The effects of polyphenols found in a Mediterranean diet on the symptoms of depression: A systematic literature review

Jessica Bayes[a], Dr Janet Schloss[b] and Prof David Sibbritt[a]

[a] Australian Research Centre in Complementary and Integrative Medicine, Faculty of Health, University of Technology Sydney, 35 Jones Street, Ultimo 2007

[b] Office of Research, Endeavour College of Natural Health, 2/269 Wickham St, Brisbane City, QLD, 4006, Australia

Corresponding author details: Jessica Bayes

Email: Jessica.bayes@yahoo.com

Phone: 0401962947

JB would like to acknowledge the support of the Australian Government Research Training Program Scholarship. No conflicts of interest.

Dr Janet Schloss

Email: janet.schloss@endeavour.edu.au

No financial support to declare and no conflict of interest

Prof David Sibbritt

Email: david.sibbritt@uts.edu.au

No financial support to declare and no conflict of interest

The review is registered with PROSPERO: CRD42019125747

Word count: 7278

Figures: 0 Supplementary figures: 1

Tables: 4 Supplementary tables: 2

List of Abbreviations: HADS – Hospital anxiety and depression score; DASS - Depression, anxiety, stress scale; ZSDS - Zung Self Rating Depression Scale; HAM-D - Hamilton Rating Scale for Depression; BDI - Becks Depression Inventory

Running Title: Effect of Polyphenols on symptoms of depression

Conflicts of Interest: None

Supplemental Figure 1 and Table 1 and 2 is available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/advances.

ABSTRACT

Depression is a mood disorder which currently effects 350 million individuals worldwide. Recently, research has suggested a protective role of diet for depression. The Mediterranean style dietary pattern has been highlighted in several systematic reviews as a promising candidate for reducing depressive symptoms. It has been speculated that this could be due to the high polyphenol content of foods commonly found in the diet. Therefore, the aim of this review was to assess the effects of polyphenols found in a Mediterranean diet on the symptoms of depression. A systematic literature review was conducted of original research which assessed the role of polyphenols on the symptoms of depression in humans. The following databases were searched: PROQUEST, SCOPUS (Elsevier), MEDLINE (EBSCO), CINAHL, and EMBase up to the 18th February 2019. The inclusion criteria consisted of both observational and experimental research in adults aged 18-80 and assessed depression scores in relation to polyphenol intake. A total of 37 studies out of 12084 met the full inclusion criteria. Of these, 17 were experimental studies and twenty were observational studies. Several different polyphenols were assessed including those from tea, coffee, citrus, nuts, soy, grapes, legumes and spices. Twenty-nine of the studies found a statistically significant effect of polyphenols for depression. This review has found both an association between polyphenol consumption and depression risk, as well as evidence suggesting polyphenols can

effectively alleviate depressive symptoms. The review uncovered gaps in the literature regarding the role of polyphenols for depressive symptoms in both young adults and men.

Keywords: Polyphenols; phytochemicals; flavonoids; depression; major depressive disorder; mental health

INTRODUCTION & BACKGROUND

Depression is a mood disorder characterised by anhedonia or lack of pleasure, a depressed mood and altered cognitive function (1). Currently, 350 million individuals suffer from depression globally (2) with the World Health Organisation (WHO) estimating that mental health conditions are now the leading cause of disability worldwide (3). Although the exact aetiology of depression is still unknown, several similarities exist between depression and inflammatory diseases such as cardiovascular disease (CVD), diabetes and cancer which include reduced insulin sensitivity, endothelial dysfunction and increased production of proinflammatory cytokines (4).

The field of *Nutritional Psychiatry* is relatively new and relates to the emerging research focusing on the role of diet and nutrition on mental health (5). New investigations into the microbiome, immune and inflammation pathways demonstrate a powerful paradigm shift in the way we understand depression (6). Research into how diet and nutrition effects these pathways could yield valuable insights into potential treatment strategies for depression. A recent review examining the role of fruit and vegetable consumption and various health outcomes suggested several possible links between these foods and depression

pathophysiology (7). The free-radical scavenging and anti-inflammatory components found in fruits and vegetables, particularly the high content of carotenoids, vitamin C and polyphenols appear to play an important role (7). Other possible therapeutic components include folate and the effects to methylation, homocysteine and vitamin B12 as well as the effect of fiber on gastric emptying and brain-derived neurotrophic factor (BDNF) (7).

Several traditional diets which are high in fruits and vegetables have been associated with a reduced risk of depression, including the traditional Japanese diet (8) and Norwegian diet (9). Currently, the diet with the most evidence for protecting against depression risk is the Mediterranean diet (MD) which has recently been hypothesised as a promising treatment strategy for improving clinical outcomes in depression (10). Several reviews on diet and depression have speculated that the efficacy of the Mediterranean diet for depression may be due to the high polyphenols content (10-12). Therefore, conducting a systematic review to examine the research on these polyphenols may assist in verifying this potential mechanism of action.

The term *Mediterranean Diet* reflects the diets of several countries in the Mediterranean Basin during the early 1960s (13). It was noted that the populations within these countries had reduced mortality and morbidity from various diseases (14). One of the common linking factors was their shared dietary pattern which has since gained much attention, particularly for preventing coronary heart disease (15). In 1993 the International Conference on the Diets of the Mediterranean defined the various components of the diet (13). They conclude that it is abundant in plant foods such as fruits, vegetables, whole grains, nuts, seeds and legumes. The principle source of dietary lipids is in the form of olive oil. Red wine is consumed in

104 moderate amounts generally with meals (13). All of these dietary components are rich in
105 polyphenols which may explain the favourable health outcomes, particularly in depression.
106
107 Polyphenols are natural compounds found in a wide variety of foods and are particularly high
108 in plant-based foods (16). Polyphenols exert protective effects on mental health via
109 upregulating the body's natural defence systems, stabilising free radicals, and reducing
110 oxidative damage (17). Additionally, neuroprotective properties have been observed, with
111 polyphenols modulating specific cellular signalling pathways involved in cognitive processes
112 (17). The main classes of polyphenols are defined according to the nature of their carbon
113 skeleton: phenolic acids, flavonoids and the less common stilbenes and lignans (18).
114
115 The aim of this literature review is to assess the effects of polyphenols on the symptoms of
116 depression.
117
118 ## METHODOLOGY
119
120 A protocol was developed according to the Preferred Reporting Items For Systematic Reviews
121 And Meta-Analysis Protocols (PRISMA-P) 2015 statement (19). The review is registered with
122 PROSPERO: CRD42019125747
123
124 **Search Strategies and Inclusion Criteria**
125 A literature search was conducted in the following databases: PROQUEST, SCOPUS (Elsevier),
126 MEDLINE (EBSCO), CINAHL, and EMBase. Search terms were divided in two groups and
127 combined within the search. Group 1: Polyphenols OR Phytochemicals OR flavonoids. Group

2: depression OR major depressive disorder OR major depression OR mental health. Initial investigations on search terms for group 1 included the search terms phenolic acids, ligands, stilbenes, and anthocyanins. These terms found no results and hence were excluded from the group.

Original research, published up to the 18th February 2019, which assessed the effect of polyphenols on the symptoms of depression were included in the review. All fruits, vegetables, nuts and seeds, wholegrains, beans and legumes, plant oils and common culinary herbs and spices were included. This is the first literature review to assess the role of polyphenols on depressive symptoms.

Articles were excluded from the review for the following reasons: articles which were not published in English; articles which were not related to the search terms such as those on Alzheimer's Disease or cognitive decline; not original research; articles which did not use a depression rating scale; studies which examined polyphenols not usually consumed as part the diet such as the medicinal herbs St. Johns wort, lavender and Ginkgo biloba.

Study Selection and Data Extraction

The initial search identified 12084 papers. After removal of 790 duplicates, articles were screened by title and by abstract. The remaining articles were then screened by full text resulting in 35 articles which met the full inclusion criteria. After hand-searching the references of the full text articles an additional 2 articles which used different key words were included. This resulted in 37 articles to be assessed in this review. Screening was performed

by JB and citations were stored and filed in EndNote X7. The article selection process is outlined in Supplemental Figure 1.

