

(REVIEW ARTICLE)



Targeting the female endocannabinoid system: A CAM intervention addressing behavioral nutrition and treating depression in women with T2DM

Clare P. Persad *

Psychology, National University, La Jolla, CA, USA.

GSC Biological and Pharmaceutical Sciences, 2023, 23(03), 128–137

Publication history: Received on 13 April 2023; revised on 25 May 2023; accepted on 27 May 2023

Article DOI: <https://doi.org/10.30574/gscbps.2023.23.3.0203>

Abstract

The following disquisition utilizes the principles of biomolecular psychology to examine the biopsychological efficacy of nutraceutical medications targeting the Female Endocannabinoid System (FECS), particularly concerning Type 2 diabetic (T2DM) women suffering from depression. Theoretical frameworks of psychoneuroimmunology linked with endocannabinoid deficiency theories and behavioral nutrition provide evidence for the efficacious use of Complimentary Alternative Medicine (CAM) interventions and treatments as a preferred option for women diagnosed with T2DM suffering from chronic depression. From a biomolecular perspective, the iatrogenic effects of synthetic drugs have demonstrated profound disadvantages for the female body. Future direction for research and implementation of alternative dietary plans and botanic cannabinoid supplementation for treating depression and other mood disorders associated with the imbalances of the Female Endocannabinoid System is discussed.

Keywords: FECS (Female Endocannabinoid System); Biomolecular Psychology; Psychoneuroimmunology; T2DM (Type 2 Diabetes); Depression; CAM (Complimentary Alternative Medicine).

1. Introduction

An amalgamation of the most current research and past findings provides a theoretical framework for utilizing CAM interventions focused on biological, psychological, and psychosocial factors influencing the behavioral nutrition of adult females diagnosed with T2DM and Depression. A detailed analysis of psychoneuroimmunology and biomolecular psychology depicts the endogenous healing approach of botanic supplements and ayurvedic diets to complement current treatment plans and interventions that use synthetic methods. The adverse effects of synthetic medicines traditionally prescribed to females resulting in iatrogenic ailments, will be discussed from a biomolecular perspective.

1.1. Overview

Women were first permitted as participants in therapeutic clinical studies in 1993, and decades later, they were physiologically and psychologically studied separately from men. This change in research methodology resulted in the FDA acknowledging that gender differences may influence the outcomes of clinical trials analyzing the efficacy of medicines. Due to females' exclusion from clinical trials over centuries, knowledge of female health science needs to be improved. Astonishingly, until 1993 women had not been included in research and scientific tests, decades after the FDA acknowledged the importance of studying females separately from men, as the gender differences in the clinical assessment of medications became more apparent. [1]

Information from the 2022 Centers for Disease Control and Prevention (CDC) reveals that in the United States, 130 million adults suffer from diabetes or prediabetes. Limited socioeconomic status and poor education, specifically among adult females, depict a more significant occurrence of diabetes linked to poverty. Demographically, there are substantial

* Corresponding author: Clare P. Persad

differences among ethnic backgrounds when investigating diabetic cases; American Indian and Alaska Native persons are recorded with the highest percentage (14.5%). Hispanic and non-Hispanic Black individuals are 11-12%, followed by Asian people (9.5%) and Caucasians (7.4%). Additionally, females with an income beneath the federal poverty level had the highest prevalence of diabetes diagnosis. [2]

1.2. Depression and T2DM (ABCS) Management

Type 2 Diabetes Mellitus is more widespread in women than men, manifesting as a greater risk of depression. Psychologically, these impacts may exacerbate unacceptable eating behaviors, raising the probability of T2DM in older females. To prevent complications with the treatment of diabetic patients, it is essential to abide by efficient and effective routines of monitoring hemoglobin A1C levels, blood pressure, and cholesterol levels, and smoking should be prevented (ABCS). The American Diabetes Association (2018) reports that from 2017–2018, U.S. diabetic patients, specifically older females, failed to meet ABCS objectives. [3]

2. How Depression Affects T2DM Patients' Behavior

Management of diabetes is complex and involves continual blood monitoring and abstaining from the intromission of unhealthy foods. Diabetic patients without adequate education and medical, peer, and family support were purported by Kalra et al. to be more susceptible to depression. [4] Prevention or minimizing complications of diabetes treatment entails a strict treatment plan that includes self-management, medication plans, glucose and blood pressure monitoring, and healthy diets customized for diabetic patients. [5] Healthcare professionals treating diabetes must be meticulous about their services, and patients' relationships with healthcare providers must be of quality to avoid poor disease management that often results in comorbidities involving depression and circulatory illness. Substantial research suggests that depression can adversely influence diabetes self-management. [6] Research proves that comorbidities of depression and diabetes drastically boost mortality probability. [7,2] From a biomolecular perspective, there is a bi-directional connection between diabetes and depression, where metabolic biomarkers and inflammation play roles in predicting both diseases.

