Original Article

Effect of green tea consumption in treatment of mild to moderate depression in Iranian patients living with HIV: A double-blind randomized clinical trial

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ABSTRACT

Objective: Depression affects people living with HIV (PLWH) compliance leading to poor control infection. Previous observational studies showed an anti-depression effect of green tea extract (GTE). The therapeutic effect of GTE on depression were investigated in PLWH receiving antiretroviral therapy (ART).
Methods: Fifty PLWH on ART with diagnose of mild to moderate of depression, participated in a double-blind, placebo-controlled trial and underwent 12 weeks of treatment with either 400 mg GTE capsules or placebo twice daily. The Hamilton depression scale of patients was measured before, 6 weeks and 12 weeks after treatment in two groups. The primary outcome measure was performed to evaluate the efficacy of GTE in improving depressive symptoms.
Results: The mean of Hamilton score showed a significant difference between the two groups after 12 weeks (P = 0.035). Repeated measures ANOVA test showed a significant effect for time × treatment interaction on the Hamilton mean score between the two groups (P = 0.000).
Conclusion: It seems the use of GTE capsules in PLWH on ART is safe and could lead to greater and more rapid improvement in depressive symptoms than placebo. Thus it can be considered as an alternative therapy for mild to moderate depression. Further studies with higher sample size and longer follow-up and comparisons with other antidepressive drugs are warranted.

1. Introduction

Antiretroviral therapy (ART) has extended the life expectancy of people living with HIV (PLWH). However, it has been reported that protease inhibitors as a component of ART could contribute to neurological damage and cognitive disorders related to HIV infection (Gannon et al., 2017). Depression is the most common psychiatric disorder in these patients (Bing et al., 2001). The prevalence of major depressive disorder (MDD) has been estimated to be between 19% and 43%, on the basis of the studied population, and these patients are known to be two times more likely to suffer from MDD compared to the normal population (Paydary et al., 2016; Ghayomzadeh et al., 2019). It is associated with poor treatment adherence (Gonzalez et al., 2011), increased medical expenditure (Katon, 2003), raised community viral load, uncontroled HIV epidemic and disease progression (Schuster et al., 2012), a significant decrease in quality of life (Razavi et al., 2012), suicidal ideation (Dabaghzadeh et al., 2015), myocardial infarction (Khambaty et al., 2016), and unsafe use of shared syringes and unprotected sex which can accelerate the transmission of HIV. Hence, successful treatment of depression improves HIV infection prognosis (Gaynes et al., 2015).

Several mechanisms such as chronic inflammation due to the microglia and astrocytes excitement and elevated cytokines, or decreased monoaminergic activity especially in dopaminergic neurons owing to neurotoxicity mediated by the direct effect of the virus or stress of negative psychosocial burden of the disease are

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involved in depression. These mechanisms might activate the hypothalamic–pituitaryadrenal axis, sympathetic system and subsequently enable the activation of cellular immunity in peripheral and central nervous system (CNS) tissues (Chaudhury et al., 2016). On the other hand, an antibiotic, minocycline, which has anti-inflammatory, neuroprotective, antioxidants and anti-glutamate excitotoxicity properties, may be effective in the treatment of mild to moderate depression among PLWH (Emadi-Kouchak et al., 2016). Antidepressants may have unintended negative effects, such as interactions with HIV-related drugs, constipation, headache, weight gain or impair sexual functioning in HIV infected patients (Fulk et al., 2004).

Green tea has been known as an antioxidant and neuroprotective beverage for thousands of years (Al-Dujaili, 2015). The origin of green tea is Chinese and preparing from the evergreen shrubs of *Camellia sinensis* with minimum oxidation. The monomeric flavonols known as catechins are the important polyphenols composing 30 to 40 percent of green tea. They include epigallocatechin gallate (EGCG), catechin gallate (CG), gallocatechin (GC), gallocatechin gallate (GCG), epigallocatechin-3,5-digallate (EGCDG) and 2′,2″-bis epigallocatechin digallate (BGCDG). Importantly, EGCG comprises approximately 50% to 60% of green tea polyphenols (Sodagari et al., 2016). Several studies showed beneficial effects of green tea polyphenols such as anticancer activity, anti-diabetes, antioxidant, anti-inflammatory, neuroprotective, cardio-protective, anti-bacterial, antifungal and antiviral activity. Polyphenols in green tea also play a role in inhibiting the pro-inflammatory cytokines and have a regulatory immune function. In addition, the reduction of the HIV neurotoxicity and its prevention and therapeutic properties in HIV-induced dementia, as well as inhibition of HIV replication in different stages by EGCG, have been shown (Giunta et al., 2006; Onakpoya et al., 2014; Vinson et al., 2004).

