



Regular consumption of black tea increases circulating kynurenine concentrations: A randomized controlled trial[☆]



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ABSTRACT

Background: Circulating neopterin and the ratio of kynurenine to tryptophan (KYN/TRP) concentrations are biomarkers of immune activation that have been linked to cardiovascular and total mortality. Several *in vitro* studies indicated that tea flavonoids and other antioxidants can modulate tryptophan breakdown rates and neopterin production in immune cells. We aimed to assess the effects of regular black tea consumption on tryptophan and neopterin metabolisms *in vivo*.

Methods: Participants were healthy individuals, with no major illnesses and having normal to mildly elevated systolic blood pressure. They were randomly assigned to consume 3 cups/day of either powdered black tea solids (tea; n = 45) or a flavonoid-free caffeine-matched beverage (control; n = 49). Serum concentrations of tryptophan, kynurenine and neopterin were assessed at baseline and again at 3 and 6 months after daily ingestion of the respective beverage.

Results: Regular consumption of tea over 6 months, compared to control, did not significantly alter neopterin ($p = 0.13$) or tryptophan ($p = 0.85$) concentrations, but did result in significantly higher kynurenine ($p = 0.016$) and KYN/TRP ($p = 0.012$). Relative to the control group, in the tea group kynurenine and KYN/TRP increased during the treatment period by 0.28 $\mu\text{mol/L}$ (95% CI: $-0.04, 0.60$) and 3.2 $\mu\text{mol/mmol}$ (95% CI: $-1.6, 8.0$), respectively at 3 months, and by 0.48 $\mu\text{mol/L}$ (95% CI: 0.16, 0.80) and 7.5 $\mu\text{mol/mmol}$ (95% CI: 2.5, 12.5), respectively at 6 months.

Conclusions: Increased circulation of kynurenine and KYN/TRP following regular black tea consumption may indicate enhanced tryptophan breakdown, possibly due to immune activation-induced tryptophan degrading enzyme indoleamine 2,3-dioxygenase.

General significance: The influence of black tea consumption on biomarkers of immune system activation could relate to its general health benefits. Data suggests that the net effect strongly depends on the individual immune state, being stimulatory in healthy individuals, while acting more immune dampening in situations with an inflammatory background.

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1. Introduction

Inflammation and immune activation play key roles in the pathogenesis of atherosclerosis [1,2]. This is reflected by an increase of inflammatory cells, such as activated macrophages, and high level production of pro-inflammatory cytokines in the atherosclerotic plaque. In the circulation, the inflammatory process manifests in elevated concentrations

of pro-inflammatory biomarkers such as interleukin-6, C-reactive protein and serum amyloid A [1,2]. Likewise, the macrophage product neopterin is formed and enhanced tryptophan breakdown is detectable by an increased kynurenine to tryptophan ratio (KYN/TRP) [3,4]. Both neopterin production and tryptophan breakdown are related to inflammation where increased formation of Th1-type cytokine interferon- γ (IFN- γ) activates neopterin production via GTP-cyclohydrolase I and induces tryptophan-degrading enzyme indoleamine 2,3-dioxygenase (IDO). Many inflammation-induced biomarkers have been found to strongly predict disease specific outcome and overall mortality in patients suffering from cardiovascular disease (CVD). Neopterin production and tryptophan breakdown may be among the most sensitive predictors of prognosis in such patients [4].

[☆] This trial was registered at the Australian New Zealand Clinical Trials Registry as ACTR12607000543482.

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Markers of antioxidant status such as vitamin C and E, as well as compounds like lycopene and lutein are reduced in patients suffering from inflammatory conditions such as CVD [5,6]. Moreover, there is evidence for a relationship between a higher degree of inflammation and immune activation and a lower vitamin status [7]. Dietary interventions are thought to be of value to slow-down inflammation. A diet rich in antioxidants and antioxidant supplements may provide benefit on cardiovascular outcomes [8,9]. In addition, a positive influence of Mediterranean diet supplemented with extra-virgin olive oil or nuts was demonstrated among persons at high cardiovascular risk [10]. A 2-year intervention trial involving healthy dietary changes had long-lasting, favorable post-intervention effects, particularly among participants receiving the Mediterranean and low-carbohydrate diets [11]. However, any positive influence of pure supplemented antioxidants like vitamins still remains to be demonstrated.