A Pharmacological study by Bourne and Kenkel [3] supported by an endocrinology study by Kalra et al. (2018) indicates that adult females with diabetes and depression suffer extra daily trials, leading to self-management challenges. [4] These studies describe the well-being of women being impacted more than men with demands on their energy and time spent on numerous responsibilities and duties that are not typically supported, such as caregiving and employment responsibilities. Environmental factors like restricted healthcare and limited access to diabetes-specific treatment programs generate significant trials for good healthcare maintenance. Daily issues adult females encounter with diabetes management adversely affect their moods (loneliness, depression, frustration, anger, and anxiety), attributing to conflicts with their self-management. [8]

3. Depression versus Distress

Untreated depression results in harmful decision-making and risky behaviors, such as smoking, stagnation, and unhealthy food consumption, causing unhealthy weight gain—all life choices that exacerbate depression. [9] Depression decreases functionality, diminishes task accomplishment, and hinders communication skills, thereby generating a more complex process of diabetes management. Typically, the medical community identifies feeling down or blue when referring to "clinical depression"; however, it is complicated for healthcare providers to decipher the differences between clinical depression and emotional reactions to stressful situations as each response differs. [3,9] Healthcare providers must take a holistic look at a patient, carefully seek insight from the patient's feelings and compare it to the environmental factors the patient faces to have an effective diagnosis and treatment process.

Depression is identified as a mental health disorder, and diabetes distress is not considered a mental sickness but instead proposed by scientists to illustrate emotional responses to surviving a life-threatening disease that entails chronic, demanding self-management. Diabetes distress encapsulates an individual's understanding of the difficulties correlated with diabetes. [3,9]

4. Nutritional Issues and T2DM Women with Depression

Recent studies indicate that several dietary compounds and nutrients intensify depressive disorders. [10,11] Particular nutrients affect neurotransmitters tied to depression, enhancing the development of obesity, diabetes, and depression. Logically following the premises of "we are what we eat," scientific studies involving ayurvedic diets have demonstrated success in diabetes management and depressive symptoms. Ayurvedic meal plans such as diabetic-specific vegetables,

fruits, oils, nuts, lean meats, and dairy are linked with reducing depression and healing diabetic symptoms. [12] Western dietary patterns, specifically the intromission of sugary drinks, refined food, processed meats, and high-fatty-based products, are associated with the threat of depression. [13]

5. Factors that Influence Nutritional Behavior

In 1977, George Engel introduced a biopsychosocial model, which offered the theory that illnesses form through a combination of biological factors, for instance, genetic, psychological, and physiological. He purported that psychological factors that promote sickness are rooted in an individual's health beliefs, behavioral patterns, personality traits, and lifestyle (Amsah et al., 2022). [14] He also pointed out that social factors like family connections, socioeconomic status, and social support, when lacking in efficiency, can be responsible for the onset of disease development. (Amsah et al., 2022). The alliance between the physical and mental health of diabetic individuals has been clearly expressed in research by McKenna et al. (2007), principally by socially induced eating disorders and depression, two frequent mental health encounters in women with diabetes. Rahimi et al. (2019) claimed that these difficulties with eating and depression notably impede the achievement of ideal metabolic control. Hence outcomes of the heightened risk of diabetes-related medical complications are evident. Furthermore, statistics investigating triggers to women's emotions confirm that the prevalence of eating disorders directly correlates to gender-related factors, which, compared to men, have been identified as more easily triggered. [15] Socioeconomic factors and adverse life experiences such as poverty, lack of family support, work, and maternal burdens place women at a higher risk of depression than men.

6. Biomolecular Psychological Perspective

Sex-related differences can be found in every aspect of physiological health, in every part of medicine, and in any disease or illness. Still, these differences have proven to be particularly profound in biomolecular psychology. Pharmacological data on outpatients with major depressive disorder between 2001 and 2017, accumulated by Seifert et al., revealed that women are more likely than men to be treated with psychotropic drugs. [16] However, Schwalsberger et al. purported that no evidence-based recommendations for sex-based differences in significant depression exist and that pharmaceutical treatment approaches are sporadically based on trial and error. [17]

Sramek et al. purported a lack of consensus as to whether there are sex-related differences in the effectiveness of antidepressants despite it being well-known that major depressive disorder is more prevalent in women. [18] An analytical study conducted by Kornstein et al. and replicated by Young et al. examined gender differences in responses to a selective serotonin reuptake inhibitor compared to a tricyclic antidepressant in treating chronic depression. [19,20] Both results revealed that the selective serotonin reuptake inhibitor was more efficacious for women, while men were significantly more likely to show favorable responses to the tricyclic antidepressant.

The Kornstein et al. study further revealed that this efficacy diminishes when women enter menopause. [19] This suggests that selective serotonin reuptake inhibitors are more effective when high estrogen concentrations. It additionally means that women's biopsychological reactions are undeniably distinct from males'; therefore, when administering pharmacodynamics and antidepressant pharmacokinetics to female patients, healthcare providers must practice meticulous care and consider female health separately from males. [3,21] Still, Rush et al. research revealed that unrelated to sex, up to 50% of patients do not respond to traditional pharmaceutical antidepressant treatment protocols. [22] This implies a longer infliction duration, with all its associated consequences. It further means that a novel treatment approach is necessary.

