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Effect of coffee (caffeine) against human cataract blindness

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Abstract: Previous biochemical and morphological studies with animal experiments have demonstrated that caffeine given topically or orally to certain experimental animal models has significant inhibitory effect on cataract formation. The present studies were undertaken to examine if there is a correlation between coffee drinking and incidence of cataract blindness in human beings. That has been found to be the case. Incidence of cataract blindness was found to be significantly lower in groups consuming higher amounts of coffee in comparison to the groups with lower coffee intake. Mechanistically, the caffeine effect could be multifactorial, involving its antioxidant as well as its bioenergetic effects on the lens.

Keywords: caffeine, cataract, cataract blindness, cataractogenic process, intraocular pressure, vision impairment

Introduction

Cataract development is one of the major causes of visual impairment and eventual blindness.[1,2] While cataract surgery has the potential of decreasing blindness due to this disease, the problem is so huge that it is difficult to eliminate it to the desired level, even by 2020. In fact, despite enhancement of surgical programs being undertaken in certain countries, the number of people with such vision impairment has been estimated to either remain stationary or even increase because of the simultaneous rise in population of the people over the age of 50. For example, in India, where there is a highly serious effort to increase the number of surgery, the number of people with cataract-related visual impairment and blindness is projected to increase from 7.75 million noted in 2001 to 8.25 million in 2020 because of the increase in the population in general, as well in the population of people over 50 years of age.[3] Additionally, its overall incidence is expected to remain relatively stationary because of the replacement of people with cataracts by the newer people and increasing the global incidence of diabetes including that in the developing countries. This is expected to have additional impact on the incidence of cataracts as well as some retinal diseases. As determined by the World Health Organization (WHO), the overprevalence of blindness due to cataract has remained steady to approximately 50% through 2010. Additionally, it is recognized that country-wise differences in cataract-related blindness is also related to certain other confounders such as genetics, environmental, and various nutritional factors known to be involved in maintaining the lens in a transparent state. For example, the cataractogenic process starts at a much younger age in Southeast Asia than in the Western countries. The prevalence of cataract is also related to the intensity and duration of solar radiation at particular places. This is largely demonstrated by the higher incidence of cataracts in the tropics.

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We have previously shown that an intraocular penetration of visible and ultraviolet (UV) radiation initiates photochemical formation of certain highly reactive species of oxygen in the aqueous humor and lens. These species are commonly referred to as reactive oxygen species (ROS). The common species are superoxide, hydrogen peroxide, hydroxyl radical, and singlet oxygen that play a central role in inflicting oxidative stress to the tissue and its opacification.[4–6] Thus, the formation of cataract is expected to be highly modulated by the presence of antioxidant nutrients in the diet and their passage through the blood aqueous barrier, such as ascorbate and vitamin E, known to act as potent scavengers of the ROS. Thus, the local nutritional culture, adopted or native, can have a significant modulating role. An immediate effect of ROS generation is to deplete the lens of its antioxidant reserves such as glutathione, which in turn can lead to oxidative modifications of its membrane lipids and proteins. We have recently shown that this depletion of antioxidants can also be followed soon by an overall genetic dysregulation, induced by an upregulation of the generation of microRNAs (miRNAs) and consequent gene silencing.[7,8] Initial evidence to the involvement of oxidative stress in the etiology of cataract formation was provided by a number of organ culture studies showing biochemical and structural damage to the tissue induced by various ROS. Addition of ROS scavengers including vitamin C, α-tocopherol, bioflavonoids, chlorogenic acid, and pyruvate to the culture medium has been found to be highly protective.[9–14] The role of oxidative stress in the pathogenesis of cataract has been demonstrated in vivo by the preventive effect of ROS scavengers against cataract formation in intact experimental animal models,[15–19] as well as by a number of human studies with antioxidant vitamins.[20–23] More recently, we have shown that caffeine, a common constituent of many food products, can also protect the lens against oxidative stress in vitro as well as in vivo.[24–28] The in vivo effectiveness has been demonstrated by its preventive effect against cataract formation in rats fed a diet rich in galactose, a highly active cataractogenic sugar that simulate the formation of diabetic cataracts. It is effective if given systemically mixed with the diet,[29] as well as when administered topically by application of caffeine drops.[27,28] Additionally, it also inhibits UV-induced cataract in vitro as well in vivo. In the former case, it was shown by its protective effect against damage to the lens organ culture in the absence as well as in the presence of kynurenine.[24,25] In the latter case, its topical application has been found to be effective against cataract formation induced by exposing rabbits to UV-B.[30] That its actions are attributable to its ability to act as scavenger of ROS was further proven by electron spin resonance studies.[31–33] While acting as a ROS scavenger, it also represses the transcription of toxic miRNAs.[34] Based on these studies showing anticataractogenic effect of the compound in experimental animals, it was considered desirable to investigate if its use as a dietary constituent could be involved as a factor in modulating the formation of cataracts in humans also.

