properties of this unique natural product.

INTERNATIONAL COFFEE ORGANIZATION

COFFEE AND HEALTH

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INTERNATIONAL
COFFEE ORGANITATION

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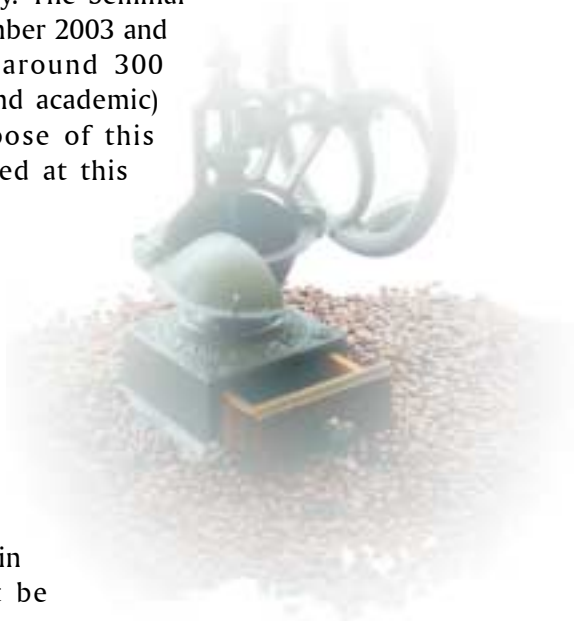
INTRODUCTION

ERNESTO ILLY
DIEGO PIZANO

Coffee is not only one of the most important commodities in international trade but also the world's second most popular drink, after water. Coffee has been described as "the intellectual fuel of the contemporary world"[1] and the human brain has been defined as "a machine for converting coffee into mathematical theorems."[2] People have been drinking coffee for the last thousand years and throughout its history all sorts of theories have been advanced on its possible effects. Only in the last 10 to 15 years, however, have any rigorous scientific conclusions been reached. These research findings are published in highly specialized periodicals and have not been sufficiently publicized among members of the medical community and still less among current and potential coffee drinkers.

In these circumstances it is easy to understand why the International Coffee Organization gave such an enthusiastic welcome to the idea of the Colombian delegation that a Seminar on Coffee and Health should be held as part of the celebration of the Organization's 40th anniversary. The Seminar duly took place in Cartagena, Colombia, on 15 September 2003 and was attended by distinguished scientists and around 300 participants from various sectors (public, private, and academic) representing more than 60 countries. The purpose of this publication is to summarize the themes considered at this important Seminar.



A casual observer could ask: How important is research on coffee and health in terms of promoting world coffee consumption? One way of answering this question is to refer to recent econometric studies measuring the price elasticity of demand for coffee in different markets[3]. These studies showed that this elasticity has diminished over time, that is, consumption levels respond less and less to cuts in coffee prices. On the other hand, the growth in consumption recorded in some markets cannot be

1 Bernard Rothfos, Kaffee, Der Verbrauch, Gordian, Hamburg, 1984.
2 Phrase attributed to Professor Paul Erdös, one of the 20th century's most prolific mathematicians, who was a great coffee drinker.
3 See, for example, the ICO/FAO studies on the development of an econometric model of the world coffee market.

explained simply in terms of variables such as increased incomes or variations in price. There are doubtless other significant factors associated with the behaviour of consumption, one of the most significant being the quality of the beverage.

What do we mean by quality? The term covers a number of aspects, since it is associated not only with a low number of defects in the final product and excellence in all the processes involved in the value-added chain but also with final consumer satisfaction[4]. In the case of coffee, quality is associated with the way in which the human brain processes sensory perceptions and distinguishes between pleasant and unpleasant tastes[5].

As Professor Martin indicated at the Cartagena Seminar, many of the world's doctors were educated in the belief that coffee is harmful to health. Several scientific studies now indicate that moderate consumption of coffee (between five and six cups a day) not only poses no risks for a normally healthy person but also has important benefits. The Centre of Scientific Information on Coffee (COSIC), based in Oxford, England[6], has identified several positive effects backed by solid scientific evidence:

1. Coffee increases the level of alertness, improves short-term memory and permits better use of the prefrontal cerebral cortex.

2. Coffee has antioxidant and antitoxic properties at cellular level.

3. Coffee reduces the risk of hepatic cirrhosis and prevents the formation of gallstones.

4. Coffee provides protection against degenerative brain diseases like Alzeimer's and Parkinson's.

5. Coffee provides protection against colon and skin cancers.

6. Coffee combats caries and has anti-inflammatory properties.

7. Coffee has a moderate slimming effect and improves performance in sports.

8. Coffee helps to alleviate asthma symptoms and helps to calm hyperactive children.

It was not possible to study all these topics at the Seminar but new evidence was presented on a number of these effects as well as on other beneficial properties of coffee. Professor Peter Martin of Vanderbilt University spoke of the possible anti-depressive and anti-addictive properties of certain coffee compounds. He also referred to coffee's antioxidant properties and its protective effects against diabetes.

Dr. Astrid Nehlig of the French National Health Institute presented an important paper on the effects of coffee on the central nervous system. This distinguished researcher provided convincing evidence that moderate consumption of coffee does not cause addiction and helps to combat fatigue, improve intellectual performance and stimulate the "feel good" factor in individuals. She also argues that certain coffee compounds help to prevent Parkinson's disease and possibly Alzheimer's.

Professor Andy Smith of Cardiff University (United Kingdom) produced a fascinating paper explaining the cerebral mechanisms responsible for improving attention and memory. He also has evidence that coffee helps to prevent accidents on the road and at work as well as helping to improve performance of various tasks.

Professor Kazumi Yagasaki of the Tokyo Noko University in Japan has been studying the inhibiting effects of certain coffee compounds on proliferation and metastasis in animal cells affected by cancer.

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4 Diego Pizano, 'Quality, Health Standards and Research with Reference to Coffee'. Capítulo 23 del libro, International Commodity Organisations in Transition. Londres, Cameron, 2002

5 Ernesto Illy, 'The Complexity of Coffee', Scientific American, June 2002.

6 www.cosic.org

The scientific findings he presented to the Seminar reinforce the validity of the hypothesis that coffee has protective effects against certain types of cancer.

Dr. Cristina Scaccini of the National Institute of Nutrition in Rome (Italy) collaborated with her research colleagues on an important study of the antioxidant effects of coffee. Antioxidants provide protection against free radicals, which can cause damage to cells and may contribute to the development of cancer.

Professor Mario Maranhão, until recently President of the World Heart Foundation, found that a high percentage of patients with cardiovascular diseases suffer from depression. Coffee has been shown to have significant anti-depressive effects and moderate consumption of the beverage could help millions of persons suffering from heart disease worldwide.

The Seminar ended with a presentation by Professor Manuel E. Patarroyo, Director of FIDIC (Colombia). This distinguished researcher reminded the audience that a cup of coffee contains over a thousand different compounds, including various acids, minerals, vitamins, proteins, lipids and amino-acids. This does not mean that coffee is a complete food, since several of these elements are present in very small quantities. Nevertheless, these compounds have positive effects on the human organism and coffee should, therefore, be part of a balanced diet.

A reading of the papers presented at the Seminar is a good intellectual investment. This is why we are inviting all those interested in coffee and health to read the papers contained in this publication.

Finally, we wish to thank Dr. Gabriel Silva, Dr. Néstor Osorio and the directors of Colcafé for their cooperation and support for this Seminar. Now we must continue to support research and intensify efforts to publicize these scientific findings worldwide.

OPENING STATEMENTS

DR. GABRIEL SILVA LUJAN
GENERAL MANAGER OF THE NATIONAL FEDERATION OF COFFEE GROWERS OF COLOMBIA

First and foremost I wish to welcome all participants in this important event and to thank the following speakers for their contribution:

- Professor Peter Martin of Vanderbilt University (USA) and Director of the Institute of Coffee and Health
- Dr. Astrid Nehlig, Director of Research at the French National Institute of Health and Medical Studie<s (INSERM)
- Professor Andy Smith, Director of the Mental Health and Occupational Therapy Centre of Cardiff University
- Professor Kazumi Yagasaki of Tokyo Noko University, Japan
- Dr. Cristina Scaccini, Head of Research at the National Institute of Food and Nutrition, Italy
- Professor Mario Maranhão of the University of São Paulo (Brazil)
- Professor Manuel E. Patarroyo, Director of FIDIC (Colombia)

I also wish to thank Dr. Beatriz Londoño, Director of the Colombian Family Welfare Institute, and Dr. Ernesto Illy, distinguished scientist and entrepreneur and Chairperson of the ICO Promotion Committee, for their presence.

A year ago the delegation of Colombia proposed that the International Coffee Organization hold this international seminar on Coffee and Health as part of the commemorative activities for the Organization's 40th anniversary. The idea was enthusiastically welcomed and was supported by Dr. Néstor Osorio, Executive Director of the ICO.

Coffee has been stigmatized by the medical community for the last 30 years and has earned a reputation in relation to the negative effects of caffeine which has no real scientific basis.

Some of the myths attributed to coffee are:

1. Parents should not give their children beverages containing caffeine!
2. Caffeine causes hyperactivity in children!
3. Women should not drink coffee because it causes breast cancer.
4. Its addictive effects are similar to those of dangerous drugs.

However, a large number of studies published by prestigious research centres all over the world have proved that these medical myths are false and that moderate consumption of caffeine, both by children and by pregnant women, is harmless.

On the contrary, moderate consumption – between five and six cups of coffee a day – can have important beneficial effects on health in various types of illness, quite apart from its anti-depressive, antioxidant, anti-inflammatory and anti-carcinogenic effects, among others.

These results have obviously been a vital step for promoting global consumption, which has been growing by less than 2% annually in the last 12 years. An aggressive strategy is needed to update the medical community on research findings that disprove old ideas.

These efforts need to be intensified both in producing and consuming countries; since, despite the well-structured programmes being carried in countries like France and the United Kingdom, dissemination of information is still inadequate.

In order to make available the results of some of the studies carried out, we have produced a compilation which will be distributed at the end of this seminar. It is derived from a number of sources and is based on serious and solid scientific literature. Some of the texts were aimed at non-specialized readers but others are somewhat more technical. The idea is to reach various audiences.

STATEMENT BY DRA. BEATRIZ LONDOÑO
DIRECTOR OF THE
COLOMBIAN FAMILY WELFARE INSTITUTE

Mr. Mick Wheeler, Mr Jacques Thinsy, Chairperson of the International Coffee Council, Dr. Gabriel Silva, President of the National Federation of Coffee Growers, Dr. Néstor Osorio, Executive Director of the International Coffee Organization, Dr. Manuel Elkin Patarroyo, Fellow Delegates, Ladies and Gentlemen:

It is an honour to be with you at the opening of this Seminar on Coffee and Health, which is being held on the historic occasion of the first meeting of the International Coffee Organization in Colombia in celebration of its 40th anniversary. I wish to extend a warm welcome to all international delegates who will be spending a week as guests of this splendid Caribbean city or the lush coffee areas of the country's heartland.

I will begin this presentation by sharing with you a very personal feeling. I feel at home with coffee people. I have coffee in my soul. Many of my childhood holidays were spent among the coffee trees on my grandfather's farm. Many marvellous images are engraved in my memory but also some of the reflections of my elders on matters of concern to you today. Despite living so close to coffee, I only learned to drink it as an adult and, over the years, I've acquired a personal style of drinking my morning coffee. I cannot begin the day without drinking a delicious cup of coffee with ice-cold milk. If I don't prepare it myself, my husband does this for me, and as he hands me the cup he always says: "I have a great survival instinct". There must be a good reason!

I am here at the kind invitation of Gabriel Silva and Néstor Osorio. For Colombians, the Institute I direct *(Instituto Colombiano de Bienestar Familiar – ICBF)*, the Colombian Family Welfare Institute, conjures up two images: the first relates to periodic payments since the Institute's resources come entirely from a payroll tax. The second because it is the national institution that reaches most Colombian homes through a number of programmes carried out

with the participation of local municipalities and departments, among others. To sum up in a few words all the services we provide, I can say that we are directly responsible for carrying out school nutrition programmes nationwide as well as giving priority to early childhood care in highly vulnerable populations. Protection of children whose rights are being violated is a key element of our work. We are far from satisfied with everything we do but we are working very hard to provide better tools, opportunities and services for the poorest families, thus helping to improve their living conditions.

Ladies and Gentlemen,

We have come to this Seminar both to learn and to "unlearn"!

Coffee and Health. The ICO cannot focus only on the effects of consuming coffee. This is why I'm very glad that apart from promoting solid commercial relations, the industry is genuinely concerned that consumers be made aware of an ethical agenda promoted among producing countries with a view to discouraging absenteeism from school among children of coffee growing families and ensuring that they are given proper respect so that they are not overburdened with an inappropriate work load.

A great deal of research has been done and much has been written on the effects of coffee on the human organism. At least 19,000 studies have been published. Caffeine has been studied exhaustively, as if it were the only element present in coffee. There has been direct contact with coffee for centuries as well as consumption, but many attitudes, not always scientifically based, need to be seen in proper perspective. There seems to be a consensus in the scientific community that coffee consumed in moderation has no harmful effects on human health. There is greater knowledge, however, of what happens in the case of adults.

Coffee is better known for all its positive effects in the prevention of colon cancer, Parkinson's disease and the formation of gallstones. Its negative effects are also known: the possibility of arrhythmic heartbeats among heavy consumers, or its effects among Scandinavians who customarily boil their coffee...

Sensitivity to caffeine depends on many factors such as how often and how much coffee is consumed, body weight, and the individual's physical condition. Other factors include the type of bean, the grind, and the preparation and processing methods used.

The average daily amount of caffeine consumed by a North American child, namely between 30 and 40 mg. carries no health risk whatsoever. There is also no evidence that this amount can contribute to hyperactivity or attention-deficit syndrome. The available scientific evidence suggests that children are not more sensitive to caffeine than adults. What happens in the case of children to the antioxidant effect of the chlorogenic compounds and other polyphenoles? What would constitute an effective protective dose? Does it really prevent later use of psycho-active addictive substances? How much milk should be mixed with coffee to ensure there is no loss of the benefits of the two products? We will have the opportunity to listen to a number of delegates whose research has helped to enrich our knowledge of the effects of caffeine. We are very much looking forward to hearing them. It would be useful to have their opponents among us. As a specialist doctor, as a public health officer and as someone now responsible for promoting the development of public policies, I can assure you that the Colombian Government, and we in the ICBF in particular, are interested in listening to them with the greatest interest, without prejudice and fully aware of the multi-dimensional nature of any political proposal. Geopolitical, economic, nutritional and developmental elements are all involved and we should, of course, be careful to heed the available scientific evidence. The use of coffee in school canteens has been encouraged in many areas of our country, for example in the city of Manizales and in the Department of Cundinamarca. Family use and approval is greater among the rural population, particularly among coffee farmers.

Research work must continue in order to establish a solid basis for providing better guidance to parents, carers and teachers on the positive effects which moderate coffee consumption can have on a child's alertness, motivation, activity and concentration, as well as on school performance and overall behaviour.

What we do will not change the lives of the 600,000 Colombian families involved in coffee farming and millions of families in more than 60 countries but we must remember that producers throughout the world depend on coffee for their livelihoods.

People throughout the world are hoping that meetings such as this will not serve merely to reunite old friends but also to find "concrete and durable solutions for the crisis" as the General Manager of the Federation put it in inviting you all to come to Colombia. I hope that your stay in our country, under the guidance of Dr. Néstor Osorio and the Colombian team, will be very pleasant and, above all, that it will prove fruitful for the welfare of millions of families worldwide.

STATEMENT BY DR. NÉSTOR OSORIO LONDOÑO
EXECUTIVE DIRECTOR OF THE
INTERNATIONAL COFFEE ORGANIZATION

In welcoming you most cordially to this important event, which brings together distinguished scientists, members of the medical profession and coffee researchers, I would like, first and foremost, to thank the Colombian authorities and, in particular, the National Federation of Coffee Growers of Colombia, for their decisive contributions to the organisation of this Seminar on Coffee and Health.

I would also like to express my gratitude to the distinguished academics who have generously accepted our invitation and agreed to share with us the results of their investigations and studies.

During the 40 years of its existence, which is being commemorated at the same time as this event, the International Coffee Organization has actively encouraged scientific research on coffee and analysis of the effects of coffee drinking on human health. In this respect, we have developed specific programmes and projects and supported research groups and institutions, always safeguarding the independence and autonomy of researchers.

In a society increasingly aware of and concerned with the influence of food and drink on health, coffee stands out as one of the most studied and researched, but also most maligned of products destined for human consumption. Our analyses of consumer behaviour have shown that a factor limiting consumption, in particular in developed countries, is the fear that coffee is a risk to health.

Unfortunately, this is a result of negative attitudes derived from outdated scientific literature, much of which is currently being re-assessed. Certain myths have been created and are still being perpetuated because of the widespread ignorance concerning new scientific findings which contradict them. Nowadays, given the evidence of the health benefits of coffee, which is in many cases overwhelming, it is imperative to develop a policy to educate and inform consumers.

The International Coffee Organization, in association with the Institute for Scientific Information on Coffee (ISIC) which includes representatives of the European coffee industry, is developing activities for this purpose through the "Positively Coffee" programme, which was initiated in the United Kingdom and is now being extended to other countries. The aim of this programme is to provide the medical profession, nutritionists, and the general public with objective information based on independent scientific studies, which show the health benefits of coffee.

If this information becomes sufficiently well-known and effective, it will be possible to dispel prejudices and create positive attitudes that could lead to an increase in consumption.

During the course of this week, an Action Plan to increase world coffee consumption will be submitted for consideration to the ICO Promotion Committee under the chairmanship of Dr. Ernesto Lilly. Projects related to health form a major part of this plan. I would like to take this opportunity, Dr Illy, to express, before this distinguished audience, my appreciation and admiration of your selfless work and your enormous contribution to the defence of coffee.

I would also like to take this opportunity to acknowledge and bear witness to the significant contribution which scientists like those present have made to the coffee sector and to renew my appeal both to the Governments of Member countries and to the coffee industry to give their support to these initiatives.

I hope that this seminar will be illustrative and enlightening in respect of the health benefits of coffee, contributing to the process of educating consumers.

Many thanks.

FUNDAMENTAL RESEARCH, EDUCATION, AND DISSEMINATION OF FINDINGS ON COFFEE AND HEALTH

Peter R. Martin, M.D.
Professor of Psychiatry and Pharmacology
Director of Division of Addiction Medicine,
Vanderbilt Addiction Center,
and Institute for Coffee Studies
AA-2206 Medical Center North,
Vanderbilt University Medical Center,
Nashville, Tennessee 37232-2647, USA

Good Afternoon,

Let me begin by offering my warm congratulations to the International Coffee Organization on its 40th anniversary. It is a great honor to be invited to participate in this Symposium on Coffee and Health. I would very much like to have been with you, in person, today; however, previous commitments made it impossible for me to travel to Cartagena.

We at the Institute for Coffee Studies at Vanderbilt University Medical Center in Nashville, Tennessee, indeed appreciate the recent endorsement by the ICO of our research and educational activities related to the health benefits of coffee. I want to thank Dr. Osorio for his continued support of our work.

Special thanks to Mr. Pizano for his leadership on behalf of the Colombian Coffee Federation in making this symposium a reality.

The theme of this meeting represents a significant change in the coffee world over the last half decade. The following videotape, which appeared in 2002 on U.S. national television, summarizes the major issues on Coffee and Health, and emphasizes recent changes in attitudes about whether coffee is healthful or harmful.

Video tape presentation

With apologies to petroleum this is America's fuel. Kick starting a nation of bleary eyed foggy headed sleep walkers into the citizen soldiers of Café Nation. America's melting pot perhaps, America's coffee pot for sure.

One could really make the argument that coffee is the American lubricant. It lubricates social situation and it also lubricates the work place. Bob Thompson is a professor of popular culture in Syracuse University. He started a whole course on Starbucks.