Green tea consumption also has protective effects on ART hepatotoxicity (Wondimnew, 2016). Furthermore, it is useful in weight control (Cabrera et al., 2006). In a cross-sectional study, Niu K. et al. showed more green tea consumption decreased the prevalence of depression among community-dwelling elderly Japanese (Niu et al., 2009). Another study revealed consumption of green tea extract (GTE) at a dose of 10 mg/kg or 20 mg/kg daily for 7 consecutive days had anti-depressant effects in rats, probably due to inhibition of the hypothalamic pituitary adrenal axis (Zhu et al., 2012). Several studies showed 800 mg EGCG consumption per day (equally 8 to 16 cups of green tea depending on the cup size), when taken with food was safe in healthy individuals (Chow et al., 2003; Sarma et al., 2008; Schönthal, 2011). In addition, the use of EGCG at a dose of 2000 mg twice daily for six months in patients with non-symptomatic chronic lymphocytic leukemia was well tolerated (Shanafelt et al., 2013).

Green tea polyphenols should not take with an empty stomach since hepatotoxicity due to EGCG elevated plasma level may develop. In clinical trials to produce beneficial cardiovascular effects, glucose homeostasis, and weight loss, 400 to 716 mg of catechins per day in divided doses, 84 to 386 mg of EGCG daily, 270 to 800 mg EGCG per day, were all effective, respectively. However, it seems that taking green tea at higher doses may associate with the risk of hepatotoxicity in mice (Green Tea, 2019). Therefore, in liver failure, it should use with caution. Contraindications for green tea consumption are not well known. Headache, dizziness, gastrointestinal symptoms such as nausea and vomiting and rarely hepatotoxicity at high doses were reported in the previous studies. Notably, no significant interaction between green tea and antiretroviral drugs observed (Green Tea, 2019).

The US Pharmacopeia (USP) Dietary Supplements Information Expert Committee (DSIEC) categorized green tea as class 2 in the classification of dietary supplement safety information; Therefore, by using this warning labeling statement "Take with food. Discontinue use and consult a healthcare practitioner if you have a liver disorder or develop symptoms of liver trouble such as abdominal pain, dark urine, or jaundice." it could be accepted into the USP Diety Supplement (Sarma et al., 2008).

In this study, we investigated the effect of 400 mg GTE consumption twice daily on mild to moderate depression in PLWH receiving ART.

2. Materials and methods

2.1. Study design and participants

From February 2017 to October 2017, three hundred and forty six of PLWH referred to Voluntary Counseling and Testing (VCT) center located in Imam Khomeini Hospital in Tehran, Iran were assessed and fifty patients attended in a 12-week randomized, double-blind, placebo-controlled parallel trial to receive either GTE or placebo capsules. Fifty patients just completed the trial and took part in all follow-up visits (Fig. 1).

2.2. Eligibility criteria

Patients who met the eligibility criteria were recruited and randomized in the two groups. The eligibility criteria are described in Table 1.

2.3. Random allocation

Following simple randomization with a computerized random number generator, eligible patients were received either GTE (provided by Iranian Institute of Medicinal Plants, Tehran, Iran) or placebo (provided by Iranian Institute of Medicinal Plants, Tehran, Iran) capsules twice daily for 12 weeks (allocation ratio 1:1). A third-party assignment was used for the allocation concealment. The GTE and placebo capsules were identical regarding their size, shape, color, texture, and odor. The patients and investigators were blinded to the treatment assignment.

2.4. Sample preparation

Dried green tea leaves (*Camelia sinensis*) were supplied by Institute of Medicinal Plants, Iran. The leaves were ground using hammer mill and then passed through 10 mm mesh. The ground leaves (2 kg) was extracted with 30 L acidified water (pH was controlled at 5.0 using citric acid) at 70 °C for 120 min. All of the solids were filtered off and the extract was concentrated by vacuum evaporator to give solutions contained 10% total solid. The concentrated extracts were mixed with maltodextrin (DE = 19) with the ratio of 3, and 8%, respectively. Finally, it was stored in a container at 4 °C until required.

