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Literature Review

Coffee as a Potential Nutraceutical

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Received: February 02, 2021; **Published:** February 27, 2021

Abstract

Global coffee production nearly doubled over the last decade, making coffee one of the most popular beverage in current society. However, recent consumer studies suggest concerns of potential health detriments from regular coffee consumption. Given its popularity, any health benefits or detriment can have substantial public health impact. Here, we examined several potential benefits and risks with regards to coffee drinking. Evidence is non-conclusive in several cases and warrants further studies. Despite so, there is likely more health benefits than harm, especially when moderation is applied. Hence, we are in the view that coffee is a potential nutraceutical when consumed in moderation and with adequate hydration.

Keywords: *Coffee; Nutraceutical; Health Complications*

Introduction

International Coffee Organization global coffee production data shows 92% increase between crop year of 1990/1991 (2.44 billion kg) and 2018/2019 (4.70 billion kg)[1]. This suggests that coffee consumption has been increasing and studies have suggested that coffee may have health benefits. However, some consumers are unsure of the effects of coffee consumption, whether beneficial or harmful, and in moderate or high amounts, suggested by consumer's attitude [1]. In a recent study, 16% of United States consumers know about the benefits of drinking coffee but 66% of them limit their coffee intake [2]. Similarly, 49% of Europeans believe that coffee may result in health complications from information through internet and social media [3].

In Japan, coffee consumption has been exponentially increasing for the last 40 years [4] with several possible reasons: such as, (a) change in society with "Westernization" of consumption habits, (b) process of product innovation including the vigorous promotion and sales of canned drink coffee, (c) growth of coffee shops with a peak of 162,000 in 1982, and (d) marketing technique whereby there is an initial emphasis of soluble coffee followed by roasted and ground coffee.

[1]http://www.ico.org/historical/1990%20onwards/Excel/1a%20-%20Total%20production.xlsx

Some consumers drink coffee for health benefits [1] while others avoid due to medical reasons such as nervousness and restlessness [5]. It has been suggested that the caffeine content in coffee can have an impact on the health [1]. Although, coffee is generally perceived as a stimulant, most consumers are usually unaware of other beneficial components in coffee [3]. Nevertheless, a cup of coffee contains more than just caffeine. In this review, we will examine several potential health benefits and risks for coffee consumption. Overall, there is likely more benefits than detriment; suggesting that coffee is a potential nutraceutical when consumed in moderation and with adequate hydration.

Potential genetic basis of habitual consumption

A consortium-wide genome-wide association meta-analysis in 2016 uncovered 6 genetic loci associated with habitual coffee consumption [6]. A study by Japan Multi-Institutional Collaborative Cohort (J-MICC) in 2018 [7] on Japanese population attempted to identify the genetic variations affecting coffee consumption. In the discovery stage with 6312 subjects, two independent loci were associated with habitual coffee consumption (12q34.12-13 and 5q33.3). However, in the replication stage with 4949 subjects, only 12q24.12-13 (rs2074356) demonstrated a high degree of association with habitual coffee consumption. These studies suggest that there may be a genetic basis for habitual coffee consumption.

Gastric cancer

Gastric Cancer (GC) is the fourth leading cause of cancer deaths worldwide with median survival rate of less than 12 months at advanced stage [8]. GC development is influenced by multiple genetic and environmental factors [9]. Being one of the first major organs to receive drank coffee, it is often wondered whether coffee has any association GC. Studies concerning the association of GC and coffee consumption are inconsistent, with conflicting results [10]. This resulted in a meta-analysis of thirteen prospective cohort studies in 2015 to examine the association of GC and coffee consumption [11]. The study involved 3,368 individuals with gastric cancer and 1,372,881 participants with a follow up period between 4.3 to 8 years. The pooled-relative risk of GC when compared to the lowest consumption level of coffee is 1.13 (95 % CI: 0.94 - 1.35). For dose-response association of GC and coffee consumption, the risk ratio per 3 cups/day increase in coffee consumption is 1.03 (95 % CI, 0.95 - 1.11). When comparing to individuals without coffee consumption, the relative risks of gastric cancer for 1 cup/day; 0.98 (95 % CI; 0.89 - 1.08), 2 cups/day; 0.98 (95 % CI; 0.85 - 1.13), 6 cups/day; 1.06 (95% CI; 0.91 - 1.25), and 8 cups/day; 1.06 (95 % CI; 0.90 - 1.25) are estimated from the resulting cubic spline model [11]. Thus, this meta-analysis suggests no significant association between GC and coffee consumption.

