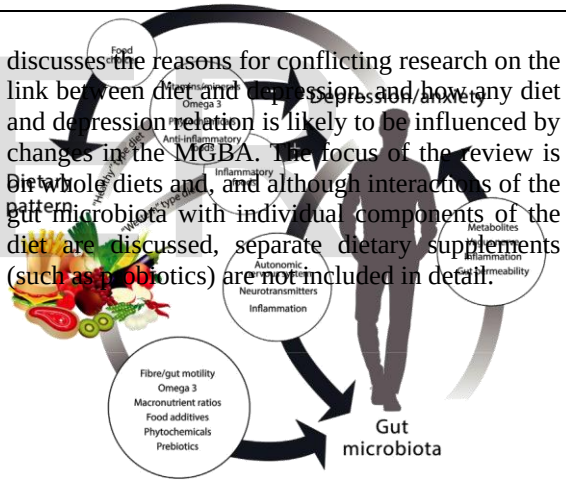
The Purpose of The Gut Microbiota in Nutritional Interventions for Depression and Anxiet

Dr. Namra Hanif

Abstract-- There is growing evidence that unhealthy diets can increase the risk of depression or anxiety, while healthy diets can reduce it. Recent research suggests that dietary interventions can help prevent stress and anxiety. However, this relationship is complex, set by a number of confusing variables and can even be bilateral, while food choices are also fraught with stress and depression. This complexity is reflected in statistics, sometimes with contradictory results between studies. As research progresses, we need to consider all aspects of the relationship to ensure that we have a full understanding that could be translated into clinical practice. A parallel and rapidly growing research group shows that the intestinal microbiota is in a two-way relationship with the brain, often called the brain axis of the intestinal microbiome. Evidence suggests that this axis plays a key role in regulating brain functions and behavior. In this review, we discuss the possible causes of the contradictory consequences of eating temperament - mood research and updated examples of current nutritional areas related to mood that could involve diet-induced intestinal microbiota. Explain the conflicting results. The study of depression. This review examines the complex interactions between the gut microbiota, nutrition, and health.

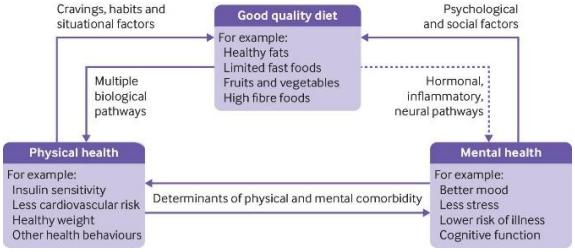
Keywords--*microbiome–gut–brain axis, depression, anxiety, mood, mental health, nutritional psychiatry, microbiota, diet, nutrition*

Introduction: Around 20–25% of people will experience mental health disorders such as a depressive episode or anxiety disorder in their lifetime (1, 2), and anxiety and depression are ranked in the top 10 causes of the global burden of disease (3, 4). Unfortunately, our understanding of these disorders and ability to effectively treat them are poor; for example, ~30%–40% of those with depression do not adequately respond to pharmacological or psychological treatment (5). The high impact on individual quality of life, as well as on the public health system, means that preventing and treating anxiety and depression is a global priority. Consequently, there has been a call for a broader research approach with more interdisciplinary efforts (6, 7). Recent approaches in depression and anxiety research are investigating 1) the links between diet and mood, and 2) the influence of gut microbiota on neurobiology and behavior, termed the microbiome–gut–brain axis (MGBA). There is emerging evidence showing a strong influence of both diet and gut microbiota on emotional behavior and neurological processes, and because the gut microbiota is strongly affected by diet (8), these 2 factors are also intertwined (Figure 1). With increasing understanding of the mechanisms involved in the complex interplay between diet and the gut microbiome and its impact on anxiety/depression, specific dietary patterns that can help prevent anxiety and mood disorders can be identified. In addition, the use of dietary intervention may prove to be an attractive and cost-effective alternative or adjuvant therapy to clinically treat these disorders. This review discusses the reasons for conflicting research on the link between diet and depression, and how any diet and depression relation is likely to be influenced by changes in the MGBA. The focus of the review is on whole diets and, and although interactions of the gut microbiota with individual components of the diet are discussed, separate dietary supplements (such as probiotics) are not included in detail.



