

The Effect of Therapeutic Horticulture Activities on People in Depression and Kynurenine Pathways

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Abstract

The article presents the results of a study conducted to assess change in depression severity, and modification in the kynurenine pathway at participants. Presently, depression is one of the most regularly encountered mental illnesses. Research based on experimental studies indicated the beneficial effects of activities conducted in nature are reducing self-reported anger, fatigue, anxiety, stress and depression. The present study was conducted by measuring depression on both the subjective (Beck Depression Inventory) and the objective (spectrophotometric analysis) levels, to obtain more relevant information regarding the real change in depression levels, during the therapeutic horticulture intervention. Consequently, depression is assessed with the BDI doubled the data by assessing the levels of kynurenine and kynurenic acid obtained from biological samples. Results indicate that the levels of depression measured with the BDI have significantly decreased after the Therapeutic Horticulture Sessions. An even better result regards the fact that the significance of this change was not only statistical, but also clinical. Analysing the kynurenine and kynurenic acid concentrations, differences were observed amongst subject during the research study.

Keywords: biomarker; gardening activities; mental health; nature-based interventions

Abbreviations: BDI: Beck Depression Inventory; HT: horticulture therapy; KYN: kynurenine; KYNA: kynurenic acid; TH: therapeutic horticulture

Introduction

The last four-five decades have witnessed an unprecedented increase in the number and the diversity of life-challenges. This phenomenon has additionally been aggravated by the disruption of the traditional and stable life-guiding interpretive frameworks (Amundson, 2006; Nolen-Hoeksema, 2003), which have seriously challenged humans' abilities to adapt to the new life-conditions (Woolfolk *et al.*, 2007). Not surprisingly, a constantly increase of population fraction has presented significant symptoms of stress, impairing different aspects of

functioning (physiological, behavioral, cognitive, emotional, social etc.) (Falvo, 2005; Levenson, 2006; Aldwin, 2007; Banyard *et al.*, 2009; Kendall-Tackett, 2009; National Comprehensive Cancer Network, 2009; Lanius *et al.*, 2010; Pennebaker and Chung, 2011). The number of those who suffer of mental illness of clinical intensity has been constantly increase along the years, depression being one of the most frequently encountered mental illnesses (Andrade *et al.*, 2003; Cunningham *et al.*, 2006; Cuijpers *et al.*, 2007; Weehuizen, 2008). The lifetime prevalence of depression ranges between 3-16.9% and 4.4% of the global population suffering of this extremely debilitating mental health conditions (Kessler *et al.*, 2003; WHO, 2017). Worldwide, depression is estimated to affect 5.8% of all men and 9.5% of

all women in any given year (Gonzalez *et al.*, 2009), the female:male ratio of major depression remained similar along the years, 1.7:1 respectively (Albert, 2015). In order to illustrate this increase in mental illness, only in the USA, the prescription of antidepressants (the third most frequently prescribed drugs during 2005-2008) has recorded a 400% increase between 1988-1994 to 2005-2008 (Pratt *et al.*, 2011). Being a huge socio-economic burden, depression is predicted to become the second most serious disease by 2030 (Mathers and Loncar, 2006; Gustavsson *et al.*, 2011; Wittchen *et al.*, 2011).

Unfortunately, only a small percentage of those diagnosed with different forms of depression benefits of specialized treatment. In the USA and Western Europe, approximately 20% of those received psychotherapy (Weddington, 1983; Brody *et al.*, 1997) and almost half of the patients drop out of therapy before completion. The major impediments in receiving treatment are: financial expenses, availability of specialized therapist, especially for sub-syndromal symptomatology (Amstadter *et al.*, 2009), perception of stigma associated with mental illness (Klein *et al.*, 2009), lack of spatial and/or temporal access to therapy etc. (Przeworski and Newman, 2006).