Assessment of Risk of Bias and Data Summary Table:

Each paper was critically appraised for methodological consistency using critical appraisal tools. For the 17 experimental studies the Joanna Briggs Institute Critical Appraisal tool for Systematic Reviews Checklist for Randomized Control Trials was used (20). For the 20 observational studies the STROBE checklist for cohort, case-control, and cross-sectional studies was used (21). Overall, the appraisals found reliable methodology and no papers were excluded from the review. **Supplemental Table 1** displays the results for randomized control trials (RCTs) and **Supplemental Table 2** displays the results for the observational studies. During this process data was extracted from the final articles and summarised in **Tables 1** and **2**.

RESULTS

Study Characteristics:

All included studies provided quantitative data on human subjects. The observational studies included both longitudinal cohort and cross-sectional designs and had an average number of 10301 participants. The experimental studies were randomized control trials with either a placebo or an anti-depressant medication with an average number of 80 participants. The experimental studies varied in time duration from two weeks to two years with the most common time frame being eight weeks. The majority of the studies assessed both genders (*n=23),* twelve assessed only females and only two studies assessed only men. Twenty-six of

the studies were in adults aged between 23-55 years, ten were in older adults, either postmenopausal or the elderly aged between 40-80 years, and only one study was in young adults aged 18-25 years. Twelve studies looked at depression in disease states. These include major depressive disorder (22-26) chronic fatigue syndrome (27), osteopenia (28), obesity (29, 30), breast cancer (31), type 2 diabetes (32) and irritable bowel syndrome (33). An overview of these study characteristics can be viewed in **Table 5.**

Critical Appraisal:

Over all the results from the critical appraisal tools showed good methodology. Results can be seen in Supplemental Tables 1 and 2. A common weakness observed in the experimental studies was the lack of information in regards to blinding. Although the majority of studies claimed to be double blinded in either the title or the abstract, many failed to provided details of how the assessors and those delivering the interventions were blinded in the methodology section. In the observational studies common weaknesses included failure to explain how loss of follow-up was addressed, not describing study design bias, not providing a flow diagram to show included participants and failing to indicate number of participants with missing data for each variable of interest. These limitations were considered when synthesising the results from this review.

Depression scales:

The most common depression scale used in the observational studies was the Center for Epidemiologic Studies Depression Scale (CESD) which was used in six of the twenty studies (34-37). The CESD is a 20-item measure that asks subjects to rate how often over the past week they experienced symptoms associated with depression, such as restless sleep, poor

appetite, and feeling lonely (38). In the experimental studies the most common scale used was the Hamilton Depression Rating Scale (HDRS) which was used in five of the seventeen studies (22, 24, 26, 39, 40). The second most popular scale was the Hospital anxiety and depression scale (HADS) which was used in four of the studies (25, 27, 33, 41). HADS is a fourteen-item scale used to measure anxiety and depression in a hospital or community setting (42). Another popular depression scale used was the Zung Self Rating Depression Scale (ZSDS) which was used in both observational (43, 44) and experimental designs (28, 39). ZSDS is a 20-item self-report questionnaire covering affective, psychological and somatic symptoms associated with depression (45).

Polyphenols:

A variety of different polyphenols are assessed in the articles included in this review. The observational studies looked at polyphenols consumed in their biological whole food form and the majority of experimental studies assessed the effect of polyphenols consumed via a capsule (22-26, 28-30, 33, 39-41), powder (46), dried herbal tea (47) or liquid (48). Only two experimental studies assessed polyphenols consumed in their whole food form (27, 49). The most commonly tested group of polyphenols were flavanols from tea (n=9 observational) and cocoa (n=2 experimental), isoflavones from soy (n=3 observational and n=4 experimental) and hydroxycinnamic acids from coffee (n=5 observational) and curcumin (n=6 experimental). Other classes of polyphenols tested include flavanones in the form of citrus (n=2 experimental), stilbenes in the form of resveratrol (n=1 experimental) and flavonols in the form of nuts (n=1 observational and n=1 experimental). Three of the observational studies considered the combined effect of all dietary sources of polyphenols in depression risk (35, 36, 50).

Intervention/variable effect:

The majority of studies (*n*=29) found a statistically significant positive and protective effect of consuming polyphenols on the symptoms and risk of depression. Five studies noted a positive effect which was not statistically significant (22, 24, 27, 43, 49) two studies reported mixed result (34, 44) and only two studies showed no difference after the intervention (30, 48). An overview of polyphenol effect on depression is displayed in **Table 3.** *P*-values are given for experimental studies in Table 1 and odds ratios, relative risk and *P*-values are given for observational studies in table 2.

DISCUSSION

This systematic review provides important insights into the role polyphenols play in depression. The cross-sectional and cohort studies reported on represent the polyphenol intake of individuals in a real life setting and estimate the prevalence of depression among low, moderate and high consumers of polyphenols. The majority (*n*=17) of these studies found a statistically significant result (31, 32, 35-37, 50-61) suggesting that a higher polyphenol intake is associated with decreased prevalence of depression. Polyphenol intake was measured via various different food frequency questionnaires and diet history forms. Several challenges exist with these methods such as under or over reporting consumption and measurement error (62) and these factors must be considered when interpreting the results. However, the results from these observational studies provide a strong foundation for suggesting that polyphenols play a role in depression, but they can only infer correlation about disease risk and prevalence.

The seventeen experimental trials included in this systematic review can provide more information about causation in regards to polyphenols exerting a therapeutic benefit for depressive symptoms. These experimental results demonstrate a positive therapeutic benefit for depression with various different polyphenols appearing to reduce depressive symptoms. In contrast to the observational studies which looked at depression risk in healthy individuals, the experimental studies assessed individuals presenting with depressive symptoms or who were diagnosed with depression prior to the commencement of the intervention. The majority (*n*=9) looked at depressive symptoms (27-30, 33, 41, 47-49) with eight of the studies assessing participants with diagnosed clinical depression (22-26, 39, 40, 46). Of these studies, several also included anti-depressant use either as the active control or in combination with a polyphenol. These include escitalopram (22, 26), venlafaxine (22), fluoxetine (24, 39) and sertraline (39). The studies which used polyphenols in combination with antidepressants found that the anti-depressive effects of the polyphenol/anti-depressant combination was greater when compared to the anti-depressant as a monotherapy (22, 24, 26, 39). Further investigations into the effects of polyphenols in individuals with clinical depression are needed and should be the focus of future studies in this area.

The findings of this systematic review of polyphenols are in part supported by a recent meta-analysis which highlighted the protective role of adhering to a Mediterranean diet for depression risk (63). The authors suggest that the protective role of the Mediterranean diet could be multidimensional, encompassing both anti-inflammatory functions and protection from oxidative stress (63, 64). Depression is commonly associated with a subclinical

inflammatory status characterised by an increase in pro-inflammatory cytokines and neuronal damage (36) which could be the pathways targeted by this dietary pattern.

The polyphenols that this review has highlighted as being effective include soy isoflavones (28, 37, 39, 41, 44, 51), tea (31, 52, 53, 56-60) and cocoa flavanols (27, 29), curcumin (23, 25, 26) and coffee hydroxycinnamic acid (32, 54, 55, 58, 61), walnut flavonols (43, 49), citrus flavanones (46) and the stilbene resveratrol (40). Polyphenols are naturally produced plant compounds which form part of the plants defence mechanisms protecting it from pathogens and ultraviolet radiation (17). Several animal studies have demonstrated that polyphenols reduce depression like behaviour in rodents (16). Studies have suggested an interaction between polyphenols and monoamine oxidase (MAO), an enzyme utilised in the catabolism of monoamines thus reducing the breakdown of monoaminergic neurotransmitters, and increasing serotonin and dopamine levels (17). Another possible mechanism for how polyphenols exert their beneficial effects on mental health include their anti-inflammatory properties via inhibition of proinflammatory cytokines, free radical scavenging and antioxidant activity as well as neuroprotective properties (65).