Laboratory spray dryer equipped with two-fluid nozzle was used in the spray drying process. In all experiments, the blower speed, the feed temperature and the outlet temperature were kept at 2000 rpm, 65 °C and 85 °C , respectively. The products from separated run were weighed and sealed in aluminum foil bags at room temperature and kept for physical and chemical analysis.

2.5. Measurements and procedures

Depreesion was assessed at baseline, 6 and 12 weeks later using HDRS validated 17-item. Hamilton Depression Rating Scale (HDRS) was applied in several clinical trials in Iran for measuring respons to treatment and severity of depressive symptoms (Emadi-Kouchak et al., 2016). The CD4 count was also evaluated using
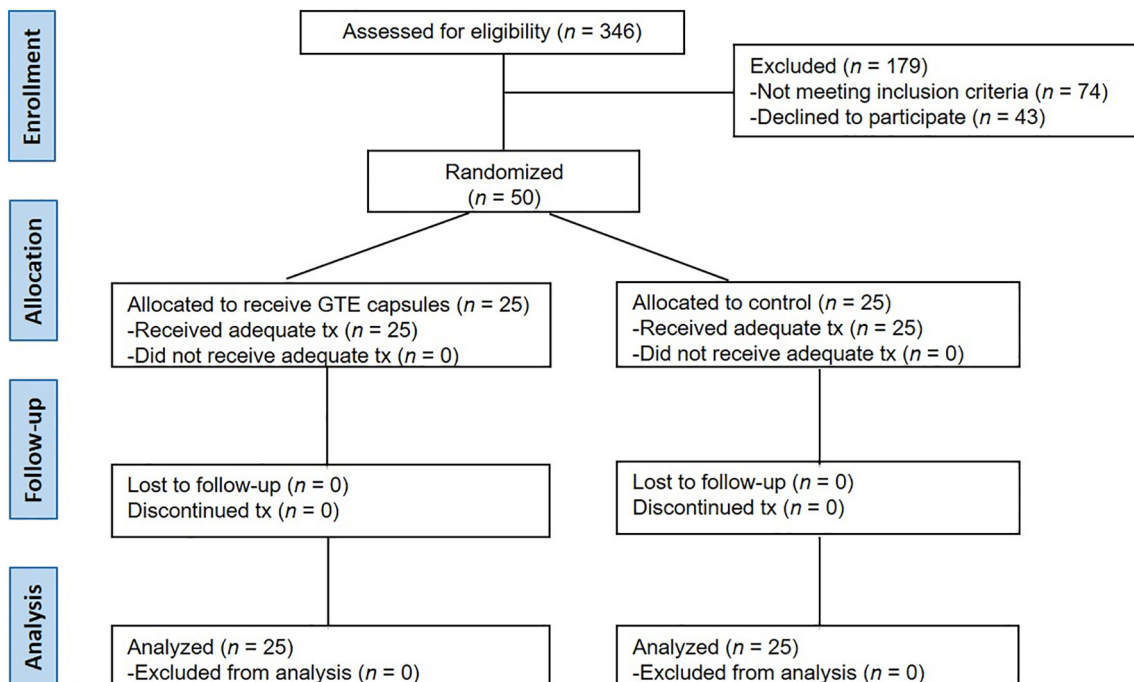
Fig. 1. Flow of participants through study.

Table 1
Eligibility criteria for the study in Imam Khomeini Hospital of Tehran from 2017 to 2018.

Inclusion criteria	Exclusion criteria
Between 18 and 65 years	Severe depression or suicidal tendency based on the Hamilton suicide score scale ≥ 2.
HIV infection based on the ELIZA and Western blot tests	Current use of antidepressants or other psychiatric medications
Receive ART	Fever
Have a diagnose of mild to moderate of depression based on Diagnostic and Statistical Manual of mental disorders (DSM) IV criteria	Presence of active infection or any history of opportunistic infections
Have a Hamilton Depression Rating Scale (HDRS) (17 items) < 20	Active addiction or alcohol consumption
Lack of other psychiatric and cognitive diseases (including AIDS Dementia Complex)	Inability to withhold tea containing products and limiting caffeinated beverages consumption which does not exceed 12 oz per day
Agree to follow the study protocol	Presence of Inflammatory Bowel Disease or chronic pancreatitis
	Patients with iron deficiency anemia or folate deficiency
	Pregnancy

the Partec kit (Partec GmbH, Münster, Germany) for all participants at baseline, 6 and 12 weeks later. The primary outcome was the assessment of GTE safety and efficacy to decrease severity of depressive symptoms compared to placebo in PLWH who were treated with ART using general linear model repeated measures. Partial responders and responders defined as 25%–50% and $\geq$ 50% reduction in HDRS score, respectively. Two groups were analyzed considering the HDRS scores from the baseline at each time point as well as the time needed to respond to treatment.

