Potential therapeutic application of probiotics in the treatment of neuropathic pain: A mechanistic aspects of brain-gut axis

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ABSTRACT

The “gut-brain axis” or “brain-gut axis” communication mechanism has a bidirectional approach because it depends on showing top-down or bottom-up channels to function. It is one of the few systems in the body that combines neuronal routes with humoral pathways, which include cytokines, hormones, and neuropeptides as chemical messages. It was also discovered to be diverse because it contains spinal, vagus, sympathetic, and intestinal nerves. The role of microbes as signaling agents in the gut-brain axis has been proven by the most recent research, which is primarily based on animal models. Probiotics are living bacteria that improve one’s health when ingested in large enough doses. Gut microbes are suspected to play a role in a variety of psychiatric disorders, making them a potential therapeutic target. The stomach and the brain are linked via a two-way communication pathway called the microbiota-gut-brain axis. Current interventional research on probiotics and the gut-brain axis has been evaluated for its findings in the treatment of depression, anxiety, and schizophrenia. Neuropathic pain is brought on by a lesion or injury to the nerve system, which is further demonstrated by a malfunction of the somatosensory system. Such a developed form of pain affects both peripheral and central nervous system neurons. According to research, probiotics can enhance the gut’s dynamic environment and are good for both the gut and the brain. Therefore, the focus of this review is on how probiotics, the microbiota-gut-brain axis, and the gut-brain axis relate to neuropathic pain.

Keywords: neuropathic pain; allodynia; hallmarks; probiotics; gut; brain

1. Introduction

Neuropathic pain

The somatosensory nervous system can become damaged or ill in the peripheral or central nervous system, leading to neuropathic pain. It affects about 20% of patients, and is a chronic condition brought on by diseases or lesions of the somatosensory nervous system[1]. Neuropathic pain accounts for 40% of patient visits to primary care doctors annually, and 20% of patients report having pain that lasts longer than six months. Unwanted effects that are perceived as “pain” by our senses and emotions might be managed or really cause tissue damage. George Riddoch, an English neurologist, wrote in a classic study from 1938 that “pain is periodically experienced in healthy life in many circumstances and it acts as an indicator or signal of development of discomfort. This pain remains inactive in normal condition. However it is an alarm of vigilance[2,3]. Our sensory and emotional systems perceive
unfavorable effects that are deemed to be “pain” and which are either tolerable or actually cause tissue damage. This situation has an occurrence of 7%–10% in the world population[2]. The ability to feel pain plays a protective role by alerting us to impending or actual tissue damage and inducing coordinated reflex and behavioural actions to keep it to a minimum. Only uncontrolled or harmful noxious stimuli that activate high threshold nociceptor central sensory neurons typically cause pain to be felt[4,5].

Peripheral neuropathic pain demonstrates an instinctive pain or pain hypersensitivity elicited by using various stimulus. Once the damage of tissue takes place causes alterations in sensory neurons[5]. As per the International Association for the Study of Pain (IASP) observed that the neuropathic pain is begins with the disturbance, mismanagement and major lesions in anxious/nervous system[4,6]. According to IASP 7%–8% of adults are suffering from chronic neuropathic pain. Muscle weakness, hyperalgesia, dysesthesias are the symptoms of neuropathic pain[7,8]. Peripheral and central nervous systems have somatosensory pathways and the lesions produced in it due to tissue trauma, surgery, metabolic disorders like diabetes, and human immunodeficiency virus (HIV) causes the development of neuropathic pain[4,8]. Many of the researchers conveyed that the occurrence of neuropathic pain is normal in the today’s population which also impacts on social level as well[9].

Peripheral nerves may cause pain which is affected by trauma and disease which leads to nerve damage[9]. Neuropathic pain is irritating to individual who shows an increased sensitivity to feeling pain and an extreme response to pain (hyperalgesia) and pain due to a stimulus that does not normally provoke pain it may considered as innocuous stimuli as painful (allodynia)[10]. The Vagus Nerve: Feedback from the gastrointestinal end is transmitted by afferent spinal and vagal sensory neurons to the brain stem, which then triggers the limbic system and hypothalamus (responsible for the regulation of emotion, among other functions)[11]. In recent years, there has been an increased interest in improving the accuracy of assessments for neuropathic pain. This is not only because symptoms and signs can provide insight into underlying mechanisms, but also because there is a need for measures of treatment response that may be more responsive than ratings of general pain intensity. Despite various symptoms and signs being considered characteristic of neuropathic pain, there have been few studies that have systematically compared pain quality in patients with neuropathic and non-neuropathic pain syndromes[12,13].

