

St. Catherine University
SOPHIA

Master of Arts in Holistic Health Studies Research
Papers

Holistic Health Studies

5-2019

The Relationship Between Fermented Foods and Depression: A Systematic Review

M. Beth Hanssens
Bethhanssens@yahoo.com

Susan Patterson
susanpatterson84@gmail.com

Cathy Wagner
cathywagner6@icloud.com

Follow this and additional works at: https://sophia.stkate.edu/ma_hhs

 Part of the [Alternative and Complementary Medicine Commons](#)

Recommended Citation

Hanssens, M. Beth; Patterson, Susan; and Wagner, Cathy. (2019). The Relationship Between Fermented Foods and Depression: A Systematic Review. Retrieved from Sophia, the St. Catherine University repository website: https://sophia.stkate.edu/ma_hhs/21

This Thesis is brought to you for free and open access by the Holistic Health Studies at SOPHIA. It has been accepted for inclusion in Master of Arts in Holistic Health Studies Research Papers by an authorized administrator of SOPHIA. For more information, please contact amshaw@stkate.edu.

Running head: FERMENTED FOODS AND DEPRESSION

The Relationship Between Fermented Foods and Depression: A Systematic Review

M. Beth Hanssens, Susan Patterson, and Cathy Wagner

St. Catherine University

May 15, 2019

Abstract

Depression is a global health issue that is socially and economically expensive. The gut microbiome influences depression, and fermented foods contain bacteria that contribute to the ecology of the gut microbiome. We performed a systematic review of clinical research that examines the relationship between fermented food and depression by conducting an electronic search of four academic databases using the search terms fermented, fermented foods, fermentation, and depression. The inclusion criteria are: inpatient, outpatient, and community settings; human participants age 5-110 years old; any diagnosis of depression; daily ingestion of fermented foods regardless of ingredients; written in English; published full text articles accessible through St. Catherine University; random controlled trials, case reports, cross-sectional studies, cohort studies, and clinical trials; and any measured change in depression after daily ingestion of fermented food. We identified 64 articles, and only two met the inclusion criteria. Both studies indicate a positive trend between fermented food supplementation and improvement in depression. Results are presented in a narrative synthesis, however, there were too few studies to draw major or significant conclusions. Researching multifaceted issues including the gut microbiome and depression in a reductive manner is paradoxical and inadequate. We suggest a more holistic approach with epistemological and ontological assumptions that account for the complexities and synergies in the human body.

Acknowledgements

Thank you to our families and friends for supporting us on this research journey.

Table of Contents

Introduction..... 6

Literature Review..... 9

 Human Gut Microbiome 9

 Food digestion..... 10

 Metabolism. 11

 Immunity..... 12

 Inflammation..... 13

 Dysbiosis 13

 Gut-brain axis..... 14

 Hypothalamus-pituitary-adrenal-axis..... 16

 Depression..... 17

 Fermentation 19

 Literature Review Summary 22

Lenses 24

 Research Paradigm and Culture of Inquiry..... 24

 Theoretical Lenses 25

 Holism theory..... 25

 Reductionism theory 26

 Gut-brain-axis theory..... 27

 Community ecology theory..... 28

 Individual and Collective Lenses 28

 Beth..... 28

 Susan..... 29

 Cathy..... 29

 Collective..... 31

Method..... 32

 Rationale for Study Design..... 32

 Instrumentation 34

 PRISMA..... 35

 RoB 2..... 35

AMSTAR 2.....	36
Sampling and Data Collection	37
Sampling.....	37
Data Collection.....	41
Included PRISMA Flow Diagram.....	43
Data Analysis.....	45
Design Rigor.....	46
Ethical considerations	47
Bias in the literature.....	47
Researcher bias.....	47
Publication bias.....	47
Design Specific Strengths and Limitations.....	48
Results.....	50
Study 1	50
Study 2	51
Discussion.....	54
Findings Supported by the Literature.....	54
Unexpected Findings.....	54
Implications for Holistic Health.....	55
Conclusion	56
References.....	58
Appendix A.....	79
PRISMA 2009 Checklist.....	79
Appendix B.....	81
RoB 2	81
Appendix C.....	110
AMSTAR 2.....	110

Introduction

With all the hype around the benefits of ingesting fermented food is there evidence that what we eat can affect depression? In this research, we describe the relationship between the human gut microbiome, fermented food, and depression. The role of diet links to alterations in mental health status (Li et al., 2017; Molendijk, Molero, Sánchez-Pedreño, Van der Does, & Martínez-González, 2018; Quirk et al., 2013). Our food choices affect our mood (Jacka, Cherbuin, Anstey, & Butterworth, 2015; Stanga et al., 2007). Depression is the leading cause of mental suffering for individuals and is a global mental health burden (Brody, Pratt, & Hughes, 2018; Kessler, 2012; Siu et al., 2016; WHO, 2017). Emerging research suggests a connection between food and depression (Akbaraly, Sabia, Shipley, Batty, & Kivimaki, 2013; Jacka, 2017; Kaplan, Rucklidge, Romijn, & McLeod, 2015; Kiecolt-Glaser, 2010; Quirk et al., 2013; Sánchez Villegas et al., 2015; Vermeulen et al., 2016).

The human gastrointestinal tract houses a complex community of microorganisms commonly called the gut microbiome (Mosca, Leclerc, & Hugot, 2016). Gut microbiota outnumber human DNA by a 10 to 1 ratio (Cryan & Dinan, 2012). The effect of bacteria on human physical and mental health (Aarts et al., 2017; Adams, Johansen, Powell, Quig, & Rubin, 2011; Allen et al., 2016; Bailey et al., 2011; Bharwani et al., 2016; Dominianni et al., 2014; Lyte, 2013; Mayer, Tillisch, & Gupta, 2015; Mosca et al., 2016; Sandhu et al., 2016), including depression (Evrensel & Ceylan, 2015), is a developing field of study. The microbiota aid in the digestion of food, including fermented food, that the human gut is unable to digest on its own (Conlon & Bird, 2015; Devaraj et al., 2013; Neish, 2009; Qin et al., 2010; Puertollano, Kolida, Yaqoob, 2014; Mayer, et al., 2015; Huttenhower et al., 2012; Manichanh et al., 2006).

Fermentation of food is an ancient form of food preservation and has practical and nutritional health benefits (Foroutan, 2012; Selhub, Logan, & Bsted, 2014), and transports bacteria to the gut (Marco et al., 2017; Raak, Ostermann, Boehm, & Molsberger, 2014). Fermented foods introduce functional microorganisms that inoculate the gut with beneficial bacteria (Aslam et al., 2018) and enhance the ecology of the gut (Rastall et al., 2005). Fermentation of food introduces microorganisms, including bacteria and yeasts, to begin the process (Aslam et al., 2018) whereby the nutritional value and bioavailability of food is transformed (Aslam et al., 2018; Conlon & Bird, 2015; Marco et al., 2017; Raak et al., 2014; Tamang, Shin, Jung, & Chae, 2016; Selhub et al., 2014). Bacterial metabolites affect the gut-brain axis (GBA) and hypothalamus-pituitary-adrenal (HPA) axis which have a known effect on behavior (Carabotti, Scirocco, Maselli, & Severi, 2015; Wang & Jia, 2016; Gorvitovskaia, Holmes, & Huse, 2016; Li, Dowd, Scurlock, Acosta-Martinez, & Lyte, 2009; Zhou et al., 2014; Diaz-Heijtz et al., 2011; Mayer et al., 2015; Lyte, 2013; Siddharth, Holway, & Parkinson, 2013; Bruce-Keller, Salbaum, & Berthoud, 2018).

Depression is one of the most prevalent domestic disorders (NIMH, 2017; WHO, 2017) and is the preeminent cause of disability worldwide (American Psychiatric Association, 2018). Furthermore, it creates an annual domestic economic cost of \$210.5 billion (APA, 2018). This number excludes the indirect costs of days not worked and diminished productivity (APA, 2018). Major depression is defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) as loss of pleasure or feeling combined with a depressed mood for two weeks or longer (NIMH, 2017), and an inability to function due to a combination of lifestyle factors including disordered energy, sleep or eating, self-image issues, and/or suicidal thoughts (NIMH, 2017). Research supports multiple therapies for the treatment of depression yet, the dominant

medical model continues with a singular treatment method utilizing pharmacological agents as first line of defense (Freeman et al., 2010; Larzelere, James, & Arcuri, 2015; Olfson, Blanco, & Marcus, 2016; Siu et al., 2016). The ingestion of fermented, fiber-rich foods affects depression through a complex series of relationships between the central nervous system (CNS), the enteric, immune, and neuroendocrine systems (Selhub et al., 2014; Chilton, Burton, & Reid, 2015) which modulate one another (Daruna, 2012) bi-directionally (Li et al., 2009; Zhou et al., 2014). Many researchers agree the ingestion of fermented foods affects physical and emotional health, including depression (Tamang et al., 2016; Foroutan, 2012; Mugula, Nnka, & Sorhaug, 2003; Selhub et al., 2014; Chilton, Burton, & Reid, 2015; Pham et al., 2014; Zhu et al., 2011; Sonedstedt et al., 2011; Keszei, Schouten, Goldbohm, & van den Brandt, 2009). Therefore, the purpose of this research is to explore the relationship between fermented foods and depression.

Following this introductory chapter, we present a review of the literature including the human gut microbiome, gut-brain axis, hypothalamus-pituitary-adrenal (HPA) axis, depression, fermentation, and summary. In the lenses chapter, we define the theoretical lenses and paradigm that provide a framework for this research and include a description of researcher lenses as well as the collective lens of the team. Next, we discuss the research method for this project. Finally, we present the results and discuss the findings.

Literature Review

The purpose of this chapter is to review the current research regarding the relationship between the gut microbiome, fermented food, and depression (Perna, Intaglietta, Simonetti, & Gambacorta, 2013; Marco et al., 2017; Raak et al., 2014). First, we define the human gut microbiome and discuss its importance to human health and behavior, including food digestion, metabolism, immunity, inflammation, and dysbiosis. Second, we address the gut-brain axis, its bi-directionality and communication between the enteric and central nervous systems. Third, we present the HPA axis and how it relates to stress and immunity. Fourth, we define depression as a complex disease with multiple causative factors. Fifth, we explain fermentation, and its practical and physiologic roles as well as concerns of ingestion of fermented food. Lastly, after exposing the research gap in the literature, we present a summary of the reviewed literature and propose our research question.

Human Gut Microbiome

The gut microbiome plays a complex and varied role in human health and behavior (Aarts et al., 2017; Adamset al., 2011; Allen et al., 2016; Bailey et al., 2011; Bharwani et al., 2016; Dominianni et al., 2014; Lyte, 2013; Mayer et al., 2015; Mosca et al., 2016; Sandhu et al., 2016). Specifically, microbiota have a role in food digestion, which affects metabolism, inflammation, immunity, and dysbiosis (Neish, 2009; Hooper, Midtvedt & Gordon, 2002; Topping & Clifton, 2001; Besten; Qin et al., 2010; Kau, Ahern, Griffin, Goodman, & Gordan, 2011; Fukuda et al., 2011; den Besten et al., 2013), all of which may contribute to depression (Perna et al, 2013; Marco et al., 2017; Raak et al., 2014). Citizen science projects involving crowd sourced data, from any individual providing a sample, allow for a large number of samples to be collected and studied regarding the effects of microbiota on human health (Del

Sivio, Prainsack & Buyx, 2016). Simultaneously, genetic sequencing, algorithms, and software advancements provide the ability to identify and organize bacterial data which lead to a fuller understanding of human biomes (Del Sivio et al., 2016).

Several distinct microbiomes exist in/on the human body; including mouth, lung, genitalia, and skin, (Slattery, MacFabe, Kahler, & Frye, 2016). However, the gut is the center for microbial activity, as 99% of human microbial population resides there (Mosca et al., 2016; Slattery et al., 2016). The human gut is host to over trillions of microscopic, uni- and multi-cellular microorganisms (Mangiola, 2016), each containing their own DNA. These microorganisms are so vast they outnumber human DNA 10 to 1 (Cryan & Dinan, 2012; Wiley et al., 2017). Microorganisms are collectively known as microbiota and include commensal (communal), symbiotic (interdependent), and pathogenic (disease producing), bacteria, yeasts, fungi and viruses (Marieb, 2015), which interact with the environment and develop an ecosystem known as a microbiome (Mosca et al., 2016). The gut microbiome's role in food digestion affects metabolism, inflammation, immunity, and dysbiosis (Mayer et al., 2015).

Food digestion. Individuals require symbiotic bacteria to digest food nutrients (Conlon & Bird, 2015; Huttenhower et al., 2012; Manichanh et al., 2006; Neish, 2009). Symbiotic bacteria constitute approximately one third of an individual's gut-bacteria, are common among healthy adults, and vary along the length of the digestive tract (Huttenhower et al., 2012). Common gut-bacteria include: *Bifidobacterium*, *Lactobacillus*, *Bacteroides*, *Clostridium*, *Escherichia*, *Streptococcus*, and *Ruminococcus* (Conlon & Bird, 2015). Additionally, different bacteria reside in varied locations along the digestive tract. For example, an abundance of *Firmicutes* and *Bacteroidetes* reside in the large intestine, and *Streptococcaceae* and *Actinobacteria* reside in the colon (Conlon & Bird, 2015). Bacterial abundance and location assist the fermentation of

undigested food, thus enabling absorption of nutrients, particularly complex carbohydrates (Conlon & Bird, 2015).

Plants, such as fruits and vegetables, are complex carbohydrates which contain saccharides and dietary fiber (Kau et al., 2011). The human digestive system has an inadequate store of enzymes to digest plant polysaccharides derived from the consumption of complex carbohydrates (Qin et al., 2010; Kau et al., 2011). Therefore, the human host relies on the help of bacteria to produce necessary enzymes for complete digestion via fermentation (Conlon & Bird, 2015; Devaraj et al., 2013; Neish, 2009; Qin et al., 2010). Specifically, the microbiota break down the indigestible by the human host dietary complex carbohydrates (Conlon & Bird, 2015; Devaraj et al., 2013; Neish, 2009, Qin et al., 2010; Puertollano et al., 2014) into oligo- and monosaccharides (Puertollano et al., 2014), which they then ferment, resulting in organic acid metabolites, known as short-chain fatty acids (SCFAs) specifically, propionate, acetate, and especially butyrate (Puertollano et al., 2014). Short chain fatty acids are linked to intestinal homeostasis (Puertollano et al., 2014). *Clostridium* and *Bifidobacterium* are particularly efficient bacteria at producing SCFAs (Neish, 2009; Turnbaugh et al., 2006.) and provide 5-15% of the human energy required for healthy colonic epithelium (Neish, 2009). Digestion is the mechanical process to break down food into smaller components and metabolism is the physiologic process to utilize food for energy (Braun, 2017; Austin, 2010).

Metabolism. Microbial colonies in the gut affect metabolism by fermenting dietary fiber to produce SCFAs (den Besten et al., 2013). Short chain fatty acids are transported via the bloodstream to various organs (den Besten et al., 2013). The most abundant SCFAs include: butyrate, acetate, and propionate (Neish, 2009; Hooper et al., 2002; Topping & Clifton, 2001; Qin et al., 2010; Kau et al., 2011; Fukuda et al., 2011; den Besten et al., 2013), which “appear in

a 3:1:1 ratio” (Puertollano et al., 2014, p. 140). Although all three SCFAs are important for energy, butyric acid is especially important to epithelial cells of the colon (colonocytes) which take up most of the butyric acid (den Besten et al., 2013). The epithelial cells depend upon butyric acid for over 60% of their energy (den Besten et al., 2013), which is needed for regeneration and maintaining a healthy epithelial intestinal barrier (Puertollano et al., 2014; den Besten et al., 2013; Chang, Hao, Offermanns, & Medzhitov, 2014). A healthy epithelial lining prevents leakage of toxic substances and microbiota into the bloodstream, maintaining intestinal wellness (Kau et al., 2011; Fukuda et al., 2011). The remaining butyrate, propionate and acetate travel via the bloodstream (den Besten et al., 2013; Puertollano et al., 2014, Slavin, 2013) to various tissues providing energy and executing roles in regulating fatty acid metabolism (den Besten et al., 2013), glucose metabolism (den Besten et al., 2013) and cholesterol metabolism (den Besten et al., 2013). However, the mechanism for uptake from the bloodstream to tissue is not yet understood (den Besten et al., 2013). The SCFAs also affect immunity and inflammation (Kau et al., 2011; Bird et al., 1998; den Besten et al., 2013; Puertollano et al., 2014; Kim, Gocevski, Wu, & Yang, 2010; Chang et al., 2014).

Immunity. The intestines provide most of the body’s immunity (Chassaing, Kumar, Baker, Singh, & Vijay-Kumar, 2014) and affect the relationship between the host and the gut-bacteria (Chassaing et al., 2014). The bacteria and the host remain in constant connection acting as partners to maintain homeostasis of the gut (Chassaing et al., 2014). Due to the sensitivity of this balance, a mucosal immune system (MIS) is required to protect the host from pathogens (Chassaing et al., 2014). The mucosal lining is a chemical and physical barrier between the gut and the bloodstream (Chassaing et al., 2014). It contains proteins, whose proliferation cause

cancer and their deficit can cause inflammation (Chassaing et al., 2014; Kau et al., 2011; Bird et al., 1998).

The absence of appropriate gut bacteria can lead to poor signaling and inadequate epithelial lining of the intestine, which leads to metabolite leakage from the gut into the bloodstream (Hsiao et al., 2013) inducing anxiety-like behavior in mouse models (Hsiao et al., 2013). Normal metabolite serum levels in the mice were restored by introducing *Bacteroides fragilis* through food (Hsiao et al., 2013). Microbiota metabolites may affect neurodevelopmental processes among other systems in the body and may be managed with commensal therapies (Hsiao et al., 2013). Immune function requires the action of T-cells (Gomez, Luckey, & Taneja, 2015). Adequate levels of butyrate suppress the immune reaction through the action of macrophages and inflammation markers (Chang et al., 2014).

Inflammation. Healthy commensal bacteria produce butyrate, a product of carbohydrate fermentation (Puertollano et al., 2014). When an individual lacks enough carbohydrate in the form of fiber which feeds the butyrate producing bacteria, the body mistakes having a low fiber intake as having pathogenic gut bacteria and initiates an immune response resulting in inflammation (Kuo, 2013; Chang et al., 2014). Appropriate levels of butyrate also increase the efficiency of T cells, which are essential in the regulation of intestinal inflammation, (Puertollano et al., 2014) and help restore balance to intestinal inflammation (Puertollano et al., 2014). An overabundance of *Bilophila wadsworthia* in animal-based diets affects inflammation (Manichanh et al., 2006). Too few microbiota and low bacterial diversity lead to dysbiosis (Huttenhower et al., 2012; Turnbaugh et al., 2009; Qin et al., 2010).

Dysbiosis. An imbalance of gut organisms creates dysbiosis of the gut (Hooks & O'Malley, 2017). Inflammation is one of the causes of dysbiosis, characterized by a decrease in

diversity or abundance of beneficial bacteria, and an increase in pathogenic bacteria (Hooks & O'Malley, 2017). A mutually beneficial or commensal relationship exists between the microflora and the human gut host (DeGruttola, Low, Mizoguchi, & Mizoguchi, 2016). Gorvitovskaia et al. (2016) indicate that considerable research has focused on what an unhealthy (dysbiotic) microbial community in the gut looks like, as well as a healthy (eubiotic) gut community. These characterizations are not independent and can occur simultaneously (DeGruttola et al., 2016). Certain bacteria are markers in dysbiosis depending upon their abundance (or lack of) in the gut. These bacteria include: *bacteroidetes*, *firmicutes*, *bifidobacteria*, *lactobacillus*, and *prevotella* (DeGruttola et al., 2016). While certain bacteria are actors within the play of dysbiosis, dysbiosis is associated with the imbalance of the whole ecosystem of the gut versus relating a single bacterium to a disease state (DeGruttola et al., 2016).

Dysbiosis is prevalent in multiple disease states including diabetes, obesity, irritable bowel disease (IBD), autism spectrum disorder (ASD), anxiety, depression, cognitive dysfunction, and cancer (DeGruttola et al., 2016). However, dysbiosis as a cause or an effect of these differing diseases is still unknown (DeGruttola et al., 2016; Hooks & O'Malley, 2017). These diseases do not exist in isolation and it is difficult to look at them in a reductive manner. Homeostasis is the desired state to avoid the possible causal effects of dysbiosis (DeGruttola et al., 2016). A dysbiotic gut affects digestion and immunity by way of the gut-brain-axis (GBA) (Carabotti et al., 2015; Wang & Jia, 2016; Gorvitovskaia et al., 2016; Li et al., 2009; Zhou et al., 2014; Diaz-Heijtz et al., 2011; Lyte, 2013; Siddharth et al., 2013).

Gut-brain axis. The GBA is a bi-directional axis running between the gut and the brain (Carabotti et al., 2015; Wang & Jia, 2016; Gorvitovskaia et al., 2016; Li et al., 2009; Zhou et al., 2014; Diaz-Heijtz et al., 2011; Mayer et al., 2015; Lyte, 2013; Siddharth et al., 2013). Possible

pathways of the GBA include communication between the central nervous system (CNS) and the enteric nervous system (ENS) (Sherman, Zaghouani, & Niklas, 2015). The communicative relationship between the central and enteric nervous systems effects gastrointestinal homeostasis and behavioral patterns (Carabotti et al., 2015). The ENS includes neural circuits that control mucosal and secretion transport, blood flow, motor functions, immune modulation, and the function of the endocrine system (Marieb, 2015). This communication links the brain including cognitive and emotional centers with the peripheral intestinal function. The signaling occurs via neural, endocrine humoral links (Li et al., 2009; Zhou et al., 2014) that travel in a bi-directional manner.

