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The Effect of Green Tea on Sildenafil Pharmacokinetics in Egyptian Healthy Volunteers

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Author's contribution

Author SKH designed the study, performed the statistical analysis, and wrote the manuscript. All authors read and approved the final manuscript.

Original Research Article

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ABSTRACT

Aim: To investigate the interaction of sildenafil and green tea in normal healthy male volunteers using probe drugs (midazolam, CYP3A4 activity).

Study Design: Ten healthy males were included in random crossover single dose study. Each volunteer received one tablet of sildenafil 50 mg and one tablet of midazolam 7.5 mg concurrently either after drinking 250 ml of water or 250 ml of fresh extract of 2 gram of green tea. After one week washout period, each volunteer received the other intervention. Plasma samples were analyzed for sildenafil and midazolam using HPLC.

Place and Duration of Study: The Laboratory of Pharmaceutical Research Center of Faculty of Pharmacy, Tanta University, Egypt, between June to July 2013.

Methodology: Blood samples were obtained after the insertion of peripheral cannula into the forearm. Samples were obtained before sildenafil and midazolam intake (blank) and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 5, 8, 10, and 12 hours after sildenafil and midazolam administration. The samples were collected in clean heparinized tubes. Plasma was obtained by centrifugation and was stored at -20° until assay. Plasma samples were analyzed for sildenafil and midazolam using HPLC.

Results: Coadministration of green tea with sildenafil tea increased the extent but not the rate of sildenafil absorption. It resulted in higher plasma concentrations (AUC_{∞} increased

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from $484.2 \pm 67.27 \mu\text{g hr/L}$ to $731.5 \pm 111.01 \mu\text{g hr/L}$ (90% CI 1.50 (1.36-1.66) and the C_{max} from $318.9 \pm 46.8 \mu\text{g/L}$ to $414.9 \mu\text{g/L} \pm 67.0 \mu\text{g/L}$ (90% CI 1.29 (1.15-1.43). The elimination rate constant of sildenafil was significantly decreased and the elimination half life was prolonged by about 36%. However, AUC_{∞} of midazolam increased by 16% and C_{max} by 14%; suggesting a small reduction CYP 3A4 activity.

Conclusion: Increased bioavailability of sildenafil after green tea intake may be caused by the effect of catechins which can alter spontaneous activity of small intestine or an effect on transporters. Patients who are taking green tea may need smaller doses of sildenafil, and those at higher risk of developing sildenafil adverse effects and are taking green tea should seek medical advice before taking their sildenafil therapy.

Keywords: Sildenafil; green tea; pharmacokinetics; bioavailability.

1. INTRODUCTION

Sildenafil is the first oral therapeutic agent introduced for the management of male erectile dysfunction. This drug is a potent and selective inhibitor of phosphodiesterase type 5 (PDE5), the predominant isoenzyme responsible for the metabolism of cyclic guanosine monophosphate (cGMP) that is capable of enhancing penile corpus cavernosum relaxation and therefore has the potential to improve penile erectile function [1]. Sildenafil is rapidly absorbed after oral administration, with absolute bioavailability of about 40%. This low bioavailability is due to the extensive first-pass metabolism [2,3]. Its pharmacokinetics is dose proportional over the recommended dose range. It is eliminated predominantly by hepatic metabolism (mainly by cytochrome P450 3A4) after absorption and is converted to an active metabolite with properties similar to itself. Sildenafil and its metabolite have terminal half-lives of approximately 4–5 h. The maximum observed plasma concentration of sildenafil is reached within 30–120 (median 60) min of an oral dosing in a fasting state [2-4]. CYP 3A is the largest subfamily of CYP enzymes expressed in the human liver and gastrointestinal tract and is involved in the metabolism of many clinically used drugs and other chemicals. Concomitant intake of grapefruit juice causes inhibition of CYP3A4-mediated first-pass metabolism of many drugs in the gut and thereby increases the bioavailability of these orally administered agents [5]. Grapefruit increased the C_{max} of sildenafil by 42% without significant change in the AUC from a single elderly male subject [6]. Jetter *et al*, [7] reported that the AUC of sildenafil increased 1.23 fold and a trend toward prolongation of t_{max} after grapefruit juice intake was observed. C_{max} did not differ significantly. Al Ghazawi *et al*, [8] demonstrated that pummelo juice reduced the rate and extent of sildenafil bioavailability to around 60%, and area under the plasma concentration time curve from zero to infinity (AUC infinity); to around 68%.

