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Exploring the Link between Stress, Gut Health, and Medicinal Plants in Disease Management

Arionget Jemima

Department of Pharmacoepidemiology Kampala International University Uganda
Email: jemima.arionget@studwc.kiu.ac.ug

ABSTRACT

This study explores the complex and bidirectional relationship between stress, gut health, and the therapeutic use of medicinal plants in the management of stress-related diseases, including cancer and inflammatory bowel disease (IBD). Chronic stress has been found to disrupt gut homeostasis, increase intestinal permeability, and alter the microbiome, leading to a cascade of immune and metabolic dysfunctions. This review outlines the physiological stress responses and their interaction with the hypothalamic-pituitary-adrenal (HPA) axis, highlighting the role of the gut-brain-microbiome axis in disease progression. Furthermore, the study investigates the pharmacological potential of medicinal plants with anti-inflammatory, anxiolytic, and antioxidant properties, such as *Psidium guajava*, *Mentha piperita*, and *Curcuma longa*, in modulating gut health and reducing stress-induced disorders. Drawing from emerging clinical evidence and traditional medicine, the paper emphasizes how botanical therapies can be integrated into holistic approaches for managing complex diseases and improving patient quality of life.

Keywords: Chronic stress, Gut-brain axis, Gut microbiota, Inflammatory bowel disease (IBD), Hypothalamic-pituitary-adrenal (HPA) axis, Medicinal plants, Phytochemicals, Intestinal permeability.

INTRODUCTION

Cancer and inflammatory bowel disease (IBD), which encompasses conditions such as Crohn's Disease (CD) and Ulcerative Colitis (UC), unfortunately afflict millions of individuals around the globe. These debilitating conditions significantly diminish the overall quality of life and contribute to increased mortality rates among those affected [1-4]. Despite the extensive studies conducted on these diseases, as well as other ailments related to the gut, effective long-term strategies designed to mitigate these pathologies remain woefully underdeveloped. At present, available therapies primarily focus on delaying disease progression or alleviating symptoms experienced by patients [5-6]. However, it is concerning that patients often find themselves facing a limited lifespan in the years following their diagnosis. This alarming reality underscores the urgent need to thoroughly explore alternative or adjunctive treatments that have the potential to noticeably improve clinical outcomes for those suffering from these debilitating diseases. In light of the recent advancements made in understanding the intricate gut-brain-microbiome axis, this chapter will investigate the promising potential of medicinal plants and plant-derived compounds to serve as therapeutic agents in the management of these complex ailments [7-9].

Understanding Stress

Stress is a significant concern across various research areas, often linked to health issues. Mental illnesses, chronic pain, and other diseases are prevalent workplace health challenges. Abnormal conditions that require diagnosis and treatment can be more distressing than typical mental disorders, with stress

continuing to affect life even after hospital discharge [10-14]. Effective handling of workplace health challenges is crucial for achieving societal sustainability. Stress connects to various issues, indicating its relevance to societal well-being. It relates to aging and anxiety, with environmental stressors such as job insecurity and financial downturns leading to both mental and physiological problems [15-18]. Work-related stress remains a major factor in environmental challenges and is associated with diseases like prostate cancer and heart issues due to social isolation. Stress can be viewed as a state, stimulus, and response. It represents a bodily state where tension disrupts physiological balance, serves as a stimulus provoking this tension, and denotes the physiological response to stressors. This understanding aids organizations in assessing stressors and their health impacts. Stress research can investigate the state independently, explore environmental contents that provoke the state, or analyze responses to stimuli. Workplace stress factors can be categorized into internal and external stressors, initiating behavioral and physiological responses when perceived as disruptive [19-23].

