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## Antidepressant foods: An evidence-based nutrient profiling system for depression

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### Abstract

#### AIM

To investigate which foods are the most nutrient dense sources of nutrients demonstrated by the scientific literature to play a role in the prevention and promotion of recovery from depressive disorders.

#### METHODS

A systematic literature review was conducted to derive a list of Antidepressant Nutrients from the 34 nutrients known to be essential for humans using level of evidence criteria. Nutritional data was extracted for a subset of foods with a high content of at least 1 Antidepressant Nutrient using a USDA database. These foods were analyzed for Antidepressant Nutrient density resulting in an Antidepressant Food Score (AFS). Plant and animal foods were analyzed separately.

#### RESULTS

Twelve Antidepressant Nutrients relate to the prevention and treatment of depressive disorders: Folate, iron, long-chain omega-3 fatty acids (EPA and DHA), magnesium, potassium, selenium, thiamine, vitamin A, vitamin B6, vitamin B12, vitamin C, and zinc. The highest scoring foods were bivalves such as oysters and mussels, various seafoods, and organ meats for animal foods. The highest scoring plant foods were leafy greens, lettuces, peppers, and cruciferous vegetables.

#### CONCLUSION

The AFS is based on a nutrient profiling system devised to identify foods with the highest nutrient density of nutrients with clinical evidence to support their

role in depressive disorders. This list of foods and food categories with the highest density of the 12 Antidepressant Nutrients, the Antidepressant Foods, should be considered by researchers in the design of future intervention studies and clinicians as dietary options to support prevention and recovery from depression disorders.

**Key words:** Depressive disorder; Mental disorders; Diet; Diet therapy; Food

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**Core tip:** The Antidepressant Food Score was designed to identify the most nutrient-dense individual foods to prevent and promote recovery from depressive disorders and symptoms. Results can be used to inform the design of future research studies or clinical dietary recommendations. This tool is based on a systematic literature review, evidence-informed list of Antidepressant Nutrients, and nutrient density calculation. The highest scoring animal foods were bivalves such as oysters and mussels, various seafoods, and organ meats. The highest scoring plant-based foods were leafy greens, lettuces, peppers, and cruciferous vegetables. These foods can be integrated into any dietary pattern.

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## INTRODUCTION

Mental illnesses are highly prevalent, disabling, costly, and inadequately treated. Among individuals aged 15-44, depressive disorders are the leading cause of disability worldwide<sup>[1]</sup>. Improving public awareness and increasing treatment options for psychiatric illnesses is imperative to public health. A growing evidence base, including the first randomized controlled trial<sup>[2]</sup>, suggests that dietary pattern and food choice may play a role in the treatment and prevention of brain-based disorders, particularly depression. The first nutritional guidelines to prevent depression were published this year. They recommend following a traditional dietary pattern such as the Mediterranean diet, consuming adequate amounts of omega-3 fatty acids, and avoiding processed foods, for example those high in refined carbohydrate or sugar<sup>[3]</sup>. Furthermore, an international consortium of mental health and nutrition researchers recently recommended "nutritional psychiatry" become a routine part of mental health clinical practice<sup>[4]</sup>.

A number of nutrients are implicated in the pathophysiology of depression, for instance: the long-chained