However, the antioxidant activity, bioavailability and enzyme and cell-receptor interactions vary greatly depending on the chemical structure of different polyphenols (18). The structure of polyphenols effects the rate and extent of intestinal absorption which in turn, effects the metabolites circulating in the plasma (18). In addition, the polyphenols which are the most common in the diet may not necessarily be the most active due to poor intestinal absorption or from high metabolism and excretion from the body (66). Studies suggest that the majority

of polyphenols are not actually absorbed through the intestinal barrier, but are metabolised by colonic microflora further down the digestive tract (18). Research even suggests that metabolism pathways and metabolites of polyphenols may be one of the responsible characteristics for their therapeutic effects (66). A recent review found that gallic acid and isoflavones have the best absorption rates with proanthocyanins displaying the poorest absorption (67). The differences in bioavailability and absorption rates of various polyphenols is an important limitation of this review and should be considered when interpreting the results.

Several studies have demonstrated that the absorption rate of curcumin is relatively poor (68-70) and the inclusion of piperine in order to enhance absorption is often recommended (70). Of the six studies included in this review which tested curcumin, three included an absorption enhancer (22, 25, 30) and three did not (23, 24, 26), which may have affected the results. All six studies were randomized clinical trials, with three displaying statistically significant results (23, 25, 26). More studies on the therapeutic use of curcumin for depression are needed before firm conclusions can be drawn. Other promising polyphenols include those from tea and coffee. Tea and coffee are two of the most commonly consumed beverages worldwide (71) and act as a major source of total dietary polyphenol intake (18). All of the twelve studies on tea and coffee included in this review were observational studies. Randomised control trials are needed to determine if a cause and effect relationship also exists for these polyphenols.

A common theme present throughout several of the studies is the use of isoflavones for women, either during menopause or in postmenopausal and elderly women. Isoflavones are

flavonoids abundant in legumes which are able to influence hormone levels by binding to some estrogen receptors and are thus referred to as phytoestrogens (41). It has been suggested that isoflavones may alleviate the symptoms of depression which commonly accompany menopause by modulating the dramatic fluctuations in ovarian hormones which occurs during this period (37). This potential mechanism of action suggests that isoflavones may only be effective in this specific demographic.

This hypothesis is further supported by the study by Li et al which found mixed results when comparing the results between men, women and menopausal status (34). The researchers found that in premenopausal women consumption of legumes was associated with an increased risk of depression. However, moderate consumption was associated with a lower risk of depression among perimenopausal women. No significant association was found among men and postmenopausal women (34). Together, these finding support the theory that isoflavones may exert their beneficial effect for depression by acting as phytoestrogens and therefore may only be appropriate for use in specific population groups.

This review has limitations of its own which need to be acknowledged. The initial search resulted in a large number of very diverse studies. Refinement of the inclusion and exclusion criteria allowed for a more focused review, however, the large exclusion criteria may limit the applicability of this review. The limited number of studies per polyphenol intervention is another key limitation of this review, which may have impacted the overall findings and conclusions drawn from this review. Given the heterogeneous mix of studies included in this review, no cumulative statistical meta-analysis was conducted. This was due to the large diversity of polyphenols tested and variety of depression scales used. The lack of reported

data on effect sizes is another important limitation of this review which effects both the meaningfulness and practical importance of these results. A narrative synthesis of the results has been provided which comes with a risk of interpretation bias from the authors. Only published trials available on the preselected databases were available to be reviewed, which may have skewed the findings.

The review also highlighted a lack of research assessing polyphenols for depression in both men and young adults. Emerging research is beginning to highlight differences in which men and women express symptoms of depression, however, it still remains unclear if these differences affect treatment outcomes (72). Studies in young adults are also needed. Over 75% of mental health problems occur before the age of 25 (73). According to the Australian Bureau of Statistics (ABS) National Survey of Mental Health and Wellbeing: Summary of Results 2007, younger people were more likely to have a mental disorder than older people (74). The lack on studies on young adults and men included in this review limits the relevance of these finding to a broader audience.

CONCLUSION

This was the first systematic literature review to assess the effects of polyphenols on the symptoms of depression. The review has identified a strong foundation for suggesting that polyphenols do play an important role in the disorder. The inclusion of both observational and experimental designs has allowed for a comprehensive synthesis of both depression prevalence as well as intention to treat analysis. There appears to be a protective role of

consuming higher amounts of polyphenols in reducing depression risk across several populations. In addition to the reduced prevalence, there also appears to be a therapeutic benefit of consuming certain polyphenols in reducing depressive symptoms. In the case of isoflavones this could be due to their phytoestrogen effect. Of the polyphenols included in this review, coffee and curcumin, soy isoflavones, tea and cocoa flavanols, walnut flavonols, citrus flavanones and the stilbene resveratrol show the most promise and would be good candidates for future research. The review also identified that further research is required to investigate the role of polyphenols for depression in men and young adults. Additional studies are needed to confirm these finding.

ACKNOWLEDGMENTS

The authors' contributions were as follows: JB, DS, and JS designed the research question and developed the search terms; JB conducted the literature search, analysed the data and drafted the manuscript with edits from DS and JS. All authors read and approved the final manuscript. JB would like to acknowledge the support of the Australian Government Research Training Program Scholarship.

CONFLICTS OF INTEREST

There are no conflicts of interest and no competing financial interests exist.

References:

1. Schmidt HD, Shelton RC, Duman RS. Functional biomarkers of depression: diagnosis, treatment, and pathophysiology. Neuropsychopharmacology. 2011;36(12):2375.
2. Marcus M, Yasamy MT, van Ommeren M, Chisholm D, Saxena S. Depression: A global public health concern. 2012.
3. McCall WV, Kintziger KW. Late life depression: a global problem with few resources. Psychiatric Clinics. 2013;36(4):475-81.
4. Howren MB, Lamkin DM, Suls J. Associations of depression with C-reactive protein, IL-1, and IL-6: a meta-analysis. Psychosomatic medicine. 2009;71(2):171-86.
5. Jacka FN. Nutritional psychiatry: where to next? EBioMedicine. 2017;17:24-9.
6. Foster JA, Neufeld K-AM. Gut–brain axis: how the microbiome influences anxiety and depression. Trends in neurosciences. 2013;36(5):305-12.
7. Angelino D, Godos J, Ghelfi F, Tieri M, Titta L, Lafranconi A, Marventano S, Alonzo E, Gambera A, Sciacca S. Fruit and vegetable consumption and health outcomes: an umbrella review of observational studies. International journal of food sciences and nutrition. 2019:1-16.
8. Suzuki T, Miyaki K, Tsutsumi A, Hashimoto H, Kawakami N, Takahashi M, Shimazu A, Inoue A, Kurioka S, Kakehashi M. Japanese dietary pattern consistently relates to low depressive symptoms and it is modified by job strain and worksite supports. Journal of Affective Disorders. 2013;150(2):490-8.
9. Quirk SE, Williams LJ, O'Neil A, Pasco JA, Jacka FN, Housden S, Berk M, Brennan SL. The association between diet quality, dietary patterns and depression in adults: a systematic review. BMC psychiatry. 2013;13(1):175.
10. Sánchez-Villegas A, Delgado-Rodríguez M, Alonso A, Schlatter J, Lahortiga F, Majem LS, Martínez-González MA. Association of the Mediterranean dietary pattern with the incidence of depression: the Seguimiento Universidad de Navarra/University of Navarra follow-up (SUN) cohort. Archives of general psychiatry. 2009;66(10):1090-8.
11. Opie R, Itsiopoulos C, Parletta N, Sanchez-Villegas A, Akbaraly TN, Ruusunen A, Jacka F. Dietary recommendations for the prevention of depression. Nutritional neuroscience. 2017;20(3):161-71.
12. Taylor AM, Holscher HD. A review of dietary and microbial connections to depression, anxiety, and stress. Nutritional neuroscience. 2018:1-14.
13. Serra-Majem L, Trichopoulou A, de la Cruz JN, Cervera P, Álvarez AG, La Vecchia C, Lemtouni A, Trichopoulos D. Does the definition of the Mediterranean diet need to be updated? Public health nutrition. 2004;7(7):927-9.
14. Willett WC, Sacks F, Trichopoulou A, Drescher G, Ferro-Luzzi A, Helsing E, Trichopoulos D. Mediterranean diet pyramid: a cultural model for healthy eating. The American journal of clinical nutrition. 1995;61(6):1402S-6S.
15. Nestle M. Mediterranean diets: science and policy implications. 1995.
16. Pathak L, Agrawal Y, Dhir A. Natural polyphenols in the management of major depression. Expert opinion on investigational drugs. 2013;22(7):863-80.
17. Gomez-Pinilla F, Nguyen TT. Natural mood foods: the actions of polyphenols against psychiatric and cognitive disorders. Nutritional neuroscience. 2012;15(3):127-33.
18. Scalbert A, Williamson G. Dietary intake and bioavailability of polyphenols. The Journal of nutrition. 2000;130(8):2073S-85S.
19. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Systematic reviews. 2015;4(1):1.
20. The Joanna Brigs Institute. Checklist for Quasi-Experimental Studies (non-randomized experimental studies)2016. Available from: Retrieved from http://joannabriggs.org/research/critical-appraisal-tools.html.