Definition And Types Of Stress

When an individual perceives a potentially harmful event as stressful, they undergo physiological and metabolic alterations collectively called the “stress response”. Stress may be acute or chronic and can include traumatic events, maltreatment, neglect, or poverty experienced during early child development. It can also take the form of emotional inferiority, conflicts, injurious accidents, bereavement, burnout, or other life crises experienced by adults [24-28]. Stress response is not uniform but varies markedly among individuals, affecting various physiological systems. Effects depend on the duration of stress and whether the stressor is ongoing or intermittent. Importantly, the stress response also depends on the type of stress: physical, psychological, or psychosocial. Almost all known stressors cause physiological, metabolic, and immunological changes that are produced, at least in part, by changes in activity of the sympathetic nervous system, hypothalamic-pituitary-adrenal (HPA) axis, and the immune system [29-34]. The HPA axis drives the synthesis and release of corticosteroids, whereas the sympathetic nervous system orchestrates a ‘fight or flight’ response that ramps up physiological functions necessary for responses to stress. In humans, the sympathetic nervous system also activates the hypothalamic-pituitary-gonadal and the hypothalamic-pituitary-thyroid axes. Immune compounds that mediate or modulate stress functions are many and varied. Cytokines affect inflammation and the actions of immune cells, whereas acute phase proteins act systemically, and local effects may be mediated by neutrophils, mast cells, eosinophils, and macrophages [35-39].

Physiological Responses To Stress

From an evolutionary perspective, responses to stress coordinate physiological demands to manage threats to health and survival. The stress response system modulates locally at mucosal surfaces to maintain barrier function. The higher vertebrates developed the hypothalamic-pituitary-adrenal (HPA) axis to amplify an organism-wide response to stressors. Activation of the HPA axis has both a circadian rhythm and a dynamic pattern in response to stressors [40-42]. The gut microbiota can influence the development and regulation of the HPA axis throughout the lifespan. Individuals with compromised sanitation and limited access to healthcare can be subject to sustained activation, resulting in “chronic, uncontrollable” stress. Sustained HPA axis activation has detrimental consequences to health and exerts a powerful influence on the composition of the gut microbiota. Shifts in microbial composition and metabolite production can cause fibrosis and alter immune functions, impacting host health. Stress can become disruptive to host physiology through a wide range of mechanisms, including gut dysmotility, altered immune responsiveness, increased intestinal permeability, compromised intestinal barrier function, increased levels of visceral sensitivity, changes in intestinal secretion, and altered gut microbiota composition [7-8].

Chronic Stress And Its Effects

Stress refers to an organism’s response to external influences, causing physiological changes that alter homeostasis. An organism’s response to these external stimuli can be classified as either distress or eustress; the former is detrimental, the latter is beneficial [10-14]. Chronic stress is often categorized as distress because, if prolonged, it adversely affects the overall health and well-being of an organism. Physiological reaction to stress involves the networks of innate and adaptive immunity as indicated by a feedback relationship between the immune system and the stress system of the body (a complex network involving the autonomic nervous system and the hypothalamic-pituitary-adrenal (HPA) axis). The stress system recognizes the activation of inflammatory pathways upon exogenous stimulation and the resulting increase in pro-inflammatory cytokines, which consequently modulates the different areas of the central

nervous system (CNS) to produce specific behavioral effects. Dysregulation of the CNS together with that of the gut microbiota results in increased vulnerability to chronic stress and the development of stress-related diseases such as irritable bowel syndrome and ulcerative colitis [9-10].

Gut Health Overview

The human gastrointestinal tract serves as a vast and remarkably intricate ecosystem, home to a diverse community of microorganisms, collectively known as the gut microbiota. This fascinating and complex community encompasses over 1,000 different species along with more than 7,000 distinct strains of these microorganisms [12-15]. These microbes play essential roles in maintaining gut health, as they are integral to the host's physiology, metabolism, and overall well-being. A person is typically regarded as having a healthy gut when they consistently experience normal bowel movements; these movements should be free from issues such as diarrhea and constipation. Furthermore, the distinct characteristics of the stool are also critical indicators of gut health; for instance, it should possess an appropriate odor and a healthy color. A stool that is considered healthy is usually observed to be yellow, soft, and non-sticky. These particular parameters can serve effectively as reliable indicators of gut health, reflecting the complex and dynamic interplay between the host and its diverse microbiota. The relationship between humans and their gut microbiota is a topic of ongoing research and has profound implications for understanding various health conditions [11-12].