omega-3 fatty acids, B-vitamins, zinc, magnesium, and vitamin D<sup>[5,6]</sup>. Deficiencies of these nutrients can cause depressive symptoms, and in supplement form are used in clinical treatment<sup>[7-9]</sup>. Recent literature on nutrition and psychiatry has shifted from studying individual nutrients to evaluating overall dietary patterns. Prospective epidemiological studies have repeatedly found that "traditional" or "whole foods" dietary patterns are significantly correlated with a decreased prevalence and incidence of depressive disorders or symptoms. A Western dietary pattern has been found to be associated with an increased relative risk of the same<sup>[4,10-12]</sup>. The SUN cohort study followed 10094 university students for 4 years and found those with the highest adherence to the Mediterranean dietary pattern (MDP) showed a greater than 30% reduced risk of developing depression over the study period compared with participants with the lowest adherence to the Mediterranean dietary pattern<sup>[13]</sup>. Studies of traditional diets in Japan, Norway, and China found similar results<sup>[14-16]</sup>. A systematic review and meta-analysis of whole-diet interventions for depression and anxiety symptoms attempted by Opie *et al*<sup>[17]</sup> found the heterogeneity of the studies precluded analysis. However, among the 47% of studies that found a positive impact of a dietary intervention, common recommendations were to increase consumption of fruit, vegetables, fiber, and fish<sup>[17]</sup>. Dietary counselling used as an active control in a trial of problem-focused therapy for the prevention of depression in 122 elderly adults with sub-syndromal depressive symptoms, found a significant and sustained 40% reduction in Beck Depression Inventory scores at two years in participants who received 5.5 h of food counselling over 6-12 wk<sup>[18]</sup>. The SMILES (Supporting the Modification of Lifestyle in Lowered Emotional States) trial, the first randomized controlled trial of a dietary intervention to treat major depressive disorder, found that prescribing a modified Mediterranean diet as an adjunctive treatment resulted in 31% achieving remission compared with placebo and a number needed to treat of 4.1<sup>[19]</sup>.

Brain health and mental illness are impacted by nutrition *via* several mechanisms. A full discussion is beyond the scope of the current paper, though we would like to highlight a few relevant mechanisms here. Nutrients such as the long-chained omega-3 fatty acids, zinc, magnesium, and a number of phytonutrients promote the expression of Brain Derived Neurotrophic Factor (BDNF) and thus influence neuroplasticity<sup>[20]</sup>. Additionally, food is a modifiable determinant of systemic inflammation, which has been described as a major cause and consequence of depression according to the neuroinflammatory hypothesis of this disorder<sup>[21]</sup>. Finally, the emerging role of gut flora (*i.e.*, the microbiome) as a possible key player in the regulation of mood, cognition, and anxiety suggests that we are only beginning to discover the potential of food as medicine<sup>[22]</sup>. Dietary fiber is a prebiotic and its consumption can alter the composition of the microbiota<sup>[22]</sup>.

Table 1 Levels of evidence

Levels of evidence: Observational studies	Levels of evidence: Experimental studies
1. At least 2 prospective cohort studies with adequate sample size and/or meta-analysis with narrow confidence intervals	1. At least 2 RCTs with adequate sample sizes, preferably placebo-controlled, and/or meta-analysis with narrow confidence intervals
2. At least 1 prospective cohort study with adequate sample size and/or meta-analysis with wide confidence intervals	2. At least 1 RCT with adequate sample size and/or meta-analysis with wide confidence intervals
3. Cross-sectional or case control studies	3. Non-randomized, controlled prospective studies (open-label) or high-quality retrospective studies ( <i>i.e.</i> , case series)
4. Expert opinion/consensus	4. Expert opinion/consensus
5. Evidence is equivocal/unavailable	5. Evidence is equivocal/unavailable

RCT: Randomized controlled trial.

There are inherent challenges in prescribing a dietary pattern that is foreign to an individual. A Japanese or MDP may not be practical or palatable for many patients. Instead, ranking foods and highlighting food categories with a high density of nutrients demonstrated to be beneficial for depression could lead to specific food recommendations that can be incorporated into a whole-foods dietary pattern of the patient's choosing<sup>[3]</sup>. For the purpose of the current paper, nutrient density is defined as the ratio of a foods' nutrient value to its caloric content.

A review of 23 existing nutrient profiling schemas found them to be oriented towards improving a number of health outcomes. While many nutrient profiling scales currently exist, created by government agencies, researchers, and the food industry, none focus on mental disorders or brain health<sup>[23]</sup>. Additionally, no scale is based on nutrients that are supported by scientific literature to be involved in the prevention of and recovery from psychiatric disorders. The objective of this study is to determine which foods are the most nutrient dense sources of nutrients demonstrated by human studies published in the current scientific literature to play a role in the prevention and promotion of recovery from depressive disorders.