Under these conditions, a very important mission of research and practice in mental-health care becomes the investigation of treatment methods, which are more accessible and cost-effective than traditional ones (Kazantzis and L'Abate, 2007). Recognizing the importance of timely interventions which would target recuperation and facilitate adaptive processes, the National Institute for Health and Clinical Excellence (NICE, 2002) has recommended several forms of psychotherapeutic interventions that proved to be highly effective in the amelioration of symptoms (Anderson, 2004; Litz *et al.*, 2007).

Therapeutic horticulture

Presently, a rapid pace of urbanization may be noticed all around the world, with over half of the world's population living in urban areas (Bratman *et al.*, 2015). In many societies, urbanization, resource exploitation and lifestyle changes have diminished the number of possibilities for humans to maintain contact with nature. Therapeutic horticulture activities were conceived to be person-centred in order to achieve evidence-based approaches in practice (Bragg and Atkins, 2016).

But, the two notions as Horticultural Therapy and Therapeutic Horticulture are often used interchangeably. The differences between them are that the Horticultural Therapy (HT) is centred on a specific person needs and implemented by trained therapists (Gonzalez *et al.*, 2009), while Therapeutic Horticulture (TH) is a more open program defined as "a process that uses plant-related activities through which participants strive to improve their well-being through active or passive involvement" (Sempik *et al.*, 2003; Gonzalez *et al.*, 2009; Kam and Siu, 2010; Adevi and Mårtensson, 2013).

Studies reported strong evidence of restorative benefits by using nature as an alternative form of therapy (Hartig *et al.*, 2014). Gardening was considered as the second most

common and most popular outdoor activity among adults, older than 65 years (Sommerfeld *et al.*, 2010). It may be considered part of a nature-based active horticulture therapy schedule, like as seeding and planting (Gonzalez *et al.*, 2010; Kamioka *et al.*, 2014), maintenance of green space (Gonzalez *et al.*, 2009, 2011; Kam and Siu, 2010; Vujcic *et al.*, 2017) and indoor ornamental plants (Kamioka *et al.*, 2014).

A plethora of research indicates the existence of a significant relationship between the emergence of mental disorders and exposure to natural environments, highlighting the benefits of nature-based activities (e.g., gardening) on the physical, social, emotional and cognitive functioning (Ulrich, 1993; Frumkin, 2001; Patel *et al.*, 2007; Annerstedt and Währborg, 2011). More specifically, less exposure to nature facilitates the development of different mental and emotional dysfunctions (Marsella, 1998; Annerstedt *et al.*, 2010). Individuals residing in urban areas were found to be 38% more likely to develop a mental illness, 21% more likely to suffer from anxiety and 39% more likely to develop a mood disorder than those living in rural areas (Wood *et al.*, 2016). Briefly put, access to less green spaces may contribute to the experience of higher levels of stress (Roe *et al.*, 2013).

These findings get serious implications if we consider that by 2050 urbanization will exceed 70% (Bratman *et al.*, 2015). Traditionally, gardening activities are associated with the amelioration of stress symptoms, inducing mood relaxation and recovery from everyday tasks (van den Berg and Custers, 2011). Recently, research based on experimental studies indicate the existence of beneficial effects of activities conducted in nature, reducing self-reported anger, fatigue (Hartig *et al.*, 2014), anxiety (Rodiek, 2002; Lee *et al.*, 2004; Stepney and Davis, 2005; Kam and Siu, 2010; Song *et al.*, 2010; Hartig *et al.*, 2014), stress (Kam and Siu, 2010; van den Berg *et al.*, 2010; Gonzalez *et al.*, 2011; Hawkins *et al.*, 2011) and depression (Son *et al.*, 2004; Wichrowski *et al.*, 2005; Gonzalez *et al.*, 2009; Min *et al.*, 2014; Ghanbari *et al.*, 2015; Wood *et al.*, 2016).