As you are working during the day, coffee becomes the equivalent of an in- flight fuelling station, you grab a cup on the way to work, you've got it in your little commuter holder in your car, there is a pot at the work place, there is a sense in which this is really the stuff which keeps us fuelled and keeps us going. And I think that it's really appropriate that oil and coffee look the same because there are a lot of ways in which oil and coffee are doing the same job.

And after oil, coffee is the second most valuable commodity in the world. More than 50% of Americans drink coffee everyday. Three to four cups a piece. More than 330 million cups a day and counting. But for all the new flavours and varieties it's not the taste driving coffee popularity, it's the feeling.

End of videotape presentation.

In 1998, when first approached by scientific and other colleagues from Brazil, Colombia, and Central America, to establish at Vanderbilt University an institute devoted to increasing mechanistic understanding of the health benefits of coffee consumption, I was reluctant to do so. I was taught in medical school that coffee consumption was both addictive and detrimental to health (the so-called "old school" mentioned in the videotape). Only after an extensive review of the relevant scientific literature did I change my opinion about the harmful effects of coffee consumption.

It was apparent that early studies, which showed harmful effects of coffee, suffered from significant methodological weaknesses.

Confounding lifestyle variables, such as smoking, were not adequately controlled in these population studies. Also, coffee frequently was equated with caffeine, thereby not taking into consideration that coffee is a complex mixture of biologically active compounds.

It was not unusual for scientists to assume that the effects of coffee consumption were identical to caffeine in pill form. For example, caffeine pills were found to increase blood pressure and pulse. Because chronically elevated blood pressure is a well known risk factor for heart attacks, it is easy to draw the fallacious conclusion that coffee causes hypertension, heart disease, and heart attacks.

Little consideration is given to the fact that coffee also contains other compounds that may antagonize the actions of caffeine; that some compounds in coffee are antioxidants, of benefit to heart health; and that some putative effects of coffee, namely

antidepressant actions, may all greatly alter the coffee=caffeine equation.

In conclusion, on careful examination of the recent scientific literature, there is little compelling evidence that coffee consumption in moderation is detrimental. On the contrary, population studies suggest potential health benefits of coffee consumption (the so-called "new school" in the videotape). For example, increased coffee consumption is associated with reduced rates of suicide, cirrhosis of the liver, cancer, atherosclerosis, Parkinson's and Alzheimer's diseases, and most recently, diabetes.

It clearly behooves us to attempt to elucidate the fundamental mechanisms of such health benefits of coffee consumption.

We at the Vanderbilt Institute for Coffee Studies have attempted to design mechanistic research on coffee constituents by following the exciting leads given us by population studies. I believe that such studies may help us better understand, prevent, and treat some of the most common diseases that affect mankind. Because population studies can only show associations, and not causality, investigations at a more fundamental level are needed to unravel the basis for these associations.

Basic studies may also help counter the prevailing viewpoint that coffee is harmful.

A significant reason most people believe that coffee consumption is harmful, may be because physicians are still taught in medical schools that coffee is detrimental to health. Consequently, when physicians counsel their patients regarding general health or a newly diagnosed illness, their advice is not to consume coffee, or else to cut back. Physicians are not interested in marketing-driven research that has been the emphasis of the coffee industry; however, they would likely be captivated by rigorous scientific work that appears in medical journals. Thus, research directed at fundamental mechanisms underpinning health benefits of coffee consumption would affect the content of medical school curricula, specifically, what physicians in training are taught about coffee.

This has clear implications for physician attitudes, and ultimately, what society considers accepted health behaviors.

To restate this point: Coffee is healthful, rather than harmful, but unless your physician can tell you that, you will continue believing what you have always been told.

Mechanistic research on coffee and health should be multidisciplinary, because studies must be conducted using test tube measures of function, laboratory animal models, and experiments in healthy humans and in disease states. Let me mention one particularly interesting example of the research to which I am referring. It is well established that caffeine inhibits the actions of insulin, and thereby, exacerbates some of the abnormalities found in diabetics.

This includes both those of Type I diabetes [insufficient insulin production] and Type II diabetes [the inability of organs to respond to insulin in the blood].

Type II diabetes exacts a huge toll in money and human suffering, accounting for 15% of all medical costs in the United States. The number of cases worldwide is estimated at 150 million. This is a minimum number, because for each diagnosed case, there is thought to be one undiagnosed case in First World countries and eight in Third World. An explosion in prevalence is occurring due to overeating, at about 50% per decade. Because the epidemic is just beginning in the world's two most populous countries, India and China, by the year 2010, more than half of the world's diabetics will be Asians. (Interestingly, in these countries, tea, not coffee, is the beverage of choice.)

In at least two epidemiologic studies over the last year, of which I am aware, the interesting observation was made that increasing consumption of coffee seems to reduce the prevalence of Type II diabetes. So, even though accepted knowledge about the actions of caffeine would indicate that individuals with diabetes should avoid coffee, these population studies actually suggest the opposite, that coffee may be protective with respect to the

development of Type II diabetes. The only logical conclusion that can be drawn from these conflicting data is that something in coffee, other than caffeine, may have potentially beneficial effects on diabetes! Work begun at the ICS over a year ago by Dr. Jane Shearer, a visiting research fellow from Canada, has shown that a non-caffeine constituent of coffee, synthesized by Dr. Tomas de Paulis, increased the capacity of the liver to remove glucose from the blood by 55 percent in the laboratory rat. Besides the potential utility of such a compound to treat diabetes, it could perhaps also explain the population findings of reduced rates of Type II diabetes associated with increased coffee consumption. Much work is clearly needed to expand these promising findings. Such results may eventually lead physicians NOT to discourage their diabetic patients from consuming coffee.

Furthermore, the potential for coffee to reduce the rates of Type II diabetes may have significant implications with respect to health, especially in populations, in which the prevalence of Type II diabetes is rising precipitously, and who do not already drink coffee.

In the last part of my talk, I would like to provide an overview of biological mechanisms that may explain findings from the population studies, to which I referred above. For example, that coffee consumption is inversely associated with the prevalence of suicide, suggests that if we better understand this association we may gain insight into the causation and treatment of depression and anxiety, both very common causes for suicide.

We have devoted considerable attention to the actions of coffee constituents on drive, mood, and pain via the opioid and adenosine systems of the brain. The focus has been to demonstrate that certain chlorogenic acid quinides can antagonize the effects of morphine at its brain receptor. In addition, we found that these compounds can increase the levels of the neuromodulator adenosine in the vicinity of nerve cells. Adenosine is an extremely important anti-anxiety and anti-depression molecule produced by the brain. Caffeine specifically antagonizes these effects. Our findings suggest that certain coffee constituents may potentially oppose the anxiety- and depression-provoking effects of caffeine.

Dr. James May, Associate Director for Basic Research at ICS, and his colleague, Dr. Huang, a post-doctoral research fellow from China, have investigated antioxidant effects of chlorogenic acids in roasted coffee. They have demonstrated that dihydrocaffeic acid, a major metabolite of coffee constituents in humans, can improve functioning of cultured blood vessel cells, and thereby, may be protective against atherosclerosis and related diseases. By adding dyhydrocaffeic acid to these cells, they found that the cell's own vitamin E [a very strong natural antioxidant] was preserved in a dose-dependent manner, and in concentrations that are typically obtained in drinking coffee.

Dyhydrocaffeic acid also increased the activity of nitric oxide synthase in these cells, an effect that should dilate blood vessels via a similar mechanism as the well known drug Viagra, and thereby could oppose hardening of the arteries.

I would like to close by discussing the relationship between coffee consumption and addiction. This area is dear to my heart, since I am an Addiction Psychiatrist, and regularly face the challenge of treating patients addicted to alcohol, cocaine, morphine, etc. I would like to underline that there is no evidence that coffee, or even caffeine, is addictive in the way the previously mentioned drugs are. People do not destroy their lives and their marriages, rob banks, and commit assault or murder in order to obtain coffee.

On the contrary, I believe we are beginning to discover that coffee may have beneficial effects in individuals who are suffering from addiction. For example, naltrexone is a medication that reduces relapse to alcoholism. The compounds we have uncovered in coffee, block the actions of brain opioid receptors, just like naltrexone. We do not yet know conclusively, whether coffee constituents may reduce the severity of addiction to alcohol, cocaine, or morphine. However, Dr. Ruggero Gallici, a visiting research fellow at the ICS from Italy, has preliminary data suggesting some of these compounds may alter the actions of cocaine in laboratory mice.

Ultimately, if coffee were rigorously demonstrated to have a beneficial effect on addiction, this could have tremendous importance to mankind, because these illnesses are some of the most destructive to society.

To me, it is ironic that in the U.S., it is not customary to allow youngsters to drink coffee, when what parents actually fear is alcoholism and drug addiction. We do not yet have strong mechanistic evidence to recommend that parents change this practice. However, there seems to be heuristic value in posing the following question, as Professor Darcy Lima has done: Could we actually prevent these devastating addictive disorders, or reduce the associated suffering to a significant degree, by permitting coffee drinking at a younger age?

This is a provocative question, indeed, that requires intensive fundamental research; research to be conducted by a new generation of coffee scientists who are trained in both basic and translational research. An important aspect of our mission at the ICS is to help train some of these young scientists.

Once again, my apologies for not being able to be with you today, and my best wishes to the International Coffee Organization for much success in the future.

EFFECTS OF COFFEE ON THE CENTRAL NERVOUS SYSTEM

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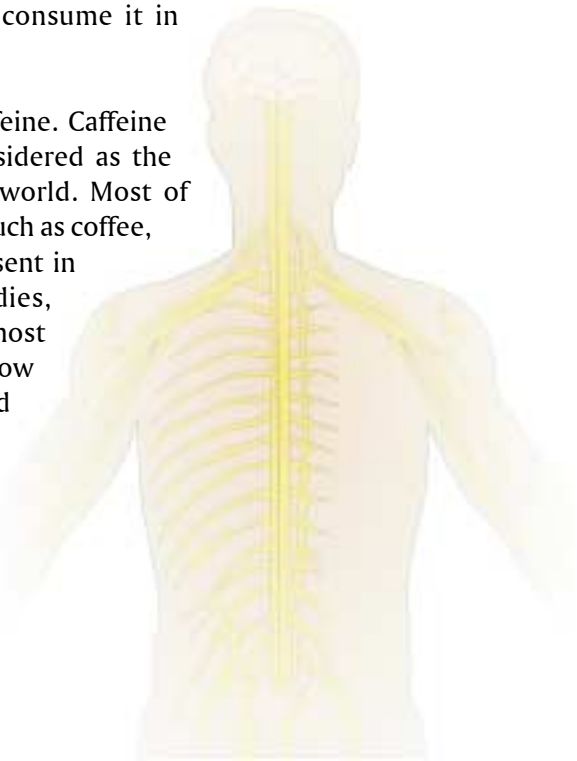
Historically, coffee was first consumed as a "medical nutrient" because of its stimulatory effects on digestion. These virtues of coffee were described by Razes, a Persian of the late 9th century and Avicenne, an Arab living in the 11th century. Then, Prosper Albin, an Italian botanist and medical doctor studied coffee during a trip to Egypt in 1580 and mentioned that "Arabs and Egyptians use it to make a kind of infusion that is popular and that they drink in place of wine". The first citations of coffee are from Antoine de Jussieu in 1713 and Carl von Linné in 1753. The Encyclopedia by Diderot and d'Alembert (1751-1752) described the virtues of coffee in "obesity or headaches" and mention that "it can be harmful to people who consume it in large quantities".



The main psychoactive component in coffee is caffeine. Caffeine was isolated from coffee beans in 1820. It is considered as the most widely used psychoactive substance in the world. Most of the caffeine consumed comes from dietary sources such as coffee, tea, cola drinks and chocolate. Caffeine is also present in many non-prescription drugs such as cold remedies, analgesics, slimming drugs and stimulants. The most notable behavioral effects of caffeine occur after low to moderate doses (50-300 mg) and are increased alertness, energy and ability to concentrate. Moderate caffeine consumption leads very rarely to health risks (Benowitz, 1990). Higher doses of caffeine rather induce negative effects such as anxiety, restlessness, insomnia and tachychardia, these effects being seen primarily in a small subset of caffeine sensitive individuals. In the present paper we will review the available and most recent data on caffeine

consumption and the known effects of caffeine on the central nervous system.

1. Coffee and caffeine consumption

Caffeine is present in a number of dietary sources consumed worldwide, i.e., tea, coffee, cocoa beverages, candy bars, and soft drinks. The content of caffeine of these various food items ranges from 70-220 mg/150 ml for coffee to 30-50 mg/150 ml for tea, 32-70 mg/330 ml for cola and 4 mg/150 ml for cocoa (Debry, 1994). A low to moderate consumption represents 1-3 cups of coffee per day while a high consumption is considered to be over 5 cups daily. According to a recent survey (Barone and Roberts, 1996), the daily mean daily intake for the whole world population reaches 1-2 mg/kg/day (70-140 mg in a 70 kg individual, i.e. about 1-2 cups of coffee). In the United States, the intake of caffeine from all sources reaches 2.4 to 4.0 mg/kg (2-4 cups of coffee), two thirds of it coming from coffee in subjects aged more than 10 years. In Scandinavia, the mean daily intake of caffeine reaches 7.0 mg/kg/day (about 7 cups of coffee). In children, the mean daily consumption of caffeine recahes 1.0 mg/kg/day in the United States and 1.8 mg/kg/day in Danemark. In the young population, soft drinks represent 55%, chocolate foods and beverages 35-40% and tea 6-10% of the total caffeine intake (Ellison et al., 1995).

2. Mechanism of action of caffeine

Caffeine, at low concentrations reached after the consumption of one or two cups of coffee, acts as a non specific antagonist of both A1 and A2a adenosine receptors (Fredholm, 1995; Fredholm et al., 1999). Adenosine, by acting at the level of presynaptic A1 receptors, inhibits the release of numerous neurotransmitters such as glutamate, GABA, acetylcholine and monoamines and is more efficient at the level of excitatory than inhibitory neurotransmission. Thus, caffeine by antagonizing the effects of endogenous adenosine increases the firing rate of central neurons which is reflected by the changes in the pattern of the electroencephalogram (EEG) of arousal induced by caffeine ingestion. While the effects of caffeine acting at A1 receptors concern all brain regions because of the wide distribution of these receptors, the effects of caffeine at A2a receptors are limited to the striatum, the only area where these receptors can be found (Fredholm et al., 1999).

3. Effects of caffeine on locomotion

In the brain, locomotion is mediated by the nigrostriatal dopaminergic system. This system originates in neurons located in the substantia nigra, mainly pars compacta. They project to the globus pallidus and terminate in the caudate nucleus which is connected to the sensorimotor cortex (Figure 2.1).

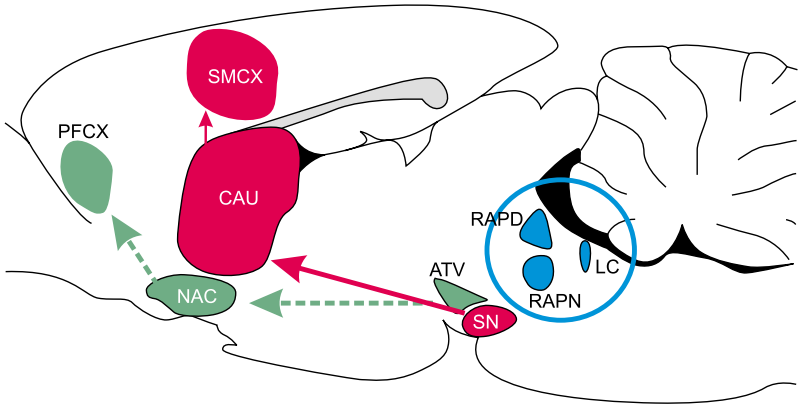


Figure 2.1. Localization of the different brain regions involved in locomotion (red), regulation of the sleep-wake cycle (blue), and reward and dependence (green).
Abbreviations: striato-nigral pathway in red: SN: substantia nigra, CAU: caudate nucleus, SMCX: sensorimotor cortex; areas involved in the regulation of the sleep-wake cycle: LC: locus coeruleus, MRAP: median raphe, DRAP: dorsal raphe; ares involved in reward and dependence: ATV: ventral tegmental area, NAC: nucleus accumbens, PFCX: prefrontal cortex.

In rats subjected to increasing doses of caffeine, the metabolic activity is already significantly increased in the caudate nucleus after the administration of the lowest dose of caffeine, 1 mg/kg to adult male rats (the mean human daily consumption, Figures 2.2 and 2.3). The functional activity of this nucleus is further increased at 2.5 mg/kg at which dose the activation spreads also to the substantia nigra pars compacta and globus pallidus. In the sensorimotor cortex the increase in metabolic activity is present only at 5 mg/kg, dose at which all the other structures remain activated. These 3 doses are in the range of the reported daily human consumption. There is a good correlation between caffeine-induced functional activation of structures belonging to the nigrostriatal pathway and the well-known stimulant effects of caffeine on locomotion. Indeed, the minimal dose of caffeine necessary to increase locomotion is 1.5 mg/kg and the direct administration of caffeine into the caudate nucleus modifies the spontaneous electrical activity of neurons (Okada et al., 1997).

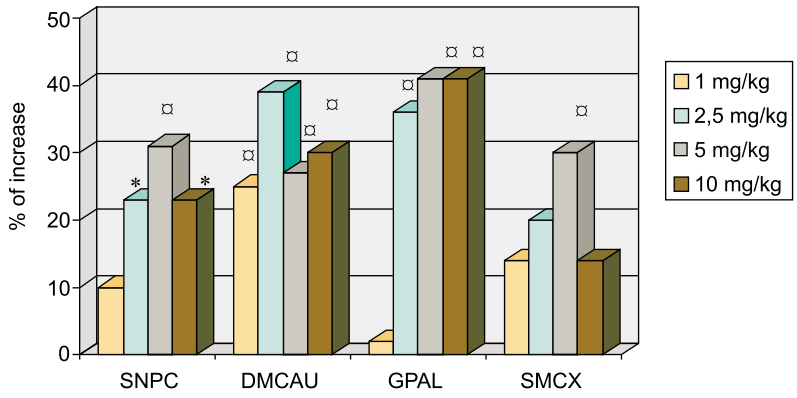


Figure 2.2. Effects of of the administration of increasing doses of caffeine on cerebral metabolism in the striatonigral pathway of rats.
Abbreviations: SNPC: substantia nigra pars compacta, DMCAU: dorsomedian caudate nucleus, GPAL: globus pallidus, SMCX: sensorimotor cortex. * $p < 0.05$, ¤ $p < 0.01$, statistically significant differences from control.

4. Effects of caffeine on sleep

The serotoninergic cell groupings, the medial and dorsal raphe nuclei as well as the noradrenergic cell grouping, the locus coeruleus that mediate the sleep-wake cycle (Figure 2.1) are very sensitive to caffeine. These structures are involved in the control of sleep, mood and well-being. In these 3 structures, metabolic activity is already activated after 1 mg/kg and remains increased at the higher doses of caffeine used, 2.5-10 mg/kg (Figures 2.3 and 2.4). These data correlate well with the known sensitivity of sleep and mood to caffeine (Nehlig et al., 1992). In humans, sleep seems to be the physiological function most sensitive to caffeine. Generally more than 200 mg caffeine are needed to affect sleep significantly. Caffeine prolongs sleep latency, shortens total sleep duration but preserves the dream phases of sleep.