Despite the dearth of clinical trials, new uses for probiotics have emerged as a result of the academic community’s intense interest in their study. Recently studies have also presented an assertive correlation.
between gut microbiota and pain modulation. Therefore, the current work encourages the development of research to examine the advantages of probiotics and their therapeutic application in neuropathic pain conditions.

1.1.1. Causes of neuropathic pain

The major cause of development of Neuropathic pain is due to differ in geographical condition. Various infectious diseases affecting most of the countries are like HIV\textsuperscript{[14,15]}, leprosy\textsuperscript{[16]}, trauma (like; due to loss or removal of body parts)\textsuperscript{[17]}, radiculopathy (which is a condition related to spinal cord, which leads to weakness, numbness, pain and tingling sensation)\textsuperscript{[18]} these are the common causes of neuropathic pain.

Several types of neuropathic pain conditions can be problematic for individuals (Table 1). Examples of such conditions include postherpetic neuralgia, painful diabetic neuropathy, and central post-stroke pain. These conditions can cause a range of symptoms, including chronic pain, numbness, tingling, and burning sensations, which can significantly impact an individual’s quality of life\textsuperscript{[12]}. There are various drugs that can develop neuropathic pain condition to the individuals (Figure 2).

<table>
<thead>
<tr>
<th>Condition</th>
<th>Epidemiology</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral neuropathic pain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radiculopathy</td>
<td>37%, prolonged low back pain</td>
<td>[19,20,21]</td>
</tr>
<tr>
<td>Polyneuropathy Postherpetic neuralgia</td>
<td>16%, diabetes mellitus</td>
<td>[22]</td>
</tr>
<tr>
<td>Postsurgical neuralgia</td>
<td>26%, type2 diabetes; 8%, herpes zoster; ~30%–40% breast cancer</td>
<td>[23]</td>
</tr>
<tr>
<td>Nerve trauma</td>
<td>5%, trigeminal nerve injury</td>
<td>[24]</td>
</tr>
<tr>
<td>Entrapment neuropathy</td>
<td>Not known</td>
<td>[25]</td>
</tr>
<tr>
<td>Trigeminal neuralgia</td>
<td>Incidence of 27/100,000 person-yr.</td>
<td>[24,26]</td>
</tr>
<tr>
<td>Central neuropathic pain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>8%, stroke</td>
<td>[26,27]</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>28%, multiple sclerosis</td>
<td>[28]</td>
</tr>
<tr>
<td>Spinal cord injury</td>
<td>67%, spinal cord injury</td>
<td>[29]</td>
</tr>
<tr>
<td>Phantom limb pain</td>
<td>Incidence of 1/100,000-yr.</td>
<td>[26]</td>
</tr>
</tbody>
</table>

1.1.2. Hallmarks of neuropathic pain and diagnosis: A basic for extensive research

The role of signs and symptoms helps to figure out pathophysiological mechanisms of neuropathic pain and receives expanded interest for the research\textsuperscript{[30]}. It is important to differentiate different types of pain.
which include stimulus-evoked and spontaneous pain. Spontaneous pain is present in the absence of any stimulation, and it can be both continuous and intermittent\(^\text{(31,32)}\). More than one type of symptoms are described by the patients about spontaneous pain and they are of different quality which include burning, vibrations, and tingling kind of sensations. Hence, such pain generally occurs to them all of the time. This pain continuously increases if not treated properly in terms of intensity\(^\text{(43)}\). In addition to this, in patients of continuous and stimulus-evoked pain, dysesthesias and paresthesia are reported frequently which is unpleasant abnormal sensations and abnormal sensations. These characteristics hallmarks of neuropathic pain may manifest as itching, numbness, tingling, and pins-and-needles, etc.