A more recent study by Parra-Lara., *et al*. [12] on the incidences and mortality rates of gastric cancer and coffee consumption in 25 countries shows an inverse Spearman's correlation between coffee consumption in kg per person per year and estimated age-adjusted incidence ($r_s = -0.5984$, p-value = 0.0016) and mortality ($r_s = -0.5877$, p-value = 0.0020) of gastric cancer. This suggests that coffee consumption may reduce incidence and mortality from gastric cancer. The concern of possible cancer-causing potential of coffee stems from the formation of acrylamide, a human carcinogen, during the roasting process [13]. However, coffee roasting also forms antioxidants and reduces the initially formed acrylamide [14], suggesting that the benefits and detriment of a single compound in a mixture should be examined in isolation [15].

Colorectal cancer

Caffeine, caffeic acid, chlorogenic acids, and kahweol display anti-carcinogenic effects in human cell cultures and in animal models and there is a possibility that it plays a protective role against colorectal cancer [16]. There have been reports of chemoprotection against

oxidative stress and DNA damage by coffee consumption *in vitro* research in the studies of rats and mice [17,18]. Both coffee and caffeine inhibits the expression of cyclooxygenase-2 (COX-2) for inflammatory response [18]. The content of bioactive compounds in coffee is very much dependent on many conditions; such as species of coffee, location of plantations, roasting time and the procedure of processing coffee and the preparation methodology [16].

A meta-analysis of 19 prospective cohort studies [19] involving 2,046,575 participants and 22,629 patients with colorectal cancer suggests a 7% non-significant (p-value = 0.177) decrease in colon cancer risk when 4 cups of coffee (237ml of coffee as 1 cup) daily. However, there is significant (upper 95% confidence boundary of relative risk < 1.0) reduction of both colon and colorectal cancer between 5 to 8 cups of coffee daily, when accounted for gender, study location, cancer subsites, duration of follow-up, dietary assessment method, body mass index, smoking, alcohol, physical activity, dairy products/calcium intake, energy intake, folate intake, and consumption of red and processed meat (p-value > 0.05 for each). In addition, decaffeinated coffee significantly (relative risk = 0.89, 95% CI = 0.80 to 0.99) reduces colorectal cancer risk compared to caffeinated coffee (relative risk = 0.99, 95% CI = 0.90 to 1.10), suggesting a potential benefit in decaffeinated coffee over caffeinated coffee.

Type 2 diabetes mellitus

There has been an increasing rate of type 2 diabetes mellitus globally [20] and among the Asian populations [21]. A meta-analysis of 7 studies suggests that coffee consumption may reduce short-term insulin sensitivity [22]. The caffeine-induced impairment of insulin is likely to involve adenosine receptors in skeletal muscle as epinephrine, a potent inhibitor of insulin actions [23], is elevated after caffeine ingestion. However, meta-analyses of prospective studies [24,25] suggest that coffee and caffeine intake to be inversely associated with the incidence of type 2 diabetes. Yet, a study by Kwok., *et al*. [28] striating samples based on genetically predicted coffee consumption using previously identified genetic markers [6] shows no association between coffee consumption and type 2 diabetes (odds ratio = 1.02, 95% CI: 0.76 to 1.36). This suggests an interplay between genetics and the effects of coffee in terms of type 2 diabetic risk, which warrants further studies.

A study [26] by the Korea National Health and Nutritional Examination Survey (KNHANES) reports increased rate of diabetes from 10.6% in 2015 to 13.0% in 2016 and higher consumption of coffee (11.3 times/week) over both kimchi (9.7 times/week) and multigrain rice (8.1 times/week). The prevalence of diabetes in Korea has reached levels of Western countries [27]; hence, the relationship between coffee consumption and diabetes was studied [26]. The study finds that coffee consumption is inversely correlated with diabetic prevalence when adjusted for covariates in middle-aged adults (40 to 64 years old) - odds ratio of 0.89 (95% CI: 0.86 to 0.92, p-value < 0.001) for women and odds ratio of 0.93 (95% CI: 0.90 to 0.95, p-value = 0.003) for men, with each 1-teaspoon (5 ml) increment in daily coffee intake. However, the odds of diabetes is not significantly associated with the daily amount of coffee consumption by young adults (19 to 39 years old), suggesting that the effects of coffee on type 2 diabetic risk may also be age-related.