There is increasing evidence that beverages rich in antioxidant polyphenols like tea, cacao and red wine, could provide a positive influence on cardiovascular health. We recently reported that black tea can affect blood pressure beneficially [12,13]. Interestingly, antioxidant compounds and extracts of antioxidant-rich beverages such as tea were observed to suppress immune activation cascades, pro-inflammatory cytokines, neopterin and tryptophan breakdown in mitogen-stimulated human peripheral blood mononuclear cells (PBMC) *in vitro* [14]. These effects appear to be shared with other compounds and extracts prepared from plants and fruits with suggested anti-inflammatory and/or antioxidant properties like salicylic acid [14], resveratrol [15] and cannabinoids [14], black tea [16], wine [17], cacao [14] and coffee [18]. For the effect of black tea, flavonoid compounds are considered to be of importance [13, 15,19]. However, in resting immune cells, the effects of compounds like resveratrol or beverages like wine or tea were found to be stimulatory rather than immunosuppressive [12,13]. Thus, results from *in vitro* studies only provide a limited picture.

We have previously reported the results from the primary outcome of the present study demonstrating that regular ingestion of black tea results in lower blood pressure and lower blood pressure variation [13]. Recently, kynurenine was shown to mediate vasorelaxation and lower blood pressure [19]. Thus, the objective of the current analysis was to assess the effects of longer-term regular consumption of black tea, over 6 months, on neopterin formation and tryptophan metabolism in healthy individuals with mild to moderate elevations in systolic blood pressure. We have also explored the relationships of any change in kynurenine concentrations with observed changes in blood pressure.

2. Subjects and methods

2.1. Study subjects

Volunteers were recruited from the general population of Perth, Australia, by using print media advertisements. Participants were tea drinkers, aged 35–75 years, had BMI of 19–35 kg/m², were non-diabetic, had not taken nutritional supplements or antibiotics from 4 weeks before beginning the trial, and had no major illness [13]. The trial was approved by the University of Western Australia Ethics Committee and registered at the Australian New Zealand Clinical trials Registry as ACTR12607000543482. Procedures followed were in accordance with institutional guidelines.

2.2. Study design

A randomized, controlled, double-blind, 6-month parallel-designed intervention study was performed [13]. The 6-month intervention was preceded by a 4-week run-in period during which participants consumed 3 cups of regular leaf tea each day prepared in the usual manner. During the fourth week of the run-in period, participants attended the School of Medicine and Pharmacology research unit located at Royal Perth Hospital, where all baseline measurements were performed. During the 6-

month intervention period, participants consumed 3 cups/day of either powdered black tea solids, which supplied 429 mg total polyphenols (primarily flavonoids)/day and 96 mg caffeine (tea)/day or a flavor-matched, flavonoid-free, and caffeine-matched placebo (control). Participants were advised to consume tea or control products at the time that they would normally consume tea. For further details see ref. [13].

After random assignment, participants were required to follow a low-flavonoid diet throughout the trial. Apart from the prescribed tea intake, participants did not consume any additional tea, they did not consume dark chocolate or red wine, the intake of fruit juices was limited to <4 glasses/week, and coffee intake was limited to <1 cup/day on average (<7 cups/week). A dietitian monitored each participant's progress every 4 weeks to ensure compliance. Participants were instructed to add the contents of a sachet of powdered tea solids or placebo to ~200 mL boiled hot water and stir the solution until the powder completely dissolved. The addition of sugar, milk, cream or other additives was not allowed, and the product was consumed while still hot.

2.3. Laboratory measurements and blood pressure assessment

The 24 h 4-O-methylgallic acid (4OMGA) excretion was used as a biomarker of black tea intake and black tea-derived flavonoid exposure and to assess compliance [13]. To monitor immune activation status of study participants, free serum concentrations of tryptophan and kynurenine were determined by high-performance liquid chromatography, as described elsewhere [20]. KYN/TRP was calculated as an index of tryptophan breakdown [20]. Serum neopterin concentrations were measured by commercially available enzyme-linked immunosorbent assay (BRAHMS Diagnostics, Hennigsdorf, Germany). The 24 h ambulatory blood pressure (BP) was measured as previously described [12,13].