The signal travels from the gut to the brain through gut microbiota that affect dysbiosis or intestinal permeability (Butwicka et al., 2017; Gungor, Suna-Celioglu, Ozel-Ozcan, Gungor-Raif, & Ayse-Selimoglu, 2013, Luna et al., 2017; Mayer et al., 2015; Niederhofer, 2011; Kang et al., 2017) which affects neuroendocrine signaling (Aarts et al., 2017; Sandhu et al., 2016; Sudo et al., 2004) via the hypothalamus-pituitary-adrenal (HPA) axis. For example, stress affects the function of the immune system which affects the expression of depression (Sarris et al., 2015; Cryan & Dinan, 2012).

Hypothalamus-pituitary-adrenal-axis. The HPA axis is the primary system through which the human body responds to stress (Daruna, 2012). Stress influences the hypothalamus to secrete corticotropin releasing hormone (CRH) (Daruna, 2012) which alerts the pituitary gland to release adrenocorticotrophic hormone (ACTH) into the bloodstream (Spinedi & Negro-Vilar, 1983) through which it travels to the adrenal glands, where it influences the release of cortisol (Spinedi & Negro-Vilar, 1983). Serotonin affects the release of ACTH from the pituitary gland (Spinedi & Negro-Vilar, 1983; Coewen, & Browning, 2015; Reigstad et al., 2014) and bi-directionally increases CRH release (Daruna, 2012; Coewen & Browning, 2015; Reigstad et al., 2014) which affects the immune response which influences tryptophan metabolism (Jenkins, Nguyen, Polglaze, & Bertrand, 2016; Bouchard, Bellinger, Wright, & Weisskopf, 2010; Shultz et al., 2015). Tryptophan metabolism (de Theije et al., 2014; Bailey et al., 2011; Petra et al., 2015; Luna et al., 2017) and metabolite production (Bouchard et al., 2010; Shultz et al., 2015) via the vagus nerve (Petra et al., 2015; Sandhu et al., 2016) result in potentially poor behavioral expressions (Carabotti et al., 2015) such as depression (Cryan & Dinan, 2012). An imbalance of healthy gut flora initiates an immune response causing the release of pro-inflammatory cytokines, chemical messengers that communicate with other immune cells in the brain and throughout the body (Carabotti et al., 2015). A change in cytokine levels originating in the gut activates the microglia causing neurons of the brain to inappropriately fire, creating over sensitivity to external stimulation disabling focus and resulting in frustration and behavior issues (Carabotti et al., 2015). The signal can change direction and flow from brain to gut in situations of stress (Aarts, et al., 2017; Allen et al., 2016; Bailey et al., 2011; Bharwani et al., 2016; Rucklidge et al., 2014; Shultz et al., 2015) which influences our mental health, behavior, and potentially, depression (Jenkins et al., 2016).

Depression

The leading cause of global adverse health and disability is depression (WHO, 2017; American Psychiatric Association [APA], 2018). Globally, over 300 million people live with depression (WHO, 2017). Additionally, depression is the projected primary contributor to lowered worldwide health by 2030 (Lopez & Mathers, 2006). Depression is defined by a significant mood change lasting at least two weeks, irrespective of grief, medical conditions or substance abuse, accompanied by more than one of the following: disordered sleep, appetite, or energy, poor concentration, feelings of worthlessness or guilt, and suicidal thoughts (APA, 2017; Belmaker & Agam, 2008; Depressive Disorders, 2013). Additionally, Nesse and Ellsworth, (2009) state depression may be an adaptation to overcome scarcity and overly challenging situations such as climate, stress, poverty, insufficient social support, unemployment (Chentsova-Dutton, Tsai, & Gotlib, 2010; National Institutes of Mental Health [NIMH], 2001).

Data from the United States National Health and Nutrition Examination Survey (NHANES) 2013-2016 indicates that 8.1% of adults over the age of 20 report experiencing depression (Brody et al., 2018). Eighty percent of adults with depression report difficulty with daily activities resulting in an escalating challenge to individuals and society that includes emotional suffering, increased time off work, lost wages, termination of education, deterioration of relationships, and impaired parental functioning (Brody et al., 2018; Kessler, 2012; Siu et al., 2016; APA, 2018). Furthermore, depression creates an annual domestic economic cost of \$210.5 billion (APA, 2018) which excludes the indirect costs of days not worked, and diminished productivity (APA, 2018).

Depression is a complex disease with multiple causative factors including stress, genetics, biological, social, environmental, and cultural (APA, 2017; Belmaker & Agam, 2008;

Bembnowska & Josko-Ochalska, 2015). For the purposes of this research, we address the influence of stress. The CNS, enteric, immune, and endocrine systems collaboratively govern physical and emotional stress (Varghese & Brown, 2001). For example, the brain influences the rate of digestion and affects the epithelial lining of the intestinal wall which affects immunity (Selhub et al., 2014; den Besten et al., 2013). In turn, bacteria of the gut aid in digestion and immunity by way of the GBA (Carabotti et al., 2015; Wang & Jia, 2016; Gorvitovskaia et al., 2016; Li et al., 2009; Zhou et al., 2014; Diaz-Heijtz et al., 2011; Lyte, 2013; Siddharth et al., 2013) and HPA (Bruce-Keller et al., 2018) which together respond to stressors affecting our mind, and influencing our brain, thus, affecting our behavior and potentially depression (Selhub et al., 2014; Jenkins et al., 2016). Specifically, stress influences the hypothalamus to release corticotropin releasing hormone (CRH) (Daruna, 2012) which signals the pituitary gland to release adrenocorticotrophic hormone (ACTH) into the bloodstream (Spinedi & Negro-Vilar, 1983), through which it travels to the adrenal glands, where it influences the release of cortisol (Spinedi, & Negro-Vilar, 1983). Serotonin affects the release of ACTH from the pituitary (Spinedi, & Negro-Vilar, 1983; Coewen, & Browning, 2015; Reigstad et al., 2014) and bi-directionally, serotonin increases CRH release (Daruna, 2012; Coewen, & Browning, 2015; Reigstad et al., 2014), affecting the immune response which influences tryptophan metabolism (Jenkins et al, 2016, Bouchard et al., 2010; Shultz et al., 2015). Tryptophan affects serotonin synthesis (Jenkins et al., 2016; Reigstad et al., 2014) and decreased serotonin affects depression (Jenkins et al., 2016; Reigstad et al., 2014). Individuals with depression experience this feedback loop as decreased plasma level of tryptophan influences peripheral inflammation (Coewen & Browning, 2015) which further affects depression by decreasing plasma tryptophan, thus, decreasing the influence of serotonin on brain function and depression (Coewen & Browning,

2015; Reigstad et al., 2014). Similarly, the ingestion of fermented fiber-rich foods affects depression through a complex series of relationships of the central nervous system (CNS), the enteric, immune, and neuroendocrine systems (Selhub et al., 2014; Chilton, Burton, & Reid, 2015) which modulate one another (Daruna, 2012) bi-directionally (Li et al., 2009; Zhou et al., 2014) and affect serotonin synthesis (Spinedi & Negro-Vilar, 1983; Coewen & Browning, 2015; Reigstad et al., 2014; Daruna, 2012; Coewen & Browning, 2015; Reigstad et al., 2014); thus, depression (Jenkins et al., 2016; Reigstad et al., 2014).

Experimentally, fermented foods show an increase in anti-depressive qualities (Selhub et al., 2014; Chilton, Burton, & Reid, 2015; Pham et al., 2014; Zhu et al., 2011; Sonedstedt et al., 2011; Keszei et al., 2009) and a decreased risk of depression in humans by 25-30% (Selhub et al., 2014; Chilton, Burton, & Reid, 2015). Many researchers agree, that ingestion of fermented foods affect physical and emotional health, including depression (Tamang et al., 2016; Foroutan, 2012; Mugula et al., 2003; Selhub et al., 2014; Chilton, Burton, & Reid, 2015; Pham et al., 2014; Zhu et al., 2011; Sonedstedt et al., 2011; Keszei et al., 2009).

Fermentation

Fermentation is typically an anaerobic process involving functional and non-functional bacteria and yeasts (Conlon & Bird, 2015; Marco et al, 2017; Raak et al., 2014; Tamang et al., 2016; Selhub et al., 2014). The biological process of fermentation detoxifies, preserves, enriches, and enhances the nutrients in food (Marco et al., 2017; Raak et al., 2014). However, bacterial populations are challenging to capture across studies as bacteria in fermented foods such as sauerkraut and kimchi, vary by batch, location, and timing of production. (Kaplan & Hutkins, 2000). This is one reason why fermented foods are not probiotics (Dennett, 2018). Probiotics

have a specific number of documented live microbes with observed health benefits (Mack, 2005), and are identified in reproducible, clinical trials (Kaplan & Hutkins, 2000).

Fermented food has a long history among worldwide cultures (Marco et al., 2017; Chilton, Burton, & Reid, 2015, Kim et al., 2016) with their earliest record of existence in the Fertile Crescent in 6,000 B.C.E. (Foroutan, 2012) contributing up to one third of the human diet worldwide (Chilton, Burton, & Reid, 2015). Numerous combinations of microbes and food can be made to create fermented foods. Examples of traditional foods include sauerkraut from Germany, cheese from the United Kingdom, soy from Japan, kimchi from Korea, and yogurt from Greece (Chilton, Burton, & Reid, 2015; Selhub et al., 2014). Practically, fermentation preserves foods, decreases the need for refrigeration (Tamang, Tamang, Schillinger, Guigas & Holzappel, 2009; Marco et al, 2017; Raak et al., 2014) and transforms some poisonous foods to edible foods (Tamang, et al., 2009), such as West African fish garra (Foroutan, 2012) and Tanzanian maize-sorghum togwa (Foroutan, 2012; Mugula et al., 2003). Additionally, fermented food promotes hospitality and feelings of friendship within and across cultures (rank.org, 2018) therefore, the ingestion of fermented food may be beneficial to overall health (Chilton, Burton, & Reid, 2015; Torres, Driscoll, & Voell, 2012), including the potential to globally influence rates of depression in a positive way (Leary, 1990).

Fermentation is the process whereby different microbiota convert carbohydrates into simpler sugars producing various metabolites and energy (Marco et al., 2017; Chilton, Burton, & Reid, 2015). Specifically, fermentation increases the nutritional value of food, provides short chain fatty acid metabolism, B vitamins, amino acids, antioxidants (Perna et al., 2013; Marco et al., 2017; Raak et al., 2014) and antimicrobials (Marco et al., 2017; Raak et al., 2014) creating compounds such as alcohol and energy (Conlon & Bird, 2015; Devaraj et al., 2013; Neish, 2009;

Puertollano et al., 2014; Chilton, Burton, & Reid, 2015; Kim et al., 2016). For example, yeast produces alcohol and carbon dioxide; *Acetobacter* produce acetic acid; *Leuconostoc*, *Lactobacillus* and *Streptococcus* produce lactic acid; *Propionibacterium freudenreichii* produce propionic acid; and *Bacillus* or molds produce ammonia and fatty acids (Marco et al., 2017; Chilton, Burton, & Reid, 2015). The ingestion of fermented foods transports bacteria into the host gut (Marco et al., 2017; Raak et al., 2014) potentially outcompeting pathogens, aiding gut-barrier function, and benefiting metabolite production (Kaplan & Hutkins, 2000), thereby, enhancing the basic nutritional components of a food beyond its inherent nutritional components (Raak et al., 2014).

Positive attributes of fermented food related to health are well documented in the literature (Kim et al., 2016; Marco et al., 2017; Selhub et al., 2014; Chilton, Burton, & Reid, 2015) yet, research on daily dosage is lacking (Aslam et al., 2018). Concerns regarding fermented food also exist (Islami, Ren, Taylor, & Kamangar, 2009; Ren, Kamangar, Forman, & Islami, 2012; Aslam et al., 2018). For example, fermented vegetables have been linked with esophageal (Islami et al., 2009) and gastric (Ren et al., 2012) cancers, antibiotic resistance (Mathur & Singh, 2005), and histamine intolerance (Maintz & Novak, 2007). Both positive and negative aspects of the bacteria in fermented food have the potential to affect the gut, digestion and immunity by way of the GBA (Carabotti et al., 2015; Wang & Jia, 2016; Gorvitovskaia et al., 2016; Li et al., 2009; Zhou et al., 2014; Diaz-Heijtz et al., 2011; Lyte, 2013; Siddharth et al., 2013) and HPA (Bruce-Keller et al., 2018). These bi-directional and complex pathways are influenced by stress, affecting our mind, mood and brain activity (Kim et al., 2016) potentially leading to depression (Selhub et al., 2014; Jenkins et al., 2016).

Literature Review Summary

The relationship or ecosystem that develops between microbiota and their environment is called a microbiome (Mosca et al., 2016). The gut is one of several distinct microbiomes that exists in the human body (Slattery et al., 2016). A diverse population and balance of microbiota are necessary within the gut microbiome to digest carbohydrates which are un-digestible by the human host (Conlon & Bird, 2015; Devaraj et al., 2013; Neish, 2009; Qin et al., 2010; Puertollano et al., 2014; Mayer, et al., 2015; Huttenhower et al., 2012; Manichanh et al., 2006). This bacterial digestion process results in metabolite production (Puertollano et al., 2014) and neuroendocrine signaling (Bouchard et al., 2010; Shultz et al., 2015; Aarts et al., 2017; Sandhu et al., 2016; Sudo et al., 2004; Evrensel & Ceylan, 2015) via the bi directional (Li et al., 2009; Zhou et al., 2014) gut-brain axis (GBA) (Carabotti et al., 2015; Wang & Jia, 2016; Gorvitovskaia et al., 2016; Li et al., 2009; Zhou et al., 2014; Diaz-Heijtz et al., 2011; Mayer et al., 2015; Lyte, 2013; Siddharth et al., 2013) and hypothalamus-pituitary axis (HPA) (Bruce-Keller et al., 2018) which affects human physical and mental health (Aarts et al., 2017; Adams et al., 2011; Allen et al., 2016; Bailey et al., 2011; Bharwani et al., 2016; Dominianni et al., 2014; Lyte, 2013; Mayer et al., 2015; Mosca et al., 2016; Sandhu et al., 2016), including depression (Evrensel & Ceylan, 2015). An imbalance of population and/or lack of diversity of bacteria within the gut microbiome is known as dysbiosis (Hooks & O'Malley, 2017) and has the potential to affect physical health (Butwicka et al., 2017; Gungor et al., 2013, Luna et al., 2017; Mayer et al., 2015; Niederhofer, 2011; Kang et al., 2017) and mental health through neuroendocrine signaling (Aarts et al., 2017; Sandhu et al., 2016; Sudo et al., 2004), tryptophan metabolism (de Theije et al., 2014; Bailey et al., 2011; Petra et al., 2015; Luna et al., 2017), and metabolite production (Bouchard et al., 2010; Shultz et al., 2015).

One way to facilitate a balanced and varied gut microbiome is the ingestion of fermented food which introduces beneficial bacteria into the diet (Marco et al., 2017; Raak et al., 2014). Bacterial metabolites affect the GBA and HPA which have a known effect on behavior (Carabotti et al., 2015; Wang & Jia, 2016; Gorvitovskaia et al., 2016; Li et al., 2009; Zhou et al., 2014; Diaz-Hejtz et al., 2011; Mayer et al., 2015; Lyte, 2013; Siddharth et al., 2013; Bruce-Keller et al., 2018). Depression is the leading cause of global adverse health and disability (WHO, 2017) and is a complex disease with multiple influencing factors, including the gut microbiome (Reichenberg et al, 2001; Evrensel & Ceylan, 2015). We explored the literature and found that no systematic review of the relationship between fermented foods and depression exists. Moreover, the literature demonstrates complexities and challenges due to interdisciplinary and multi-faceted approaches complicated by jargon. Therefore, the research question is, does the ingestion of fermented foods affect depression?

Lenses

The purpose of this chapter is to articulate the relevant research lenses that have influenced the development and implementation of this study. While lenses are not always specifically noted in published studies, we recognize how important it is to expose them given the changing landscape of research including the multiple epistemologies, axiologies, and cultures of inquiry, not to mention multiple methods of data collection and types of data collected. When researchers do not specify their underlying assumptions, readers can only speculate as to how these assumptions may have influenced the design of the study, data collection, data analysis, and conclusions drawn by the researchers. When researchers are transparent about these assumptions, they encourage their readers to think more critically about how these assumptions impact any type of research. Moreover, researchers who do this make it possible for readers to hold them accountable to the researcher's standards, rather than impose other potentially irrelevant standards. The reliability and validity of this study's findings may thus be more accurately assessed considering this full disclosure.

In this chapter, we first elaborate on how our research paradigm and culture of inquiry frames this research. Next, we describe the theoretical lenses guiding our study. This is followed by the articulation of individual and collective lenses and how they have influenced the development, implementation and interpretation of this study.

Research Paradigm and Culture of Inquiry

Our post-positivist paradigm with its critical realist ontology and its objective epistemology led us to the conclusion that a systematic review method was most appropriate for this study. The empirical approach taken in this study applies a systematic, scientific and reductionist approach. This empirical culture of inquiry called for a systematic review method to

find, synthesize and analyze the existing published clinical research. Four theoretical frameworks provide the necessary conceptual grounding for this study. They are: Holism Theory, Reductionism Theory, Gut-Brain-Axis Theory, and Community Ecology Theory. These theoretical lenses individually frame a certain aspect of our research and provide the framework to understand and interpret our results. We describe the four theories and illustrate how each theory pertains to our research. These theories are important to our discussion.

Theoretical Lenses

Four theoretical lenses frame this study: Holism Theory, Reductionism Theory, Gut-Brain-Axis Theory, and Community Ecology Theory. We briefly describe each theory below and articulate how it influenced the development, implementation, and interpretation of this systematic review.

Holism theory. The term holism, originally coined by Smuts, author of the book *Holism and Evolution* (Smuts, 1936), is derived from the Greek term *holos*, meaning whole or entire (Holism, 2019). The idea of holism contends that the properties of any system are more than the sum of its parts (McMillan, Stanga, & Van Sell, 2018; Smuts, 1936; McLeod, 2008). Rather than focusing on a discrete part of a system, holism considers the entire system. For example, a change in the body may affect the mind, and/or spirit (McMillan, Stanga, & Van Sell, 2018). Researching the connection of fermented foods, gut-brain-axis, and depression requires a holistic lens where any part of the system is more than the sum of its parts. However, we did not fully recognize this until we had completed the study. We attempted to conduct this research project by reducing the focus to how fermented foods influence depression. What we found is at this point in human research, it is too early to use this narrow of a lens, and holism theory would be more appropriate. First, we need to understand how the entire system - the gut microbiome, the

gut-brain-axis, and mental health are interconnected and influence each other. We do envision a time in the not too distant future that conducting this type of systematic review may help guide practice. Ultimately, depression affects the mind, body and spirit and must be viewed through a holistic lens. Holism is the antagonist of reductionism which considers systems at their most discrete level providing an incomplete scope (McMillan, Stanga, & Van Sell, 2018). This theoretical lens highlights the tension we encountered in this study between holism and reductionism.

Reductionism theory. There are three types of reductionism: ontological, methodological, and theoretical (New World Encyclopedia, 2015). Ontological reductionism accepts that all things can be reduced to fewer substances, considering their matter and motion. (New World Encyclopedia, 2015). Methodological reductionism attempts to explain phenomena in its most discrete measure (New World Encyclopedia, 2015). Theoretical reductionism is the process by which one theory absorbs another through bridging concepts (New World Encyclopedia, 2015). We used a reductionist view to develop, implement, and interpret this research project. By nature, a systematic review is the definition of reductionism because it attempts to review the published literature and distill it to a few key points. Because of this, reductionism significantly influenced our research process. Most research requires a reductionist perspective because the amount of data that is available is overwhelming and hard to synthesize and analyze. Our job as researchers is to condense overwhelming amounts of data into key data sets or key data points. A reductionist view influenced every aspect of our paper including the method of systematic review, researcher lenses and the empirical data we collected. As an example, our method of systematic review started with 64 articles and ended with two that we

used for analysis, however, the level of reductionism was too great - the two final articles were not comparable and were not useful in terms of providing suggestions for practice.