Medicinal Plants And Their Role

Medicinal plants protect the digestive system from stress-related gastrointestinal diseases and are valued for their low toxicity and historical acceptance. They contain phytochemicals like terpenes, phenolics, and alkaloids, offering antispasmodic, cytoprotective, and anti-inflammatory effects [15-19]. In the Mediterranean, plants like *Olea europaea* and *Rosmarinus officinalis* target inflammatory processes. Bioactive molecules with anxiolytic effects, including pomegranate, lavender, hops, and valerian, have been widely studied. Pomegranate's phytochemicals—anthocyanins, flavonoids, tannins, and organic acids—combat oxidative stress and inflammation, which are crucial in digestive diseases, causing mucosal damage. Traditionally, these plants are consumed raw or dried to minimize harmful microorganisms, but bacterial strains associated with human pathogens have been found, particularly in oregano. While these bacteria can aid plant growth, ingestion may lead to infections. Extracts from Chinese medicinal plants show effectiveness against pathogens like *Staphylococcus aureus*, supporting traditional medicinal uses. Similarly, Mexican plants have demonstrated activity against multidrug-resistant pathogens. The medicinal plants and their microbiomes offer an untapped resource of bioactive compounds for applications in medicine, agriculture, and pharmaceuticals, warranting further investigation [20-25].

Interconnection Between Stress And Gut Health

There is substantial evidence linking stress to the gut, significantly affecting the gut barrier, microbiome, and its metabolic environment. Stress accounts for the impact of the microbiome and gut health on mental states like anxiety and depression, applicable to various stress types [26-30]. This connection has historical roots in physiology, as the definition of stress emerges from the gut and hypothalamic axes. The gut mediates allostatic load and dysfunction during chronic stress, with the brain-gut axis crucial for regulating gastrointestinal functions. Communication pathways integrate gut functions with metabolic and reproductive needs, as well as stress responses. Beyond homeostasis, gut-to-brain signals also affect mood, motivation, and cognitive processes. Main signaling occurs in interconnected brain areas, such as the brainstem and hypothalamus, influenced by gut microbiota that impact brain-gut interactions. Research shows that short-term stress modifies gut microbial composition, affecting stress responses, brain function, and anxiety-like behaviors. Chronic stress models display altered brain functions and behavioral issues akin to a dysfunctional brain-gut axis. Changes in caecum microbial composition relate to increased pro-inflammatory signals and harmful metabolites, indicating the microbiome's role in stress-related disorders like depression [31-35].

Medicinal Plants Targeting Gut Health

Mediterranean herbal active compounds demonstrate notable anti-inflammatory and antioxidant effects that are highly relevant to various gastrointestinal disorders and issues. Psychological stress plays a significant role in disrupting gut homeostasis through a range of mechanisms that prominently involve corticotropin-releasing hormone and mast cells [36-40]. These disruptions lead to an increased susceptibility to numerous digestive diseases that can severely affect an individual's quality of life. Certain specific bacterial strains have been shown to positively influence overall mental health and effectively modulate gastrointestinal dysfunction that is induced by stress. This beneficial effect is mediated through

several complex pathways, which include the activation of the vagus nerve, the production of microbial metabolites, and the nuances of enteroendocrine signaling. Moreover, phytochemicals that are derived from medicinal plants that have relevance to stress-related gastrointestinal diseases—including well-known species such as *Psidium guajava*, *Mentha piperita*, *Curcuma longa*, and *Panax quinquefolius*—exert significant therapeutic activity. This activity is achieved through complementary mechanisms that include robust anti-inflammatory and antioxidant activities, which collectively contribute to the alleviation of stress-induced gastrointestinal issues [41-42].

