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## Review Article

A cross comparison between *Ayurvedic* etiology of Major Depressive Disorder and bidirectional effect of gut dysregulation

Eliot Steer

Teachers College, Columbia, USA

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## ABSTRACT

*Ayurveda*, an Indian medical science has been practiced for thousands of years. What makes *Ayurveda* relevant today is its subtle understanding of the environment and its focus on the generation of good health through one's own lifestyle choices. The digestive system has long been an area of critical importance within the *Ayurvedic* system and is only now being acknowledged by modern science as a key component in the regulation of physical and mental well-being. The gut microbiome and enteric nervous system are two particular areas in which the onset of psychiatric disorders, such as depression, have been associated. There are some striking similarities between this biomedical understanding of the gastrointestinal system and the *Ayurvedic* perspective of disease development. Major Depressive Disorder (MDD) is becoming increasingly linked with gut dysregulation in contemporary literature and is a pathology explored within both the *Ayurvedic* and Western systems of medicine. This literature review seeks to draw parallels between these two areas of study and highlight the importance of the digestive system when diagnosing and treating MDD.

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## 1. Introduction

According to the World Health Organization, depression is the most common cause of YLD (years lived with disability) globally and ranks as one of the leading causes of disability [1]. The 'Diagnostic and Statistical Manual of Mental Disorders – V' describes symptoms of Major Depressive Disorder (MDD) as: a depressed mood, suicidal ideation, fatigue or loss of energy, psychomotor agitation, and insomnia, persisting most of the day, nearly everyday for a period of two weeks [2]. MDD is increasingly linked with gut dysregulation in contemporary literature and is a pathology explored within both the *Ayurvedic* and Western systems of medicine. *Ayurveda* has long proposed a mechanism of causation for depression which is strikingly similar to a new biomedical understanding which links MDD to a dysregulation of the GI tract. The following review of an *Ayurvedic* and biomedical understanding of depression seeks to highlight the importance of the digestive system when diagnosing and treating MDD.

## 2. Methods

## 2.1. Searching

A review was conducted using PubMed and Google Scholar with search terms: *depression*, combined with *gut*, *GI*, *inflammation*, *Ayurveda*, *diet*, and *lifestyle*. Both, original research articles and reviews were chosen for further analysis and ranged from the first available year to March 2017. A manual review was conducted of reference lists of relevant literature found from the database searches. The literature which was perceived to be of relevance was chosen for further study. Secondly, several *Ayurvedic* text books written by some of the highest authorities in the field were reviewed as a means to convey classical *Ayurvedic* theory.

## 2.2. Selection

Studies and reviews were coded under four categories of (1) *Depression*, (2) *GI* (3) *Ayurveda*, and (4) *Treatment*. The studies were selected if (a) they included a link between cognition and the GI tract (b) depression was studied in relation to inflammatory changes (c) they studied treatment modalities for depression which were targeting the GI tract (d) they identified a mechanism of action between the brain and gut (e) an *Ayurvedic* understanding of

E-mail: [ezs2105@tc.columbia.edu](mailto:ezs2105@tc.columbia.edu).

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depression and/or the digestive system was reviewed. Studies were excluded which either did not address depression or provide some reference to psychology as mediated via the digestive system. The text books chosen for insight into *Ayurvedic* theory were those written by Dr. V. Lad, Dr D. Frawley, Dr. A.R.V. Murthy, and Maya Tiwari. A three volume series by Dr. Vasant Lad was used as the primary reference point for the *Ayurvedic* content presented due to the authors' simple albeit thorough descriptions of *Ayurvedic* theory and practice.

### 2.3. Extraction and synthesis

Further coding was used to break the literature apart into (1) *Cause of Depression* (2) *Result of Depression* (3) *Treatment of Depression* under two headings of (1) *Ayurveda* and (2) *Bio Medicine*. The literature was then compared and contrasted to identify key similarities and differences between both systems of medicine. Finally, the information was sorted into categories according to the stage of development of disease.