In mental illnesses, depression may be correlated with an imbalance in the kynurenine (KYN) pathway (Wurfel *et al.*, 2017). Evidence-based research suggests that the KYN pathway may be implicated in the pathophysiology of depression. Réus highlights the importance of the kynurenine pathway according to depression, based on the results obtained by clinical and preclinical studies (Réus *et al.*, 2015). Based on the tryptophan metabolic pathway, kynurenine is generated by the tryptophan degradation, one of the precursors of serotonin (Ogyu *et al.*, 2018), which can be a start to future research into alternative treatments for depression. Almost 99% of tryptophan contribution is transformed in the liver into kynurenine and kynurenic acid (Reus *et al.*, 2015).

The major objective of the present pioneering study was to investigate the possible effect of a Therapeutic Horticulture intervention on people in depression amelioration.

Materials and Methods

Method design and participants

The present study was an experimental research based on pre- and post-test assessments, conducted among randomly selected volunteer subjects at University of Agricultural Sciences and Veterinary Medicine Cluj-Napoca, Romania.

Hypothesis 1: it was intended to decrease the level of depression for the volunteer involved in Therapeutic Horticulture Intervention, measured with the Beck Depression Inventory, using BDI_T1 for the date collected before therapeutic horticulture investigation, and BDI_T2 after the last session.

Hypothesis 2: the expect results of the changes in the kynurenine pathway after the Therapeutic Horticulture Intervention the levels of depression measured through contribution of kynurenine and kynurenic acid to change significantly, based on the contribution of kynurenine (KYN_T1) and kynurenic acid (KYNA_T1) before and after (KYN_T2, KYNA_T2) Therapeutic Horticulture Intervention.

Moreover, the study was conducted by measuring depression both on the subjective and the objective levels, in order to obtain more relevant information regarding the real change in depression levels. Consequently, the investigation of depression level was assessed with the Beck Depression Inventory (BDI) and doubled the obtained data by assessing the levels of biomarkers - kynurenine and kynurenic acid contribution obtained from biological samples (urine). We chose to investigate in a non-invasive way, the kynurenine and kynurenic acid levels based on the other research results which indicates that changes in these indicators may be related to changes in the levels of depressions.

In the first stage of the study were randomly selected an assessed 85 volunteer subjects with the Beck Depression Inventory questionnaire (BDI score) made by Beck (Beck and Steer, 1987). Thirty minutes after the distribution, the questionnaires were collected and coded. The age of the 85 participants (37 men, 48 women) ranged from 19 to 32 years ($M = 21.1$ years), 72% attaining BDI scores ≤ 10 ; the rest attaining BDI scores was above 10. From the questioned participants ($N = 24$) during the study, in the TH group were selected eight participants (1 man, 7 women) who attended 10 consecutive days (excepting Saturdays and Sundays). After completing the therapeutic horticulture sessions, biologic fluid - urine samples were collected by the participants and preserved in laboratory conditions (pre-post TH). All the participants who have done and finished the study declared that during the experimental period and until the post-test, none of them received any form of medical treatment, including also tryptophan.

Research setting

The study was part of a larger "green care and maintenance" program performed by subjects. For this research study, the University of Agricultural Sciences and Veterinary Medicine Cluj-Napoca green space was selected

and used to perform therapeutic horticultural based activities.

Procedures

It was conducted a 2-week Therapeutic Horticulture (TH) program in 10 consecutive days (including 2 days of break in one week-end). It included ordinary and easy gardening activities, both active and passive. The active parts of the program included sowing, potting, planting, composing beds, rooting herbs and pruning orchard and vineyard planting. Similar activities were effectuated by Gonzalez *et al.*, 2011. The passive parts included walking around, sitting on benches, watching birds, insects, butterflies, the weather and the landscape, activities use in other research studies (Kam and Siu, 2010; Cooper Marcus and Sachs, 2014; Vujcic *et al.*, 2017). Participations in the project implied attendance in the TH activities every day in four-hour group sessions.