Research by Bourne & Kenkel, and LeBlanc et al. disclosed that from a biomolecular psychological perspective, females are more susceptible to developing depressive symptoms due to gender variations in brain compositions, hormonal configurations, neurochemistry, and societal influences. [3,10] This indicates that when recommending antidepressant pharmacokinetics or pharmacodynamics to women, it is crucial to be vigilant and imperative to consider female health independently, as their effects are indisputably different for males. [3,21]

7. Iatrogenic Effects on Female Health

Steed et al. and Deuschle revealed that drugs prescribed to females in Western medicine, particularly when merged with other synthetic drugs similar to antidepressants, cause severe damage to a woman's health, for example, the combination of diabetic pharmacological drugs with female-prescribed drugs like estrogen and birth control. [23,24] This implies that lifestyle alterations and uncompromising duties of self-management might considerably affect the quality of life of diabetic women experiencing depression. Research by Ridosh et al. described diabetic females battling

depression as presenting more indications of barriers to coping with the gravity of their symptoms than others whose spirits remain high. [8] According to the teachings from the biomolecular field of science, all intrusions into the human body are metabolized by the same process. Ingestion and Digestion of natural molecules do not cause sickness in the body to develop as long as it is moderately administered to create balance. [25] However, synthetic molecules like pharmaceutical drugs harm the human body. It has been demonstrated that when the body ingests or digests artificial material, it is analogous to enzymes trying to eat plastic. [26] Due to the human systems' inability to degrade synthetic material, proteins are triggered to store the artificial bits in locations such as the liver, arteries, kidneys, and numerous organs, generating inflammation that expresses itself in either pain or mood disorders like depression. [25]

8. The Female Endocannabinoid System and Psychoneuroimmunology

The female endocannabinoid system (FECS) regulates neurotransmitter activity in the female brain. Trezza and Campolongo defined it as the system in the body responsible for generating homeostasis throughout the other bodily systems by lipid signaling and neuroactive processes. [27] Psychoneuroimmunology connects mood disorders to inflammation in the body, and the female endocannabinoid configurations of operations in limbic segments of the brain are in control of emotional reactions to stress and mood. Studies conducted by Russo and Compton and American offer the theoretical framework of endocannabinoid deficiencies and irrefutable evidence of correlations between serotonin and dopamine levels to depression and anxiety expressions, leading to the premise of management of the female endocannabinoid system in quelling discrepancies related to emotional imbalances by use of phytocannabinoid supplementation. [28,29]

Dantzer illustrated a psychoneuroimmunological methodology established on the continual interfaces of the central nervous system and immune systems employing distinct biomolecular couriers. Biomolecular psychology distinguishes communication of the nervous system by classifying its hormonal and neurotransmitter functions, as opposed to the immune system, which is identified through its utilization of proteins labeled cytokines. [30] Although a diverse number of cytokines have been established through neurological studies, the focus of physiological and psychological stressors that active proinflammatory cytokines have been the main focus in the study of psychoneuroimmunology. [31] Gorman pointed out that not all inflammation manifests in the brain as pathological pain. [32] Later studies demonstrated that brain inflammation, when chronically induced, promotes behavioral symptoms correlated to mood disorders, notably depression. [1]

Furthermore, when increased progressively, various prolonged inflammation types reveal that the mood of the female body is intensely impacted. Ong et al. conducted an emotion diversity and biomarker study of inflammation and demonstrated that systemic inflammation greatly influences mood and increases variety in daily optimistic feelings. In contrast, an improved sense of well-being is associated with enhanced rates of circulation and lowering of inflammation levels. [33]

The study of psychoneuroimmunology is essentially the interaction of processes of the human body's immune and nervous systems, utilizing the comprehension of how the human's physiological and psychological well-being is expressed while combating inflammation. Isung et al. explained that this field of biomolecular exploration is highly complex, with great potential for alleviating chronic depression and mood and autoimmune disorders. [34] The emotional states that constitute everyday life are described by Cohen et al. as highly complex. [35] Rossi et al. purport that traumatic stressors are linked to the inception and prolongation of mood disorders and endocannabinoid deficiencies that manifest as particular ailments and different autoimmune syndromes. [36]

Experiments involving neuroendocrine endpoints historically overshadowed research on the biomolecular psychological perspective of depressive conditions. However, paradigm shifts throughout science made it evident that the immune system is significantly connected to depressive psychophysiology. Additionally, Schiepers et al. hypothesized that the immune system dramatically affects the functional symptomology adjustments associated with depression. [37]

The pathophysiological organizations of chronic depressive conditions are complicated and similar to other psychological disorders. It is doubtful that every case of depression contributes to a similar fundamental mechanism. [38] Limited findings have analyzed immune variations in diabetic patients suffering from depressive ailments. Yet, research studies prove that the immune system performs a vital role in the body's psychopathology and the comorbid psychological signs of depression syndromes. [39]