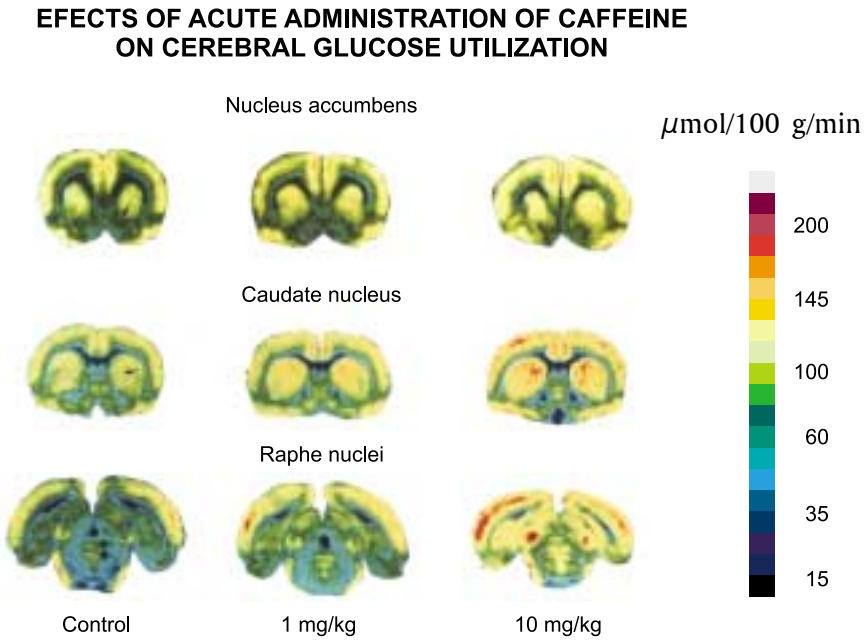


Figure 2.3. Effects of the administration of increasing doses of caffeine on cerebral metabolism in the brain of rats. On the autoradiograms of coronal rat brain sections taken at selected levels, it appears clearly that glucose metabolism is increased after 1 mg/kg caffeine compared to control levels in both the caudate nucleus and the raphe nuclei (indicated by black arrows). This effect persists at the dose of 10 mg/kg. Conversely, in the nucleus accumbens, glucose metabolism is only activated at the highest dose of caffeine, 10 mg/kg.

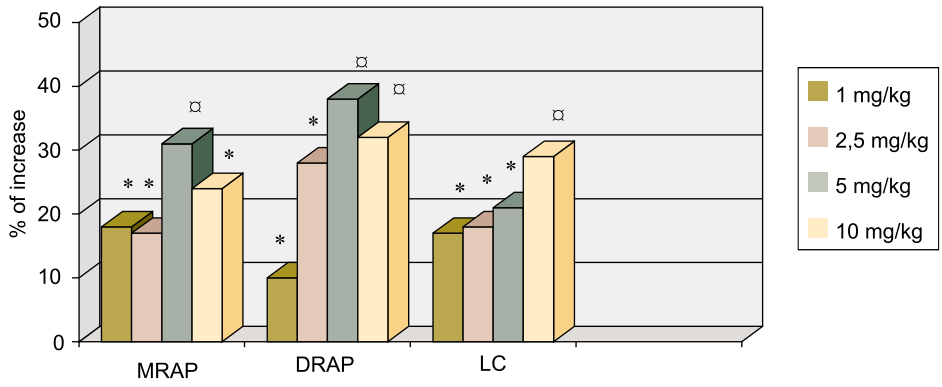


Figure 2.4. Effects of of the administration of increasing doses of caffeine on cerebral metabolism in the structures involved in the regulation of the sleep-wake cycle in rats.
Abbreviations: LC: locus coeruleus, MRAP: median raphe, DRAP: dorsal raphe.
* p< 0.05, ¤ p < 0.01, statistically significant differences from control.

5. Effects of caffeine on alertness, mood and performance

Low doses of caffeine act positively on mood; subjects ingesting 20-200 mg of caffeine report that they feel energetic, imaginative, efficient, self-confident, alert, able to concentrate and motivated to work (Griffiths and Mumford, 1995; Silverman et al., 1994). Recent studies reported that positive effects of low doses of caffeine (40-60 mg) on performance and well-being may be more beneficial in situations of low arousal, such as the post-lunch decrease in vigilance, the common cold (Smith et al., 1997, 1999), fatigue in drivers (Reyner et al., 2000) or during attention-requiring tasks (Lorist et al., 1994). The alerting effects of caffeine are also able to reverse the deleterious effects of a 36 h sleep deprivation (Patat et al., 2000). The influence of low doses of caffeine on mood correlates well with the significant increases in cerebral functional activity recorded in the areas involved in the regulation of wakefulness, mood and well-being, namely the locus coeruleus, and the median and dorsal raphe nuclei that occur after the administration of 1 mg/kg of caffeine to rats (Figure 2.3).

6. Effects of caffeine on headache and migraine

Coffee or caffeine present in analgesic medications are able to relieve people from pain triggered by various types of headaches. The efficacy of caffeine in relieving headache induced by caffeine withdrawal which leads to cerebral vasodilatation has been repeatedly shown and seems to reflect the central vasoconstrictive properties of the methylxanthine. In tension-type headache, there are no vascular changes related to the attack and therefore the analgesic of caffeine per se or combined to other anti-pain medication is most likely mediated by other phenomena although it cannot be totally excluded that the vasoconstrictive effect of caffeine could add to the mechanisms involved in pain relief. Finally for migraine attacks, the literature is rather in favor of a decrease in cerebral blood flow during the attacks. The origin of pain in this pathology remains to be clearly defined; pain is attributed to the dilatation of the ipsilateral medial cerebral artery and also to the dilatation and increased pulsations of the superficial temporal artery and other extracranial arteries. The role of caffeine in pain relief in migraine is not clearly understood and has not been fully explored since the effect of caffeine per se or the comparison of anti-pain drug combinations with and without caffeine is missing (for review, see Nehlig, 2003).

7. Effects of caffeine on anxiety

Caffeine has been reported to generate anxiety when absorbed in excessive amounts in the general population or in low doses in specifically sensitive individuals (for review see Hughes, 1996). Non-usual or low consumers of caffeine appear to be more sensitive to anxiogenic and psychostimulant effects of caffeine than usual consumers (Uhde, 1990). The level of anxiety is also more markedly increased in naturally anxious individuals or subjects suffering from panic attacks compared to the normal population. These individuals show the tendency to reduce or stop their caffeine consumption because of the secondary unpleasant effects of the methylxanthine (Uhde, 1990) and their health status clearly improves after caffeine cessation (Bruce and Lader, 1989). Indeed, in sensitive subjects, panic attacks can occur after the absorption of a single cup of coffee (80-110 mg caffeine) (Uhde, 1988) while in normal individuals, only caffeine doses higher than normal consumption levels can induce significant anxiogenic effects (James and Crosbie, 1987).

8. Preventive effects of caffeine on Parkinson's disease

Parkinson's disease is caused by a severe degeneration of dopamine neurons in the substantia nigra which causes an incapacity to control voluntary movements and leads to tremor, akinesia, rigidity and postural instability. It is presently treated by the precursor of dopamine, L-dopa, not very active on tremor. However, this treatment leads to long term complications, including loss of drug efficacy and dyskinesia (Marsden, 1990) and psychic side effects at high doses (Montastrue et al., 1994).

Experimental evidence suggests that the antiparkinsonian effects of dopamine agonists could be improved if an adenosine antagonist, like

caffeine or theophylline is used in a combined therapy. In human parkisonian patients, the combination of caffeine with L-dopa may lead to improvements in tremor, but only after prolonged treatment (Mally and Stone, 1994). It has also been repeatedly shown that cafffeine consumption could delay the onset or even prevent the occurrence of Parkinson's disease. Coffee intake is protective and inversely related to the occurrence of Parkinson's disease (Ascherio et al., 2001; Benedetti et al., 2000; Checkoway et al., 2002; Grandinetti et al., 1994; Fall et al;, 1999; Hellenbrand et al., 1994; Jimenez-Jimenez et al., 1992; Ross et al., 2000). The mechanisms by which this protective effect occurs are not yet clear.

However, although this effect was clearly demonstrated in men, the conclusions appear less clear in women. A recent study showed that there is a possible interaction between the effects of caffeine and post-menopausal hormonal treatment.

As a result, women that consume less than a cup of coffee per day are protected against the occurrence of Parkinson's disease while those who drink more than 6 cups daily have a relative risk 4-fold higher than non drinkers to develop Parkinson's disease (Ascherio et al., 2003). Finally, in the elderly population that already suffers from the disease, the consumption of coffee is ineffective in reducing the symptoms of the disease (Louis et al., 2003).

9. Effects of caffeine on Alzheimer's disease

One recent study reported the neuroprotective effects of coffee and caffeine in Alzheimer's disease (Maia and de Mendonça, 2002). Caffeine exposure appears to be inversely associated with Alzheimer's disease independently of other confounding factors. The risk to develop the disease was reduced to 0.40 in people consuming 200 mg of caffeine daily (2 cups of coffee) while it was 1.0 in the patients diagnosed with Alzheimer's disease who consumed an average quantity of 70 mg caffeine daily (less than one cup of coffee). However, these properties of coffee and caffeine need to be confirmed in future prospective studies.

10. Effects of caffeine in stroke and epilepsy

In man, chronic caffeine consumption is inversely related to the risk of fatal and non fatal stroke (Grobbee et al., 1990). In fact, one paper advised to drink enough coffee to allow an increase in the number of adenosine receptors but also to stop drinking caffeine-containing beverages when a stroke occurs to prevent caffeine from inducing a blockade at the level of cerebral adenosine receptors (Longstreth and Nelson, 1992). Likewise, a chronic caffeine treatment leads to decreased susceptibility to seizures (for review, see Nehlig, 2002) and has neuroprotective effects in the hippocampus (Rigoulot et al., 2003).

However, in these two diseases, more research remains necessary to assess the extent of potential neuroprotective properties of coffee and caffiene consumption.

11. Are we dependent on coffee and caffeine

11.1. Criteria for drug dependence

Drug dependence has been defined as "a pattern of behavior focused on the repetitive and compulsive seeking and taking a psychoactive drug". The recent diagnostic manuals from the World Health Organization (WHO) and the American Psychiatric Association (APA) proposed a set of criteria for dependence. The diagnosis of dependence requires the fulfillment of three criteria. The seven criteria of dependence as proposed by the APA in DSM-IV (*Diagnostic and Statistical Manual of Mental Disorders*, 4th edn) are: (i) tolerance (not specified for severity), (ii) substance specific withdrawal syndrome (psychic or physiological, not specified for severity), (iii) substance is often taken in larger amounts or over a longer period than intended, (iv) persistent desire or unsuccessful efforts to cut down or control use, (v) a great deal of time spent in activities necessary to obtain, use, or recover from the effects of the substance, (vi) important social, occupational or recreational activities given up or reduced because of substance use, (vii) use continued despite knowledge of a persistent or recurrent physical

or psychological problem that is likely to have been caused or exacerbated by the substance.

11.2. Arguments in favor of dependence on caffeine

The possible dependence on caffeine has been considered for over a decade (for review, see Nehlig, 1999). In one recent study, a dependence on caffeine was shown in a subset of the general population (Strain et al., 1994) The dependence was not related to the daily caffeine intake which ranged from 129 to 2548 mg/day (1-20 cups daily). However, the conclusions of this study need to be taken with care since in 11 of the 16 persons diagnosed with "caffeine dependence", the prevalence of psychiatric disorders was higher than the one encountered in the general population.

Among the seven criteria for drug dependence that have been cited above, caffeine withdrawal has been reported. A small percentage of the population may experience withdrawal symptoms following sudden cessation of caffeine consumption while gradual cessation over 2-3 days has not been shown to result in such symptoms. The most often reported are headaches, weakness and drowsiness, impaired concentration, fatigue and work difficulty, depression, anxiety, irrritability. Withdrawal symptoms generally begin about 12-24 h after sudden cessation of caffeine consumption and reach a peak after 20-48 h. Withdrawal symptoms do not relate to the quantity of caffeine ingested daily (for review, see Nehlig, 1999). Caffeine withdrawal symptoms disappear soon after absorption of caffeine.

11.3. Arguments against the dependence on caffeine

There is no tolerance of the central nervous system to the effects of caffeine. Tolerance to a drug refers to an acquired change in responsiveness of a subject repeatedly exposed to the drug. Tolerance might indicate that the dose necessary to achieve the desired euphoric or reinforcing effects will increase with time thus inciting people to gradually consume more drug. This has not been reported in indivuals who consume coffee or caffeine. Indeed, most people maintain their consumption at a quite constant level. Likewise, cerebral energy metabolism does not become tolerant to caffeine since an acute administration of caffeine induces quite similar metabolic increases whether rats have been pre-exposed daily to caffeine or saline for 15 days. Thus, every single exposure to caffeine is able to produce cerebral stimulant effects, mainly in the areas that control locomotor activity and the sleep-wake cycle (Nehlig et al., 1986).

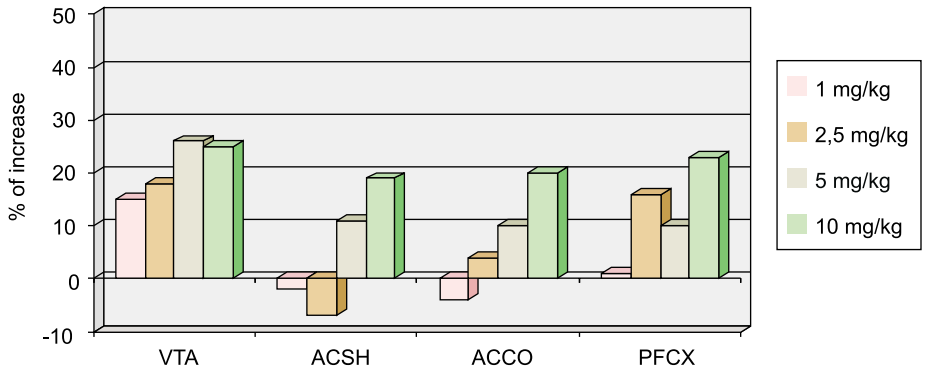


Figure 2.5. Effects of of the administration of increasing doses of caffeine on cerebral metabolism in the structures involved in dependence and reward in rats.
Abbreviations: VTA: ventral tegmental area, ACSH: nucleus accumbens, shell, ACCO: nucleus accumbens, core; PFCX: prefrontal cortex. * p< 0.05, ¤ p < 0.01, statistically significant differences from control.

The molecular mechanisms underlying reinforcement and drug dependence were recently reviewed (Self and Nestler, 1995) and the critical role of the mesolimbic dopaminergic system emphasized. The mesolimbic dopaminergic system consists of the dopaminergic neurons originating in the ventral tegmental area and ending in the shell of the nucleus accumbens. The specificity of cocaine, amphetamine, morphine and nicotine is to selectively activate the dopaminergic neurotransmission in the shell of the nucleus accumbens (Pontieri et al., 1995, 1996), a property that has been related to the strong addictive properties of these drugs. Conversely to the drugs of abuse, caffeine does not increase the release of dopamine in the shell of the nucleus accumbens when injected at doses ranging from 0.5 to 5.0 mg/kg (Acquas et al., 2002). This data is consistent with the low addictive potential of caffeine. Conversely, at the latter doses, caffeine stimulates dopamine release in the prefrontal cortex, the terminal area of the mesolimbic dopaminergic system which reflects its psychostimulant properties (Acquas et al., 2002).

Caffeine increases cerebral energy metabolism in the structures of the mesolimbic dopaminergic system only at quite high doses, 5 mg/kg for the area of origin, the ventral tegmental area and 10 mg/kg for the two subdivisions of the nucleus accumbens, the shell and the core and the medial prefrontal cortex (Figure 2.4). These data show that at the doses daily consumed by most people (2-2.5 mg/kg), caffeine does not activate the brain circuitry of dependence and reward involved in the action of psychostimulants. Moreover, the activation of functional activity in the shell of the nucleus accumbens, specific of the drugs of abuse, occurs only at high doses of caffeine (10 mg/kg, i.e., about 4-5 times the average daily human consumption which would correspond to 8-10 cups of coffee in one sitting) at which the methylxanthine activates also the core of the nucleus not involved in dependence and reward, and induces widespread non specific metabolic increases in a majority of brain regions (for review, see Nehlig et al., 1992).

These widespread effects of high doses of caffeine on brain functional activity are likely to reflect the numerous adverse side effects of the ingestion of large amounts of caffeine.

12. Conclusion

The areas controlling locomotor activity and the sleep-wake cycle appear to be highly sensitive to low amounts of coffee and caffeine. Coffee and caffeine also ameliorate mood and performance and alleviate pain to due various types of headaches. Caffeine and coffee have neuroprotective and preventive properties in Parkinson's disease and these properties need to be confirmed in Alzheimer's disease. Coffee and caffeine may be anxiogenic in a subfraction of sensitive individuals.

The structures involved in addiction and reward are not sensitive to low to moderate amounts of coffee and caffeine and are only activated after high doses of caffeine that are already toxic and far higher than the usual human consumption. These doses activate also numerous brain regions and are likely to induce also the adverse effects occurring after the ingestion of large doses of caffeine. The present data are rather in favor of caffeine acting as a positive reinforcer at doses reflecting the general human consumption and do not support the participation of the brain circuitry of addiction and reward in the biological effects on caffeine. Altogether, it apperars that moderate consumption of coffee and caffeine has rather beneficials effects and coffee can contribute to a healthy and balanced diet.

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COFFEE, ATTENTION, MEMORY AND MOOD: FROM THE BRAIN TO THE WORKPLACE

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ABSTRACT

Coffee is a major source of caffeine, which has been shown to have a number of behavioural effects. For example, caffeine increases alertness, improves sustained attention and psychomotor performance. These beneficial effects often increase with dose (within the limits consumed by the majority of the population). Caffeine has less effect on memory but has recently been shown to improve retrieval from general knowledge and the ability to think logically. Improvements following ingestion of caffeinated coffee are most easily observed when alertness is low (e.g. after sleep deprivation; in the early morning; after lunch; when performing at night; after prolonged work; when the person has a minor illness such as the common cold). Caffeine influences many neurotransmitter systems and the beneficial effects seen in low arousal contexts probably reflect its effects on central noradrenaline. Other effects, such as the increased speed of encoding new information after caffeine, reflect changes in other neurotransmitter systems (e.g. the cholinergic system). It has been suggested that the positive effects of caffeine merely reflect removal of negative effects of withdrawal. This is unlikely as effects can be demonstrated in non-consumers and also consumers who have not had caffeine withdrawn.

The beneficial effects of caffeine can be demonstrated using realistic consumption patterns. Similarly, simulations of real-life activities (e.g.driving) show improved performance after caffeine. Furthermore, recent epidemiological analyses suggest that those with above average intake of caffeine report fewer errors at work and are involved in fewer accidents. Overall, these findings suggest that the levels of caffeine in coffee consumed by most people have largely beneficial effects on behaviour.

CAFFEINE IN COFFEE

Coffee is one of the major sources of caffeine. Instant coffee typically contains about 60 mg per cup whereas coffee prepared by the drip method can have nearly twice that amount of caffeine per cup. While it is quite plausible that other compounds in coffee may produce behavioural change previous research has largely focused on caffeine. The present article is, therefore, largely concerned with the behavioural changes that might be associated with consumption of caffeinated coffee.

Caffeine (1,3,7 – trimethylxanthine) is one member of a class of naturally occurring substances termed methylxanthines. Absorption from the gastrointestinal tract is rapid and reaches 99% in humans in about 45 minutes after ingestion. The hydrophobic properties of caffeine allow its passage through all biological membranes and there is no blood-brain barrier to caffeine. The time for peak plasma concentration is variable (15-120 minutes) and caffeine half-lives range from 2.5 to 4.5 hours.

CNS MECHANISMS

The effects of caffeine on the CNS have been reviewed in detail by Fredholm *et al*. (1999). Most of the data suggest that caffeine, in the doses that are commonly consumer, acts primarily by blocking adenosine A_1 and A_{2a} receptors. Even though the primary action of caffeine may be to block adenosine receptors this leads to very important secondary effects on many classes of neurotransmitters, including noradrenaline, acetylcholine, dopamine, serotonin, glutamate and GABA (Daly, 1993). Such effects show that caffeine has the ability to increase alertness, a possible reason underlying why people consume caffeine-containing beverages.