Side effects were measured monthly during the study using a specific checklist. In addition, participants were warned to notice the researchers any unexpected symptom during the study course immediately.

This trial was a proof of concept study; However, we assumed a significant difference of 3 on the HDRS score, a SD of 4, a two-sided significance level of 0.05, a power of 80% based on our previous study (Emadi-Kouchak et al., 2016), and a loss to follow up rate 20%. Thus, the sample size was calculated 50 (25 patients in each arm).

2.6. Ethical considerations

The authors considered the declaration of Helsinki and subsequent revisions and obtained written informed consent from all the patients before the study participation. Participants knew they could leave the study when they wanted without any interruption in the standard care. Moreover, institutional review board (IRB) of Tehran University of Medical Sciences (TUMS) approved the study protocol.

2.7. Statistical analysis

Quantitative and qualitative variables are reported as mean ± SD and number (%), respectively. The independent t-test was used for comparison of HDRS scores between the two groups at the baseline, 6 weeks and 12 weeks, as well as the reduction in HDRS scores from baseline to each time point in both groups. Mann-Whitney Test uesed for evaluation of HDRS scores changes during the trial course. The ANOVA's repeated-measure analysis was used to compare HDRS scores between the two groups during the trial course. Qualitative variables were analyzed using Fisher's exact test. The time needed to partially respond to treatment compared between the two groups usuing Kaplan–Meier estimation with log-rank test.

All tests were in two domains and a P-value<0.05 was considered statistically significant. All statistical analysis were performed with the statistical package of social science (SPSS) software (version 22; IBM Company, Armonk, New York, USA). The repeated-measure test graphs were drawn with Sigma plot (version 12; Systat Software Inc., San Jose, California, USA).

Table 2
Baseline characteristics of patients according to treatment in two groups in Imam Khomeini Hospital of Tehran from 2017 to 2018.

General information		Green Tea (n = 25)	Placebo (n = 25)	P-value
Age	<30	5 (20.0%)	7 (28.0%)	0.2
	30–40	11 (44.0%)	14 (56.0%)	
	40<	9 (36.0%)	4 (16.0%)	
Gender	Female	8 (32.0%)	10 (40.0%)	0.7
	Male	17 (68.0%)	15 (60.0%)	
Marital	Single	5 (20.0%)	7 (28.0%)	0.1
	Married	19 (76.0%)	12 (48.0%)	
	Divorced	1 (4.0%)	6 (24.0%)	
Education	Under diploma	13 (52.0%)	14 (56.0%)	0.9
	Diploma	5 (20.0%)	6 (24.0%)	
	Associate Degree	1 (4.0%)	0 (0.0%)	
	Bachelor	5 (20.0%)	4 (16.0%)	
	Master's degree	1 (4.0%)	1 (4.0%)	
HDRS score baseline		15.72 ± 2.5	15.92 ± 2.3	0.8
CD4 count baseline	<500	11 (44.0%)	10 (40.0%)	0.9
	500–1000	13 (52.0%)	13 (52.0%)	
	1000<	1 (4.0%)	2 (8.0%)	

3. Results

3.1. Demographic characteristics

Finally, intention to treat (ITT) analysis was preformed. Basic participants' demographic data as shown in Table 2 were not significantly different between the two groups. Primarily participants were male, with the average age of (35 ± 6) and (34 ± 7) in green tea and placebo groups, respectively. Baseline CD4 count means were (547 ± 170) in green tea, and (606 ± 228) in the placebo group. In addition, baseline HDRS scores was no significant difference between the green tea and the placebo groups [(15.72 ± 2.5) *vs.* (15.92 ± 2.3), respectively, mean difference (MD) (95% confidence interval) = − 1.57 to 1.173), df (48)].

3.2. Outcomes

A significant finding was reported for effect for time × treatment interaction on the HDRS score according to general linear model repeated measures (P = 0.001) (Fig. 2).

