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Review Article

Nutritional therapy can reduce the burden of depression management in low income countries: A review

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ABSTRACT

Depression is a serious mental and mood disorder with global health and economic burden. This burden may be overwhelming in low income countries, although there are insufficient data. Most antidepressant formulations are predicated on the monoamine, neuroendocrine and neuro-inflammation hypotheses, with little or no cognizance to other neurochemicals altered in depression. A nutritional strategy with or without conventional antidepressants is recommended, as nutrition plays vital roles in the onset, severity and duration of depression, with poor nutrition contributing to its pathogenesis. This review discusses nutritional potentials of utilizing omega-3 fatty acids, proteins, vitamins, minerals and herbs or their phytochemicals in the management of depression with the aim of reducing depression burden. Literature search of empirical data in books and journals in data bases including but not limited to PubMed, Scopus, Science Direct, Web of Science and Google Scholar that might contain discussions of sampling were sought, their full text obtained, and searched for relevant content to determine eligibility. Omega-3 fatty and amino acids had significant positive anti-depression outcomes, while vitamins and minerals although essential, enhanced omega-3 fatty and amino acids activities. Some herbs either as whole extracts or their phytochemicals/metabolites had significant positive anti-depression efficacy. Nutrition through the application of necessary food classes or herbs as well as their phytochemicals, may go a long way to effectively manage depression. This therefore will provide inexpensive, natural, and non-invasive therapeutic means with reduced adverse effects that can also be applied alongside clinical management. This nutritional strategy should be given more attention in research, assessment and treatment for those with depression and other mental illness in low income countries, especially in Africa.

1. Introduction

Depression is a serious mental or mood disorder whose etiology is not understood still. However, genetic, biological and environmental factors have been suggested. This disorder can arise due to any form of dilapidating conditions including, but not limited to chronic stress, traumatic experience, diseases, infection, stroke and even senescence (Oni et al., 2018; Pappa et al., 2020; Park et al., 2020). Depression manifests with symptoms not limited to depressed mood, lethargy, anhedonia, decreased energy, feelings of guilt or low self-esteem, disturbed sleep or appetite and poor concentration among others. These can lead to substantial impairments, and ultimately suicide (Roca et al., 2019; WHO, 2020), resulting in high health burden and management costs (Popa and Ladea, 2012; Egede et al., 2016).

According to the World Health Organization (WHO), depression is reported with a global burden of over 264 million people worldwide, cutting across low-, middle- and high- income countries (WHO, 2020). The incidence is more prevalent in the female population compared to the male (Pappa et al., 2020), attributable to the female changing hormonal levels (Albert, 2015). Depression cuts across age, sex, social class, and educational and professional status (Lloyd-Sherlock et al., 2019; Pappa et al., 2020).

Most treatment for depression is by pharmacotherapy, where different antidepressants feature. The current treatment of depression is not sustainable as even with different treatment strategies, there is delayed onset of antidepressant effects, just as the overall depression effects also persist. These inadequacies together with good outcome against depression by certain diets motivated the reassessment of dietary provisions and their potential in depression management towards reducing health and economic burden to the benefit of low income countries and especially in Africa. This review discusses depression classification, its burden in a global scale, the associated brain and

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neurochemicals, treatment strategies and nutritional roles of diets with focus on omega-3 fatty acids, proteins, vitamins, minerals, as well as herbs or their phytochemicals in the management of depression.

2. Literature search

Approximately, a thousand articles were searched for empirical data, including books and journals in the following data bases arranged chronologically: African Journals Online (AJOL), Bielefeld Academic Search Engine (BASE), Book Review Index Online, CAB Abstracts, Cochrane Library, Directory of Open Access Journals (DOAJ), Excerpta Medica dataBASE (EMBASE), Europe PubMed Central, Food Science and Technology Abstracts (FSTA), Global Health, Google Scholar, Index Copernicus, IngentaConnect, JournalSeek, Journal Storage (JSTOR), Medical Literature Analysis and Retrieval System Online (MEDLINE), Mendeley, Microsoft Academic, National Diet Library Collection, Open Researcher Community ID (ORCID), PsycINFO, PubMed, PubMed Central (PMC), Publons, PubPsych, ResearchGate, Scientific Electronic Library Online (SciELO), Scientific Information Database, Science Direct, Scopus, Semantic Scholar, SpringerLink, Web of Science and WorldCat. Only data with information and discussions on depression and food/nutrition were selected, and their full text obtained, and searched for relevant content to determine eligibility. This amounted to four hundred and fifteen relevant articles. In other instances, review materials were also consulted.

3. Classification of depression

It is important to understand that depression is not a one-cap-fit it all condition. Hence, its treatment is based on the severity. This however cannot be determined without following some guidelines known as depression scales. There are different scales used in the classification of the severity of depression, some of which will be discussed. Depression is classified as mild, moderate and severe. The classification criteria differ however, depending on which diagnostic method is applied. According to the 10th version of the International Classification of Diseases (ICD–10) and the Diagnostic and Statistical Manual of Mental Disorders (DSM–IV) depression is classified as clinically important based on the number, type and severity of symptoms present, and the degree of functional impairment (APA, 2000; Sajatovic et al., 2015).

In the Beck Depression Inventory-II (BDI-II), depression is classified based on non-cognitive (somatic-affective) and cognitive dimensions. Non-cognitive factor is represented by somatic symptoms such as loss of energy, and affective symptoms, such as irritability. Cognitive factor composed of psychological symptoms, such as self-dislike and worthlessness. Accordingly, the diagnostic range mean value of the BDI-II for patients indicates the overall level of depression (Steer et al., 2000; Sajatovic et al., 2015).

The Hamilton Depression Rating Scale (HAM-D) is an observer-rated scale that evaluates core symptoms of depression. HAM-D focuses on the somatic symptoms of depression such as sleep and appetite. Scoring values obtained is used to classify depression (Sajatovic et al., 2015). HAM-D validation/research base is excellent, with ease of administration.

The Montgomery-Åsberg Depression Rating Scale (MADRS) addresses core mood symptoms such as apparent sadness, reported sadness, inner tension, lassitude, inability to feel, and pessimistic thoughts. Scores of MADRS are used as diagnostic values to classify depression (Sajatovic et al., 2015). This classification into mild, moderate and severe also determines the treatment strategies applied, as well as treatments for children and adolescents. It is important to note that these scales may not be used alone without validation with one another.

4. Economic burden of depression

Globally, depression is of great burden, health-wise and economically. Health-wise, depression cuts across functional impairment, comorbidity and reduced health associated work productivity and loss (Greenberg et al., 2015; Egede et al., 2016; WHO, 2020). Economically, depression ranges from high healthcare cost to high health budgetary cost allocation. In the United States of America, as at 2010, the total healthcare cost (direct and indirect) was over 210.5 billion US Dollars (Greenberg et al. 2015). In Europe, the total healthcare cost (direct and indirect) for twenty eight countries as at 2004 was 132 billion US Dollars (Sobocki et al., 2006).

In the Asia-Pacific region as at 1997–1998, the depression healthcare cost for Australia was 1.8 billion US Dollars, while earlier in 1994, Taiwan spent 1.4 billion US Dollars. In 2004, depression healthcare cost China 6.264 million US Dollars (Hu, 2004; Hu et al., 2007). In 2005, South Korea spent 4.049 US Dollars (Chang et al., 2012), while in 2008, Japan spent 11 billion US Dollars (Okumura and Higuchi, 2011).

In Africa, there are limited and small scale data. Depression is reported among Ghanaians, Nigerians and Ugandans (Gureje et al., 2010; Sanni et al., 2018), but data in terms of healthcare to budgetary expenditures is not available. Nevertheless, in South African adults, the total health cost was 3.659 billion US Dollars (Lund et al., 2013).