Outcome measures

Severity of depression was measured with the BDI, a 21-item self-report questionnaire according to Beck Depression Inventory (Beck and Steer, 1987). The maximum score on the BDI accepted is 63 and the instrument further demonstrates good discrimination between patients with varying degrees of depression, and it accurately reflects changes in depression severity over time (Gonzalez *et al.*, 2011). Also, the participants of the research study were asked to bring urine sample (first urine in the morning, of the same day), at the first and last TH program activities. Each biological urine sample was processed in the Spectroscopy Laboratory of Life Sciences Institute, where were analysed the urinary biomarkers like tryptophan, tryptophan-related metabolites pathway concentration by high performance liquid chromatography with fluorimetric detection. Thus, our study was based on the research of Ogyu *et al.* (2018) which reported that the biological mechanisms underlying depression should be explored to lead to the development of a more effective treatment strategy for depression, abnormalities of the kynurenine (KYN) pathway may be implicated in the pathophysiology of this disease.

Beck depression inventory-II

Depressive tendencies were measured with the Beck Depression Inventory-II (BDI) used by Beck (Beck *et al.*, 1979; Romanian adaptation David and Dobrea, 2012). The BDI contain 21-item, multiple-choice format inventory, designed to measure the presence of depression in adults and adolescents. Each of the 21 items assesses a symptom or attitude specific to depression, inquiring its somatic, cognitive, mood and behavioural aspects. By its assessments, single scores are produced, which indicate the intensity of the depressive episode. Scores ranging from 0 to 9 represent normal levels of depression. Scores situated between 10 and 18 represent mild to moderate depression; values between 19 and 29 represent moderate to severe depression, while scores above the value of 30 represent severe depression. Internal consistency indices of the BDI are usually above 90.

Ethical considerations

The research study was approved by the Committee for Bioethics in University of Agricultural Sciences and Veterinary Medicine Cluj-Napoca, Romania. The volunteer subjects provided written informed consent, and they received printed information about the research study. All data were analysed in a confidential manner, without imparting private matters of the subjects involved.

Spectrofluorimetry analysis

The spectrofluorimetric analysis of urine from non-depressed and depressive patients was performed with a Jasco FP 8200 spectrofluorometer. It was analysed a quantity of 2 ml of urine without prior centrifugation. In order to obtain not only a proper emission for kynurenic acid (KYNA) and kynurenine (KYN), but also a good comparison between the collected urine samples, several excitation wavelengths (λ_{ex}) were used (330 and 380 nm). The emission spectra were recorded in a range of 345 to 750 nm, for KYNA and of 395 to 750 nm for KYN, with maximum of emission at 380 nm for KYNA and at 480 nm for KYN respectively as described in dedicated literature

(Lesniak *et al.*, 2013). The gathered spectra were further fitted with the Gaussian deconvolution algorithm as illustrated in Fig. 1 and 2, where can be seen a deconvolution example made on one of participants biological sample, collected before and after the TH intervention, using spectrofluorimetric analysis. The OriginPro Version 8.5.1 OriginLab Corporation, Northampton, MA, USA was used to analyse the fluorescence data in order to obtain the contribution of searched fluorophores to the total fluorescence of urine samples (KYN and KYNA).

Results

Based on the investigations made by measuring the effects of the therapeutic horticulture investigation, to achieve changes in the BDI score and contribution of the fluorophores in the kynurenine pathway, the evidence-based research reveals that TH can have a possible positive effect decreases in depression level. By measuring depression on both the subjective and the objective levels, it was obtained more relevant information regarding the real