A significantly improvement was seen in HDRS score from baseline to 12 weeks in the green tea group than placebo group (P = 0.035) (Table 3). At weeks 6 and 12, a significantly plausible percent of partial responders were seen in the green tea group than placebo group (Table 4).

No participants in the placebo group experienced response to treatment (≥50% reduction in HDRS score). Kaplan-Meier estimation partial for response to treatment was seen at shorter time in green tea group than placebo group (P < 0.001).

3.3. Adverse effects

Incidence of overall adverse effects was 1 (4%) in green tea group and 1 (4%) in placebo group reported (P = NS)

4. Discussion

This study showed taking GTE capsule twice daily for 3 months in PLWH improved the symptoms of mild to moderate depression significantly. Considering the basic clinical characteristics of the participants did not differ substantially between the green tea and placebo groups, the anti-depression effects observed in the treatment group can be attributed to the therapeutic effect of GTE. Since the side effects were not significantly different in the two groups, it can be concluded that the use of GTE was well tolerated in addition, no significant serious adverse effects noted.
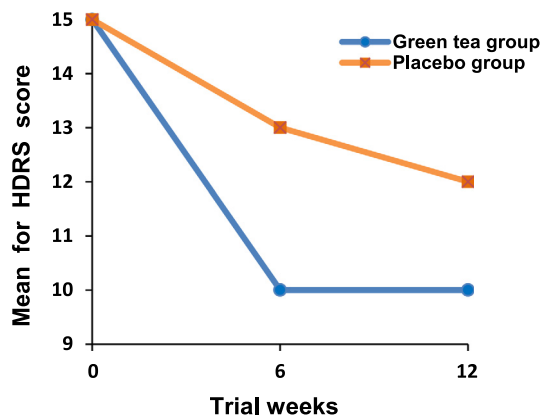
Fig. 2. Repeated measure for comparison of two study groups on HDRS score.

Table 3
Comparison of mean HDRS and CD4 count between two groups in Imam Khomeini Hospital of Tehran from 2017 to 2018 (mean ± SD, n = 25).

Groups	HDRS score at week 6th	HDRS score at week 12th	CD4 count at week 12th
Green tea	10.68 ± 3.60	10.13 ± 3.04	574.80 ± 202.63
Placebo	13.04 ± 4.80	12.63 ± 4.70	631.71 ± 157.20
P value	0.06	0.04	0.56

Table 4
Comparison of outcome indexes between the two groups in Imam Khomeini Hospital of Tehran from 2017 to 2018.

Groups	Number (%) of partial responders at week 6th	Number (%) of partial responders at week 12th
Green tea	9 (36%)	15 (62.5%)
Placebo	1 (4%)	0 (0%)
P value	0.01	< 0.001

No significant interactions between GTE and ART were reported. The mean of CD4 count in both groups did not differ significantly at the beginning and the end of the study.

In a study in Iran based on Depression Anxiety Stress Scales (DASS), 68% of PLWH had depression, and the disease was very severe in 17% of the participants. Seventysix percent of PLWH were

anxious, and 27% experienced very severe anxiety disorder. The prevalence of stress among the PLWH was 73%, of which 14% had very severe stress (SeyedAlinaghi et al., 2019; Paydary et al., 2015).

Several mechanisms have been purposed for anti-depressant properties of green tea. Green tea is rich in polyphenols, especially catechins, which can exert anti-depressant effects through reducing corticosterone (cortisone in men) and corticotropin. It has also been shown that epigallocatechin (EGCG), a major catechin in green tea, can reduce the concentration of dopamine in the brain which plays a major role in pathogenesis of depression. Approximately fifty percent of the amino acids in green tea composed with thiamine. Animal studies showed thiamine could increase dopamine concentration in the brain. Folate, another tea component, has also been shown to protect against depression (Dong et al., 2015).

In addition, green tea as a strong antioxidant agent can also protect depression by reducing the oxidative stress, a potential mechanism involved in depression pathogenesis (Pham et al., 2014; Nathan et al., 2006). Moreover, polyphenols can reduce anxiety and depression through adult hippocampal neurogenesis (AHN) (Dias et al., 2012). Polyphenols are also effective in increasing the serotonin (5-HT) and norepinephrine (NE) concentrations in the hippocampus and the glutathione (GSH) (Liu et al., 2013).