The relation between diet and depression: Research shows that there is a relation between diet and depression; however, there are conflicting results from studies and the directionality and mechanism of the relation are currently unclear. Many correlative studies in healthy adults show that a lower incidence of depression occurs in those who eat according to "healthy" dietary patterns,

characterized by an abundance of vegetables, fruits, cereals, nuts, seeds, and pulses, as well as moderate amounts of dairy, eggs, and fish and unsaturated fats (9), including the Mediterranean diet (10, 11), Japanese diet (12, 13), and Norwegian diet (14). In contrast, a "Western" dietary pattern, consisting of sweet and fatty foods, refined grains, fried and processed foods, red meat, high-fat dairy products, and low fruit and vegetable intake, is associated with higher depression incidence (10, 15, 16). However, not all studies show an association, with many finding no association (17–20) or showing an effect only from a specific food [e.g., tomatoes (18)]. Conflicting results from studies are potentially due to many factors. There is possible recall bias due to the use of FFQs, and difficulty in controlling for all confounding variables (21). The recall bias has not been addressed and may be a specific problem for assessing diet and depression, because depression can affect memory (22). Participant and researcher expectation bias is another issue in randomized controlled trials. Because the variables being measured rely on participant reporting, blinding is important to prevent expectation bias. However, blinding of the participants to the hypothesis is difficult. Dieticians/nutritionists and psychologists who deliver the separate arms of the trial should also be blinded as to the study hypothesis, but in practice this is rarely done. Reverse causality is possible. Stress and depression can also alter taste thresholds (23), perception of sugary and fatty foods (24, 25), and food choices (26–28). A 10-y longitudinal study in France showed an association between depression incidence and poor diet, but found that there was probably reverse causality, with depression increasing the risk of poor eating behaviors (29). A reanalysis of a longitudinal study in Australia showed that those with an existing depressive episode had a poorer diet, but not those with only historical depression (30). The authors suggest that this could be due to reverse causality, but alternatively could be due to altered dietary habits after depression treatment in order to prevent depression recurrence, an interpretation that is supported by a study showing that 20% of people with depression intentionally improve their diet (31). An understudied aspect in the diet–depression relation which could explain some of the inconsistencies is the diet– microbiota–mood relation. Emerging evidence shows that the gut microbiota is linked to emotional behaviors thought to represent symptoms of both depression and anxiety, and because the gut microbiota is highly influenced by diet, diet can influence this relation.



The link between the gut microbiota, depression, and anxiety: Research into the MGBA began with the observation that there is a high comorbidity of anxiety and depression in those with inflammatory bowel disease (79, 80) and irritable bowel syndrome (79–82). In addition, gut microbiota composition in individuals with anxiety or depression (including those in remission) differs from that in healthy controls (83–85), and animal models of depression show altered gut microbiota compared with controls (46). Early studies in mice showed that gut infections or chemically induced colitis caused an increase in patterns of behavior thought to represent anxiety, including decreased exploration (86) and increased behavioral inhibition (87, 88). The direct effect of gut microbiota on emotional behaviors was shown in studies which identified that anxiety-like behaviors differ between germ-free (GF) rats and mice (born and raised in a microbiota-free environment) and animals with normal, specific pathogen–free (SPF) gut microbiota (89–92). Colonization of GF animals with SPF gut microbiota has been shown to ameliorate the behavioral differences (90, 92, 93). Fecal transplants from anxious-type mice into a more resilient strain increase anxiety-like behaviors in the resilient strain, and vice versa (94). Probiotic supplementation has also shown promise, with a reduction in anxiety and depression reported in many human and animal studies (95–99). Probiotics seem to also be protective against the development of anxiety due to gut infection (88) and immunodeficiency (100).