Case Studies And Clinical Trials

Chronic stress stands as a significant contributing factor in the development and progression of various diseases. Individuals who endure prolonged stressors typically find themselves more susceptible to a range of health issues, particularly infectious diseases, autoimmune disorders, and neurodegenerative pathologies. There is a rising body of evidence that supports the therapeutic potential of medicinal plants to enhance overall health by leveraging the complex interactions along the microbiota-gut-brain axis. This axis offers a promising target for interventions aimed at improving the health of the microbiome, alongside enhancing neurological and gastrointestinal well-being. By delving into and investigating the intricate interactions between herbal medicine and the gut microbiota, we can unlock valuable insights into how complementary and alternative medicine effectively modulates the microbiome and subsequently influences host physiology. Such understanding has the potential to contribute to the reduction of the onset of various pathologies that are associated with long-term stress exposure. This report endeavors to provide a comprehensive and detailed outline of the medicinal plants that have demonstrated significant impact on the gut-brain axis and may thereby serve as effective tools in the modulation of disease outcomes [19-20].

Practical Applications In Disease Management

Dyspeptic disorders are frequent in patients infected with *Helicobacter pylori* (*H. pylori*) or other microorganisms that perturb the normal gut flora. The infection is closely linked to the development of gastritis and peptic ulcers and also correlates with increased risk of gastric mucosa-associated lymphoid tissue lymphoma and adenocarcinoma. The key virulence factor associated with gastroduodenal disease is the bacterial oncoprotein CagA. Gut dysbiosis can induce health problems such as anxiety, depression, and irritable bowel syndrome (IBS). Several phytochemicals that regulate microRNAs and the gut microbiome might be useful in colorectal cancer treatment. Effective pacification of stress and inflammation is important to prevent the initiation of stress-related diseases such as Alzheimer's disease. A variety of medicinal and aromatic plants can be effectively applied to combat stress and treat related ailments and infections. Stress is a worldwide problem. Persistent stress leads to oxidative damage affecting various bodily organs through the release of stress hormones. Many disorders, like gastrointestinal diseases, cardiovascular diseases, and diabetes, are linked to oxidative stress. Because of the side effects associated with chemical drugs, researchers are interested in herbal drugs. Extracts from many plants have been shown to effectively treat diseases and their stress-related complications [21-22].

Future Directions In Research

Although initial breakthroughs have recently been achieved in revealing the potential of medicinal plants as complementary agents in reducing psychological and physiological stress effects in several stress-related musculoskeletal inflammation pathologies, promising new research directions remain unexplored. For example, in Sudha et al.'s study, only skeletal muscle inflammation of stress-linked disorders was focused on, but many other conditions, such as rheumatoid arthritis and psychotic disorders that belong to this group, need to be addressed, particularly in identifying common biological markers to elucidate the involved complementary mechanisms. Furthermore, research should focus on exploring how medicinal plants can contribute to the prevention of musculoskeletal disorders other than their simple alleviation, with emphasis on safeguarding against maladaptive tissue remodelling, which often leads to the permanent loss of tissue and joint function, increasingly reported not only in rheumatoid arthritis and psychotic disorders but also in osteoporosis and chronic back pain. In addition, the narrowing role of gut microbial mediators has been introduced, but the responsible metabolic pathways still require thorough investigation, which will impact pharmacotherapeutic efficacy when administering medicinal plants or biologically active principles thereof. Further exploitation of the health-promoting benefits of medicinal plants and their derived agents could provide a sustainable business model that contributes to alleviating the financial burden on individuals and healthcare systems around the world, while simultaneously addressing algia related to stress-linked musculoskeletal inflammatory syndromes [23-24].

CONCLUSION

The intricate interplay between stress and gut health forms a cornerstone in understanding the onset and progression of various chronic diseases, particularly gastrointestinal disorders and neuroinflammatory conditions. This review underscores the significance of the gut–brain–microbiome axis in mediating the physiological effects of stress and its implications on disease management. Medicinal plants offer a promising, low-toxicity alternative or adjunctive therapy due to their rich phytochemical composition and multifaceted mechanisms of action, including anti-inflammatory, antioxidant, and anxiolytic properties. By modulating microbial composition, restoring intestinal barrier integrity, and influencing stress-response pathways, these botanicals emerge as vital tools in the therapeutic arsenal against stress-related diseases. Future research and clinical trials are imperative to standardize their use and further validate their efficacy within integrative medical frameworks.

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