Green tea, which is derived from *Camellia sinensis* plant is the most consumed beverage in the world [9]. The major catechins in green tea are epicatechin (EC), epigallocatechin (EGC), epicatechin-3-gallate (ECG) and epigallocatechin-3-gallate (EGCG) which is the most abundant, accounting for 50-80% of the total catechins in green tea [10]. A previous study using bacterial membrane fraction expressing human CYP demonstrated that ECG and EGCG inhibited the activity of human CYP enzymes, including CYP1A1, 1A2, 2A6, 2C9, 2E1 and 3A [11]. Similarly, green tea extract (GTE), in which catechins are more than 60% of total weight, inhibited *in vitro* testosterone 6-hydroxylation, a probe reaction to evaluate CYP3A activity in human liver microsomes [12]. Kumazoe *et al*, [13] reported that the green tea polyphenol (–)-epigallocatechin-3-O-gallate (EGCG) can bind to the 67-kDa laminin

receptor (67LR) to promote cancer cell death in a cyclic GMP–dependent manner. They found that a phosphodiesterase 5 inhibitor, which increases cyclic GMP levels, potentiated EGCG-induced cell death through the 67LR pathway without affecting normal cells and that this combination therapy increased survival time in a mouse xenograft model. For this reason, it is very important to ensure the safety of this drug in a variety of conditions, and to study the potential drug-drug interactions with a wide variety of drugs.

The wide variety of putative medical uses of green tea suggests that the possibility for coadministration with synthetic medications, and accordingly, the potential for drug interaction is high.

The current study was performed to investigate the interaction of sildenafil and green tea in normal healthy male volunteers using probe drugs (midazolam, 7.5 mg, CYP3A4 activity) which was administered orally at baseline, and again after treatment with green tea.

2. MATERIALS AND METHODS

2.1 Materials

Sildenafil was obtained from Medical Union Pharmaceuticals; MUP (Ismailia, Egypt), midazolam was obtained from Amoun Pharmaceutical Co. (Cairo, Egypt), and propyl paraben was obtained from Sigma Chemical Co. (St.Louis, MO, USA). Acetonitrile, methanol, ammonium dihydrogen phosphate, and phosphoric acid were purchased from Riedel-De Haen, Germany. All solvents were HPLC grade. Diethyl ether of analytical grade was obtained from Honil Limited (London, UK).

2.2 Subjects

Ten healthy males were included in the study. The average age of the volunteers ranged from 18-40 years and the average weight was 78 kg (range 60-93 kg). The study protocol was approved by the Ethical Committee of Tanta University in accordance with the Declaration of Helsinki (World Medical Association, 1996) [14]. Participants signed for a written consent form. All the volunteers had normal kidney and liver functions, and were free from ischemic heart disease, diabetes, hypertension, or hypotension.

2.3 Study Design

A random crossover single dose study was employed. The subjects were instructed not to take any drugs for at least 72 hours prior to and throughout each study period and to fast over night for at least 8 hours before drug administration. All the volunteers were given the same meals throughout the study period. On the day of the study, each volunteer received one tablet of sildenafil 50 mg (Viagra® 50 mg, Pfizer, Cairo, Egypt), and one tablet of midazolam 7.5 mg (Mediathetic® 7.5 mg, Amoun, Cairo, Egypt) concurrently either after drinking 250 ml of water or 250 ml of fresh extract of 2 gram of green tea (Green tea packets 2 grams, Mepaco, Anshas El-Raml, Sharqia, (3 g catechins /100g of green tea powder). After one week washout period, each volunteer received the other intervention. All volunteers took the same standardized meal 3 hours after sildenafil administration and no smoking was allowed during the study period.

Blood samples were obtained after the insertion of peripheral cannula into the forearm by a skilled certified nurse. Samples were obtained before sildenafil and midazolam intake (blank) and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 5, 8, 10, and 12 hours after sildenafil and midazolam administration. The samples were collected in clean heparinized tubes. Plasma was obtained by centrifugation (Hettich EAB 12 Centrifuge, Germany) and was stored at -20°C until assay. Plasma samples were analyzed for sildenafil and midazolam using HPLC.