The economic burden of depression persists, partly because of the widespread underuse of otherwise efficacious and tolerable depression treatments. Those of the low- and middle- income countries may arise due to limited spending on the treatment and prevention of mental disorders accounting for the gap between treatment and its availability. For example, in Nigeria there is underfunding of the health sector in general, with specifically non-provision of affordable health insurance cover for mental health challenges (Abdulmalik et al., 2019). This gap in treatment affects the health of depressed individuals and their families, and consequently productivity at work for employers and governments, as well as increased healthcare resource use (Greenberg et al. 2015; Egede et al., 2016).

5. Brain structures and functions in depression

Depressive effects have been studied structurally in the orbitofrontal cortex, the basal ganglia, anterior cingulate cortex, hippocampus, amygdala, thalamus, and the parahippocampus. Both structural and functional abnormalities in these brain areas have been reported in depressives, including reduced hippocampal/parahippocampus volumes and larger amygdala (Weniger et al., 2006; Disabato et al., 2016; Zhou et al., 2016). These depressive effects also include increased neuronal density in the medio-dorsal and antero-ventral/antero-medial nuclei of the thalamus (Young et al., 2004), and decreased asymmetry in the globus pallidus volume with correlation to length of illness and number of prior depressive episodes (Lacerda et al., 2003). Another effect is the thinning of orbitofrontal cortex gray matter in patients with severe depression symptom has also been reported (Yu et al., 2018).

A decreased amygdala volume and its diminished functional connectivity with the prefrontal cortex were reported in depressives with suicidal tendency (Wang et al., 2020). Depressives who remit with treatment have been shown to have larger hippocampal volumes (MacQueen et al., 2008; Nogovitsyn et al., 2020), while those who failed to remit had smaller dorsal and rostral anterior cingulate gray matter volumes (Gunning-Dixon et al., 2009). There are also reported abnormalities of metabolism and cerebral blood flow. These abnormalities disrupt the limbic-cortico-striato-pallido-thalamic circuit causing functional network impairments (Cowen et al., 2012; Disabato et al., 2016).

Aside the morphology of the brain, neurochemical changes are known to occur; these reported abnormalities are seen in neurotransmitters, neuropeptides, hormones and inflammatory biomarkers (Fig. 1). Hypotheses abound on the role of monoamines in the pathogenesis of depression. Thus, most antidepressants target this

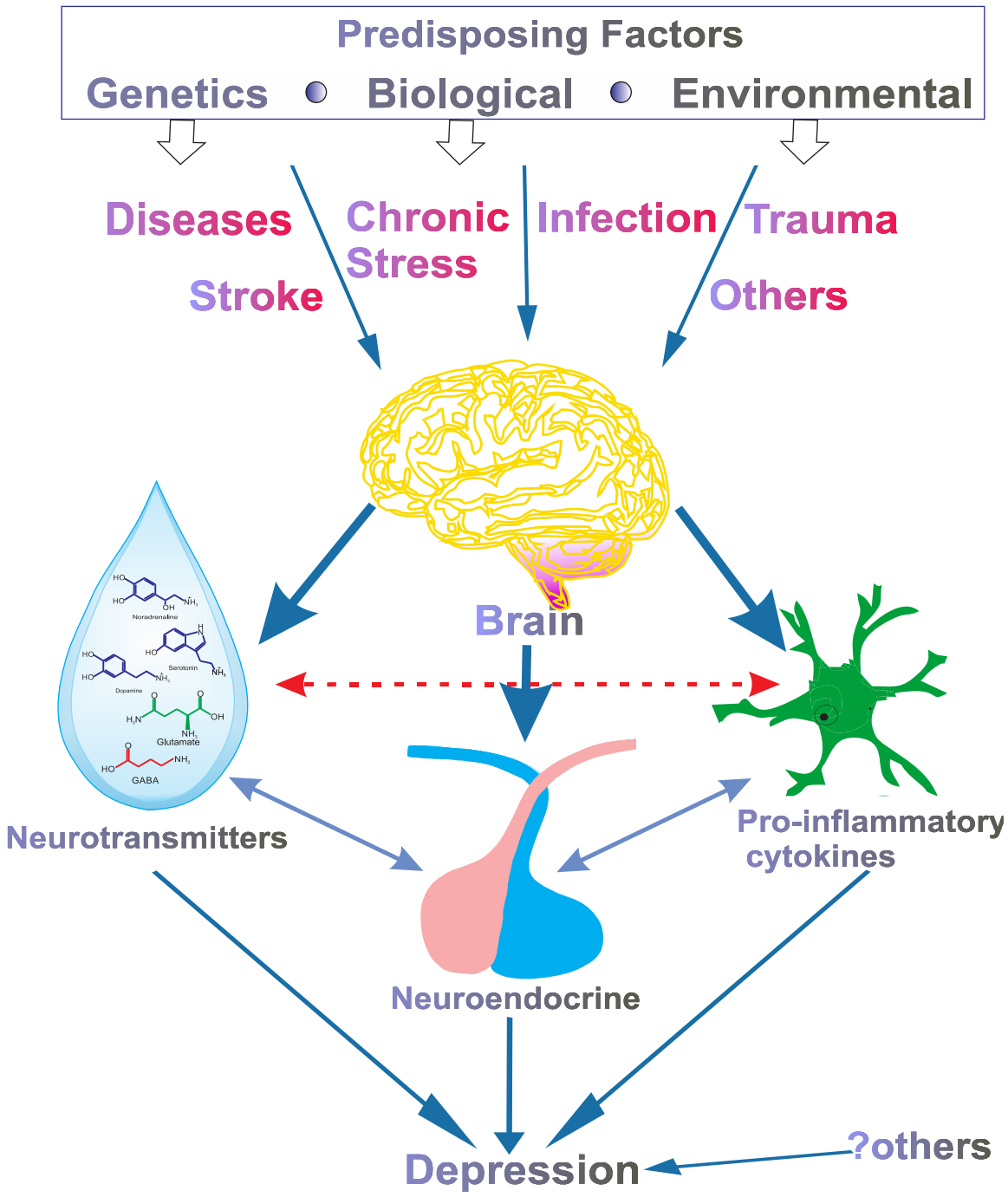

Fig. 1. Simplistic schema of the predisposing factors of depression. Genetics, biological and environmental factors are involved. The hypothetical changes which are dependent on each other include the neurotransmitters, serotonin, dopamine, noradrenaline, glutamate and gamma amino butyric acid; the neurochemicals and hormones; pro-inflammatory cytokines and others still unknown.

monoaminergic pathway (Jeon and Kim, 2016). These antidepressants are formulated to regulate the abnormal levels of the monoamines; serotonin, noradrenaline and dopamine reported in different brain areas mostly implicated in depression (Haase and Brown, 2015). Decreased serotonin precursor, tryptophan and alteration in the serotonin synthesis pathway have been reported in depression (Cowen, 2015). One of such is the up-regulation of the kynurenine pathway, which diminishes serotonin production resulting in its decreased availability for normal brain function (Khan and Khan, 2016). Another part is the increase amount of monoamine oxidase (MAO) which degrades the monoamines more than it should (Meyer et al., 2006).

Abnormal levels of noradrenaline and dopamine are also associated with depression. Altered sensitivity and density of adrenergic receptors and its associated decreased noradrenaline transporter binding are some of the noradrenaline activities in depressive disorders (Maletic et al., 2017). Depressive disorder patients and animal models have also been observed with reduced dopamine level either from diminished release from presynaptic neurons or impaired signal transduction (Belujon and Grace, 2017). Increased density of monoamine oxidase-A is reported in depressed patients, whose activity is suspected to also result in increased catabolism of the monoamines with associated decreased levels (Meyer et al., 2006).