The diagnosis of NP is based mainly on experience, physical tests, and clinical assessments. In 2008, IASP released specific diagnostic criteria which show that neuropathic pain is present when

- Pain has a neuroanatomically possible distribution (under a peripheral or central interior or representational territory).
- A lesion or underlying disorder that can affect the somatosensory nervous system is indicated in history.
- Both conditions (1) and (2) have been demonstrated either clinically or ancillary testing.

The third criterion involves various examinations, such as standard electromyography, standardized sensory assessments, brain and/or spinal cord imaging, nerve or skin biopsies which can be used to recognize and classify the possible underlying neurological lesions\(^\text{(33–35)}\). In addition burning, prickling, and tingling along with normal pain are the most significant descriptors for assessment of neuropathic pain as they distinguish neuropathic pain from nociceptive pain up to large extent\(^\text{(38)}\).

Screening tools have been designed in a very simple manner to provide valuable new information on neuropathic pain and help clinicians (doctors, pharmacists, dentists, and nurses) to identify neuropathic pain easily. Such tools are essentially created and validated as questionnaires using various specific verbal pain descriptors, such as burning, prickling, tingling, needling, and pins. Over the 15 years, many of the screening tools have been developed including Michigan Neuropathy Screening Instrument, Neuropathic pain Scale, Neuropathic pain Questionnaire, Neuropathic pain Symptom Inventory, etc.\(^\text{(37–39)}\) In Germany, three-quarters of clinicians use Pain Direct for the identification of neuropathic pain\(^\text{(40)}\). In countries like India, Australia and China, most clinicians love to use Leeds Assessment of Neuropathic Symptoms (LAANS) as a screening tool for diagnosing neuropathic pain\(^\text{(41,42)}\).

The McGill Pain Questionnaire (MPQ) is a commonly used tool for assessing the quality and intensity of a patient’s spontaneous pain. It includes a range of sensory, affective, and evaluative descriptors of pain that can be used to better understand the patient’s experience. The use of the MPQ and other assessment tools can help clinicians develop more targeted treatment plans for patients with neuropathic pain\(^\text{(43,44)}\). Subsequent studies examining the use of the McGill Pain Questionnaire (MPQ) have demonstrated its ability to differentiate between various types of pain. For example, MPQ has been shown to discriminate between trigeminal neuralgia and atypical facial pain, as well as painful diabetic neuropathy and non-neuropathic leg or foot pain. The questionnaire has also been used to differentiate between different types of peripheral neuropathic pain and persistent benign pain. In addition, the MPQ has been used to distinguish individuals with chronic pain following a complete spinal cord injury from those with partial injury. These findings highlight the utility of the MPQ in providing more accurate diagnoses and targeted treatments for patients with different types of pain\(^\text{(45–47)}\). Recent study on animal about the partial nerve injury states that at the site of injury along the peripheral leads to sensory nerve is certainly a necessary factor in the manifestations of neuropathic pain\(^\text{(48,49)}\).

An important diagnostic feature of neuropathic pain is the presence of a mixed peripheral nerve with a cutaneous branch or a central somatosensory pathway involvement. In such cases, there is almost always an area of abnormal sensation, and the patient’s maximum pain is coextensive with or within an area of sensory
deficit. This feature is significant in diagnosing neuropathic pain. The sensory deficit typically affects noxious and thermal stimuli, indicating damage to small-diameter afferent fibers. Therefore, clinicians must perform careful sensory testing to assess the quality and extent of sensory loss and to evaluate the pain distribution accurately. This information can help in developing more targeted treatment plans for patients with neuropathic pain. In addition to negative somatosensory signs, which indicate a deficit in function, positive symptoms are also characteristic of neuropathic conditions. Paresthesia is a burning or prickling feeling which is usually painless and described as tingling or numbness, skin crawling, or itching. Painful positive signs include spontaneous ongoing pain and spontaneous shooting, electric-shock-like sensations.

Many patients with neuropathic pain also experience evoked types of pain, which are characterized by several sensory abnormalities and may be adjacent to or intermingled with skin areas of sensory deficit. Hyperalgesia is one such evoked type of pain and is defined as an increased sensitivity to pain and an extreme response to pain, such as that caused by a pinprick.

1.1.3. Treatment of neuropathic pain

Antidepressants, antiepileptics, opioids, and antiarrhythmic drugs are commonly utilized in the treatment of neuropathic pain.