2.4 Determination of Sildenafil and Midazolam by HPLC

Plasma samples were analyzed for sildenafil and midazolam in one run using validated HPLC method developed in the laboratory of Pharmaceutical Research Center of Faculty of Pharmacy, Tanta University, Egypt. A clean test tube were spiked with 50 μl of the internal standard solution "5 $\mu\text{g}/\text{ml}$ propyl paraben in methanol" and the methanol was left to evaporate in a water bath adjusted at 50°C . , then 0.5 ml of the collected plasma sample was added and the tube contents were vortex mixed for 3 min. The plasma samples already spiked with the internal standard were extracted with 4 ml of ether following mixing by vortex for 3 minutes. After centrifugation for 10 min, the ether layer was transferred to a clean test tube and was evaporated in a water bath at 50°C . The residue was dissolved in 150 μl of the mobile phase and 50 μl of the resulting solution was injected onto the HPLC. The mobile phase consisted of acetonitrile and 50 mmol ammonium dihydrogen phosphate buffer (PH adjusted at 3.5 with phosphoric acid) at a ratio 35:65. Separation was achieved at ambient temperature using reversed phase column (15 cm x 3.9 mm) C18, 4 μm Novapack (Waters® Inc., MA, USA) at a flow rate of 1.5 ml/min. The column effluent was monitored by UV detector at 220 nm. The retention time (RT) for sildenafil was 6.6 min and (RT) for midazolam was 14.2 min. The concentrations of sildenafil and midazolam in the unknown samples were determined from the calibration curves. The lower limit of quantification was 0.025 $\mu\text{g}/\text{ml}$. The within-run (intraday) and between-run (interday) coefficients of variance (CV) were always within $\pm 0.15\%$ in the entire range of the calibration curve. The intraday accuracy ranged between 89.51 and 107%, whereas the interday accuracy ranged between 94.0 and 106%. The assay was fully validated for linearity, selectivity, precision, accuracy and stability.

2.5 Pharmacokinetic and Statistical Calculations

The pharmacokinetics of sildenafil and midazolam after a single oral administration were characterized by determining the peak concentration in plasma (C_{max}), time to C_{max} (t_{max}), elimination half-life ($t_{1/2}$), and the area under the plasma concentration – time curve from zero to infinity ($\text{AUC}_{0-\infty}$). The C_{max} and t_{max} values were taken directly from the original data. The log-linear part of each plasma concentration-time curve was identified visually, and the elimination rate constant (k_e) was determined by linear regression analysis of the log-linear part of the concentration-time curve. The $t_{1/2}$ was calculated by the equation $t_{1/2} = \ln 2/k_e$. The AUC values were calculated by the linear trapezoidal rule with extrapolation to infinity by division of the last measured concentration by k_e . Statistical comparisons were made with one-way analysis of variance (ANOVA) with factors for treatment, period, and sequence and for subjects nested within sequence. The area under the curve from zero to infinity (AUC_{∞}) and C_{max} were evaluated after logarithmic transformation, providing point estimates and 90% confidence intervals. ANOVA and 90% confidence intervals (90% CIs) were obtained using WinNonlin (Version 5.2.1). All statistical analyses were performed using the Minitab Statistical Package ver. 13 (Minitab, State College, PA) on an IBM PC.

3. RESULTS AND DISCUSSION

Mean systolic and diastolic blood pressures (BPs) and electrocardiograph (ECG) were similar after sildenafil alone as well as with green tea.

Fig. 1 shows the HPLC spectra of sildenafil and midazolam (A) before and (B) after green tea administration.