CAFFEINE AND PERFORMANCE

Early research on this topic has been reviewed by Lieberman (1992). This research has suggested that caffeine improves sustained attention and psychomotor speed but has little effect on memory. More recent studies of effects of caffeine on performance have confirmed many of the earlier results. For example, the beneficial effects of caffeine on psychomotor speed and vigilance have been replicated (e.g. Fine *et al*., 1994; Frewer and Lader, 1991). Similarly, the absence of effects in episodic memory tasks has also been confirmed (e.g. Loke, 1990; Smith et al., 1997a).

Consideration of other aspects of memory

The effects of caffeine on other aspects of memory have also been investigated. For example, components of Baddeley's working memory model have been examined and the results show no effects of caffeine on the articulatory loop (Smith, Clark and Gallagher, 1999) or the visuo-spatial sketchpad (Warburton, 1995) but improved central executive function as shown by improved speed and accuracy of performing a logical reasoning task (Smith et al., 1992; Smith, Maben and Brockman, 1994). Semantic memory has also been studied and results show that caffeine improves the speed of retrieval of semantic information. Indeed, this effect appears to be very consistent with the majority of studies showing improved performance after caffeine (Smith, Kendrick and Maben, 1992; Smith et al., 1994; Smith, Sturgess and Gallagher, 1999).

CAFFEINE AND LOW ALERTNESS SITUATIONS

Caffeine often has its biggest effect when alertness is low (e.g. in the early morning or when working at night). Research has shown that the decreased alertness produced by consumption of lunch can be eliminated by consumption of caffeinated coffee (see Figure 3.1 - Smith *et al*., 1991; Smith and Phillips, 1993).

Furthermore, alertness is often reduced by minor illnesses such as the common cold, and caffeine can remove the impaired performance and negative mood associated with these illnesses (Smith *et al*., 1997a). The ability of caffeine to counteract the effects of fatigue has been confirmed using simulations of driving (Horne and Reyner, 1996; Reyner and Horne, 1997). A study of simulated assembly line work (Muehlbach and Walsh, 1995) also demonstrated significant improvements after caffeine on five consecutive nights and showed no decrements when caffeine was withdrawn.

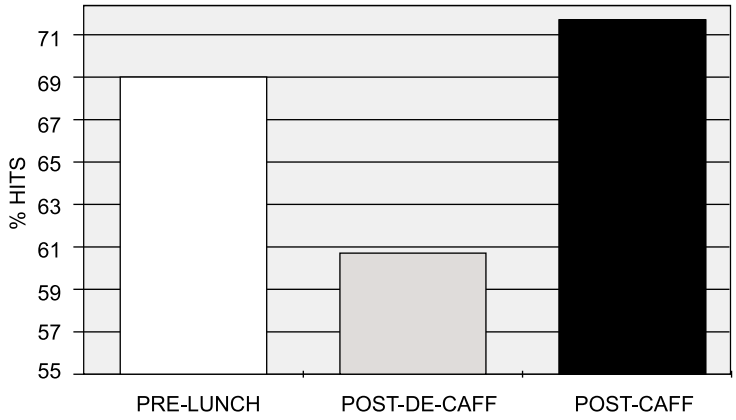

Figure 3.1. Effects of caffeine on the post-lunch dip in sustained attention (Smith and Miles, 1987; pre-lunch = performance before lunch; post-de-caf = performance after lunch and de-caffeinated coffee; post-caf = performance after lunch and caffeinated coffee)

Some of the above studies allow one to assess the magnitude of the effects of caffeine. For example, Smith *et al*., (1993) found that consumption of caffeine at night maintained individuals at the levels seen in the day. Another approach has been to compare the effects of caffeine with other methods aimed at counteracting sleepiness. Bonnet and Arand (1994a,b) report that the combination of a prophylactic nap and caffeine was more effective in maintaining nocturnal alertness than was the nap alone. Other studies have continued to demonstrate that caffeine can remove impairments produced by sedative drugs (*e.g.* alcohol - Hasenfratz *et al*., 1993; scopolamine - Riedel *et al*., 1995; lorazepam - Rush *et al*., 1994a; triazolam - Rush *et al*., 1994b).

One issue is whether positive effects of caffeine are largely restricted to low alertness situations. Battig and Buzzi (1986) argued that caffeine can improve performance beyond a mere restoration of fatigue. Other studies have shown that fatigued subjects show larger performance changes after caffeine than do well-rested volunteers (Lorist, Snel and Kok, 1994; Lorist *et al*., 1994). Another issue is whether caffeine exacerbates negative effects produced by stressful conditions (*e.g.*,electrical shocks - Hasenfratz and Battig, 1992; noise - Smith *et al*., 1997b) and results suggest that it does not.

DIFFERENT DOSES OF CAFFEINE

A number of studies (e.g Lieberman *et al.,* 1987; Smith, Sturgess and Gallagher, 1999) have shown that beneficial effects of doses of caffeine typically found in commercial products can now be demonstrated in both measures of mood and performance. A linear dose response curve has also been shown in a number of studies (Amendola, Gabrieli and Lieberman, 1998; Smith, 1999) although, like the animal literature, beneficial effects often disappear at very high doses.

The strongest evidence for beneficial effects of regular caffeine consumption comes from a study by Jarvis (1993). He examined the relationship between habitual coffee and tea consumption and cognitive performance using data from a cross-sectional survey of a representative sample of over 9,000 British adults. Subjects completed tests of simple reaction time, choice reaction time, incidental verbal memory and visuo-spatial reasoning, in addition to providing self-reports of usual coffee and tea intake. After controlling extensively for potential confounding variables, a dose-response trend to improved performance with higher levels of coffee consumption (best performance associated with about 400mg caffeine per day) was found for all tests. Estimated overall caffeine consumption

showed a dose-response relationship to improved cognitive performance that was strongest in those who had consumed high levels for the longest time period (the 55 years plus age group).

BENEFICIAL EFFECTS OF CAFFEINE OR REMOVAL OF NEGATIVE EFFECTS OF WITHDRAWAL?

Overall, the previous sections confirm that the effects of caffeine on performance are largely beneficial. However, this view has been questioned by James (1994) who argues that the beneficial effects of caffeine are really only removal of negative effects produced by caffeine withdrawal. Smith (1995) has argued against this general view of caffeine effects on a number of grounds. First, it cannot account for the behavioral effects seen in animals or non-consumers, where withdrawal cannot occur.

Secondly, caffeine withdrawal cannot account for behavioral changes following caffeine consumption after a short period of abstinence (Warburton, 1995; Smith, Maben and Brockman, 1994) or the greater effects of caffeine when arousal is low. Finally, claims about the negative effects of caffeine withdrawal require closer examination as they can often be interpreted in ways other than caffeine dependence (e.g. expectancy - Smith, 1996; Rubin and Smith, 1999). Indeed, in most of the studies that have demonstrated increases in negative affect following caffeine withdrawal, the volunteers have not been blind but have been told or even instructed to abstain from caffeine. This is clearly very different from the double-blind methodology typically used to study effects of caffeine challenge.

The view that beneficial effects of caffeine reflect degraded performance in the caffeine-free conditions (James, 1994) crucially depends on the strength of the evidence for withdrawal effects. James states that "there is an extensive literature showing that caffeine withdrawal has significant adverse effects on human performance". If one examines the details of the studies cited to support this view one finds that some of them do not even examine performance, and that where they do, any effects are selective, not very pronounced, and largely unrelated to the beneficial effects of caffeine reported in the literature.

Rogers, Richardson and Dernoncourt (1995) have reviewed a number of studies of caffeine withdrawal and performance. They conclude that " ...in a review of recent studies we find no unequivocal evidence of impaired psychomotor performance associated with caffeine withdrawal". Indeed, they found that caffeine improved performance in both deprived volunteers and non-consumers (Richardson *et al*., 1994). Furthermore, other studies which suggest that withdrawal may impair performance (e.g. Bruce *et al*., 1991; Rizzo, Stamps and Lawrence, 1988) can be interpreted in other ways than deprivation (e.g, changes in state).

The effects of caffeine withdrawal are still controversial. James (1998) showed that caffeine withdrawal impaired short-term memory performance but caffeine ingestion had no effect. In contrast, Smith (1999) reported that caffeine improved attention in both those who had been deprived of caffeine for a short period and those who had no caffeine for 7 days (see Figure 3.2).

Other studies (e.g. Comer *et al.*, 1997) suggest that effects of withdrawal are restricted to mood and that performance is unaltered. Like many areas of caffeine research, some of the effects that have been attributed to withdrawal are open to other interpretations. For example, Lane (1997), Phillips-Bute and Lane (1997) and Lane and Phillips-Bute (1998) compared days when mid-morning coffee was either caffeinated or de-caffeinated. Caffeine consumption was associated with better performance and mood. The authors interpret this as a negative effect of caffeine withdrawal whereas one could interpret it as a positive effect of caffeine. Other studies of caffeine withdrawal effects have methodological problems such as the lack of pre-drink baselines (e.g. James, 1998; Robelin and Rogers, 1998) or failure to consider possible asymmetric transfer when using within subject designs (e.g. James, 1998). This topic will be returned to when very recent research is considered.

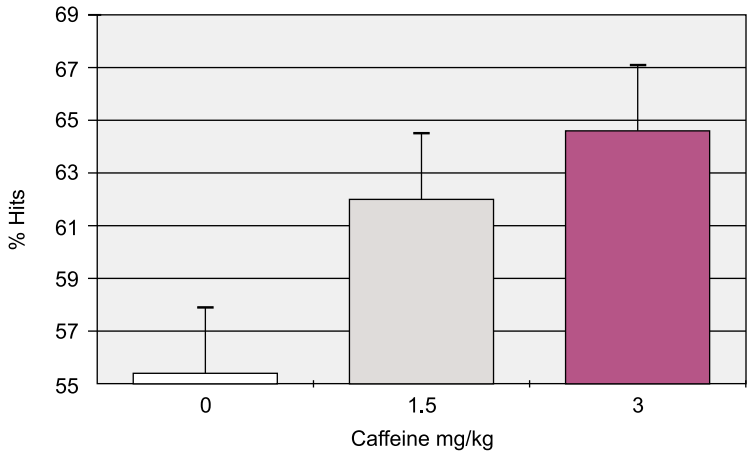

Figure 3.2. Effects of caffeine in volunteers who had been deprived of caffeine for 7 days: hits in cognitive vigilance task. (Smith, 1999)

Caffeine withdrawal

Recent research in this area has been concerned with two main topics, namely what underlies the increase in symptoms following caffeine withdrawal, and, secondly, whether the effects of caffeine reflect removal of negative effects of withdrawal. Dews, O'Brien and Bergman (2002) have considered factors underlying caffeine withdrawal and conclude that "non pharmacological factors related to knowledge and expectation are the prime determinants of symptoms and their reported prevalence on withdrawal of caffeine after regular consumption ". In contrast, some researchers still suggest that caffeine only has beneficial effects on performance when the person has had caffeine withdrawn. Yeomans *et al.* (2002) report that caffeine improved performance on a sustained attention task and increased rated alertness when volunteers had been caffeine deprived but had no such effects when they were no longer deprived. However, the results showed an effect of order of treatments with those who received caffeine first continuing to show better performance even when subsequently given placebo.

Smith, Christopher and Sutherland (submitted) examined effects of caffeine in the evening after a day of normal caffeine consumption. Caffeine improved performance (see Figure 3.3) which casts doubt on the view that reversal of caffeine

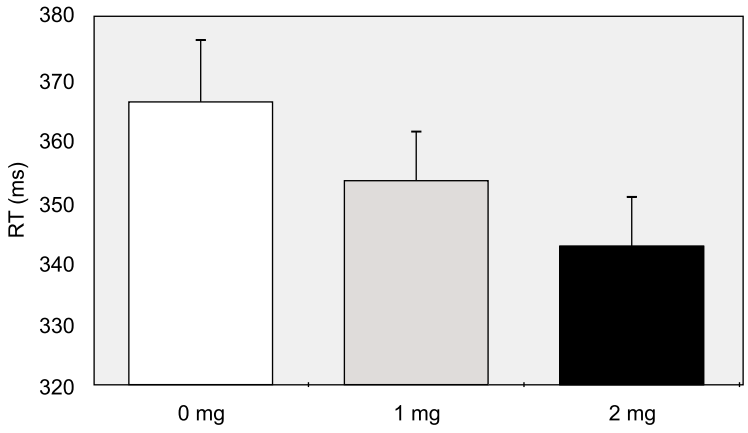

Figure 3.3. Effects of caffeine on simple reaction time of fatigued volunteers following a day of normal caffeine consumption (Smith, Christopher and Sutherland, submitted)

withdrawal is a major component underlying effects on performance.

Further evidence against the caffeine withdrawal explanation comes from recent studies of non-consumers (Smith, Brice and Nguyen van Tam, 2001). These studies not only detected few negative effects of withdrawal but showed that caffeine improved the performance of both withdrawn consumers and non-consumers, a finding that argues strongly against the withdrawal reversal explanation.

REAL LIFE PERFORMANCE

Recent research has shown that caffeine can have beneficial effects on performance when it is consumed in a realistic way (Brice and Smith, 2001b) and in real life situations. Lieberman *et al.* (2002) investigated whether caffeine would reduce the adverse effects of sleep deprivation and exposure to severe environmental and operational stress. They studied U.S. Navy Sea-Air-Land trainees and found that even in the most adverse circumstances moderate doses of caffeine improved vigilance, learning, memory and mood state. A dose of 200 mg appeared to be optimal under such conditions. Lieberman *et al.* (2002) conclude that "When cognitive performance is critical and must be maintained during exposure to severe stress, administration of caffeine may provide a significant advantage ". Such beneficial effects of caffeine have been reported in many real life activities (Weinberg and Beale, 2002) and a recent study suggests that performance at work may be improved (Brice and Smith, 2001a). Smith (submitted) examined associations between caffeine consumption and accidents at work in a sample of 1555 blue-collar workers. The results showed that those who consumed higher levels of caffeine than average had half the risk of having an accident. Similarly, white collar workers (N=1253) who consumed more than 150 mg/caffeine a day were less likely to make errors of memory, attention and action at work.

UNDERLYING CNS MECHANISM: HUMAN STUDIES

Animal studies of the CNS effects of caffeine show that it can potentially influence behaviour through a number of mechanisms. In contrast to this, research with human volunteers is often based on the assumption that all the observed changes can be accounted for by a single mechanism. Evidence for distinct effects of caffeine comes from pharmacological challenge studies. Low states of alertness can be induced by reducing the turn over of central noradrenaline by giving clonidine. In a recent study (Smith *et al.,* 2003) we have shown that caffeine can reverse the effect of clonidine (see Figure 3.4).

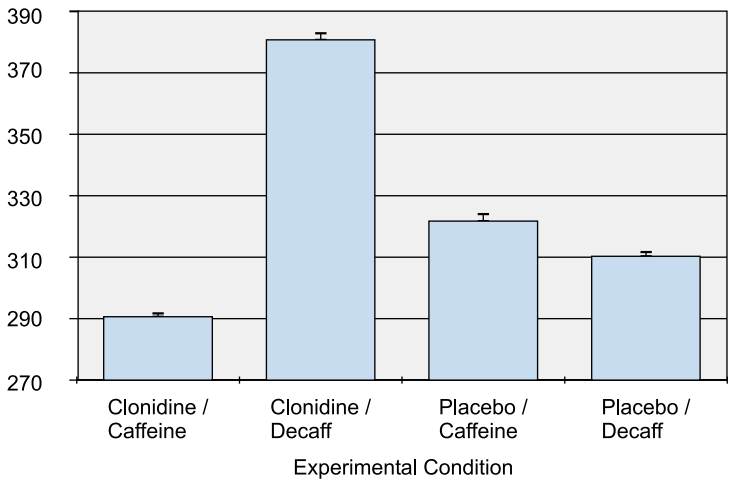

Figure 3.4. Effects of Caffeine and Clonidine on Mean Reaction Time in a Simple Reaction Time Task.

However, certain types of task (e.g. a cognitive vigilance task) were not impaired by clonidine yet showed significant improvements following ingestion of caffeine. These tasks are known to be sensitive to cholinergic challenges and prior research has shown that caffeine can reverse these (Riedel *et al.,* 1995). These cholinergic effects reflect an increase in the speed of encoding of information and a reduction in variability in performance (Warburton, Bersellini and Sweeney, 2001) and are not restricted to low alertness situations. This dual mechanism model is clearly an over simplification of the effects of caffeine but it represents a move towards mapping the behavioural effects with the underlying neurotransmitter changes.

CONCLUSIONS

The present article has reviewed the effects of caffeine on mood and mental performance. Most of the research has examined acute effects of single doses, and further studies are needed to produce a more detailed profile of effects of regular levels of consumption. However, the general picture to emerge is that when caffeine is consumed in moderation by the majority of the population there are unlikely to be many negative effects. Indeed, the positive effects may be important in maintaining efficiency and safety in both the workplace and other environments. Excessive consumption of caffeine will produce problems, and appropriate information should be given to minimise effects in psychiatric patients and other sensitive groups. It is important to balance this with information on the benefits of caffeine, for most consumers can usually control their intake to maximise the beneficial effects and reduce or prevent adverse effects due to over-consumption or consumption at inappropriate times. The behavioural effects of caffeine may reflect a variety of different neurotransmitter changes and further research is needed to identify the mechanisms underlying specific effects. The beneficial effects of caffeine can be demonstrated using realistic consumption patterns. Similarly, simulations of real-life activities (e.g.driving) show improved performance after caffeine. Furthermore, recent epidemiological analyses suggest that those with above average intake of caffeine report fewer errors at work and are involved in fewer accidents. Overall, these findings suggest that the levels of caffeine in coffee consumed by most people have largely beneficial effects on behaviour.

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POSSIBILITY OF COFFEE'S ANTI-CANCER ACTIVITY IN ANIMAL CELL EXPERIMENTS

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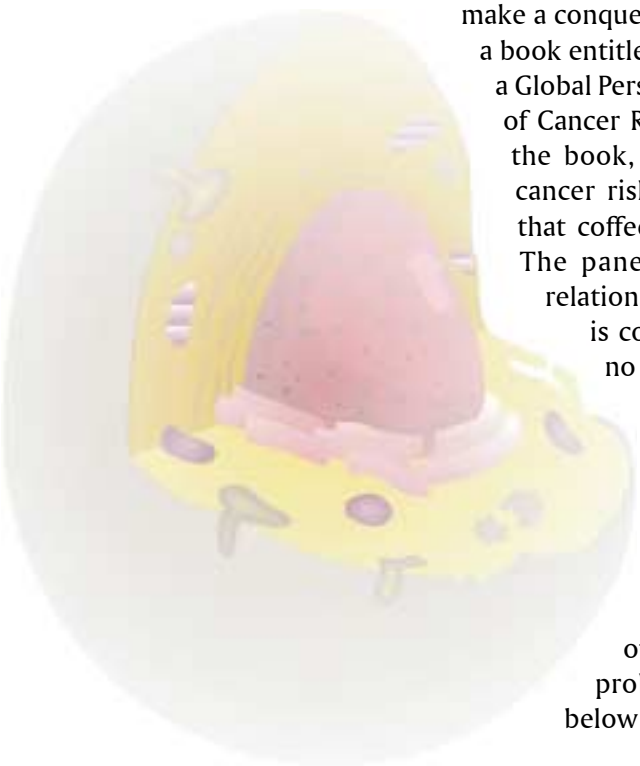
1. Introduction

Factors modulating various physiological functions have been recently found in various foods. These so-called "food factors" include non-nutrients as well as nutrients. Coffee contains various food factors. In this paper, "possibility of coffee's anti-cancer activity" will be discussed on the basis of results obtained from "animal cell experiments".