## MATERIALS AND METHODS

A list of 34 essential nutrients for humans was compiled based on the Institute of Medicine's Dietary Reference Intakes<sup>[24]</sup>. A reference librarian at Columbia University was consulted to develop a systematic search strategy to further refine an evidence-based list of Antidepressant Nutrients. Computerized searches of OVID Medline, Embase, and Embase Classic dating back to 1946 were conducted during February 2017 using the search terms "Depressive Disorder, Major (MeSH)" and "Depression (MeSH)" in combination with the following nutrients: Arsenic, biotin, boron, calcium, carotenoids, choline, chromium, copper, dietary fiber, fluoride, folic acid, iodine, long chain omega-3 fatty acids (docosahexanoic acid and eicosapentanoic acid), magnesium, manganese, molybdenum, niacin, nickel, phosphorus, potassium, pyridoxine, riboflavin, selenium, sodium, silicon, sulfates, vanadium, vitamin A, vitamin B12, vitamin C, vitamin

E, vitamin K, and zinc. Search terms were adapted to different databases. Titles and abstracts were read by both of the study authors to determine if retrieved papers were relevant to the topic under study according to the following inclusion criteria: Observational or experimental studies of an essential nutrient for the treatment or prevention of depressive disorders or symptoms (unipolar) in humans. Exclusion criteria included non-English language articles, review articles, and opinion pieces. Next, nutrient by nutrient, relevant articles underwent full-text review and data extraction by both study authors. Study findings were coded as positive, negative, or equivocal in regard to the prevention or recovery from depressive disorders. Discrepancies were resolved by both authors *via* consensus.

### Statistical analysis

A system to rank the level of evidence in support of each potential antidepressant nutrient was developed based on level of evidence criteria used in various clinical practice guidelines in psychiatry<sup>[25]</sup>. The level of evidence was established for both observational and experimental human studies for each nutrient under consideration using the following guidelines shown in Table 1. Nutrients were included in the list of Antidepressant Nutrients if they had a combined score of less than or equal to 5. For example, magnesium received a total score of 4. There was one positive RCT and one positive prospective cohort study, both with adequate sample sizes, resulting in a level of evidence score of 2 for both experimental and observational studies.

Lists of the top 20 plant and animal whole food sources of each Antidepressant Nutrient were compiled in July 2017 based on the USDA nutrient database<sup>[26]</sup>. After duplicates were removed, this preliminary list consisted of 213 foods. An additional 23 commonly recommended healthy foods such as whole wheat, blueberries, and yogurt were added to this list to assess their AFS.

The nutrient content for each Antidepressant Nutrient was gathered using the database for each of the 236 foods. Nutrient content was expressed as a percent daily value. When percent daily values were not available, such as for long chain omega-3 fatty acids, we extracted the absolute nutrient amount per 100 g raw serving. This was then later converted to a percent daily value. For

**Table 2 Antidepressant foods**

Antidepressant animal foods	AFS range	Antidepressant plant foods	AFS range
Oyster	56%	Watercress	127%
Liver and organ meats (spleen, kidneys, or heart)	18%-38%	Spinach	97%
Poultry giblets	31%	Mustard, turnip, or beet greens	76%-93%
Clam	30%	Lettuces (red, green, romaine)	74%-99%
Mussels	28%	Swiss chard	90%
Octopus	27%	Fresh herbs (cilantro, basil, or parsley)	73%-75%
Crab	24%	Chicory greens	74%
Goat	23%	Pummelo	69%
Tuna	15%-21%	Peppers (bell, serrano, or jalapeno)	39%-56%
Smelt	20%	Kale or collards	48%-62%
Fish roe	19%	Pumpkin	46%
Bluefish	19%	Dandelion greens	43%
Wolffish	19%	Cauliflower	41%-42%
Pollock	18%	Kohlrabi	41%
Lobster	17%	Red cabbage	41%
Rainbow trout	16%-17%	Broccoli	41%
Snail or whelk	16%	Brussels sprouts	35%
Spot fish	16%	Acerola	34%
Salmon	10%-16%	Butternut squash	34%
Herring	16%	Papaya	31%
Emu	16%	Lemon	31%
Snapper	16%	Strawberry	31%

AFS: Antidepressant food score.

long chain omega-3 fatty acids, we based this calculation on a recommended daily intake of 1000 mg of long chain omega-3 fatty acids (EPA + DHA) based on a review of available guidelines<sup>[27]</sup>.