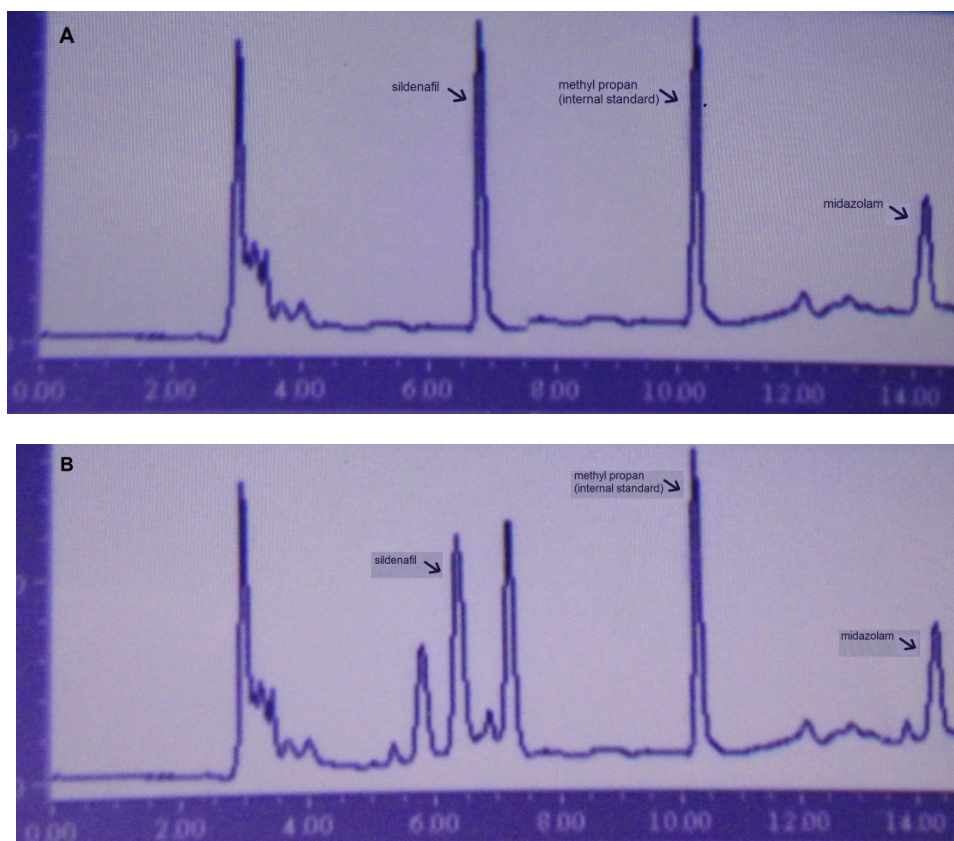


Fig. 1. HPLC spectra of sildenafil and midazolam (A) before and (B) after green tea administration

The mean plasma concentration-time profile after a single dose of sildenafil 50 mg alone and after green tea 2 gm are shown in Fig (2). Coadministration of green tea with sildenafil produced a significant increase in AUC_{∞} (90% CI= 1.5) and the C_{max} (90% CI=1.29). The elimination of sildenafil was also significantly delayed.

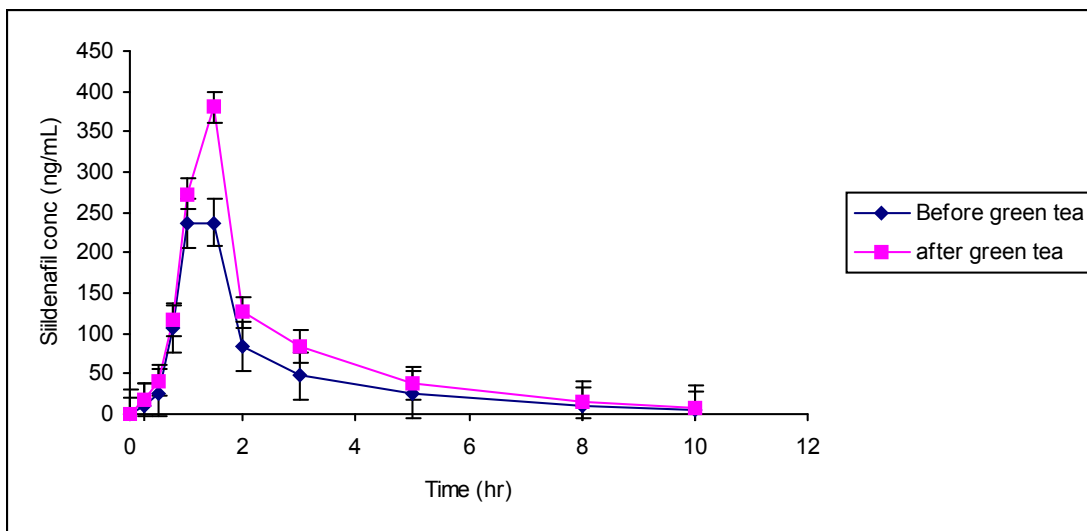


Fig. 2. Mean sildenafil plasma concentration-time profile after a single dose of sildenafil 50 mg alone (♦) and after green tea 2 gm (■).

Data are presented as mean ± S.D, n=10

The mean plasma concentration-time curve of midazolam before and after green tea is shown in Fig. (3). Area under the curve of midazolam increased insignificantly (16%), and C_{max} increased by 14% compared to before green tea.