Our study showed the beneficial effects of GTE on the improvement of depression symptoms in HIV patients. To the best of our knowledge, this trial is the first study on HIV patients. Pham and colleagues in a cross-sectional survey on 537 Japanese workers revealed the prevalence of depression symptoms in whose consumed four or more cups of green tea a day was significantly lower compared to those who consumed one or fewer cups daily (Pham et al., 2014). In a study by Hintikka et al., which was conducted on a 2011 Finnish woman using the Depression Inventory (BDI Beck), people who were drinking tea daily were less depressed than others, and none of whom drunk five cups or more tea per day were depressed. However, in contrast to our study it was a cross-sectional survey; so the causal relationship between green tea consumption and depression was not well investigated. Furthermore, the type of tea was not defined in this paper (Hintikka et al., 2005). Conversely, a cross-sectional study of Ruusune et al. did not show a relation between reducing the risk of severe depression and taking tea or caffeine in 2,232 middle-aged Finnish men. This survey performed on patients with severe depression required hospital admission, while our study conducted on people with mild to moderate depression. Moreover, while approximately 43% of participants were tea drinkers, the average tea consumption was relatively low (Ruusunen et al., 2010). Eventually, Dong et al., in a *meta*-analysis of 11 observational papers regarding tea consumption and the risk of depression revealed that drinking more three teacups daily was associated with a 37% reduction in the risk of depression. Hence, they suggested tea consumption is an independent protective factor for depression (Dong et al., 2015).

In contrast to other papers noted, our study was a double-blinded clinical trial, using a valid instrument for measuring depression (Emadi-Kouchak et al., 2016). Moreover, demographic characteristics and Hamilton mean score did not differ significantly between the two groups at the beginning of the study. Therefore, they provided a valid comparison of the anti-depressant effect between the two groups. In this study, although consumption of tea and other caffeine products was limited in participants, but the type of diet, the socioeconomic status, the existence of social support versus social isolation and lifestyle factors (such as physical activity, alcohol consumption, and smoking) which are potentially confounding factors might not be perfectly controlled in the both groups. Furthermore, we could not measure the factors involved in the green tea anti-depression mechanisms such as serum or urine catechins, serum folate, cortisone serum levels.

Also, sample size and follow-up duration were relatively low. This is especially important in chronic diseases such as depression that is likely to recur.

5. Conclusions

It seems that taking GTE 400 mg twice daily in PLWH receiving ART is safe and could improve mild to moderate symptoms of depression. Since depression is prevalent in HIV infected patients and synthetic antidepressants are sometimes unpleasant among HIV infected patients with occasionally severe side effects, green tea can be considered in a case of mild to moderate depression. However, further studies with higher sample sizes and a longer follow-up period and comparison with other depressive drugs are recommended.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

Al-Dujaili, E. A. (2015). Natural polyphenols: Potential for disease prevention. *EC Nutrition, 2*(2), 337–345.

Bing, E. G., Burnam, M. A., Longshore, D., Fleishman, J. A., Sherbourne, C. D., London, A. S., et al. (2001). Psychiatric disorders and drug use among human immunodeficiency virus–infected adults in the United States. *Archives of General Psychiatry, 58*(8), 721–728.

Cabrera, C., Artacho, R., & Giménez, R. (2006). Beneficial effects of green tea—a review. *Journal of the American College of Nutrition, 25*(2), 79–99.

Chaudhury, S., Bakhla, A. K., & Saini, R. (2016). Prevalence, impact, and management of depression and anxiety in patients with HIV: A review. *Neurobehavioral HIV Medicine, 7*, 15.

Chow, H. S., Cai, Y., Hakim, I. A., Crowell, J. A., Shahi, F., Brooks, C. A., et al. (2003). Pharmacokinetics and safety of green tea polyphenols after multiple-dose administration of epigallocatechin gallate and polyphenon E in healthy individuals. *Clinical Cancer Research, 9*(9), 3312–3319.

Dabaghzadeh, F., Jabbari, F., Khalili, H., & Abbasian, L. (2015). Associated factors of suicidal thoughts in HIV-positive individuals. *Iranian Journal of Psychiatry, 10*(3), 185.

Dias, G. P., Cavegn, N., Nix, A., do Nascimento Bevilaqua, M. C., Stangl, D., Zainuddin, M. S. A., et al. (2012). The role of dietary polyphenols on adult hippocampal neurogenesis: Molecular mechanisms and behavioural effects on depression and anxiety. *Oxidative Medicine and Cellular Longevity, 2012.* https://doi.org/10.1155/2012/541971 541971.