Methods

This possibility has been investigated by correlating the prevalence of cataract blindness in different countries with the amount of caffeine consumed there in, per person. Data on the prevalence of cataract blindness were obtained from the population-based studies, where the blindness due to cataract was determined along with the contribution of various other eye diseases such as glaucoma, age-related macular degeneration, corneal opacities, diabetic retinopathy, childhood blindness, trachoma, onchocerciasis, and others, consolidated by WHO in 2004.[2] Cataract has been found to account for approximately 50% of the total blindness, a figure found to be little affected at least until 2010 and expected to remain so at least till 2020.

Since coffee is the primary source of caffeine, its intake was determined from its per capita coffee consumption (kg/year). This information was obtained from the Food and Agriculture Organization of the United Nations (http://www.griequity.com/resources/BusinessGuides/DemographicsData/energy/energy-resourceconsn.pdf Table ERC.5),[35] as well as from the alphabetical listings and maps available online with www.ChartsBin.com. They all describe consumption of *Coffea arabica*, the primary variety of the coffee used throughout the world.[33,34] Additional data were obtained from www.wiseGEEK.com.[38] The amount of caffeine derived from the coffee consumed was calculated from its percentage composition in the arabica beans, which is close to 1% (10 mg/g). The beans for beverage preparation are normally roasted at 220°C for improving its taste and aroma. Since its melting point is rather high (238°C), its loss during the roasting process is small.[39,40] On the other hand, other possible physiologically active agents present in the beans such as the chlorogenic acids,[41] are destroyed by isomerization, hydrolysis, and pyrolysis during roasting. The small traces likely to be left over during roasting are destroyed further by heating of the roast with steaming hot water during beverage preparation by the continuous drip method or by heating with microwave irradiation. The physiological activity of the coffee is thus largely attributable to its caffeine content, acting by virtue of its effectiveness as a scavenger of hydroxyl radical or other modes such as the inhibition of phosphodiesterase or as an adenosine antagonist.

The amount of caffeine present in the beverage prepared from tea (*Camellia sinensis*), despite a higher concentration of caffeine per gram of the tea leaves, is known to be much lower than the coffee prepared from arabica. This is due to the relatively much smaller quantity of the tea leaves used in the beverage preparation. This is consistent also with the much higher incidence of cataracts in most tea-consuming countries instead of coffee, such as India, Pakistan, Bangladesh, Myanmar, People's Republic of China, and other Southeast regions, as compared with the coffee-consuming countries with some exceptions where tea is used in excessive amounts, such as Turkey where the use of tea is maximum in the world, deriving 376 mg of caffeine per day. The caffeine they derive from the coffee is only approximately 10 mg/day, and yet they have lower incidence of cataract attributable to the high amounts they derive from tea.