21. Vandenbroucke JP, von Elm E, Altman DG, Gøtzsche PC, Mulrow CD, Pocock SJ, Poole C, Schlesselman JJ, Egger M, Initiative S. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. International journal of surgery. 2014;12(12):1500-24.
22. Bergman J, Miodownik C, Bersudsky Y, Sokolik S, Lerner PP, Kreinin A, Polakiewicz J, Lerner V. Curcumin as an add-on to antidepressive treatment: a randomized, double-blind, placebo-controlled, pilot clinical study. Clinical neuropharmacology. 2013;36(3):73-7.
23. Lopresti AL, Maes M, Maker GL, Hood SD, Drummond PD. Curcumin for the treatment of major depression: a randomised, double-blind, placebo controlled study. Journal of affective disorders. 2014;167:368-75.
24. Sanmukhani J, Satodia V, Trivedi J, Patel T, Tiwari D, Panchal B, Goel A, Tripathi CB. Efficacy and safety of curcumin in major depressive disorder: a randomized controlled trial. Phytotherapy research. 2014;28(4):579-85.
25. Panahi Y, Badeli R, Karami GR, Sahebkar A. Investigation of the efficacy of adjunctive therapy with bioavailability-boosted curcuminoids in major depressive disorder. Phytotherapy Research. 2015;29(1):17-21.
26. Yu J-J, Pei L-B, Zhang Y, Wen Z-Y, Yang J-L. Chronic supplementation of curcumin enhances the efficacy of antidepressants in major depressive disorder: a randomized, double-blind, placebo-controlled pilot study. J Clin Psychopharmacol. 2015;35(4):406-10.
27. Sathyapalan T, Beckett S, Rigby AS, Mellor DD, Atkin SL. High cocoa polyphenol rich chocolate may reduce the burden of the symptoms in chronic fatigue syndrome. Nutrition Journal. 2010;9:55.
28. Atteritano M, Mazzaferro S, Bitto A, Cannata ML, D'Anna R, Squadrito F, Macrì I, Frisina A, Frisina N, Bagnato G. Genistein effects on quality of life and depression symptoms in osteopenic postmenopausal women: a 2-year randomized, double-blind, controlled study. Osteoporosis International. 2014;25(3):1123-9.
29. Ibero-Baraibar I, Perez-Cornago A, Ramirez MJ, Martínez JA, Zulet MA. An increase in plasma homovanillic acid with cocoa extract consumption is associated with the alleviation of depressive symptoms in overweight or obese adults on an energy restricted diet in a randomized controlled trial. J Nutr. 2016;146(4):897S-904S.
30. Esmaily H, Sahebkar A, Iranshahi M, Ganjali S, Mohammadi A, Ferns G, Ghayour-Mobarhan M. An investigation of the effects of curcumin on anxiety and depression in obese individuals: A randomized controlled trial. Chin J Integr Med. 2015;21(5):332-8.
31. Chen X, Lu W, Zheng Y, Gu K, Chen Z, Zheng W, Shu XO. Exercise, tea consumption, and depression among breast cancer survivors. J Clin Oncol. 2010;28(6):991.
32. Omagari K, Sakaki M, Tsujimoto Y, Shiogama Y, Iwanaga A, Ishimoto M, Yamaguchi A, Masuzumi M, Kawase M, Ichimura M. Coffee consumption is inversely associated with depressive status in Japanese patients with type 2 diabetes. Journal of clinical biochemistry and nutrition. 2014:14-30.
33. Kazemian A, Toghiani A, Shafiei K, Afshar H, Rafiei R, Memari M, Adibi P. Evaluating the efficacy of mixture of Boswellia carterii, Zingiber officinale, and Achillea millefolium on severity of symptoms, anxiety, and depression in irritable bowel syndrome patients. Journal of Research in Medical Sciences. 2017;22(11).
34. Li Y, Dai Q, Tedders SH, Arroyo C, Zhang J. Legume consumption and severe depressed mood, the modifying roles of gender and menopausal status. Public health nutrition. 2010;13(8):1198-206.
35. Chang S-C, Cassidy A, Willett WC, Rimm EB, O'Reilly EJ, Okereke OI. Dietary flavonoid intake and risk of incident depression in midlife and older women. The American journal of clinical nutrition. 2016;104(3):704-14.

386 36. Godos J, Castellano S, Ray S, Grosso G, Galvano F. Dietary Polyphenol Intake and Depression:
387 Results from the Mediterranean Healthy Eating, Lifestyle and Aging (MEAL) Study. Molecules (Basel,
388 Switzerland). 2018;23(5).
389 37. Miyake Y, Tanaka K, Okubo H, Sasaki S, Furukawa S, Arakawa M. Soy isoflavone intake and
390 prevalence of depressive symptoms during pregnancy in Japan: baseline data from the Kyushu
391 Okinawa Maternal and Child Health Study. European journal of nutrition. 2018;57(2):441-50.
392 38. Herge WM, Landoll RR, La Greca AM. Center for Epidemiologic Studies Depression Scale
393 (CES-D). Encyclopedia of Behavioral Medicine. 2013:366-7.
394 39. Nina Estrella RE, Landa AI, Lafuente JV, Gargiulo PA. Effects of antidepressants and soybean
395 association in depressive menopausal women. Acta Pol Pharm Drug Res. 2014;71(2):323-7.
396 40. Davinelli S, Scapagnini G, Marzatico F, Nobile V, Ferrara N, Corbi G. Influence of equol and
397 resveratrol supplementation on health-related quality of life in menopausal women: A randomized,
398 placebo-controlled study. Maturitas. 2017;96:77-83.
399 41. Hirose A, Terauchi M, Akiyoshi M, Owa Y, Kato K, Kubota T. Low-dose isoflavone aglycone
400 alleviates psychological symptoms of menopause in Japanese women: a randomized, double-blind,
401 placebo-controlled study. Archives of Gynecology and Obstetrics. 2016;293(3):609-15.
402 42. Bjelland I, Dahl AA, Haug TT, Neckelmann D. The validity of the Hospital Anxiety and
403 Depression Scale: an updated literature review. Journal of psychosomatic research. 2002;52(2):69-
404 77.
405 43. Su Q, Yu B, He H, Zhang Q, Meng G, Wu H, Du H, Liu L, Shi H, Xia Y. Nut consumption is
406 associated with depressive symptoms among Chinese adults. Depression and anxiety.
407 2016;33(11):1065-72.
408 44. Yu B, Yu F, Su Q, Zhang Q, Liu L, Meng G, Wu H, Xia Y, Bao X, Shi H, et al. A J-shaped
409 association between soy food intake and depressive symptoms in Chinese adults. Clinical Nutrition.
410 2018;37(3):1013-8.
411 45. Zung WW, Richards CB, Short MJ. Self-rating depression scale in an outpatient clinic: further
412 validation of the SDS. Archives of general psychiatry. 1965;13(6):508-15.
413 46. Kamalifard M, Khalili AF, Namadian M, Herizchi S, Ranjbar Y. Comparison of the effect of
414 lavender and bitter orange on depression in menopausal women: A triple-blind randomized
415 controlled trial. Int J Women's Health Reproduction Sci. 2017;5(3):224-30.
416 47. Chang SM, Chen CH. Effects of an intervention with drinking chamomile tea on sleep quality
417 and depression in sleep disturbed postnatal women: a randomized controlled trial. Journal of
418 advanced nursing. 2016;72(2):306-15.
419 48. Mirghafourvand M, Charandabi SMA, Hakimi S, Khodaie L, Galeshi M. The effect of orange
420 peel essential oil on postpartum depression and anxiety: A randomized controlled clinical trial.
421 Iranian Red Crescent Medical Journal. 2017;19(2).
422 49. Pribis P. Effects of walnut consumption on mood in young adults—A randomized controlled
423 trial. Nutrients. 2016;8(11).
424 50. Mofrad MD, Siassi F, Gilani B, Bellissimo N, Azadbakht L. The association of dietary
425 phytochemical index and mental health in women: A cross-sectional study. British Journal of
426 Nutrition. 2019.
427 51. Yu S, Guo X, Yang H, Zheng L, Sun Y. Soybeans or soybean products consumption and
428 depressive symptoms in older residents in rural Northeast China: a cross-sectional study. The journal
429 of nutrition, health & aging. 2015;19(9):884-93.
430 52. Hintikka J, Tolmunen T, Honkalampi K, Haatainen K, Koivumaa-Honkanen H, Tanskanen A,
431 Viinamäki H. Daily tea drinking is associated with a low level of depressive symptoms in the Finnish
432 general population. European journal of epidemiology. 2005;20(4):359-63.
433 53. Niu K, Hozawa A, Kuriyama S, Ebihara S, Guo H, Nakaya N, Ohmori-Matsuda K, Takahashi H,
434 Masamune Y, Asada M. Green tea consumption is associated with depressive symptoms in the
435 elderly. The American journal of clinical nutrition. 2009;90(6):1615-22.