Dong, X., Yang, C., Cao, S., Gan, Y., Sun, H., Gong, Y., et al. (2015). Tea consumption and the risk of depression: A meta-analysis of observational studies. *The Australian and New Zealand Journal of Psychiatry, 49*(4), 334–345.

Emadi-Kouchak, H., Mohammadinejad, P., Asadollahi-Amin, A., Rasoulinejad, M., Zeinoddini, A., Yalda, A., et al. (2016). Therapeutic effects of minocycline on mild-to-moderate depression in HIV patients: A double-blind, placebo-controlled, randomized trial. *International Clinical Psychopharmacology, 31*(1), 20–26.

Fulk, L. J., Kane, B. E., Phillips, K. D., Bopp, C. M., & Hand, G. A. (2004). Depression in HIV-infected patients: Allopathic, complementary, and alternative treatments. *Journal of Psychosomatic Research, 57*(4), 339–351.

Gannon, P. J., Akay-Espinoza, C., Yee, A. C., Briand, L. A., Erickson, M. A., Gelman, B. B., et al. (2017). HIV protease inhibitors alter amyloid precursor protein processing

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via β-site amyloid precursor protein cleaving enzyme-1 translational up-regulation. *American Journal Pathology, 187*(1), 91–109.

Gaynes, B. N., Pence, B. W., Atashili, J., O'Donnell, J. K., Njamnshi, A. K., Tabenyang, M. E., et al. (2015). Changes in HIV outcomes following depression care in a resource-limited setting: Results from a pilot study in Bamenda, Cameroon. *PLoS One, 10*(10) e0140001.

Ghayomzadeh, M., Earnest, C. P., SeyedAlinaghi, S., Wesson, P., Taj, L., Rezaei, S., et al. (2019). Effects of aerobic dance training on psychological well-being and immune function of women living with HIV. *Journal of the Association of Nurses in AIDS Care, 30*(2), 238–244.

Giunta, B., Obregon, D., Hou, H., Zeng, J., Sun, N., Nikolic, V., et al. (2006). EGCG mitigates neurotoxicity mediated by HIV-1 proteins gp120 and Tat in the presence of IFN-γ: Role of JAK/STAT1 signaling and implications for HIV-associated dementia. *Brain Research, 1123*(1), 216–225.

Gonzalez, J. S., Batchelder, A. W., Psaros, C., & Safren, S. A. (2011). Depression and HIV/AIDS treatment nonadherence: A review and meta-analysis. *Journal of Acquired Immune Deficiency Syndromes, 58*(2), 181–187.

Tea, Green (2019). Clinical Overview Retrieved from https://www.drugs.com/npp/green-tea.html. Accessed March 23, 2019.

Hintikka, J., Tolmunen, T., Honkalampi, K., Haatainen, K., Koivumaa-Honkanen, H., Tanskanen, A., et al. (2005). Daily tea drinking is associated with a low level of depressive symptoms in the Finnish general population. *European Journal of Epidemiology, 20*(4), 359–363.

Katon, W. J. (2003). Clinical and health services relationships between major depression, depressive symptoms, and general medical illness. *Biological Psychiatry, 54*(3), 216–226.

Khambaty, T., Stewart, J. C., Gupta, S. K., Chang, C. C. H., Bedimo, R. J., Budoff, M. J., et al. (2016). Association between depressive disorders and incident acute myocardial infarction in human immunodeficiency virus–infected adults: Veterans Aging Cohort Study. *JAMA Cardiology, 1*(8), 929–937.

Liu, Y., Jia, G., Gou, L., Sun, L., Fu, X., Lan, N., et al. (2013). Antidepressant-like effects of tea polyphenols on mouse model of chronic unpredictable mild stress. *Pharmacology Biochemistry and Behavior, 104*, 27–32.

Nathan, P. J., Lu, K., Gray, M., & Oliver, C. (2006). The neuropharmacology of *L*-theanine (N-ethyl-*L*-glutamine) a possible neuroprotective and cognitive enhancing agent. *Journal of Herbal Pharmacotherapy, 6*(2), 21–30.

Niu, K., Hozawa, A., Kuriyama, S., Ebihara, S., Guo, H., Nakaya, N., et al. (2009). Green tea consumption is associated with depressive symptoms in the elderly. *The American Journal of Clinical Nutrition, 90*(6), 1615–1622.