**Antidepressants**: Antidepressants and anticonvulsants are used for the treatment of different condition. Tricyclic antidepressants are used for the treatment of diabetic’s neuropathy. It inhibits the uptake of serotonin and noradrenaline which is balanced by taking drugs like amitriptyline, imipramine and clomipramine. The reuptake of serotonin inhibition is used by the compound itself while the reuptake of noradrenaline inhibition is by their respective metabolite’s nortriptyline, desipramine and desmethylclomipramine. Tricyclic antidepressants, including tertiary amines and secondary amines are commonly recommended to treat neuropathic pain. However, some studies suggest that these drugs may not be effective in treating neuropathies if the patients have critical kind of suffering. In a patient of HIV, cancer, and chronic lumbar root pain these conventional used amines are not a good approach to treating neuropathic pain. It is also very important to consider serotonin syndrome. Tricyclic antidepressants are used in this case more diversely because it is responsible to act on various receptors. These receptors are alpha-adrenergic, histaminergic (H1), and muscarinic cholinergic receptors. They also have N-methyl-D-aspartate (NMDA) antagonistic effects and can block sodium and voltage-gated calcium channels.

**Gabapentin and pregabalin**: Pregabalin and gabapentin are both successful in treating neuropathic pain. These medications diminish calcium influx into neurons and block the release of neurotransmitters like...
substance-P, glutamate, and norepinephrine because they have an affinity for the voltage-gated calcium channel’s 2 subunits. While both gabapentin and pregabalin are effective in treating neuropathic pain, only pregabalin has been approved by the Food and Drug Administration (FDA) for the treatment of both diabetic peripheral neuropathy and post-herpetic neuralgia (PHN). But gabapentin has been found to be ineffective in treating painful neuropathy caused by chemotherapy. Compared to gabapentin, pregabalin is more effective at lower doses. The effective dose range for pregabalin is 150–600 mg/day, whereas for gabapentin. It is 1800–3600 mg/day. It takes about 2 weeks to observe the effects of pregabalin. Some common side effects of pregabalin include dizziness, somnolence, peripheral edema, weight gain, and dry mouth.

Lamotrigine: It is effective for the treatment of neuropathic pain which starts from HIV, central stroke pain, and spinal injury patients. Its side effect is skin rash which frequently arrives. The side effects are minimized by taking a starting dose as low as 25 mg/day and increasing it slowly every week up to a maximum of 400 mg/day.

Opioids: The effect of opioids in the treatment of neuropathic pain is still controversial. But the studies say that the protective effect shown by opioids over the placebo effect which leads to reduce the neuropathic pain. The recent studies say that strong opioids good to nortriptyline and naproxen as a pain relief in chronic non cancer pain. Opioids are used for the patients which are failed to respond with first line regimen, for episodic discharge in sever chronic pain. Adverse effects are nausea, vomiting, sedation, and constipation. Long term use of opioids leads to hypogonadism which result in infertility in males and females, decrease libido, aggression and galactorrhea.

Carbamazepine: It has analgesic effect. It shows recovery rate of voltage gated sodium channel in a frequency dependent. Its dosage is from 300–1000 mg/day. Dizziness, skin rash, balance difficulties, thrombocytopenia, hepatic damage and rarely leucopenia are the side effects of the drug. It shows effective result in treatment of trigeminal neuralgia.

Anti-epileptics: Anti-epileptics are used to manage pain and they are hydantoin derivatives like; phenytoin which is used for the treatment of trigeminal neuralgia. Anti-epileptics which are available are carbamazepine, oxcarbazepine, gabapentin, lamotrigine, phenytoin, valproate and topiramate these drugs show effective result for treatment of neuropathic pain.

Combination therapy: Combination pharmacotherapy of neuropathic pain involves combination of opioids and TCAs, gabapentin/pregabalin, cholecystokinin, gabapentin and nortriptyline, gabapentin, and alpha-lipoic acid, fluphenazine and TCAs these show frequent result in form of adverse effects on central nervous system such as sedation and depression. Depression is known to cause mood disorder that might impair the brain-gut axis. In combination of gabapentin with morphine, gabapentin with nortriptyline show most efficacious for the relief of pain except the drugs gives alone. Gabapentin in combination with oxycodone shows better relief from pain having side effects of sleep disturbance.