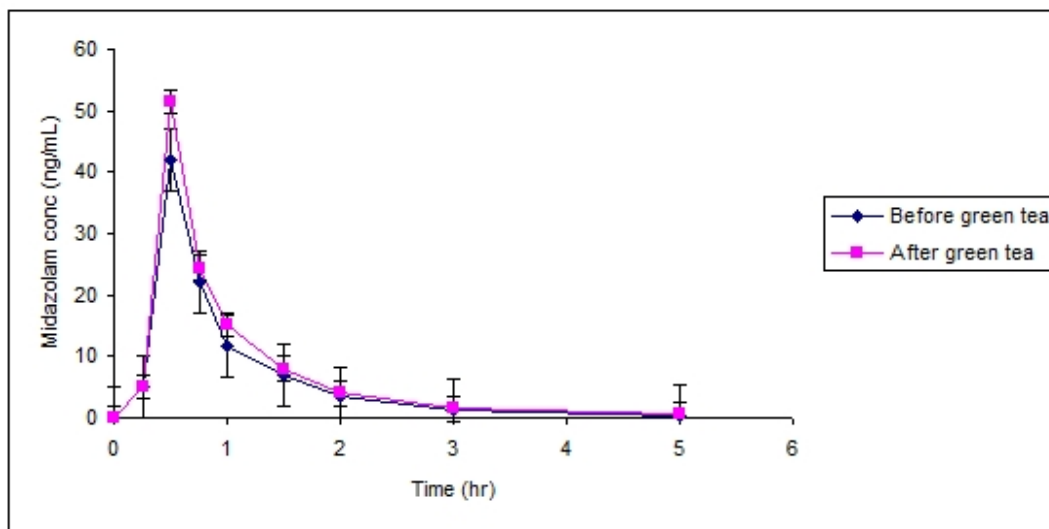


Fig. 3. Mean midazolam plasma concentration-time profile after a single dose of midazolam 7.5 mg alone (♦) and after green tea 2 gm (■).

Data are presented as mean ± S.D, n=10

The mean pharmaco-kinetic parameters of sildenafil and midazolam before and after a green tea are shown in Table 1.

Table 1. The effect of green tea coadministration on sildenafil and midazolam pharmacokinetic parameters

Parameter	Sildenafil (before green tea)	Sildenafil (after green tea)	Midazolam (before green tea)	Midazolam (after green tea)
AUC ∞ ($\mu\text{g hr/L}$)	484.2 \pm 67.27	731.5* \pm 111.01	329.4 \pm 31.2	382.7 \pm 34.6
Cmax ($\mu\text{g/L}$)	318.35 \pm 46.8	414.9* \pm 6.0	41.98 \pm 1.19	46.98 \pm 1.18
T max (hr)	1.25 \pm 0.26	1.38 \pm 0.21	0.5 \pm 0.01	0.5 \pm 0.02
K (hr $^{-1}$)	0.38 \pm 0.1	0.27* \pm 0.06	0.46 \pm 0.08	0.42 \pm 0.03
t $\frac{1}{2}$ (hr)	1.92 \pm 0.4	2.63* \pm 0.66	1.4 \pm 0.1	1.3 \pm 0.09

Data are presented as mean \pm S.D, n=10

*significantly different from before green tea ($P < 0.05$).

AUC ∞ , area under the curve from zero to infinity, Cmax, maximum plasma concentration, tmax, time required to achieve maximum plasma concentration, K, elimination rate constant, t $\frac{1}{2}$, half-life

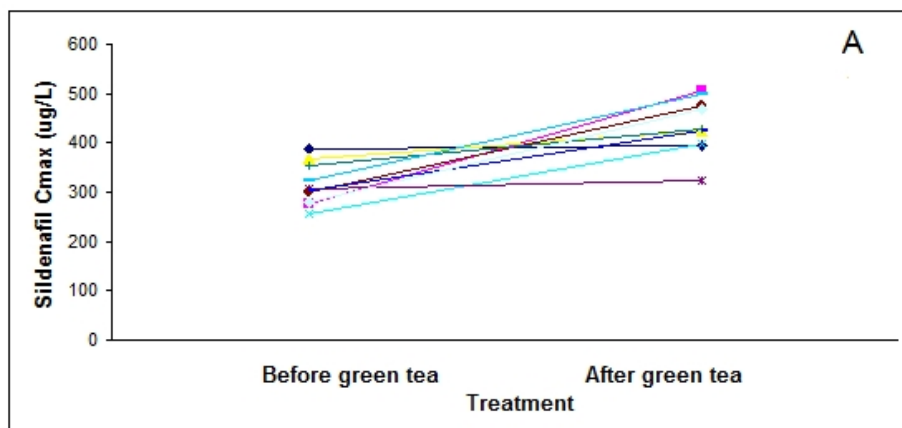
Table (2) shows that the ratios for the pharmacokinetic parameters of sildenafil were $< 80\%$ and none of the intervals passed the 100% points.

Table 2. Ninety percent confidence intervals (90% CI) for the equality of mean Cmax and AUC of sildenafil

Parameter	Ratio (Before/After green tea)	Geometric Mean (90% CI)	Lower limit of the 90% CI	Upper limit of the 90% CI
C max	76.8%	1.29	1.15	1.43
AUC ∞	78.8%	1.50	1.36	1.66

Cmax, maximum plasma concentration, AUC ∞ , area under the curve from zero to infinity

Fig. (4) shows the individual pharmacokinetic parameters of sildenafil area under the plasma concentration time curve (AUC ∞), and maximum plasma concentration (Cmax) after green tea intake.