Cancer cells are believed to arise out of normal cells through three phases called initiation, promotion and progression. The best policy to make a conquest of cancer is to prevent its occurrence. In 1997, a book entitled "Food, Nutrition and the Prevention of Cancer: a Global Perspective" was published by the American Institute of Cancer Research and World Cancer Research Fund[1???]. In the book, the relationship between coffee drinking and cancer risk is argued. Most evidence on coffee suggests that coffee drinking has no relationship with cancer risk. The panel judges that the evidence that there is no relationship between coffee drinking and breast cancer is convincing, that coffee consumption probably has no relationship with the risk of stomach, pancreatic and renal cancer, and that coffee drinking possibly has no relationship with the risk of prostate cancer. It is also described that coffee drinking decreases colorectal cancer for higher consumption, although the evidence is insufficient. In contrast, high consumption of coffee is mentioned to possibly increase the risk of bladder cancer at high levels of intake, but is probably not associated with risk at consumption below five cups/day. Recently, coffee drinking has been

reported to prevent oral, pharyngeal and esophageal cancer[2]. Very recently, a new anti-cancer compound called methylpyridinium is found in coffee[3], and it is formed during the roasting process from its chemical precursor, trigonelline, which is common in raw coffee bean. Methylpyridinium is found to increase activities of phase II detoxyfying enzymes in rats fed this compound, suggesting this compound is one of cancer fighter in coffee.

Cancer cells have two biological properties, that is, endless proliferation and metastasis. Therefore, once cancer is caused, the suppression of these two properties of cancer cells seems to be the second best policy.

2. Effect of coffee on the proliferation and invasion of cancer cells

During proliferation, some cancer cells get ability to secede from primary tumor tissues. Then, they are transported in vessels to a target tissue or organ, adhere to endothelial cells, invade and proliferate again (Figure 4.1). The invasion of cancer cells is an important and characteristic step of cancer metastasis. We attempted to seek for food factors that have potential to suppress the growth and metastasis of cancer cells by using *in vitro* assay systems for both the proliferation and invasion of cancer cells[4].

2.1 *In vitro assay systems*

We employed a rat ascites hepatoma cell line of AH109A, as model cancer cells. The hepatoma cells are known to proliferate well both *in vitro*, that is, in a cell culture system[5] and *in vivo*, that is, in abdominal cavity and under the skin[6].

These cells form some metastatic foci in lung, mesentery and lymphatic nodes[7]. The hepatoma cells were cultured in Eagle's Minimum Essential Medium containing 10% calf serum. Using the hepatoma cells, we constructed *in vitro* assay

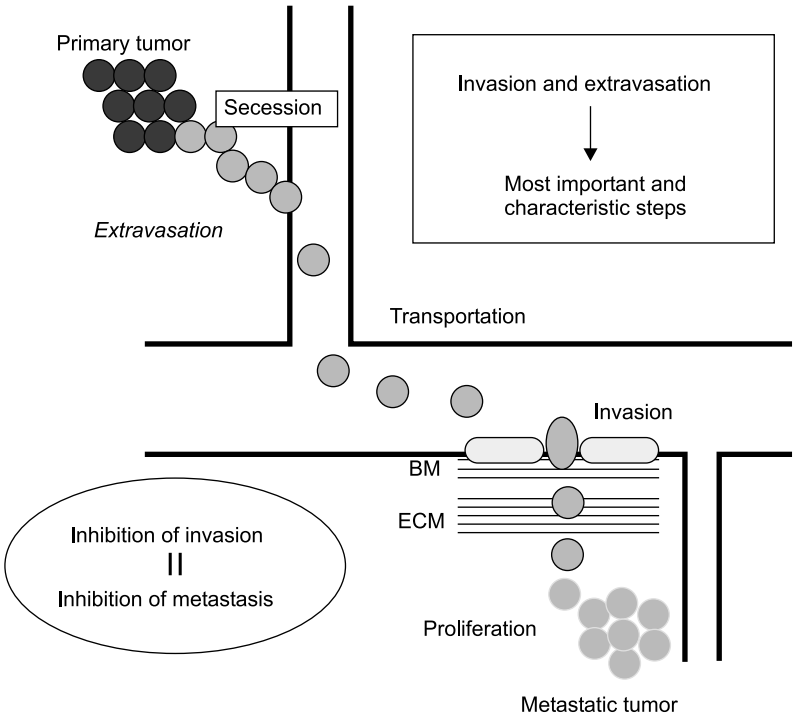


Figure 4.1. Schematic representation for proliferation and metastasis of cancer cells.

systems for both the proliferation and invasion of cancer cells[8]. Briefly, the proliferation of hepatoma cells was estimated by [^{3}H]thymidine incorporation method (Figure 4.2). The invasion of hepatoma cells was estimated by a co-culture system of hepatoma cells with mesentery-derived mesothelial cells. Mesothelial cells were primarily cultured from a rat mesentery and cultured for 7 to 10 days to attain a confluent state. On the monolayer of mesothelial cells, hepatoma cells were overlaid and cultured for 24-48 hours (Figure 4.2). The invasive activity of AH109A cells was measured by counting invaded hepatoma cells and colonies underneath the monolayer with a phase-contrast microscope.

2.2 *In vitro effect of coffee*

Using these *in vitro* assay systems, we investigated the effects of various food extracts and food components on the proliferation and invasion of hepatoma cells[4]. Coffee as well as teas was found to suppress both the proliferation and invasion of hepatoma cells. We used a commercially available instant coffee powder (ICP) as the coffee sample. ICP suppressed significantly and dose-dependently the proliferation and invasion of hepatoma cells, when ICP was directly added to the experimental medium[9].

It is important to estimate whether or not effective components in foods would be also effective when orally given, because foods should be orally ingested. We therefore examined the bioavailability of ICP. Rats were fasted overnight, and 10 o'clock in the next morning, they were given oral administration of ICP aqueous solution at a dose of 100 mg/100 g body weight, and blood was obtained 0, 0.5, 1, 2, 3 and 5 hours after oral administration of ICP solution. Serum prepared from blood was used instead of calf serum, and subjected to the proliferation and invasion assays. ICP-loaded rat serum obtained after oral administration significantly and time-dependently suppressed the proliferation and invasion as compared with 0 hr value of ICP-loaded rats[9]. The anti-proliferative and anti-invasive effects lasted for 5 hours after oral

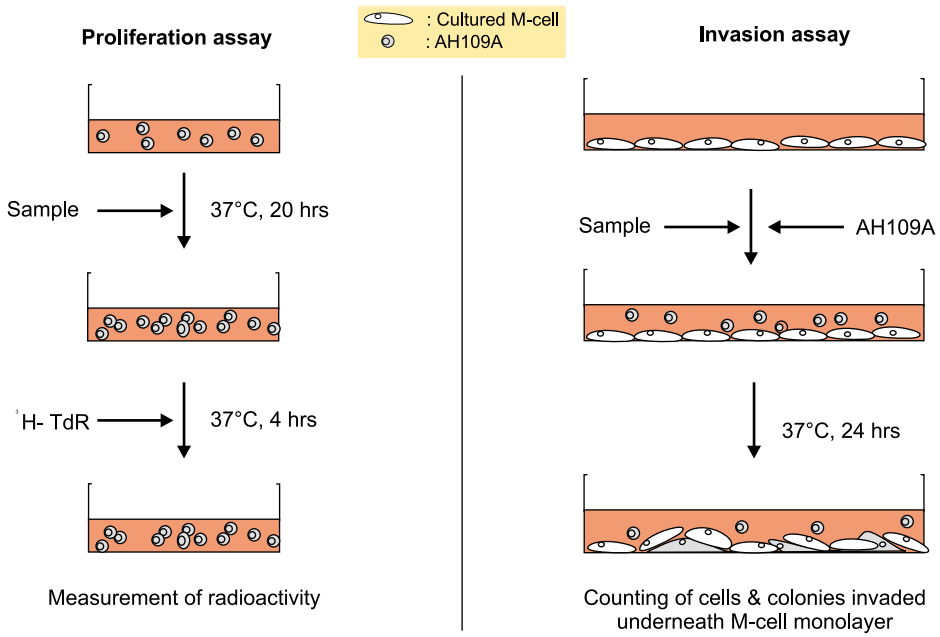


Figure 4.2. Proliferation assay and invasion assay of AH109A.

administration. The significant inhibitory effect appeared at the dose of 10 mg/100 g of body weight[9].

These results obtained from *in vitro* and *ex vivo* experiments suggest that ICP may be effective *in vivo*.

2.3 ***In vivo effect of coffee***

So, we conducted a preliminary *in vivo* experiment to examine whether or not ICP would be effective in hepatoma-bearing rats by feeding a 20% casein diet containing 0.1% ICP for 2 weeks[10]. The content of 0.1% ICP in the diet is approximately equivalent to the above-mentioned oral dose of 10 mg/100 g of body weight. ICP could significantly inhibit the size of solid hepatoma, and hence weight of primary solid tumors. Although three of eleven control rats exhibited some metastatic foci, none of ICP-fed rats exhibited any metastatic foci. These results suggest that ICP may have a suppressive effect on the *in vivo* proliferation and invasion of AH109A cells, the latter leading to suppression of metastasis. However, further large-scale experiments are required to confirm this possibility.

3. Modes of actions of coffee on the proliferation and invasion of cancer cells

3.1 ***Mechanism for the suppression of hepatoma cell proliferation by coffee***

Possible mechanisms for the suppression of cancer cell proliferation are considered to be cell cycle arrest, induction of apoptosis, inhibition of angiogenesis (inhibition of new blood vessel formation). Of these possibilities, we examined the effect of ICP on cell cycle and apoptosis.

Cells progress cell cycle from the gap 1 phase (G1 phase), DNA synthetic phase (S phase), gap 2 phase (G2 phase) and mitotic phase (M phase), and cells proliferate.

The hepatoma cells were cultured in the medium containing 300 mg/ml of ICP for 0, 12 and 24 hours, and cell cycle was analyzed by flow cytometry. The fraction of cells in the S phase was found to increase at 12 and 24 hours after addition of ICP, when compared with 0 hour control cells[10]. This result suggests ICP induces cell cycle arrest in the hepatoma cells by elongating S phase.

We next examined whether or not ICP could induce apoptosis, the programmed cell death, in AH109A cells. The hepatoma cells were cultured in the medium containing 1,200 mg/ml of ICP for 24 hours, and the induction of apoptosis was detected by DNA laddering method. ICP was found to induce apoptosis in AH109A cells.

These results indicate that ICP suppresses the proliferation of hepatoma cells by arresting cell cycle at a lower concentration and by inducing apoptosis at a higher concentration, like teas and their components[11].

3.2 ***Mechanism for the suppression of hepatoma cell invasion by coffee***

Possible mechanisms for the suppression of cancer cell invasion are considered to be an inhibition of cancer cell adhesion, inhibition of cancer cell motility, inhibition of ECM degradation, and inhibition of angiogenesis. We have focused our attention on the motility of hepatoma cells. In our separate experiment, we found that the invasive activity significantly increased when cancer cells were exposed to the reactive oxygen species (ROS)-generating system, and this rise was canceled if food factors with anti-oxidative activity such as β– carotene co-existed with the ROS-generating system[12]. We therefore examined whether or not ICP could suppress ROS-potentiated invasive activity by producing superoxide radical extracellularly using hypoxanthine-xanthine oxidase as a ROS-generating system[10].

Hepatoma cells were preliminary cultured for 4 hours with or without hypoxanthine-xanthine oxidase in the presence or absence of ICP, and then the hepatoma cells were washed. The same number of hepatoma cells were overlaid on the monolayer of mesothelial cells, and cultured for

another 24 hours without ICP. The invasive activity significantly increased when cancer cells were exposed to ROS-generating system, and this rise was canceled when ICP co-existed with ROS-generating system (Fugure 4.3). Serum from rats orally given ICP aqueous solution also canceled the ROS-induced rise in the hepatoma cell invasion[10].

The intracellular peroxide levels can be determined by flow cytometry using a reagent called DCFH-DA. We examined the effect of ICP on the endogenous and exogenous peroxide levels in the hepatoma cells by this method (Figure 4.3). The intracellular peroxide level was elevated by ROS treatment. ICP was found to decrease not only the exogenous peroxide level but also the endogenous peroxide, indicating ICP has ROS-scavenging activity. Serum from rats orally given ICP aqueous solution also scavenged both the exogenous and endogenous peroxide levels in the hepatoma cell[10].

Tumor cell invasion has three steps, that is, adhesion of cancer cells, movement of cancer cells, and degradation of ECM. Of these three steps, we studied the relationship among cell motility, ROS and food components with antioxidative activity[13,14]. Several motility factors have been reported so far. That is, autocrine motility factor (AMF), scatter factor (SF)/ hepatocyte growth factor (HGF) and other factors. Genes of AMF, HGF and their receptors were already cloned. In AH109A cells and mesothelial cells, mRNAs of AMF and its receptor AMFR were not detected, while mRNAs of HGF and its receptor c-met were detected in AH109A cells[13]. These results suggested an involvement of HGF in the invasion of the hepatoma cells. Exposure of hepatoma cells to ROS notably increased the

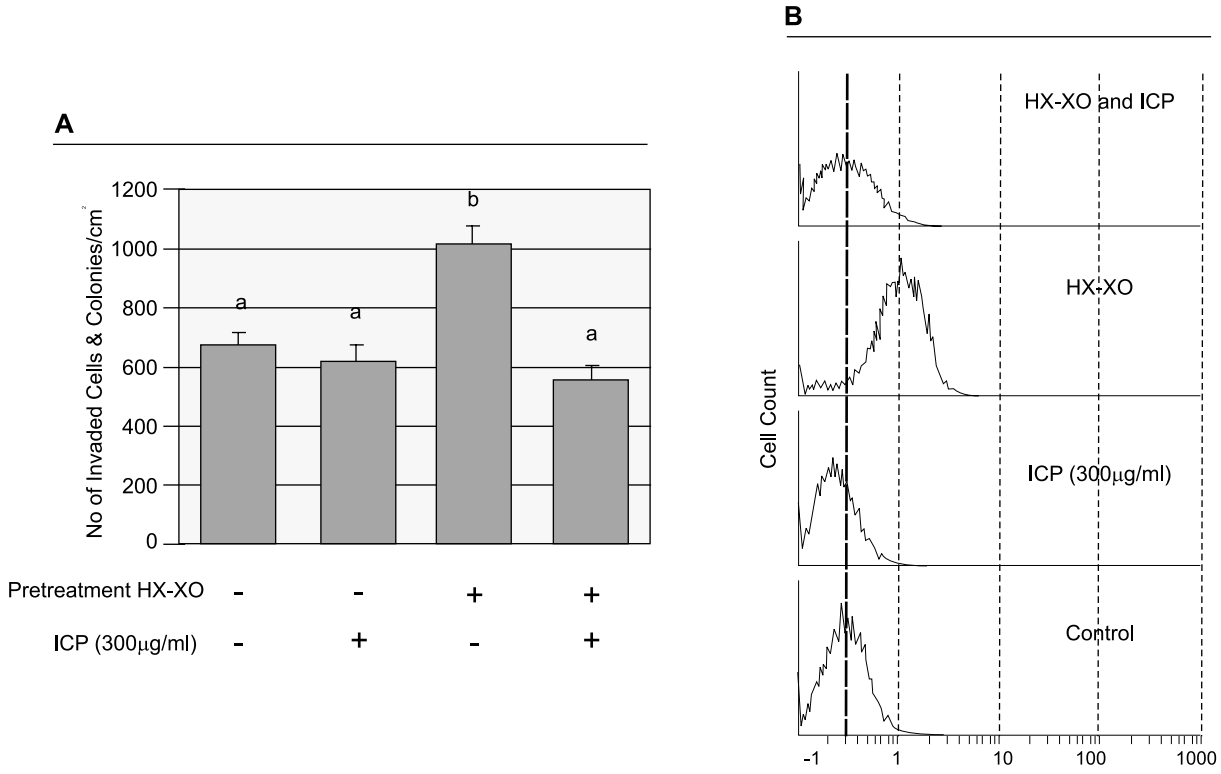


Figure 4.3. Effect of ICP on AH109A cell invasion and intracellular peroxide level in AH109A cells. AH109A cells were pretreated for 1hr. Thereafter, invasive activity (A) and cellular peroxide levels were determinated (B).

expression of HGF mRNA and HGF protein[13]. These results strongly suggested the relationship among ROS, HGF and AH109A cell invasion. Thus, we examined this possibility using anti-HGF antibody. HGF significantly increased the hepatoma cell invasion, and anti-HGF antibody canceled not only this HGF-potentiated invasion but also spontaneous invasion. These results indicated the involvement of HGF in the hepatoma cell invasion. Resveratrol, a known antioxidant in grapes, was found to suppress the expression of HGF mRNA and secretion of HGF protein[14].

From the results obtained so far, we propose that:

1) The invasion of AH109A cells is regulated by autocrine action of HGF,
2) exogenous ROS and probably endogenous ROS stimulate the expression of HGF in AH109A cells,
3) ROS potentiate the invasive activity via autocrine loop of HGF in AH109A cells, and
4) ICP may suppress the invasion of AH109A cells by inhibiting the autocrine loop through its ROS-scavenging activity.
Further intensive studies are required to clarify these aspects.

4. Effective components in coffee

What are the effective components in coffee? So far, we have examined four major components in coffee, namely, chlorogenic acid, caffeic acid, quinic acid[15,16] and trigonelline[16]. Chlorogenic acid is an ester compound of caffeic acid and quinic acid.

Chlorogenic acid inhibited the hepatoma cell invasion at concentrations of 5 to 40 mM without affecting the proliferation at the same concentrations. Caffeic acid and quinic acid are constituents of chlorogenic acid, and both acids also inhibited the invasion, although the inhibitory effect of chlorogenic acid was stronger than those of caffeic and quinic acids at the same concentration of 10 μM. Trigonelline also inhibited the invasion of hepatoma cells at concentrations of 5 to 40 μM, while this component failed to suppress the proliferation at the same concentrations.

Caffeic acid-loaded rat sera obtained 0.5, 1, 2, 3, 6 and 12 hours after oral administration significantly suppressed the invasion as compared with serum obtained immediately after oral administration. The inhibitory acivity was the strongest 30 minutes after oral administration, and thereafter weakened as time went on. Serum from rats received oral administration of chlorogenic or quinic acids also inhibited the invasion of hepatoma cells, although the strongest time was different between the components. Trigonelline-loaded rat sera obtained 0.5, 1, 2, 3, 6 and 12 hours after oral administration significantly suppressed the invasion as compared with serum obtained immediately after oral administration. The inhibitory acivity was the strongest 2 hours after oral administration, and thereafter weakened as time went on.

Caffeic acid was found to suppress the ROS induced increase in the AH109A invasion. Caffeic acid-loaded rat serum also canceled the ROS-potentiated invasion. The same tendency was found in the actions of other 2 components. Trigonelline was found to suppress the ROS-induced increase in the AH109A invasion. Likewise, trigonelline-loaded rat serum also canceled the ROS-potentiated invasion. Thus, the antioxidative property of these coffee components may play an important role in their anti-invasive actions.

These four coffee components suppressed the invasion of hepatoma cells, but so far we have not identified coffee components that inhibit the proliferation, and to be identified in the future. It is interesting whether or not methylpyridinium, a newly found anticancer compound[3], is involved in the suppression of hepatoma cell proliferation.

5. Conclusion

From animal cell experiments, we could demonstrate a possibility that coffee may prevent the progression of cancer. In other words, coffee may prevent the aggravation of cancer. Further extensive studies are required to confirm the possibility.