Gut-brain-axis theory. The human enteric system, central nervous system, and the mechanism of the HPA are complex and bi-directionally interconnected and influenced by gut-bacteria via the GBA (Miller, 2018). Signals travel from the gut to the brain (Butwicka et al., 2017; Gungor et al., 2013, Luna et al., 2017; Mayer et al., 2015; Niederhofer, 2011; Kang et al., 2017) which affect neuroendocrine signaling (Aarts et al., 2017; Sandhu et al., 2016; Sudo et al., 2004), tryptophan metabolism (de Theije et al., 2014; Bailey et al., 2011; Petra et al., 2015; Luna et al., 2017), and metabolite production (Bouchard et al., 2010; Shultz et al., 2015) via the vagus nerve (Petra et al., 2015; Sandhu et al., 2016). During stress, the signal can change direction and flow from brain to gut (Aarts, et al., 2017; Allen et al., 2016; Bailey et al., 2011; Bharwani et al., 2016; Rucklidge, Johnstone, Gorman, Boggis, Frampton, 2014; Shultz et al., 2015). Our understanding of the GBA is what led us to our particular research question, what is the relationship between fermented foods and depression? In particular, the bi-directional nature between the gut and the brain led us to wonder if eating fermented food might help with depression symptoms, an idea that is prevalent in the popular press and makes sense based on what we know about the gut-brain-axis theory. After completing the study, we are aware that it is the bi-directional nature of GBA relationships that makes our research question more complex than we initially anticipated because we can't definitively delineate how the triangular relationship among the gut, brain and the microbiome influence one another. We know that the abundance and prevalence of bacteria as well as their ability to function within a community of the gut is important to homeostasis (Chassaing et al., 2014) and maintaining homeostasis within

the community of the gut is critical to an individual's health and wellbeing (Davison & Kaplan, 2012; Stanga et al., 2007).

Community ecology theory. The framework for interactions of living organisms in communities including distribution and abundance of existing organisms within a population (Sahney & Benton 2008) as well as competition between taxonomic groups is the community ecology theory (Costello et al., 2012). This includes the cooperation or non-cooperation between different taxonomic populations, including the study of species abundance and diversity, productivity, and hierarchy within a community (Sahney & Benton, 2008). Species abundance fluctuates based on environmental influences (Costello et al., 2012).

We believe the community ecology theory should be considered in the research surrounding the ecology of the gut microbiota. What is unclear in the current literature is how changing one species/type of microbiota may influence the rest of the microbiota community. In addition, researchers could use community ecology theory to explore species counts, environmental influences, and the influence of the brain on the gut and the gut on the brain.

Individual and Collective Lenses

Next, we describe our individual lenses and how they influenced the development, implementation, and interpretation of this research project. We conclude by describing our collective lens.

Beth. My yoga and fitness professional lens and my personal lens are one and the same, and are rooted in post-positivist ontology, and in an empirical culture of inquiry. I value verifiability, accuracy, and consistency in knowledge, as it pertains to one reality. I further believe measurements and observations have the potential to be flawed by the measurer and observer. Specifically, my observations are limited by my critical ability to know what I

absolutely observe, and my observations are biased by my worldview and cultural lens.

Furthermore, I believe we humans individually hold worldviews and lenses which uniquely bias our individual observations; therefore, my lens dictates that the only way to get close to the truth is to look at it through multiple perspectives. This is the basis of my belief in holism, as it does not consider one aspect of an individual or one individual in isolation. Rather, its premise of wellness is based on all aspects of the individual, including wholeness, body, mind and spirit.

Susan. My professional worldview influences my approach to this research. I am situated in the post-positivist paradigm with an empirical axiology. By acknowledging my lens, the reader has a greater understanding of the evolution of the research. My professional lens stems from the post-positivist quasi-experimental model of the current dominant paradigm of research. It is from this frame of reference that I conduct my research. Professional experience as a researcher enables me to approximate objectivity when considering data and led to conducting a systematic review. My personal lens blends personal experiences with data to develop understanding. It incorporates the mind body spirit approach to interpreting life events.

Cathy. My professional training, first as a Registered Dietitian and a Registered Nurse, has been guided by the positivist paradigm. With positivism, scientific methodology is used for the order, prediction and control of life experiences. Order and control in nursing allows me to consistently provide safe care and promote health.

During my 25-year nursing career, I have cared for many who are suffering. The human condition and all its imperfections complicate the positivist ontology, rooted in the belief that there is one truth. Bearing witness to suffering has shifted my perspective to allow for human imperfections and I find myself more aligned with the post-positivist paradigm. The post-

positivist paradigm guides my research as I seek to approximate one truth and acknowledge that I cannot achieve absolute truth.

My professional role as a Registered Nurse exists in the biomedical model of health care. Nursing practice is unique in biomedicine in that it is evidence-based yet the tenets of nursing that focus on the health and wellbeing of the whole person bridge the gap to complementary and alternative medicine. My nursing philosophy, grounded in Jean Watson's Theory of Human Care (Watson, 2012) recognizes that inner harmony and healing can occur when the body, mind and spirit are in balance. Nurses, acting as facilitators, guide patients toward balance and healing. It can be challenging to practice nursing and facilitate personal wholeness in a complex, outcome focused biomedical system. This challenge propelled me to study holistic health and work to make this evidence-based care model accessible to everyone.

I witness the multifactorial effects of depression on many of the patients under my care. The suffering caused by depression significantly impacts individuals and families. Allopathic, evidence-based treatment protocols for depression do not consider the whole person and are often inadequate. In my own practice I want patients to have evidence-based complementary / alternative treatment options for depression.

As a graduate student in the Holistic Health Studies program at St. Catherine University, I have been immersed in a course of study that is changing my perception of health and wellness. Holistic health is not about the utilization of individual modalities for healing but rather a fundamental way of knowing and acceptance of the connection between the mind, body, and spirit to bring health and wholeness. The path to wholeness begins with food and the choices we make to nourish our bodies.

My desire to study the role of nutrition in health is rooted in my agricultural background. Though I grew up as a Caucasian female in a Midwestern suburb, my paternal grandfather was a vegetable farmer and I married a farmer. For thirty-five years, I have lived in a rural area and participated in the cycle of life that is agriculture eventually becoming co-owner of a small farm. I am interested in what influences our food choices and the consequences of those decisions. Food is central to our existence as humans and either contributes to or deters our state of health. I have observed with great curiosity and excitement the growing interest in farm-to-table and whole, natural foods to promote health. The fundamental shift in how we nourish our bodies, returning to our ancestral roots of simple, whole foods supports holistic health.

Collective. The experience of working as a team influences our project in two important ways. First, working as a team did not allow any one of our worldviews or biases to dominate our collective work. We collaborated and achieved consensus on every decision and wrote every word together which managed any one of our lenses from dominating the research process. Second, performing a systematic review forced us to consider the lenses, methods and results of other researchers. Their methodology informed our collective lens rather than having our collective lens bias their methodology. Consequently, results of this systematic review were potentially less biased by our team lens as we were forced to consider the lens of researchers outside of our team.

Method

The purpose of this chapter is to describe the research method used to systematically review the existing academic published body of literature to answer the question: Does the ingestion of fermented food affect depression? We are post-positivist researchers examining the relationship of gut microbiome, fermentation, and depression. Research on the relationship between gut microbiome and depression, which has increased over the last decade, presents a challenge to health care providers and academia to adopt clinical findings into practice. Theory, popular press, and emerging academic data suggest using fermented food to help with depression. However, to date, no one has systematically analyzed the academic data that does exist. Therefore, the empirical inquiry of a systematic review isolates insignificant and unsubstantial data from critical studies of significance and generalizes scientific findings (Boland, Cherry, & Dickson, 2017; Mulrow, 1994).

Complexities and challenges in the literature are due to inter-disciplinary and multi-faceted approaches to research complicated by language, necessitating critical comparison and distillation of data. Based on time, funding, and accessibility of literature, an empirical culture of inquiry is the best approach to distill and synthesize the available phenomenon to address our research question. The chapter includes first, a rationale for study design. Next, there is a description of instrumentation, sampling and data collection, and data analysis. Then comes a detail of design rigor. Finally, there is a discussion of ethical considerations and design-specific limitations.

Rationale for Study Design

This study is framed in a post-positivist paradigm with an empirical culture of inquiry using a systematic review of the literature as the method. The post-positivist paradigm is non-

dogmatic and does not allow for one truth (Ryan, 2006). While positivists require reproducible results from established scientific methods to evidence a truth, a post-positivist accepts this truth and realizes that their senses, biases, and lenses affect the way they interpret the truth, therefore, multiple truths may exist (Ryan, 2006). The postpositivist ontology, the nature of reality, is based on researcher interpretation (Wahyuni, 2012) of one truth. The epistemology, how we know what we know, focuses on observable data to describe phenomena in an objective manner (Wahyuni, 2012). The axiology, research values, of the post-positivists include order, prediction, and control. As such, a benefit of the post-positivist paradigm allows for flexibility in learning in place of rigid testing (Ryan, 2006). An inadequacy of this paradigm is the lack of consideration for the complexity and non-empirical evidence of phenomena, which may lead to dismissal of data (Ryan, 2006).

Observation and research are the foundation of empirical evidence (Bradford, 2017). The empirical culture of inquiry records observations and experiences to gather data (Bradford, 2017). We used the empirical culture of inquiry, grounded in the scientific method, to search the literature and methodically distill the individual studies to a final number of articles, that are evaluated and presented in narrative synthesis (Boland et al., 2017; Popay et al., 2006). A strength of the empirical culture of inquiry is its generalizability and reproducibility, enhancing validity and reliability, which are paramount (Boland et al., 2017). A drawback of this culture of inquiry is the inability to suggest new theories as theory is the foundation that guides the empirical culture of inquiry (Weibelzahl & Weber, 2002). This was the only culture of inquiry that spoke to us as post-positivist researchers as it used observable and measured data to describe phenomena in an objective reproducible manner, therefore, we did not consider other research methods.

Within our empirical culture of inquiry, we used the systematic review method which locates, assigns quality, and synthesizes published evidence to answer our research question (Boland et al., 2017; Popay et al., 2017). The rigorous design and use of protocol in a systematic review reduces researcher bias, allows for replication of studies and evaluates consistencies and inconsistencies of data (Mulrow, 1994). We used a transparent and reproducible methodology including a comprehensive search of the literature to identify possible studies for inclusion. We used three tools to assess risk of bias: Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA), Revised Cochrane Risk of Bias Tool for Randomized Trials (RoB2), and A Measurement Tool to Assess systematic Reviews (AMSTAR 2). We provided synthesis and orderly presentation of study characteristics and outcomes (Liberati et al., 2009). The strength of this method is well defined transparent steps, allowing for reproducibility (Boland et al., 2017). Researchers undertaking a systematic review develop critical analytical skills and a breadth of understanding of multiple research methods (Boland et al., 2017). Results of systematic reviews can identify where evidence is lacking and propose new areas of study (Egger et al., 2008).

A potential limitation of a systematic review is publication bias, where studies with positive findings are more likely to be published (Egger, Dickersin, & Smith, 2008). Another limitation is researcher bias where inclusion criteria has the potential to bias results if the research team has knowledge of specific study outcomes they want to include (Egger et al., 2008).

Instrumentation

In conducting this systematic review of scientific articles related to fermented food and depression, we used three tools validated and accepted by the research community (Kim et al.,

2013, Boland et al., 2017, Shea et al., 2017): PRISMA, Revised Cochrane Risk of Bias Tool for Randomized Trials (RoB2), and A Measurement Tool to Assess Systematic Reviews (AMSTAR 2). Standardized tools enhance the rigor and validity in a systematic review (Boland et al., 2017). Tools help reduce researcher bias and allow for study replication and evaluate consistencies and inconsistencies of data (Mulrow, 1994). We describe each in more detail below.

PRISMA. PRISMA includes a 27 item, evidence-based standard protocol and checklist (see Appendix A) as well as a flowchart (see Figure 1), used for transparency and reporting consistency in systematic reviews in health care (Boland et al., 2017; Liberati et al., 2009). Developed by a multi-disciplinary group of individuals, PRISMA reduces flawed reporting and improves transparency of data (Liberati et al., 2009). We used the PRISMA flowchart to determine which articles to review for inclusion (see Figure 1). There is little data to state its effectiveness, validity, and reliability; however, author compliance to the guidelines may improve the quality of systematic reviews (Liberati et al., 2009). The PRISMA checklist identifies the most relevant items when reporting systematic reviews including: abstract, introduction, methods, results, discussion, and funding (Liberati et al., 2009). A strength of using PRISMA is the identification of critical components for evaluation across studies (Liberati et al., 2009). A PRISMA drawback is its emergence in 2007 and testing confinement to systematic reviews of randomized controlled trials and the limitation of choices on the checklist (Liberati et al., 2009, Shea et al., 2009).

RoB 2. RoB 2 (see Appendix B) is the revised COCHRANE risk of bias tool for randomized trials. RoB 2 provides a framework to assess risk of bias found in randomized controlled trials, parallel group trials, cluster-randomized trials, and cross-over trials and other matched designs (Higgins, Savovic, Page, & Sterne, 2016). The tool assesses bias based on five

domains including “(1) Bias arising from the randomization process, (2) Bias due to deviations from intended interventions, (3) Bias due to missing outcome data, (4) Bias in measurement of the outcome, and (5) Bias in selection of the reported result” (Higgins, Savovic, Page, & Sterne, 2016, p. 2). We used the entire RoB 2 to assess risk of bias of individual studies meeting criteria for inclusion in the systematic review, see Appendix B. A strength of the tool is its application to specific outcomes within a study or to the study overall (Higgins, Savovic, Page, & Sterne, 2016). A drawback is that the tool is relatively new, developed in 2013 (Kim et al., 2013) and updated in 2018 (Higgins, Savovic, Page & Sterne, 2016) therefore, has “moderate reliability and promising feasibility and validity” (Kim et al. 2013, p. 408). A second drawback of this tool is the reviewers’ judgement in answering the questions within the criteria (Higgins, Savovic, Page & Sterne, 2016) and therefore, we each independently applied it to the articles and then collaboratively talked about the results. Furthermore, researcher understanding of the individual articles affects how the authors use the tool and therefore influences the tool’s assessment outcome (Higgins, Savovic, Page & Sterne, 2016). Researcher judgement influences reliability and validity (Babic, Pijuk, Brazdilova, Georjjeva, Pereira, et al., 2018).

AMSTAR 2. AMSTAR 2 (see Appendix C) is a 16-question quality assessment tool to evaluate methodological quality in a systematic review (Shea et al., 2017). AMSTAR 2 focuses on the quality of reporting in a systematic review (Shea et al., 2017). A strength of AMSTAR 2 is that it is an empirically valid, reliable, and feasible tool which is easy to use on a variety of systematic reviews (Shea et al., 2009). A drawback of AMSTAR 2 may be inconsistencies in assessing methodological and reporting quality (Faggion, 2015). Developed for independent reviewers to evaluate systematic reviews, we used the tool as a guide and checklist to strengthen reliability and validity of this systematic review.

Sampling and Data Collection.

Sampling. Sampling is a discovery process of screening a broad scope of data in the form of published articles among the body of literature and identifying specific studies for inclusion in a systematic review (Boland et al., 2017; Linares-Espinos, et al., 2018). We collectively conducted a search of the literature using five academic databases from individual database inception through January 2019, available to us as student researchers (Table 1). The five databases, CINAHL, PubMed, PsychInfo, Cochrane, and ScienceDirect represent multiple disciplines and provide unique references (Table 1). The literature search identified published human clinical trials written in English, and available in full text. Keywords included: fermented, fermented food, fermentation, and depression. Keywords entered into each database resulted in a syntax search for the individual database. See Table 1 for Boolean drop down syntax search strategy developed for individual databases.

Table 1.

Database Description and Syntax (drop down Boolean method)

Database	Inception	Description	Boolean syntax
PubMed	January 1996	PubMed free database including literature including life sciences, behavioral sciences, chemical sciences and bioengineering literature maintained by the National Institutes of Health’s (NIH) United States National Library of Medicine https://www.ncbi.nlm.nih.gov/books/NBK3827/#pubmedhelp.PubMed_Quick_Start)	(fermentation) OR fermented) OR fermented foods) AND depression)
CINAHL	1961	Cumulative Index to Nursing and Allied Health Literature includes articles from nursing and allied health (https://www.sciencedirect.com/topics/nursing-and-health-professions/cinahl)	fermented OR fermented food OR fermentation AND depression
PsychINFO	1967	Includes articles from psychological, behavioral and social sciences (https://www.sciencedirect.com/topics/nursing-and-health-professions/cinahl)	fermented OR (fermented food) OR fermentation AND depression
Cochrane	1995	A collection of databases containing quality evidence for the purposes of health care decision makers (https://www.cochranelibrary.com/about/about-cochrane-library)	'fermented in All Text OR fermented food in All Text OR fermentation in All Text AND depression in All Text - (Word variations have been searched)'
Science Direct	1997	Peer reviewed articles on the topics of 1. Physical Sciences and Engineering, 2. Life Sciences, 3. Health Sciences and 4. Social Sciences and Humanities literature available by subscription (https://www.elsevier.com/solutions/sciencedirect)	fermented or fermented food or fermentation and depression

We searched the databases resulting in 863 articles. We did not conduct additional article searches outside the listed databases. Deduplication yielded 811 articles. We applied advanced search strategy in RefWorks using the keywords: fermented, fermented food, fermentation, and depression to 811 articles. This strategy resulted in elimination of 806 articles resulting in 5 full text articles which we reviewed against inclusion criteria.

Each researcher individually applied inclusion criteria: Studies settings include inpatient, outpatient, and community, human participants age 5-110 years old, any diagnosis of depression, daily ingestion of fermented foods regardless of ingredients, written in English, published full text articles accessible through St. Catherine University and InterLibrary Loan Internet Accessible Database (ILLIAD) accessed through St. Catherine University, random controlled trials, case reports, cross-sectional studies, cohort studies, clinical trials, and measured change in depression after daily ingestion of fermented foods. All five studies did not have a daily dose of fermented food and were excluded. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart summarizing this process is outlined in Figure 1.

Keywords were lacking in all five of the resulting articles, calling into question the accuracy of the search. Therefore, we conducted additional Boolean searches with the same search terms, in a different search hierarchy from the initial search, resulting in a different number of articles in each database. We questioned the algorithms used in the individual databases. Upon counsel by the St. Catherine University librarian, we ran searches on one line rather than the drop-down method in each database. Subsequently, we conducted a second systematic review base on a new Boolean method listed in Table 2.

We removed ScienceDirect from the included databases in the second search due to the difficulty with filtering for human studies.

Table 2.
Database Description and Syntax (one-line Boolean method)

Database	Inception	Description	Boolean syntax
PubMed	January 1996	PubMed free database including literature including life sciences, behavioral sciences, chemical sciences and bioengineering literature maintained by the National Institutes of Health’s (NIH) United States National Library of Medicine (https://www.ncbi.nlm.nih.gov/books/NBK3827/#pubmedhelp.PubMed_Quick_Start)	((fermentation) OR fermented) OR fermented foods) AND depression)
CINAHL	1961	Cumulative Index to Nursing and Allied Health Literature includes articles from nursing and allied health (https://www.sciencedirect.com/topics/nursing-and-health-professions/cinahl)	fermented OR fermented food OR fermentation AND depression
PsychINFO	1967	Includes articles from psychological, behavioral and social sciences (https://www.sciencedirect.com/topics/nursing-and-health-professions/cinahl)	fermented OR (fermented food) OR fermentation AND depression
Cochrane	1995	A collection of databases containing quality evidence for the purposes of health care decision makers (https://www.cochranelibrary.com/about/about-cochrane-library)	'fermented in All Text OR fermented food in All Text OR fermentation in All Text AND depression in All Text - (Word variations have been searched)'

Records identified through database searching resulted in 64 articles. We did not conduct additional article searches outside the listed databases. There were no duplicate articles. We applied advanced search strategy in RefWorks using keywords: fermented, fermented food, fermentation, and depression to 64 articles. We eliminated fifty-four articles resulting in ten

identified records. We excluded one record because it was a trial in progress. We excluded a second record as it was a protocol. We pulled the remaining eight records for full text review against inclusion criteria.