Other neurotransmitters indicted in depression include the excitatory glutamate and the inhibitory gamma-amino butyric acid (GABA).

Abnormal activities of glutamate and GABA and their receptors in the brain, as well as in other body fluids have been reported in depression. Increased glutamate and decreased GABA levels are associated with depression (Croarkin et al., 2011; Cowen, 2015). Decreased density of GABAergic interneurons have been reported in some brain regions (Maciag et al., 2010), alternatively, there is reduced expression of mGluR2/3 receptors in the anterior cingulate cortex, and elevated expression levels of mGluR and iGluR genes was reported in the dorsolateral prefrontal cortex of major depressive disorder individuals (Gray et al., 2015; McOmish et al., 2016). There is also the associated decreased glutamate reuptake by astrocytes.

Neuropeptides, crucial in modulating behavior and also playing roles in stress response have also been associated with depression, and their abnormalities reported in subjects with major depressive disorder. Such neuropeptides as corticotropin-releasing factor, nerve growth factor inducible (VGF) and calcitonin gene-related peptide among others, have

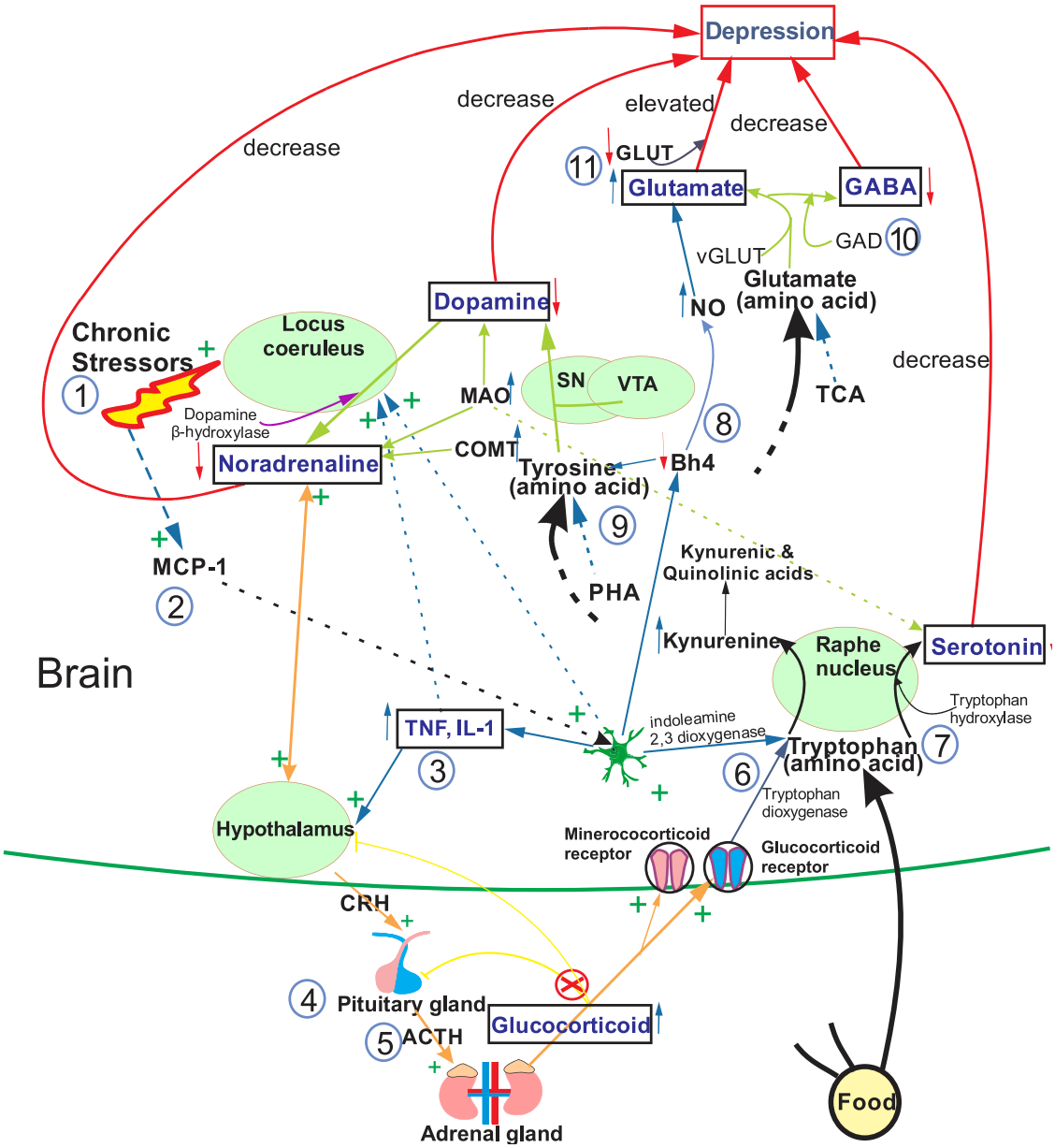

Fig. 2. Simplistic schema of the molecular processes involved in depression. Chronic stress stimulates (1) locus coeruleus to release noradrenaline sustained by reciprocal stimulation by the hypothalamus and also pro-inflammatory cytokines (interleukin, IL −1, tumor necrotic factor, TNF etc.) increase; and (2) monocyte chemoattractant protein (MCP-1) increase to activate monocytes release of pro-inflammatory cytokines. (3) Pro-inflammatory cytokines stimulate hypothalamus release of corticotropin releasing hormone (CRH) that (4) activates the pituitary to release the adrenocorticotropic hormone (ACTH). (5) ACTH activates the adrenal gland to release the glucocorticoids which enters the brain by activating glucocorticoid receptors. The feedback to the hypothalamus and pituitary is inhibited increasing circulating glucocorticoid level. (6) Glucocorticoid activates monocytes to sustain the release of pro-inflammatory cytokines; together they activate the kynurenine instead of the serotonin pathway. (7) Serotonin is normally synthesized from tryptophan by the action of tryptophan hydroxylase, which declines (8) Pro-inflammatory cytokines stimulated in the presence of tetrahydrobiopterin (BH4) result in the release of nitric oxide (NO) to activate the synthesis of more of glutamate neurotransmitter, already supplied through the tricarboxylic acid (TCA) cycle, and less GABA production. (9) Phenylalanine in the presence of BH4 is converted to tyrosine and then dopamine by the tyrosine hydroxylase, with its subsequent conversion to noradrenaline by dopamine β-hydroxylase: these activities decrease the monoamines and further compounded by increase degradation by the monoamine oxidase (MAO) and catechol-0-methyltransferase (COMT). (10) Glutamate decarboxylase (GAD) coverts glutamate to gamma amino butyric acid (GABA). (11) Glutamate is transported by the vesicle glutamate transporter (vGLUT), while the reuptake glutamate transporter (GLUT) is insufficient to remove excess glutamate.

been reported in depressives (Serafini et al., 2013), and are activated through the stress response pathway (Chávez-Castillo et al., 2019). Brain-derived neurotrophic factor (BDNF), which plays an important role in the maintenance and survival of neurons and in synaptic plasticity is reportedly decreased in the serum and plasma in depressed patients (Molendijk et al., 2011; Karege et al., 2002). Its depletion may be a reason for hippocampal shrinkage in depressives.