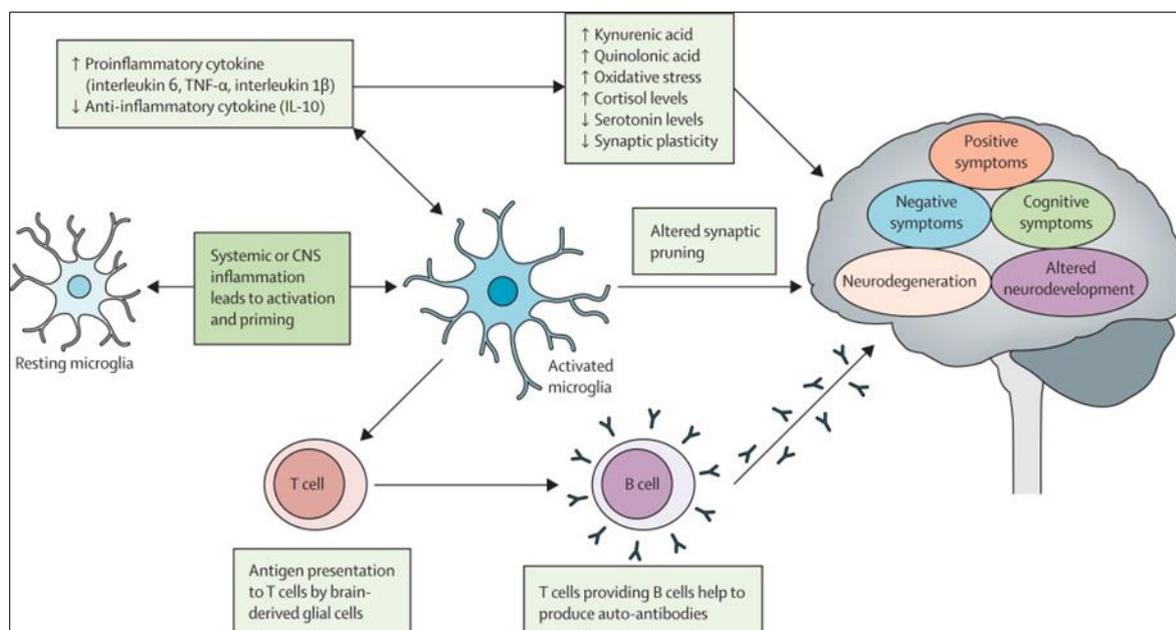


Figure 1 Complex Interactions between the Immune System and the Brain

Courtesy of the following;

Dantzer, R., O'Connor, J. C., Freund, G. G., Johnson, R. W., & Kelley, K. W. (2008). From inflammation to sickness and depression: when the immune system subjugates the brain. *Nature reviews. Neuroscience*, 9(1), 46–56. <https://doi.org/10.1038/nrn2297>.

9. CAM Approach for T2DM and Women with Depression

9.1. Diabetic Mood Enhancement (Nutraceutical Transdermal Patch)

Countless studies portray current pharmacological options for treating depression and diabetic patients as failing to reach optimal levels of success. Paradigm shifts in medical research and globalization have produced newfound knowledge and efforts to seek improved healing methods rather than suppressing symptoms. The study of the Female Endocannabinoid System is a reputable framework for healing mood conditions by endogenous alteration of dopamine and serotonin levels in the female body. [40] Mood enhancement has been proven successful through the cutting-edge nanogold technology applied in manufacturing transdermal medical patches for the intramission of nutraceutical molecules into the bloodstream to mitigate dopamine and serotonin levels. [40] Intramission of botanic cannabinoids that are 100% pure isolated molecules such as CBG, CBD, CNC, and THCV combined with 100% pure natural terpenes such as limonene and myrcene is proven efficacious, generating positive side effects, like inflammation reduction and boosting of the immune system. The ingredients of these nutraceutical transdermal patches consist of 100% plant-based molecules that are required to be third-party lab-tested by the FDA and "Generally Regarded As Safe" (GRAS) by the FDA, and designed for effective treatments of anxiety, immune system deficiencies, depression, blood sugar monitoring, and weight control. [25,28,40]

9.2. Female Endocannabinoid System Balancing with Ayurvedic Diets

As new research and developments arise in a globalized world, medical studies involving ayurvedic practices have spread to the Westernized world. Unique to Western culture, this ancient medical practice has recently emerged in the United States. Complementary and Alternative Medicine (CAM) has become a more popular treatment for chronic illnesses such as diabetes and cardiovascular diseases. Studies show that T2DM is a chronic illness with considerable long-term repercussions for people experiencing the condition and those struggling with access to the failing healthcare system. [3,12,4]

A dire need for nutrition and behavioral modifications is crucial in successful treatment plans designed specifically for healing rather than suppressing symptoms of type 2 diabetic females. A holistic approach is best, especially when considering the female endocannabinoid system and its ability to regulate the rest of the bodily systems through

balancing deficiencies. [12,28] This ancient Indian medicinal practice of Ayurveda primarily utilizes herbal supplements to clean and replenish the body, healing and curing ailments where the symptoms are permanently diminished instead of suppressing them. Ayurvedic treatments designed specifically for healing signs of T2DM aim to maintain hemoglobin A1c (HbA1c) levels in a therapeutic range. [12] However, its approach, when compared to Western medicine, is significantly more effective because it takes into consideration the whole body's functionality and context of balancing life forces or doshas that each individual possesses, which are proven to affect the body through emotions that reveal itself in physical pain, physiological disorders mood disorders or mental disorders. The Female Endocannabinoid System is imbalanced when inflammation results in ailments expressing themselves as pain or mood disorders such as depression and anxiety. [12] The Ayurvedic diet is based on food choices that boost immunity and cleanse and strengthen the system from an endogenous approach, thereby balancing the human system responsible for creating homeostasis in all the other systems of the human body. Specifically, women suffer from mood disorders at a higher level than men, and female patients with diabetes are more susceptible to developing depressive systems. [3,4,28,41] Therefore, using ayurvedic diets to combat these symptoms is another way of balancing the female Endocannabinoid System, eliminating signs of depression, and boosting the immune system.