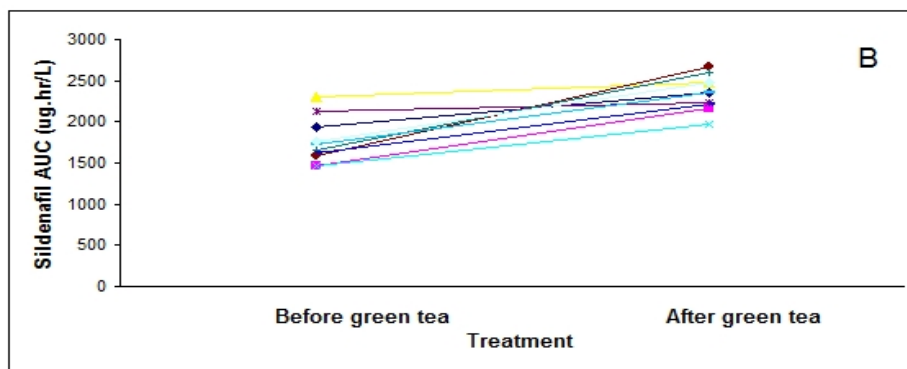


Fig. 4. Individual sildenafil pharmacokinetic parameters area under the plasma concentration time curve (AUC_{∞}) (A), and maximum plasma concentration (C_{max}) (B)

3.1 Effect of Administration of Green Tea on the Pharmacokinetics of Sildenafil

Administration of sildenafil after taking green tea significantly increased the AUC_{∞} and C_{max} by about 30%. It also prolonged the elimination half life of sildenafil by about 36%. Prolongation of the half life can result from decreasing the total body clearance or increasing the volume of distribution of the drug. It is likely that green tea's constituent (catechins) which is highly bound to plasma protein (close to 100%) [15] can affect the volume of distribution of sildenafil. This result is in agreement with Salminen et al. [16] who demonstrated that green tea extract provided protection against acetaminophen-induced hepatotoxicity when administered prior to the acetaminophen dose. It dramatically decreased acetaminophen covalent binding to protein indicating that less reactive metabolite was available to cause hepatocellular injury.

Also, taking in consideration the small (36%) but significant increase in elimination half life, we can conclude that green tea significantly increased sildenafil bioavailability and to lesser extent decreased its clearance. This result is consistent with Yang et al. [17] who demonstrated that green tea catechins may bind to certain drugs to affect their absorption and bioactivities; it may inhibit the activities of drug-metabolizing enzymes and drug transporters or affect the expression of these proteins, either upregulation or downregulation.

Few studies have investigated the interaction between green tea and other drugs. Misaka et al. [18] found that green tea catechins cause clinically relevant interactions with substrates for CYP2B6 and CYP2C8 in addition to CYP3A. In addition, a case study reported that consumption of green tea might lead to a significant increase in the plasma concentration of simvastatin in a hypercholesterolemic patient [19]. Vischini et al. [20] demonstrated that there was an increased plasma level of tacrolimus after ingestion of green tea.

3.2 Effect of Administration of Green Tea on the Pharmacokinetics of Midazolam

Midazolam (MDZ) is a commonly used benzodiazepine in clinical practice. In addition, its metabolic oxidation is used as a surrogate marker (*in vivo* probe) for Cytochrome P450 3A enzyme activity as well [21]. In this study, area under the curve of midazolam increased

insignificantly (16%) and C_{max} increased by 14% compared to before green tea suggesting a small reduction CYP 3A4 activity. Chow et al, [22] demonstrated that repeated green tea catechin administration is not likely to result in clinically significant effects on the disposition of drugs metabolized by CYP enzymes. Donovan et al. [23] showed that chronic treatment with a decaffeinated green tea supplement did not affect pharmacokinetic disposition of alprazolam, a CYP3A substrate, in healthy volunteers.

In the present study, coadministration of green tea with sildenafil produced a non-significant effect on the rate of sildenafil absorption; this was apparent from the insignificant change in the t_{max}. The results of this study indicated that green tea could increase the extent but not the rate of sildenafil absorption in humans. The green tea-sildenafil interaction may have been caused by the effect of catechins which can alter spontaneous activity of small intestine [24]. Kim et al. [25] demonstrated that this modulation is mediated *via* acting on intracellular Ca²⁺ mobilization in cAMP and cGMP-independent manner. However, other possible mechanism is possible; carrier- mediated uptake transports, such as organic anion-transporting polypeptides (OATPs), have been shown to play a central role in drug disposition [26]. For example, OATP1A2 facilitates intestinal uptake and systemic availability of many orally administered drugs [27]. It has been demonstrated that as green tea catechins modulate the function of some OATPs [28]. Roth *et al.*[29] showed that the green tea compounds ECG and EGCG are substrates for OATP1A2 and OATP1B3 suggesting that these two transporters could be involved in the disposition of these two catechins.