### 2.4. Depression

The etiology of depression has been identified by Sue et al. as comprising of four dimensions: biological, psychological, social, and sociocultural [3]. All four of these dimensions have their own distinct effects and often combine to create a depressive episode [3]. Currently, many doctors rely on anti-depressant medication as a means to relieve symptoms of depression. The most commonly used class of anti-depressant are serotonin re-uptake inhibitors (SSRI's) which are often prescribed by general practitioners [4]. Approximately 12%–20% of depressed patients are resistant to psychotropic medications which are estimated to add a societal cost of between \$106 and \$118 billion [5]. This resistance can be coupled with “functional impairment, poor quality of life, suicide ideation and attempts, self-injurious behavior, and a high relapse rate” [6]. There is also the possibility of anti-depressant use having a ‘pro-depressant’ effect, resulting in the onset of chronic depression; also known as ‘tardive dysphoria’ [7]. Moreover, treatment resistant depressed patients may also not respond to standard treatment protocols such as MBCT and CBT [6]. As a result, there is a growing interest in alternative treatments such as acupuncture, homeopathy and *Ayurveda* which offer a varied and holistic approach towards disease [8].

### 2.5. Basic concepts of Ayurveda

*Ayurveda* is a medical system which is individualized in its assessment and treatment of illnesses whilst maintaining a strong focus on the prevention of disease [9]. The *Ayurvedic* definition of health goes beyond the typical paradigm of an absence of disease, and rather refers to a state of optimal functioning on a physical, psychological and spiritual level. Suśruta (one of the classical authorities of *Ayurveda*) defines health as the following:

“Health is the state of having balanced *doshas* (biological energies which maintain one's physiology and psychology), balanced digestion, balanced tissues, and proper expulsion of wastes. It is a state of peace/contentment in the soul, senses and mind.” [10].

As a result of this definition of health, *Ayurveda* takes an entirely holistic view of the persons reality, looking at “physical health, mental stability, spiritual well-being, social welfare, environmental considerations, dietary and lifestyle habits, daily living trends, and

seasonal variations in lifestyle, as well as treating and managing specific disease” [9].

### 2.6. Ayurvedic system of disease development

*Ayurveda* is based on the understanding that we are a microcosm of our environment which is composed of five elements (earth, water, fire, air, space) [11]. In the human body, these 5 elements are grouped into three bio-energetic humors (also known as ‘*doshas*’) [11]. These *doshas* are called *kapha* (earth and water), *pitta* (fire and water), and *vata* (air and space) [11]. All three *doshas* exist in an individual and each govern specific functions throughout the body. Depending on the genetic traits and health of ones parents, a set ratio (*prakruti*) of these three *doshas* is formed at birth which can be associated with a state of homeostasis [11]. As one is subject to environmental changes, these *doshas* can increase or decrease causing fluctuations in ones health – possibly leading to pathological changes (known as *vikruti*) [11]. Therefore, each *dosha* is associated with psychophysiological qualities which can be either health promotive or pathological depending on the state of balance of the individual [11].

*Ayurvedic* medicine highlights the importance of self-care in order to prevent diseases from manifesting. The etiology of many illnesses in *Ayurveda* originate from the improper functioning of the digestive system which alludes to a therapeutic understanding that differs from conventional Western medicine. The *Ayurvedic* process of disease formation takes a longitudinal approach which builds sequentially overtime. This process is comprised of six key steps:

1. Accumulation – A *dosha* is disturbed whilst localized in one of the three core *dosha* sites: stomach (*kapha*), small intestine (*pitta*) and colon (*vata*).
2. Aggravation – Without proper care, the symptoms mentioned above will worsen and continue to accumulate in GI tract.
3. Overflow – The imbalanced *dosha* spreads throughout the body, moving into the blood stream.
4. Moving and Localization – The *dosha* begins to move into organs and bodily tissues which are susceptible to disturbance, staying dormant until the disease is apparent.
5. Manifestation – The first signs of the illness develop which can be measured and named. Names given to such disease include cancer, diabetes and bronchitis.
6. Chronic Complications and Distinction – The disease takes a complex and/or chronic form. Meaning that the disease might have advanced into a further stage of aggravation, for example an abscess becoming a chronic ulcer [12].

Most importantly, the site of origination for all *dosha* imbalance is considered to be the digestive tract, regardless of which *dosha* has been vitiated. Once a *dosha* starts to move outside the digestive tract, it will start circulating throughout the body via blood [12]. If there is no therapeutic intervention to stop the *dosha* from spreading, it will move into the fourth stage of localization. This is the stage where disease will take shape, including all relevant symptomatology, by impacting tissues and vital organs throughout the body [12].

To explain this process further, one must look at *ama*, the result of undigested food. *Ama* is defined as a toxic, pro-inflammatory waste product that blocks the body's channels, triggers negative immune reactions and is considered to be a primary cause of internal disease [13]. The body may also produce *ama* as a result of externally-manifested diseases [13]. Psychological distress also produces a psychological form of *ama* which manifests from misperception and disturbed emotions; giving rise to potentially harmful mental states such as anger, selfishness, and greed [14].