Acknowledgement
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EFFECTS OF COFFEE ON THE TOTAL PLASMA ANTIOXIDANT CAPACITY IN HUMANS AND BIOAVAILABILITY OF COFFEE POLYPHENOLS

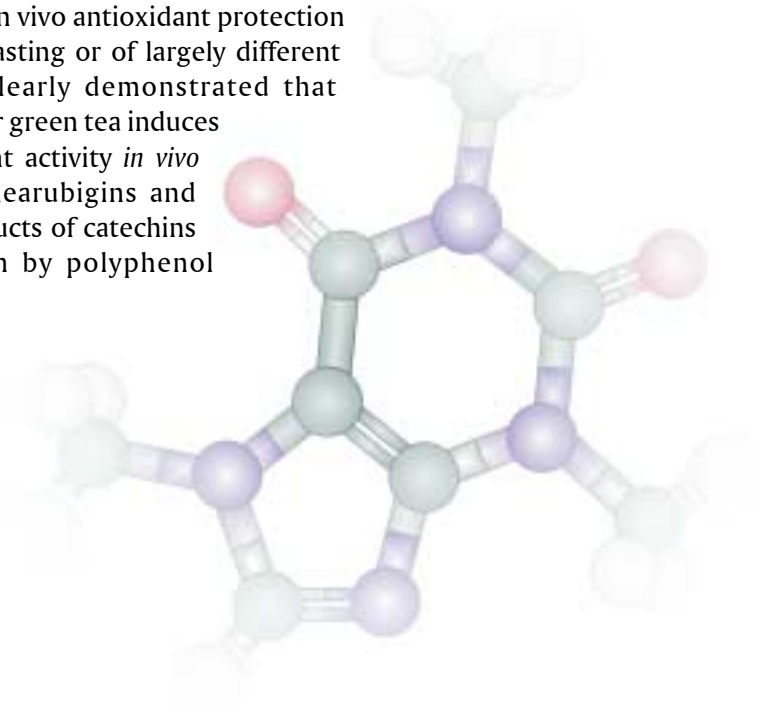
Mirella Nardini, Fausta Natella and Cristina Scaccini

Background

Polyphenols have been reported to exert a variety of biological actions, such as free radical scavenging, metal chelation, modulation of enzymatic activity and, more recently, to affect signal transduction, activation of transcription factors and gene expression (1-4). Epidemiological studies have suggested associations between the consumption of polyphenols-rich foods and beverages and the prevention of many human diseases.

Despite extensive literature describing the effects of polyphenols, our knowledge about their absorption from diet is scarce, one major question arising on the absorption of bound forms of phenolic compounds:

A number of beverages derived from vegetables have been tested for their in vitro and in vivo antioxidant activity (white and red wine, green and black tea, beer) (5-7). In particular, in the last years, a number of studies focused on the capacity of tea to elicit in vivo antioxidant protection in humans, giving pictures both contrasting or of largely different extent. However, a recent paper clearly demonstrated that consumption of a single dose of black or green tea induces a significant rise in plasma antioxidant activity *in vivo* (8). Black tea contains catechins, thearubigins and theaflavines, which are oxidation products of catechins formed during enzymatic oxidation by polyphenol oxidase in fresh tea leaves.



Although coffee is as rich as tea in phenolic antioxidants and is equally consumed in the world, its antioxidant activity in vivo has been never studied.

Coffee contains several phenolic components, other than tocopherols,

endowed with antioxidant capacity, and the total polyphenols amount ranges from 200 to 550 mg per cup. Among the phenolic compounds identified are chlorogenic acids, a family of esters formed between quinic acid and several cinnamic acids such as caffeic, ferulic and p-coumaric acid, caffeoylquinic acid being by far the most abundant. Based on 10 g coffee per cup of brew, a cup content of chlorogenic acid (5'-caffeoyl quinic acid, the most abundant isomer) can range from 15 to 325 mg. A value of 200 mg/cup has been reported for coffee, brewed by drip filtering.

The aims of our studies were:

- To assess the capacity of coffee in affecting the plasma redox homeostasis in humans in fasting conditions, using tea as control. Total antioxidant capacity and the concentration of the main antioxidants were measured on plasma before and after the supplementation of a standard cup of coffee or black tea. Metabolic parameters in plasma were also measured to control the eventual effect of acute coffee and tea consumption on lipid metabolism.

- To determine the bioavailability of phenolic acids, with particular concern on the conjugated forms. The preliminary set up of a hydrolysis method was necessary to avoid the degradation of phenolic acids in the alkaline conditions commonly used.

Design of the study and brief description of methods utilized

In vitro study on detection of bound phenolic acids in coffee and compared analysis of antioxidant capacity and phenolic concentration in coffee and tea

Coffee brew was prepared using a commercial automatic brewing machine (60 g of roasted and ground coffee from an Italian brand per liter water) and used within 10 min from preparation. Coffee (non-hydrolyzed or subjected to alkaline hydrolysis in the presence of EDTA and ascorbic acid) was analyzed using an HPLC system, consisting of a Perkin-Elmer Series 4 Liquid Chromatograph with gradient pump, column thermoregulatory, auto sampling injector equipped with electrochemical coulometric detector

The total antioxidant capacity of coffee and tea (prepared by 5 min infusion of 20 g in 1 liter of water at 100°C) was measured using two different systems, the loss of fluorescence of r-phycoerithryn (TRAP test) and the competition kinetic with the bleaching of a carotenoid, the crocin (Crocin test), triggered by the peroxyl radicals generated by thermal decomposition of 2,2'-azobis(2-amidinopropane) HCl (AAPH).

Total phenols were measured by the Folin Ciocalteau method after deproteinization of samples with ammonium sulfate (9). Caffeine, theobromine and theophylline were detected by HPLC (10).

In vivo study on modulation by coffee and tea drinking of plasma antioxidant capacity in humans

A standard amount (200 ml) of brewed coffee was administered in fasting conditions to 10 healthy non-smoker moderate-coffee drinkers. In a different session (2 weeks apart) black tea was administered as control. Beverages were ingested within 10 min from brewing.

The total antioxidant capacity of plasma was measured using the same methods employed for the analysis of beverages. Single molecules with antioxidant capacity were individually measured (SH groups, ascorbic and uric acid, alpha tocopherol).

Plasma total cholesterol and triacylglycerols, HDL-cholesterol and LDL-cholesterol, total homocysteine were also measured to control any metabolic effect.

Bioavailability of phenolic acids from coffee in humans

Aliquots of plasma samples (0.5 ml) from each subject were thawed and treated according to one of the three following procedures: no treatment, to detect free phenolic acids; b-glucuronidase treatment (used to selectively hydrolyze glucuronidated forms of hydroxycinnamic acids) and alkaline hydrolysis treatment (used to liberate phenolic acids from bound complexes) to detect total

(free + bound) phenolic acids. *o*-Coumaric acid was selected as internal standard due to the absence of detectable amounts of this compound in human plasma samples before and after coffee administration, with or without b-glucuronidase or alkaline hydrolysis treatments.

The presence of phenolic acids in treated and untreated samples was assessed by HPLC-ECD.

Results

In vitro study on detection of bound phenolic acids in coffee (11) and compared analysis of antioxidant capacity and total phenols concentration in coffee and tea (12)

Coffee brew was analyzed for phenolic acids composition, before and after hydrolytic treatment. Chlorogenic acid (5'-caffeoyl quinic acid) was present in non-hydrolyzed coffee at high concentration, while free caffeic acid, *p*-coumaric acid and ferulic acid were undetectable. After hydrolysis, ferulic acid, *p*-coumaric acid and high levels of caffeic acid were detected. The amount of caffeic acid released upon hydrolysis was higher than the amount expected from hydrolysis of chlorogenic acid based on 1 to 1 stoichiometry. This result is explained by the fact that coffee also contains dicaffeoylquinic acid derivatives and different isomer of caffeoylquinic acids besides 5'-caffeoylquinic acid, the one detected in our experiments. From our data, we calculated that a cup of coffee (200 ml) contained 95.8±4.6 mg chlorogenic acid (5'-caffeoylquinic acid). After hydrolytic treatment, the total phenolic acids content of a cup of coffee was: caffeic acid, 166.0 ± 14.0 mg, *p*-coumaric acid 2.8 ± 0.2 mg, ferulic acid 28.6 ± 2.5 mg.

The measure of the antioxidant capacity of the two beverages, using both TRAP and Crocin test methods indicates that coffee is more powerful in scavenging peroxyl radicals than tea, at least in an hydrophilic environment. Total phenols, expressed as gallic acid equivalents, are still higher in coffee than in tea, but the difference is not as dramatic (+ 40%) as for the antioxidant capacity. Thus, the antioxidant capacity of the beverages cannot be explained by the mere measure of total phenols.

To further characterize the two beverages, we measured the concentration of 1,3,7-trimethyl xanthine (caffeine), 3,7-dimethyl xanthine (theobromine) and 1,3-dimethyl xanthine (theophylline). Caffeine in a cup of coffee (200 ml), as administered in the in vivo study, corresponded to 181 mg, while 200 ml of tea contained 130 mg of caffeine. The figures for theobromine were 28.9 and 5.9 mg/200 ml, respectively for coffee and tea. In both samples, theophylline was under the detection limit of our method.

As trimethyl xanthines don't have antioxidant activity against peroxyl radicals, we can postulate that the higher antioxidant activity of coffee in respect to tea is probably linked to its different pattern in antioxidant compounds. Alpha-tocopherol was present in negligible amount in coffee and it was absent in tea (data not shown). Thus, we can exclude a participation of a-tocopherol to the beverage's AC. Finally, the contribution of other compounds with antioxidant activity present in roasted coffee, namely Maillard products or melanoidins, can not be excluded.

In vivo study on modulation by coffee and tea drinking of plasma antioxidant capacity in humans (12)

The ingestion of 200 ml of coffee in bolus produced a statistically significant increase at t = 1 (5.5%, $P<0.05$) in the plasma antioxidant capacity, measured by the TRAP method, maintaining a 4% increase after two hours. The 4.7 % increase of TRAP 1 hour after tea administration did not reach statistical significance.

In the case of coffee, the Crocin test gave a similar trend in the modulation of antioxidant activity, even if the differences were not statistically significant. In the case of tea, the AC measured by the Crocin test, decreased significantly ($P<0.005$) after 2 hours, paralleling the decline of the reduced form of ascorbic acid.

The apparent lack of statistical significance in the increases of AC by TRAP test for tea and by Crocin test for coffee disappears when inter-individual differences are taken into account. In fact, analyzing

individual data, we found that subjects did not reach the maximum value at the same time. Prevalently the peak time was 1 hour. However, in the case of the measurement of AC by Crocin test, 4 subjects reached the maximum value 2 hours after coffee drinking and in the case of the measurement of AC by TRAP, 3 subject reached the peak 2 hour after tea drinking. This event can be linked to differences in the efficiency of absorption and/or metabolism of antioxidant compounds. Comparing the individual AC at time 0 with the AC at the peak time (1 hour or 2 hours depending on the subjects), we observed a significant increase in plasma AC using both methods after coffee drinking. The increase in plasma AC after tea drinking reached statistical significance only when measured by TRAP method.

The two methods employed to measure AC differ for their capacity to be affected by uric acid: in fact plasma uric acid contribution to TRAP is about 60%, while its contribution to the Crocin test is equal to zero. Because coffee and tea drinking induced a significant increase of plasma uric acid, we can speculate that the increase in plasma AC measured by the TRAP method was largely affected by the increase of plasma uric acid concentration. After coffee drinking, we observed a significant increase of AC also using the Crocin test. As uric acid do not contribute to the Crocin test, we can speculate that molecules other than uric acid (probably phenolic acids) are responsible for the observed increase of antioxidant capacity.

Caffeic acid is the most abundant phenolic compound in coffee brew and it is endowed with strong antioxidant activity in vitro and in vivo. As caffeic acid is present in human plasma at μmolar concentration after coffee drinking (*13*), we can assume that it is at least in part directly responsible for the increase in plasma antioxidant capacity observed in this study.

Therefore, whilst the contribution of phenolic compounds from tea to the AC is essentially indirect, 'influencing' the plasma uric acid level (even if a slight direct contribution can not be ruled out) phenolic compounds from coffee could act both directly and indirectly.

Bioavailability of caffeic acid from coffee in humans (13)

In order to study the absorption of coffee phenolic acids, plasma samples collected before and after coffee administration were analyzed for content of both free and total (free + bound) phenolic acids, using two different procedures of hydrolysis to release phenolic acids from bound forms. In the first procedure, b-glucuronidase was used to selectively hydrolyze glucuronidated forms of hydroxycinnamic acids. In the second procedure, an alkaline hydrolytic treatment was used to liberate phenolic acids from bound complexes.

Less than 12.6±7.4 ng/ml of free caffeic acid (corresponding to 0.07 μM) was detected in the untreated control plasma samples taken immediately prior to coffee brew administration (time 0). A significant increase in free caffeic acid plasma levels was found in untreated plasma samples 1 h after coffee brew consumption in respect to time 0.

After b-glucuronidase treatment, total caffeic acid in plasma was significantly higher at both 1 h and 2 h after coffee administration than at time 0 with a maximum absorption peak at 1 h for all subjects. Alkaline hydrolysis treatment of plasma samples gave similar results, with significantly higher levels of total caffeic acid at 1 h and 2 h in respect to time 0 and maximum absorption peak at 1 h. Both b-glucuronidase and alkaline hydrolysis treatment released a considerable amount of caffeic acid at 1 h and 2 h after coffee consumption. Interestingly, the plasma levels of caffeic acid measured after both hydrolysis procedures were very similar and no significantly different by ANOVA.

Conclusions

1. Following our experimental conditions, coffee drinking increases plasma antioxidant capacity, probably due to bioavailability and antioxidant activity of its peculiar group of phenolic compounds (chlorogenic acids).

2. Coffee administration resulted in increased total plasma caffeic acid concentration, with an

absorption peak at 1h. Caffeic acid was the only phenolic acid found in plasma samples after coffee administration, while chlorogenic acid was undetectable. Most of caffeic acid was present in plasma in bound form, mainly in the glucuronate/sulfate forms. Due to the absence of free caffeic acid in coffee, plasma caffeic acid is likely to be derived from hydrolysis of chlorogenic acid in the gastrointestinal tract.

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Table 5.1 Plasma caffeic acid levels (ng/ml) before and after coffee consumption

Treatment	Time = 0	Time = 1h	Time = 2h
No treatment	12.6 ± 7.4 range 0-21	20.9 ± 4.4* range 15-26	18.4 ± 5.3 range 9-30
β- glucuronidase	14.5 ± 8.8 range 0-25	91.1 ± 33.2* range 58-176	57.0 ± 21.4 range 31-105
Alkaline hydrolysis	13.9 ± 8.4 range 0-23	91.3 ± 31.1* range 5-166	61.2 ± 25.1* range 31-121

Data are means ± SD (n=10). * $p<0.05$ from time 0 level (paired t-test).

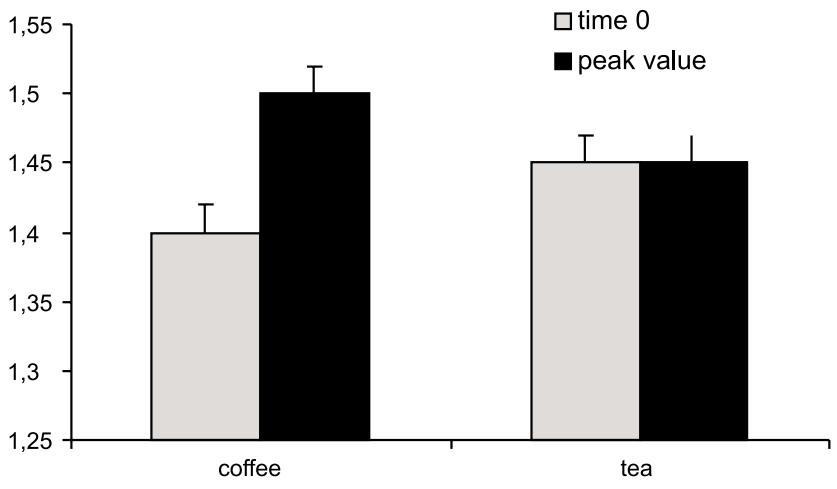

Figure 5.1 Plasma total antioxidant capacity:changes at peak points

COFFEE HEART STUDY

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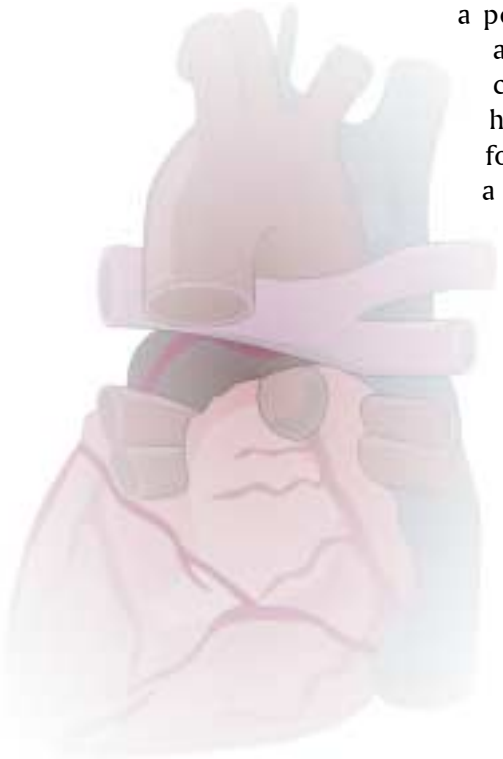
1.INTRODUCTION

Coronary atherosclerotic heart disease (CAHD) is the commonest cause of cardiovascular disability and death into the U.S.A. Men are more often affected than women. Epidemiological studies have identified a number of important risk factors for premature heart disease. These include a positive family history, age, male gender, blood lipid abnormalities, hypertension, physical inactivity, cigarette smoking, diabettes mellitus and hypoestrogenemia in women. Recent research has focused on abnormalities of lipid metabolism, which play a role in the pathophysiology of this condition. Risk increases progressively with higher levels of LDL cholesterol and declines with higher levels of HDL cholesterol. It appears that other abnormalities of lipid metabolism may also play a role in the pathogenesis of coronary artery disease such as elevated levels of apolipoprotein(a) (“little a”) and of small, dense LDL lipoprotein particles. Accumulating evidence suggests that hypertriglyceridemia is an independent risk factor for coronary artery disease as well.



Depression is present in over 45 % of patients admitted to hospital after a myocardial infarction and is an independent risk factor for increased mortality and increased morbidity after myocardial infarction. Depression may precede myocardial infarction,

although this is not certain. Research in this area has been limited to studies of small numbers of highly selected hospital patients, often without any control group. Furthermore, the overall relation between depression, ischaemic heart disease and cholesterol concentration is unclear. So far, research into wether depression precedes myocardial infarction has been limited. But recent case-controlled studies have suggested that depression may be a risk factor for ischaemic heart disease in men but not women and that it is independent of smoking status, diabetes or hypertension.

Depending on the population studied, the lifetime prevalence of major depression in the United States is five to 20 percent. Improved recognition and treatment of mood and anxiety disorders by primary care physicians would have a major impact on health in the United States, where mood and anxiety disorders are the most common serious psychiatric illnesses. Depending on stringency of the criteria used to define mood and anxiety disorders, perhaps 10 percent of the population will at some point experience a depressive episode that would benefit from treatment. Despite the availability of effective treatments, however, depression is very commonly missed during patient evaluations, and even when it is identified, it is often inadequately treated. Undertreatment of depression results in needless individual suffering, increased medical morbidity, decreased ability to work, and increased risk of suicide. Patients with untreated or inadequately treated depressive disorders, including patients with chronic minor depression or even isolated depressive symptoms, have worse physical, social, and role functioning, worse perceived health, and more somatic complaints than healthy persons. These impairments may be chronic and are equivalent to, or worse than, those associated with major chronic medical conditions such as diabetes, hypertension, and arthritis. In addition, depression and chronic medical conditions have additive deleterious effects on patients' ability to function. Undertreatment of depression also increases the risk of suicide. Mood disorders involve serious morbidity and a substantial risk of death. Among patients with recurrent depression, 15 percent commit suicide. Patients with mood disorders also have a higher mortality than age-matched control subjects because of a higher incidence of accidents and other illnesses.

In developing countries the leading cause of death is infection of the lower respiratory tract. But the second commmonest cause of death is ischaemic heart disease. Of the 50 million people who died in 1990, 6.3 million succumbed to coronary disease, 57 % of who lived in developing countries.