Results

Table 1 summarizes the global data on the incidence of cataract blindness in different countries, expressed as a percentage of total blindness by WHO,[1,2] along with the consumption of coffee in terms of caffeine intake per day,

Table 1 Cataract prevalence and caffeine consumption

Zone	Country name	Cataract incidence (% of total blindness)	Caffeine consumption (mg/day)
Zone 1	Benin	64	0
	Ghana	62.5	0
	Nigeria	50	0
	Congo	55	0
	Mali	50	0
	Togo	50	0
Zone 2	Kenya	55	2.70
	Sierra Leone	50	2.74
	Mauritania	50	2.74
	Tanzania	55	2.80
	Paraguay	40	5.47
	Niger	50	4.76
	Cameroon	50	5.47
	Guinea	50	8.22
	Vanuatu	65	8.20
	Central African Republic	55	8.20
	Tunisia	48.5	10.13
Zone 3	South Africa	55	11.00
	Morocco	49	24.65
	Oman	48.5	27.39
	Saudi Arabia	48.5	43.8
	Barbados	40	27.39
	Brazil	40	26.00
	Bulgaria	28.5	79.0
Zone 4	Turkey	28.5	10.95
	Turkmenistan	35.5	54
	Belarus	24	16
	Hungary	24	84.93
	Latvia	24	93.15
	Lithuania	24	112
	Ukraine	24	38.5
Zone 5	USA	7.6	226
	Canada	5	178
	Denmark	5	271
	Finland	5	328
	France	5	148
	Iceland	5	246
	Ireland	5	104
	Italy	5	162
	the Netherlands	5	230
	UK	5	200
	Norway	5	271
	Australia	5	202

Note: The zones labeled 1–5 represent countries in areas specified with the following WHO abbreviated names: Afr D, Afr E, Emr B and D, Eur C, and Eur A, respectively.
Abbreviation: WHO, World Health Organization.

per person. The grouping of the countries used in the table is identical to that done by WHO. However, for convenience, the group name has been replaced by numbered zones. The numbered geographic zones represent the countries as indicated in Table 1. Information on caffeine consumption (mg/day/person) in the individual countries of the groups was derived from the country-wise listing of per capita coffee consumption in sources as mentioned earlier.

A first glance of the table clearly suggests that the incidence of cataract blindness in the countries varies noticeably with the variation in caffeine intake. It indicates a relatively higher incidence of cataracts in countries with lower intake of coffee, also showing vice versa that the incidence of cataract blindness is lower in countries with its higher intake, with expected data scatter. However, a decreasing correlation between the increase in caffeine intake and lowering of cataract incidence was more convincingly demonstrated if the caffeine intake and the cataract prevalence data were analyzed interzonally, and group-wise, as summarized in Table 2.

As can be seen by reference to groups in Table 2, the percentage of cataract blindness in zone 1 is as high as 64%, which corresponds to coffee consumption of near zero. The mean cataract blindness in this group was 55%±6%. That a consumption of coffee by this group and consequent availability of caffeine in their diet could have attenuated this high incidence of cataract was inferable from the reference to the cataract incidence summarized in zone 2. The cataract blindness incidence in this group decreased perceptibly from the mean of 55% in zone 1 to 52%, with an increase in caffeine intake from 0 to 5.6±2.72 mg/day. Although this decrease in cataract was not statistically significant, it was adequate to suggest that a further increase in caffeine intake could lead to a more significant and visible decrease of cataract development. That indeed has been found to be the case. As noticeable in zone 3, increase in caffeine use to 34.2 mg/day was now associated with the further decrease in cataract generation to 44.21%. Increasing the caffeine consumption to 48 mg/day, the cataract blindness decreased to 26.2%±3%. Increase of caffeine consumption to 198 mg/day, the cataract blindness was now highly minimized, the cataract incidence being now only approximately 7.6%, in the USA. The effect of caffeine was significant also in the eastern European regions such as Latvia, Lithuania, Hungary, Ukraine, Belarus, Turkey, and Turkmenistan. Other areas of the world including India, People's Republic of China, and other South Asian countries where caffeine consumption is <2.0–5 mg/day, cataract is also known to be very high, the contribution of cataract to blindness reaching up to 70%.[3] The lower consumption of coffee in Turkey and Turkmenistan with a relatively lower incidence of cataract blindness was initially intriguing. But this is explainable by the finding that Turkish (culturally) have the highest tea consumption in the world, 6.87 kg/year (18.8 g/day) with a caffeine content of 20 mg/g. The daily consumption comes out to be 376 mg/day. Turkmenistan uses 0.82 kg/day, given caffeine intake data of 45 mg. This obviously has an additive factor with its coffee consumption. The results therefore show a significant relationship between the higher caffeine intake and lower incidence of cataract blindness. Statistical analysis of the data in Table 2 is shown in Table 3. It is clear that the significance of findings (the *t* values determined by Student's *t*-test and *P*-values determined from standard *t* table) increases from lower to the higher level of caffeine consumption, the final *P* level reaching to 0.0001.