54. Ruusunen A, Lehto SM, Tolmunen T, Mursu J, Kaplan GA, Voutilainen S. 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. 2010;13(8):1215-20.
55. Lucas M, Mirzaei F, Pan A, Okereke OI, Willett WC, O'reilly ÉJ, Koenen K, Ascherio A. Coffee, caffeine, and risk of depression among women. Archives of internal medicine. 2011;171(17):1571-8.
56. Feng L, Li J, Kua EH, Lee TS, Yap KB, John Rush A, Ng TP. Association between tea consumption and depressive symptoms in older Chinese adults. J Am Geriatr Soc. 2012;60(12):2358-60.
57. Feng L, Yan Z, Sun B, Cai C, Jiang H, Kua EH, Ng TP, Qiu C. Tea Consumption and Depressive Symptoms in Older People in Rural C hina. J Am Geriatr Soc. 2013;61(11):1943-7.
58. Pham NM, Nanri A, Kurotani K, Kuwahara K, Kume A, Sato M, Hayabuchi H, Mizoue T. Green tea and coffee consumption is inversely associated with depressive symptoms in a Japanese working population. Public health nutrition. 2014;17(3):625-33.
59. Li F-D, He F, Ye X-J, Shen W, Wu Y-P, Zhai Y-J, Wang X-Y, Lin J-F. Tea consumption is inversely associated with depressive symptoms in the elderly: A cross-sectional study in eastern China. Journal of affective disorders. 2016;199:157-62.
60. Chan S-P, Yong P, Sun Y, Mahendran R, Wong J, Qiu C, Ng T-P, Kua E-H, Feng L. Associations of long-term tea consumption with depressive and anxiety symptoms in community-living elderly: findings from the diet and healthy aging study. The journal of prevention of Alzheimer's disease. 2018;5(1):21-5.
61. Navarro A, Abasheva D, Martínez-González M, Ruiz-Estigarribia L, Martín-Calvo N, Sánchez-Villegas A, Toledo E. Coffee consumption and the risk of depression in a middle-aged cohort: The sun project. Nutrients. 2018;10(9):1333.
62. Brown D. Do food frequency questionnaires have too many limitations? Journal of the American Dietetic Association. 2006;106(10):1541-2.
63. Lassale C, Batty GD, Baghdadli A, Jacka F, Sánchez-Villegas A, Kivimäki M, Akbaraly T. Healthy dietary indices and risk of depressive outcomes: a systematic review and meta-analysis of observational studies. Molecular psychiatry. 2018:1.
64. Psaltopoulou T, Sergentanis TN, Panagiotakos DB, Sergentanis IN, Kosti R, Scarmeas N. Mediterranean diet, stroke, cognitive impairment, and depression: a meta-analysis. Annals of neurology. 2013;74(4):580-91.
65. Dias GP, Cavegn N, Nix A, do Nascimento Bevilaqua MC, Stangl D, Zainuddin MSA, Nardi AE, Gardino PF, Thuret S. The role of dietary polyphenols on adult hippocampal neurogenesis: molecular mechanisms and behavioural effects on depression and anxiety. Oxidative medicine and cellular longevity. 2012;2012.
66. Manach C, Scalbert A, Morand C, Rémésy C, Jiménez L. Polyphenols: food sources and bioavailability. The American journal of clinical nutrition. 2004;79(5):727-47.
67. Manach C, Williamson G, Morand C, Scalbert A, Rémésy C. Bioavailability and bioefficacy of polyphenols in humans. I. Review of 97 bioavailability studies. The American journal of clinical nutrition. 2005;81(1):230S-42S.
68. Akram M, Shahab-Uddin AA, Usmanghani K, Hannan A, Mohiuddin E, Asif M. Curcuma longa and curcumin: a review article. Rom J Biol Plant Biol. 2010;55(2):65-70.
69. Nagpal M, Sood S. Role of curcumin in systemic and oral health: An overview. Journal of natural science, biology, and medicine. 2013;4(1):3.
70. Chauhan M, Saha S, Roy A. Curcumin: a review. Journal of Applied Pharmaceutical Research. 2014;2(1):18-28.
71. Ferruzzi MG. The influence of beverage composition on delivery of phenolic compounds from coffee and tea. Physiology & behavior. 2010;100(1):33-41.
72. Weissman MM. Treatment of depression: men and women are different? : Am Psychiatric Assoc; 2014.

73. Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. Archives of general psychiatry. 2005;62(6):593-602.
74. Slade T, Johnston A, Oakley Browne MA, Andrews G, Whiteford H. 2007 National Survey of Mental Health and Wellbeing: methods and key findings. Australian and New Zealand Journal of Psychiatry. 2009;43(7):594-605.

493 **Table 1. Data Summary of Experimental Trials assessing polyphenols in depressed participants**

Author	Year	Country	Study Design	Intervention	Subjects	Depression Scale	Other Measurements	Results
Sathyapalan et al.(27)	2010	England	Randomized placebo-controlled trial. Duration: 8 weeks of initial intervention followed by a 2 week wash out period followed by 8 weeks of the crossover intervention.	1: Polyphenol rich chocolate with 85% coco solids 2: Placebo chocolate	10 subjects (*n*=6 women) (*n*=4 men) Condition: Chronic fatigue	Hospital anxiety and depression scale (HADS)	Chalder fatigue scale and London handicap scale	Depression scores improved after the high polyphenol chocolate but deteriorated after the placebo chocolate. Coco group HADS median scores: Baseline = 10, conclusion = 5.5. Placebo baseline = 6, conclusion = 12. However, the results were non-significant: Wilcoxon signed rank sum test *Z* value: -2.68 (0.01).
Bergman et al. (22)	2013	Israel	Randomized, double blinded, placebo controlled, pilot clinical trial. Duration: 5 weeks	1: 500 mg/d curcumin plus antidepressant 2: Placebo plus antidepressant	40 subjects (*n*=23 women) (*n*=17 men)	Hamilton Depression rating scale and Montgomery-Asberg Depression Scale (MADRS)	Global Impression Severity Scale	Both groups had a significant improvement in depressive symptoms. MADRS Score for the Curcumin group 95% CI, 7.2-13.7; *P= <0.001* and Placebo group 95% CI. 2.1-8.5; *P=* <0.01. Although no significant differences were observed between the intervention and placebo, the curcumin group displayed a more

								rapid improvement in symptoms compared to the placebo. Curcumin group MADRS mean scores: Baseline = 34.4, conclusion = 14.0. Placebo baseline = 32.8, conclusion = 15.4.
Nina Estrella et al.(39)	2014	Dominican Republic	Pilot randomized clinical study. Duration: 3-month duration with four intervention arms	1: Fluoxetine (10mg/day) 2: Soy isoflavones concentrate (100mg/day) 3: Sertraline (50mg/day) 4: Soy (100mg/day) and Sertraline (50mg/day)	40 women aged 45-55yrs. Condition: menopausal depressive	Zung self-rating depression scale (ZSDS) Hamilton Rating Scale for Depression (HAMD)	Not reported	ANOVA for both ZSDS and HAMD showed statistically significant differences between groups (F= 24.06, *P* = < 0.0001) and (F= 31.73, -*P* = < 0.0001) respectively. Soybean has antidepressant effect and may increase the effects of anti-depressants.
Atteritano et al.(28)	2014	Italy	Double blinded randomized control trial Duration: 2 years	1: Isoflavone Genistein (45mg/day) 2: Placebo	262 women Condition: Osteopenic postmenopausal	Zung self-rating depression score (ZSDS)	Health rated quality of life (HRQL) assessed via Italian version of Short Form-36 (SF-36)	The genistein group saw a decrease in depression scores after 1 and 2 years. The difference between groups was statistically significant (*P*=<0.01 vs placebo). Genistein group ZSDS mean scores: Baseline = 41, conclusion = 36. Placebo baseline = 41, conclusion = 43.