Although the sample size in this study was low (ten volunteers), it should be noted that the points of estimates of the pharmacokinetic parameters were above the limits of bioequivalence acceptance zone (80-125%). The individual plots show that the increase in the measures of bioavailability after green tea intake was consistent in most volunteers, with no trend toward any significant decrease.

4. CONCLUSION

Increased bioavailability of sildenafil after green tea intake may be caused by the effect of catechins which can alter spontaneous activity of small intestine or an effect on transporters. Although there were no clinically relevant changes in ECG or BP and administration of sildenafil with green tea is well tolerated, it's recommended that patients at higher risk of developing sildenafil adverse effects and are taking green tea should seek medical advice before taking their sildenafil therapy, because the ingestion of tea catechins from dietary supplements, which could be in large bullet doses, may produce more profound effects on drug metabolism [30], and such effects with drugs need to be further investigated.

CONSENT

The author declares that 'written informed consent was obtained from the volunteers for publication of this study.

ETHICAL APPROVAL

"The author hereby declares that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki."

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Boolell M, Allen MJ, Ballard SA, Gepi-Attee S, Muirhead GJ, Naylor AM, Osterloh IH, Gingell C. Sildenafil: an orally active type 5 cyclic GMP-specific phosphodiesterase inhibitor for the treatment of penile erectile dysfunction. *Int J Impot Res.* 1996;8(2):47–52.
2. Nichols DJ, Muirhead GJ, Harness JA. Pharmacokinetics of sildenafil after single oral doses in healthy male subjects: absolute bioavailability, food effects and dose proportionality. *Br J Clin Pharmacol.* 2002;53(Suppl 1):5S–12S
3. Walker DK, Ackland MJ, James GC, Muirhead GJ, Rance DJ, Wastall P, Wright PA. Pharmacokinetics and metabolism of sildenafil in mouse, rat, rabbit, dog and man. *Xenobiotica.* 1999;29(3):297–310.
4. Muirhead GJ, Rance DJ, Walker DK, Wastall P. Comparative human pharmacokinetics and metabolism of single-dose oral and intravenous sildenafil. *Br J Clin Pharmacol.* 2002;53(Suppl 1):13S–20S
5. Ku YM, Min DI, Flanigan M. Effect of grapefruit juice on the pharmacokinetics of microemulsion cyclosporine and its metabolite in healthy volunteers: does the formulation difference matter? *J Clin Pharmacol.* 1998;38(10):959-65.
6. Lee M, Min DI. Determination of sildenafil citrate in plasma by high performance liquid chromatography and a case for the potential interaction of grapefruit juice with sildenafil citrate. *Ther Drug Monit.* 2001;23(1):21-26.
7. Jetter A, Kinzig-Schippers M, Walchner-Bonjean M, Hering U, Bulitta J, Schreiner P, Sorgel F, Fuhr U. Effects of grapefruit juice on the pharmacokinetics of sildenafil. *Clin Pharmacol Ther.* 2002;71(1):21-29.
8. Al-Ghazawi MA, Tutunji MS, AbuRuz SM. The effects of pummelo juice on pharmacokinetics of sildenafil in healthy adult male Jordanian volunteers. *Eur J Clin Pharmacol.* 2010;66(2):159-63. doi: 10.1007/s00228-009-0738-0.
9. Graham HN. Green tea composition, consumption and polyphenol chemistry. *Prev Med.* 1992;21:334-50.
10. Feng WY. Metabolism of green tea catechins: an overview. *Curr Drug Metab.* 2006;7:755-809.
11. Muto S, Fujita K, Yamazaki Y, Kamataki, T. Inhibition by green tea catechins of metabolic activation of procarcinogens by human cytochrome P450. *Mutat. Res.* 2001;479:197–206