*Ama* is also regarded as the “root cause of all diseases” and its elimination is one essential component of treatment [13].

### 2.7. Agni

The governing process of the digestive system is ‘*agni*’, a Sanskrit word that translates as ‘digestive fire’. *Agni* is associated with digestion, metabolism and the assimilation of nutrients [13]. A proper functioning of *agni* is noted to produce many physiological benefits such as good strength, resistance to infection, and good skin luster [13]. Since a disturbance of *agni* is considered to promote the formation of *ama* (inflammatory waste), “the whole treatment methodology in *Ayurveda* revolves around the modulation and management of *agni*” [13]. When the functioning of *agni* is compromised, *ama* is produced and a range of psychophysiological responses can occur ranging from nausea to osteoporosis [13]. There are three pathological expressions of *agni* which are called *vishama*, *tikshna* and *manda*. They are associated with an excess of *vata*, *pitta*, and *kapha dosha* respectively. *Manda agni*, also referred to as hypo-metabolism, is the term for describing *agni* when it is too low. Symptoms include excessive sleep, slow metabolism, poor appetite, a feeling of weakness, and depression [12]. Causes of low *agni* include *kapha* aggravating foods, unprocessed emotions, stress, and a lifestyle of inertia [11,12].

### 2.8. Ayurvedic psychology and depression

The three constituents/*guṇas* of the mind in *Ayurveda* are *sattva* (clarity, balance), *rajas* (activity, arogance), and *tamas* (darkness, inertia) [14]. The mind is always being affected by these three *guṇas* which, after being further influenced by memory and discernment, is synthesized into experience and the egoic self. *Manas vikruti* is the current state of psychological imbalance which deviates from one’s ‘normal’ functioning [15]. This means that if someone was naturally *Sattva* 3, *Rajas* 2, *Tamas* 1, a diagnosis of *Tamas* 2 (increased from 1) would indicate an elevation of this state – tending towards inertia [15]. Factors which affect *manas vikruti* include diet, lifestyle, stress, relationships, one’s response to challenges, and repressed emotions [11]. If these cognitive energies are left to accumulate over time they can also give rise to imbalance and might cause mental disturbances like “anxiety ..., depression and insomnia” [16]. Although all three *guṇas* play a role in psychological health, this review will focus on *tamas* due to its association with depression [15].

Mental illness is mostly considered to arise as a result of an interplay between *dosha* (biological humors) and the *guṇas* (psychological qualities) [14]. Imbalances of the three *doshas* are representative of different cognitive and somatic symptoms: *vata* being associated with anxiety and hyperactivity, *kapha* linked to passivity and lethargy, and *pitta* connected to strong emotions such as anger [11].

Negative psychological states have a bidirectional impact on the body and, in particular, the homeostasis of *agni* [17]. In other words, if *agni* is disturbed through physical means, such as eating foods which cause imbalance, then psychological difficulties like insomnia and disturbed thoughts will likely ensue. The same is true from a top-down perspective, implying that emotional imbalance caused by *rajas* or *tamas* can disturb *agni*, possibly leading to pathology [17].

In an anthropological study on ‘appropriating depression in *Ayurvedic* psychiatry’, Lang & Jansen (2013) wrote on the recent ‘scientification’ of *Ayurveda*, stating that it is now common for *Ayurvedic* psychiatrists to draw from the classical theories of *dosha unmada* (mental illness resulting from *dosha* imbalance) whilst reinterpreting them into a modern framework [18]. In the same

paper it was identified that depression is commonly associated with an imbalance of two of the three *doshas*, *vata* and *kapha*, depending on the symptomatology [18].

*Kapha unmada* (depression) was considered to result from “external factors such as tension, bereavement, loss, or a wrong diet” and is similar conceptually with the DSM-V diagnosis of major depression [18]. A *vata* induced depression, also known as *viśadam*, is considered to be mild in comparison to *kapha unmada* and is usually associated with psychological rumination and worries [18]. *Viśadam* was said to be treatable through *Ayurvedic* drugs and counseling, whereas *kapha unmada* “must be treated further with purgatory and purifying procedures: internal (*snēhapana*) and external (*abhyāṅga*) oilation of the body, sweating (*svēdana*), therapeutic vomiting (*vamana*), and nasal treatment (*nasya*)” [18]. Although *viśadam* is associated with a depressed mood, this review primarily emphasizes *kapha unmada* due to its similarity with the DSM-V diagnostic criteria for depression.