Lopresti et al. (23)	2014	Australia	Randomized double blinded, placebo control trial Duration: 8 weeks	1: 500mg twice daily of Curcumin 2: Placebo	56 subjects (*n*=40 women) (*n*=16 Men)	Inventory of Depressive Symptomatology self-rated scale (IDS-SR 30)	Spielberger State-Trait Anxiety Inventory	From weeks 4-8 the Curcumin group demonstrated significantly more efficacy that placebo. IDS-SR Total Score ($F_{1,53}$ = 4.22, *P*= 0.045) and Mood Score ($F_{1,53}$ = 6.51, *P*= 0.014). Curcumin group IDS-SR Total mean scores: Baseline = 33, conclusion = 22.7. Placebo baseline = 33, conclusion = 25.8.
Sanmukhani et al. (24)	2014	India	Double blinded randomized control trial. Duration: 6 weeks	1: Fluoxetine 20mg/day 2: Curcumin 1000mg/day (500mg BD) 3: Fluoxetine 20mg/day plus curcumin 1000mg/day (500mg BD)	40 subjects (*n*=24 women) (*n*=16 men)	Hamilton Depression Ratting Scale (HAM-D_{17})	Clinical Global Impression – severity of illness scale	A greater response was observed in the combined Fluoxetine and curcumin group (77.8%) compared to the fluoxetine group (64.7%) and curcumin group (62.5%). However, the differences between groups were not statistically significant (*P*=0.58). Group 1 HAM-D mean scores: Baseline = 21, change from baseline at conclusion = -13.6. Group 2 baseline = 19.3, change at conclusion = -13.3. Group 3 baseline = 21.9, change at conclusion = -14.6.

Esmaily et al. (30)	2015	Iran	Double blind, cross over, placebo controlled randomized control trial Duration: 4 weeks with a 2 week wash out between groups	1: Curcumin 1g/day 2: Placebo	30 subjects (*n*=24 women) (*n*=6 men) Condition: Obese	Becks Depression Inventory (BDI)	Beck Anxiety Inventory (BAI)	No significant differences in BDI scores were observed for the curcumin group *P*= >0.05
Panahi et al. (25)	2015	Iran	Open label randomised control trial Duration: 6 weeks	1: Standard anti-depressant therapy 2: Standard antidepressant therapy plus curcuminoids 1000mg and 10mg piperine.	111 subjects (*n*=60 women) (*n*=51 men)	Hospital Anxiety and Depression Scale (HADS) and Becks Depression Inventory (BDI)	Not Reported	Significantly reduced HADS and BDI scores in the curcumin group compared to the control group. HADS Score *P*= <0.001 and BDI Score *P*= <0.001. Curcuminoids group BDI mean scores: Baseline = 38.66, conclusion = 29.66. Placebo baseline = 40.44, conclusion = 37.60. Curcuminoids group HADS mean scores: Baseline = 42.59, conclusion = 30.90. Placebo baseline = 38.82, conclusion = 36.10.
Yu et al. (26)	2015	China	Double blinded, placebo controlled, pilot randomized control trial Duration: 6 weeks	1: Curcumin 1000mg/day 2: Placebo soybean powder	108 male subjects	Chinese version of the 17-item Hamilton Depression Rating Scale	Blood pathology: plasma cytokines IL-1β, TNF-α and	Significant reduction in depressive symptoms in the curcumin group for both the HDRS and MADRS *P*=<0.05. Significant reduction in cytokines IL-1β, TNF-α and BDNF

						(HDRS) and Montgomery-Asberg Depression Rating Scale (MADRS)	brain-derived neurotropic factor (BDNF)	for the curcumin group *P*=<0.001. Curcumin group HDRS mean scores: Baseline = 14.06, change from baseline at conclusion = 4.52. Placebo baseline = 14.28, change from baseline at conclusion = 3.30. Curcumin group MADRS mean scores: Baseline = 18.22, change from baseline at conclusion = 6.26. Placebo baseline = 18.68, change from baseline at conclusion = 4.52.
Ibero-Baraibar et al.(29)	2016	Spain	Double blinded, randomized, placebo-controlled trial. Duration: 4 weeks	1: 15% energy restriction diet plus 1.4g coco extract (645mg total polyphenols) 2: 15% energy restriction diet only	50 subjects (*n*=27 women) (*n*=23 men) Condition: Overweight or obese adults	Spanish translation of the Beck Depression Inventory (BDI)	3-day food recall questionnaire	Depressive symptoms were reduced significantly in both experimental groups (*P*=<0.05). However, no differences were observed in depression scores between the two groups. Coco group BDI mean scores: Baseline = 9.4, conclusion = 5.7. Placebo baseline =11.8, conclusion = 6.1.
Pribis (49)	2016	USA	Double blinded, randomized, placebo-controlled, cross over design.	1: Banana bread with 60g of ground walnuts 2: Banana bread without walnuts	49 subjects (*n*=29 women) (*n*=20 men)	The profile of mood states (POMS)	Lifestyle survey and Food frequency questionnaire (FFQ)	Males, but not females, had a significant medium effect size improvement in total mood disturbances. Both men and women had a non-statistically

			Duration: 8-week intervention followed by 6 weeks wash out period followed by 8 weeks cross over intervention		Condition: Students between 18-25yrs			significant improvement in depression *P*=0.103.
Hirose et al.(41)	2016	Japan	Randomized, double blinded, placebo-controlled trial Duration: 8 weeks	1: Isoflavone aglycone (12.5mg/day) 2: isoflavone aglycone (25mg/day) 3: Placebo	90 women aged 40-60yrs Condition: Menopausal	Hospital Anxiety and Depression Scale (HADS)	Menopausal symptom scale and Athens Insomnia Scale	Low dose (25mg/day) isoflavone aglycone significantly reduced symptoms of depression (*P*=0.033).
Mirghafourvand et al.(48)	2017	Iran	Randomized control trial Duration: 8 weeks	1: Orange peel essential oil (10 drops 3x/day) 2: Placebo	48 women Condition: Postpartum	The Edinburg Postnatal Depression Questionnaire	The Spielberger state-trait anxiety inventory	No statistically significant difference between intervention and placebo (*P*=0.956). Orange peel group depression mean scores: Baseline = 8.0, conclusion = 6.7. Placebo baseline = 8.1, conclusion = 6.7.
Kamalifard et al.(46)	2017	Iran	Triple blind randomized control trial Duration: 8 weeks	1: Bitter orange powder (500mg/day)	156 women aged 45-60 Condition: menopausal	Beck Depression Inventory	Socio-demographic questionnaire	Both orange and lavender were effective at reducing symptoms of depression compared to placebo (*P*=0.001). There was no significant difference between orange and

				2: Lavender flower powder (500mg/day) 3: Placebo – starch (500mg/day)				lavender. Bitter orange group BDI mean scores: Baseline = 21.38, conclusion = 14.48. Lavender baseline = 20.82, conclusion = 14.07. Placebo baseline =20.01, conclusion = 16.78.
Davinelli, et al.(40)	2017	Italy	Randomized, double blinded, placebo-controlled trail Duration: 12 weeks	1: Capsule containing 200mg of fermented soy (80mg of isoflavone aglycones and 10mg equol) and 25mg of resveratrol per day 2: Placebo capsule	60 women aged 50-55yrs Condition: menopausal	Hamilton Rating Scale for Depression (HAM-D)	Health rated quality of life (HRQL) Menopause Rating Scale (MRS)	Treatment group saw improvements in depression scores in comparison to the placebo group (*P*=0.001).
Kazemian et al.(33)	2017	Iran	Randomized controlled trial Duration: 1 month	1: Capsule containing Zingiber Officinale (ginger), Boswellia carterii (frankinsence) and Achillea millefolium (yarrow) daily. 2: Placebo	42 subjects (*n*=19 women) (*n*=23 men) Condition: Irritable bowel syndrome (IBS)	Hospital Anxiety and Depression Scale (HADS)	IBS-severity scoring system (IBS-SSS)	Symptoms of depression reduced significantly in the intervention group (*P*=0.001) with no significant changes in the placebo group (*P*=0.31). Herb group HADS mean scores: Baseline = 17.4, conclusion = 12.5. Placebo baseline = 18.0, conclusion = 17.22.