Scientific data have also implicated endocrine and inflammatory response system in the pathophysiology of depression (Leonard, 2010; Boku et al., 2017). Although the neuroendocrine and inflammatory response systems hypotheses are plausible, the actual mechanism is not fully understood. In the neuroendocrine response system, abnormalities in the hypothalamic–pituitary–adrenal (HPA) axis lead to hyper-secretion of the cortisol, glucocorticoid, released in stressful situations (Cowen, 2015), where the failure of the negative feedback to the hypothalamus and pituitary gland is associated with depression (Leonard, 2010). Boku et al. (2017) suggests the involvement of this hormonal pathway during hippocampal size reduction in depression. Patients with depression also show abnormal responses to thyroid-stimulating and thyrotropin-releasing hormones, as well as elevated cerebrospinal fluid concentrations of thyrotropin-releasing hormone (Bahls and de Carvalho, 2004).

Abnormalities in the levels of inflammatory biomarkers, C-reactive protein and cytokines such as interleukin (IL)-1, IL-6 and alpha tumor necrosis factor (TNF)-α in depression have been reported (Cowen, 2015; Mikkelsen et al., 2017). Depressive episodes associated with increased levels of the cytokines are as a result of hyperactivity and loss of negative feedback of the HPA axis, with consequential elevations in the levels of corticotropin-releasing hormone which activates a chain of other hormones, including adrenocorticotropic hormone (ACTH) and cortisol (Pace et al., 2007). These abnormal hormonal levels as also seen in other medical conditions, triggers the release of the pro-inflammatory cytokines characteristic of inflammatory responses (Schiepers et al., 2005). Anti-inflammatory treatments in patients with depression also yielded promising results (Köhler et al., 2014). On the whole, it is very important to note these systems do not function independent of each other, indicating that treatment strategy should also be holistic (Fig. 2).

6. Treatment/management strategies in depression

Different treatment/management strategies already in place have been used to reduce the burden of depression; these include psychotherapy, electroconvulsive therapy and pharmacotherapy:

Psychotherapy involves the utilization of psychological means such as behavioral activation, cognitive and interpersonal sessions with experts. Psychotherapy may be applied alone for the treatment of mild depression. But in moderate to severe depression, psychotherapy is combined with antidepressant medications. Psychotherapy may involve the depressed individual alone, or may include other individuals either with similar condition or whose presence may help in quick recovery. Psychotherapy focuses on reality and the ability to solve problems, thereby helping the depressives to recognize these. Such therapy as applied in psycho-education and yoga, as well as in educational intervention using guided internet-assisted intervention have been reported with good outcomes (Niemi et al., 2016; Ofoegbu et al., 2020).

Electroconvulsive therapy is used for patients with severe major depression who have not responded to other treatment strategies, especially in treatment-resistant depression. This therapy reported with some level of success, involves a brief electrical or magnetic stimulation of the brain (Fitzgerald et al., 2003). Electrical stimulation is an invasive procedure while the patient is under anesthesia. The electrical stimulation of the subgenual cingulate white matter diminishes symptoms of treatment-resistant depression, with suggestion of disrupting focal pathological activity in limbic-cortical circuits (Mayberg et al., 2005). Other reports of long and short pulse width subcallosal cingulate stimulation have been shown to have good outcome (Lozano et al., 2012; Ramasubbu et al., 2020). However, treatment may be up to four months or more to derive maximum benefits (Fitzgerald et al., 2003). Non-invasive transcranial magnetic and electrical stimulation have also been reported. They exert their effect by inducing changes in cell activity, resulting in changing connectivity, and network structure and function. These changes emergent properties of the networks, clinically expressed as altered symptom presentation or enhancement of specific functions (De Ridder et al., 2017). Electroconvulsive shock therapy is reported to also increase the levels of BDNF in the serum of treatment resistant depressed patients (Marano et al., 2007).

7. Pharmacological treatment regimes for depression

Pharmacotherapy is the most widely used form of depression treatment, involving medication either alone or with other treatment strategies. Medications include antidepressants such as the selective serotonin reuptake inhibitors (for example; citalopram, fluoxetine and sertraline), serotonin-noradrenaline reuptake inhibitors (for example; venlafaxine, duloxetine and milnacipran) and tricyclic antidepressants (for example; amitriptyline, imipramine and nortriptyline). Other antidepressants include atypical antidepressants (for example; mirtazapine, agomelatine and bupropion) and monoamine oxidase inhibitors (for example; selegiline, isocarboxazid and phenelzine) (Jakobsen et al., 2020). These antidepressants act by modifying brain chemistry to improve depressive conditions (Molendijk et al., 2011; Gabbay et al., 2017).

Most therapies for depression are based on the hypothesis that the shortage of serotonin, dopamine or noradrenaline in the brain deteriorates depression disorder (Meyer et al., 2006; Cowen, 2015). The selective serotonin reuptake inhibitors (SSRI) and the serotonin-noradrenaline reuptake inhibitors (SNRI) regarded as second generation antidepressants, inhibit the reuptake of serotonin, and serotonin and/or noradrenaline, respectively in the brain by binding with presynaptic monoamine transporters, allowing the availability of these monoamines for their normal functional activities. The tricyclic antidepressants considered as the first generation antidepressants, have a range of activities including monoamine reuptake inhibition as well as antagonism of serotonin 2A (5-HT2A) receptors (Jakobsen et al., 2020). Other antidepressants such as the monoamine oxidase inhibitors inhibit the activities of the monoamine oxidase A and/or B preventing the degradation of the monoamines, while the atypical antidepressants act in an atypical manner in contrast to the other antidepressant types. All of these mechanisms result in an enhanced neurotransmission of serotonin and/or noradrenaline.

The onset of clinical efficacy of depression treatment may be up to three to four weeks, and well-being extending to months, with its associated adverse reactions (Adell et al., 2005). Even with pharmacotherapy, treatment-resistant depression still arise warranting special attention. Thus, the pharmacological deficiencies in depression treatments led to the WHO cautioning, against the use of antidepressants in children, as well as for the treatment of mild depression, and with adolescents not eligible for first line treatment (WHO, 2020).

8. Other treatments for depression

Hormone therapy has been reported with promising results. The adrenal hormone, corticosterone is reported with potentials in the treatment of depression in animal models (Berger et al., 2019). The thyroid hormone, thyrotropin-releasing hormone showed greater arousal and improved cognitive functions (Khan et al., 1993). Estrogen, the ovarian hormone has been reported useful in managing postpartum depression (Gregoire et al., 1996). Hormone may be used as mono-therapies or concomitantly with antidepressants: The limiting factor is their tendency to lead to other health complications.

Physical and sport activities have also been suggested in depression treatment. Participation in physical or sport activities was associated

with fewer depressive symptoms and increase hippocampal volume (Hayward et al., 2016; Gorham et al., 2019). There are other inconclusive reports, with resulting suggestions that physical or sport activities may be used in addition to antidepressants (Blake, 2012).

Despite the availability of different classes of antidepressant drugs, most of them are not completely effective, coupled with delayed onset of antidepressant effects, and are also associated with serious adverse effects. Their use in treatments is based on the different hypotheses on the etiology of depression. There is a need for newer approaches to either prevent depression or delay its progression, as well as whole treatment strategy that may capture the entire hypotheses of etiology.

9. Application of nutrition in depression management

9.1. Overview

Nutrition can be exploited in depression treatment. This is important because there are hypotheses that certain nutrients needed for the brain to function effectively also influences biological and neurochemical actions involved in the development and progression of depression (Popa and Ladea, 2012). There are also mounting evidence linking dietary patterns to major depression development and also those supporting the importance of nutrition in maintaining good mental health (German et al., 2011; Kaner et al. 2015; Hayward et al., 2016; Sinclair et al., 2016). Nutrition is reported to be involved in the synthesis of the monoamines (Lopresti et al., 2013), glutamate and GABA implicated in depression. Depressed individuals also have elevated levels of monoamine oxidase (Meyer et al., 2006), which equally breaks down more serotonin, dopamine, and noradrenaline necessary for mood regulation.