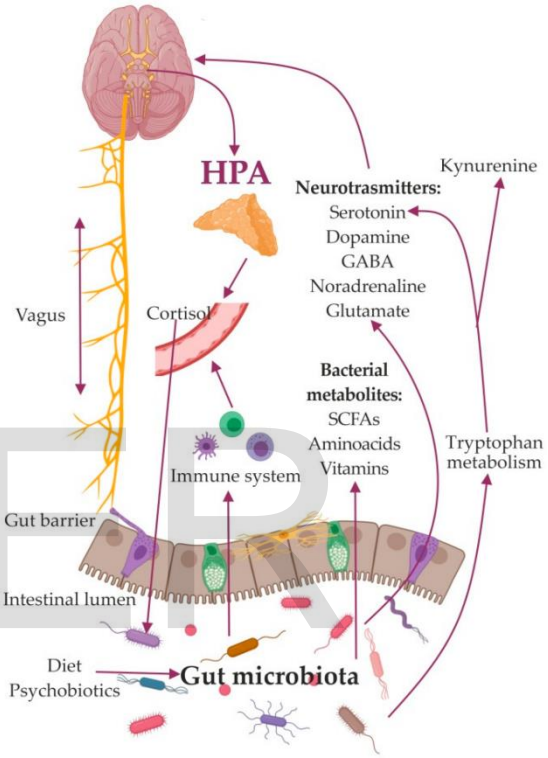
Changes in gut microbiota with depression and anxiety: The MGBA findings of behavioral effects with probiotic or inflammatory bacteria broadly fit with the microbial profiles associated with positive or negative mental health, although there is no specific gut microbiota composition profile linked to anxiety or depression. Comparisons of microbial changes in humans with depression show a variety of changes compared with healthy controls but show a general pattern of increases in potentially harmful and inflammatory bacteria such as Proteobacteria, which are normally minor in relative abundance, alongside a decrease in commensal bacteria, which are normally more abundant (83, 84, 113, 143– 145). In those with Generalized Anxiety Disorder, fewer changes were

found but a similar reduction in commensal bacteria was seen (85). The lack of an identified depression or anxiety "gut microbiota profile" is likely to be due to variation in the methods used to evaluate gut microbiota composition and gene abundance, and individual variation in the human gut microbiota (146). Although there are still many unknowns relating to the MGBA and its mechanisms, the emerging evidence, combined with the effect of diet on microbiota, supports its important role in the diet–mood relation.

Interactions of Diet with the MGBA

Whole diet: There is a paucity of research measuring the effects of whole diet on microbiota as well as depressive symptoms, and studies on diet and anxiety in humans are still needed. However, dietary patterns associated with a risk of depression are in line with changes in microbial composition and functions, which MGBA research shows can affect emotional behavior in rodents. Adherence to the Mediterranean diet reduces the numbers of inflammatory/pathogenic bacteria such as Escherichia coli, and increases key commensal bacte-ria such as Bifidobacteria (147), Clostridium cluster XVIa, and Faecalibacterium prausnitzii (148). It also increases microbial metabolites including fecal SCFA concentrations (149), phe-nolic metabolites, benzoic acid, and 3-hydroxyphenylacetic acid (148). Vegetarian or entirely plant-based diets have been shown to alter microbial composition (150–152) and reduce gut inflammation (150). A dietary pattern defined by fast-food consumption reduced Lactobacilli (149). A high-fat/low-carbohydrate diet, regardless of the type of fat, decreases total bacteria (153). Many of the individual dietary elements that are asso-ciated with an increased or decreased risk of developing depression also alter the gut microbiota (refer to Table 1). It is plausible that the effect of a dietary component on the gut microbiota may partially or wholly mediate the effect of that dietary component on mood.

Prebiotic foods: A "healthy" dietary pattern contains a larger amount of fruit, vegetables, and wholegrains, which contain prebiotics such as fermentable carbohydrates, polyols, and phytochemicals (208). Prebiotic compounds selectively promote the growth and microbial activity of beneficial bacteria and confer positive health outcomes (208). The higher prebiotic content characteristic of healthy diets may be why the association of depression with diet is stronger for healthy dietary patterns and more variable for poor dietary patterns (9, 32, 157). Prebiotic compounds typically have been shown to increase concentrations of Bifidobacteria and Lactobacillus but as microbial research techniques have become more sophisticated, we now understand that there are many other beneficial bacteria that are promoted with prebiotics, such as butyrate-producing bacteria. Some dietary fibers are considered prebiotic but not all. Dietary fiber that promotes the growth of all gut bacteria is not considered a prebiotic because numbers of pathogenic bacteria are also increased (208). The most well-researched prebiotics are the soluble fibers "fructans" [fructooligosaccharides (FOSs) and inulin] and galactans [galactooligosaccharides (GOSs)]. Mannanoligosaccharides and xylooligosaccharides are also considered prebiotic.