### 2.9. Role of gastrointestinal (GI) system and inflammation in depression

Recent discovery has alerted us about the essential role that our gastrointestinal system plays in maintaining our physical and mental health as mediated through our microbiome. The human microbiome is a collection of microbial flora of at least 10,000 species accounting for 90% of our cell mass [19]. In terms of our DNA, the human body has roughly 20,000 human genes, compared to an approximate 3.3 million microbial genes [19]. Over the past decade, there has been a huge body of work dedicated to the discovery of the microbiome’s effect on regulating health, as well as being a potential cause for disease [20]. Intestinal flora has shown to aid digestion, act as a physical barrier against pathogens, help to detoxify that which passes through the intestines, aid in stress management, produce and release important biological enzymes and chemicals (such as neurotransmitters), and the control of inflammation [21]. However, as a result of impairment, the gastrointestinal tract can allow toxins to escape into the blood stream and locate in different parts of the body – causing inflammation and eventually disease [21]. This is known as ‘impaired intestinal permeability’ and is often caused by microbial dysbiosis (an imbalance of harmful bacteria in relation to healthy bacteria).

More specifically, the GI system can play a role in the formation of depression. The enteric nervous system (ENS), commonly regarded as the second brain, is a collection of neurons located in the GI system and is home to approximately 100 million neurons and over 30 different neurotransmitters [22]. When addressing the biological cause of depression in Western conventional medicine, most look to the disruption of serotonergic systems in the body and attempt to increase serotonin stimulation by medicating with antidepressant medication; most commonly Selective Serotonin Reuptake Inhibitors (SSRI’s) [5]. Most of the body’s serotonin is found within the GI tract [22] and is produced primarily by diet, exercise, exposure to light, and positive emotional states [23]. Tryptophan (the precursor of serotonin) is metabolized from food within the GI tract which, after absorption, is transformed into serotonin by “enterochromaffin cells of the gastrointestinal tract” [24].

A current conception of depression views it as a biological symptom associated with an inflammatory response, as opposed to a standalone disease. The inflammatory model of depression has been extensively researched and is a possible mediating pathway between the causes of MDD and its symptoms. Inflammatory markers, known as cytokines, are chemical messengers which alert the body when inflammation is occurring. Factors associated with depression as a result of an inflammatory response include a poor

diet, obesity, smoking, disturbed sleep, gut permeability, stress and trauma [25].

A meta-analysis containing more than fifty studies identified a positive association between depression and the inflammatory markers C-reactive protein (CRP), interleukins one (IL-1) and interleukins six (IL-6) [26]. Another study reported that up to 50% of patients receiving the administration of interferon- $\alpha$  (used for illnesses like hepatitis C) experience depression as a symptom of the therapy, inferring a causal association between cytokines and depression [27]. Psychological stress can also “promote inflammatory responses through effects on sympathetic and parasympathetic nervous system pathways” [27]. This evidence indicates a bi-directional effect between inflammation acting as a trigger for a depressive episode whilst also becoming aggravated by the stress of being depressed.

As discussed previously, *Ayurvedic* medicine has long been familiar with the interconnection between psychological well-being and gut homeostasis. In relation to this understanding, the GI system is scientifically understood to be particularly sensitive to stress activation. One biological explanation for this interaction has been linked to the stimulation of the hypothalamic–pituitary–adrenal (HPA) axis through the stress response. Corticosteroids are released as a result of HPA activation which have the ability to impact the composition of microbial communities within the gut [28]. In a 2016 study, Kanuri et al. found that it was common amongst patients with irritable bowel syndrome (IBS) to have a prior history of physical, sexual, and emotional abuse [29]. Comorbid mood disorders (anxiety and depression) were also identified as being a potential mediator for IBS, suggesting a resilience to those with stronger emotional coping skills [29]. Most importantly, this study demonstrates the effect of stress upon the GI system which, when left untreated, can cause further inflammation and mood dysfunction.

Surdea-Blaga et al.'s review on the psychosocial determinants of IBS also suggests a “link between psychosocial factors and gastrointestinal function” [30]. A bidirectional communication “between the gastrointestinal tract and brain through neural, neuroimmune and neuroendocrine pathways” was noted as the mediating factor of many common psychological comorbidities with IBS, including depression [30].