The AyurVAID clinic in Bangalore, India, successfully featured the Ayurvedic mediation applied to reduce diabetic patients' HbA1c from 11.2 to 5.7 over nine months. The principal technique used in Ayurveda is the supplementation of herbs in diets curtailed for fighting specific ailments and diseases, along with physical and mental exercises guided by and rooted in spiritual practices (Gordon et al., 2019). The herbs proven most beneficial for lessening glucose levels consist of holy basil, Coccinia India, Gymnema Sylvestre, Cinnamomum Tamala, Curcumin, D-400, Eugenia jambolana, botanic cannabinoids, terpenes, Ayush-82, and Momordica charantia. The preparation and intromission of these herbal supplements must be carefully followed in the ayurvedic practices for them to be effective. For example, some herbal formulas are for adequate oral ingestion, while others are for skin absorption. The abhyanga herbs are used in a hot oil massage. In contrast, botanic cannabinoids can be used in tea, inhaled into the respiratory system directly, or rubbed on the skin, and Udvantanam is a powder massaged directly into the skin. [12]

Each herb applied for specific ailments targeting the immune system in Ayurvedic practice is classified with a unique and dominating therapeutic property. The biomolecular mechanisms engaged in the cleansing, strengthening of the immune system, and regeneration of beta cells proposed for the hypoglycemic action of ayurvedic herbs have been notably included in diabetic treatment and depressive treatments. Ayurvedic practitioners have successfully treated diabetic patients by customizing appropriate herbal formulations with ingredients such as *Momordica charantia*, *Pterocarpus marsupium*, and *Trigonella foenum greacum*, along with specific diet and exercise routines (Gordon et al., 2019). Scientific research has designated the most effective plant-based ayurvedic formulas in the treatment of T2DM as, Fenugreek, ginger root, turmeric root, curcumin, bitter melon (*M. charantia*), Indian Kino Tree, Holy basil, Pomegranate, almond, chia seeds, flax seeds, Gymnema, lemon, Tinospora, Margosa Tree, Holy Fruit Tree, garlic, and Ivy Guard (Gordon et al., 2019). Studies have depicted that every herb used in ayurvedic diabetic medical treatments all have a different way of helping reduce symptoms of diabetes and depression. For instance, bitter melon lowers polyuria, to some extent inhibiting renal hypertrophy while reducing urinary albumen secretion. Indian Kino Tree produces a water extract; science has discovered that 400 mg/dL decreases hyperglycemia and insulin levels significantly. The effectiveness of herbal formulations used in ayurvedic treatments is founded based on customization to an individualized host, where each herb has been researched in human and animal experiments that identified specific uses with vastly different properties and the premise of each person having diverse manifestations of the doshas; therefore, the formulas used and dosing is different across patients. [12]

The human body endogenously produces Chromium, an element found in the exact location of the pancreas where insulin is generated. This element is vital in maintaining regular glucose metabolism. Chromium has been demonstrated to benefit insulin production, and some findings have revealed chromium deficiency in diabetic patients. Herbs such as Babbul and Karranj Beej, used in ayurvedic practices, have been found to contain Chromium, which supports glucose metabolism analogous to how insulin synchronizes blood glucose concentrations. [12]

9.3. Psychosocial Aspects of Pharmaceutical and Nutraceutical Interventions of Healthcare

The Pharmaceutical and nutraceutical approaches to cure endocannabinoid deficiency ailments conflict in remarkable ways. The medical system has the easy distribution of synthetic drugs with the advantage of legal claims to FDA consent, but nutraceuticals by law are at a disadvantage from limitations on research and development. [40,24] History has shown that our society has chosen to be a synthetic one and is conditioned to believe "FDA approved" indicates "safe," although this opinion is undertaking modifications as the iatrogenic effects of FDA-approved medications are progressively revealed. [40,24] In contrast to synthetic drugs, the body naturally degrades herbal-based medicines. This gives nutraceutical medicines biological superiority due to limited iatrogenic effects. [42]

Depression can entrap people into engaging in unhealthy lifestyles and poor decision-making, resulting in behavior patterns that result in poor nutrition and suicidal ideation, which can become a domino effect in challenges faced with chronic illnesses such as diabetes. [43] Government sectors must improve the healthcare system to ensure people have proper access to diabetic-specific treatments and communal support, especially targeting populations of adult women in impoverished sectors. [14] Coping mechanisms such as a diet plan and access to healthcare are necessary for treating chronic diseases, and depression enhances the complexity of healing. In preventing iatrogenic effects, healthcare providers must be aware of comorbidity issues and careful when prescribing medicine for interrelated conditions such as diabetes and depression, especially in women. [43] The economic cost of accessing holistic medicine is excessive in Western society, and medical insurance plans do not cover the costs of traditional healing methods included in CAM practices such as Ayurveda treatments. [14]

Limited research indicates that women are more likely to be emotionally triggered than men, implying that females suffer more negative emotions than males and hence a greater risk of developing depression. [3,21] For decades, scientific examinations have overlooked females' health as being distinct, and it is essential to progress with caution concerning female-specific needs and their uniqueness in healthcare. Nutraceutical methodologies used in Ayurveda account for gender differences but are expensive and often difficult to afford, leaving many people without the education or access to complementary approaches.