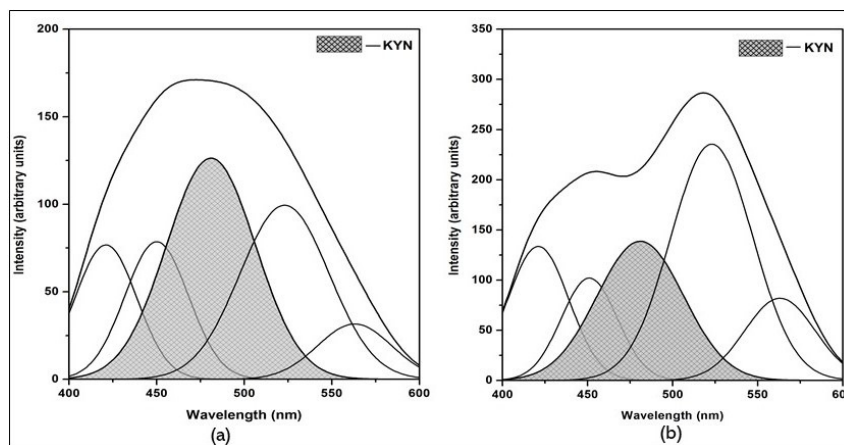


Fig. 1. The deconvoluted urine spectra of one subject collected before (a) and after (b) the therapeutic horticulture intervention, concerning the kynurenine contribution

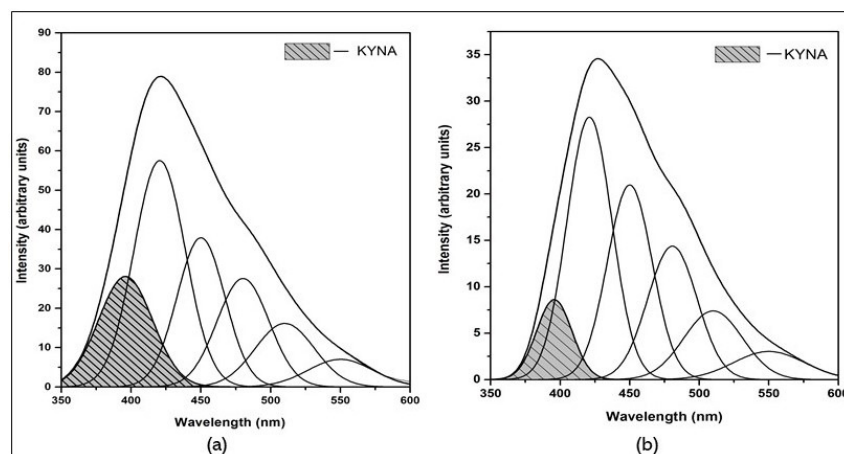


Fig. 2. The deconvoluted urine spectra of one subject collected before (a) and after (b) the therapeutic horticulture intervention, concerning the kynurenic acid contribution

Table 1. Descriptive statistics analysis according to the collected data during therapeutic horticulture intervention

Measure	Measurement point	Value			
		Min.	Max.	Mean	St. Dv.
BDI	T1	10.00	22.00	14.00	3.77
BDI	T2	5.00	11.00	7.87	2.41
KYN	T1	26.23	44.85	33.48	5.64
KYN	T2	24.11	40.11	33.27	4.83
KYNA	T1	7.88	31.07	20.60	7.26
KYNA	T2	12.90	26.64	18.02	4.72

Table 2. Pre and post-test differences in levels of depression (BDI, KYN, KYNA) during therapeutic horticulture intervention

	BDI _{T2} - BDI _{T1}	KYN _{T2} - KYN _{T1}	KYNA _{T2} - KYNA _{T1}
Z	-2.37*	-0.56	-0.98
p	0.018	0.575	0.327

change in depression levels. Consequently, depression was assessed with the Beck Depression Inventory (BDI) and doubled the obtained data by assessing the levels of kynurenine and kynurenic acid obtained from urine samples.

The investigation of the kynurenine and kynurenic acid levels with a non-invasive procedure is relevant based on the literature which indicates that changes in the contributions of these markers may be related to changes in the levels of depressions (Reus *et al.*, 2015; Ogyu *et al.*, 2018). Firstly, it was presented the descriptive characteristics of the data processed with SPSS 20.0 (Table 1).