Data was gathered for a 100 g serving of each food in the raw form. This was done because various cooking methods can alter the nutrient content, nutrient bioavailability, and water content of foods. In addition, nutrients vary largely with respect to bioavailability and form between plant and animal foods. For instance, heme-iron is only found in animal foods, and with the exception of certain sea vegetables, long chain omega-3 fatty acids are not found in plant foods. Separating plant and animal foods also served to minimize heterogeneity in bioavailability and content of nutrients across foods.

The mean Antidepressant Nutrient density was calculated for each food included in our list. This generated a nutrient density score, which was expressed as a percentage. The percent daily value for each nutrient was capped at 100% so that one nutrient would not overly influence the AFS. Our methods were adapted from a recent nutrient profiling study of "powerhouse" fruits and vegetables<sup>[28]</sup>. The following formula was used to calculate the Antidepressant Food Score:  $[(\sum \% \text{ daily value per Antidepressant Nutrient} / 12) / \text{calories per 100 g serving}] \times 100$ .

## RESULTS

### Literature review

Our initial searches resulted in 1628 results and screening by title and abstract resulted in 213 relevant results eligible for full-text review. The following 12 nutrients met level

of evidence criteria and were considered Antidepressant Nutrients: Folate, iron, long chain omega-3 fatty acids (EPA, DHA), magnesium, potassium, selenium, thiamine, vitamin A, vitamin B6, vitamin B12, vitamin C, and zinc.

### Antidepressant food score

The top Antidepressant Foods based on the AFS are displayed in Table 2. Foods were grouped into categories and ranked in Table 3. Grouping foods into categories serves to ease implementation of results by providing the researcher or clinician with more flexibility<sup>[29]</sup>. The complete list of foods analyzed, Antidepressant Nutrient content per 100 g serving, AFS, and level of evidence per nutrient are displayed in the Supplementary Materials. The authors excluded the following 6 foods from analysis, as data was not available for greater than two nutrients: whale liver, caribou liver, blackfish, boar, antelope, and longan.

## DISCUSSION

To our knowledge, The Antidepressant Food Score (AFS) is the first nutrient profiling system created to inform dietary recommendations concerning mental health. This evidence-based approach is unique in that it is based on Antidepressant Nutrient density. That is, nutrients considered have been shown in human studies to be beneficial with regards to treatment or prevention of depressive disorders. Our findings include a list of individual foods as well as food rankings within categories that can be incorporated in the design of subsequent research studies or recommended to patients as part of a healthy dietary pattern of their choosing.

**Table 3 Food categories and mean antidepressant food score**

Food category	Mean AFS
Vegetables	48%
Organ meats	25%
Fruits	20%
Seafood	16%
Legumes	8%
Meats	8%
Grains	5%
Nuts & seeds	5%
Dairy	3%

AFS: Antidepressant food score.

Interestingly, many foods with a high AFS are not commonly eaten as part of the Western dietary pattern. Specifically, the majority of the United States adult population does not meet daily recommendations for vegetables. The Healthy People 2010 initiative aimed to increase vegetable consumption of adults and found that only 27.2 percent ate three or more servings of vegetables per day<sup>[30]</sup>. Average annual seafood intake for Americans is 14.6 pounds, and the USDA estimates that 80-90 percent of the population fails to meet the recommendation of two servings of seafood per week<sup>[31]</sup>. On the contrary, top scoring foods on the AFS; seafood, leafy greens, cruciferous vegetables, and nuts are commonly consumed as part of a variety of traditional diets. The Mediterranean dietary pattern is but one example of a consistent pattern: traditional diets contain more nutrient dense foods and fewer highly processed foods. The evidence linking dietary patterns and depressive disorders supports the consumption of a whole-foods based traditional diet as opposed to a Western dietary pattern to prevent and promote recovery from depression. This emerging literature provides some external validity to the results of the AFS while our study serves to identify what some of the “active ingredients” of these traditional diets may be.