Nutrition can be regarded as a way of life because it is generally acceptable and easy to administer. This can be exploited for health interventions as a safe, natural and inexpensive treatment for depression (Sublette et al., 2011). Nutritional factors having beneficial effects on mental health include polyunsaturated fatty acids, especially the omega-3 polyunsaturated fatty acids, proteins, vitamins and minerals among others (Lim et al., 2016).

9.2. Role of Omega 3 polyunsaturated fatty acid in depression

The polyunsaturated fatty acids, especially the omega-3 polyunsaturated fatty acids (ω-3 fatty acids) are normal constituents of cell membranes essential for normal brain functions (Deacon et al., 2017). They function in the regulation of brain cell membrane fluidity, membrane-bound enzymes, dopaminergic and serotoninergic transmission, and cellular signal transduction, as well as in brain eicosanoid synthesis, which is connected to depression (Liperoti et al., 2009). Additionally, ω-3 fatty acids influence the production of neurotrophic factors that regulate neurogenesis, cognition and emotion, support cognitive processes, and also up-regulate genes that are important for maintaining synaptic function and plasticity (Deacon et al., 2017).

The main forms of ω-3 fatty acids are the α-linolenic acid, found mainly in plants such as walnut, soy and canola oil, and the long-chain, docosahexanoic and eicosapentaenoic acids whose richest source is in seafood. In the body, α-linolenic acid is converted into docosahexanoic and eicosapentaenoic acids. Fishes such as salmon, mackerel, herring, anchovies, sardines and trout, as well as certain eggs and animal products are rich sources of docosahexanoic and eicosapentaenoic acids (Mischoulon et al., 2015). High fish consumption is reported in decrease risk of depression (Sublette et al., 2011).

Omega-3 fatty acids are essential fatty acids; depressed individuals have been reported to have lower blood levels of ω-3 fatty acids and reduced levels of docosahexaenoic and eicosapentaenoic acids (Lin et al., 2010; Panagiotakos et al., 2010; Liao et al., 2019). Deficiency of ω−3 fatty acids result in neural functional impairment (Sinclair et al., 2016), probably due to alteration of the structure and/or functions of membrane-bound enzymes, protein receptors and ion channels.

Dietary intake of ω-3 fatty acids is reported in depression scores improvement (Banikazemi et al., 2015), as well as increased adaptive coping in stressful events (Gonzales et al., 2015). The eicosapentaenoic acid form of ω-3 fatty acid is also reported with clinical benefits on depressive symptoms (Liao et al., 2019). The ω-3 fatty acids protect against depression, may be by regulating the serotoninergic, dopaminergic and adrenergic transmission (Liperoti et al., 2009), through the production of neurotrophic factors necessary for neurogenesis (Deacon et al., 2017). In contrast to the health effects, high content of ω-3 fatty acids adversely affect cognitive performance and cause a reduction of hippocampal levels of BDNF-related synaptic plasticity (Molteni et al., 2002).

9.3. The role of proteins in depression

The neurons of the brain communicate with each other by means of proteins release from synaptic vesicles, protein transporters or membrane receptors and ion channels. Protein deficiency induces abnormal neurotransmitter levels and cognitive behavior deficits (Sato et al., 2020). Proteins are macromolecules consisting of one or more long chain amino acid group required as building blocks and as an energy source for cell repair, survival, regeneration and growth. There are 22 amino acids; nine amino acids considered “essential” cannot be synthesized endogenously in humans. Thus, dietary proteins are key sources of these essential amino acids. These amino acids include histidine, isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan and valine. Amino acids considered “non-essential” and synthesized endogenously include alanine, arginine, asparagine, aspartate, glutamate, glutamine, glycine, proline and serine synthesized from glucose; while cysteine is synthesized from the metabolism of methionine, tyrosine is synthesized from the metabolism of phenylalanine. Selenocysteine and pyrrolysine are rare amino acids made by modifying genetically encoded amino acids, cysteine and lysine, respectively, a process known as post-translational modification (Clark et al., 2019).

Neurotransmitters are derivatives of amino acids; two of them, tryptophan and tyrosine are precursors of serotonin, and dopamine and noradrenaline, respectively, while glutamate is the precursor of glutamate and GABA. Tryptophan and tyrosine are abundant in milk, cheese, meat, eggs, chicken, fish, beans, oats, nuts and whole grains (Grunewald, 2012). Tryptophan readily crosses the blood-brain barrier where it is converted into serotonin or 5-hydroxytryptophan (5-HT) in neurons, through the sequential actions of tryptophan hydroxylase and 5-hydroxytryptophan decarboxylase in the presence of pyridoxal phosphate. Serotonin is unable to cross the blood-brain barrier (Khan and Khan, 2016), requiring tryptophan continuous supply from diet.

Poor tryptophan diets lead to reduced serotonin in the brain, resulting in anxiety, obsessions and compulsions, which are symptoms of depression (Chávez-Castillo et al., 2017; Chávez-Castillo et al., 2019). Serotonin production in the raphe nuclei are also affected in chronic stressful conditions and reduced ω-3 fatty acids level, with subsequent unregulated rise in the glucocorticoids and pro-inflammatory cytokines. These unregulated rise predisposes serotonin depletion by stimulation of the tryptophan-metabolizing enzymes, indoleamine 2,3-dioxygenase, and tryptophan dioxygenase, instead of tryptophan hydroxylase, causing increased production of quinolinic acid, a potential neurotoxic metabolite (Dantzer et al., 2008; Cowen, 2015). In remitted depressed patients, temporarily lowering tryptophan levels can result in an acute depressive relapse (Booij et al., 2005). Dietary intake of tryptophan reduces stress and cortical hormones which are associated with depression (Koopmans et al., 2005).

Tyrosine also known as 4-hydroxyphenylalanine, is a non-essential amino acid obtained from diets or through the hydroxylation of phenylalanine by tyrosine hydroxylase (National Center for Biotechnology Information, 2020). Tyrosine or L-tyrosine readily crosses the blood-brain barrier where it is converted into dopamine and noradrenaline in neurons. The enzyme tyrosine hydroxylase first converts

L-tyrosine to 3,4-dihydroxy-L-phenylalanine (L-DOPA) and subsequently decarboxylated to dopamine by DOPA decarboxylase. The enzyme, dopamine β-hydroxylase then hydroxylates dopamine to noradrenaline. Phenylethanolamine N-methyltransferase, another enzyme, transfers a methyl group from S-adenosylmethionine to the nitrogen of noradrenaline forming adrenaline. These processes take place in discrete neurons of the ventral tegmental nucleus, substantia nigra, locus coeruleus as well as the hypothalamus (Moret and Briley, 2011; Robertson et al., 2013; Poulin et al., 2018).

Deficiency of tyrosine or the abnormalities in tyrosine hydroxylase leads to decrease dopamine, associated with anhedonia and lack of motivation as observed in depression (Harmer et al., 2001; McLean et al., 2004; Grunewald, 2012). Decreased dopamine may also be due to changes in the density of dopamine transporter binding (Sarchiapone et al., 2006). Deficiency in noradrenaline associated with decreased alertness, problems of inattention, concentration and cognitive abilities may also arise from tyrosine deficiency. Dietary intake of tyrosine improves cognitive behavior in acute and chronic stress models (Jongkees et al., 2015; Alabsi et al., 2016), and this reduced stress effects may be due to the enhanced production of noradrenaline (McLean et al., 2004).

Glutamate is another amino acid obtained in diets, but mostly produced in the body from glucose through alpha-ketoglutarate in the tricarboxylic acid cycle. Food such as milk, cheese, meat, fish, mushrooms and vegetables are rich in glutamate. The neurotransmitters, glutamate and GABA do not cross the blood-brain barrier and therefore, require their synthesis within the brain. Astrocytes generate glutamate via *de novo* synthesis or by "recycling" glutamine from GABA and glutamate after reuptake. GABA is synthesized from the neurotransmitter, glutamate in the presynaptic neuron by the enzyme glutamate decarboxylase (GAD), which requires pyridoxal phosphate as a co-factor (Waagepetersen et al., 2007; Leke et al., 2011).