Psychosocial stressors are also suggested as a bidirectional facilitator of depression. Stress, as mediated through the sympathetic nervous system (SNS) is known to increase heart rate, raise blood pressure and slow digestive functions as a survival mechanism. Through repeated exposure to cortisol (the steroidal molecule released by the adrenal cortex during moments of stress), the body can start to experience a high allostatic load which can contribute to a dysregulation of the HPA-axis – resulting in depression [31].

Gut microbiota play a potential role in modulating psychological stress via the vagus nerve – the longest cranial nerve running between the brain and abdomen. Yarandi et al. (2016) explain a system in which gut microbiota are stimulating the “stress response and the activity of the corticosterone pathway orchestrated by the HPA-axis” [32]. Their proposed mechanism takes into account both possible directions of interaction whilst highlighting the specific biological pathways through which it occurs. Meaning that an increase in gut permeability can cause “bacteria or metabolic products” to leak through the intestinal barrier and trigger an inflammatory response. Stress activation can also cause the release of cortisol which can stimulate the release cytokines, resulting in a permeable gut [32].

Although research concerning this area of study is new and relatively sparse, a number of studies highlight the mechanisms of interaction between the gut and stress activation. Through a study

using germ free mice, it was identified that the stress of maternal separation disrupted colonic homeostasis, thus, altering the environment of the hosts gut causing dysbiosis [33]. Similar results have been found with human subjects. Through analysis of urine lactulose/mannitol ratio (LMR) used to measure small intestinal permeability after a stressful stimulus, Vanuytsel et al. (2013) concluded that permeability was increased as a result of “endocrinological signs of stress activation” [34]. Cortisol secretion was also identified as a mediator for small intestinal permeability – leading to the hypothesis that gut permeability is ‘strongly associated’ with the activation of the HPA axis and autonomic nervous system [34].

Furthermore, by transferring the fecal microbiota from thirty four patients with a diagnosis of major depression into microbiota deficient rats, Kelly et al. (2016) were able to identify a significant disruption to “behavioral and physiological homeostasis”. Most importantly, this study indicates that depressive symptoms, such as anhedonia, can be induced through alterations to the gut microbiota. This suggests that the gut plays a “causal role in the complex mechanisms underlying the development of depression” [35].

#### 2.10. Comparative assessment of Ayurveda, depression, and gut dysfunction

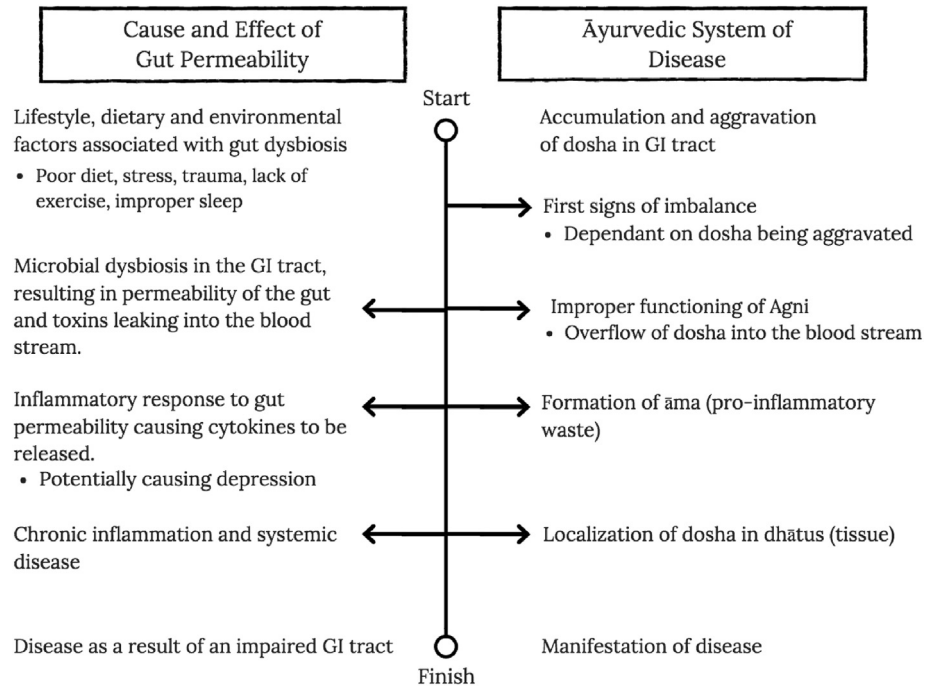
As discussed previously, both *Ayurveda* and current approaches in biomedicine seek to understand the causation of depression as it relates to the GI system, as well as identifying treatment modalities which specifically target this link. Although these two systems have many similarities with a potential for partnership, there is no available literature at this time which seeks to understand the similarities between these two understandings of depression. The following section compares the *Ayurvedic* system of disease development to the biomedical understanding of the role of the GI tract in MDD to identify their similarities. Fig. 1 shows a pictorial representation of some key associations between these two forms of understanding.