Educating healthcare professionals and patients, especially females, on the benefits of choosing nutraceutical medications and holistic treatments is challenging due to costs, institutional resistance, and paradigm conditioning of healthcare professionals. The psychosocial conditioning of American society towards artificial and patentable medicines also complicates the understanding and acceptance of natural approaches for healing chronic ailments. Scientists are limited in research, and funding is determined for experiments to be conducted for further knowledge on the effectiveness of healing using nutraceuticals instead of synthetic drugs.

Nutraceutical approaches such as female endocannabinoid system mitigation and CAM interventions that use Ayurveda practices focus on healthcare holistically from a biomolecular perspective. They may effectively treat the root causes of depression in diabetic women (Bies et al., 2003). Healthy ayurvedic diets that supplement botanic cannabinoids and other herbal medicines in quelling female endocannabinoid deficiencies related to diabetes and depression are recommended as safe and efficacious treatment choices. Still, these approaches have not been widespread due to limitations in medical advancements and laws governing the research and development of nutraceuticals.

Future healthcare advancement is paramount, and establishing a healthy routine for patients suffering from chronic illnesses such as diabetes and depression is crucial. Implementing innovative technology to generate effective nutraceuticals comparable to synthetic drugs' effectiveness is a preferred approach to eradicate the iatrogenic effects caused by artificial medicine. In a society that is conditioned to choose synthetic options for suppression of symptoms, challenges to normalize natural remedies for healing lay in the education of healthcare providers and patients, government funding and control of medical practices to include and cover costs of holistic medicines and the governing the development of nutraceuticals medicine through laws that permit the efficacious study.

10. Conclusion

This disquisition explores the use of nutraceutical medications targeting the Female Endocannabinoid System (FECS) to treat depression in Type 2 diabetic (T2DM) women using principles of biomolecular psychology. It discusses the efficacy of Complimentary Alternative Medicine (CAM) interventions and treatments, emphasizing the disadvantages of synthetic drugs for women. The study stresses the need for improved research on female health, given the prevalence of T2DM in women and the impact of depression on self-management. It also explores the influence of nutrition on T2DM and depression, highlighting the success of ayurvedic diets in managing these conditions. This article addresses the interplay between biological, psychological, and social factors that influence nutritional behavior and discusses the iatrogenic effects of synthetic drugs on female health. The role of the Female Endocannabinoid System and psychoneuroimmunology in understanding and managing depression is examined, with a focus on endocannabinoid deficiencies and the potential of phytocannabinoid supplementation. The disquisition concludes by accentuating the need for further research and implementation of alternative dietary plans and botanical cannabinoid supplementation for treating depression and mood disorders associated with imbalances in the Female Endocannabinoid System. Incorporating CAM interventions, addressing gender-specific healthcare needs, promoting preventive measures, and considering the biomolecular perspective, this research has the potential to benefit society in various ways. It offers a more holistic and personalized approach to managing T2DM and depression in women, ultimately improving healthcare outcomes, advancing scientific knowledge, and promoting overall well-being in communities.

Compliance with ethical standards

Acknowledgments

I would like to extend my sincere thanks to my mentor David A. Dawson.

References

- [1] Liu KA, Mager NA. Women's involvement in clinical trials: historical perspective and future implications. *Pharmacy practice*. 2016 Jan-Mar;14(1):708. doi: 10.18549/PharmPract.2016.01.708.
- [2] Centers for Disease Control and Prevention. National diabetes statistics report 2020. U.S. Department of Health and Human Services, CDC. Published 2022. Accessed April 13, 2023. <https://www.cdc.gov/diabetes/library/features/diabetes-stat-report.html>.
- [3] Bourne C, Kenkel L. Treatment of Depression in Women. *Handbook of experimental pharmacology*. 2019;250:371-387. doi: 10.1007/164_2018_163.
- [4] Kalra S, Jena BN, Yeravdekar R. Emotional and psychological needs of people with diabetes. *Indian J Endocrinol Metab*. 2018 Sep-Oct;22(5):696-704. doi: 10.4103/ijem.IJEM_579_17.
- [5] American Diabetes Association. Economic Costs of Diabetes in the U.S. in 2017. *Diabetes Care*. 2018;41(5):917-928. doi: 10.2337/dci18-0007.
- [6] Alexandre K, Campbell J, Bugnon M, et al. Factors influencing diabetes self-management in adults: an umbrella review of systematic reviews. *JBI evidence synthesis*. 2021;19(5):1003-1118. doi: 10.11124/JBIES-20-00020.
- [7] Moulton CD, Pickup JC, Ismail K. The link between depression and diabetes: the search for shared mechanisms. *Lancet Diabetes Endocrinol*. 2015 Jun;3(6):461-471. doi: 10.1016/S2213-8587(15)00134-5.
- [8] Ridosh MM, Roux G, Meehan M, Penckofer S. Barriers to self-management in depressed women with type 2 diabetes. *Can J Nurs Res*. 2017 Dec;49(4):160-169. doi: 10.1177/0844562117736699
- [9] Jeffery A, Maconick L, Francis E, Walters K, Wong IC, Osborn D, Hayes JF. Prevalence and characteristics of antidepressant prescribing in adults with comorbid depression and type 2 diabetes mellitus: A systematic review and meta-analysis. *Health Sci Rev*. 2021 Jun;1:100002. doi: 10.1016/j.hsr.2021.100002.
- [10] LeBlanc EL, Patnode CD, Webber EM, Redmond N, Rushkin M, O'Connor EA. Behavioral and pharmacotherapy weight loss interventions to prevent obesity-related morbidity and mortality in adults: an updated systematic review for the U.S. Preventive Services Task Force. *Agency for Healthcare Research and Quality (U.S.)*; 2018.
- [11] Oluma A, Abadiga M, Mosisa G, Fekadu G, Turi E. Perceived self-efficacy and associated factors among adult patients with type 2 diabetes mellitus at public hospitals of western ethiopia, 2020. *Patient Prefer Adherence*. 2020 Sep 21;14:1689-1698. doi: 10.2147/PPA.S275887.
- [12] Gordon A, Buch Z, Baute V, Coeytaux R. Use of Ayurveda in the Treatment of Type 2 Diabetes Mellitus. *Glob Adv Health Med*. 2019;8:2164956119861094. doi: 10.1177/2164956119861094.
- [13] Jin F, Zhang J, Shu L, Han W. Association of dietary fiber intake with newly-diagnosed type 2 diabetes mellitus in middle-aged Chinese population. *Nutr J*. 2021 Jan 6;20(1):8. doi: 10.1186/s12937-021-00740-2.
- [14] Amsah N, Md Isa Z, Ahmad N. Biopsychosocial and nutritional factors of depression among type 2 diabetes mellitus patients: A systematic review. *Int J Environ Res Public Health*. 2022;19(8). doi: 10.3390/ijerph19084888.
- [15] Rahimi Z, Kooshan M, Akrami R, Rad M. Effect of peer support group on the level of depression in type 2 diabetic patients: A randomized clinical trial. *J Evid Based Care*. 2019;9(3):23-31. doi: 10.22038/EBCJ.2019.14020.
- [16] Seifert, J., Führmann, F., Reinhard, M. A., Engel, R. R., Bernegger, X., Bleich, S., Stübner, S., Rütger, E., Toto, S., Grohmann, R., Sieberer, M., & Greil, W. (2021). Sex differences in pharmacological treatment of major depressive disorder: Results from the AMSP pharmacovigilance program from 2001 to 2017. *J. Neural Transm.*, 128(6), 827-843. <https://doi.org/10.1007/s00702-021-02349-5>