Onakpoya, I., Spencer, E., Heneghan, C., & Thompson, M. (2014). The effect of green tea on blood pressure and lipid profile: A systematic review and meta-analysis of randomized clinical trials. *Nutrition, Metabolism and Cardiovascular Diseases, 24*(8), 823–836.

Paydary, K., Ekhtiari, H., Noori, M. V., Rad, M., Hajiabdolbaghi, M., & SeyedAlinaghi, S. (2015). Evaluation of the association between addiction severity index and depression with adherence to anti-retroviral therapy among HIV infected patients. *Infectious Disorders-Drug Targets (Formerly Current Drug Targets-Infectious Disorders), 15*(3), 177–183.

Paydary, K., Mahin Torabi, S., SeyedAlinaghi, S., Noori, M., Noroozi, A., Ameri, S., et al. (2016). Impulsivity, sensation seeking, and risk-taking behaviors among HIV-positive and HIV-negative heroin dependent persons. *AIDS Research and Treatment, 2016*(5323256), 1–9.

Pham, N. M., Nanri, A., Kurotani, K., Kuwahara, K., Kume, A., Sato, M., et al. (2014). Green tea and coffee consumption is inversely associated with depressive symptoms in a Japanese working population. *Public Health Nutrition, 17*(3), 625–633.

Razavi, P., Hajifathalian, K., Saeidi, B., Esmaeeli Djavid, G., Rasoulinejad, M., Hajiabdolbaghi, M., et al. (2012). Quality of life among persons with HIV/AIDS in Iran: Internal reliability and validity of an international instrument and associated factors. *AIDS Research and Treatment, 2012*. https://doi.org/10.1155/2012/849406

Ruusunen, A., Lehto, S. M., Tolmunen, T., Mursu, J., Kaplan, G. A., & Voutilainen, S. (2010). Coffee, tea and caffeine intake and the risk of severe depression in middle-aged Finnish men: The Kuopio Ischaemic Heart Disease Risk Factor Study. *Public Health Nutrition, 13*(8), 1215–1220.

Sarma, D. N., Barrett, M. L., Chavez, M. L., Gardiner, P., Ko, R., Mahady, G. B., et al. (2008). Safety of green tea extracts. *Drug Safety, 31*(6), 469–484.

SeyedAlinaghi, S., Dehghan Manshadi, A., & Golrokhi, R. (2019). *Assessing coping strategies and examining the relationship between adaptation used by HIV-positive patients with depression, anxiety and stress: Project Report [In Persian]*. Tehran: Iranian Research Center for HIV/AIDS.

Schönthal, A. H. (2011). Adverse effects of concentrated green tea extracts. *Molecular Nutrition & Food Research, 55*(6), 874–885.

Schuster, R., Bornovalova, M., & Hunt, E. (2012). The influence of depression on the progression of HIV: Direct and indirect effects. *Behavior Modification, 36*(2), 123–145.

Shanafelt, T. D., Call, T. G., Zent, C. S., Leis, J. F., LaPlant, B., Bowen, D. A., et al. (2013). Phase 2 trial of daily, oral polyphenon E in patients with asymptomatic, Rai stage 0 to II chronic lymphocytic leukemia. *Cancer, 119*(2), 363–370.

Sodagari, H. R., Bahramsoltani, R., Farzaei, M. H., Abdolghaffari, A. H., Rezaei, N., & Taylor-Robinson, A. W. (2016). Tea polyphenols as natural products for potential future management of HIV infection-an overview. *Journal of Natural Remedies., 16*(2), 60–72.

Vinson, J. A., Teufel, K., & Wu, N. (2004). Green and black teas inhibit atherosclerosis by lipid, antioxidant, and fibrinolytic mechanisms. *Journal of Agricultural and Food Chemistry, 52*(11), 3661–3665.

Wondimnew, T. (2016). *Effect of green tea (Camellia sinensis) leaf extract on highly active antiretroviral therapy induced dyslipidemia and non alcoholic fatty liver disease in Albino Wistar rats (Doctoral dissertation*. Addis Ababa University).

Zhu, W. L., Shi, H. S., Wei, Y. M., Wang, S. J., Sun, C. Y., Ding, Z. B., et al. (2012). Green tea polyphenols produce antidepressant-like effects in adult mice. *Pharmacological Research, 65*(1), 74–80.