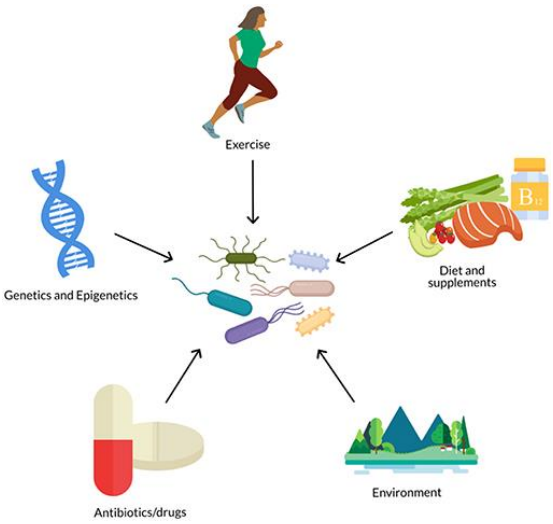


Phenolics and phytochemicals show prebiotic effects, although some of the health benefits may be from microbially produced secondary metabolites. Conjugated linoleic acid (18:2n–6) and PUFAs are also considered candidate prebiotics (208). The biological activity of many phytochemicals has been shown to have possible positive health ef fects, including antidepressant-like or anxiolytic effects (70) and a prebiotic effect (213). The actions of phytochemicals may also be due to secondary metabolites created by microbial utilization (213). Research examining the effect of phytochemicals on both mood and microbiota is lacking.

Macronutrients: A large driver of the effect of diet on the composition of the gut microbiota is variation in macronutrient ratios, amounts, and types. Carbohydrate fermentation tends to increase overall microbial fermentation and SCFA production. The amount of fermentation depends on how much reaches the colon, which is

influenced by the amount and type of dietary fiber and prebiotic carbohydrates (214). A plant-rich diet promotes the phylum Bacteroidetes, specifically the genera Prevotella and Xylanibacter, which ferment plant fiber. Some evidence for an effect of macronutrient intake on emotional behavior has been found in rodent studies, mostly with an HFD. Increased anxiety-like behavior has been found in mice fed an HFD comprising 60% kcal unspecified unsaturated FAs (225), 58% kcal hydrogenated coconut oil (226), or 45% kcal lard and soybean oil (227), compared with control diets of ~10% kcal fat. Decreased anxiety-like behaviors have also been found with an HFD (Crisco and corn oil, 90% kcal), compared with a diet high in protein (90% kcal) or carbohydrate (90% kcal), which did not alter these behaviors (228). Another study found no change in anxiety-like behaviors with an HFD (60% kcal), but did find alterations in memory, and also found decreased anxiety-like behaviors with a high-sucrose diet (70% kcal) (202). Support for the role of the gut microbiota as a mediator of any behavioral changes with an HFD comes from a study where a fecal transplant from mice fed an HFD (60% kcal fat) into mice with antibiotic-depleted microbiota (fed a normal diet, 13% kcal fat) increased anxiety-like behaviors (229).

Food additives: Western diets include a high proportion of processed foods containing food additives to improve attributes such as shelf life, texture, and palatability. Studies in mice showed that emulsifiers can alter the gut microbiota composition (234, 205), increase the proinflammatory potential of the gut microbiota (234), increase microbiota infiltration of the gut mucosa layer (234), and alter anxiety-like behavior (205). Salt is another food additive that tends to be in high concentration in processed foods and Seck et al.



(235) found that high fecal salinity alters gut microbe composition, including a decrease in the beneficial bacteria Akkermansia muciniphila and Bifidobacterium spp., specifically B. longum and B. adolescentis. Maltodextrin reduces mucus production and increases gut inflammation by increasing endoplasmic reticulum stress (236). The links between a Western diet and depression may include an effect of food additives on the gut microbiota. Evidence from human studies is needed.

Other considerations: Fermented foods typically contain strains of Lactobacillus as well as yeasts, and are likely to be important because they contain both probiotic microbiota and microbial metabolites. Most studies investigating the effect of fermented foods on the gut microbiota or mood have been undertaken using commercially produced yoghurts with very specific microbiota and fall more into the category of supplements than diet, so are not discussed here. However, there is huge scope for research into fermented drinks such as wine and kombucha, or foods such as breads, sauerkraut, kimchi, and yoghurt, and their effect on the gut microbiota and mood. There is some evidence that altered gut motility may be associated with mood (250) and that the gut microbiota composition is altered by changes in motility and vice versa (251). Foods that directly affect factors such as gut motility, e.g., those containing soluble or insoluble fiber, may also be able to affect mood by correcting problems with motility, which could be a confounding variable or could be related to changes in the gut microbiota. More research in this area is needed, and it would be useful for food intervention studies to measure changes in gut function concurrently with assessing changes in mood. Other cofactors usually considered in depression research, such as exercise and sleep, also have independent impacts on microbiota (252, 253) and should be considered when assessing relations between foods, mood, and the microbiome.