The excitatory glutamate and the inhibitory GABA work together to control many processes, including the brain's overall level of excitation. After release into the synaptic cleft, GABA can bind to GABA receptors, be recycled into the presynaptic neuron, or taken-up by astrocytes where it is degraded. Within the astrocyte, the enzyme GABA-transaminase degrades GABA into succinic semialdehyde, and into succinate by succinate semialdehyde dehydrogenase. Succinate then enters the tricyclic acid cycle, and is transformed to α-ketoglutarate, which converts into glutamate. Glutamine synthase then converts glutamate into glutamine, and is subsequently transported to the presynaptic neuron, where it is converted again into glutamate by phosphate-activated glutaminase (Waagepetersen et al., 2007; Leke et al., 2011). Deficiency in essential proteins is reported to not only affect the monoamine and catecholamine levels, but also glutamate and GABA levels. However, intake of these essential proteins has shown a reversal of depressive symptoms (Sato et al., 2020). Administration or consumption of glutamate is reported to exacerbate depression symptoms, possible because it causes excessive glutamate release, which is toxic to the brain and linked to many neurodegenerative diseases, and associated with exposure to chronic stress, and excessive glutamate release and uptake (Reiner and Levitz, 2018; Mesripoura et al., 2019; Kraal et al., 2020).

Other amino acids also contribute to the formation of neurochemicals that are necessary for the proper functioning of the brain. Histidine and arginine for example are used by the brain for the synthesis of various neurotransmitters and neuromodulators (Betz et al., 1994).

9.4. The role of vitamins and minerals in depression

Vitamins and minerals are essential substances needed for the development and proper functioning of the body. They are reported to play key roles in the etiology of depression, although vitamins' regulation of depression is not unequivocal. Several reports indicate lower intake of vitamins and minerals in individuals with depression (Kaner et al. 2015; Nguyen et al., 2017). Food rich in vitamins include fish, lean meats, eggs, poultry, milk and fruits.

Vitamins include A, B, C, D, E and K. Vitamins A, D, E and K are classified as fat-soluble, while vitamins B and C are water-soluble. Vitamins A, C, and E are major non-enzymatic antioxidants that serve as the body's defense mechanism against oxidative stress and protects against cognitive decline and mental disorders including anxiety disorders, attention-deficit/hyperactivity disorder, and depression (Brown and Roffman, 2014). Lim et al. (2016) reported that the brain is vulnerable to oxidative stress because its lipid-rich area especially in neuronal membrane is metabolically active. High-dose antioxidant supplementation has been shown to slow the progression of neuronal damage and vascular disease, and therefore, may be effective in preventing or treating major depressive disorders.

Vitamin A is present in cod liver oil, liver, egg, milk, butter, sweet potato, carrot, broccoli, tomatoes, pepper and pawpaw among other fruits and vegetables (Bourre, 2006). It is also essential for growth and development and cognition, as well as immune system and vision maintenance. Vitamin A's role in depression is not known, but deficiency is reported in depression (Husson et al., 2004; Bremner et al., 2012), while supplementation improves depression symptoms (Bitarafan et al., 2016; Nguyen et al., 2017).

Vitamin C or ascorbic acid is present in black current, broccoli, citrus fruits, tomatoes, potatoes, pepper, guava, kiwi and strawberry among other fruits and vegetables. This vitamin is also involved in the synthesis of the monoamine neurotransmitters, dopamine and noradrenaline (Diliberto et al., 1991). Its deficiency is associated with depression (Pullar et al., 2018). Short-term supplementation of vitamin C significantly decreased anxiety levels in diabetic patients through alleviating oxidative damage (Mazloom et al., 2013), and reverses depressive symptoms (Nguyen et al., 2017; Pullar et al., 2018).

Vitamin E is rich in goose meat, seafood, wheat germ oil, sunflower, almond, peanut, avocado, mango and kiwi among other fruits. It also maintains neurological structure and function (Muller and Goss-Sampson, 1990). Its deficiency associated with depression symptoms, alters the levels of glutamate and GABA in developmental neurogenesis by inducing changes in the enzymes involved in their metabolism (Pereira et al., 2013; Banikazemi et al., 2015). Vitamin E intake reduces depressive symptoms (Banikazemi et al., 2015; Nguyen et al., 2017).

The B vitamins are involved in deoxyribonucleic acid (DNA) synthesis, membrane maintenance, and are essential for monoamine oxidase synthesis, and neuronal function. They are rich in salmon, liver, eggs, milk, beef, leafy greens, legumes, yogurt and fortified cereals among others. Vitamin B complex nutritional supplement showed significant continuous improvements in depressive and anxiety symptoms (Lewis et al., 2013). These vitamin B complex include B_1 (thiamine), B_2 (riboflavin), B_3 (niacin), B_5 (pantothenic acid), B_6 (pyridoxine), B_9 (folate), B_{12} (cobalamin) and biotin. Their deficiency may contribute to cognitive impairment, dementia and depression (Mikkelsen et al., 2016, 2017; Nguyen et al., 2017).

Vitamin B_1 or thiamine is essential for neuronal function especially in energy production, anti-nociception and cognitive performance (Eisinger, 1997). Its deficiency in animals showed less brain glutamate, 2-oxo-glutarate and GABA (Page et al., 1989; Braga et al., 2020). Vitamin B_2 or riboflavin is essential for cellular metabolism, energy production, anti-nociception, as well as regulation of vitamins B_1 and B_3. Its deficiency may affect the glycolysis pathway, as well as iron deficiency (Braga et al., 2020). Vitamin B_3 or niacin is relevant in the production of serotonin, deficiency of vitamin B_3 results in negative effect on mood (Bourre, 2006). Vitamin B_6 (pyridoxine) is necessary for serotonin and GABA formation. Its deficiency may affect the glycolysis pathway and depression (Khan and Khan, 2016).

Vitamin B_9 or folate is relevant in the production of serotonin and other monoamine neurotransmitters and catecholamines, and is essential in pregnancy for the normal formation of the nervous system and mood regulation. Deficiency is observed in MDD individuals (Kaner et al., 2015; Ahmed et al., 2020). Vitamin B_{12} or cobalamin is essential

for red blood cell formation. It is also involved in the synthesis and metabolism of monoamine and catecholamines neurotransmitters (Grunewald, 2012). Lower level of vitamins B_{12} is reported in depression (Kaner et al., 2015; Ahmed et al., 2020).

Vitamin D is essential for calcium homeostasis, bone growth and regulation of neurodevelopment and function. The main source of vitamin D is sunlight, while dietary sources include fish and fortified margarine (Anjum et al., 2018). Vitamin D regulates formation and utilization of the neurotransmitters, glutamine, noradrenaline, dopamine and serotonin (Kesby et al., 2017). The deficiency of this vitamin, either due to the decreased cutaneous synthesis or dietary intake deficiency is reported in depression (Moy et al., 2017; Hansen et al., 2019), with a behavioral and anatomical change in the hippocampus reported in animal studies (Berridge, 2017). Dietary supplementation of vitamin D is associated with decrease depression symptoms in older females (Bertone-Johnson et al., 2011); however, Hansen et al. (2019) reported no positive results in depression.

Vitamin K is involved in blood clotting and in membrane sphingolipids metabolism in the brain (Ferland, 2013). Deficiency is reported in elastin degradation and chronic obstructive pulmonary disease, as well as in depression (Nguyen et al., 2017; Piscaer et al., 2019). High dietary vitamin K intake was significantly associated with lower depressive symptoms (Bolzetta et al., 2019).