The inhibitory effect of caffeine in humans is also indicated by the graphical representation of the total data in Table 1 and the trend line as shown in Figure 1. A negative correlation between the caffeine intake and the incidence

Table 2 Zone-wise data showing decreasing incidence of cataract with increase in caffeine intake

Zone	Caffeine intake (mg/day)	Cataract incidence (%)	n
1	0	55.25±6.56 (2.66)	6
2	5.6±2.720 (0.860)	51.68±6.51 (1.93)	10
3	34.28±21.94 (8.95)	44.21±8.74 (3.56)	6
4	48.02±46.28 (18.88)	26.28±4.39 (1.79)	6
5	213.83±61.58 (19.48)	5.21±0.75 (0.23)	13

Note: The values are expressed as mean ± standard deviations and standard errors of the means.
Abbreviation: n, the number of countries in each zone.

Table 3 Intergroup *t* and (*P*) values for caffeine intake and cataract blindness

Interzone	Caffeine intake	Cataract blindness
Between 2 and 1	5.02 (0.005)	1.16 (0.23)
Between 3 and 1	3.81 (0.0034)	2.48 (0.03)
Between 4 and 1	2.54 (0.0293)	9.04 (0.0001)
Between 5 and 1	8.35 (0.0001)	16.77 (0.0001)
Between 3 and 2	4.16 (0.001)	2.12 (0.0626)
Between 4 and 2	2.96 (0.0103)	8.87 (0.0001)
Between 5 and 2	10.62 (0.001)	27.77 (0.001)
Between 4 and 3	0.662 (0.5527)	6.05 (0.001)
Between 5 and 3	6.75 (0.0001)	16.52 (0.001)
Between 5 and 4	5.84 (0.001)	17.33 (0.0001)

Notes: Data were analyzed for means, standard deviations, and errors by using routine statistical formulas. They were then further analyzed for statistical significance by Student's *t*-test. The corresponding *P*-values were then read from standard *t* tables. As may be noted, all the *P*-values showing inhibition of cataract formation with increasing caffeine content were notably significant, except that between the zones 2 and 1.

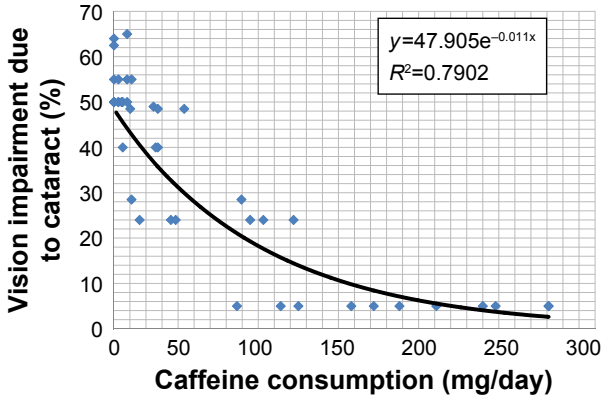


Figure 1 Regression analysis.
Notes: The graph shows an inverse correlation between vision impairment (%) due to cataract and caffeine intake (mg/day). As may be noted, the downward correlation between caffeine intake and the cataract incidence is highly apparent with coefficient of correlation and inhibition of cataract blindness with caffeine is highly significant, with R^2 value approaching 8. The Spearman's rank-order correlation coefficient and the overall *P*-value are –0.89 and 0.0001, respectively.