Conclusions: Research shows that there is a link between diet and depression, but conflicting results and limited research mean that we do not yet understand the nature of the relation. There is likely to be a bidirectional relation and it may be of more importance in vulnerable individuals. Because diet is a large influencer of the gut microbiota composition and function, it is likely that changes in the gut microbiota contribute to how diet (whole diet and individual components of diet) may affect depression and anxiety. Limited research in this area is sometimes contradictory and mostly in rodents but does show a pattern of results indicating that the gut microbiota may play a significant role and should be considered in dietary

intervention studies. Dietary patterns for positive mental health will likely support the growth of commensal microbiota, decrease the growth of pathogenic and colitis-inducing bacteria, and affect gut barrier permeability and inflammation. In addition, because a change in whole dietary patterns changes the ratio of many dietary components, investigation into these individual components is also impor-tant. In dietary studies for depression and anxiety, types and amounts of dietary components (e.g., fat, prebiotics) within the dietary patterns should be identified.

Although examining the changes in microbial profile is interesting, it is important to remember that it is the collective function and characteristics of the gut microbiota that interact with the host, and that >1 microbe can occupy a particular ecological niche within their environment. Therefore, similar functions can be carried out by different microbiota structures and the same functional outcome could occur with different changes in microbiota. This par-ticularly supports food as an effective intervention, because it can shift the microbial profile at all taxonomic levels and may also affect composition and function separately. The type and strength of the effect of diet on the gut microbiota will be determined by existing microbiota composition and function and the host phenotype, including interactions with immune function. Research needs to include examination of the gut microbiota function as well, using metabolomics and/or metagenomics techniques.

Research, in both humans and animals, into mecha-nisms of the MGBA will continue to help to elucidate the mechanisms by which the gut microbiota affect depression and anxiety symptoms, as well as other psychological and neurological effects. Food interventions have the dual benefit of a direct impact on gut and brain physiology and an indirect effect via the gut microbiota. With continued research investigating these aspects of the MGBA, we will further our understanding and make advances in obtaining a well-understood and well-guided holistic approach to treating and preventing anxiety and depression.

References

1.Somers JM, Goldner EM, Waraich P, Hsu L. Prevalence and incidence studies of anxiety disorders: a systematic review of the literature. Can J Psychiatry 2006;51(2):100–13.

2.Lépine J-P, Briley M. The increasing burden of depression. Neuropsychiatr Dis Treat 2011;7(Suppl 1):3–7.

3.Baxter AJ, Vos T, Scott KM, Ferrari AJ, Whiteford HA. The global burden of anxiety disorders in 2010. Psychol Med 2014;44(11):2363–74.

4.World Health Organization. Depression fact sheet [Internet]. Geneva: World Health Organization; 2016. [Accessed 2019 Jan 13]. Available from: www.who.int/mediacentre/factsheets/fs369/en/.

5.DeRubeis RJ, Siegle GJ, Hollon SD. Cognitive therapy versus medication for depressions: treatment outcomes and neural mechanisms. Nat Rev Neurosci 2008;9(10):788–96.

6.Marquez PV, Saxena S. Making mental health a global priority. Cerebrum 2016:cer–10-16.

7.McLaughlin KA. The public health impact of major depression: a call for interdisciplinary prevention efforts. Prev Sci 2011;12(4):361–71.

8.Oriach CS, Robertson RC, Stanton C, Cryan JF, Dinan TG. Food for thought: the role of nutrition in the microbiota-gut–brain axis. Clin Nutr Exp 2016;6:25–38.

9.Lai JS, Hiles S, Bisquera A, Hure AJ, McEvoy M, Attia J. A systematic review and meta-analysis of dietary patterns and depression in community-dwelling adults. Am J Clin Nutr 2014;99(1):181–97.

10.Ford PA, Jaceldo-Siegl K, Lee JW, Youngberg W, Tonstad S. Intake of Mediterranean foods associated with positive affect and low negative affect. J Psychosom Res 2013;74(2):142–8.

11.Crichton GE, Bryan J, Hodgson JM, Murphy KJ. Mediterranean diet adherence and self-reported psychological functioning in an Australian sample. Appetite 2013;70:53–9.

12.Suzuki T, Miyaki K, Tsutsumi A, Hashimoto H, Kawakami N, Takahashi M, Shimazu A, Inoue A, Kurioka S, Kakehashi M, et al. Japanese dietary pattern consistently relates to low depressive symptoms and it is modified by job strain and worksite supports. J Affect Disord 2013;150(2):490–8.