Physical performance

One of the stimulation effects of coffee is through increase in plasma epinephrine [28], which increases aerobic fitness [29] and is increased after combat sports [30]. Hence, it is conceivable that coffee consumption has an impact on physical performance. However, studies reported mixed results. Trexler., *et al*. [31] hypothesized that caffeine anhydrous ingestion improve strength and sprint performance more than coffee or placebo and studied 54 male participants (54 out of 56 participants completed the study). The first test consists of one-repetition maximum and repetitions to fatigue for leg press and bench press, as well as a repeated sprint protocol to determine the peak power and the total work output. In the second visit after at least 48 hours, participants were randomly assigned to either 3 of the

groups consisting of either caffeine anhydrous (CAF), caffeine-matched dose of coffee (COF), or placebo (PLA). After thirty minutes of consumption, the tests were repeated. Trexler., *et al*. [31] report no significant interaction effects for bench press one-repetition maximum and no difference in the score between each treatment. However, there is a significant improvement in leg-press one-repetition maximum for COG when compared to CAF, with no difference between COF and PLA. There is no significant difference between the 3 treatment groups in terms of sprint performance over a few trials. Overall, this suggests that neither CAF and COF resulted in any greater improvement as compared to PLA [31].

Similarly, Marques., *et al*. [32] report no improvement in ingestion of caffeinated coffee in time trial performance of 800 metre run when compared to decaffeinated coffee, with no changes in blood pressure levels, and blood glucose and lactate concentrations between trials. However, there have been claims that there are bioactive compounds in COF; such as chlorogenic acids, which are produced from the roasting process of coffee [33]; may reduce the efficacy of caffeine. Pickering and Kiely [34] suggest the lack of caffeine effects may be associated with polymorphisms in CYP1A2 (responsible for 95% of caffeine metabolism) and ADORA2A (adenosine receptor) genes.

Clarke., *et al*. [35] investigated whether gender plays a role in the performance and affective responses following the ingestion of caffeinated coffee by examining 39 recreational active cyclists on completing a 5 km cycling trial on a cycle ergometer before and after the ingestion of coffee, a placebo or control; on the same day. Nescafe original coffee was used in the coffee trials and dissolved in 300 mL of hot water and served in lidded cups. Result show that coffee drinkers (about 482 seconds) are faster than in placebo (about 491 seconds) with males moderately faster than females. Men and women improve by approximately 9 and 6 seconds after coffee ingestion compared to placebo and control, respectively. However, no significant gender and trial interaction is observed.

Cognition and mood

The cognitive benefits of coffee ingestion are associated to caffeine [36] by non-selective antagonism of adenosine receptors [37], which is supported by a study showing that caffeine can significantly affect the mental performance, mood and thirst at doses equal to or lower than the amount of caffeine contained in a single serving of popular caffeine drinks [38]. Haskell-Ramsay., *et al*. [36] examined the effects of a single dose of caffeinated or decaffeinated coffee on cognition and mood in both healthy young (20 to 34 years old, n = 29) and older (61 to 80 years old, m = 30) adults. The three treatments were (a) 220 ml of 2.5g coffee flavouring (placebo), (b) 220 ml of regular coffee without milk and sugar containing 100 mg caffeine, and (c) 220 ml of decaffeinated coffee without milk and sugar containing about 5 mg caffeine. Results show that consumption of 220 mL of regular coffee containing 100 mg of caffeine leads to a faster response during the information processing tasks when they are compared to placebo. At the same time, overall alertness and mood are higher and mental fatigue ratings are lower in the regular coffee group as compared to placebo. Moreover, decaffeinated coffee improves alertness when compared to placebo. The findings are consistent with the reported effects of coffee on attention task productivity and alertness [38-40].

Parkinson's disease

Parkinson's Disease (PD) is a neurodegenerative disorder from the loss of dopaminergic neurons found in the striatum and substantia nigra pars compacta, affecting the nigrostriatal pathway of movement [41], with clinical features of resting tremor, rigidity, bradykinesia, and postural instability which can occur at a later stage of PD [42]. Caffeine is known to have a neuroprotective effect by antagonising the A2A adenosine receptor which is abundantly found in the striatum, olfactory cortex, basal ganglia, and the hippocampus, which offers neuroprotection against dopaminergic degeneration and could influence the start and progression of PD [43]. Hence, coffee may be protective against PD [44].