According to the data obtained, the mean value of BDI score measured with the Beck Depression Inventory dropped off from 14.00 (mild to moderate depression) to 7.87 (normal levels of depression). Concerning the spectrofluorimetric analysis, it can be noticed that the contribution of either kynurenine (KYN) and kynurenic acid (KYNA) in the urine sample collected pre-test, and post-test, before and after Therapeutic Horticulture Intervention were lower. The obtain result are similarly as other research studies (Gabbay *et al.*, 2010; Raison *et al.*, 2010; Sublette *et al.*, 2011; Myint *et al.*, 2013; Savitz *et al.*, 2015). Previous similar studies noted by Ogyu *et al.*, 2018 showed an abnormal contribution of KYNA and QUIN,

relevant metabolites of KYN pathway, in subjects with depression.

Wilcoxon non-parametric t-test for 2 related samples was used consequently to the number of participants in the present experiment. The results obtained were presented in Table 2.

Obtained results indicate that only depression measured with the Beck Depression inventory has changed significantly [$Z = -2.37^*$, $p < 0.05$], decreasing from Mean T1 = 14.00 to Mean T2 = 7.87. The effect size ($r = 0.59$) of this decrease was calculated with the following formula: $r = Z/\sqrt{N}$ (where, N = number of participants * number of observations), which according to Cohen's (1988) classification is a large statistical effect.

Analysing the results, it may be observed that changes in the concentration of either kynurenine or kynurenic acid between the two assessments are not significant. The results indicated a decrease in the levels of kynurenine (T1_{mean} = 33.48, T2_{mean} = 33.27) and kynurenic acid contribution (T1_{mean} = 20.60, T2_{mean} = 18.02), however this change has not proved significant.

Continuing the investigation, it was noticed that most of the participants presented a pattern of depression symptoms decrease; moreover, depression dropped with a category of severity, from mild-moderate to normal (Fig. 3).

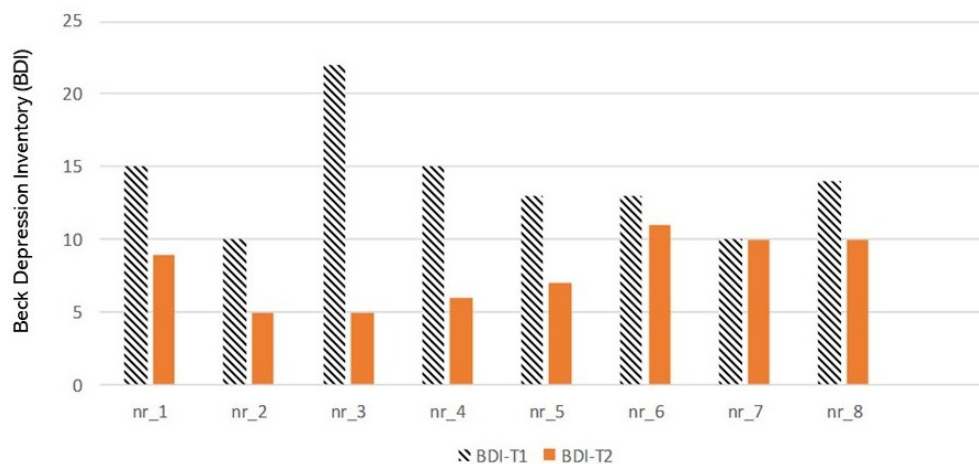


Fig. 3. Changes in BDI in individual cases of participants (BDI-T1, based on samples from the first day of the experiment; BDI-T2, based on samples from the last day of the experiment, after the TH)

Analysing the results can be concluded that in the case of participant no. 1 the depression level dropped from 15 to 9, in no. 2 from 10 to 5, in no. 3 from 22 to 5, in no. 4 from 15 to 4, no. 5 from 13 to 7, in no. 6 from 14 to 11, in no. 8 from 14 to 10 in the case of participant no. 7.