Chang et al. (60)	2018	Taiwan	Single blinded. Placebo controlled, randomized clinical trial Duration: 2 weeks	1: Camomile tea (1 cup per day which included 2g of dried flowers and 300ml hot water steeped for 10-15 minutes) 2: Regular care with no camomile tea.	80 women Condition: 6 weeks postpartum	Edinburgh Postnatal Depression Scale	Postpartum Fatigue Scale	The camomile teat group significantly lowered depressive symptoms compared with the control group (*T*=-2.372, *P*=0.020). Camomile group depression mean scores: Baseline = 7.86, conclusion = 7.26. Placebo baseline = 9.71, conclusion = 9.51.

507 **Table 2. Data Summary of Observational Studies assessing polyphenols on depressive symptoms**

Author	Year	Country	Study Design	Main Variable	Subjects	Depression Scale	Other measures	Results
Hintikka et al. (52)	2005	Finland	Cross Sectional Study	Tea consumption	2011 participants from the Kuopio Depression Study aged 25-64 (*n*=1121 women) (*n*=890 men)	Beck Depression Inventory (BDI)	Food Frequency Questionnaire	Daily tea drinkers had a significantly reduced risk of being depressed (*OR* 0.46, 95% *CI* 0.3-0.7).
Niu et al. (53)	2009	Japan	Cross Sectional Study	Green tea consumption	1058 elderly participants >70 years old	30-item Geriatric Depression Scale	Height and weight, blood tests for C reactive protein. A 75-item diet history questionnaire	The prevalence of depressive symptoms was 44% lower for participants who consumed ≥4 cups of green tea compared to those who consumed ≤1 cup per day 9Bonferroni corrected *P*=<0.01.
Chen et al. (31)	2010	China	Prospective Cohort Study	Tea consumption	1399 women Condition: Breast cancer survivors	20-item Center for Epidemiological Studies Depression Scale	Quality of Life and Medical outcome short form 36 health survey	Regular tea consumption (>100g dried tea leaves/month) was inversely associated with overall depression (*OR*, 0.64; 95% CI, 0.41-0.99).

Ruusunen et al. (54)	2010	Finland	Prospective Cohort Study	Coffee and tea consumption	2232 middle aged men	18-Item Human Population Laboratory (HPL) Depression Scale	4 day food record, BMI.	Heavy coffee drinkers had a decreased risk of depression compared to non-drinkers (*RR*=0.28, 95% CI 0.08, 0.98). No associations were observed for tea consumption and depression (*RR*=1.19, 95% CI 0.54, 2.23).
Li et al.(34)	2010	USA	Longitudinal cohort study Duration: cohort from 1971-1982	Legume consumption	4869 adults who participated in the National Health and Nutrition Examination Survey (NHANES I)	Centre for Epidemiological Studies Depression Scale (CES-D)	3-month food frequency questionnaire (FFQ)	In premenopausal women, consumption of legumes was associated with an increased risk of depression (*P*=0.0148). However, moderate consumption was associated with a lower risk of depression among perimenopausal women (*RR*=0.52 (0.27,1.00). No significant association was found among men and postmenopausal women.
Lucas et al. (55)	2011	USA	Prospective longitudinal study Duration: 10 year follow up.	Coffee consumption	50739 women (mean age 63 years)	36 item short form health survey	Food frequency questionnaire	Depression risk decreases with increasing coffee intake. Multivariate relative risk for those consuming 4 cups per day or more was 0.80 (95% CI, 0.68-0.95; *P* for trend = 0.02).

Feng et al. (56)	2012	Singapore	Prospective Cohort Study	Tea consumption	1615 older participants aged 55-93 years	15-item Geriatric Depression Scale	Food frequency questionnaire	Risk of depression decreased with increasing tea consumption. Odds Ratio for low, medium and high tea consumption was 1.15, 0.55 and 0.37, respectively. (*P* for linear trend = 0.01).
Feng et al. (57)	2013	China	Cross Sectional Study	Tea consumption	1368 older aged participants ≥60 years	15-item Geriatric Depression Scale	Mini mental state examination. Tea consumption questionnaire	Daily tea consumption is associated with a reduced risk of depressive symptoms. Weekly tea consumption OR=0.86; 95% CI=0.56-1.32 and daily consumption OR=0.59; 95% CI=0.43-0.81. (*P* for linear trend = 0.001).
Omagari et al. (32)	2014	Japan	Cross Sectional Study	Coffee consumption	89 participants with type 2 diabetes (*n*=34 women) (*n*=55 men)	Japanese version of the Hospital Anxiety and Depression Scale (HADS)	Food frequency questionnaire and BMI	Coffee consumption was inversely associated with depressive symptoms with participants who drink 3 or more cups per day having a significantly reduced risk of depression (*P*=0.032)
Pham et al. (58)	2014	Japan	Cross Sectional Study	Green tea and coffee consumption	537 men	Center for Epidemiological Studies	Diet history questionnaire C reactive protein and	Higher green tea consumption ≥4 cups/day was associated with a lower prevalence of

						Depression Scale	folate blood test.	depressive symptoms (51% significantly lower prevalence odds) (*P* for trend = 0.01). Coffee consumption was also inversely associated with depressive symptoms with ≥2 cups/day compared to 1 cup/d: (*OR*=0.61; 95% CI 0.38, 0.98).
Yu et al.(51)	2015	China	Cross Sectional Study	Soybean and soybean product consumption	1717 Liaoning Province residence aged>65 years (*n*=849 women) (*n*=868 men)	Patient Health Questionnaire-9	Food frequency questionnaire	Frequent consumption of soybeans and soybean products is associated with a decrease in the likeliness of depressive symptoms. Consumption 2-3 times per week (*P*=0.23) *OR* 95% CI= 0.36 (0.15,0.87) Consumption >4 times per week (*P*=0.001), *OR* 95% CI= 0.50 (0.34,0.74).
Li et al. (59)	2016	China	Cross Sectional Study	Tea consumption	9371 elderly (≥60 years of age) participants (*n*= 4853 women) (*n*= 4518 men)	Patient Health questionnaire (PHQ-9)	Daily living scale and the Mini Mental State Examination. Food frequency questionnaire	The black tea drinkers had a significantly decreased risk of depressive symptoms (*P*= < 0.01), Compared with non-drinkers, the adjusted OR 95% CI =0.48 (0.23, 0.99) and 0.35 (0.17, 0.72) for participants consuming

								< 3 cups and ≥3 cups of black tea per day, respectively (*P* for trend: <0.01
Chang, et al.(35)	2016	USA	Longitudinal cohort study Duration: 1976-2001	Dietary flavonoid intake	82648 women who participated in the Nurses' Health Study	The 5 item mental health index and the Center for Epidemiologic Studies Depression Scale (CESD-10) and the Geriatric Depression Scale (GDS)	Food frequency questionnaire	Greater intakes of dietary flavonoids were significantly associated with a modest reduction in depression risk. Participants in the highest flavonoid consumption group had a 7-10% reduction in depression risk compared to the lowest intake group. There was evidence of an inverse linear trend across consumption groups (-*P*-trend=0.08, 0.0004 and 0.0007, respectively)
Su et al.(43)	2016	China	Cross sectional Study	Nut consumption	13626 adults who participated in the Tianjin Chronic Low-grade Systemic Inflammation and Health Cohort. Recruited during 2013-2014	Zung Self Rating Depression Scale (ZSDS)	Food frequency questionnaire	Frequent nut consumption is associated with lower prevalence of depression. *OR* 95% CI= 0.82 (0.75, 0.90) for consumption 1-3 times per week and *OR* 95% CI= 0.82 (0.73,0.92) for consumption ≥ 4 times per week.