Minerals include a wide range of natural occurring elements necessary for normal body functions. Some of them affect brain cognitive and metabolic processes, and their deficiency or abundance pose a problem. Lower levels of such minerals as sodium, potassium, magnesium, calcium, phosphorus, iron and zinc have been reported in individuals with depression, and mainly associated with lower intake either as supplements or in diets (Kaner et al., 2015; Nguyen et al., 2017). Low intake of zinc, copper, and manganese is associated with depression and anxiety symptoms (Nguyen et al., 2017; Nakamura et al., 2019). High zinc, iron, copper and selenium intake is inversely associated with depression (Li et al., 2018).

Two of these elements, sodium and potassium are complementary to each other; essential in maintaining water and electrolyte balance, especially in neural transmission (Pivovarov et al., 2018). They tend to determine healthy dietary patterns, with high urine sodium associated with consumption and implicated in depressive symptoms (Moore et al., 2017). On the other hand, high urine potassium was also associated with consumption, but showed less depressive symptoms (Mente et al., 2009), with the former mostly derived from junk food and salty diets, the latter is from fruits and vegetables.

Magnesium is essential as cofactor in many enzymatic reactions in the body, and in the nervous system is involved in nerve transmission and neuromuscular regulation (Grober et al., 2015). The deficiency of magnesium is associated with symptoms of depression and other mood disorders, while moderate intake is inversely associated with the risk of depression (Li et al., 2017). Iron is another cofactor for numerous enzymatic processes, which modulates neuronal development and regulates dopaminergic neurotransmission (Youdim et al., 1983). It exacerbates depressive symptoms upon higher body intake in young adult males (Richardson et al., 2015); while their deficit decreases oxygen supply to the brain, brain energy production, as well as deregulation of the dopaminergic system and depression lower levels (de Deungria et al., 2000; Matak et al., 2016). Calcium is very essential in the body for muscle contraction, blood-clotting, bones and teeth formation, and maintenance. In the nervous system it is essential in neural and synaptic transmission, as well as heart beat and fluid balance regulations (Pravina et al., 2013). Dietary deficiency of calcium was associated with depression symptoms in a female population (Bae and Kim, 2012). However, Jamilian (2020) reported that calcium level does not affect depression outcome.

Phosphorus is essential in the formation of bones and teeth, as well as adenosine tri-phosphate, DNA and membrane synthesis, as well as protein phosphorylation (Foster, et al., 2008). High energy phosphate metabolism, intracellular pH and membrane phospholipid metabolism are altered in depressive disorders (Kato et al., 1992), although Jamilian (2020). reported that phosphorus level is not affected in depression. Zinc influences numerous cellular functions, with most enzymatic actions being zinc-dependent (Osredkar and Sustar, 2011). It is essential at low concentrations; deficiency impairs whole-body accumulation of polyunsaturated fatty acids and alters mood and depression (Cunnane and Yang, 1995; Li et al., 2018). Zinc intake is associated with decrease in depressive and anxiety symptoms (Li et al., 2018), but high concentration is detrimental to the GABAergic pathway (Blakemore and Trombley, 2017).

Copper is essential in some enzymatic actions. Its deficiency can affect brain development, and also in dopamine depletion and probably depression (Osredkar and Sustar, 2011; Li et al., 2018). Copper accumulates in the brain in psychiatric and behavioral abnormalities (Desai and Kaler, 2008). Selenium is essential in some enzymatic actions and the maintenance of the antioxidant capacity of the brain, where it is bound to the amino acid, selenocysteine (Zoidis et al., 2018; Clark et al., 2019). Selenium supplementation appears to exert antioxidant effect (Zoidis et al., 2018), although high selenium intake is inversely associated with depression (Nguyen et al., 2017; Li et al., 2018).

Other trace compounds important in brain function include chromium and boron. Chromium is required for carbohydrate metabolism and is known to potentiate insulin action. Chromium-deficient patients develop glucose intolerance, impaired energy utilization and nerve and brain disorders (Vincent, 2017). Chromium or its supplement, chromium picolinate reduced serum triglyceride and shows promising antidepressant effects in atypical depression (Lee and Reasner, 1994; Davidson et al., 2003). Boron is essential for several metabolic activities in the body including anti-oxidation, bone maintenance, wound healing, regulation of hormone, vitamin and magnesium activities, and in the nervous system improves the brains electrical activity and cognitive performance (Pizzorno, 2015). Low dietary boron is reported to cause significantly poorer performance on various cognitive and psychomotor tasks (Naghii et al., 1996).

9.5. *Application of herbs in depression management*

Another area of research is the use of herbs, including nutraceuticals, fruits and vegetables, and their bioactive metabolites. Herbs or their bioactive metabolites with psychotropic effects can be exploited for the treatment of depression (Matraszek-Gawron et al., 2019). Summary of phytochemicals/metabolites and herbal whole extracts with antidepressant activity can be found in Tables 1 and 2. Dietary antioxidants from fruits and vegetables are beneficial against depression and its associated symptoms (Saghafian et al., 2018).

Herbs contain phytochemicals with different properties essential in maintaining the nervous system, which generally help to repair damaged cells, decrease inflammation in brain cells, while also restoring neurotransmitter balance and cognitive deficits. One vital phytochemical reported with enormous antidepressant effect is the polyphenols. Some of them are discussed based on their effects on depressive symptoms. In an animal model, p-Coumaric, a polyphenol derivative of cinnamic acid from fruits and diets improved behavioral, biochemical and electrophysiological measures of lipopolysaccharides (a bacteria-derived endotoxins)-induced depressive symptoms (Jakupovic et al., 1990; Lee et al., 2018) possibly by activating the antioxidant pathway, indicating its benefit in combating depression.

Quercetin (3,3′,4′,5,7-pentahydroxyflavone), a polyphenolic flavonoid found in many fruits, vegetables, and medicinal herbs, has antioxidant action and prevents depression-like behaviors. It acts by blocking the monoamine oxidase inhibitor (Dhiman et al., 2019), preventing the reuptake and degradation of the monoamines, thereby increasing the amount of serotonin, dopamine, and noradrenaline in the brain. It also activates the HPA axis in animals (Bhutada et al., 2010). Foods with high levels of quercetin include apples, kale, berries, grapes,

Table 1
Summary of phytochemicals/metabolites of herbs with antidepressant activity.

Phytochemical	Source	Role	Reference
Quercetin	Fruits, vegetables, and medicinal herbs	Antioxidant action. Prevents depression-like behaviors. Blocks MAO inhibitor. Limits hyper-activation of the HPA axis.	Bhutada et al. (2010);Dhiman et al. (2019)
Carvacrol	Aromatic herbs such as oregano and thyme	Enhance 5-HT and dopamine levels	Melo et al. (2011);Zotti et al. (2013)
Curcumin	*Curcuma longa*	Restores stress-induced behavioral and biochemical changes. Reduced immobility time in forced swimming test. Decrease MAO activity, 5-HT level and hippocampal 5-HT1A mRNA	(Xu et al., 2007; Kulkarni et al., 2008; Bhutani et al., 2009)
Resveratrol	Red wine, grapes, grape juice, peanuts, cocoa, and berries	Reduced immobility period in the despair tests, as well as sucrose preference and deficits. Raised 5-HT, dopamine, and noradrenaline concentrations and reduced MAO activity.	Xu et al. (2010); Yu et al. (2013)
Polyphenol	*Camellia sinensis*	Decreased immobility time in forced swim test. Decreased serum level of corticosterone Regulate the HPA axis	Zhu et al. (2012)
Saponin	*Rauwolfia vomitoria*	Anti-depressive effect in behavioral activities in scopolamine model of memory impairment	Bisong et al. (2019)
Alkaloid	*Vernonia amygdalina*	in vitro antioxidant properties, while also inhibiting brain enzymatic activities involving the MAO, as well as reversing these activities in scopolamine model of depression.	Oboh et al. (2020).