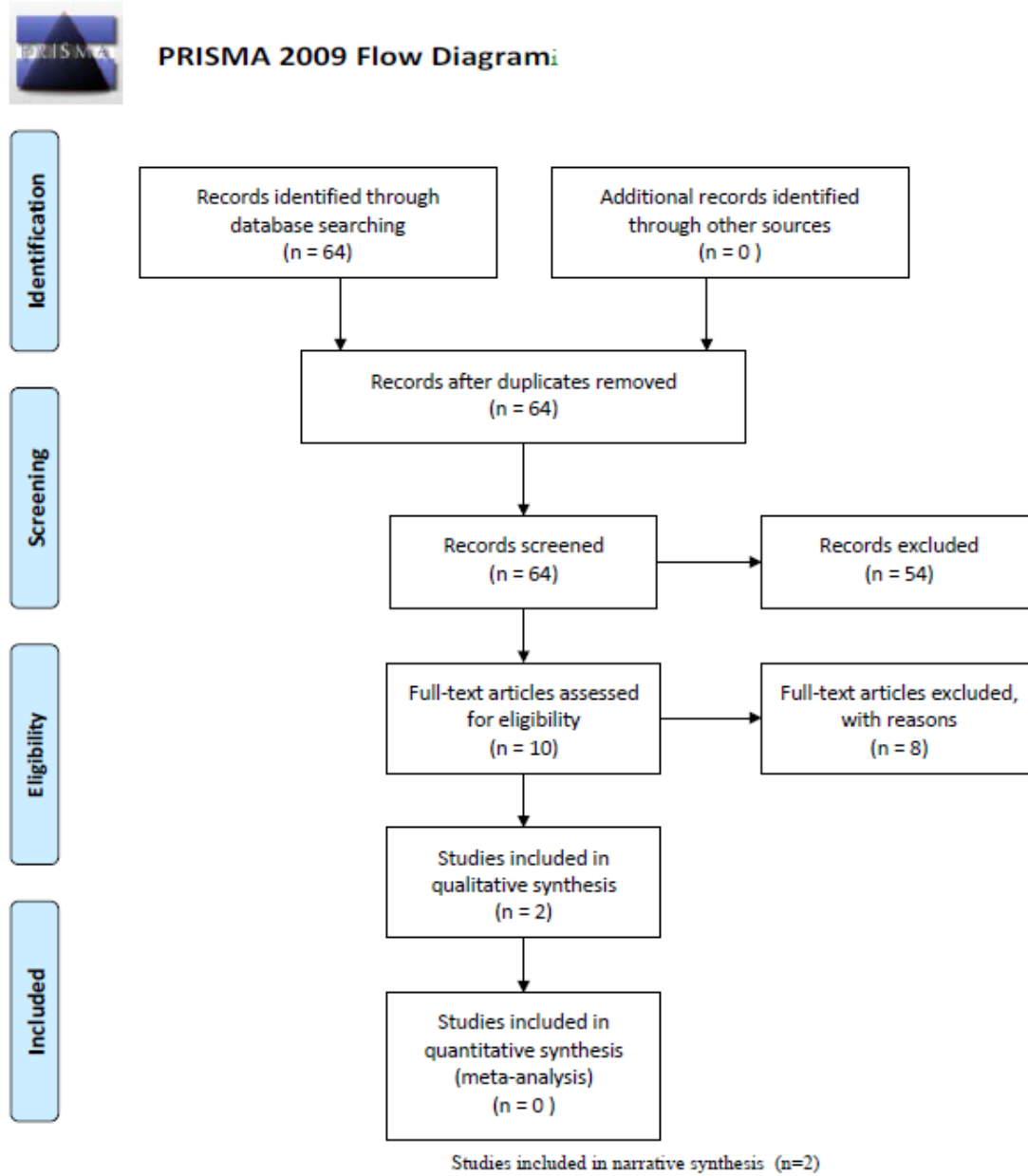
Each researcher individually applied inclusion criteria: Studies settings include inpatient, outpatient, and community, human participants age 5-110 years old, any diagnosis of depression, daily ingestion of fermented foods regardless of ingredients, written in English, published full text articles accessible through St. Catherine University and InterLibrary Loan Internet Accessible Database (ILLIAD) accessed through St. Catherine University, random controlled trials, case reports, cross-sectional studies, cohort studies, clinical trials, and measured change in depression after daily ingestion of fermented foods. We met to discuss our individual results and achieve consensus on articles for inclusion, resulting in two articles. We stored all articles in RefWorks and used an Excel spreadsheet to track the data. Our analysis is based on systematic review 2. We collectively executed data sampling. We searched four databases including CINAHL, PubMed, Cochrane, and PsychINFO, using keyword searches (see table 2). We used a PRISMA flow diagram to document research article selection (Figure 1). We stored articles electronically in RefWorks between January 2- March 1, 2019 and we imported them into an Excel spreadsheet and documented them by title and author. We conducted article deduplication in RefWorks. Keyword search in RefWorks resulted in ten articles. We excluded two articles as they were study protocols without published results.

Data Collection. We conducted a full text review on the eight articles that we individually read and rated for inclusion and documented in a shared Excel spreadsheet under the following headings: Article title, Author, Year, Country of study, Number of subjects, Age, Sex. We compared, discussed, and agreed upon the final two studies for data extraction. We contacted

one author to clarify the reported data; to date we do not have clarification. We documented data extraction from included individual studies in Table 3 by: Study (author), N (number of subjects), Age, Sex, Population description, Type of fermented food, Depression assessment tool, and Objective. See Figure 1 for the PRISMA flow diagram.

Included PRISMA Flow Diagram

Figure. 1. PRISMA 2009 Flow Diagram



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed.1000097

For more information, visit www.prisma-statement.org.

Table 3.*Summary of Studies that met inclusion criteria*

Study	N	Age	Sex	Population description	Type of fermented food	Depression assessment tool	Objective
Davinelli et al. (2016) Italy	N = 60 30=treatment 30= Placebo	50-55	Female	Postmenopausal women, BMI between 20- 25; case history of menopause related symptoms	200 mg of fermented soy (including 80 mg of isoflavone aglycones and 10 mg of euol) and 25 mg of resveratrol from vinifera	(HAM - D)	Evaluate the effects of equol and resveratrol supplementation on health-related quality of life (HRQoL) in otherwise healthy menopausal women with hot flashes, anxiety and depressive symptoms
Divsalar et al. (2018) Iran	Screened N = 101 Randomized N = 56 R/YR = 28 Placebo = 28	R/YR 43.52 ± 6.36 Placebo 44.32 ± 5.47	R/YR treatment group 18 Male 7 Female	Outpatient Iranian men and women with a history of coronary angioplasty and MDD	200 mg sertraline and R/YR ..	(DSM-V), and (HDRS)	Access the efficacy of R/YR (neuroprotective effects) for treatment of depression in patients with recent history of percutaneous coronary intervention

Data Analysis

The cornerstone of a systematic review is the synthesis of findings and the formation of conclusions from included research articles (Popay et al., 2006). In a systematic review, there are three ways to analyze data: 1) quantitatively, which highlights objective measurements and applies statistical data analysis (Creswell, 2018); 2) qualitatively, which emphasizes non-numeric information that organizes and distills data to create meaning (Creswell, 2018); and 3) mixed method, which analyzes quantitative and qualitative data within the framework of a single study (Driscoll, Appiah-Yeboah, Salib, & Rupert, 2007). We applied narrative synthesis as a mixed method approach.

Narrative synthesis “tells a story” of the findings (Popay et al., 2006). The story combines qualitative and quantitative data in a format to bridge the gap between practice and research (Popay et al., 2006). We used narrative synthesis to enable the comparison and synthesis of only two articles. One strength of this method is the ability to integrate quantitative and qualitative results which are otherwise difficult or seemingly incomparable (Popay et al., 2006), enabling the synthesis of results through narration. One weakness of this method is that it may be prone to the bias of researcher interpretation and lenses (Higgins & Green, 2011; Popay et al., 2006). Author interpretation may lead to potentially poor reliability and opacity (Campbell, Katikireddi, Sowden, McKenzie & Tomson, 2018). In an effort to increase reliability and transparency, we kept a continuous shared chronicle of all discussions and decisions (Popay et al., 2006). To increase validity and assess robustness, we emailed a primary author to confirm data results; to date we have not received clarification. We used standardized tools designed to enhance validity of a systematic review. Furthermore, as a team, we were in frequent dialogue

regarding the systematic review process, collectively making decisions, documenting decisions, and holding each other accountable.

Design Rigor

Our post-positivist paradigm requires us to look at quantitative and qualitative data to approximate one truth, through the use of empirical data. Hence, we used a systematic review method within an empirical culture of inquiry that necessitates the use of evidence-based instrumentation allowing for reproducibility. In this research project we meticulously kept notes of our process, the decisions we made, and the outcomes as a way of being transparent and increasing the potential for replicability. To address investigator responsiveness, individual researchers referred to the group tenet stating all researchers will have a common understanding and acceptance at each step of the process. We debated issues and addressed questions until consensus was achieved. Tangential questions were documented in a Google doc for future discussion. When the initial systematic review did not yield qualifying studies, our investigator responsiveness required we reexamine our search process in the individual databases by running practice searches to determine whether drop down or one-line searches revealed different results. We found they did yield different results. Subsequently, we conducted a second systematic review where we changed the database search technique from a drop-down Boolean method to a one-line Boolean technique. Feedback from university and online librarians confirmed our decision to conduct a one-line Boolean search. To support our analytical stance, we emailed the lead author of one of our included studies to clarify their intention in the way they reported their data; to date we have not received clarification. We utilized PRISMA, RoB2, and AMSTAR2 to enhance rigor of this systematic review.

Ethical considerations

The Program Director of the Master of Arts in Holistic Health Studies at St. Catherine University approved this study. The study did not require Institutional Review Board (IRB) approval because we conducted a systematic review of published literature. However, ethical considerations are still important. In this project, ethical considerations included: bias in the literature, researcher bias, and publication bias. We address each of these below.

Bias in the literature. Bias in the literature includes plagiarism, ethically flawed studies and author conflict of interest (Vergnes, Marchal-Sixou, Nabet, Maret, & Hamel, 2010; Wager & Wiffen, 2011). To mitigate these concerns, we used RoB2 to review the method section for alignment of methodology with study design, and the statistical plan and statistical analysis for each study. We also looked for author conflict of interest and ethical flaws. We relied on the peer reviewed academic journals to filter for plagiarism. We did not find bias in our two included studies.

Researcher bias. Researcher bias includes funding sources and neutrality and impartiality (Wager & Wiffen, 2011; Vergnes et al., 2010). To mitigate these concerns, we emailed one primary author to clarify their rationale for reporting only four of the seventeen items of the HAM-D. Neither of our included studies reported conflict of interest or funding source concerns.

Publication bias. Publication bias favors positive results over negative or null findings of research (Boland et al., 2017; Vergnes et al., 2010). Our study may be biased due to the absence of unpublished studies that did not match publishing criteria. All studies meeting inclusion criteria, regardless of results, were included in the systematic review. Maintaining a high level of credibility in a systematic review, we considered the ethical integrity of original research. There

was a continuous two-tiered quality evaluation to maintain ethics and integrity. The first tier was on the individual study level and employed the use of RoB2. We used RoB2 on both included articles. The second tier was an overall quality assessment of the systematic review using AMSTAR2 as a guide and checklist specifically to enhance reliability and validity of this systematic review. Furthermore, the determination to include all data did not blind us to potentially flawed studies with unethical study design (Vergnes et al., 2010). In summary, an ethical assessment is good practice to elevate the integrity of a systematic review and strengthen the study results (Weingarten, Paul, & Leibovici, 2004).

Design Specific Strengths and Limitations

We recognize that our post-positivist paradigm is a strength and a weakness in this systematic review. As three post-positivists, we find meaning and interpret reality similarly and are simultaneously limited in our ability to see reality differently. Additionally, the shared paradigm allows for an understanding of one's ideas and concepts within the team. However, these similarities can also be a challenge because it confines our ability to think creatively when interpreting the data when it is reported in a way that is different from our paradigm. We feel supported by the use of tools, systematic approaches, and deliberate documentation of the process, as we are aware that we are flawed by our biases. Therefore, intentional choices made regarding instrumentation, sampling, and method are consistent with our post-positivist paradigm and help us to remain aware of our biases and strengthen the systematic review. This continual check of our biases is the thread that connects the systematic review process. For example, the use of external tools checks our bias. The sampling comes from multiple databases thus, we are not relying on the bias of one database. The method calls for research from multiple authors, consequently we are not relying on the results of one author.

A potential limitation is that all the researchers employ the same paradigm that may limit what we read and interpret. Additionally, there were times when we needed to make decisions regarding next steps that were impacted by our individual interpretations and lenses. Another potential limitation was that we are novice researchers completing our first systematic review. Also, our status as students of St. Catherine University limited access to studies, time constraint to complete the review, and our confined knowledge of the field. Furthermore, we periodically were boxed in by our culture of inquiry with protocols and systematic processes that did not allow for deviation from stated protocols, minimizing our ability to explore and create. Also, our empirical culture of inquiry challenged the investigation of the complex topics of depression and fermentation in a reductive manner. Finally, our systematic review is based on an emerging topic, absent of common definitions and use of jargon. Despite these challenges, a heightened awareness of design strengths and limitations reinforces the power of our paradigm.

Results

The purpose of this chapter is to provide the results of the articles identified through the systematic review. A search of four databases including: CINAHL, Cochrane, PubMed, and PsychINFO; using the following search criteria: fermented OR fermented food OR fermentation AND depression, was used to answer the research question “Does fermented food affect depression?” and resulted in 64 articles. After applying the inclusion criteria, two studies remained for evaluation: (Study 1) *Influence of equol and resveratrol supplementation on health-related quality of life in menopausal women: A randomized placebo-controlled study* (Davinelli et al., 2017) and (Study 2) *Red yeast rice as an adjunct to sertraline for treatment of depression in patients with percutaneous coronary intervention: Placebo-controlled trial* (Divsalar et al., 2018). Both studies utilized the Hamilton Depression Rating Scale (HAM-D, alternate abbreviation HDRS) to assess the severity of depression. The HAM-D is an adequately reliable 17 item tool, to determine a patient’s severity of depression before, during, and after a treatment (Rohan et al., 2016). Below is a summary of results from the two included studies.

Study 1

Davinelli (2017) conducted a randomized, double-blind, placebo-controlled 3-month trial with 60 Caucasian women aged 50-55 who had a case history of menopausal depression. The authors researched plant-based therapies due to the link between hormone replacement therapy (HRT), breast cancer, cardiovascular disease, and quality of life factors, including depression. The treatment arm of the study received a daily dose of 200 mg of fermented soy and 25 mg of resveratrol. The control group received a pre-packaged placebo. Davinelli (2017) used the Hamilton Depression Rating Scale (HAM-D), a 17-item scale to measure depression at one month and three months and recorded the results as percentage. Davinelli (2017) only reported 4

items of the HAM-D scale and we are unclear whether he/she administered the entire scale or only the 4 items related to 1) work and activities, 2) agitation, 3) anxiety (psychological), and 4) anxiety (somatic). The treatment group achieved statistical significance on the four reported items of the HAM-D by the end of the study, suggesting fermented soy and resveratrol may be helpful in menopausal depression. No adverse events were reported.

Study 2

Divsalar (2018) conducted a randomized, double-blind, placebo-controlled trial of 50 male and female subjects, age 18-60, to assess the efficacy of red yeast rice in patients with major depression who also had a recent history of percutaneous coronary intervention (PCI), more commonly known as angioplasty with a stent. In the treatment group, subjects received a daily dose of 2400 mg. of Jarrow Formulas Red Yeast Rice (RYR) along with 200 mg. of the antidepressant, Sertraline. The control group only received the antidepressant. Divsalar (2018) used the HAM-D, a 17-item scale that measures depression at 3 weeks and 6 weeks of treatment. Results approached significance for the treatment group, indicating that RYR may be beneficial in treating depression. While this study was designed to treat depression, it is worth noting that there were no significant differences in the treatment and control group in lipid profiles, liver function tests, or adverse events.

The authors sought an alternative to statins, a common lipid-lowering agent, in an effort to avoid adverse effects, most frequently muscle related, which are responsible for non-adherence and drug discontinuation. Furthermore, Divsalar (2018) addresses monacolin K, an active compound in red yeast rice (RYR), chemically comparable to statins. The study notes possible reproducibility issues due to the manufacturer of supplements and possible inconsistency in RYR produced with different manufacturers.

Davinelli (2017) achieved statistical significance on the 4 reported items of HAM-D scale. Divsalar (2018) approached statistical significance on the mean of the 17 item HAM-D scale. Both studies (Davinelli et al., 2017; Divsalar et al., 2018) demonstrated improvement of depressive symptoms with the ingestion of a fermented food supplement. Table 4 summarizes the reported results from *Influence of equol and resveratrol supplementation on health-related quality of life in menopausal women: A randomized placebo-controlled study* (Study 1) and *Red yeast rice as an adjunct to sertraline for treatment of depression in patients with percutaneous coronary intervention: Placebo-controlled trial* (Study 2).

Table 4.

Summary of Included Study Results

Study	HAM-D								AE
Study 1 Davinelli et al. (2017) Italy									
	Symptoms*	Active (%)			Placebo (%)				
		T0	T1	T3	T0	T1	T3		
	Anxiety (psychological) (Subjective tension and irritability)	63.3	43.3	20***	63.3	53.8	50.6§§		0 AE
	Anxiety (somatic) (Moderate)	63.3	43.3	23.3***	60.0	48.6	45.7§		
	Work and activities (Loss of interest in activity)	56.7	13.3***	3.3***	60.0	40.0	36.7§§§		
	Agitation (Fidgetiness)	70.0	19	33.3*	66.7	54	47.6§		
Study 2 Divsalar et al. (2018) Iran									
		Mean (SD) Score		Mean (SD) Change in Score		Mean Difference in Score Change (CI 95%)	t (df)	P-value	11 AEs RZR
	Follow up	Sertraline + RZR (%)	Sertraline + Placebo(%)	Sertraline + RZR (%)	Sertraline + Placebo(%)				14AEs Placebo
	W0	22.12 (1.42)	22.36 (1.80)						
	W3	12.44 (2.35)	11.84 (2.94)	-9.68 (3.06)	-10.52 (2.43)	0.84 (- 0.73 to 2.41)	1.07 (48)	.289	
	W6	7.56 (2.02)	9.04 (1.93)	-14.56 (2.43)	-13.32 (2.01)	-1.24 (- 2.51 to 0.03)	-1.96 (48)	.056	

Intragroup analysis vs baseline: *p<0.05; **p<0.01; ***p<0.001; Intergroup analysis at the same time: §p<0.05; §§p<0.01; §§§p<0.001.

HDRS, Hamilton Depression Rating Scale. a Degrees of freedom (df) and concordant p-values were calculated based on the results of Levene’s test for assessment of equality of variances in independent samples t-test.

Discussion

The purpose of this chapter is to interpret and discuss the results from the systematic review to answer the question: What is the relationship of fermented foods and depression? First, we discuss findings supported by the literature. Second, we discuss unexpected findings. Next, we describe implications of this project for holistic health and future research. Finally, we conclude with a summary and ending remarks.

Findings Supported by the Literature

Two studies (Davinelli et al., 2017; Divsalar et al., 2018) met our inclusion criteria and indicate that the ingestion of a fermented supplement may have the potential to affect depression. While Divsalar et al. (2018) approached significance and Davinelli et al., (2017) demonstrated statistical significance toward the benefit of a fermented product on depression, the outcomes did not consider the confounding variables of diet intake and inconsistent administration and reporting of depression scale (HAM-D).

Unexpected Findings.

Based on our literature review, we expected to find more human clinical trials that met our criteria that suggest the potential effects of fermented food on depression (Selhub et al., 2014; Chilton, n, et al., 2015; Pham et al., 2014; Zhu et al., 2011; Sonedstedt et al., 2011; Keszei et al., 2009). However, we found that the specific use of language in the method of a systematic review matters, specifically, the terms fermented food and fermentation. The body of literature frequently refers to the term fermented food (Kim et al, 2016; Marco et al., 2017; Selhub et al., 2014; Chilton, Burton, & Reid, 2015; Raak et al., 2014; Lang, Eisen, & Ziykovic, 2014), yet, the two studies (Davinelli et al., 2017; Divsalar et al., 2018) we found indicated that a fermented supplement (rather than a fermented food) can have an influence on depression. Additionally, the term fermentation can refer to fermentation in food with the purpose of preservation (Tamang et

al., 2009; Marco et al., 2017; Raak et al., 2014; Aslam et al., 2018) or it can refer to the metabolic process of fermentation in the gut (Marco et al., 2017; Raak et al., 2014; Aslam et al., 2018). The consideration of language led us to investigate our Boolean strategy. We found the order of terms listed, as well as the one-line method versus a drop-down method yielded different results within the same database and varied among databases. Due to this challenge in the Boolean search strategy, we question whether relevant studies were left out that may have affected our conclusions and implications for future studies. Subsequently, we question the reproducibility of any systematic review.

Ethical considerations potentially complicate studies on depression. When studying individuals with major depressive disorder, ethically, researchers must treat them for depression. For example, in Divsalar et al. (2018) both randomized and treatment groups received Sertraline, while only the treatment group received the RYR supplement. Claiming the benefit of RYR in isolation when sertraline and/or the synergies of sertraline and RYR are in play may confound results.

Further confounding our findings is the difficulty of studying a holistic system including complex, synergistic, fluid, multi-dimensional, inter-relating, bi-directional, and synergistic components in a reductive way. Our research of the microbiome and its bi-directional relationship to depression falls at the intersection of Holism and Reductionism. We are challenged to interpret this intersection in a post-positivist and empirical way.

Implications for Holistic Health

A post-positivist lens is paradoxical to holism. We are using an empirical reductive lens to look at the holistic ecology of the gut microbiome that has many outside influences, synergies, complexities and bi-directionalities. Conducting research about a topic that is complex and

synergistic, such as the relationship between depression and fermented foods, is problematic in at least three ways.

First, using the post-positivist lens and reducing our research to look at specific bacteria related to depression is too simplex and reductionist. During our research, we realized that we couldn't actually answer our research question from a post-positivist lens because of the complexities, synergies, and bi-directional nature of the relationship between fermented foods and depression. Second, the underlying epistemological, ontological, and axiological assumptions of the post-positivist paradigm are not only incongruent, but also paradoxical in holistic health where the focus is on the whole. Third, asking a question that in and of itself is linear, limits the scope, results, and implications of the research in ways that artificially reduce the question to something that cannot be answered in a holistic manner. In fact, the result of a systematic review is a reduction of complex research studies leading to simplistic outcomes that can be taken out of context. Thus, one of the implications of conducting research in holistic health is the finding or creation of research methodologies that hold complexities and synergies while not being trapped by the imposed constrictions of the dominant empirical paradigm. Simultaneously, we acknowledge that the value research derives from the empirical paradigm is useful and necessary, yet, may not be the answer for all questions. We encourage inquiry from multiple perspectives and recommend that future research address the same question from diverse paradigms and research methodologies.