Ketamine in low dose with gabapentin causes reduction in pain with spinal cord injury patients. Other combination therapy like: Morphine with amitriptyline, morphine with nortriptyline, duloxetine with methadone, amitriptyline with ketamine and carbamazepine, ketamine with calcitonin, and doxepin with capsaicin these are the combination which show unsuccessful toward the neuropathic pain.

1.1.4. Pharmaceutical challenges in the treatment of neuropathic pain

In present time, the drugs which are used to treat neuropathic pain like, antidepressants, lidocaine patches, capsaicin patches, pregabalin, gabapentin, this drug shows effective result for neuropathic pain. Gabapentin is a drug which was initially developed for the treatment of antiepileptic drug because it mimics GABAergic activity (Table 2). But according to studies it doesn’t act via GABA, while it affects other spinal
or, supraspinal mechanism\textsuperscript{[90,91]}. Morphine is one of the pain killers for the treatment of pain caused by neuropathic pain. It is the most effective drug used for the treatment of long-term pain caused by nerve damage which is not easy to treat and diagnose. It may cause addiction and have various side effects like, nausea, dizziness, and drowsiness\textsuperscript{[76]}. Cancer patients having complain of specific pain which indicate the diseases, the pain which simplifies the cause of diseases by its pain, syndrome, and pathophysiology and other to checks the other factor which may affect the condition of diseases or cause illness burden\textsuperscript{[92]}. it may also cause by diabetic which is most common. Mainly anti-epileptics and antidepressants are used to treat neuropathic pain. Mainly anti-epileptics and antidepressants are used to treat neuropathic pain.

National Institute for Health and Care Excellence (NICE) guidelines recommended to choose amitriptyline, duloxetine, gabapentin, or pregabalin for the initial treatment, and if there is no relief from then then switch to other one of these drugs\textsuperscript{[93]}. By using duloxetine\textsuperscript{[94]}, lacosamide\textsuperscript{[95]}, gabapentin\textsuperscript{[96]} and pregabalin\textsuperscript{[97]} the pain can be reduced by > 50% over 12 weeks or for tropical capsacin the pain is reduced by > 50% within 2–12 weeks\textsuperscript{[98]}. Some of patients have benefit but some of them show adverse effect\textsuperscript{[99]}.

\begin{table}
\begin{center}
\caption{Drugs and the doses which are used in the treatment of diabetic neuropathy and postherpetic neuralgia.}
\begin{tabular}{lll}
\hline
\textbf{Drugs} & \textbf{Structure} & \textbf{Doses (mg/day)} \\
\hline
Diabetic neuropathy & & \\
Duloxetine & & 60–120 \\
Gabapentin & & 1200 \\
Pregabalin & & 600 \\
Postherpetic neuralgia & & \\
Pregabalin & & 600 \\
Amitriptyline and nortriptyline & & 10–25 \\
\hline
\end{tabular}
\end{center}
\end{table}
2. Novel concept of neuropathic pain treatment through gut brain axis (GBA)

2.1. Gut brain axis

Direct cell-to-cell communication includes various organs and organ system and also the central nervous system. ‘Microbiota-gut-brain axis’ is also considered as ‘gut-brain axis’ concept. It was 1st introduced by William James and Carl Lange in 1880 that gut brain axis is bidirectional transmission between intestinal organs and central nervous system (CNS)\(^{100-102}\). The intestine microbiota consist of trillions of microorganisms within the gastrointestinal tract and include over 100 times extra genes than the human genome\(^{103,104}\). Healthy gut function represents good CNS function. Gut releases various elements like hormones, neurotransmitter, and immunological factors which send signal by brain autonomic neurons\(^{102,104}\).

The stomach is colonized with an intricate local area of microscopic organisms (microbiota), which assists with molding the resistant framework, metabolic capability and conduct in wellbeing and infection over the course of life\(^{105}\). As of late, studies have arisen focused on varieties in the microbiome and the impact on different CNS issues, including, however, not restricted to nervousness, burdensome issues, schizophrenia, and autism. This survey centers around the GBA with regards to uneasiness and burdensome problems\(^{101}\). The term probiotic is generally connected with the intestinal climate and works, for example, the homeostasis or equilibrium of stomach microbiota\(^{106,107}\).