Selecting foods based on nutrient density is one way to meet daily nutrient requirements without consuming excessive calories, which may have benefits beyond mental health<sup>[32]</sup>. This is particularly important considering that a number of Antidepressant Nutrients have high rates of dietary insufficiency, meaning many individuals do not meet the Recommended Dietary Allowance (RDA). For example, 55% of the American population does not meet the RDA for vitamin A, 75% for folate, and 68% for magnesium<sup>[33]</sup>.

It is worth discussing how our results differ from certain currently accepted dietary guidelines and nutrient profiling systems<sup>[28,32,34]</sup>. For instance, the AFS is focused on depression and does not consider dietary constituents to avoid such as saturated fat, cholesterol, and sodium. A recent review suggests that nutrient profiling scales designed to improve consumer food choices should be based on nutrients known to be beneficial for health as opposed to nutrients to avoid<sup>[29]</sup>. Moreover, the

harmfulness and potential benefit of nutrients such as saturated fat, cholesterol, and sodium for both physical and mental health is being called into question based on more recent research, and cholesterol is no longer considered a nutrient of concern according to the most recent Dietary Guidelines for Americans<sup>[35-37]</sup>. Lastly, the AFS only ranks whole, unprocessed foods free of added sodium and fats. Recommending that patients continue to avoid fat, cholesterol, and sodium can potentially steer them away from consuming entire potentially nutritious food categories, such as seafood.

Certain nutrients, such as long-chain omega-3 fats, vitamin B12, and heme-iron are only found in animal foods such as seafood, meat, eggs, and dairy and these foods are generally absent from existing nutrient profiling scales. This may occur because a certain scale incorporates dietary cholesterol, saturated fat, or sodium as nutrients to avoid while others simply omit animal foods entirely. As health recommendations have trended towards more “plant-based” diets, one must consider the higher rates of B vitamin deficiencies in both vegetarian and vegan populations. A recent large study found higher levels of depressive symptoms in vegetarian men<sup>[38]</sup>. Our findings highlight the importance of including animal foods as an important part of a healthy dietary pattern to prevent and promote recovery from depressive disorders. That being said, there is a divergence between the animal foods that score highly on our scale such as organ meats and seafoods, and the processed meats typically consumed as part of the Western dietary pattern. The results of our study add to the current discussion in the nutrition literature about the importance of “plant based” diets by presenting a complimentary recommendation: Consuming animal products such as seafoods, organ meats, and small amounts of other traditionally-raised minimally processed meats is an important part of a healthy diet for depression. This is relevant as the majority of eaters consume animal products.

Gut health is increasingly understood as critical for brain health<sup>[22]</sup>. Along with being nutrient-dense sources of vitamins and minerals, two components of plants are relevant to mental health, but not well represented in the literature: fiber and phytonutrients. Generally, fiber is lacking in Western diets, and this influences the population and diversity of bacterial species that comprise the microbiome, the collection of bacteria that reside in the gut<sup>[39]</sup>. Phytonutrients are plant-based compounds, such as lycopene and quercetin, that are traditionally thought of as “antioxidants” but play clear cell signaling roles that influence genetic expression and modulate inflammation<sup>[40]</sup>. Ranking foods by phytonutrients content was not feasible, nor is there sufficient evidence linking individual phytonutrients to brain health. Fiber did not reach our level of evidence cutoff for inclusion and clearly more studies are needed.