of cataract was exponential. With the regression line starting with the cataract incident of approximately 55%, the R^2 value comes out to near 0.8, with the Spearman's rank-order correlation coefficient of –0.89 and the *P*-value of <0.0001. The inhibitory effect of caffeine against cataract formation is thus statistically highly significant. The cataract-lowering effect becomes highly visible as the caffeine consumption levels reach near 50 mg and then nearly complete at 100 mg/day. Therefore, there is evidence of saturation kinetics coming into play, characteristic of the biological effectiveness of treatment with exogenous agents. In the USA, using one cup of ordinary coffee (8 Oz, 237 mL) provides 95–200 mg of caffeine. Thus, it lies close to the amount found positively correlated with lower incidence of cataract blindness.

The lower incident of cataract blindness in countries with higher levels of caffeine use is in line with the experimental findings referred earlier, showing inhibition of cataract formation in animals given caffeine either systemically with the diet or through topical eye drops in galactosemic animals, and also through eye drops in rabbits exposed to UV irradiation. This is also in agreement with other studies, where we have shown that caffeine can inhibit cataractogenesis induced directly by photochemical generation of ROS in vitro.

Discussion

Cataract development is the major cause of visual impairment and blindness throughout the world.[1–3] Etiologically, its origin and formation is related to several confounding factors such as aging by itself, genetic factors, increasing incidence of diabetes, nutritional deficiencies, smoking, continued penetration of light into the eye, and consequent induction of oxidative stress through intraocular formation of oxygen free radicals. The latter has been suggested to be one of the primary factors involved in the formation of cataracts, as evident by its higher prevalence in countries that receive excessive solar radiation and consume diets that are low in nutritional antioxidants and scavengers of oxygen free radicals. Accordingly, the attempt of cataract surgery in removing blindness due to cataracts gets significantly minimized. In India, for example, the number of people with cataract blindness is likely to remain the same as it is today or most likely to increase.[3] Further studies on the prevention of cataracts by methods such as preventing the increase in obesity and diabetes, modulating light exposure penetrating in the eye, and increasing use of antioxidant nutrients are considered highly desirable. Previously described studies with experimental animals as well as with certain human epidemiological studies strongly suggest that the use of certain antioxidant nutrients is highly effective in inhibiting the formation of cataracts. Therefore, the primary aim of this investigation was to assess the significance of these experimental studies with regard to the prevalence of cataract blindness in humans as determined by the consumption of coffee as a source of caffeine. While coffee does contain certain other antioxidants, such as chlorogenic acids, they are destroyed while roasting the raw coffee beans before their use for the preparation of coffee. The present investigations seeking to correlate the amount of coffee consumption with cataract incidence were also prompted by reports showing that its consumption decreases the risk of the development of type 2 diabetes,[41,42] a disease known to accelerate the formation of age-dependent cataract. In addition, it has been suggested to prevent liver cirrhosis and certain cancers.[43–45] Thus, the significance of any toxic effects of caffeine as reported in earlier literature has now been greatly minimized. The US Food and Drug Administration has listed caffeine as a fairly safe compound. Clinically, the most compelling evidence of its nontoxicity has been proven by its wide use in treating diseases associated with neural and muscular dysfunctions, such as the common age-associated dementia, and the Alzheimer's and Parkinson's diseases,[46–53] with significant success. While the biochemistry of these diseases is yet only partially understood, it is widely believed that their pathogenesis is strongly related to oxidative damage[55] to the neural and muscular tissues in question, especially in the case of Alzheimer's disease.[55] Thus, there are significant similarities in the biochemistry of these diseases with that of the

pathogenesis of cataracts, at least in terms of the formation of lipid peroxidation products such as malondialdehyde[55] and the presence of DNA degradation products such as 8-hydroxyguanosine and 8-hydroxydeoxyguanosine[56–58] in the neural tissues, similar to that in the lens. Their formation in the neural tissues may precede the formation of intracellular Tau-based fibrous tangles and the appearance of extracellular plaques due to β-amyloid deposition. Apparently, all these processes are initiated by an early generation of ROS by the interaction of trace metals and oxygen.[59–61] The β-amyloid can itself lead to the generation of oxygen free radicals.[62] The concept of oxidative stress is also supported by the effectiveness of ascorbate in treating the disease,[59] similar to that in the case of cataracts.[20–23] Treatment with caffeine has also been seen to delay the formation of plaques and the tangles, while also minimizing memory loss.