A prospective study [45] involving 48,532 men and 63,590 women suggests reduction in risk between coffee intake PD (relative risk of 0.43; 95% CI: 0.26 to 0.71) when comparing the highest intake of caffeine (475 mg/day) to the lowest intake of caffeine (9.2 mg/day) in men. In women, there is also a non-significant reduction in risk from coffee consumption (relative risk of 0.61; 95% CI: 0.34 to 1.09) when comparing the highest intake of caffeine (433.2 mg/day) to the lowest intake of caffeine (5.6 mg/day). Qi and Li [46] performed a meta-analysis on 13 studies involving 901,764 participants for coffee and 492,724 participants for caffeine to assess the risk of PD for coffee/caffeine consumption. In terms of coffee consumption, the relative risk of PD for highest consumption of coffee (7 cups/day) was 0.65 (95% CI: 0.56 to 0.74) when compared to the lowest consumption of coffee (1 cup/day) with the maximum protection against PD at approximately 3 cups daily (relative risk of 0.72; 95% CI: 0.65 to 0.81). In terms of caffeine consumption, the relative risk of PD for highest consumption of caffeine (700 mg/day) was 0.55 (95% CI: 0.43 to 0.71) when compared to the lowest consumption of caffeine (100 mg/day).

The protection effect of caffeine in women may be impaired by hormone replacement therapy (HRT) as both caffeine and estrogen compete for the same enzyme, CYP1A2, for metabolism [43]. As a result, women not involved in HRT has a stronger protection against PD (relative risk of 0.32) compared to women in HRT (relative risk of 0.81, and p-value of interaction = 0.15) when comparing to the highest intake of caffeine (433.2 mg/day) to the lowest intake of caffeine (5.6 mg/day) [45]. The studies suggest that the risk of PD is reduced with coffee consumption, men being offered the highest protection, followed by women not on HRT and offering the lowest protection to women on HRT.

Besides potentially protective against PD, coffee may also have positive effects on PD symptoms [47,48]. Cho., *et al*. [47] examined 196 PD patients (136 coffee drinkers and 60 (non-drinkers) and suggest that total scores on Non-Motor Symptom Scale is significantly lower (p-value = 0.047) in coffee drinkers compared to non-drinkers, especially in reduced severity of the mood and cognition (p-value = 0.003). This is supported by a later study from the same group [48] on 284 PD patients and suggest that coffee drinkers have lower tremor scores compared to non-coffee drinkers in a dose-dependent manner.

Diuretic effects

Compounds in coffee, such as caffeine and related methylxanthine compounds, are known to have diuretic effects [49]. For example, caffeine causes acute diuresis by reducing sodium reabsorption in the proximal and distal nephron tubules [50] by antagonism of adenosine A1 receptor, which have been shown in animal studies and resulting in increased renal fluid and sodium excretion [51]. A study by Seal., *et al*. [52] on 10 healthy individuals (8 males and 2 females) indicate that high caffeine in coffee (6 mg/kg) resulted in higher diuresis (613 ± 101 ml, p-value < 0.05) compared to consumption of coffee with low caffeine (3 mg/kg) which induces lower diuresis (316 ± 38 ml) and water (356 ± 53 ml). The study also suggest significant cumulative urinary osmotic excretion is greater in coffee with high caffeine (425 ± 92 mmol, p-value < 0.05) as compared to coffee with low caffeine (177 ± 16 mmol) and water (249 ± 36 mmol). This suggests that caffeine content in coffee has a diuretic effect, which can lead to dehydration; which in turn is a potential cause of urolithiasis or urinary stone formation [53]. This leads to current recommendation of high fluid intake as prophylaxis against kidney stone formation [54,55]. Hence, there is a concern on whether coffee intake can lead to urolithiasis. A recent systematic review of 13 studies [56] suggests that moderate coffee consumption with adequate hydration has no effect on stone formation despite the diuretic effect of caffeine.

Conclusion

Coffee is a popular beverage in current society; hence, its benefits or detriment can have substantial impact on public health. In this review, we examined several potential benefits and risks with regards to coffee drinking. In several cases, evidence is non-conclusive and

warrants further studies. However, there appears to be likely more benefits than harm by taking the current evidence in totality, especially when moderation is applied. Hence, we are in the view that coffee is a potential nutraceutical when consumed in moderation and with adequate hydration.

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Volume 16 Issue 3 March 2021