The biomedical understanding of gut homeostasis portrays a very similar picture to the *Ayurvedic* model of depression. Where the former identifies bacteria leaking through an impaired intestinal wall and spreading throughout the body as a clinical cause of depression [36], *Ayurveda* defines a potential cause as the spreading of vitiated *doshas* from the digestive system to particular tissue sites. The etiology responsible for this gastrointestinal dysbiosis is primarily associated with a poor diet, stress and lifestyle choices. Other factors including antibiotic usage, poor sleep, lack of exercise, birth by C-section, birth control pills and exposure to environmental chemicals like herbicides have all been noted to have a negative effect on the proper functioning of gut microbiota, potentially leading to a depressive episode [22,25]. Although beyond the scope of this review, there are numerous chronic diseases which have been correlated with a dysbiosis of the GI tract, including “atopic diseases, IBD, diabetes, obesity and neuropathologies” [36]. Further exploration is required to find the correlation between diseases relating to depression and the GI system.

The effect of diet, lifestyle, and stress will now be explored for an insight into the similarities between modern science and *Ayurvedic* theory as it relates to the onset of MDD.

#### 2.11. Diet and lifestyle

The medicinal properties of food play a key role in *Ayurveda* as a form of treatment, as well as a means to prevent the occurrence of psychological and physiological diseases. Foods which have the potential to slow *agni* and induce depression are those which are ‘*tamasic*’ in nature (causing inertia). These are foods which are



**Fig. 1.** A pictorial comparison between the *Ayurvedic* system of disease and the cause/effect of gut permeability. The specific cause of accumulation is dependent on the individuals environment, lifestyle and genetic susceptibility towards imbalance. Once an imbalance has occurred, the gut/*agni* will be affected – causing *ama* and vitiated *doshas* to spread throughout the body. From a biomedical perspective, a dysbiosis of microbial flora is followed by a permeable gut and the release of toxins into the blood. Finally, an inflammatory response occurs within the body and disease is potentially set to manifest.

processed, frozen, fried, high in sugar, and substances like alcohol, drugs and chemicals, which will likely increase *tamas* and cause a lethargic state in the body and mind [11].

Similarly, Jacka et al. published a recent intervention where adults with MDD were given a controlled diet, emphasizing whole foods and limiting the consumption of refined and sugary food [37]. Results showed a significant decrease in depression symptomatology to those in a social support group. This relationship is potentially related to the 'Western' diet (characterized by a high saturated fat and refined sugar intake) [37] having the potential to induce depression through an inflammatory response by increasing intestinal permeability and negatively altering the microbial composition of the gut [38]. A 2016 study using both human and animal subjects demonstrated that a diet high in both sugar and fat was correlated with a dysbiosis of intestinal mucosa "characterized by an overgrowth of pro-inflammatory proteobacteria" [39]. Other factors associated with a Western diet include a reduction in protective gut bacteria and a thinning of the gastric mucus layer; inducing permeability and inflammation [38,39].

Lifestyle and stress management play a fundamental role in *Ayurvedic* treatment methodology. *Kapha dosha* is primarily aggravated through *tamas* (inertia promoting) and sedentary lifestyle choices which have both been noted as causative of depression [12]. A life of inertia and excess sleeping are likely to increase *kapha* and thus form symptoms of depression, whilst also causing hypo-metabolism. As proposed by this *Ayurvedic* principle, MDD is directly associated with sedentary behavior [40]. Several studies have linked a sedentary lifestyle to a pro-inflammatory response in the body [41,42], further suggesting a relationship between inflammation, depression and *kapha dosha*.

Furthermore, psychological distress plays an intrinsic role in the ecology of the digestive system. Chronic exposure to inflated cortisol can directly change the ecology of the gut, causing

permeability and increasing inflammation [34] which are both associated with a diagnosis of depression [25].