Conclusion

The body of academic literature demonstrating the effects of fermented food on depression is limited and includes animal studies and sparse human studies even though popular press claims fermented food helps with depression. Our systematic review identified two articles

that met our inclusion criteria and only included a fermented food supplement, no actual fermented foods. Additionally, clarity on definitions is needed to help facilitate the research when comparing data. It may be too early to draw evidence-based conclusions regarding the effect/s of fermentation on depression in humans. We suggest consideration of the paradox of researching multifaceted issues (fermented foods and depression) in a reductive manner.

Therefore, we propose a more holistic approach that considers the complexities and synergies in the human body. Specifically, we advise a more phenomenological approach that accounts for lifestyle factors relating to health and the microbiome, including diet, sleep, movement, stress and emotional management as well as more specifics about depression and fermented foods. The answer resides at the intersection between the art of interpreting holism and the science of reducing, measuring and reproducing data.

References

- Aarts, E., Ederveen, T., Naaijen, J., Zwiers, M., Boekhorst, J., Timmerman, H., . . . Arias Vasquez, A. (2017). Gut Microbiome in ADHD and its relation to neural reward anticipation. *Plos One*, *12*(9), 1-17. doi.org/10.1371/journal.pone.0183509
- Adams, J., Johansen, L., Powell, L., Quig, D., & Rubin, R. (2011). Gastrointestinal flora and gastrointestinal status in children with autism-comparisons to typical children and correlation with autism severity. *BMC Gastroenterology*, *11*(22), 1-13. Retrieved from: <http://biomedcentral.com/1471-230X/11/22>
- Allen, A.P., Hutch, W., Borre, Y.E., Kennedy, P.J., Temko, A., Boylan, G., . . . Clarke, G. (2016). *Bifidobacterium longum*1714 as a translational psychobiotic: Modulation of stress, electrophysiology and neurocognition in health volunteers. *Translational Psychiatry*, *2016*(6), 1-7. doi:10.1038/tp.2016.191
- Akbaraly, T. N., Sabia, S., Shipley, M. J., Batty, G. D., & Kivimaki, M. (2013). Adherence to healthy dietary guidelines and future depressive symptoms: Evidence for sex differentials in the Whitehall II study. *American Journal of Clinical Nutrition*, *97*(2), 419-427. doi:10.3945/ajcn.112.041582
- American Psychiatric Association [APA], (2018). *Quantifying the cost of depression*. Retrieved from: <http://www.workplacementalhealth.org/Mental-Health-Topics/Depression/Quantifying-the-Cost-of-Depression>
- American Psychiatric Association (2017). What is depression?. Retrieved from: <https://www.psychiatry.org/patients-families/depression/what-is-depression>
- Aslam, H., Green, J., Jacka, F., Collier, F., Berk, M., Pasco, J., & Dawson, S. (2018). Fermented foods, the gut and mental health: A mechanistic overview with implications for

depression and anxiety. *Nutritional Neuroscience*, doi: 10.1080/1028415X.2018.1544332

Retrieved from: <https://doi.org/10.1080/1028415X.2018.1544332>

Austin, S. F. (2010). *Lifetime nutrition and wellness: Principles of digestion and metabolism*.

Retrieved from: [http://cte.sfasu.edu/wp-](http://cte.sfasu.edu/wp-content/uploads/2012/01/2_Principles_of_Digestion_and_Metabolism.html)

[content/uploads/2012/01/2_Principles_of_Digestion_and_Metabolism.html](http://cte.sfasu.edu/wp-content/uploads/2012/01/2_Principles_of_Digestion_and_Metabolism.html)

Babic, A., Pijuk, A., Brazdilova, L., Georgieva, Y., Pereira, R., Poklepovic, T., & Puljak, L.

(2018). Judgements of other bias in Cochrane systematic reviews of interventions are highly inconsistent and thus hindering use and comparability of evidence. Retrieved

from: <https://doi.org/10.1101/292425>

Bailey, M., Dowd, S.E., Galley, J., Hufnagle, A.R., Allen, R., & Lyte, M. (2011). Exposure to a

social stressor alters the structure of the intestinal microbiota: Implications for stressor-induced immunomodulation. *Brain, Behavior, and Immunity*, 25(3), 397-407.

doi:10.1016/j.bbi.2010.10.023

Belmaker, R.H., & Agam, G. (2008). Major depressive disorder. *The New England Journal of*

Medicine, 358(1), 55-68. doi:10.1056/NEJMra073096

Bembnowska, M., & Josko-Ochalska, J. (2015). What causes depression in adults? *Polish*

Journal of Public Health, 125(2), 116-120. <https://doi.org/10.1515/pjph-2015-0037>

den Besten., G., van Eunen, K., Groen, A., Venema, K., Reijngoud, D.J., & Bakker, B.M.

(2013). The role of short-chain fatty acids in the interplay between diet, gut microbiota, and host energy metabolism. *Journal of Lipid Research*, 54(9), 2325-2340. doi:

10.194/jlr.R036012

Bharwani, A., Firoz Mian, M., Foster, J., Surette, M., Bienenstock, J., & Forsythe, P. (2016).

Structural & functional consequences of chronic psychosocial stress on the microbiome.

Psychoneuroendocrinology, 63(2016), 217-227. doi.org/10.1016/j.psyneuen.2015.10.001

Bird, J., Brown, D., Mullen, A., Moskowitz, N., Mahowald, M., Sider, J., . . . Wang, C. (1998).

Helper T-cell differentiation is controlled by the cell cycle. *Immunity*, 9(2), 229-237.

Retrieved from: <https://www.cell.com/immunity/home>

Boland, A., Cherry, M. G., & Dickson, R. (2017). *Doing a systematic review: A student's guide*.

Los Angeles: Sage Publication

Bouchard, M., Bellinger, D.C., Wright, R.O., & Weisskopf, M.G. (2010). Attention

deficit/hyperactivity disorder and urinary metabolites of organophosphate pesticides in

U.S. children 8-15 years. *Pediatrics*, 125(6), 1270-1277. doi:10.1542/peds.2009-3058

Bradford, A. (2017) *Empirical evidence: A definition*. Retrieved from:

<https://www.livescience.com/21456-empirical-evidence-a-definition.html>

Braun, D., (2017). *The process of metabolism and how it works*. Retrieved from:

<https://www.natural-holistic-health.com/process-metabolism-works/>

Brody, D. J., Pratt, L. A., & Hughes, J. P. (2018). Prevalence of depression among adults aged

20 and over: United States, 2013-2016. *NCHS data brief*, (303), 1-8. Retrieved from:

<https://www.cdc.gov/nchs/products/databriefs/db303.htm>

Bromet, E., Andrade, L. H., Hwang, I., Sampson, N. A., Alonso, J., de Girolamo, G., . . . Kessler,

R. (2011). Cross-national epidemiology of DSM-IV major depressive episode. *BMC*

Medicine, 9(90), 1-16. Retrieved from: <http://www.biomedcentral.com/1741-7015/9/90>

- Bruce-Keller, A.J., Salbaum, J.M., & Berthoud, H.R. (2018). Harnessing gut microbes for mental health: Getting from here to there. *Biological Psychiatry*, 83(3), 214-223. doi: 10.1016/j.biopsych.2017.08.014
- Butwicka, A., Lichtenstein, P., Frisé, L., Almqvist, C., Larsson, H., & Ludvigsson, J. F. (2017). Celiac disease is associated with childhood psychiatric disorders: A population-based study. *The Journal of Pediatrics*, 184(5), 87-93. doi:10.1016/j.jpeds.2017.01.043
- Campbell, M., Katikireddi, S. V., Sowden, A., McKenzie, J. E., & Thomson, H. (2018). Improving conduct and reporting of narrative synthesis of quantitative data (ICONS-quant): Protocol for a mixed methods study to develop a reporting guideline. *BMJ Open*, 8(2), e020064. doi:10.1136/bmjopen-2017-020064
- Carabotti, M., Scirocco, A., Maselli, M. A., & Severi, C. (2015). The gut-brain axis: Interactions between enteric microbiota, central and enteric nervous systems. *Annals of Gastroenterology: Quarterly Publication of the Hellenic Society of Gastroenterology*, 28(2), 203-209. Retrieved from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4367209/pdf/AnnGastroenterol-28-203.pdf>
- Chang, P.V., Hao, L., Offermanns, S., & Medzhitov, R. (2014). The microbial metabolite butyrate regulates intestinal macrophage function via histone deacetylase inhibition. *PNAS*, 111(6), 2247-2252. doi.org/10.1073/pnas.1322269111
- Chassaing, B., Kumar, M., Baker, M., Singh, V., & Vijay-Kumar, M. (2014). Mammalian gut immunity. *Biomedical Journal*, 37(5), 246-258. doi: 10.4103/2319-4170.130922
- Chentsova-Dutton, Y.E., Tsai, J.L., & Gotlib, I.H. (2010). Further evidence for the cultural norm hypothesis: Positive emotion in depressed and control European American and Asian

- American women. *Cultural Diversity and Ethnic Minority Psychology*, 16(2), 284-295.
doi: 10.1037/a0017562
- Chilton, S., Burton, J.P., & Reid, G. (2015). Inclusion of fermented foods in food guides around the world. *Nutrients*, 7(2015), 390-404. doi:10.3390/nu7010390
- Coewen, P.J., & Browning, M. (2015). What has serotonin to do with depression? *World Psychiatry*, 14(2), 158-160. doi:10.1002/wps
- Cryan, J.F., & Dinan, T.G., (2012). Mind-altering microorganisms: The impact of the gut microbiota on brain and behavior. *Nature Reviews Neuroscience*, 13(10), 701-712. doi: 10.1038/nrn3346
- Daruna, J.H. (2012). *Introduction to psychoneuroimmunology*. London, UK: Academic Press
- Davinelli, S., Scapagnini, G., Marzatico, f., Nobile, V., Ferrara, N., & Corbi, G. (2017). Influence of equol and resveratrol supplementation on health-related quality of life in menopausal women: A randomized, placebo-controlled study. *Maturitas*, 96(2017), 77-83. doi:10.1016/j.maturitas.2016.11.016
- Del Sivio, L. Prainsack, B., & Buyx, A. (2016). Crowdsourcing the human gut. *Journal of Science Communication*, 15(3) 1-16. Retrieved from:
https://jcon.sissa.it/site/default/files/documents/JCOM_1503_2016_A03.pdf
- Depressive Disorders (2013). *Diagnostic and Statistical Manual of Mental Disorders, 5th edition*. American Psychiatric Association. Retrieved from:
<https://doi.org/10.1176/appi.books.978089042559>
- Devaraj, S., Hemarajata, P., & Versalovic, J. (2013). The human gut microbiome and body metabolism: Implications for obesity and diabetes. *Clinical Chemistry*, 59(4), 617-628.
doi: 10.1373/clinchem.2012.187617

- DeGruttola, A. K., Low, D., Mizoguchi, A., & Mizoguchi, E. (2016). Current understanding of dysbiosis in disease in human and animal models. *Inflammatory Bowel Diseases*, 22(5), 1137-1150. doi:10.1097/mib.0000000000000750
- Dennett, C., (2018). *The facts about fermented foods*. Retrieved from: <https://www.todaysdietitian.com/newarchives/0418p24.shtml>
- Devaraj, S., Hemarajata, P., & Versalovic, J. (2013). The human gut microbiome and body metabolism: Implications for obesity and diabetes. *Clinical Chemistry*, 59(4), 617-628. doi:10.1373/clinchem.2012.187617
- Diaz Heijtz, R., Wang, S., Anuar, F., Quian, Y, Bjorkholm, B., Saelsson, A., . . . Pettersson, S. (2011). Normal gut microbiota modulates brain development and behavior. *Proceedings of the National Academy of Sciences of the United States of America*, 108(7), 3407-3052. doi/10.1073.pnas.1010529108
- Divsalar, P., Noorbala, A. A., Moazen-Zadeh, E., Jafarinia, M., Shakiba, M., Shahmansouri, N., . . . Akhondzadeh, S. (2018). Red yeast rice as an adjunct to sertraline for treatment of depression in patients with percutaneous coronary intervention: Placebo-controlled trial. *Advances in Integrative Medicine*, 5(2), 69-74. doi:10.1016/j.aimed.2018.01.001
- Dominianni, C., Sinha, R., Goedert, J.J., Pei, Z., Yang, L., Hayes, R, & Ahn, J. (2015). Sex, body mass index, and dietary fiber intake influence the human gut microbiome. *Plos One*, 10(4), 1-14. doi:10.1371/journal.pone.0124599
- Driscoll, D., Appiah-Yeboah, A., Selib, P., & Rupert D., (2007) *Merging qualitative and quantitative data in mixed methods research: How to and why not*. Retrieved from <https://digitalcommons.unl.edu/cgi/viewcontent.cgi?article=1012&context=icwdmee>

Evrensel, A., & Ceylan, M. E. (2015). The gut-brain axis: The missing link in depression.

Clinical Psychopharmacology and Neuroscience the Official Scientific Journal of the Korean College of Neuropsychopharmacology, 13(3), 239-244. doi:
10.9758/cpn.2015.13.3.239

Faggion, C. M., (2015) Critical appraisal of AMSTAR: Challenges, limitations, and potential solutions from the perspectives of an assessor. *BMC Medical Research Methodology* 15(63), 1-5. doi :10.1186/s12874-015-0062-6

Foroutan, R. (2012). *The history and health benefits of fermented food*. Retrieved from:

<https://foodandnutrition.org/winter-2012/history-health-benefits-fermented-food/>

Freeman, M. P., Mischoulon, D., Tedeschini, E., Goodness, T., Cohen, L. S., Fava, M., & Papakostas, G. I. (2010). Complementary and alternative medicine for major depression disorder: A meta-analysis of patient characteristics, placebo-response rates, and treatment outcomes relative to standard antidepressants. *Journal of Clinical Psychiatry*, 71(6), 682-688. doi:10.4088/JCP.10r05976blu

Fukuda, S., Toh, H., Oshima, K., Nakanishi, Y., Yoshimura, K., . . . Ohno, H. (2011).

Bifidobacteria can protect from enteropathogenic infection through production of acetate. *Nature*, 469(7331), 543-549. doi:10.1038/nature09646

Gomez, A., Luckey, D., & Taneja, V. (2015). The gut microbiome in autoimmunity: Sex matters.

Clinical Immunology, 159(2), 154-162. doi:10.1016/j.clim.2015.04.016

Gorvitovskaia, A., Holmes, S. P., & Huse, S. M. (2016). Interpreting *Prevotella* and *Bacteroides* as biomarkers of diet and lifestyle. *Microbiome*, 4(1), 3-12. doi:10.1186/s40168-016-0160-7

Gungor, S., Suna Celioglu, O., Ozel Ozcan, O., Gungor Raif, S., & Ayse Selimoglu, M. (2013).

Frequency of celiac disease in attention deficit hyperactivity disorder. *Journal of Pediatric Gastroenterology and Nutrition*, 56(2), 211-214.

doi:10.1097/MPG.0b13e318272b7bc

Holism. (2019). In Wikipedia. Retrieved from: <https://en.wikipedia.org/wiki/Holism>

Hooks, K. B., & O'Malley, M. A. (2017). Dysbiosis and its discontents. *American Society for Microbiology*, 8(5), 1-11. doi:10.1128/mbio.01492-17

Hooper, L., Midtvedt, T., & Gordon, J. (2002). How host-microbial interaction shape the nutrient environment of the mammalian intestine. *Annual Review of Nutrition*, 2002(22), 283-307.

doi: 10.1146/annualrev.nuty.22.011602.092259

Hsiao, E., McBride, S.W., Hsien, S., Sharon, G., Hyde, E.R., McCue, T, ... Mazmanian, S.K., (2013). Microbiota modulate behavioral and physiological abnormalities associated with neurodevelopmental disorders. *Cell*, 155(7),1451-1463.

doi.org/10.1016/j.cell.2013.11.024

Huttenhower, C., Gevers, D., Knight, R., Abubucker, S., Badger, J.H., Chinwalla, A.T., Fulton, R.S., . . . White, O. (2012). Structure, function and diversity of the healthy human microbiome. *Nature*, 486(2012), 207-214. doi:10.1038/nature11234

Islami, F., Ren, J. S., Taylor, P.R., & Kamangar, F. (2009). Pickled vegetables and the risk of oesophageal cancer: A meta-analysis. *British Journal of Cancer*, 101(9), 641-1647.

Retrieved from: <https://doi.org/10.1016/j.ijfoodmicro.2005.03.008>

Jacka, F. N., Cherbuin, N., Anstey, K. J., & Butterworth, P. (2015). Does reverse causality explain the relationship between diet and depression? *Journal of Affective Disorders*, 175, 248-250. doi:10.1016/j.jad.2015.01.007

- Jenkins, T.A., Nguyen, J.C.D., Polglaze, K.E., & Bertrand, P.P. (2016). Influence of tryptophan and serotonin on mood and cognition with a possible role of the gut-brain axis. *Nutrients*, 8(1), 1-15. doi:10.3390/nu8010056
- Kaplan, H., & Hutkins, R.W. (2000). Fermentation of fructooligosaccharides by lactic acid bacteria and *Bifidobacteria*. *Applied and Environmental Microbiology*, 66(6), 2682-2684. Retrieved from: <https://aem.asm.org/content/aem/66/6/2682.full.pdf>
- Kaplan, B. J., Rucklidge, J. J., Romijn, A., & McLeod, K. (2015). The emerging field of nutritional mental health: Inflammation, the microbiome, oxidative stress, and mitochondrial function. *Clinical Psychological Science*, 3(6), 964-980. doi:10.1177/2167702614555413
- Kang, D-W., Adams, J., Gregor, A., Borody, T., Chittick, L., Fasano, A., . . . Krajmalnik-Brown, R. (2017). Microbiota transfer therapy alters gut ecosystem and improves gastrointestinal and autism symptoms: An open-label study. *Microbiome*, 5(10), 1-16. doi: 10.1186/s40168-016-0225-7
- Kau, A., Ahern, P., Griffin, N., Goodman, A., & Gordan, J., (2011). Human nutrition, the gut microbiome and the immune system. *Nature*, 2011(474), 327-336. doi:10.1038/nature10213
- Kessler, R. C. (2012). The costs of depression. *The Psychiatric Clinics of North America*, 35(1), 1-14. doi: 10.1016/j.psc.2011.11.005
- Keszei, A.P., Schouten, L.J., Goldbohm, A., & van den Brandt, P.A. (2009). Dairy intake and the risk of bladder cancer in the Netherlands cohort study on diet and cancer. *American Journal of Epidemiology*, 4(171) 436–446. doi:10.1093/aje/kwp399

- Kiecolt-Glaser, J. K. (2010). Stress, food, and inflammation: Psychoneuroimmunology and nutrition at the cutting edge. *Psychosomatic Medicine*, 72(4), 365-369.
doi:10.1097/PSY.3e3181dbf489
- Kim, B., Hong, V.M., Yang, J., Hyun, H., Im, J.J., Hwang, J., . . . Kim, J. (2016). A review of fermented foods with beneficial effects on the brain and cognitive function. *Preventive Nutrition and Food Science*, 21(4), 297-309. doi:[10.3746/pnf.2016.21.4.297]
- Kim, G-W, Gocevski, G., Wu, C-J., & Yang, X-J. (2010). Dietary, metabolic, and potentially environmental modulation of the lysine acetylation machinery. *International Journal of Cell Biology*, 2010(Article 632739), 1-14. doi.org/10.1155/2010/632739
- Kuo, S-M. (2013). The interplay between fiber and the intestinal microbiome in the inflammatory response. *Advances in Nutrition*, 4(1), 16-28. doi:10.3945/an.112.003046
- Larzelere, M. M., James, E., & Arcuri, M. (2015). Treating depression: What works besides meds? *The Journal of Family Practice*, 64(8), 454-459. Retrieved from:
<https://www.mdedge.com/jfponline>
- Leary, M.R. (1990). Responses to social exclusion: Social anxiety, jealousy, loneliness, depression, and low self-esteem. *Journal of Social and Clinical Psychology*, 9(2), 221-229. Retrieved from: <https://doi.org/10.1521/jscp.1990.9.2.221>
- Li, W., Dowd, S.E., Scurlock, B., Acosta-Martinez, V., & Lyte, M. (2009). Memory and learning behavior in mice is temporarily associated with diet-induced alterations in gut-bacteria. *Physiology & Behavior*, 96(2009), 557-567. Retrieved from:
<https://doi.org/10.1016/j.physbeh.2008.12.004>
- Li, Y., Lv, M., Wei, Y., Sun, L., Zhang, J., Zhang, H., & Li, B. (2017). Dietary patterns and depression risk: A meta-analysis. *Psychiatry Research*, 253, 373-382.

doi:10.1016/j.psychres.2017.04.020

- Lopez, A. D., & Mathers, C. D. (2006). Measuring the global burden of disease and epidemiological transitions: 2002-2030. *Annals of Tropical Medicine and Parasitology*, *100*(5-6), 481-499. doi:10.1179/136485906X97417
- Luna, R.A., Oezguen, N., Balderas, M., Venkatachalam, A., Runge, J.K., Versalovic, J., . . . Williams, K. (2017). Distinct microbiome-neuroimmune signatures correlate with functional abdominal pain in children with autism spectrum disorder. *Cellular and Molecular Gastroenterology and Hepatology*, *3*(2), 219-230. doi.org/10.1016/j.jcmgh.2016.11.008
- Lyte, M., (2013). Microbial endocrinology in the microbiome-gut-brain axis: How bacterial production and utilization of neurochemicals influence behavior. *Plos Pathogens*, *9*(11), 1-4. doi:org/10.1371/journal.ppat.1003726
- Mack, D.R. (2005). Probiotics, *Canadian Family Physicians*, *51*(11), 455–1457. Retrieved from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1479485/>
- Maintz, L., & Novak, N. (2007). Histamine and histamine intolerance. *The American Journal of Clinical Nutrition*, *85*(5), 1185-1196. doi:https://doi.org/10.1093/ajcn/85.5.1185
- Mangiola, F. (2016). Gut microbiota in autism and mood disorders. *World Journal of Gastroenterology*, *22*(1), 361-368. doi:10.3748/wjg.v22.i1.361
- Manichanh, C., Rigottier-Gois, L., Gloux, K., Pelletier, E., Nalin, R., . . . Dore, J. (2006). Reduced diversity of faecal microbiota in Crohn's disease revealed by a metagenomic approach. *Gut*, *55*(2), 205-211. doi: 10.1136/gut.2005.073817