- [17] Schwalsberger K, Reininghaus B, Reiter A, Dalkner N, Fleischmann E, Fellendorf F, Platzer M, Reininghaus EZ. Sex-related differences in the pharmacological treatment of major depression - are women and men treated differently? *Psychiatria Danubina*. 2022;34(2):219-228. doi: 10.24869/psyd.2022.219.
- [18] Sramek, J. J., Murphy, M. F., & Cutler, N. R. (2016). Sex differences in the psychopharmacological treatment of depression. *Dialogues in Clinical Neuroscience*, 18(4), 447-457. <https://doi.org/10.31887/DCNS.2016.18.4/jsramek>
- [19] Kornstein, S. G., Schatzberg, A. F., Thase, M. E., Yonkers, K. A., McCullough, J. P., Keitner, G. I., Gelenberg, A. J., Davis, S. M., Harrison, W. M., & Keller, M. B. (2000). Gender differences in treatment response to sertraline versus imipramine in chronic depression. *The American Journal of Psychiatry*, 157(9), 1445-1452. <https://doi.org/10.1176/appi.ajp.157.9.1445>
- [20] Young EA, Kornstein SG, Marcus SM, Harvey AT, Warden D, Wisniewski SR, Balasubramani GK, Fava M, Trivedi MH, John Rush A. Sex differences in response to citalopram: A STAR*D report. *J Psychiatr Res*. 2009;43(5):503-511. doi: 10.1016/j.jpsychires.2008.07.002.
- [21] Karasu T, Marczylo TH, Maccarrone M, Konje JC. The role of sex steroid hormones, cytokines, and the endocannabinoid system in female fertility. *Hum Reprod Update*. 2011;17(3):347-361. doi: 10.1093/humupd/dmq058.
- [22] Rush, A. J., Trivedi, M. H., Wisniewski, S. R., Nierenberg, A. A., Stewart, J. W., Warden, D., Niederehe, G., Thase, M. E., Lavori, P. W., Lebowitz, B. D., McGrath, P. J., Rosenbaum, J. F., Sackeim, H. A., Kupfer, D. J., Luther, J., & Fava, M. (2006). Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: A STAR*D report. *American Journal of Psychiatry*, 163(11), 1905-1917. <https://doi.org/10.1176/ajp.2006.163.11.1905>
- [23] Steed, L., Cooke, D., & Newman, S. (2003). A systematic review of psychosocial outcomes following education, self-management, and psychological interventions in diabetes mellitus. *Patient Education and Counseling*, 51(1), 5–15. [https://doi.org/10.1016/S0738-3991\(02\)00117-4](https://doi.org/10.1016/S0738-3991(02)00117-4)
- [24] Deuschle M. Effects of antidepressants on glucose metabolism and diabetes mellitus type 2 in adults. *Curr Opin Psychiatry*. 2013;26(1):60-65. doi: 10.1097/YCO.0b013e32835a4206.
- [25] Hill, M. N., & Gorzalka, B. B. (2009). The endocannabinoid system and the treatment of mood and anxiety disorders. *CNS & neurological disorders drug targets*, 8(6), 451–458. <https://doi.org/10.2174/187152709789824624>
- [26] Dawson, D. A. (2018). Synthetic cannabinoids, organic cannabinoids, the endocannabinoid system, and their relationship to obesity, diabetes, and depression. *Molecular Biology*, 7(2), 219. <https://doi.org/10.4172/2168-9547.1000219>
- [27] Trezza, V., & Campolongo, P. (2013). The endocannabinoid system is a possible target to treat both the cognitive and emotional features of post-traumatic stress disorder (PTSD). *Frontiers in Behavioral Neuroscience*, 7. doi: 10.3389/fnbeh.2013.000100
- [28] Russo, E. B. (2016). Clinical endocannabinoid deficiency reconsidered: Current research supports the theory in migraine, fibromyalgia, irritable bowel, and other treatment-resistant syndromes. *Cannabis and Cannabinoid Research*, 1(1), 154-165. <https://doi.org/10.1089/can.2016.0009>
- [29] Compton MT, American Psychiatric Association. Marijuana and mental health. American Psychiatric Association Publishing. 2016.
- [30] Dantzer R. Neuroimmune interactions: From the brain to the immune system and vice versa. *Physiol Rev*. 2018;98(1):477-504. doi: 10.1152/physrev.00039.2016.
- [31] Kelso, A. (1998). Cytokines: Principles and prospects. *Immunology & Cell Biology*, 76(4), 300-317. doi: 10.1046/j.1440-1711.1998.00763.x.
- [32] Gorman JM. Comorbid depression and anxiety spectrum disorders. *Depress Anxiety*. 1996;4(4):160-168. doi: 10.1002/(SICI)1520-6394(1996)4:4<160::AID-DA2>3.0.CO;2-J.
- [33] Ong, A. D., Benson, L., Zautra, A. J., & Ram, N. (2018). Emodiversity and biomarkers of inflammation. *Emotion (Washington, D.C.)*, 18(1), 3-14. <https://doi.org/10.1037/emo0000343>
- [34] Isung, J., Williams, K., Isomura, K., Gromark, C., Hesselmark, E., Lichtenstein, P., Larsson, H., Fernández de la Cruz, Lorena, Sidorchuk, A., & Mataix-Cols, D. (2020). Association of primary humoral immunodeficiencies with