Chan et al. (60)	2018	Singapore	Prospective Cohort Study	Tea consumption	614 elderly participants aged 60 years and above	15-item Geriatric Depression Scale (GDS)	Geriatric Anxiety Scale. Tea consumption questionnaire	Long term tea consumption was significantly associated with reduced odds of depressive symptoms. Tea consumption for over 15 years resulted in lower GDS Scores (*OR*: 0.82, *P*=0.01).
Navarro et al. (61)	2018	Spain	Longitudinal Cohort Study	Coffee consumption	14413 middle aged participants	Validated physician diagnosis of depression using the Structured Clinical Interview for DSM-IV (SCID-I)	Food frequency questionnaire	Greater coffee consumption is associated with reduced risk of depression. Participants who drank ≥4 cups/day showed a significantly lower risk of depression than participants who drank less than one cup of coffee per day (HR: 0.37 (95% CI 0.15–0.95).
Miyake et al.(37)	2018	Japan	Cross sectional study	Soy isoflavones	1745 pregnant women who participated in the KOMCHS study (an ongoing prospective pre-birth cohort study)	Center for Epidemiologic Studies Depression Scale (CESD)	Diet history questionnaire	Isoflavone intake was associated with a lower prevalence of depressive symptoms during pregnancy. Prevalence ratios (95 % confidence intervals, *P* for trend) 0.63 (0.47–0.85, 0.002), 0.72 (0.54–0.96, 0.007), 0.74 (0.56–0.98, 0.04), 0.57 (0.42– 0.76, <0.0001), 0.73 (0.55–0.98, 0.03), 0.65 (0.49–0.87, 0.003), and 0.63 (0.46–0.86, 0.002).

Yu et al.(44)	2018	China	Cross sectional study	Soy isoflavones	13760 adults who participated in the Tianjin Chronic Low-grade Systemic Inflammation and Health Cohort.	Zung Self Rating Depression Scale (ZSDS)	Food frequency questionnaire	Moderate intake of soy foods may reduce the incidence of depression while high intakes may worsen depressive symptoms. *OR* 95% CI for <1/week) were 0.80 (0.67, 0.95) for 1-3/week, 0.69 (0.55, 0.86) for 4-7/week, and 1.85 (1.21, 2.80) for ≥ 2/day.
Godos et al.(36)	2018	Italy	Cross sectional study	Dietary polyphenols	1572 adults who participated in the Mediterranean Healthy Easting and Lifestyle and Aging (MEAL) Study	Center for Epidemiologic Studies Depression Scale (CESD)	Food frequency questionnaire	Higher dietary flavonoid intake may be inversely associated with depressive symptoms. (-*P* for trend <0.001) Dietary intake of phenolic acid (*OR* = 0.64, 95% CI: 0.44, 0.93), flavanones (*OR* = 0.54, 95% CI: 0.32, 0.91), and anthocyanins (*OR* = 0.61, 95% CI: 0.42, 0.89) showed significant inverse association with depressive symptoms, when comparing the highest with the lowest quartile.
Mofrad et al.(50)	2019	Iran	Cross sectional study	Dietary phytochemicals	488 women aged 20-50yrs	Depression, anxiety, stress scale (DASS)	Food frequency questionnaire	Higher consumption of dietary phytochemicals is associated with a decrease in depressive symptoms

	(*OR*: 0.22; 95% CI: 0.12–0.38; -*P* = <0.001)

508

Table 3. Effect of Polyphenols on Symptoms of Depression

Author	Positive Effect: Statistically Significant	Positive Effect: Not Statistically Significant	Mixed results	No Difference Observed
Experimental:				
Sathyapalan et al. (27)		X		
Bergman et al. (22)		X		
Nina Estrella et al. (39)	X			
Atteritano et al. (28)	X			
Lopresti et al. (23)	X			
Sanmukhani et al. (24)		X		
Esmaily et al. (30)				X
Panahi et al. (25)	X			
Yu et al. (26)	X			
Ibero-Baraibar et al. (29)	X			
Pribis (49)	X*	X		
Hirose et al. (41)	X			
Mirghafourvand et al. (48)				X
Kamalifard et al. (46)	X			
Davinelli et al. (40)	X			
Kazemian et al. (33)	X			
Chang et al. (47)	X			
Observational:				
Hintikka et al. (52)	X			
Niu et al. (53)	X			
Chen et al. (31)	X			
Ruusunen et al. (54)	X			
Li et al. (34)			X	
Lucas et al. (55)	X			
Feng et al. (56)	X			
Feng et al. (57)	X			

Omagari et al. (32)	X			
Pham et al. (58)	X			
Yu et al. (51)	X			
Li et al. (59)	X			
Chang et al. (35)	X			
Su et al. (43)		X		
Chan et al. (60)	X			
Navarro et al. (61)	X			
Miyake et al. (37)	X			
Yu et al. (44)			X	
Godos et al. (36)	X			
Mofrad et al. (50)	X			

Key:

X indicates that the study contains this item.

*Only significant in males

514 **Table 4. Characteristics of included articles**

Author	Sex			Age					Disease	Polyphenols									
Experimental	M	F	B	Young adult	Adult	Pregnancy or postpartum	Menopause	Post-menopausal or elderly	Disease state	Soy	Citrus	Resveratrol	Cocoa	Nut	Legume	Herb and spice	Coffee	Tea	All poly-phenols
Sathyapalan et al. (27)			X						X				X						
Bergman et al. (22)			X		X				X							X			
Nina Estrella et al. (39)		X			X		X			X									
Atteritano et al. (28)		X						X	X	X									
Lopresti et al. (23)			X		X				X							X			
Sanmukhani et al. (24)			X		X				X							X			
Esmaily et al. (30)			X		X				X							X			
Panahi et al. (25)			X		X				X							X			
Yu et al. (26)	X				X				X							X			
Ibero-Baraibar et al. (29)			X		X				X				X						
Pribis (49)			X	X										X					
Hirose et al. (41)		X			X		X			X									
Mirghafourvand et al. (48)		X			X	X					X								

Kamalifard et al. (46)		X			X			X					X											
Davinelli et al. (40)		X			X			X				X			X									
Kazemian et al. (33)			X		X						X									X				
Chang et al. (47)		X				X														X				

515

516

Author	**Sex**			**Age**					**Disease**	**Polyphenols**											
Observational	**M**	**F**	**B**	**Young adult**	**Adult**	**Pregnancy or postpartum**	**Menopause**	**Post-menopausal or elderly**	**Disease state**	**Soy**	**Citrus**	**Resveratrol**	**Cocoa**	**Nut**	**Legume**	**Herb and spice**	**Coffee**	**Tea**	**All poly-phenols**
Hintikka et al. (52)			X		X													X	
Niu et al. (53)			X					X										X	
Chen et al. (31)		X			X				X									X	
Ruusunen et al. (54)	X				X												X	X	
Li et al. (34)			X		X			X							X				
Lucas et al. (55)		X						X									X		
Feng et al. (56)			X					X										X	
Feng et al. (57)			X					X										X	
Omagari et al. (32)			X		X				X								X		

Pham et al. (58)		X	X					X	X	
Yu et al. (51)		X			X	X				
Li et al. (59)		X			X				X	
Chang et al. (35)	X		X		X					X
Su et al. (43)		X	X				X			
Chan et al. (60)		X			X				X	
Navarro et al. (61)		X	X					X		
Miyake et al. (37)	X		X	X		X				
Yu et al. (44)		X	X			X				
Godos et al. (36)		X	X							X
Mofrad et al. (50)	X		X							X

Key: M = Male
F = Female
B = Both Genders

43