- Marco, M., Heeney, D., Binda, S., Cifelli, C. J., Cotter, P. D., Foligne, B., . . . Hutkins, R. (2017). Health benefits of fermented foods: Microbiota and beyond. *Current Opinions in Biotechnology*, 44(94), 94-102. doi.org/10.1016/j.copbio.2016.11.010
- Marieb, E. N. (2015). *Essential of human anatomy and physiology*. Boston MA: Pearson.
- Mathur, S. & Singh, R. (2005). Antibiotic resistance in food lactic acid bacteria-a review. *International Journal of Food Microbiology*, 105(3), 281-295. Retrieved from: <https://doi.org/10.1016/j.ijfoodmicro.2005.03.008>
- Mayer, E., Tillisch, K., & Gupta, A. (2015). Gut/brain axis and microbiota. *The Journal of Clinical Investigation*, 125(3), 926-938. doi:10.1172/jc176304
- McMillan E., Stenga, N., & Van Sell., S. (2018). Holism: A Concept Analysis International. *Journal of Nursing & Clinical Practices*, 5(282), 1-6. doi: <https://doi.org/10.15344/2394-4978/2018/282>
- Miller, I. (2018). The gut-brain axis: Historical reflections. *Microbial ecology in health and disease*, 29(1), 1-9. doi: 10.1080/16512235.2018.1542921
- Molendijk, M., Molero, P., Sánchez-Pedreño, F.O., Van der Does, W., & Martínez-González, M.A. (2018). Diet quality and depression risk: A systematic review and dose-response meta-analysis of prospective studies. *Journal of Affective Disorders*, 226, 346-354. doi:10.1016/j.jad.2017.09.022
- Mosca, A., Leclerc, M., & Hugot, J. (2016). Gut microbiota diversity and human diseases: Should we reintroduce key predators in our ecosystem? *Hypothesis and Theory*, 7(455), 1-11. doi:10.3389/fmicb.2016.00455
- Mugula, J.K., Nnka, S.A., & Sorhaug T. (2003). Microbiological and fermentation characteristics of togwa, a Tanzanian fermented food. *International Journal of Food*

- Microbiology*, 80(3), 187-199. Retrieved from: [https://doi.org/10.1016/S0168-1605\(02\)00141-1](https://doi.org/10.1016/S0168-1605(02)00141-1)
- National Institute of Mental Health (NIMH). (2001). *Mental Health: Culture, Race, and Ethnicity: A Supplement to Mental Health: A Report of the Surgeon General*. Retrieved from: <https://www.ncbi.nlm.nih.gov/books/NBK44249/>
- National Institutes of Mental Health (NIMH). (2017). *Depression*. Retrieved from: <https://www.nimh.nih.gov/health/topics/depression/index.shtml>
- Neish, A., (2009). Microbes in gastrointestinal health and disease. *Gastroenterology*, 2009(136), 65-80. Retrieved from: [http://www.gastrojournal.org/article/S0016-5085\(08\)01978-1/pdf](http://www.gastrojournal.org/article/S0016-5085(08)01978-1/pdf)
- Nesse, R. M., & Ellsworth, P. C. (2009). Evolution, emotions, and emotional disorders. *American Psychologist*, 64(2), 129-139. doi:10.1037/a0013503
- Niederhofer, H. (2011). Association of attention-deficit/hyperactivity disorder and celiac disease: A brief report. *The Primary Care Companion for CNS Disorders*, 13(3), 1-7. doi:10.4088/pcc.10br01104
- Olfson, M., Blanco, C., & Marcus, S. (2016). Treatment of adult depression in the United States. *JAMA Internal Medicine*, 176(10), 1482-1491. doi:10.1001/jamainternmed.2016.5057
- Perna, A., Intaglietta, I., Simonetti, A., & Gambacorta, E. (2013). Effect of genetic type and casein haplotype on antioxidant activity of yogurts during storage. *Journal of Dairy Science*, 96(2013), 3435-3441. doi:10.3168/jds.2012-5859
- Petra, A. I., Panagiotidou, S., Hatzigelaki, E., Stewart, J. M., Conti, P., & Theoharides, T. C. (2015). Gut-Microbiota-Brain Axis and its effect on neuropsychiatric disorders with suspected immune dysregulation. *Clinical Therapeutics*, 37(5), 984-995. doi:10.1016/j.clinthera.2015.04.002

- Pham, N.M., Nanri, A., Kurotani, K., Kuwahara, K., Kume, A., Sata, M., ... Mizoue, T. (2014). Green tea and coffee consumption is inversely associated with depressive symptoms in Japanese working population. *Public Health and Nutrition*, 17(3), 625-633. doi: 10.1017/S1368980013000360
- Puertollano, E., Kolida, S., & Yaqoob, P. (2014). Biological significance of short-chain fatty acid metabolism by the intestinal microbiome. *Current Opinion Clinical Nutrition Metabolism Care*, 17(2), 139-144. doi:10.1097/MCO.0000000000000025
- Qin, J., Li, R., Raes, J., Arumugam, M., Burgdorf, K.S., Manichanh, C., ... Wang, J. (2010). A human gut microbial gene catalogue established by metagenomic sequencing. *Nature*, 464(4), 59-67. doi:10.1038/nature08821
- Quirk, S. E., Williams, L. J., O'Neil, A., Pasco, J., A., Jacka, F. N., Housden, M. B., & Brennan, S. L. (2013). The association between diet quality, dietary patterns and depression in adults: A systematic review. *BMC Psychiatry*, 13(175), 1-22. doi:10.1186/1471-244X-13-175
- Raak, C., Ostermann, T., Boehm, K., & Molsberger, F. (2014). Regular consumption of sauerkraut and its effect on human health: A bibliometric analysis. *Global Advances in Health and Medicine*, 3(6), 12-18. doi:10.7453/gahmj.2014.038
- Rank.org. (2018). *Food and culture*. Retrieved from: <http://family.jrank.org/pages/639/Food-Food-Culture.html>
- Rastall, R. A., Gibson, G. R., Gill, H. S., Guarner, F., Klaenhammer, T. R., Pot, B., Reid, G... Sanders, M. E. (2005). Modulation of the microbial ecology of the human colon by probiotics, prebiotics and synbiotics to enhance human health: An overview of enabling

- science and potential applications. *FEMS Microbiology Ecology*, 52(2), 145-152. doi: 10.1016/j.femsec.2005.01.003
- Reductionism. (2015, July). Retrieved from New World Encyclopedia website: <http://www.newworldencyclopedia.org/entry/Reductionism>
- Reichenberg, A., Yirmiya, R., Schuld, A., Kraus, T., Haack, M., Morag, A., & Pollma, T. (2001). Cytokine associated emotional and cognitive disturbances in humans. *Archives of General Psychiatry*, 58(5), 445-452. doi:10.1001/archpsyc.58.5.445
- Reigstad, C.S., Salmonson C.E., Rainey, J.F., Szurszewski, J.H., Linden, D.R., Sonnenburg, J.L., . . . Kashyao, P.C. (2014). Gut microbes promote colonic serotonin production through an effect of short-chain fatty acids on enterochromaffin cells. *The Journal of the Federation of American Societies for Experimental Biology*, 29(4), 1935-1403. doi:[10.1096/fj.14-259598: 10.1096/fj.14-259598]
- Ren, J.S., Kamangar, F., Forman, D., & Islami, F. (2012). Pickled food and risk of gastric cancer: A systematic review and meta-analysis of English and Chinese literature. *Cancer Epidemiology, Biomarkers & Prevention*, 1(6), 905-915. doi:10.1158/1055-9965.EPI-12-0202
- Rucklidge, J., Johnstone, J., Gorman, B., Boggis, A., & Frampton, M. (2014). Moderators of treatment response in adults with ADHD treated with a vitamin-mineral supplement. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, 50(4), 163-171. doi:org/10.1016/j.pnpbp.2013.12014
- Ryan, A. B. (2006). Post-positivist approaches to research. In *Researching and writing your thesis: A guide for postgraduate students*. MACE: Maynooth Adult and Community Education. Retrieved from <http://eprints.maynoothuniversity.ie/874/>

- Sahney, S., & Benton, M. J. (2008). Recovery from the most profound mass extinction of all time. *Proceedings of the Royal Society B: Biological Sciences*, 275(1636), 759–765. doi:10.1098/rspb.2007.1370
- Sánchez-Villegas, A., Henríquez-Sánchez, P., Ruiz-Canela, M., Lahortiga, F. Molero, P., Toledo, E., & Martínez-González, M. A. (2015). A longitudinal analysis of diet quality scores and the risk of incident depression in the SUN project. *BMC Medicine*, 13(1), 1-12. doi:10.1186/s12916-015-0428-y
- Sandhu, K., Sherwin, E., Schellekens, H., Stanton, C., Dinan, T., & Cryan, J. (2016). Feeding the microbiota-gut-brain axis: Diet, microbiome, and neuropsychiatry. *Translational Research*, 179, 223-243. doi:org/10.1016/j.trsl.2016.10.002
- Sarris, J., Logan, A. C., Akbaraly, T. N., Amming, G.P., Balanza-Martinez, V., Freeman, M.P., . . . Jacka, F. (2015). Nutritional medicine as mainstream in psychiatry. *The Lancet Psychiatry*, 2(3), 271-274. http://dx.doi.org/10.1016/S2215-0366(14)00051-0
- Selhub, E., Logan, A. C., & Bested, A. (2014). Fermented foods, microbiota, and mental health: Ancient practice meets nutritional psychiatry. *Journal of Physiological Anthropology*, 33(2), 1-12. doi:10.1186/1880-6805-33-2
- Sherman, M., Zaghouni, H., & Niklas, V. (2015). Gut microbiota, the immune system and diet influence the neonatal gut-brain axis. *Pediatric Research*, 77(2015), 127-135. doi:10.1038/pr.2014.161
- Shultz, S.R., Aziz, N.A.B., Yang, L., Sun, M., MacFabe, F., & O'Brien, T.J. (2015). Intracerebroventricular injection of propionic acid, an enteric metabolite implicated in autism, induces social abnormalities that do not differ between seizure-prone (FAST) and

seizure-resistant (SLOW) rats. *Behavioral Brain Research*, 278(2), 542-548.

doi.org./10.1016/j..bbr.2014.10.050

Siddharth, J., Holway, N., & Parkinson, S.J. (2013). A western diet ecological module identified from the “humanized” mouse microbiota predicts diet in adults and formula feeding in children. *Plos One*, 8(12), 1-12. Retrieved from:

<https://doi.org/10.1371/journal.pone.0083689>

Siu, A. L., Bibbins-Domingo, K., Grossman, D. C., Baumann, L. C., Davidson, K. W., Ebell, M., . . . Krist, A. H. (2016). Screening for depression in adults: US Preventive Services Task Force recommendation statement. *Journal of the American Medical Association*, 315(4), 380-387. doi:10.1001/jama.2015.18392

Slattery, J., MacFabe, D., Kahler, S.G., & Frye, R.E. (2016). Enteric ecosystem disruption in autism spectrum disorder: Can the microbiota and macrobiota be restored? *Current Pharmaceutical Design*, 2016(22), 6107-6121.

doi:10.21741381612822666160905123953

Slavin, J. (2013). Fiber and prebiotics: Mechanisms and health benefits. *Nutrient*, 5(4), 1417-1435. doi:10.3390/nu5041417

Sonedstedt, E., Wirfält, E., Wallstrom, P., Gullberg, B., Orho-Melander, M., & Hedblad, B. (2011). Dairy products and its association with incidence of cardiovascular disease: The Malmö diet and cancer cohort. *European Journal of Epidemiology*, 26(2011), 609–618. doi:10.1007/s10654-011-9589-y.

Smuts, J. C. (1936/2010). *Holism and Evolution*. Whitefish, Montana: Kessinger Publishing

Spinedi, E., & Negro-Vilar, A. (1983). Serotonin and adrenocorticotropin (ACTH) release: Direct effects at the anterior pituitary level and potentiation of arginine vasopressin-

- induced ACTH release. *Endocrinology*, *112*(4), 1217-1223. Retrieved from:
<https://doi.org/10.1210/endo-112-4-1217>
- Stanga, Z., Field, J., Iff, S., Stucki, A., Lobo, D. N., & Allison, S. P. (2007). The effect of nutritional management on the mood of malnourished patients. *Clinical Nutrition*, *26*, 379-382. doi:10.1016/j.clnu.2007.01.010
- Sudo, N., Chida, Y., Aiba, Y., Sonoda, J., Oyama, N., Yu, X-N., & Kubo, C., . . . Koga, Y. (2004). Postnatal microbial colonization programs in the hypothalamic-pituitary-adrenal system for stress response in mice. *The Journal of Physiology*, *1*(558), 263-275. doi: 10.1113/jphysiol.2004.06338
- Tamang, J., Shin, D.H., Jung, S.J., & Chae, S.W. (2016). Functional properties of microorganisms in fermented foods. *Frontiers in Microbiology*, *7*(2016), 1-13. doi: 10.3389/fmicb.2016.00578
- Tamang, J. P., Tamang, B., Schillinger, U., Guigas, C., & Holzapfel, W. H. (2009). Functional properties of lactic acid bacteria isolated from ethnic fermented vegetables of the Himalayas. *International Journal of Food Microbiology*, *135*(1), 28–33. doi: 10.1016/j.ijfoodmicro.2009.07.016
- de Theije, C., G., Wopereis, H., Ramadan, M., van Eijndthoven, T., Lambert, J., Knol, J., . . . Oozeer, R. (2014). Altered gut microbiota and activity in a murine model of autism spectrum disorders. *Brain, Behavior, and Immunity*, *2014*(37), 197-206. Retrieved from:
<https://doi.org/10.1016/j.bbi.2013.12.005>
- Topping, D., & Clifton, P. (2001). Short-chain fatty acids and human colonic function: Roles of resistant starch and nonstarch polysaccharides. *Physiological Review*, *81*(3), 1031-1064. Retrieved from: <https://www.physiology.org/journal/physrev>

- Torres, L., Driscoll, M.W., & Voell, M. (2012). Discrimination, acculturation, acculturative stress, and Latino psychological distress: A moderated mediational model. *Cultural Diversity & Ethnic Minority Psychology, 18*(1), 17-25. doi: [10.1037/a0026710]
- Turnbaugh, P., Ley, R., Mahowald, M., Magrini, V., Mardis, E., & Gordon, J. (2006). An obesity-associated gut microbiome with increased capacity for energy harvest. *Nature, 444*(7122), 1027-1031. doi:10.1038/nature05414
- Turnbaugh, P., Hamady, M., Yatsunenko, T., Cantarel, B., Duncan, A., Ley, R., . . . Gordon, J. (2009). A core gut microbiome in obese and lean twins. *Nature, 457*(22), 480-485. doi:10.1038/nature07540
- Varghese, F.P. & Brown, S., (2001). The Hypothalamic-Pituitary-Adrenal Axis in major depressive disorder: A brief primer for primary care physicians. *Journal of Clinical Psychiatry, 3*(4), 151-155. Retrieved from:
<https://www.ncbi.nlm.nih.gov/pubmed/15014598>
- Vermeulen, E., Stonks, K., Visser, M., Brouwer, I. A., Schene, A. H., Mocking, R. J. T., . . . Nicolaou, M. (2016). The association between dietary patterns derived by reduced rank regression and depression symptoms over time: The Invecchiare in Chianti (InCHIANTI) study. *British Journal of Nutrition, 115*, 2145-2153. doi:10.1017/S0007114516001318
- Vergnes, J., Marchal-Sixou, C., Nabet, C., Maret, D., & Hamel, O. (2010). Ethics in systematic reviews. *Journal of Medical Ethics, 36*(2010), 771-774. doi: 10.1136/jme.2010.039941
- Wager, E., & Wiffen, P. J. (2011). Ethical issues in preparing and publishing systematic reviews. *Journal of Evidence-Based Medicine, 4*(2011), 130-134. doi: 10.1111/j.1756/5391.2011.01122.x

- Wahyuni, D. (2012). The research design maze: Understanding paradigms, cases, methods and methodologies. *Journal of Applied Management Accounting Research*, 10(1), 69-80.
Retrieved from: <http://arrow.unisa.edu.au:8081/1959.8/135405>
- Wang, J., & Jia, H. (2016). Metagenome-wide association studies: Fine-mining the microbiome. *Nature Reviews Microbiology*, 14(8), 508-522. doi:10.1038/nrmicro.2016.83
- Watson, J. (2012). *Human Caring Science: A Theory of Nursing*. Sudbury, MA: Jones & Bartlett Learning
- Weibelzahl, S. & Weber, G. (2002). Advantages, opportunities, and limits of empirical evaluations: Evaluating adaptive systems. *Kunstliche Intelligenz*, 3(2), 17-20. Retrieved from: <http://citeseerx.ist.psu.edu/viewdoc/summary?doi=10.1.1.18.7909>
- Weingarten, M. A., Paul, M., & Leibovici, L. (2004). Assessing ethics of trials in systematic reviews. *British Medical Journal*, 328(7446), 1013-1014.
doi:10.1136/bmj.328.7446.1013
- Wiley, N.C., Dinan, T.G., Ross, R. P., Stanton, C., Clarke, G., & Cryan, J. F. (2017). The microbiota-gut-brain-axis as a key regulator of neural function and the stress response: Implications for human and animal health. *Journal of Animal Science*, 95(7), 3225-3246.
doi:10.2527/jas2016.1256
- World Health Organization (2017). "Depression: Let's talk" says WHO, as depression tops list of causes of ill health. Retrieved from:
<http://www.who.int/mediacentre/news/releases/2017/world-health-day/en/>
- Zhou, Y., Mihindukulasuriya, K. A., Gao, H., Rosa, P. S., Wylie, K. M., Martin, J. C., . . . Weinstock, G. M. (2014). Exploration of bacterial community classes in major human habitats. *Genome Biology*, 15(5), 1-18. doi:10.1186/gb-2014-15-5-r66

Zhu, W.L., Shi, H.S., Wei, Y.M., Wang, S.J., Sun, C.Y., Ding, Z.B., & Lu, L. (2011). Green tea polyphenols produce antidepressant-like effects in adult mice. *Pharmacological Research*, 65(1), 74-80. doi:10.1016/j.phrs.2011.09.007

Appendix A
PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	

Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

Appendix B

RoB 2

Revised Cochrane risk-of-bias tool for randomized trials (RoB 2.0)

TEMPLATE FOR COMPLETION

Edited by Julian PT Higgins, Jelena Savović, Matthew J Page, Jonathan AC Sterne
on behalf of the ROB2 Development Group

Version of 9 October 2018

The development of the RoB 2 tool was supported by the MRC Network of Hubs for Trials Methodology Research (MR/L004933/2- N61), with the support of the host MRC ConDuCT-II Hub (Collaboration and innovation for Difficult and Complex randomised controlled Trials In Invasive procedures - MR/K025643/1), by MRC research grant MR/M025209/1, and by a grant from The Cochrane Collaboration.



This work is licensed under a [Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License](https://creativecommons.org/licenses/by-nc-nd/4.0/).

Study details Abstract Objective: This study was designed to evaluate the effects of equol and resveratrol supplementation on health-related quality of life (HRQoL) in otherwise healthy menopausal women with hot flashes, anxiety and depressive symptoms. Methods: Sixty recently menopausal women aged 50–55 years were randomized in a 12-week, placebo-controlled trial to receive 200 mg of fermented soy containing 10 mg of equol and 25 mg of resveratrol (1tablet/day). The primary outcome was the change in score on the Menopause Rating Scale (MRS), used to evaluate the severity of age-/menopause-related complaints. Additional outcome measures included the subject-reported score on the Hamilton Rating Scale for Depression (HAM-D) and Nottingham Health Profile (NHP), which was used specifically to assess sleep quality. Results: The symptoms assessed by the MRS improved during treatment in the active group. Comparison between placebo and treatment groups revealed statistically significant improvement in particular for dryness of vagina (–85.7%) (p < 0.001), heart discomfort (–78.8%; p < 0.001) and sexual problems (–73.3%; p < 0.001). On the HAM-D significant improvements at week 12 were seen in work and activities (–94.1%) (p < 0.001). Subjects treated with equol and resveratrol also had significant differences in the sleep domain of the NHP (p < 0.001). Conclusion: These findings provide evidence that 12 weeks of dietary supplementation with equol and resveratrol may improve menopause-related quality of life in healthy women.