In the past decade, the number of people dying each year of myocardial infarction has decreased significantly. Both in-hospital mortality and out-of-hospital mortality have declined as a result of substantial increases in the use of thrombolytic therapy, coronary angioplasty, aspirin, and heparin and a reduction in the risk factors for coronary artery disease. Despite these advances, approximately 1.5 million people in the United States suffer acute myocardial infarction each year, and 500,000 die. Nearly half of these deaths occur before the patient receives medical care either from emergency medical technicians or in a hospital.

The cardiovascular disease program at WHO began in 1959, but it was only in 1973 that a fully integrated community-based plan was introduced to include the developing world. The need for reliable epidemiological data was the priority but research and training in cardiovascular disease prevention were additional goals. Despite these early efforts, which have continued at a low level for more than 20 years, the widely accepted view is that they have not been sufficient. According to the WHO the two leading causes of death worldwide by 2020 will be cardiovascular diseases and depression. What can be done to prevent these problems?

2. WORLD HEART FEDERATION

The World Heart federation helps people to achieve a better and longer life with the prevention and control of the cardiovascular diseases with focus in the middle and low economies countries.

The World Heart Federation was founded in 1946 and is based in Geneva, Switzerland and represented by 167 national societies and foundations in

Cardiology in more than 100 countries. The World Heart Federation promotes science, education and training and advocacy and has two major programs: the World Heart Day - commemorated annually in the last Sunday of September and the World Heart Forum which is a parliament embodied all the organizations involved in prevention and control of cardiovascular diseases. The World Heart federation has closes ties with the World Health organization and the UNESCO, in programs of education and prevention like the World Heart Day.

COFFEE IS NOT ONLY CAFFEINE

In the early 80´s Dr. Darcy R. Lima, M.D., Ph.D (London), Professor of Medicine and History of Medicine at the Neurology Institute at Federal University of Rio de Janeiro (UFRJ) began scientific speculations about coffee and health and has raised since then scientific data showing that coffee has many bioactive compounds which could well have a more important role than that of caffeine to human health. Caffeine is the most studied chemical from coffee but not the most abundant or perhaps even the least important compound found in coffee. Since then Dr. Darcy Lima has performed basic, clinical and epidemiological studies and was able to unquestionably prove that coffee is not only caffeine and that its daily moderate intake can be good to human health. The author's studies in Brazil were lately confirmed by large epidemiological and basic studies in USA and Europe.

Around 99 % of the people who drink coffee think that coffee is only caffeine and most people know that caffeine is safe if taken into moderate amounts on a daily basis (up to 4 cups daily). There is an inverse relationship between coffee intake and depression/suicide. Depressive illness reaches during any 1 year period almost 18 millions American adults and a significant number of youth. Nearly 18 million Americans fail to recognize their illness and get treatment. Depressed mood is associated with nicotine dependence, but it is not known whether depression predisposes one to begin smoking or develops during the course of nicotine dependence. Depression significantly increases during smoking withdrawal and this is cited as one reason for relapse. 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. It is estimated an annual loss of 43.7 billions dollars, accounting work absence, productive reduction, salary expenses, medical treatment and expenses with suicidal cases. There is an inverse relationship between coffee intake and alcoholism/cirrhosis. Around 90 percent of adult people in the world drink alcoholic beverages regularly, and 40 to 50 percent of them, particularly men, have temporary alcohol-induced problems. Around 10 percent of men and 5 percent of women develop persistent alcoholism. In the United States, two- thirds of all adults use alcohol occasionally, and at least 15 percent of the users can be considered "heavy" drinkers. Alcohol dependence is a problem that affects more than 18 millions of Americans and they represent the biggest problem of public health in the United States. In 1990, in the United States, it was spent more than 136 billions of dollars with problems from direct and indirect alcohol consumption, as such accidents, violence and productivity loss.

Coffee was wrongly considered into the past as having basically or mainly caffeine. Coffee has more than 1.000 compounds such as vitamin PP (niacin), amino acids, sugars, lipids, minerals, cafestol, chlorogenic acids (CGA), among many others yet to be studied. Opioid antagonists (naltrexone) are the only FDA approved medicines to treat alcoholism, a major worldwide problem. Depressed mood is associated with nicotine dependence. Because there is evidence that nicotine activates release of endogenous opioids, the opioid antagonist naloxone has been evaluated in short-term clinical studies for its effect on nicotine abstinence and preliminary data shows that naloxone causes a small but significant decrease in craving and smoking. Recently the FDA has approved the use of an antidepressant, bupropion, as an adjunct to the treatment of nicotine addiction. Coffee has far more chlorogenic acids (6 to 9%) comparing with caffeine (1–2,5%). The chlorogenic acids (which have potent antioxidant properties) after coffee is properly roasted give birth to the quinides which have a powerful opioid antagonist activity. When people drink coffee these compounds go faster than caffeine into the blood and into the brain. In this way the good mood, lack of depression and of craving for alcohol seems to be related to the CGA content of

coffee acting into the limbic system while the improvement in attention and memory due to its caffeine content (1-2 %) acting into the brainstem and cerebral cortex.

Ongoing studies with youth at schools in Brazil are showing that higher rates of participation in school breakfast programs with coffee and milk are associated in a short-term and long-term with improved student functioning on a broad range of psychosocial and academic measures. Brazilian students who drink coffee and milk are less prone to apathy, depression and alcohol intake.

Definitively coffee beans, coffee roasting and coffee drinking has yet a lot to be studied under rigorously controlled situations either into laboratories as well as among normal consumers, youth and adults as well as depressed people, alcoholics, smokers and drug addicts, among many others. The relationship of daily coffee intake, depression and cardiovascular disease seems to be of utmost importance to human health as well.

4. COFFEE HEART STUDY

The COFFEE HEART STUDY is a Prospective Population-Based study (cohort) of doctors and patients who drink or not coffee on a daily basis and follow-up studies to evaluate the incidence of depression and morbidity and mortality due to CAHD planned by Prof. Mario Maranhão and Prof. Darcy Roberto Lima, approved by the WORLD HEART FEDERATION wich will began in Brazil under the leadership of HEART INSTITUTE from São Paulo (HC-USP) and its Director Prof. Jose Antonio F. Ramirez. The investigational sites are being determined by INCOR and WHF. The study intends to evaluate the relationship between regular daily coffee intake among doctors and patients and incidence of depression and morbidity and mortality due to CAHD. The length of the study is ten years and the Scientific Group of the Project CHS will determine the numbers of subjects.

A semi-quantitative food frequency questionnaire listing regular foods and beverages items (including coffee, tea, cola, beverages, alcohol, tobacco), each specifying a commonly used portion size will be used. Three cohort groups will be established: 1) non-smoking doctors 2) smoking doctors and 3) patients in general. Cohort members will be asked to report the average frequency of consumption of each item during the previous year. The question concerning beverages will include possible responses regarding the frequency with which subjects drank one cup of coffee or tea or one glass of cola beverage, ranging from never or almost never to four, six or more times a day. To derive the caffeine score and chlorogenic acids score of the many brands of coffee consumed by the population, samples of coffee will be analyzed to quantify the final caffeine and CGA content.

Regularly questionnaires will be given or send by post to members of each specific population and questionnaires will be recovered afterwards. Those where two or more items are blank shall be excluded as well as those with implausibly high or low scores for total food intake and subjects who did not complete the question on coffee consumption.

A recent major cohort study to relate habitual (cups per day) of tea and coffee consumption to conventional coronary risk factors and subsequent risk of coronary heart disease and death was published (1999). The Scottish Heart Health Study, a nationwide random population study included over 11.000 men and women aged 40-59 from 1984 until 1987 and participants were followed up to the end of 1993, an average of 7,7 years , for all cause mortality, coronary death, or any major coronary event (death, non-fatal infarction or coronary artery surgery). Cox´s proportional hazards regression model was usd to estimate the hazard in consumers of tea and coffee relative to the zero consumption group, both before and after correction for other factors.

Main results showed that coffee and tea consumption have a strong inverse relation. For many conventional risk factors, coffee showed a weak, but beneficial, gradient with increasing consumption, whereas increasing tea consumption showed the reverse. Increasing coffee consumption was associated with beneficial effects for mortality and coronary morbidity, whereas tea showed the opposite. The authors conclude that the study shows

epidemiological differences despite pharmacological similarities between tea and coffee, perhaps rregarding its final caffeine content. The authors do not mention the rather important difference of chlorogenic acids derivatives found in coffee with opiate receptor antagonist activity (formed after the roasting process) wich are almost absent into tea (non roasted beverage).

The SCOTTISH HEART HEALTH STUDY gives additional support to the present project, which intends to evaluate the role of coffee in preventing mortality and coronary morbidity, thus confirming these preliminary data as well as explaining the differences found comparing with tea, among other beverages without chlorogeinc acids derivatives with opiod antagonist activity. Provide coffee has appropriate amounts of chlorogenic acids/ quinides with opioid antagonist activity, its regular and moderate intake may well be an important prophylatic agent for coronary heart disease among men.

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ANALYSING COFFEE'S CHEMICAL COMPOSITION AND ITS BIOLOGICAL EFFECTS ON HUMAN HEALTH

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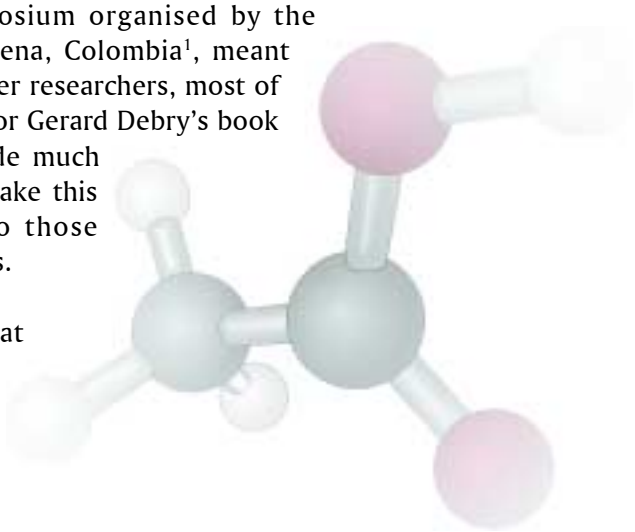
Introduction

Coffee is one of the most well known beverages drunk most around the world, acting as a stimulant for people's psychogenic activity. Coffee represents one of the most important agricultural products for producing countries' economic and social development. Such psychogenic, economic, political and social activity has thus attracted intense analysis (chemical and biological in the case of psychogenic activity) in an attempt to understand those mechanisms regarding its action, activity in relation to the nervous system and the positive or harmful effects of its consumption on the human organism. A deep knowledge of its chemical components has thus become needed for understanding its biological activity.

The concise analysis presented in the short paper presented in September 2003 during the "Coffee & Health" Symposium organised by the International Coffee Organisation in Cartagena, Colombia[1], meant summarising many studies carried out by other researchers, most of which have been carefully analysed in Professor Gerard Debry's book entitled "Coffee and Health," (1) which made much use of their information. We would like to take this opportunity for expressing our thanks to those researchers and duly recognising their efforts.



Coffee, like all biological products, has great chemical and biological complexity in which more than 1,000 substances and chemical products have been recognised, some of

[1] This event was organised by Diego Pizano

which have been clearly identified and their biological functions defined.

If one wishes to investigate human beings' chemical characteristics, then many factors must be considered, including their genetic origin, the degree of their biological development, the circumstantial setting, the analytical method used and such methodology's ability to lead to validate conclusions etc. The same applies to coffee.

The different varieties' (*robusta, arabica,* etc) degree of maturity, how they are prepared, the analytical methods used and their intrinsic limitations, etc., mean that interpretations (another variable) may sometimes differ and even be contradictory on some occasions.

We therefore wish to give a brief presentation of results from such analysis depending on variety, preparation method and methodology used, to try to give an overall view of coffee's chemistry and avoid any innate slant.

Coffee's chemical composition

Table 1 shows the composition of green or roasted coffee (*arabica, robusta* varieties) and instant analysing its bulk chemical composition by studying its general components. It can be immediately observed that instant coffee contains a greater quantity (expressed as the percentage of dry basis) of minerals (2 to 3 times) and caffeine (4 or 5 times), whilst other substances susceptible to degradation (produced by processing) disappear or their

Tabla 7.1. Composition of green and roasted coffee (acording to variety) and of instant coffee (expressed as a percentage of the dry basis)

Component	*Arabica*		*Robusta*		Instant
	Green	Roasted	Green	Roasted	
Minerals	3,0 - 4,2	3,5 - 4,5	4,0 - 4,5	4,6 - 5,0	9,0 - 10,0
Caffeine	0,9 - 1,2	Appr. 1,0	1,6 - 2,4	Appr. 2,0	4,5 - 5,1
Trigonelline	1,0 - 1,2	0,5 - 1,0	0,6 - 0,75	0,3 - 0,6	-
Lipids	12,0 - 18,0	14,5 - 20,0	9,0 - 13,0	11,0 - 16,0	1,5 - 1,6
Total chlorogenic acids	5,5 - 8,0	1,2 - 2,3	7,0 - 10,0	3,9 - 4,6	5,2 - 7,4
Aliphatic acids	1,5 - 2,0	1,0 - 1,5	1,5 - 2,0	1,0 - 1,5	-
Oligosaccharides	6,0 - 8,0	0 - 3,5	5,0 - 7,0	0 - 3,5	0,7 - 5,2
Total polysacchrides	50,0 - 55,0	24,0 - 39,0	37,0 - 47,0	-	Appr. 6,5
Amino acids	2,0	0	2,0	0	0
Proteins	11,0 - 13,0	13,0 - 15,0	11,0 - 13,0	13,0 - 15,0	16,0 - 21,0
Humic acids	-	16,0 - 17,0	-	16,0 - 17,0	15,0

concentration becomes dramatically lessened such as trigonelline, aliphatic lipids (10%) and oligosaccharide acids. (1) This is not just important from the product's physical-chemical characteristics point of view but also in terms of organoleptic characteristics such as aroma, taste, stimulant activity, etc.

Table 2 shows the differences between *arabica* and *robusta* varieties, mainly concerning green coffee beans' carbohydrate content (concerning variation in dry basis percentage) mainly in sucrose content, where it is found that the *arabica* variety's sucrose concentration is 2 to 3 times greater than that of the *robusta* variety, an important factor in characteristics regarding taste (2).

Analysing Table III gives a small illustration of the difficulty involved in breaking-down a product's composition, respecting the composition of green

Tabla 7.2. Carbohydrate contents in green coffee (% of dry basis)

Contituent	*Arabica*	*Robusta*
Monosaccharides	0,2 - 0,5	0,2 - 0,5
Sucrose	6 - 9	3,7
Polysacchrides	43,0 - 45,0	46,9 - 48,3
- arabinose	3,4 - 4,0	3,8 - 4,1
- mannose	21,3 - 22,5	21,7 - 22,4
- glucose	6,7 - 7,8	7,8 - 8,7
- galactose	10,4 - 11,9	12,4 14,0
- rhamnose	0,3	0,3
- xylose	0 - 0,2	0,2

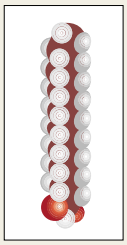
coffee's fatty acids (expressed as total lipid percentage) as analysed by three different groups of researchers (3). What is clear is that independently of variations (probably due to differences in method employed) it is found that the main fatty acids are palmitic C16:00, linoleic C18:2, oleic C: 18:1, stearic C 18:0 and arachidic C: 20: 6, some of them being saturated and others non-saturated.

Tabla 7.3. Fatty acid composition of green coffee bean oil, expressed as a %of total lipids

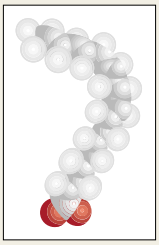
Authors	1	2	3
Myristic a. C14:0	Traces	Traces	0.2
Palmitic a. C16:0	35,20 - 38,60	30,7 - 35,3	35,2 - 36,7
Palmitoleic a. C16:1	Traces	Traces	-
Margaric a. C17:0	-	Traces	-
Stearic a. C18:0	6,60 - 8,35	6,6 - 9,0	7,2 - 9,7
Oleic a. C18:1	7,55 - 10,90	7,6 - 10,1	9,5 - 11,9
Linoleic a. C18:2	38,40 - 43,0	43,2 - 45,9	41,2 - 42,6
Linolenic a. C18:3	?	1,1 - 1,7	1,3 - 2,7
Arachidic C20:0	4,05 - 4,75	2,7 - 3,3	0,3 - 1,5
Gadoleic C20:1	-	?	
Behemic a. C22:0	0,65 - 2,60	0,3 - 0,5	

Palmitic acid

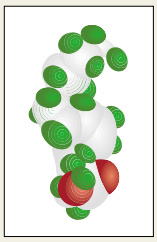
Stearic acid



Linoleic acid



Oleic acid

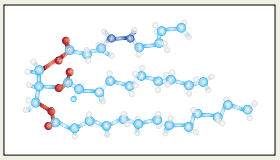
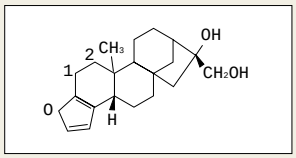


X C20;0 and higher= 4,28-6,43

1. Calzorali (C), Cerma (E) Riv ital. Sostanze Grase 1963; 40, 176-180
2. Kroplien (U), Green and Roasted CoffeeTests, Gordian, Hambourg 1963
3. Chassevent (F), Gerwing (S). Vicent (J. C.) Café, Cacao, The, 1974, 18, 49-56

Roasted coffees contain a high lipid level (around 16% for *arabica* and 11% for *robusta*), associated in two coffee-specific diterpenes (cafestol and kahweol), being those liberating their most volatile products during the roasting process and whose level can serve in determining the proportion of *arabica* and *robusta* coffee chosen for preparing blended coffees, since kahweol is present in *robusta* but not in *arabica* coffee (4).

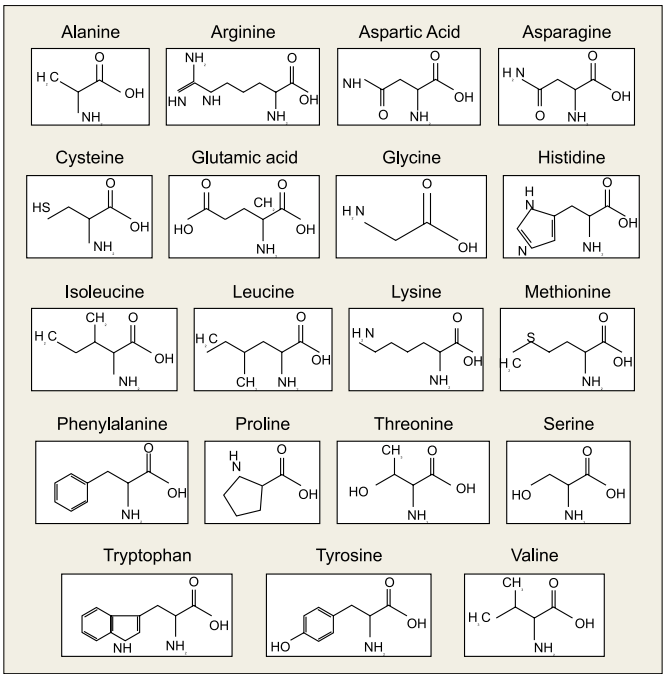
Tabla 7.4. Lipid composition of green (expressed as a %total lipids)

Lipidic fractions	%	Components
Triglycerides	70 - 80	Linoleic and palmitic acid esters 
Free fatty acids (in % of oleic acid)	0,5 - 2,0	
Diterpene esters	15 - 18,5	Linoleic and palmitic acid esters Cafestol (furokaurane) and (in *arabica*) kahweol (furokaurene), atractyligenine.
Triterpenes, sterols, methylsterol esters	1,4 - 3,2	Sytosterol, stigmasterol, campesterol 
Free diterpenes	0,1 - 1,2	
Free triterpenes and sterols	1,3 - 2,2	
Phospholipids	0,1	Squalene and nonacosane
Hydrocarbons	Traces	Arachidic, behenic and lignoceric acid amides
5-Hydroxytriptamides	0,3 - 1,0	Alpha, beta and gamma isomers
Tocopherols	0,3 - 0,7	

Both varieties' protein content is practically the same, being between 8.8% and 12.2% of green coffee's base, but free amino acid content is very poor ranging from 0.2% and 0.8%. Of total amino acids 20% to 40% are lost during the roasting process (depending on their intensity) as a result of proteins becoming denatured. The proportion of some amino acids can be increased during roasting whilst others such as arginine, glutamine, cysteine, serine and threonine can disappear as a result of such processing (5,6).