psychiatric disorders and suicidal behavior and the role of autoimmune diseases. *JAMA Psychiatry*, 77(11), 1147-1154.
<http://proxy1.ncu.edu/login?url=https://search.ebscohost.com/login.aspx?direct=true&db=edo&AN=146870078&site=eds-live>

- [35] Cohen S, Janicki-Deverts D, Doyle WJ, Miller GE, Frank E, Rabin BS, Turner RB. Chronic stress, glucocorticoid receptor resistance, inflammation, and disease risk. *Proc Natl Acad Sci USA*. 2012;109(16):5995. doi: 10.1073/pnas.1118355109.
- [36] Rossi, S., Motta, C., Musella, A., & Centonze, D. (2015). The interplay between inflammatory cytokines and the endocannabinoid system in the regulation of synaptic transmission. *Neuropharmacology*, 96, 105-112. doi:10.1016/j.neuropharm.2014.09.022
- [37] Schiepers, O. J., Wichers, M. C., & Maes, M. (2005). Cytokines and major depression. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, 29(2), 201-217.
- [38] Leonard, B. E., & Myint, A. (2009). The psychoneuroimmunology of depression. *Human Psychopharmacology: Clinical & Experimental*, 24(3), 165-175. <https://doi.org/10.1002/hup.1011>
- [39] Perrin, A. J., & Pariante, C. M. (2020). Endocrine and immune effects of non-convulsive neurostimulation in depression: A systematic review. *Brain Behavior and Immunity*, 87, 910-920. <https://doi.org/10.1016/j.bbi.2020.02.016>
- [40] Jeong, W. Y., Kwon, M., Choi, H. E., & Kim, K. S. (2021). Recent advances in transdermal drug delivery systems: A review. *Biomaterials Research*, 25(1)<https://doi.org/10.1186/s40824-021-00226-6>
- [41] O'Llenecia S. Walker, Holloway AC, Raha S. The role of the endocannabinoid system in female reproductive tissues. *J Ovarian Res*. 2019 Jan 22;12(1):1-10. doi: 10.1186/s13048-018-0478-9. PMID: 30669951; PMCID: PMC6344999.
- [42] Dawson, D. A., & Persad, C. P. (2022). Targeting the endocannabinoid system in the treatment of addiction disorders. *GSC Biological and Pharmaceutical Sciences*, 19(02), 064-074. <https://doi.org/10.30574/gscbps.2022.19.2.0175>.
- [43] Whiteford, H. A., Harris, M. G., McKeon, G., Baxter, A., Pennell, C., Barendregt, J. J., & Wang, J. (2013). Estimating remission from untreated major depression: a systematic review and meta-analysis. *Psychological medicine*, 43(8), 1569–1585.

Authors short Biography



Clare Petal Persad is a highly decorated United States retired Naval Supply Corps Officer, a passionate scholar-professional researcher, scientist, and serial entrepreneur. She is a doctoral candidate at National University studying Biomolecular Psychology with a concentration in health psychology (Ph.D.). She has a master's in global business (MBA) from National University, where she received high honors and recognition as the only student in 2014 to research the Endocannabinoid System as an endogenous way of healing.