Reference

Davinelli, S., Scapagnini, G., Marzatico, F., Nobile, V., Ferrara, N., & Corbi, G. (2017). Influence of equol and resveratrol supplementation on health-related quality of life in menopausal women: A randomized, placebo-controlled study. *Maturitas*,96, 77-83.
doi:10.1016/j.maturitas.2016.11.016

Study design

- Individually-randomized parallel-group trial
- Cluster-randomized parallel-group trial
- Individually randomized cross-over (or other matched) trial

Specify which outcome is being assessed for risk of bias

The effects of equol and resveratrol supplementation on menopausal related symptoms of hot flashes, anxiety and depression using the HAM-D depression assessment tool. Risk of bias to be assessed: Subject selection, Randomization, Treatment adherence, HRQol measurements using Menopause Rating scale , (MRS) for menopausal symptoms, Hamilton rating scale (HAM-D) for depression and the Nottingham Health Profile (NHP) health status changes over time for emotional reactions

Specify the numerical result being assessed. In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed.

Sample size calculation based on the results of previous similar studies: alpha value at 0.05 with a confidence level of 90% and considering a prevalence of menopausal symptoms of 60% and a possible response distribution of 5%, sample size of 26 for each group. With this number, differences in menopause symptom scores from baseline to week 12 between active and placebo groups could be detected.

Questionnaire results reported as means ± Standard Error (SE) or percentage values.

Percentages show the subjects with the menopausal complaints data. These percentages were calculated on the number of subjects that at the enrolment scored the symptom higher than “none”.

Subjects scoring the symptom “absent” were excluded from the analysis. Intragroup (vs. baseline) and intergroup (active vs.placebo).

Statistical analysis was carried out using a mixed effect model. A p-value < 0.05 was considered statistically significant.

Is the review team’s aim for this result...?

- to assess the effect of *assignment to intervention* (the ‘intention-to-treat’ effect)

- to assess the effect of *adhering to intervention* (the 'per-protocol' effect)

Which of the following sources were obtained to help inform the risk-of-bias assessment? (tick as many as apply)

- Journal article(s) with results of the trial
- Trial protocol
- Statistical analysis plan (SAP)
- Non-commercial trial registry record (e.g. ClinicalTrials.gov record)
- Company-owned trial registry record (e.g. GSK Clinical Study Register record)
- "Grey literature" (e.g. unpublished thesis)
- Conference abstract(s) about the trial
- Regulatory document (e.g. Clinical Study Report, Drug Approval Package)
- Research ethics application
- Grant database summary (e.g. NIH RePORTER or Research Councils UK Gateway to Research)
- Personal communication with trialist
- Personal communication with the sponsor

Domain 1: Risk of bias arising from the randomization process

Signalling questions	Description	Response options
1.1 Was the allocation sequence random?	A restricted randomization list was created using PASS 2008(PASS, LLC. Kaysville, UT, USA) statistical software running on Windows Server 2008 R2 Standard SP1 64 bit Edition (Microsoft, USA) by a biostatistician and stored in a safe place. Randomization sequence was stratified using 10% maximum allowable% deviation with a 1:1 allocation ratio. The allocation sequence was concealed from the in site study director in sequentially numbered, opaque, and sealed envelopes, reporting the unblinded treatment allocation (based on subject entry number in the study). The A4 sheet reporting the unblinded treatment was folded to render the envelope impermeable to intense light. After acceptance of the subject in the study the appropriate numbered envelope was opened. An independent technician dispensed either active or placebo products according to the card inside the envelope. The study adhered to established procedures to maintain separation between the investigator and its collaborators and the staff that delivered the intervention. Investigator and its collaborators who obtained out-come measurements were not informed on the product group assignment. Staff who delivered the intervention did not take out-come measurements. Subjects, investigator and collaborators were kept masked to products assignment.	Y
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?		Y
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	Difference in demographic and baseline characteristics of study population between the active and placebo group were measured as non-statistical.	N
Risk-of-bias judgement	Specified procedures and description in the article for signaling questions 1.1, 1.2, and 1.3	Low
Optional: What is the predicted direction of bias arising from the randomization process?	Optional did not complete	Favours experimental / Favours comparator / Towards null

		/Away from null / Unpredictable
--	--	------------------------------------

Domain 2: Risk of bias due to deviations from the intended interventions (*effect of assignment to intervention*)

Signalling questions	Description	Response options
2.1. Were participants aware of their assigned intervention during the trial?	The allocation sequence was concealed from the in-site study director in sequentially numbered, opaque, and sealed envelopes, reporting the unblinded treatment allocation (based on subject entry number in the study). Investigator and its collaborators who obtained out-come measurements were not informed on the product group assignment. Staff who delivered the intervention did not take out-come measurements. Subjects, investigator and collaborators were kept masked to products assignment.	N
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		N
2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	NA	NA
2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups?	NA	NA
2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome?	NA	NA
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Yes, Intragroup analysis vs baseline: and Intergroup analysis at the same time points were conducted, there was no deviation from the assignment to intervention listed in the flow diagram fig. 1. In the article	Y
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA	NA
Risk-of-bias judgement	Specified procedures and description in the article for signaling questions 2.1, through 2.7.	Low

<p>Optional: What is the predicted direction of bias due to deviations from intended interventions?</p>	<p>Optional did not complete</p>	<p>Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable</p>
---	----------------------------------	---

Domain 2: Risk of bias due to deviations from the intended interventions (*effect of adhering to intervention*)

Signalling questions	Description	Response options
2.1. Were participants aware of their assigned intervention during the trial?	The allocation sequence was concealed from the in-site study director in sequentially numbered, opaque, and sealed envelopes, reporting the unblinded treatment allocation (based on subject entry number in the study). Investigator and its collaborators who obtained out-come measurements were not informed on the product group assignment. Staff who delivered the intervention did not take out-come measurements. Subjects, investigator and collaborators were kept masked to products assignment.	<u>N</u>
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		<u>N</u>
2.3. If Y/PY/NI to 2.1 or 2.2: Were important co-interventions balanced across intervention groups?	NA	NA
2.4. Could failures in implementing the intervention have affected the outcome?	No as both lost to follow up and discontinued interventions were being documented. From the flow chart exclusion from analysis was listed, however there were not exclusions from analysis	<u>N</u>
2.5. Did study participants adhere to the assigned intervention regimen?	Yes, from the flow diagram, there were no lost to follow-up, or discontinuation of the intervention in either the Active or placebo group during the study	<u>Y</u>
2.6. If N/PN/NI to 2.3 or 2.5 or Y/PY/NI to 2.4: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	NA	NA
Risk-of-bias judgement	Specified procedures and description in the article for signaling questions 2.1, through 2.6.	Low
Optional: What is the predicted direction of bias due to deviations from intended interventions?	Optional did not complete	Favours experimental / Favours comparator / Towards null / Away from null / Unpredictable

Domain 3: Missing outcome data

Signalling questions	Description	Response options
3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Yes, see flow diagram Fig. 1	<u>Y</u>
3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	NA
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	NA
3.4 If Y/PY/NI to 3.3: Do the proportions of missing outcome data differ between intervention groups?	NA	NA
3.5 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	NA
Risk-of-bias judgement	Specified procedures and description in the article for signaling questions 3.1, through 3.5.	Low
Optional: What is the predicted direction of bias due to missing outcome data?	Optional did not complete	Favours experimental / Favours comparator / Towards null / Away from null / Unpredictable

Domain 4: Risk of bias in measurement of the outcome

Signalling questions	Description	Response options
<p>4.1 Was the method of measuring the outcome inappropriate?</p>	<p>To evaluate the efficacy of the intervention, we used the validated HRQoL questionnaire Menopause Rating Scale (MRS) to measure the proportion of subjects achieving an improvement in menopausal symptoms. The MRS was developed and validated to evaluate the severity of menopause-related complaints. A 5-point rating scale from zero (no complaint) to four (extremely severe symptoms) permits to describe the severity of complaints of each item. The MRS consists of eleven questions, however, the item related to anxiety was not included in the questionnaire since this symptom was assessed by Hamilton Rating Scale for Depression (HAM-D). The HAM-D is a well-known clinician standardized scale designed to measure depression severity. The original version of HAM-D contains 17 items. Each item is scored on a scale of 0 (not present) to 4 (severe), with a total score range of 0–56, where <17 indicates mild severity, 18–24 mild to moderate severity and 25–30 moderate to severe. In this study, emotional dis-tress in menopausal woman was assessed using 4 items of HAM-D pertaining to work and activities, agitation and anxiety. Sleep quality was measured using the Nottingham Health Profile (NHP). The NHP is a self-administered questionnaire consisting of 38 items that detects health status changes over time. The NHP is organised into six domains, including emotional reactions, energy, pain, physical mobility, social isolation, and sleep. The NHP scores range from 0 to 100, with lower scores indicating lower levels of distress. In the present study, we used the sleep section of the NHP to assess different aspects of sleep disturbances associated with menopause.</p>	<p><u>N</u></p>
<p>4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?</p>	<p>No, see fig. 1</p>	<p><u>N</u></p>
<p>4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the</p>	<p>No participants and clinicians were not aware of the interventions received. No major deviation was observed in the treatment regimen. All subjects were included</p>	<p><u>N</u></p>

intervention received by study participants?	in the safety analysis data set. In general, the treatment was well tolerated, and no adverse events were reported during the study period.	
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	NA
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	NA
Risk-of-bias judgement	Specified procedures and description in the article for signaling questions 4.1, through 4.5.	Low
Optional: What is the predicted direction of bias in measurement of the outcome?	Optional did not complete	Favours experimental / Favours comparator / Towards null / Away from null / Unpredictable

Domain 5: Risk of bias in selection of the reported result

Signalling questions	Description	Response options
<p>5.1 Was the trial analysed in accordance with a pre-specified plan that was finalized before unblinded outcome data were available for analysis?</p>	<p>Yes, No major deviation was observed in the treatment regimen. All subjects were included in the safety analysis data set. In general, the treatment was well tolerated, and no adverse events were reported during the study period.</p>	<p><u>Y</u></p>
<p>Is the numerical result being assessed likely to have been selected, on the basis of the results, from...</p>		
<p>5.2. ... multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?</p>	<p>No outcome measurements were defined and followed</p>	<p><u>N</u></p>
<p>5.3 ... multiple analyses of the data?</p>	<p>No, specified analysis was followed</p>	<p><u>N</u></p>
<p>Risk-of-bias judgement</p>	<p>Specified procedures and description in the article for signaling questions 5.1, through 5.3.</p>	<p>Low / High / Some concerns</p>
<p>Optional: What is the predicted direction of bias due to selection of the reported result?</p>	<p>Optional did not complete</p>	<p>Favours experimental / Favours comparator / Towards null / Away from null / Unpredictable</p>

Overall risk of bias

Risk-of-bias judgement	Low as all Specified procedures and description in the article for signaling questions 1.1, through 5.3. were addressed	Low
Optional: What is the predicted direction of bias due to selection of the reported result?		Favours experimental / Favours comparator / Towards null / Away from null / Unpredictable

Study details Abstract Objectives: Red yeast rice (RZR) has demonstrated neuroprotective effects in animal studies. The aim of this study was to assess the efficacy of RZR for treatment of depression in patients with recent history of percutaneous coronary intervention. Design: This was a 6-week double-blind placebo-controlled randomized clinical trial. Setting: Participants included outpatient men and women aged 18 to 60 years old with history of coronary angioplasty, diagnosis of major depressive disorder based on the Diagnostic and Statistical Manual of Mental Disorders (DSM-V), and Hamilton Depression Rating Scale (HDRS) score of ≥ 20 . Candidates were excluded in case of any other DSM-V disorders, use of lipid-lowering agents in the last two weeks, elevated serum aminotransferases or serum LDL ≤ 80 mg/dL. Interventions: Patients received sertraline (200 mg/day) plus either red yeast rice commercially available capsules (2400 mg/day) containing 10.05 mg/day lovastatin or placebo. Main outcome measures: The primary outcome was the difference in mean change of the HDRS score from baseline to endpoint between the two treatment arms. Results: The primary outcome approached significance (Mean difference in score change (CI95%) = -1.24 (-2.51 to 0.03), $p = .056$) and was accompanied by a significant time x treatment interaction effect [Two-way ANOVA: F (df, mean square) = 4.42 (2, 13.687), $p = .015$]. There was no significant difference between the two treatment arms in terms of lipid profile, liver function tests, or incidence of adverse events. Conclusions: This is the first report on the benefits of RZR in treatment of depression. Future studies are warranted to confirm our findings and scrutinize the mechanisms of action.

Reference

Divsalar, P., Noorbala, A. A., Moazen-Zadeh, E., Jafarinia, M., Shakiba, M., Shahmansouri, N., . . . Akhondzadeh, S. (2018). Red yeast rice as an adjunct to sertraline for treatment of depression in patients with percutaneous coronary intervention: Placebo-controlled trial. *Advances in Integrative Medicine*, 5(2), 69-74. doi:10.1016/j.aimed.2018.01.001

Study design

- Individually-randomized parallel-group trial
- Cluster-randomized parallel-group trial
- Individually randomized cross-over (or other matched) trial

Specify which outcome is being assessed for risk of bias

The difference in change of mean Hamilton Depression Rating Scale (HDRS) score from baseline to the endpoint between the RZR and the placebo treatments.

Specify the numerical result being assessed. In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed.

The Hamilton Depression Rating Scale (HDRS) was used for assessment of severity of depressive symptoms. Composed of 17 items (each on a three-point or five-point scale) An independent rater was responsible

for administration of the HDRS at weeks 0, 3, and 6. The difference in mean change of the HDRS score from baseline to week 6 between the RYR and placebo groups was considered the primary outcome of interest. Time x treatment interaction between the two treatment groups was considered as the secondary outcome. Table 2, Table3, Table 4, and fig 2.

Is the review team's aim for this result...?

- to assess the effect of *assignment to intervention* (the 'intention-to-treat' effect)
- to assess the effect of *adhering to intervention* (the 'per-protocol' effect)

Which of the following sources were obtained to help inform the risk-of-bias assessment? (tick as many as apply)

- Journal article(s) with results of the trial
- Trial protocol
- Statistical analysis plan (SAP)
- Non-commercial trial registry record (e.g. ClinicalTrials.gov record)
- Company-owned trial registry record (e.g. GSK Clinical Study Register record)
- "Grey literature" (e.g. unpublished thesis)
- Conference abstract(s) about the trial
- Regulatory document (e.g. Clinical Study Report, Drug Approval Package)
- Research ethics application
- Grant database summary (e.g. NIH RePORTER or Research Councils UK Gateway to Research)
- Personal communication with trialist
- Personal communication with the sponsor

Domain 1: Risk of bias arising from the randomization process

Signalling questions	Description	Response options
1.1 Was the allocation sequence random?	In order to randomize the participants to red yeast rice or placebo groups in a 1:1 ratio, computerized random number generation was used by one of the personnel different from raters. Treatment allocation concealment was achieved using sealed opaque envelopes with sequential numbers. RYR and placebo were in form of capsules identical in color, shape, texture, size, taste, and container. An investigational drug pharmacist was responsible to dispense the medications. All healthcare providers, participants, and caregivers were blinded during the trial.	Y
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?		Y
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	No significant difference was detected in demographics (Table 1), baseline HDRS scores (Table 2), or baseline lab tests (Table 3) between the two treatment arms.	N
Risk-of-bias judgement	Specified procedures and description in the article for signaling questions 1.1, 1.2, and 1.3	Low
Optional: What is the predicted direction of bias arising from the randomization process?	Optional did not complete	Favours experimental / Favours comparator / Towards null / Away from null / Unpredictable

Domain 2: Risk of bias due to deviations from the intended interventions (*effect of assignment to intervention*)

Signalling questions	Description	Response options
2.1. Were participants aware of their assigned intervention during the trial?	RYS and placebo were in form of capsules identical in color, shape, texture, size, taste, and container. An investigational drug pharmacist was responsible to dispense the medications. All healthcare providers, participants, and caregivers were blinded during the trial.	N
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		N
2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	NA	NA
2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups?	NA	NA
2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome?	NA	NA
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Considering a similar study on simvastatin [34], a difference of 2 and a standard deviation of 2.5 was considered for mean change in the HDRS score between the two groups. Applying a type I error of 0.05 and power of 80%, a primary sample size of 50 was calculated. Considering an attrition rate of 10%, the final sample size was estimated as 55 participants.	Y
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA	NA
Risk-of-bias judgement	Specified procedures and description in the article for signaling questions 2.1, through and 2.7	Low

<p>Optional: What is the predicted direction of bias due to deviations from intended interventions?</p>	<p>Optional did not complete</p>	<p>Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable</p>
---	----------------------------------	---

Domain 2: Risk of bias due to deviations from the intended interventions (*effect of adhering to intervention*)

Signalling questions	Description	Response options
2.1. Were participants aware of their assigned intervention during the trial?	An investigational drug pharmacist was responsible to dispense the medications. All healthcare providers, participants, and caregivers were blinded during the trial.	N
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		N
2.3. If Y/PY/NI to 2.1 or 2.2: Were important co-interventions balanced across intervention groups?	NA	NA
2.4. Could failures in implementing the intervention have affected the outcome?	No as discontinued interventions were being documented for both RYR and placebo groups.	N
2.5. Did study participants adhere to the assigned intervention regimen?	3 patients in the RYR and 3 patients in the placebo group discontinued prior to the end of the study	PY

	<pre> graph TD A[101 Patients screened] --> B[56 randomized] A --> C[45 excluded: 30 did not meet inclusion criteria 15 met exclusion criteria] B --> D[28 assigned to Red Yeast] B --> E[28 assigned to placebo] D --> F[25 completed trial] D --> G[Discontinued: 2 Withdrawn consent at week 1 1 excluded due to substance dependence at week 2] E --> H[25 completed trial] E --> I[Discontinued: 3 Withdrawn consent at week 2] </pre>	
<p>2.6. If N/PN/NI to 2.3 or 2.5 or Y/PY/NI to 2.4: Was an appropriate analysis used to estimate the effect of adhering to the intervention?</p>	<p>While documentation of discontinuations was present, the article did not discuss how adherence to taking the intervention. An assumption was made that if the investigational drug pharmacist responsible for Dispensing the medications did not mention any deviation from adherence that all of the 25 that completed the trial adhered to the intervention.</p>	<p>Y</p>
<p>Risk-of-bias judgement</p>	<p>Specified procedures and description in the article for signaling questions 2.1, through and 2.7</p>	<p>Low</p>
<p>Optional: What is the predicted direction of bias due to deviations from intended interventions?</p>	<p>Optional did not complete</p>	<p>Favours experimental / Favours comparator /</p>

		Towards null /Away from null / Unpredictable
--	--	---

Domain 3: Missing outcome data

Signalling questions	Description	Response options
<p>3.1 Were data for this outcome available for all, or nearly all, participants randomized?</p>	<p>Yes, of the 56 patients randomized all but 3 in the RYR and 3 from the Placebo group were available, data from the discontinued patients were not presented</p> <pre> graph TD A[101 Patients screened] --> B[56 randomized] A --> C[45 excluded: 30 did not meet inclusion criteria 15 met exclusion criteria] B --> D[28 assigned to Red Yeast] B --> E[28 assigned to placebo] D --> F[25 completed trial] D --> G[Discontinued: 2 Withdrawn consent at week 1 1 excluded due to substance dependence at week 2] E --> H[25 completed trial] E --> I[Discontinued: 3 Withdrawn consent at week 2] </pre>	<p>Y</p>
<p>3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?</p>	<p>NA</p>	<p>NA</p>

3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	NA
3.4 If Y/PY/NI to 3.3: Do the proportions of missing outcome data differ between intervention groups?	NA	NA
3.5 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	NA
Risk-of-bias judgement	Specified procedures and description in the article for signaling questions 3.1, through and 3.5	Low
Optional: What is the predicted direction of bias due to missing outcome data?	Optional did not complete	Favours experimental / Favours comparator / Towards null / Away from null / Unpredictable

Domain 4: Risk of bias in measurement of the outcome

Signalling questions	Description	Response options
<p>4.1 Was the method of measuring the outcome inappropriate?</p>	<p>Analysis was performed using IBM SPSS Statistics 19.0.0 (IBM Corporations) and Jamovi 0.8.1.13. Continuous and categorical data were reported as mean (SD), mean (95% confidence intervals (95% CI)), and number (%), where appropriate. Cohen’s d (95% CI) was reported as a measure of effect size for difference in score changes. Intention-to-treat analysis was performed using last observation carried forward (LOCF) method. Time X treatment interaction was estimated by application of two-way repeated measure analysis of variance (ANOVA). If the sphericity assumption was violated based on the Mauchly’s W test, Greenhouse-Geisser’s correction was considered. Independent samples t-test was used for comparison of continuous data with subsequent correction for degrees of freedom and p-values if the assumption of equality of variances was violated based on the Levene’s test. Fisher’s exact test was used to compare categorical data. Two-tailed p-values of <.05 were considered significant. Cronbach’s alpha and McDonald’s omega were reported after reliability analysis.</p>	<p>N</p>
<p>4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?</p>	<p>No Intervention vs placebo see fig. 1 and 2, and table 1-4</p>	<p>N</p>
<p>4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants ?</p>	<p>No,</p>	<p>N</p>
<p>4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?</p>	<p>NA</p>	<p>NA</p>
<p>4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was</p>	<p>NA</p>	<p>NA</p>

<p>influenced by knowledge of intervention received?</p>		
<p>Risk-of-bias judgement</p>	<p>Specified procedures and description in the article for signaling questions 4.1, through and 4.5</p>	<p>Low / High / Some concerns</p>
<p>Optional: What is the predicted direction of bias in measurement of the outcome?</p>	<p>Optional did not complete</p>	<p>Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable</p>