## 2.12. Bidirectional relationship of the gut–brain axis

A bidirectional communication between the gut and brain is highlighted by both *Ayurveda* and Western medicine as a mechanism which causes and contributes to MDD. The system of gut-brain interaction proposed by Yarandi et al. shares many of the qualities same to the *Ayurvedic* understanding of psychopathology [32]. The bidirectional element is crucial to both mechanisms. If *agni* (digestive fire) is disturbed through physical means, such as eating foods which cause imbalance, then a lack of positive emotion and disturbed thoughts will likely ensue. The same is true from a top-down perspective, implying that emotional imbalance can disturb the digestive system, possibly leading to pathology. The stress response stimulates the HPA axis and releases corticosteroids and the result of which exposes the intestinal wall to cortisol and can lead to gut permeability and depression [32].

Moreover, when comparing the *Ayurvedic* understanding of depression to this system, a *kapha* induced depression (*kapha unmada*) is most similar to the bottom-up perspective, implying an effect from external factors, such as diet, inducing permeability [18]. A disturbance of *kapha* is correlated with '*manda agni*'/low *agni*, also known as hypo-metabolism, which can induce lethargy, excessive sleep, attachment and possessiveness [12]. A *vata* induced depression (*visadam*), however, tends more towards the top-down mechanism as it is correlated with psychological disturbances, such as ruminating on negative emotions, as the causative factor [18]. When *vata dosha* is aggravated, one's *agni* becomes irregular and results in symptoms like anxiety, insecurity, cracking joints, dry skin and insomnia [11]. Similarly, exposure to sensory perception which increases *tamas*

(inertia) in the mind can affect the body through this top-down mechanism [14].

The *Ayurvedic* association between psychology and the gut can also be paralleled with the enteric nervous system. More than thirty different neurotransmitters are used by the gut in regulating functioning and is in communication with the brain via the vagus nerve [22]. The study of psychopathology and the gut is a very new area of exploration and there is little definitive evidence to suggest the specific pathway to which this relationship is mediated. The “vagus nerve, immune system, short chain fatty acids and tryptophan” have all been cited as potential routes of communication between the gut and brain [43]. Most likely, this is a multi-faceted relationship which will take much more scientific inquiry to fully understand.

### 2.13. Treatment

The genetic understanding of psychopathology can give reason to believe that depression is unavoidable. However, recent data indicates that depression is epigenetic in nature, meaning that the genetic inheritance of depression must be triggered environmentally in order to manifest symptoms [44,45]. The following section will present a summary of how *Ayurveda* and conventional medicine have utilized the gut-brain axis in formulating treatments of depression.

Starting from the first two stages of disease development where a *dosha* is localized in the GI tract, *Ayurveda* emphasizes the importance of listening to the body's warning signs. Cravings which have an opposite quality to the cause of imbalance can occur in an attempt to restore equilibrium [12]. It is during these two stages of disease when symptoms of GI disturbance can be observed. Specifically regarding depression, it is likely that *agni* will be low (*manda*) which will require a preprandial therapy called *dipana*, meaning to kindle *agni* [46]. Herbs such as *Plumbago zeylanica*, *trikatu* (a mix of *Piper longum*, *P. nigrum*, and *Zingiber officinale*), *Ocimum tenuiflorum*, *Cinnamomum verum*, and *Acorus calamus* are good for reducing symptoms of *manda agni* [46]. Not eating until one is hungry, eating light meals, avoiding cold/iced drinks, and pre-meal exercise are also helpful for kindling the digestive system [46].

During the third stage of disease (overflow) it is crucial to treat the imbalance before the *doshas* are expressed as a disease [12]. Here, an *Ayurvedic* treatment regime will take into account many of the factors which have been addressed as the causation of depression, including *tamasic* foods, a dysfunctional *agni*, unprocessed emotions, the removal of *ama* (inflammatory waste), and stress [12,18]. Certain *shodhana* (cleansing) therapies can be used to target *kapha unmada* (depression) such as therapeutic vomiting (*vamana*) to remove *kapha* from the stomach and lungs [46,18]. *Nasya* (nasal application of herbs/oils) can be used to target the mind. For depression, *vacha nasya* is effective due to its sharp and light quality – acting as an expectorant, stimulant, and nerve sedative [14]. Herbs which rejuvenate the mind are known as '*medhya rasayana*' and have a direct effect on the 'sensory mind and intellect' [46]. Some examples of *medhya rasayana* are *Withania somnifera*, *Bacopa monnieri*, *Nardostachys jatamansi*, and *Convolvulus pluricaulis*. Massaging the body with *dosha* specific oils can also be effective as a treatment for depression, known as *abhyanga* [14]. Other recommendations might include lifestyle alterations (like strong exercise and waking up before sunrise), meditation, yoga, and psychotherapy [14,46].