2.4. Statistical analysis

The sample size for this study was based on the primary outcome of 24-h ambulatory systolic BP. We estimated that 100 participants (50 participants/group) would provide 90% power at two-tailed $\alpha = 0.05$ to detect a difference of 3 mm Hg in 24-h systolic BP. Results of the primary outcome of the study (i.e., BP) have been published [12]. Collection of blood samples during the study allowed investigation of the effects of tea on tryptophan and neopterin metabolisms by measuring circulating concentrations of kynurenine, tryptophan and neopterin. Post-hoc analysis of study power indicated that we had more than 80% power to detect a 1.4 nmol/L difference in neopterin and a 0.45 μ mol/L difference in kynurenine.

Descriptive statistics are presented as means \pm SDs. Categorical variables were summarized by number in each category. A two-tailed type-1 error rate of $p < 0.05$ was the level of significance used for all hypothesis testing. At baseline, characteristics of participants in the 2 groups were compared by using the independent-samples t test on transformed data, when appropriate, and the chi-square test for categorical variables. Spearman's rank correlation coefficient was used to explore the degree and direction of associations of neopterin, kynurenine and KYN/TRP with traditional cardiovascular disease risk factors at baseline. Baseline, 3- and 6-month values for outcome measures and between-group differences are presented as least-squares means and 95% CIs. The primary analysis was a modified intent-to-treat analysis with the population defined as participants who were randomly assigned to the study for which there were complete baseline measurements of neopterin, kynurenine and tryptophan ($n = 94$). Outcomes were analyzed by using mixed models in SAS software (version 9.3; SAS Institute Inc.). The PROC MIXED command of the SAS program was used to determine the effect of tea compared with the control. Fixed effects in the model included time (baseline, 3 and 6 months; modeled as 3 separate binary indicator variables), treatment group (tea and control), and treatment group \times time (in which time was modeled as 3 separate binary indicator variables). The overall effect of treatment was established by using the

global treatment group × time interaction term. Differences between the tea and control were also assessed and reported individually at 3 and 6 months. Pearson's correlation coefficient was used to explore the degree and direction of associations of the change in neopterin, kynurenine and KYN/TRP from baseline to 6 months (6 months–baseline) with the change in 4OMGA from baseline to 6 months and the change in blood pressure from baseline to 6 months.

3. Results

3.1. Descriptive and baseline data

The study was performed between October 2007 and September 2010. Ninety-four participants had complete neopterin, kynurenine and tryptophan measurements available at baseline (Fig. 1). Baseline characteristics of the participants are presented in Table 1. Neopterin, kynurenine, tryptophan and KYN/TRP values at baseline, 3 months and 6 months are presented in Table 2.

At baseline, neopterin was positively associated with kynurenine ($r = 0.22, p = 0.03$) and KYN/TRP ($r = 0.37, p < 0.001$). In addition, during the intervention, at both 3 and 6 months significant correlations existed between neopterin and KYN/TRP in the controls (at 3 months: $r = 0.50, p < 0.001$; at 6 months: $r = 0.48, p < 0.001$) and in the tea group (at 3 months: $r = 0.51, p < 0.001$; at 6 months: $r = 0.50, p < 0.001$). Neopterin concentrations at baseline were positively associated with age ($r = 0.28, p = 0.007$), but there existed no other significant relationships. Kynurenine concentrations at baseline were positively associated with age ($r = 0.28, p = 0.007$), waist circumference ($r = 0.32, p = 0.002$) and fasting glucose ($r = 0.25, p = 0.02$). The baseline KYN/TRP ratio was positively associated with age ($r = 0.32, p = 0.002$), body mass index ($r = 0.25, p = 0.02$), waist circumference ($r = 0.28, p = 0.006$) and fasting glucose ($r = 0.21, p = 0.05$).