Domain 5: Risk of bias in selection of the reported result

Signalling questions	Description	Response options
<p>5.1 Was the trial analysed in accordance with a pre-specified plan that was finalized before unblinded outcome data were available for analysis?</p>	<p>An independent rater was responsible for administration of the HDRS at weeks 0, 3, and 6. The difference in mean change of the HDRS score from baseline to week 6 between the RYR and placebo groups was considered the primary outcome of interest. Time X treatment interaction between the two treatment groups was considered as the secondary outcome. Analysis was performed using IBM SPSS Statistics 19.0.0 (IBM Corporations) and Jamovi 0.8.1.13. Continuous and categorical data were reported as mean (SD), mean (95% confidence intervals (95% CI)), and number (%), where appropriate. Cohen’s d (95% CI) was reported as a measure of effect size for difference in score changes. Intention-to-treat analysis was performed using last observation carried forward (LOCF) method. Time x treatment interaction was estimated by application of two-way repeated measure analysis of variance (ANOVA). If the sphericity assumption was violated based on the Mauchly’s W test, Greenhouse-Geisser’s correction was considered. Independent samples t-test was used for comparison of continuous data with subsequent correction for degrees of freedom and p-values if the assumption of equality of variances was violated based on the Levene’s test. Fisher’s exact test was used to compare categorical data. Two-tailed p-values of <.05 were considered significant. Cronbach’s alpha and McDonald’s omega were reported after reliability analysis</p>	<p>Y</p>
<p>Is the numerical result being assessed likely to have been selected, on the basis of the results, from...</p>		
<p>5.2. ... multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?</p>	<p>N</p>	<p>N</p>
<p>5.3 ... multiple analyses of the data?</p>	<p>N</p>	<p>N</p>

Risk-of-bias judgement	Specified procedures and description in the article for signaling questions 5.1, through and 5.3	Low
Optional: What is the predicted direction of bias due to selection of the reported result?	Optional did not complete	Favours experimental / Favours comparator / Towards null / Away from null / Unpredictable

Overall risk of bias

Risk-of-bias judgement	Specified procedures and description in the article for signaling questions 1.1, through and 5.3	Low
Optional: What is the predicted direction of bias due to selection of the reported result?	Optional did not complete	Favours experimental / Favours comparator / Towards null / Away from null / Unpredictable

Appendix C

AMSTAR 2

AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both

<p>1. Did the research questions and inclusion criteria for the review include the components of PICO?</p>		
<p>For Yes:</p> <ul style="list-style-type: none"> <input type="checkbox"/> Population <input type="checkbox"/> Intervention <input type="checkbox"/> Comparator group <input type="checkbox"/> Outcome 	<p>Optional (recommended)</p> <ul style="list-style-type: none"> <input type="checkbox"/> Timeframe for follow-up 	<ul style="list-style-type: none"> <input type="checkbox"/> Yes <input type="checkbox"/> No
<p>2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?</p>		
<p>For Partial Yes: The authors state that they had a written protocol or guide that included ALL the following:</p> <ul style="list-style-type: none"> <input type="checkbox"/> review question(s) <input type="checkbox"/> a search strategy <input type="checkbox"/> inclusion/exclusion criteria <input type="checkbox"/> a risk of bias assessment 	<p>For Yes: As for partial yes, plus the protocol should be registered and should also have specified:</p> <ul style="list-style-type: none"> <input type="checkbox"/> a meta-analysis/synthesis plan, if appropriate, <i>and</i> <input type="checkbox"/> a plan for investigating causes of heterogeneity <input type="checkbox"/> justification for any deviations from the protocol 	<ul style="list-style-type: none"> <input type="checkbox"/> Yes <input type="checkbox"/> Partial Yes <input type="checkbox"/> No
<p>3. Did the review authors explain their selection of the study designs for inclusion in the review?</p>		
<p>For Yes, the review should satisfy ONE of the following:</p> <ul style="list-style-type: none"> <input type="checkbox"/> Explanation for including only RCTs <input type="checkbox"/> OR Explanation for including only NRSI <input type="checkbox"/> OR Explanation for including both RCTs and NRSI 		
<p>4. Did the review authors use a comprehensive literature search strategy?</p>		
<p>For Partial Yes (all the following):</p> <ul style="list-style-type: none"> <input type="checkbox"/> searched at least 2 databases (relevant to research question) <input type="checkbox"/> provided key word and/or search strategy <input type="checkbox"/> justified publication restrictions (e.g. language) 	<p>For Yes, should also have (all the following):</p> <ul style="list-style-type: none"> <input type="checkbox"/> searched the reference lists / bibliographies of included studies <input type="checkbox"/> searched trial/study registries <input type="checkbox"/> included/consulted content experts in the field <input type="checkbox"/> where relevant, searched for grey literature <input type="checkbox"/> conducted search within 24 months of completion of the review 	<ul style="list-style-type: none"> <input type="checkbox"/> Yes <input type="checkbox"/> Partial Yes <input type="checkbox"/> No
<p>5. Did the review authors perform study selection in duplicate?</p>		
<p>For Yes, either ONE of the following:</p> <ul style="list-style-type: none"> <input type="checkbox"/> at least two reviewers independently agreed on selection of eligible studies and achieved consensus on which studies to include <input type="checkbox"/> OR two reviewers selected a sample of eligible studies <u>and</u> achieved good agreement (at least 80 percent), with the remainder selected by one reviewer. 		

AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both

<p>1. Did the research questions and inclusion criteria for the review include the components of PICO?</p>		
<p>For Yes:</p> <ul style="list-style-type: none"> <input type="checkbox"/> Population <input type="checkbox"/> Intervention <input type="checkbox"/> Comparator group <input type="checkbox"/> Outcome 	<p>Optional (recommended)</p> <ul style="list-style-type: none"> <input type="checkbox"/> Timeframe for follow-up 	<ul style="list-style-type: none"> <input type="checkbox"/> Yes <input type="checkbox"/> No
<p>2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?</p>		
<p>For Partial Yes: The authors state that they had a written protocol or guide that included ALL the following:</p> <ul style="list-style-type: none"> <input type="checkbox"/> review question(s) <input type="checkbox"/> a search strategy <input type="checkbox"/> inclusion/exclusion criteria <input type="checkbox"/> a risk of bias assessment 	<p>For Yes: As for partial yes, plus the protocol should be registered and should also have specified:</p> <ul style="list-style-type: none"> <input type="checkbox"/> a meta-analysis/synthesis plan, if appropriate, <i>and</i> <input type="checkbox"/> a plan for investigating causes of heterogeneity <input type="checkbox"/> justification for any deviations from the protocol 	<ul style="list-style-type: none"> <input type="checkbox"/> Yes <input type="checkbox"/> Partial Yes <input type="checkbox"/> No
<p>3. Did the review authors explain their selection of the study designs for inclusion in the review?</p>		
<p>For Yes, the review should satisfy ONE of the following:</p> <ul style="list-style-type: none"> <input type="checkbox"/> Explanation for including only RCTs <input type="checkbox"/> OR Explanation for including only NRSI <input type="checkbox"/> OR Explanation for including both RCTs and NRSI 		
<p>4. Did the review authors use a comprehensive literature search strategy?</p>		
<p>For Partial Yes (all the following):</p> <ul style="list-style-type: none"> <input type="checkbox"/> searched at least 2 databases (relevant to research question) <input type="checkbox"/> provided key word and/or search strategy <input type="checkbox"/> justified publication restrictions (e.g. language) 	<p>For Yes, should also have (all the following):</p> <ul style="list-style-type: none"> <input type="checkbox"/> searched the reference lists / bibliographies of included studies <input type="checkbox"/> searched trial/study registries <input type="checkbox"/> included/consulted content experts in the field <input type="checkbox"/> where relevant, searched for grey literature <input type="checkbox"/> conducted search within 24 months of completion of the review 	<ul style="list-style-type: none"> <input type="checkbox"/> Yes <input type="checkbox"/> Partial Yes <input type="checkbox"/> No
<p>5. Did the review authors perform study selection in duplicate?</p>		
<p>For Yes, either ONE of the following:</p> <ul style="list-style-type: none"> <input type="checkbox"/> at least two reviewers independently agreed on selection of eligible studies and achieved consensus on which studies to include <input type="checkbox"/> OR two reviewers selected a sample of eligible studies <u>and</u> achieved good agreement (at least 80 percent), with the remainder selected by one reviewer. 		

AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both

<p>6. Did the review authors perform data extraction in duplicate?</p> <p>For Yes, either ONE of the following:</p> <table border="0"> <tr> <td><input type="checkbox"/> at least two reviewers achieved consensus on which data to extract from included studies</td> <td><input type="checkbox"/> Yes</td> </tr> <tr> <td><input type="checkbox"/> OR two reviewers extracted data from a sample of eligible studies <u>and</u> achieved good agreement (at least 80 percent), with the remainder extracted by one reviewer.</td> <td><input type="checkbox"/> No</td> </tr> </table>			<input type="checkbox"/> at least two reviewers achieved consensus on which data to extract from included studies	<input type="checkbox"/> Yes	<input type="checkbox"/> OR two reviewers extracted data from a sample of eligible studies <u>and</u> achieved good agreement (at least 80 percent), with the remainder extracted by one reviewer.	<input type="checkbox"/> No																																
<input type="checkbox"/> at least two reviewers achieved consensus on which data to extract from included studies	<input type="checkbox"/> Yes																																					
<input type="checkbox"/> OR two reviewers extracted data from a sample of eligible studies <u>and</u> achieved good agreement (at least 80 percent), with the remainder extracted by one reviewer.	<input type="checkbox"/> No																																					
<p>7. Did the review authors provide a list of excluded studies and justify the exclusions?</p> <table border="0"> <tr> <td>For Partial Yes:</td> <td>For Yes, must also have:</td> <td></td> </tr> <tr> <td><input type="checkbox"/> provided a list of all potentially relevant studies that were read in full-text form but excluded from the review</td> <td><input type="checkbox"/> Justified the exclusion from the review of each potentially relevant study</td> <td> <input type="checkbox"/> Yes <input type="checkbox"/> Partial Yes <input type="checkbox"/> No </td> </tr> </table>			For Partial Yes:	For Yes, must also have:		<input type="checkbox"/> provided a list of all potentially relevant studies that were read in full-text form but excluded from the review	<input type="checkbox"/> Justified the exclusion from the review of each potentially relevant study	<input type="checkbox"/> Yes <input type="checkbox"/> Partial Yes <input type="checkbox"/> No																														
For Partial Yes:	For Yes, must also have:																																					
<input type="checkbox"/> provided a list of all potentially relevant studies that were read in full-text form but excluded from the review	<input type="checkbox"/> Justified the exclusion from the review of each potentially relevant study	<input type="checkbox"/> Yes <input type="checkbox"/> Partial Yes <input type="checkbox"/> No																																				
<p>8. Did the review authors describe the included studies in adequate detail?</p> <table border="0"> <tr> <td>For Partial Yes (ALL the following):</td> <td>For Yes, should also have ALL the following:</td> <td></td> </tr> <tr> <td><input type="checkbox"/> described populations</td> <td><input type="checkbox"/> described population in detail</td> <td><input type="checkbox"/> Yes</td> </tr> <tr> <td><input type="checkbox"/> described interventions</td> <td><input type="checkbox"/> described intervention in detail (including doses where relevant)</td> <td><input type="checkbox"/> Partial Yes</td> </tr> <tr> <td><input type="checkbox"/> described comparators</td> <td><input type="checkbox"/> described comparator in detail (including doses where relevant)</td> <td><input type="checkbox"/> No</td> </tr> <tr> <td><input type="checkbox"/> described outcomes</td> <td><input type="checkbox"/> described study's setting</td> <td></td> </tr> <tr> <td><input type="checkbox"/> described research designs</td> <td><input type="checkbox"/> timeframe for follow-up</td> <td></td> </tr> </table>			For Partial Yes (ALL the following):	For Yes, should also have ALL the following:		<input type="checkbox"/> described populations	<input type="checkbox"/> described population in detail	<input type="checkbox"/> Yes	<input type="checkbox"/> described interventions	<input type="checkbox"/> described intervention in detail (including doses where relevant)	<input type="checkbox"/> Partial Yes	<input type="checkbox"/> described comparators	<input type="checkbox"/> described comparator in detail (including doses where relevant)	<input type="checkbox"/> No	<input type="checkbox"/> described outcomes	<input type="checkbox"/> described study's setting		<input type="checkbox"/> described research designs	<input type="checkbox"/> timeframe for follow-up																			
For Partial Yes (ALL the following):	For Yes, should also have ALL the following:																																					
<input type="checkbox"/> described populations	<input type="checkbox"/> described population in detail	<input type="checkbox"/> Yes																																				
<input type="checkbox"/> described interventions	<input type="checkbox"/> described intervention in detail (including doses where relevant)	<input type="checkbox"/> Partial Yes																																				
<input type="checkbox"/> described comparators	<input type="checkbox"/> described comparator in detail (including doses where relevant)	<input type="checkbox"/> No																																				
<input type="checkbox"/> described outcomes	<input type="checkbox"/> described study's setting																																					
<input type="checkbox"/> described research designs	<input type="checkbox"/> timeframe for follow-up																																					
<p>9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?</p> <table border="0"> <tr> <td colspan="3">RCTs</td> </tr> <tr> <td>For Partial Yes, must have assessed RoB from</td> <td>For Yes, must also have assessed RoB from:</td> <td></td> </tr> <tr> <td><input type="checkbox"/> unconcealed allocation, <i>and</i></td> <td><input type="checkbox"/> allocation sequence that was not truly random, <i>and</i></td> <td><input type="checkbox"/> Yes</td> </tr> <tr> <td><input type="checkbox"/> lack of blinding of patients and assessors when assessing outcomes (unnecessary for objective outcomes such as all-cause mortality)</td> <td><input type="checkbox"/> selection of the reported result from among multiple measurements or analyses of a specified outcome</td> <td><input type="checkbox"/> Partial Yes</td> </tr> <tr> <td></td> <td></td> <td><input type="checkbox"/> No</td> </tr> <tr> <td></td> <td></td> <td><input type="checkbox"/> Includes only NRSI</td> </tr> <tr> <td colspan="3">NRSI</td> </tr> <tr> <td>For Partial Yes, must have assessed RoB:</td> <td>For Yes, must also have assessed RoB:</td> <td></td> </tr> <tr> <td><input type="checkbox"/> from confounding, <i>and</i></td> <td><input type="checkbox"/> methods used to ascertain exposures and outcomes, <i>and</i></td> <td><input type="checkbox"/> Yes</td> </tr> <tr> <td><input type="checkbox"/> from selection bias</td> <td><input type="checkbox"/> selection of the reported result from among multiple measurements or analyses of a specified outcome</td> <td><input type="checkbox"/> Partial Yes</td> </tr> <tr> <td></td> <td></td> <td><input type="checkbox"/> No</td> </tr> <tr> <td></td> <td></td> <td><input type="checkbox"/> Includes only RCTs</td> </tr> </table>			RCTs			For Partial Yes, must have assessed RoB from	For Yes, must also have assessed RoB from:		<input type="checkbox"/> unconcealed allocation, <i>and</i>	<input type="checkbox"/> allocation sequence that was not truly random, <i>and</i>	<input type="checkbox"/> Yes	<input type="checkbox"/> lack of blinding of patients and assessors when assessing outcomes (unnecessary for objective outcomes such as all-cause mortality)	<input type="checkbox"/> selection of the reported result from among multiple measurements or analyses of a specified outcome	<input type="checkbox"/> Partial Yes			<input type="checkbox"/> No			<input type="checkbox"/> Includes only NRSI	NRSI			For Partial Yes, must have assessed RoB:	For Yes, must also have assessed RoB:		<input type="checkbox"/> from confounding, <i>and</i>	<input type="checkbox"/> methods used to ascertain exposures and outcomes, <i>and</i>	<input type="checkbox"/> Yes	<input type="checkbox"/> from selection bias	<input type="checkbox"/> selection of the reported result from among multiple measurements or analyses of a specified outcome	<input type="checkbox"/> Partial Yes			<input type="checkbox"/> No			<input type="checkbox"/> Includes only RCTs
RCTs																																						
For Partial Yes, must have assessed RoB from	For Yes, must also have assessed RoB from:																																					
<input type="checkbox"/> unconcealed allocation, <i>and</i>	<input type="checkbox"/> allocation sequence that was not truly random, <i>and</i>	<input type="checkbox"/> Yes																																				
<input type="checkbox"/> lack of blinding of patients and assessors when assessing outcomes (unnecessary for objective outcomes such as all-cause mortality)	<input type="checkbox"/> selection of the reported result from among multiple measurements or analyses of a specified outcome	<input type="checkbox"/> Partial Yes																																				
		<input type="checkbox"/> No																																				
		<input type="checkbox"/> Includes only NRSI																																				
NRSI																																						
For Partial Yes, must have assessed RoB:	For Yes, must also have assessed RoB:																																					
<input type="checkbox"/> from confounding, <i>and</i>	<input type="checkbox"/> methods used to ascertain exposures and outcomes, <i>and</i>	<input type="checkbox"/> Yes																																				
<input type="checkbox"/> from selection bias	<input type="checkbox"/> selection of the reported result from among multiple measurements or analyses of a specified outcome	<input type="checkbox"/> Partial Yes																																				
		<input type="checkbox"/> No																																				
		<input type="checkbox"/> Includes only RCTs																																				
<p>10. Did the review authors report on the sources of funding for the studies included in the review?</p> <p>For Yes</p> <table border="0"> <tr> <td><input type="checkbox"/> Must have reported on the sources of funding for individual studies included in the review. Note: Reporting that the reviewers looked for this information but it was not reported by study authors also qualifies</td> <td> <input type="checkbox"/> Yes <input type="checkbox"/> No </td> </tr> </table>			<input type="checkbox"/> Must have reported on the sources of funding for individual studies included in the review. Note: Reporting that the reviewers looked for this information but it was not reported by study authors also qualifies	<input type="checkbox"/> Yes <input type="checkbox"/> No																																		
<input type="checkbox"/> Must have reported on the sources of funding for individual studies included in the review. Note: Reporting that the reviewers looked for this information but it was not reported by study authors also qualifies	<input type="checkbox"/> Yes <input type="checkbox"/> No																																					

AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both

<p>11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?</p>	
<p>RCTs</p>	
<p>For Yes:</p>	
<p><input type="checkbox"/> The authors justified combining the data in a meta-analysis</p>	<p><input type="checkbox"/> Yes</p>
<p><input type="checkbox"/> AND they used an appropriate weighted technique to combine study results and adjusted for heterogeneity if present.</p>	<p><input type="checkbox"/> No</p>
<p><input type="checkbox"/> AND investigated the causes of any heterogeneity</p>	<p><input type="checkbox"/> No meta-analysis conducted</p>
<p>For NRSI</p>	
<p>For Yes:</p>	
<p><input type="checkbox"/> The authors justified combining the data in a meta-analysis</p>	<p><input type="checkbox"/> Yes</p>
<p><input type="checkbox"/> AND they used an appropriate weighted technique to combine study results, adjusting for heterogeneity if present</p>	<p><input type="checkbox"/> No</p>
<p><input type="checkbox"/> AND they statistically combined effect estimates from NRSI that were adjusted for confounding, rather than combining raw data, or justified combining raw data when adjusted effect estimates were not available</p>	<p><input type="checkbox"/> No meta-analysis conducted</p>
<p><input type="checkbox"/> AND they reported separate summary estimates for RCTs and NRSI separately when both were included in the review</p>	
<p>12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?</p>	
<p>For Yes:</p>	
<p><input type="checkbox"/> included only low risk of bias RCTs</p>	<p><input type="checkbox"/> Yes</p>
<p><input type="checkbox"/> OR, if the pooled estimate was based on RCTs and/or NRSI at variable RoB, the authors performed analyses to investigate possible impact of RoB on summary estimates of effect.</p>	<p><input type="checkbox"/> No</p>
	<p><input type="checkbox"/> No meta-analysis conducted</p>
<p>13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?</p>	
<p>For Yes:</p>	
<p><input type="checkbox"/> included only low risk of bias RCTs</p>	<p><input type="checkbox"/> Yes</p>
<p><input type="checkbox"/> OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results</p>	<p><input type="checkbox"/> No</p>
<p>14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?</p>	
<p>For Yes:</p>	
<p><input type="checkbox"/> There was no significant heterogeneity in the results</p>	<p><input type="checkbox"/> Yes</p>
<p><input type="checkbox"/> OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the review</p>	<p><input type="checkbox"/> No</p>
<p>15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?</p>	
<p>For Yes:</p>	
<p><input type="checkbox"/> performed graphical or statistical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias</p>	<p><input type="checkbox"/> Yes</p>
	<p><input type="checkbox"/> No</p>
	<p><input type="checkbox"/> No meta-analysis conducted</p>

AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both

16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?

For Yes:

- | | |
|---|------------------------------|
| <input type="checkbox"/> The authors reported no competing interests OR | <input type="checkbox"/> Yes |
| <input type="checkbox"/> The authors described their funding sources and how they managed potential conflicts of interest | <input type="checkbox"/> No |

To cite this tool: Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, Moher D, Tugwell P, Welch V, Kristjansson E, Henry DA. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ*. 2017 Sep 21;358:j4008.