The AFS ranks foods and nutrients with an established dietary reference intake included in the USDA database for standard reference at the time of analysis. Our

determination of Antidepressant Nutrients was based on the currently available scientific literature based on our search strategy at the time of our literature searches. As such, certain nutrients such as phytonutrients and other antioxidants were automatically excluded from our algorithm either based on a lack of established dietary reference intake, lack of inclusion in the USDA database, or lack of human studies supporting their effectiveness in treating or preventing depressive disorders. Finally, clinical trials of nutrients often use doses of supplements far beyond those possible *via* food consumption. If a high dose of vitamin B12 can promote depression recovery, it does not necessarily follow that foods with high nutrient density of vitamin B12 do as well.

Findings from the current study can be incorporated into the design of subsequent research studies. For instance, in developing a dietary intervention for depression, researchers should consider including and emphasizing foods that score highly on the AFS. Furthermore, upon publication of the current paper, the authors plan to make our database publicly available online for use by clinicians, researchers, and patients alike. Next steps also include expanding our database to include all foods listed in the USDA database.

In conclusion, a nutrient profiling system focused on mental health yielded rankings of plant and animal foods according to nutrient density of the 12 nutrients supported by current evidence: Folate, iron, long chain omega-3 fatty acids (EPA, DHA), magnesium, potassium, selenium, thiamine, vitamin A, vitamin B6, vitamin B12, vitamin C, and zinc. Evidence-informed dietary recommendations are critical to the employment of nutritional psychiatry in clinical practice. Considering cost, stigma, and access, nutritional interventions provide a unique treatment opportunity for mental health patients. Additionally, mental health professionals are well versed in supporting behavioral changes, of which dietary change is simply an example. As the evidence-base for nutrition as a modifiable factor influencing both the risk and prognosis of mental illness continues to expand, the AFS is a tool to help researchers refine nutritional recommendations to inform the design of future studies and to help clinicians guide patients towards healthier food choices today.

## ARTICLE HIGHLIGHTS

### Research background

The Western dietary pattern is insufficient in a number of essential nutrients. Evidence suggests dietary pattern is key to the prevention and treatment of depressive disorders, yet treatment rarely includes food recommendations. Nutrient profiling systems rank foods according to nutrient density and guide clinical recommendations, research study design, and patient choices. No current food rating scale focuses on nutrients required for mental health.

### Research objectives

The objective of this study is to determine which foods are the most nutrient dense sources of nutrients demonstrated by the scientific literature to play a role in the prevention and promotion of recovery from depressive disorders.

## Research methods

A systematic literature review was conducted to derive a list of Antidepressant Nutrients from the 34 nutrients known to be essential for humans using level of evidence criteria. Nutritional data was extracted for a subset of foods with a high content of at least 1 Antidepressant Nutrient using a USDA database. These foods were analyzed for Antidepressant Nutrient density resulting in an Antidepressant Food Score (AFS). Plant and animal foods were analyzed separately.

## Research results

Twelve Antidepressant Nutrients relate to the prevention and treatment of depressive disorders: Folate, iron, long-chain omega-3 fatty acids (EPA and DHA), magnesium, potassium, selenium, thiamine, vitamin A, vitamin B6, vitamin B12, vitamin C, and zinc. The highest scoring foods were bivalves such as oysters and mussels, various seafoods and organ meats for animal foods. The highest scoring plant foods were leafy greens, lettuces, peppers, and cruciferous vegetables.

## Research conclusion

The AFS is based on a nutrient profiling system devised to identify foods with the highest nutrient density of nutrients with clinical evidence to support their role in depressive disorders. This list of foods and food categories with the highest density of the 12 Antidepressant Nutrients, the Antidepressant Foods, should be considered by researchers in the design of future intervention studies and clinicians as dietary options to support prevention and recovery from depression.

## Research perspectives

The AFS was designed to identify the most nutrient-dense individual foods to prevent and promote recovery from depressive disorders and symptoms. Results can be used to inform the design of future research studies or clinical dietary recommendations. This tool is based on a systematic literature review, evidence-informed list of Antidepressant Nutrients, and nutrient density calculation. The highest scoring animal foods were bivalves such as oysters and mussels, various seafoods, and organ meats. The highest scoring plant-based foods were leafy greens, lettuces, peppers, and cruciferous vegetables. These foods can be integrated into any dietary pattern.

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