It is simply legitimate to consider and incorporate the stomach microbiota as a significant modulator of this framework and, thus, the term microbiota-stomach cerebrum pivot’s has arisen\(^{105}\) (Figure 4). Stomach organisms are fit for delivering most synapses tracked down in the human mind. While these synapses fundamentally act locally in the stomach, regulating the intestinal sensory system, proof is currently gathering to help the view that stomach microorganisms through various instruments can impact focal neurochemistry and conduct\(^{108}\). Irritable bowel syndrome (IBS) and inflammatory bowel disease are examples of chronic intestinal diseases that have been shown to alter the microbiota/gut/brain axis\(^{109,110}\). The gut brain axis is a kind of communication machinery available in human body that corelates as well as interpret all the signaling pathway, i.e., neural, hormonal and immunological information between the gut and brain\(^{111}\). The communication between Central Nervous System (CNS) and Microbiota is considered as microbiota-gut-brain axis, which is able to have an impact on neurotransmission and behavior and occur via distinctive pathways\(^{101,111,112}\). The enteric nervous system (ENS) and immune system’s growth and operation, which have an impact on CNS function, are influenced by the enteric microbiota. In response to stress or increased immunological activity, the hypothalamic pituitary adrenal (HPA) axis is a crucial part of brain-gut signaling. Top-down, bottom-up, and diverse cognitive processes can all mediate signaling. Increased levels of systemic proinflammatory cytokines or environmental stress can both trigger the HPA axis. In order to stop the HPA axis from functioning, cortisol generated by the adrenal glands feeds back to the pituitary, hypothalamus, amygdala, hippocampus, and prefrontal cortex (PFC). The systemic and gastrointestinal (GI) immune systems respond favorably to cortisol produced from the adrenals in an anti-inflammatory manner. Stress can cause changes in GI function and an increase in corticotropin releasing factor (CRF)\(^{110,113,114}\).

The flow starts from Gut (microbiota, microbial flora) → digestion → Food particles → absorbed to blood → reaches to brain → to form neuro transmitter → decreases pain.
The gut microbiome has been recognized as an important player in the communication between the CNS and ENS, forming the microbiome-gut-brain axis. (Hypothalamus (HYP), Amygdala (AMG), Hippocampus (HIPP), Corticotropin releasing factor (CRF), Adrenocorticotropic hormone (ACTH), Posterior Parietal Cortex (PPC))

Figure 4. The gut microbiome has been recognized as an important player in the communication between the CNS and ENS, forming the microbiome-gut-brain axis. (Hypothalamus (HYP), Amygdala (AMG), Hippocampus (HIPP), Corticotropin releasing factor (CRF), Adrenocorticotropic hormone (ACTH), Posterior Parietal Cortex (PPC))

The vagus nerve, immune system, and microbial metabolites are only a few of the signaling pathways that are involved in this axis, which involves bidirectional communication between the gut microbiota and the brain. It has been established that the microbiome-gut-brain axis regulates a variety of GI processes and influences cognition, behaviour, and mood. Numerous neurological and behavioural conditions, such as anxiety, melancholy, autism, and multiple sclerosis, have been linked to changes in the gut microbiome. Modulation of the gut microbiome has consequently been identified as a potential treatment approach for various disorders[115,116].

2.2. Relation with neuron

Hypothalamus has an important role in synchronizing the central control of appetite[117]. The hypothalamus serves as a hub for communication between neural, nutrient, and hormonal signals from various organs, including the gut, pancreas, liver, adipose tissue, brainstem, and other brain regions. These signals are relayed through direct and indirect pathways, forming a network that allows for bidirectional communication between the gut and the brain. The hypothalamus plays a critical role in regulating energy balance, feeding behavior, and metabolism, and is involved in the pathophysiology of a range of metabolic disorders, including obesity, type 2 diabetes, and metabolic syndrome[118]. There is a gap in the network formed by the semi-permeable blood-brain barrier, which allows peripheral signals such as hormones and nutrients to access the CNS. This gap is essential for communication between the gut, pancreas, liver, adipose tissue, brainstem, and hypothalamus[119,120].