In addition to its antioxidant effects, caffeine can help overcome the neural transmission defects by acting as an antagonist of adenosine, which is well known to modulate nerve transmission by binding to the G-protein (Gi)-linked receptors.[63–67] This binding is followed by the ultimate generation of the subunits (Gαi and βγ) that de-energize the cells by inhibiting adenylyl cyclase and cyclic adenosine monophosphate synthesis, and inhibiting neurotransmitter release by inhibiting calcium transport into the presynaptic nerve terminals. Caffeine antagonizes this process by competitively inhibiting the binding of adenosine to the receptor. Adenosine's inhibitory effects on nerve transmissions are thus reversed by caffeine. Adenosine binding to the G-protein receptor (instead of Gi) also inhibits dopamine release. Caffeine abolishes this unwanted effect as well. It is thus highly possible that the helpful effects of caffeine as an antioxidant are synergistically related to its action as an antagonist of adenosine.

Similar to the action of caffeine against oxidative stress in neural tissue and the previously reported effect against cataract formation in animal studies, its effectiveness in the observed lowering in the incidence of cataract in humans consuming greater amounts of caffeine could also be due to its oxy-radical scavenging activity as one of the possible mechanisms. The oxy-radical scavenging activity of caffeine has been more specifically confirmed in the organ culture studies showing it to act by scavenging the hydroxyl radicals detected by electron spin resonance spectroscopy.

Another action of caffeine in humans when present at appropriately high levels, as likely to be the case in the group consuming more than 200 mg of caffeine per day, is to act as inhibitor of phosphodiesterase activity, helping to maintain a higher levels of cyclic adenosine monophosphate. This is expected to activate protein kinases and subsequent stimulation of tissue metabolism including pathways leading to adenosine triphosphate generation. Indeed, we have shown that the levels of adenosine triphosphate are higher in the lenses cultured with caffeine as well as when it was given in vivo.[23,24] The presence of caffeine has also been shown to accelerate synthetic processes associated with lens cell development,[68] an effect also found useful in cloning of embryonic stem cells.[69]

We have recently reported that induction of oxidative stress during cataract formation, beside depleting the antioxidant reserves, triggers an onset of a genetic dysregulation process initiated by inducing an upregulation of certain miRNAs and consequent gene silencing caused by deactivation of the mRNAs involved in the translation of various antioxidant enzymes. Several miRNAs known to exert such silencing have been shown to be significantly upregulated with the very beginning of cataract formation in the lenses of galactosemic animals. Interestingly, such upregulation has been found to be thwarted by caffeine, suggesting another pathway of the physiologically beneficial effects of caffeine in lens.

The results thus indicate to the likelihood that the observed protective effect of caffeine against cataract formation in humans and experimental animals is likely to be multifactorial in nature, involving its action as a scavenger of oxygen free radicals, acting in combination with its property of acting as an inhibitor of phosphodiesterase and preventing gene silencing. All of them are physiologically beneficial reactions.

It has been previously reported[70–72] that intake of a coffee drink by glaucoma patients can increase the intraocular pressure by 1–2 mmHg, suggesting the possibility of a toxic effect of caffeine in the long run. However, such increases have not been observed regularly. Additionally, this is not supported by studies with pure caffeine.[73,74] The small rise in intraocular pressure with coffee drinking, if any, is obviously due to increase in water absorption in glaucoma,[75,76] a fact used for diagnosis of the disease itself.

This study indicating a possible preventive effect of coffee and caffeine against cataract formation in humans is thus considered useful for further controlled clinical studies evaluating the effect of coffee and caffeine against cataract. In addition, the study also points out the desirability of further mechanistic studies on the molecular mode caffeine's action using in vitro and in vivo experimental animal models.

Disclosure

The author reports no conflicts of interest in this work.

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