13.Nanri A, Kimura Y, Matsushita Y, Ohta M, Sato M, Mishima N, Sasaki S, Mizoue T. Dietary patterns and depressive symptoms among Japanese men and women. Eur J Clin Nutr 2010;64(8):832–9.

14.Jacka FN, Mykletun A, Berk M, Bjelland I, Tell GS. The association between habitual diet quality and the common mental disorders in community-

dwelling adults: the Hordaland Health study. Psychosom Med 2011;73(6):483–90.

15.Ruusunen A, Lehto SM, Mursu J, Tolmunen T, Tuomainen TP, Kauhanen J. Dietary patterns are associated with the prevalence of elevated depressive symptoms and the risk of getting a hospital discharge diagnosis of depression in middle-aged or older Finnish men. J Affect Disord 2014;159:1–6.

16.Akbaraly TN, Brunner EJ, Ferrie JE, Marmot MG, Kivimaki M, Singh-Manoux A. Dietary pattern and depressive symptoms in middle age. Br J Psychiatry 2009;195(5):408–13.

17.Sugawara N, Yasui-Furukori N, Tsuchimine S, Kaneda A, Tsuruga K, Iwane K, Okubo N, Takahashi I, Kaneko S. No association between dietary patterns and depressive symptoms among a community-dwelling population in Japan. Ann Gen Psychiatry 2012;11(1):24.

18.Niu K, Guo H, Kakizaki M, Cui Y, Ohmori-Matsuda K, Guan L, Hozawa A, Kuriyama S, Tsuboya T, Ohrui T, et al. A tomato-rich diet is related to depressive symptoms among an elderly population aged 70 years and over: a population-based, cross-sectional analysis. J Affect Disord 2013;144(1–2):165–70.

19.O'Neil A, Quirk SE, Housden S, Brennan SL, Williams LJ, Pasco JA, Berk M, Jacka FN. Relationship between diet and mental health in children and adolescents: a systematic review. Am J Public Health 2014;104(10):e31–42.

20. Chocano-Bedoya PO, O'Reilly EJ, Lucas M, Mirzaei F, Okereke OI, Fung TT, Hu FB, Ascherio A. Prospective study on long-term dietary patterns and incident depression in middle-aged and older women. Am J Clin Nutr 2013;98(3):813–20.

21. Sanchez-Villegas A, Martínez-González MA. Diet, a new target to prevent depression? BMC Med 2013;11:3.

22. Burt DB, Zembar MJ, Niederehe G. Depression and memory impairment: a meta-analysis of the association, its pattern, and specificity. Psych Bull 1995;117(2):285–305.

23. Heath TP, Melichar JK, Nutt DJ, Donaldson LF. Human taste thresholds are modulated by serotonin and noradrenaline. J Neurosci 2006;26(49):12664–71.

24.Platte P, Herbert C, Pauli P, Breslin PA. Oral perceptions of fat and taste stimuli are modulated by affect and mood induction. PLoS One 2013;8(6):e65006.

25.Noel C, Dando R. The ef fect of emotional state on taste perception. Appetite 2015;95:89–95.

26.Ouwens MA, van Strien T, van Leeuwe JFJ. Possible pathways between depression, emotional and external eating. A structural equation model. Appetite 2009;53(2):245–8.

27. Frost RO, Goolkasian GA, Ely RJ, Blanchard FA. Depression, restraint and eating behavior. Behav Res Ther 1982;20(2):113–21.

28.Le Port A, Gueguen A, Kesse-Guyot E, Melchior M, Lemogne C, Nabi H, Goldberg M, Zins M, Czernichow S. Association between dietary patterns and depressive symptoms over time: a 10-year follow-up study of the GAZEL cohort. PLoS One 2012;7(12):e51593.

30. Miller AH, Maletic V, Raison CL. Inflammation and its discontents: the role of cytokines in the pathophysiology of major depression. Biol Psychiatr 2009;65(9):732–41.

31. Pirotta M, Densley K, Forsdike K, Carter M, Gunn J. St John's wort use in Australian general practice patients with depressive symptoms: their characteristics and use of other health services. BMC Complement Altern Med 2014;14(1):204.

32. Molendijk M, Molero P, Ortuño Sánchez-Pedreño F, Van der Does W, Angel Martínez-González M. Diet quality and depression risk: a systematic review and dose-response meta-analysis of prospective studies. J Affect Disord 2018;226:346–54.