Table 1
Baseline characteristics of the participants in the control and tea groups.^a

	Control (n = 49)	Tea (n = 45)
Gender (M/F)	18/31	15/30
Age (year)	56.3 (10.6) ^b	57.1 (10.8)
Body mass index (kg/m ²)	25.2 (3.3)	24.8 (3.6)
Waist circumference (cm)	82 (12)	82 (11)
Total cholesterol (mmol/L)	5.2 (1.0)	5.1 (0.8)
Glucose (mmol/L)	5.1 (0.5)	5.2 (0.8)
Office systolic blood pressure (mm Hg)	119 (14)	122 (14)
Office diastolic blood pressure (mm Hg)	70 (7)	69 (7)

^a Intent-to-treat population included 94 participants; characteristics were not different between groups at baseline ($p > 0.05$ for between-group differences analyzed using independent samples t-test and the chi-square test for categorical variables).

^b Mean (SD) for all such values.

3.2. Effects on neopterin, kynurenine and tryptophan metabolisms

Regular consumption of tea compared to control did not significantly alter neopterin concentrations over the 6 month intervention period ($p = 0.13$ for global treatment × time interaction; Fig. 2, upper). At 3 months, the difference between groups was 0.7 nmol/L (95% CI: -0.5, 1.9) ($p = 0.27$); and at 6 months the difference was 1.3 nmol/L (95% CI: 0.1, 2.5) ($p = 0.03$). Regular consumption of tea compared to control resulted in a significant difference in kynurenine ($p = 0.016$ for global treatment × time interaction; Fig. 2, middle). At 3 months the difference between groups was 0.28 μmol/L (95% CI: -0.04, 0.60) ($p = 0.083$); and at 6 months the difference was 0.48 μmol/L (95% CI: 0.16, 0.80) ($p = 0.004$). Consumption of tea relative to control also resulted in a significant difference in KYN/TRP ($p = 0.012$ for global treatment × time interaction; Fig. 2, lower). At 3 months the difference between groups was 3.2 μmol/L (95% CI: -1.6, 8.0) ($p = 0.18$); and at 6 months the difference was 7.5 μmol/L (95% CI: 2.5, 12.5) ($p = 0.003$). Adjustment for age, body mass index, waist circumference and fasting glucose concentrations did not alter the observed effects on kynurenine or KYN/TRP (data not presented). Tryptophan concentrations over the 6 month intervention period were not altered ($p = 0.85$).

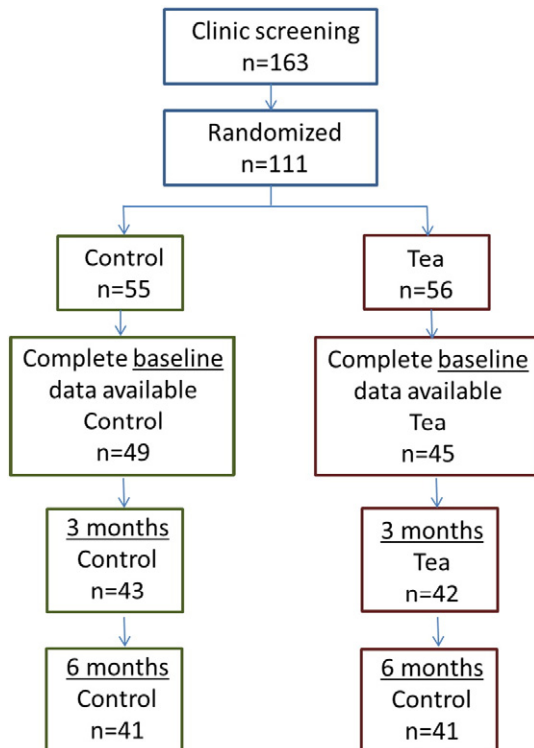


Fig. 1. Participants at each stage of the trial.

Table 2
Neopterin, kynurenine, tryptophan and KYN/TRP values at baseline, 3 months and 6 months.