The Arcuate Nucleus (ARC) is a key hypothalamic nucleus involved in the regulation of food intake and energy homeostasis. Neurons in the ARC integrate and respond to peripheral signals such as leptin, ghrelin, insulin, and glucose, as well as neuronal inputs from other hypothalamic nuclei. The ARC neurons then communicate with other hypothalamic nuclei such as the paraventricular nucleus, dorsomedial nucleus, lateral hypothalamus, and ventromedial nucleus to regulate feeding behavior, energy expenditure, and other physiological functions related to energy balance[121,122]. Signals from the gastrointestinal tract are sensed in the brainstem through similar mechanisms to those seen in the hypothalamus. The vagus nerve plays a key role in relaying these signals from the gut to the brainstem, where they are integrated with other inputs to regulate various GI functions. The brainstem also communicates with higher brain centers, such as the hypothalamus and limbic system, to modulate feeding behavior, satiety, and other physiological responses to food intake. Additionally, the gut microbiome has been shown to play a role in modulating the gut-brain axis.
through various mechanisms, including the production of neurotransmitters and metabolites that can affect CNS function\textsuperscript{[123–125]}. The gut hormones influence signaling systems and receptors, which in turn affect energy homeostasis. These effects are mediated through the vagus nerve and brainstem\textsuperscript{[126]}. The hypothalamus receives signals related to appetite from the brainstem\textsuperscript{[127–129]}. The hypothalamus integrates the signals received from the brainstem and other sources to generate efferent signals that are transmitted through the brainstem to regulate various gastrointestinal and appetite functions\textsuperscript{[122,130,131]}. The vagus nerve plays a crucial role in the communication of both afferent (sensory) and efferent (motor) signals between the gastrointestinal system and the brainstem, which can ultimately result in changes in meal patterns\textsuperscript{[127,132]}.

### 2.3. Mechanistic study of gut brain axis

The bidirectional pathway of the gut-brain axis plays a crucial role in maintaining metabolic homeostasis. The complex communication between the intestine and the CNS can provide information on nutritional status through various means, including enteroendocrine cells (EECs), the vagus nerve (VN), and the enteric nervous system (ENS). The signals can be modulated by metabolites produced by gut microbes\textsuperscript{[133,134]}. Prebiotics are described as “selectively fermented elements that result in specific changes in the composition and/or pastime of the gastrointestinal microbiota, accordingly conferring benefits upon host health”\textsuperscript{[135]}. GABA is a crucial neurotransmitter that primarily inhibits neuronal activity in the brain. It is produced from its counterpart glutamate, which is an excitable neurotransmitter. GABA has a significant role in the hypothalamic control of food intake\textsuperscript{[136,137]}.

Most of the gut disease and intestinal disorder is caused due to unbalance in microbiota and Probiotics play an important role digestive system\textsuperscript{[139]}. Probiotics have been shown to have a positive impact on the gut microflora, which can protect against various intestinal complications such as infectious diarrhea, inflammatory bowel disease (IBD), irritable bowel syndrome (IBS), Helicobacter pylori infection, lactose intolerance, and antibiotic-associated diarrhea (AAD)\textsuperscript{[140]}. Various intestinal bacteria inhibit growth of pathogenic bacteria like: lactobacilli, Clostridium botulinum\textsuperscript{[141]}, Clostridium Difficile\textsuperscript{[142]}. The gut microflora is protective which have specific microorganism that is responsible for the production of effective probiotic for its effect\textsuperscript{[143,144]}. It produces antimicrobial substances which show its effect by reduction in number of viable cells\textsuperscript{[145]} which affect the metabolism and the production of toxin in intestinal bacteria\textsuperscript{[146]}.