Discussion

The last four-five decades have witnessed an unprecedented increase in the number and the diversity of life-challenges. The number of those who cannot adequately adapt to these constant changes, and who suffers of mental illness of clinical intensity has been constantly increasing along the years, depression being one of the most frequently encountered mental illnesses (Andrade *et al.*, 2003; Cuijpers *et al.*, 2007; Cunningham *et al.*, 2006; Weehuizen, 2008). Under these conditions, a very important mission of research and practice in mental-health care becomes the investigation of treatment methods, which are more accessible and cost-effective than traditional ones (Kazantzis and L'Abate, 2007). A relatively accessible, cost effective form of intervention is Horticulture Therapy (HT, or Therapeutic Horticulture, used interchangeably), which has received increased attention along the years, due to its relative simplicity and effectiveness.

The scientific results conclude that analysing the kynurenine pathway after the tryptophan degradation, the changes can be implicated in the inflammation process in the major depressive disorder (MDD). Based on the connection between tryptophan degradation, MDD and inflammatory mediators can be a purpose for antidepressant therapies (Dantzer *et al.*, 2011; Zheng *et al.*, 2013; Bay-Richter *et al.*, 2015). Latest research studies indicate that kynurenine pathway can be a biomarker to evidence neurological diseases (Fujigaki *et al.*, 2017). Different contribution of kynurenine can be involved in depression. More research is needed to highlight the connection between depression and each metabolite of the KYN pathway (Ogyu *et al.*, 2018).

The main findings of the present study indicate that the levels of depression measured with the BDI have significantly decreased after the Therapeutic Horticulture Interventions. An even better result regards the fact that the significance of this change was not only statistical, but also clinical, since most of the participants felt from a higher depression category into a lower one, as established by cut-points. No significant change during and after a 10-day Therapeutic Horticulture session was achieved in the kynurenine pathway.

Possible reasons for this finding may be (the short interval, the implication of the participants, the personal and subjective factors or metabolism), while this research did not analyse the participants diet during the TH intervention. However, while there was no significant difference in kynurenine and kynurenic acid contribution (Myint *et al.*, 2007), further research is clearly needed (Reus *et al.*, 2015; Ogyu *et al.*, 2018).

In the scientific literature, for the sample preparation were used different fluids to analyse the kynurenine pathway (KYNA, QUIN or KYN) in blood (serum and plasma), urine, cerebrospinal fluid (CSF) and brain tissue

samples. Using the listed biofluids, results obtained at subjects with depression in comparison with HCs. Namely, the kynurenine contribution was expected to significantly increase (Myint *et al.*, 2007; Raison *et al.*, 2010; Hennings *et al.*, 2013; Quak *et al.*, 2014; Nikkheslat *et al.*, 2015; Hu *et al.*, 2016; Veen *et al.*, 2016; Krause *et al.*, 2017), and the levels of kynurenic acid to increase (Myint *et al.*, 2007; Maes *et al.*, 2011; Bay-Richter *et al.*, 2015; Nikkheslat *et al.*, 2015; Schwieler *et al.*, 2015; Young *et al.*, 2016).

The partial conformation of the results may be due to several limitations of the hereby experiment: (i) the number of participants has been relatively low (Gigliotti *et al.*, 2004; Rodiek *et al.*, 2008); however, in this domain many studies did not include a control group; (ii) the QUIN levels in urine was not investigated in the present study, which may be more directly linked to changes in biomarker kynurenine pathway (Reus *et al.*, 2015; Ogyu *et al.*, 2018). As for future directions, the authors intend to increase the number of participants, to include a control group and to use as objective marker of depression the QUIN levels.

Conclusions

The obtained results indicated that the levels of depression measured with the BDI have significantly decreased after the Therapeutic Horticulture Interventions, the effect size of this decrease being quite large at the volunteer subjects. An even better result regards the fact that the significance of this change was not only statistical, but also clinical. Based on the biological biomarkers analysis of kynurenine and kynurenic acid contributions, differences were observed, but even though results did not indicate statistical changes. Therapeutic Horticulture Interventions is a possible alternative therapy to increase people well-being measured by a non-invasive method.

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Conflicts of interest

The authors declare that there are no conflicts of interest related to this article.

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