12. Nishikawa M, Ariyoshi N, Kotani A, Ishii I, Nakamura H, Nakasa H, Ida M, Nakamura H, Kimura N, Kimura M, Hasegawa A., Kusu F, Ohmori S, Nakazawa K, Kitada M. Effects of continuous ingestion of green tea or grape seed extracts on the pharmacokinetics of midazolam. *Drug Metab Pharmacokinet.* 2004;19:280–89.
13. Kumazoe M, Sugihara K, Tsukamoto S, Yuhui Huang Y, Tsurudome Y, Suzuki T, Suemasu Y, Ueda N, Yamashita S, Yoonhee Kim 1Y, Koji Yamada K, Tachibana H. 67-kDa laminin receptor increases cGMP to induce cancer-selective apoptosis *J Clin Invest.* 2013;123(2):787–99. doi:10.1172/JCI64768
14. World Medical Association. Declaration of Helsinki. Ethical principles for medical research involving human subjects. Last amended by the Forty-eighth WMA General Assembly, Somerset West, Republic of South Africa, 1996. Published online: http://www.wma.net/e/policy/17-c_e.html
15. Kurlbaum M, Högger P. Plasma protein binding of polyphenols from maritime pine bark extract (USP). *J Pharm Biomed Anal.* 2011;54(1):127-32. doi: 10.1016/j.jpba.2010.07.038.
16. Salminen WF, Yang X, Shi Q, Greenhaw J, Davis K, Ali AA. Green tea extract can potentiate acetaminophen-induced hepatotoxicity in mice. *Food Chem Toxicol.* 2012;50(5):1439-46. doi: 10.1016/j.fct.2012.01.027.
17. Yang CS, Pan E. The effects of green tea polyphenols on drug metabolism. *Expert Opin Drug Metab Toxicol.* 2012;8(6):677-89. doi: 10.1517/17425255.2012.681375.
18. Misaka S, Kawabe K, Onoue S, Werba JP, Giroli M, Tamaki S, Kan T, Kimura J, Watanabe H, Yamada S. Effects of green tea catechins on cytochrome P450 2B6, 2C8, 2C19, 2D6 and 3A activities in human liver and intestinal microsomes. *Drug Metab Pharmacokinet.* 2013;28(3):244-49.
19. Werba J.P, Giroli M, Cavalca V, Nava MC, Tremoli E, Dal Bo, L. The effect of green tea on simvastatin tolerability. *Ann. Intern Med.* 2008;149:286–87
20. Vischini G, Niscola P, Stefoni A, Farneti F. Increased plasma levels of tacrolimus after ingestion of green tea. *Am J Kidney Dis.* 2011;58(2):329.
21. Fuhr U, Jetter A, Kirchheiner J. Appropriate phenotyping procedures for drug metabolizing enzymes and transporters in humans and their simultaneous use in the "cocktail" approach. *Clin Pharmacol Ther.* 2007;81(2):270-83.
22. Chow HH, Hakim IA, Vining DR, Crowell JA, Cordova CA, Chew WM, Xu M J, Hsu CH, Ranger-Moore J, Alberts DS. Effects of repeated green tea catechin administration on human cytochrome P450 activity. *Cancer Epidemiol. Biomarkers Prev.* 2006;15:2473–76.
23. Donovan JL, Chavin KD, Devane CL, Taylor RM., Wang JS, Ruan, Y, Markowitz J S. Green tea (*Camellia sinensis*) extract does not alter cytochrome p450 3A4 or 2D6 activity in healthy volunteers. *Drug Metab Dispos.* 2004;32:906–8.
24. Ceregrzyn M, Kuwahara A. The effect of epigallocatechin gallate on intestinal motility in mice. *Environ Health Prev Med.* 2003;8(2):47-51. doi: 10.1007/BF02897926.
25. Kim KY, Choi SJ, Jang HJ, Zuo DC, Shahi PK, Parajuli SP, Yeum CH, Yoon PJ, Choi S, Jun JY. (-)-epigallocatechin gallate inhibits the pacemaker activity of interstitial cells of cajal of mouse small intestine. *Korean J Physiol Pharmacol.* 2008; 12(3):111-15. doi: 10.4196/kjpp.2008.12.3.111.

26. Bailey DG, Dresser GK, Leake BF, Kim RB. Naringin is a major and selective clinical inhibitor of organic anion-transporting polypeptide 1A2 (OATP1A2) in grapefruit juice. *Clin Pharmacol Ther.* 2007;81:495-502.
27. Lee W, Glaeser H, Smith LH, Roberts RL, Moeckel GW, Gervasini G, Leake BF, Kim RB. Polymorphisms in human organic anion-transporting polypeptide 1A2 (OATP1A2): implications for altered drug disposition and central nervous system drug entry. *J Biol Chem.* 2005;280(10):9610-17.
28. Zhang Y, Hays A, Noblett A, Thapa M, Hua DH, Hagenbuch B . Transport by OATP1B1 and OATP1B3 enhances the cytotoxicity of epigallocatechin 3-O-gallate and several quercetin derivatives. *J Nat Prod.* 2013;76(3):368-73. doi: 10.1021/np3007292.
29. Roth M, Timmermann BN, Hagenbuch B. Interactions of green tea catechins with organic anion-transporting polypeptides. *Drug Metab Dispos.* 2011;39(5):920-6. doi: 10.1124/dmd.110.036640.
30. Chow HH, Cai Y, Hakim IA, Crowell JA, Shahi F, Brooks CA, Dorr RT, Hara Y, Alberts DS. Pharmacokinetics and safety of green tea polyphenols after multiple-dose administration of epigallocatechin gallate and polyphenon E in healthy individuals. *Clinical Cancer Research.* 2003;9:3312–19.

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