Tabla 7.5. Free and total amino acids in green coffe (% of dry basis)

Amino acid	Free amino acids		Total proteins
	Arabica	*Robusta*	
Alanine	0,05	0,09	0,5
Arginine	0,01	0,02	0,5
Aspartic acid	0,05	0,09	1,0
Asparagine	0,05	0,09	
Cysteine	0,001	0,001	0,3
Glutamic acid	0,13	0,08	1,9
Glycine	0,01	0,02	0,6
Histidine	0,01	Traces	0,2
Isoleucine	0,01	0,02	0,4
Leucine	0,01	0,02	1,0
Lysine	0,01	Traces	0,6
Methionine	0,004	0,004	0,2
Phenylalanine	0,02	0,04	0,7
Proline	0,03	0,04	0,6
Serine	0,03	0,04	0,5
Thereonine	Traces	0,01	0,3
Tyrosine	0,01	0,02	0,4
Valine	0,01	0,02	0,5
Tryptophan	0,01	0,05	0,1
Total	0,5	0,8	10,3



Amino acids can undergo Maillard's reaction during roasting or Strecker's reaction together with α-diketones, being degraded by pyrolysis. New products formed in this way are aromatic and volatile.

Purine bases can be found amongst nucleic acid derivatives and precursors whose concentration changes according to variety (7, 8).

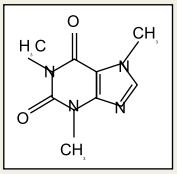
Caffeine (Table Vl) is the main alkaloid present in coffee, its concentration (in milligrams/Kgr/dry basis) varying, *arabica* (9,000–14,000) being practically half of robust (15,000-26,000). The other alkaloids such as theobromine and theophyline are found in much lesser proportions.

Nitrogenated bases are divided into two large groups; there are roasted stable ones such as ammoniac, betaine and choline and some instable ones such as trigonelline (present in around 0.6% to 1.2% *arabica* and 0.9 *robusta* varieties) which becomes decomposed to nicotinic acid or niacin.

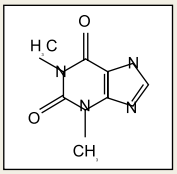
Tabla 7.6. Purine alkaloids in green coffee expressed in mg/kg/db

Components	*Arabica*	*Robusta*
Caffeine	9,000 - 14,000	15,000 - 26,000
Theobromine	36 - 40	26 - 82
Theophylline	7 - 23	86 - 344
Paraxantine	3 - 4	8 - 9
Theacrine	0	11
Liberine	5	7 - 110
Methylliberine	0	3

Caffeine



Theophylline

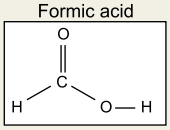


Free acid content is important in coffee's organoleptic characteristics, mainly as a result of acetic, citric and phosphoric acid formation. Phosphoric acid content (just like pyroglutamic acid derived from glutamic acid) becomes considerably higher during the roasting process (9).

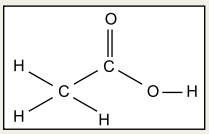
Tabla 7.7. Aliphaticacids in coffee (% db)

Components	Green coffee	Roasted coffe
Formic acid	Traces	0,06 - 0,15
Acetic acid	0,01	0,25 - 0,34
Lactic acid	Traces	0,02 - 0,03
Citric acid	0,7 - 1,4	0,3 - 1,1
Malic acid	0,3 - 0,7	0,1 - 0,4
Fumaric acid	Traces	0,01 - 0,03
Oxalic acid	0 - 0,2	?
Quinic and quinidinic acid	0,3 - 0,5	0,6 - 1,2

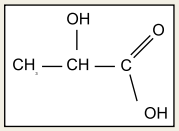
Formic acid



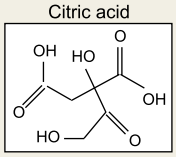
Acetic acid



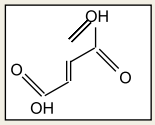
Lactic acid



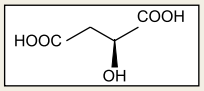
Citric acid



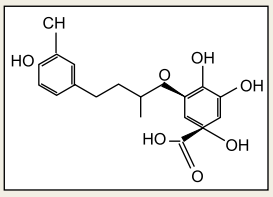
Fumaric acid



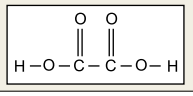
Malic acid



Quinic acid



Oxalic acid



Quinic and vinidinic acid content lying between 0.3% and 0.5% in green beans becomes increased during treatment, but from the biological point of view their derivatives are more important. One of these is n-chlorogenic acid whose proportion and derivatives depends on the degree of roasting (10,11).

Tabla 7.8. Chlorogenic acids in *arabica* and *robusta* raw coffee (% db)

Component	*Arabica*	*Robusta*
5-chlorogenic acid	3,0 - 5,6	4,4 - 6,5
4-chlorogenic acid	0,5 - 0,7	0,7 - 1,1
3-chlorogenic acid	0,3 - 0,7	0,6 - 1,0
Total	**3,8 - 7,.0**	**5,7 - 8,6**
3,4-dicaffeoylquinic acid	0,1 - 0,2	0,5 - 0,7
3,5-dicaffeoylquinic acid	0,2 - 0,6	0,4 - 0,8
4,5-dicaffeoylquinic acid	0,2 - 0,4	0,6 - 1,0
Total	**0,5 - 1,2**	**1,5 - 2,5**
3-feruloylquinic acid	Traces	0,1
4-feruloylquinic acid	Traces	0,1
5-feruloylquinic acid	0,3	1,0
5-feruloyl, 4-caffeoylquinic acid	0	Traces
Total	**1,2**	**1,2**

A coffee's quality partly depends on relative mono- and di-chlorogenic acid proportion. A di-chlorogenic excess can lead to a coffee's metallic, bitter taste associated with coffee which has been kept hot for a long time resulting from an increase in quinic acid and lactone formation and a lessening of pyridine concentration (11).

Respecting mineral content, potassium is found in the greatest proportion (around 80 milligrams in a cup of instant coffee). Even when a low copper concentration is found, such level is much greater in *robusta* coffee, leading to it being argued as an explanation for this variety's greater resistance to developing fungi due to copper's antifungal activity (12).

Tabla 7.9. Mineral content
(A cup of instant coffee approx. 200ml, corresponding to 2g of coffee)

Mineral	Milligrams	Ppm
Sodium	1	5
Potassium	80	400
Calcium	3	15
Phosphorus	7	15
Iron	0,09	0,45
Copper	0,001	0,005
Zinc	0,01	0,05

The percentage of extracted potassium in instant coffee is different, but its concentration depends on the method employed, used for indicating a determined technique's extraction rate.

It may be true that the composition of coffee represents an excellent source of nutritional requirements for the human body; however such supposition must be taken with reserve due to the great number of unidentified components which a determined physiological function may have, many of which have still not been clearly established.

Coffee's biological effects

The most studied molecule and that to which most of coffee's effects is attributed is caffeine, isolated in 1820 for the first time by Runge and Van Giese and described for the first time in 1823. It is found in more than 60 plants and trees (such as coffee, tea and cacao) and it is known that it protects coffee beans against parasites thanks to its antifungal activity (13).

Caffeine is an alkaloid from the methylxanthine family, derived from purine (14).

Caffeine becomes rapidly absorbed by the intestine and stomach within 45 minutes of being ingested, reaching its maximum concentration peak 15 to 20 minutes after being ingested. 5 mgr/Kg caffeine corresponds to people weighing about 70 Kg consuming around 600 ml of roasted coffee (i.e. 4 cups of coffee) (15).

As it is a hydrophobic molecule, it passes cell barriers, including blood brain and foetal barriers in such a way that a foetus receives the same concentration of caffeine as its mother.

Caffeine is metabolised in the liver where it undergoes successive demethylations and oxidations until being eliminated in the urine.

It has been argued that this molecule's stimulant effect on the nervous system is the result of adenosine A_1 receptor inhibitory action, these being present in large numbers in the brain and also in the heart, trachea, kidneys and adipose tissue (16). These receptors intervene in cellular exchange of potassium and calcium and thus play a part in a process of regulating cell membrane polarity, excitability of the nerves, diuresis and secreting renin, partly explaining its technological mechanisms on the nervous system and polyuria.

Caffeine also acts on phosphodiesterase (17), inducing relaxing of the trachea and bronchial tubes, meaning that it has a favourable effect on asthma attacks. It also causes mobilisation of intracellular calcium inducing changes in nerve cell function, whilst it has been shown that it is the only alkaloid within the neurotransmitters causing important physiological effects and as it is found in many drinks it is difficult to evaluate its mechanisms and biological function.

Coffee and caffeine represent human beings' most widely used and consumed central nervous system stimulants, having a slight stimulant effect, relieving minor fatigue and boredom with little risk of any harmful effects (18).

It has an effect on locomotor activity, associated with occupying adenosine A_1 receptors due to metabolising methylxanthine.

It does not increase long-term memory in human beings, but, due to previously described mechanisms, responses are faster and more efficient, perhaps due to fatigue being reduced (19,20). However, it seems that coffee postpones sleepiness, leading to lighter sleep and that its results become more prominent before bedtime. It also increases anxiety levels in those individuals who are sensitive to this substance. The central nervous system does not easily seem to develop tolerance towards caffeine but methylxanthine dependence has been shown. Children are not so sensitive to coffee or caffeine as adults; on the contrary, sensitivity to methylxanthine increases with age. Caffeine has a vasoconstrictor effect on the brain and peripheral vasodilator, leading to it being used in mechanisms against migraine; it is thus also used for boosting for some medicaments' analgesic effect.

Coffee's medicinal effects

Due to the wide consumption of coffee throughout the world, the safety of drinking it has often been questioned from the biological point of view, it being argued (without great scientific basis) that it negatively affects human health. This has led to a great number of clinical studies being done, some of them being well-designed, well-randomised case-control studies; these have had well-analysed confusion variables and clearly defined products. Their conclusions were diametrically opposed to those questioning coffee, arguing coffee's harmful effects on human health (21).

It has been found, for example, that the inotropic effect on myocardial muscular contractility was variable from specie to specie analysed and that a much greater dose was needed in humans than that obtained by drinking coffee (1 to 3 litres of instant coffee) to produce changes in cardiac frequency or functioning of the heart, tachycardia, extrasystole, etc (22).

No correlation was found between drinking coffee and heart-attack in 19 prospective studies and 18 case-control studies carried out between 1963 and 1991 in different countries (USA, UK, Canada, Scandinavia, etc).

As caffeine's action mechanisms are complex, acting as an adenosine A_2 receptor blocker on baroreceptors, renin and sympatic nervous system, it was thought that it could have effects on blood pressure. Many studies found that drinking coffee induced a small increase in blood pressure (3 mm mercury) for about 4 hours with a slight lessening in heartbeat, suggesting that it could have been acting on baroreceptors (23).

When some people drink coffee they experience a burning sensation at the mouth of the stomach. This could perhaps be a result of gastrin secretion being induced by caffeine or acidity being induced by the aforementioned acids. Nevertheless, decaffeinated coffee also induces the same symptoms, suggesting that other substances different to caffeine but present in coffee could also be mediating such gastric hyperacidity (24).

One of the most important substances in coffee, chlorogenic acids are hydrolysed to caffeic and quinic acids in humans. One or two cups of coffee stimulate gastric secretion and increases chlorhydric acid production as a result of chlorogenic acid action, whilst quinic acid has none of these activities.

It has been found in a case-control study that the burning sensation or dyspepsia was not associated with the presence of gastric ulcer. It is thus not possible to argue that coffee is a cause of dyspeptic upset.

From the digestive point of view, it can be found that drinking coffee increases the liver's enzyme activity. A study involving more than 128,000 adults concluded that people drinking 4 cups of coffee per day ran a 5 times lower relative risk of developing hepatic cirrhosis than those who did not (25). It has also been found that drinking coffee reduces the relative risk of gallstones becoming formed by 50% (26). There are circumstances in which drinking coffee has lessened glutamyltransferase serum levels.

Consuming alcohol can lead to hepatic cirrhosis as a result of alcohol's pro-oxidant effects on P450 cytochrome, biotransforming ethanol into acetaldehyde, generating oxygen-free radicals in turn binding to macromolecules or reacting with intracellular thiol reducers. Coffee contains a great amount of antioxidant agents neutralising oxygen-free radicals generated by activating P450 cytochrome; such formation seems to be mediated by cafestol and kahweol (27).

Parkinson's disease is a neuro-vegetative disorder of unknown origin characterised by bradykinesia or slowness of movement, tremor and rigidity, appears in around 1% of people aged more than 55 or 3% of those older than 65. It results from degeneration of the *substancia nigra*.

Case-control studies have found that the relative risk of developing this disease is 5.1 times lower in people drinking 4 cups of coffee per day (28). It has been argued that it results from the caffeine's

antagonism towards adenosine A_2A receptors; coffee can thus reduce Parkinson's clinical manifestations. Studies have also suggested that niacin in coffee (required for synthesising nicotinamide-adenin-dinucleotide - NADH) and its phosphodiester-derivative (NADPH) involved in reducing the brain's free radicals could also be acting on the *substancia nigra*, reducing the level of these radicals (29).

Different studies carried out from 1960-1990 in 10 countries (Europe, Japan and the USA) found that people drinking more than 4 cups of coffee a day had 24% less probability of developing colon-rectal carcinoma (30), perhaps due to biliary acid secretion becoming inhibited (these being considered promoters of this disease), higher cholesterol level induced by coffee through cafestol and kahweol action or due to the presence of substances acting as anti-oxidants, such as chlorogenic acids (caffeic, cinnamic, ferulic esters of quinic acid) which have conferring anti-oxidant activity (31).

It has also been suggested that coffee stimulates the process of detoxification on inducing glutation transferase enzymes by cafestol and kahweol action, helping to limit the action of toxic and oxidant substances, the same as the mutagenic tending to act on the liver and colon (32).

Conclusions

- Coffee's composition is very complex. It includes more than one thousand substances;
- Not all the components of coffee have been identified. Some of those which have been identified possess physiological effects, caffeine being the most well-known one;
- To determine the validity of results from experimental studies on animals, the following criteria must be taken into account:
  The dose used;
  The duration of coffee being administered; and
  Each animal specie's metabolic characteristics;
- Caffeine is the most well-known alkaloid in coffee producing significant physiological effects; others like teophilline, theobromine also induce significant biological effects;
- Coffee's metabolism is complex. Its physiological effects can be partly explained by three mechanisms:
  Adenosine receptor antagonism;
  Phosphodiesterase inhibition, and
  Intra-cellular calcium mobilisation;
- The only neurological effects that have been clearly demonstrated are increased alertness and delay before the onset of sleep. Coffee's caffeine content elicits constriction of cerebral blood vessels. It is thus present in many pharmaceutical products used to treat migraine. Caffeine also boosts some medications' analgesic effect;
- Coffee increases short-term memory, alertness and sharpness;
- Healthy people consuming coffee in moderate amounts does not modify their cardiovascular function or systolic or diastolic blood pressure, however it does increase sportspeople's performance;
- Gastric or intestinal intolerance sometimes attributed to coffee is linked to individual sensitivity which has not been reproduced in experimental studies;
- Coffee exerts a cholecystokinetic action and increase the pancreas' external secretion;
- Consuming coffee does not cause disease related to the respiratory apparatus;
- Endocrine functions do not become modified by consuming coffee;
- Consuming coffee does not have any important effect on muscle function;
- It has not been demonstrated that consuming coffee represents a risk factor in bone fracture;
- Coffee is a good source of potassium, magnesium and fluoride;

- Consuming coffee increases energy metabolism in the hours following its ingestion, but does not modify total energy expenditure;
- Consuming coffee has no harmful effects on reproduction or fertility;
- Coffee (drunk in the usual amounts by humans) does not have any teratogenic effect; and
- In terms of habitual amounts of human consumption, coffee does not have any genotoxic, mutagenic or carcinogenic potential.

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FINAL COMMENTS

Dr. Ernesto Illy

Over the course of the last decade the weight of research into the health aspects of coffee drinking has seen a shift from predominantly negative to predominantly positive.

During this period the scientific community has broadened its focus from the effects of caffeine to those of other compounds found in coffee.

Antioxidants have been shown to assist in eradicating free radicals, rogue molecules that attach themselves to normal healthy molecules with potentially serious consequences for the health of the individual. The antioxidant effect of coffee is thirty percent higher than that of tea, due to the presence of caffeic as well as uric acid.

Coffee has been found to reduce the risk of developing conditions of the central nervous system such as Alzheimer's and Parkinson's diseases. New research from Japan points to coffee providing protection against cancer by hindering the spread of cancerous cells to other parts of the body.

Coffee is an anti-depressant, aiding sufferers from this intractable condition to rediscover the joy of life. Due to its anti-inflammatory action it can help to protect against cardiovascular disease. It can be used to treat drug addiction by blocking the neuroreceptors that would normally produce a pleasurable response to the ingested drug.

These findings have changed the way we think about coffee. We have always drunk it for the wonderful taste and the way it brightens our outlook. It is now clear from research into the physiological effect of compounds found in coffee, that it helps us to live better and longer. Thus we must finally leave it to the medical profession to prescribe coffee to patients suffering from those diseases that it helps control or prevent, allowing them the pleasure of a good cup, while enjoying the medicinal benefits of this unique natural product.

BIOGRAPHICAL NOTES ON PARTICIPANTS

Gabriel Silva: General Manager of the National Federation of Coffee Growers of Colombia. He was Ambassador of Colombia at the White House and National Security Counsellor to the Colombian Presidency. He was President of the Global Education company.

Ernesto Illy: President of the ICO Promotion Committee, President of ASIC (International Coffee Science Association) and of ISIC. President of the Illycaffè company. Graduate in Chemistry of the University of Bologna, Italy. *Cavaliere del Lavoro*, of the Republic of Italy and "Lifetime Achievement Award" of the SCAA.

Beatriz Londoño: Director of the Colombian Family Welfare Institute. She is a Medical Anaesthetist and holds a Master's degree in Public Health from Harvard University. She was Health Secretary for the city of Bogotá. She has acted as a Consultant to various public and private bodies.

Néstor Osorio: Executive Director of the ICO. He was Ambassador of Colombia to the World Trade Organization and Chairman of the WTO Agricultural Committee and Trade Policy Review Body. Between 1978 and 1994 he was Permanent Representative of Colombia to the ICO.

Diego Pizano: Economic and International Adviser to FEDERACAFÉ. Alternate Representative of Colombia to the ICO. He was Economic Counsellor to the Colombian Presidency. He has acted as a Consultant to the World Bank and the Inter-American Development Bank. He has been associated with the *Universidad de los Andes* (Bogotá) for many years and is the author of several books and publications.

Peter Martin: Professor of Psychiatry and Pharmacology at Vanderbilt University (USA). Director of the Institute for Coffee Studies at that university. He was also Director of the Addiction Studies Centre. Author of several publications.

Astrid Nehlig: Director of Research at the French National Health Institute (INSERM) based in Strasbourg. Author of several publications in the field of neurology relating to coffee and health, epilepsy and other subjects.

Cristina Scaccini: Head of Research at the National Institute of Food and Nutrition, Italy (INRAN) based in Rome. She coordinates the Institute's Study Group on Free Radicals and is the author of several publications.

Manuel E. Patarroyo: Director of the Colombian Institute of Immunology. Author of numerous publications in the field of immunology and tropical medicine. He was awarded the Koch Medal in Germany and the Principe de Asturias Prize in Spain.

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