	Control (n = 49)	Tea (n = 45)	Difference (95% CI)	p-Value
Neopterin (nmol/L)				
Baseline	6.9 (3.6) ^b	5.5 (1.7)		
3 months	6.4 (2.7)	5.6 (1.9)	0.7 (-0.5, 1.9) ^a	0.27
6 months	5.8 (2.0)	5.7 (3.3)	1.3 (0.1, 2.5)	0.03
Global treatment × time interaction				0.13
Tryptophan (μmol/L)				
Baseline	68 (11)	70 (10)		
3 months	68 (11)	71 (12)	1.2 (-1.4, 5.6)	0.57
6 months	69 (13)	71 (11)	0.6 (-3.8, 5.0)	0.79
Global treatment × time interaction				0.85
Kynurenine (μmol/L)				
Baseline	3.2 (0.9)	2.9 (0.7)		
3 months	3.1 (0.9)	3.1 (0.7)	0.28 (-0.04, 0.60)	0.083
6 months	3.1 (1.0)	3.4 (0.8)	0.48 (0.16, 0.80)	0.004
Global treatment × time interaction				0.016
KYN/TRP (×1000)				
Baseline	47 (12)	42 (9)		
3 months	46 (12)	44 (9)	3.2 (-1.6, 8.0)	0.18
6 months	45 (12)	49 (14)	7.5 (2.5, 12.5)	0.003
Global treatment × time interaction				0.012

^a Least squares mean difference.

^b Observed mean values and SD in brackets.

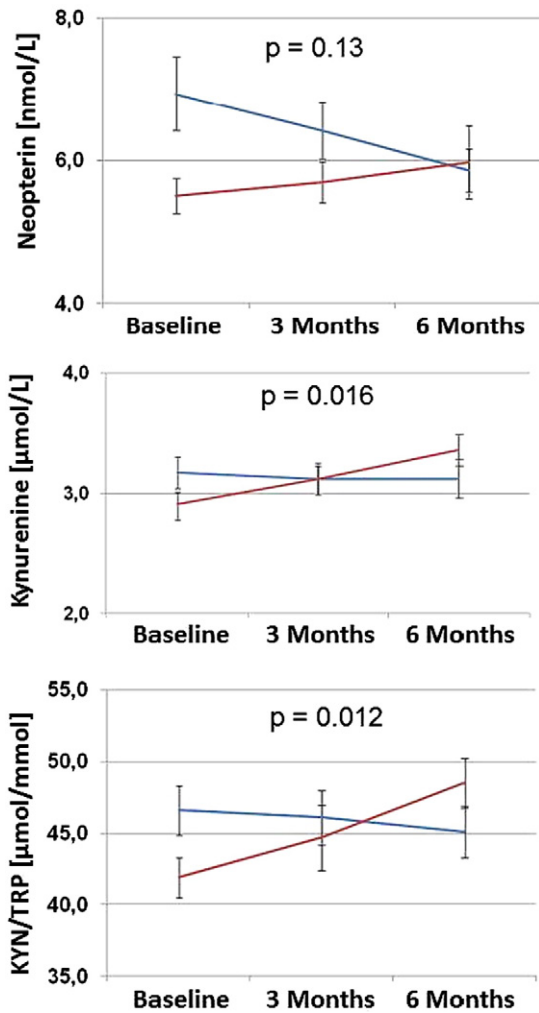


Fig. 2. Serum concentrations (mean \pm SD) of neopterin (upper), kynurenine (middle) and kynurenine to tryptophan ratio (KYN/TRP) (lower) in individuals exposed to tea during 6 months (p -values for treatment by time interactions). Participants consumed 3 cups/day of either powdered black tea solids (red lines) or a flavonoid-free caffeine-matched beverage (blue lines).

The change in 4OMGA (biomarker of tea intake and polyphenol exposure) from baseline to 6 months (6 months–baseline) was positively correlated with change (6 months–baseline) in kynurenine ($r = 0.31$, $p = 0.008$) and KYN/TRP ($r = 0.30$, $p = 0.01$) but not neopterin ($r = 0.13$, $p = 0.28$). In addition, the change in 24-h systolic and diastolic blood pressure (6 months–baseline) was negatively correlated with the change (6 months–baseline) in neopterin (systolic: $r = -0.26$, $p = 0.03$; diastolic: $r = -0.31$, $p = 0.006$), kynurenine (systolic $r = -0.20$, $p = 0.08$; diastolic: $r = -0.21$, $p = 0.06$) and KYN/TRP (systolic: $r = -0.26$, $p = 0.02$; diastolic $r = -0.23$, $p = 0.04$).