Recent findings also present therapeutic potential for the alleviation of depression through the gut-brain axis. Perhaps one of the most telling forms of treatment to highlight the correlation between the digestive system and depression is the clinical use of

probiotics. Probiotics are live micro-organisms which are often ingested orally for their health benefits on the digestive system. The bacteria present in probiotics is often the same or very similar to the healthy bacteria residing in the human body [47]. A systematic review of studies investigating the clinical effect of probiotics on depression found that majority of cases showed a decrease on 'all measures of depressive symptoms' [48]. A likely pathway of action for these clinical changes is the regulation of healthy bacteria in the gut [49]. Probiotics have also been identified to reduce abnormal behavior by controlling inflammation; 'changing how the immune system signals the brain to alter brain function' [50].

A large proportion of research regarding diet as a treatment for depression is focused on specific compounds and foods types, such as omega-3 fatty acids [51] and curcumin [52]. There are some clinical studies, however, which have investigated the therapeutic benefit of overall dietary patterns on MDD. As mentioned earlier, Jacka et al. [37] is one of the first to explore this relationship and found depression to decrease through a health promotive diet.

The 'Mediterranean diet', which is partially defined by its high consumption of monounsaturated fats (like those found in nuts, olive oil and wild fish) has gained significant attention in recent years for its wide variety of health benefits [51]. A greater adherence to a mediterranean diet has been identified in a number of clinical trails to reduce symptomatology of depression [53–55]. The mediating factor commonly cited for this link between a Mediterranean diet and reduced depression is the anti-inflammatory properties of the lipids contained in the diet, such as omega-3 fatty acids [53].

There are a number of non-diet related lifestyle choices which have been associated with the reduction of depression; further emphasizing the bidirectional nature of mood regulation. Physical activity, proper sleep and sun exposure are recognized as mood promoting lifestyle strategies and have a direct coloration with the relief of depression [56,57]. Meditation has also been extensively studied and found to induce an anti-depressant effect through the stimulation of neurological areas associated with positive states of being; strengthening them as a result of repetitive activation – also known as neuroplasticity [58]. Other effects of meditation which have been studied include a decrease in pro-inflammatory cytokines, reducing oxidative stress marker, and increasing telomerase activity [59].

### 3. Conclusion

There is a significant similarity between the way in which *Ayurveda* understands and treats depression and the biomedical understanding of depression as a symptom of psychophysiological distress with a bidirectional interaction between the gut and brain. *Ayurvedic* medicine offers an in depth understanding about the functioning of the mind and body as a non-dualistic entity which is currently not acknowledged in most practices of conventional medicine. There were several parallels found in this review which emphasize the importance of considering the gut when addressing MDD. These include (1) diet, lifestyle, and psychological stress as causative factors (2) digestive dysfunction and resulting inflammatory changes being a mediating factor, and (3) diet and lifestyle alterations being effective forms of treatment. Also, the review indicates that *Ayurveda* has a vast body of knowledge relating to gut health and emotional regulation which could prove helpful in establishing additional treatments for individuals with MDD.

More research is needed on the *Ayurvedic* treatment of psychopathology, in particular relating to the individualization associated with its treatment plans, as a way to further establish *Ayurveda* as an effective and accessible treatment modality for MDD. Future randomized and controlled studies looking at

individualized treatments of MDD focusing on the digestive system, as compared to current medications and manual based psychotherapy (like CBT), would help to highlight the clinical significance of such approaches. Focusing on treatment resistant groups might prove to be most fruitful in finding approaches which match the patients needs, particularly if other treatment modalities are not working. Other areas of study might seek to explore an integrative approach between *Ayurvedic* treatment recommendations and current therapies to find the most effective styles for select groups of people. For instance, focusing on female adolescents with treatment resistant depression – using both psychotherapy and an *Ayurvedic* prescribed diet to compare both systems individually and when used together under controlled conditions.

Finally, returning to the *Ayurvedic* definition of health, it is not enough to be free of depression. Rather, a re-emergence into optimal well-being should be the goal of any clinician seeking to incorporate *Ayurveda* into their practice. The *Ayurvedic* approach to disease is hopeful and can help cultivate a deeper awareness of how one relates to themselves and their environment. Using this approach for the treatment of MDD might prove more empowering than what is currently offered by allopathic medicine; providing an individual with a greater understanding of their psychophysiology and how best to maintain a state of health in the future.

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#### Conflicts of interest

None.

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