HPA – hypothalamic-pituitary-axis; MAO – monoamine oxidase.

onion, and green tea (Nishimuro et al., 2015).

Carvacrol is a monoterpenic phenol isolated from such aromatic herbs as oregano and thyme. It induced antidepressant effects by enhancing 5-HT and dopamine levels (Melo et al., 2011; Zotti et al., 2013), essential for normal brain function. Curcumin, a polyphenol derivative of the rhizome of *Curcuma longa* belonging to the family, Zingiberaceae, restores stress-induced behavioral and biochemical changes including immobility time and MAO activity, 5-HT level and hippocampal 5-HT1A mRNA (Xu et al., 2007; Kulkarni et al., 2008; Bhutani et al., 2009), essential for normal brain functions.

Resveratrol is a polyphenol derivative from sources such as red wine, grapes, grape juice, peanuts, cocoa, and berries, is reported to reduce immobility period in the despair tests, sucrose preference and deficits, as well as MAO activity. It raises 5-HT, dopamine, and noradrenaline concentrations in the brain (Xu et al., 2010; Yu et al., 2013), essential for normal brain functions. Polyphenols from the leaf of *Camellia sinensis* also called green tea, and belonging to the Theaceae family, is reported to improve depression-like behavior, while decreasing serum levels of corticosterone by regulating the HPA axis (Zhu et al., 2012) essential for normal brain function.

Other phytochemicals also provide antidepressant effect. For example, *Rauvolfia vomitoria* or serpent wood, an antipsychotic plant of the Apocynaceae family, is used in psychiatry treatments (Obembe, 2001; Nduohosewo and Ekong, 2020). The saponin fraction of the root bark exhibited anti-depressive effect in behavioral activities in scopolamine model of memory impairment (Bisong et al., 2019). *Vernonia amygdalina* or bitter leaf, belonging to the Asteraceae family, is eaten as food or used as decoction (Ekong et al., 2016). Its alkaloid-rich leaf extract is reported with in vitro antioxidant properties, while also inhibiting brain enzymatic activities involving the MAO, as well as reversing these activities in scopolamine model of depression (Oboh et al., 2020).

Whole plant extracts have also been reported with antidepressant activities; some of them are discussed based on their effect on depression symptoms. *Vernonia amygdalina* methanol extract exerted antidepressant on behavioral activities in animals (Onasanwo et al., 2016). *Moringa oleifera* is of the family, Moringaceae, with its leaves mostly used as food (Ghasi et al., 2000). It is rich in different classes of food and phytochemicals (Abdulkarim et al., 2005) and reported with antioxidant and neuroprotective properties (Ekong et al., 2017). Ethanol extract of *Moringa oleifera* exerted antidepressant on behavioral activity in animals, which was amplified in combination with fluoxetine (Kaur et al., 2015).

Zingiber officinale or ginger belongs to the Zingiberaceae family. Its rhizome used as spice in food is reported with anxiolytic activity and anti-nociceptive effect (Singh et al., 2012; Phukan and Adhikari, 2017). It acts as 5-HT1A receptor antagonist and an antidepressant (Phukan and Adhikari, 2017), whose activity also involves the activation of the dopaminergic system (Singh et al., 2012). *Allium cepa* or onions, belongs to the Liliaceae family. *Allium cepa* showed antioxidant activity and

Table 2
Summary of some herbal whole extracts with antidepressant activity.

Plant	Family	Part	Role	Reference
Vernonia amygdalina (bitter leaf)	Asteraceae	leaf	Antidepressant exerted on behavioral activities in animals with decreased immobility time in forced swim and tail suspension tests	Onasanwo et al. (2016).
Moringa oleifera (Moringa)	Moringaceae	leaf	In animal models antioxidant and neuroprotective properties antidepressant on behavioral activity	Kaur et al. (2015) Ekong et al. (2017)
Zingiber officinale (ginger)	Zingiberaceae	rhizome	anxiolytic activity and anti-nociceptive effect. It acts as 5-HT1A receptor antagonist and an antidepressant	Singh et al. (2012) Singh et al. (2012); Phukan and Adhikari (2017)
Allium cepa (Common onion)	Liliaceae	Bulb	In animal models showed antioxidant activity and antidepressant inhibiting MAO	Sakakibara et al. (2008); Samad and Saleem (2018)
Momordica charantia (bitter melon)	Cucurbitaceae	Whole plant	antidepressant effect. Whole extract of the plant reduced depression through the serotonergic, noradrenergic, dopaminergic, muscarinic cholinergic receptor systems	Ishola et al. (2013)
Crocus sativus (saffron)	Iridaceae	Flower	Clinically effective in depression treatment. Improves HAM-D and Beck Depression Inventory Scores	Akhondzadeh et al. (2004); Noorbala et al. (2005)
Hypericum perforatum (St John's Wort)	Hypericaceae	Flower, Leaf	Clinically effective in depression treatment. Decreases HAM-D scores	Kasper et al. (2006); Mannel et al. (2010)
Ginkgo biloba	Ginkgoaceae	Leaf	Clinically effective in depression treatment. Decreases HAM-D scores. Inhibits MAO	White et al. (1996); Dai et al. (2018)

HPA – hypothalamic-pituitary-axis; MAO – monoamine oxidase.

antidepressant effects by inhibiting MAO in animals (Sakakibara et al., 2008; Samad and Saleem, 2018).

Momordica charantia of the family, Cucurbitaceae, and commonly called bitter melon or gourd has been reported with antidepressant effect. Whole extract of the plant reduced depression through the serotonergic, noradrenergic, dopaminergic, muscarinic cholinergic receptor systems (Ishola et al., 2013). *Crocus sativus* of the Iridaceae family is best known as saffron. It is reported to improve the Hamilton Rating Scale for Depression, Beck Depression Inventory and Beck Anxiety Inventory Scores (Akhondzadeh et al., 2004; Noorbala et al., 2005). *Hypericum perforatum* (St John's Wort), is of the family Hypericaceae. It is clinically efficacious for depression management (Kasper et al., 2006; Mannel et al., 2010). *Ginkgo biloba* is of the family Ginkgoaceae. Its extract in combination with citalopram, acts as adjunctive treatment effectively improving depressive symptoms (Dai et al., 2018). It acts by inhibiting MAO (White et al., 1996), Fowler et al. (2000) reported contrary in the human brain.

Other plants not showing these antidepressant effects may either be due to the interference/masking of their polyphenols by other phytochemicals, or to the low polyphenols content within these plants. Nevertheless, they may still be beneficial to brain when applied appropriately.

10. Conclusion

Depression is a global health and economic burden, with widespread data in developed climes. Data on these is lacking or inefficiently managed in developing countries, leading to under reporting of its prevalence. Such data in management and cost in treatments in developed countries are mind blowing warranting a need for shift in treatment strategy in the middle and low income countries who may be unable to cope. One area that may interest researchers, caregivers and policy makers in depression management, and which is readily available is nutrition. Nutrition through the application of ω-3 fatty acids, proteins, vitamins and minerals present in food or through either food supplements or herbs may go a long way to provide inexpensive, natural, non-invasive and less adverse intervention that can be applied alongside standard clinical practice. Given the basic influence of nutrition on both physical and mental health, it should be given more attention in research for the assessment and treatment of depression and other mental illness in low income countries, especially in Africa.

Conflicts of Interest

Authors declare no conflict of interest.

Ethics Statement

Ethical approval was not needed as this study did not involve humans nor animals.

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