4. Discussion

Our study revealed that black tea consumption in comparison to a caffeine-matched control beverage may increase serum concentrations of immunobiochemical markers of tryptophan metabolism. Both kynurenine and KYN/TRP were significantly increased with tea over the 6 month intervention, with the largest increases observed at the 6 month time point with tea compared to control. Although a similar trend for neopterin was found and the difference in changes from baseline at 6 months was significant, there was no overall significant difference between group changes over the 6 month intervention.

Black and green tea extracts and related polyphenols were shown to exert suppressive effects on neopterin and cytokine production and on KYN/TRP *in vitro* [14–16]. Thus, the increase of kynurenine concentrations in the tea group is unexpected at first glance, because a cardioprotective activity of black tea is considered in part to be due to anti-inflammatory and immunosuppressive properties [21–23]. However, in the *in vitro* studies, the immunosuppressive properties were observed in PBMC that were pre-stimulated with mitogens such as phytohemagglutinin or concanavalin A. In contrast, there was a stimulatory effect of extracts on resting PBMC [15,16]. Thus, the findings of the present study that black tea consumption may induce neopterin formation and kynurenine production due to accelerated tryptophan breakdown are in line with the observations derived from *in vitro* studies using resting PBMC. This may be more representative of what occurs in healthy individuals, while the suppression of stimulated PBMC may reflect processes that occur in individuals with an activated immune system. Interestingly, both anti- and pro-oxidant properties have been reported for green tea catechins [12,24–26]. Induction of ROS due to superoxide formation by catechin in the presence of oxygen and transition metals is an important property for its bioactivity as phytotoxin [26], but also for its chemopreventive effects [27]. Thus, these bidirectional effects could help to explain why black tea is associated with reduced risk of CVD. This may involve both enhancing activation status of immunocompetent cells leading to increased immune surveillance and inhibiting low grade inflammation.

The correlations found between the kynurenine and KYN/TRP concentrations and the concentrations of immune activation marker neopterin suggest that they are associated with increased immune activation and inflammation. Thus, the observed association between kynurenine metabolism (KYN/TRP) and neopterin concentrations throughout the study in both groups suggests an involvement of enzyme indoleamine 2,3-dioxygenase (IDO) rather than liver enzyme tryptophan 2,3-dioxygenase (TDO) in the alterations of kynurenine concentrations. TDO is primarily controlled by tryptophan concentrations but independent from immunological stimuli. However, the association between neopterin and kynurenine levels indicates an induction of pro-inflammatory cytokine cascades in study participants to be responsible for the induction of IDO and the increase of kynurenine. We speculate that the influence of black tea on kynurenine concentrations was due to the induction of pro-inflammatory cytokines like IFN- γ . This may support protection of the human organism from infection and even malignant development in an antiproliferative milieu, which is achieved by the induction of IFN- γ -dependent effector pathways. It is possible that the situation might be different in patients that are already suffering from inflammatory diseases and thus heightened oxidative stress. Our findings in healthy individuals may not be extrapolated to those suffering from CVD, infections or malignant diseases.

The observed increase of kynurenine and KYN/TRP concentrations might also relate to the influence of black tea to lower blood pressure and its benefit for cardiovascular health [21–23,27–30]. In rats administration of kynurenine was demonstrated to beneficially influence blood pressure. In the current study we observed a negative correlation between the change in kynurenine and the change in blood pressure from baseline to 6 months. Thus, the increase of kynurenine levels in the tea group in our study may be linked to the blood pressure lowering during black tea consumption, which was described earlier [19,29].

Of note, at baseline, significant associations were found for kynurenine with parameters such as waist circumference and fasting glucose, as well as for KYN/TRP with age, body mass index, waist circumference and fasting glucose. Given the close crosstalk between metabolism and immune response, also these associations indicate an individual's immune status. An association of neopterin levels with age and immune status has been documented earlier [31].

In conclusion, our study shows that black tea consumption is associated with an increased kynurenine production in individuals with no

major illnesses and having normal to mildly elevated systolic blood pressure. It may partly relate to the positive influence of black tea on blood pressure in our study participants, and it is suggested to relate to activation of IDO. In turn, activated IDO could contribute to slowing down of immune activation and inflammation.

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