When probiotic bacteria interact with epithelial cells (E), M cells (M), or dendritic cells (DC), the bacteria or its parts are internalized. This connection increases the release of IL-6 by epithelial cells and the production of TNF- and IFN- by macrophages (MQ) and dendritic cells. The cytokine IL-4, which mast cells (MAC) or other cells are induced to generate, along with IL-6 and TGF-, causes the Tin-dependent transition from IgM to IgA on the surface of B lymphocytes (BL), hence increasing the production of IgA. IgA B cell clonal proliferation is promoted by IL-6. Moreover, there is a reduction in the release of IgE and an increase in the synthesis of IgM and IgG antibodies. IFN and TNF, are two pro-inflammatory cytokines produced by Th1 cells. IL-2 stimulates the phagocytosis and elimination of microbial pathogens and triggers the killing of viruses and malignancies by macrophages, natural killer cells, and cytotoxic T-lymphocytes\textsuperscript{[113]}. Pregabalin reduces pain by blocking voltage gated calcium channel (VGCCs), which reduces calcium influx and prevents the release of glutamate and neuropeptides (such as substance P and CGRP) at synapses. It also enhances the activity of excitatory amino acid transporters (EAATs), resulting in a further reduction in glutamate availability at synapses. This reduction in glutamate levels prevents NMDA activation, leading to a decrease in neuronal activity. Additionally, pregabalin opens ATP-sensitive potassium channels (KATP) channels, which reduces neuronal excitability. These mechanisms work together to provide significant pain relief in various neuropathic pain conditions\textsuperscript{[147]}.
2.3.1. Voltage gated calcium channels

Numerous research studies have shown that the upregulation of voltage-gated calcium channels (VGCC) occurs in dorsal horn and dorsal root ganglion in neuropathic pain. VGCC is composed of several subunits, including one pore-forming transmembrane subunit, as well as auxiliary subunits two and three\(^\text{148}\). The voltage-gated calcium channel (VGCC) is composed of various subunits, including the α1, α2, and δ subunits. Among these, the α2 and δ subunits form the 2-subunit of the VGCC. The α2 component is located outside of the cell membrane, while the δ component is embedded in the membrane. These two components are joined together by a disulfide bond, which plays a crucial role in maintaining their stable binding and ensuring the optimal expression of VGCC on the cell surface. The α2 subunit modulates the voltage-dependent calcium-dependent inactivation and facilitation of the VGCC, while the δ subunit regulates the gating properties of the channel\(^\text{149}\). The function of the β subunit is to bind to the α1 subunit and regulate the voltage-dependent inactivation, calcium-dependent inactivation, and calcium-dependent facilitation of VGCC\(^\text{150}\). The exact role of the -subunit in other types of channels is not well understood, although it is primarily associated with calcium channels in skeletal muscle\(^\text{150}-\text{152}\). Cells expressing CaV 2 and CaV 1 improve the localization of VGCC to the plasma membrane\(^\text{153}\).

2.3.2. Glutamate transporter

Glutamate is the primary excitatory neurotransmitter in the mammalian central nervous system which is stored in synaptic vesicles. The activity of glutamate is rapidly terminated, and its extracellular concentration is kept below excitotoxic levels by excitatory amino acid transporters (EAATs), which are present on the plasma membrane of neurons and glial cells\(^\text{154,155}\). Out of the five Na\(^+\)-dependent glutamate transporters (EAATs 1–5), EAAT3 has been found to be a target of pregabalin. Pregabalin can lead to a significant increase in the expression of EAAT3 at the plasma membrane of neurons and glial cells. This increase in expression may cause a notable reduction in the functional response of the excitatory neurotransmitter glutamate.

2.3.3. Potassium channels

Research has shown that pregabalin can have an impact on various types of potassium channels, such as KATP channels, which implies another possible mechanism of action for its analgesic properties. Activation of KATP channels in the spinal cord has been found to have antinociceptive effects, which reduce neuronal excitability and inhibit the release of multiple neurotransmitters, including substance P. Studies have shown that pregabalin can enhance potassium ion (K\(^+\)) currents in dorsal root ganglion (DRG) neurons regardless of whether it is applied inside or outside of the cells. This suggests that both extracellular and intracellular target sites may be affected by pregabalin’s actions. By reducing the release of norepinephrine and glutamate in the rat neocortical tissue, increased K\(^+\) current caused by pregabalin may reduce neuronal excitability\(^\text{156}\). Pregabalin-induced increases in K\(^+\) current are prevented by the injection of cAMP analogue, indicating that the activation of protein kinase A may be responsible for the intracellular response. In accordance with additional research, gabapentin drug-induced Ca\(^{2+}\) current inhibition is sensitive to cAMP analogues that can activate or inhibit PKA\(^\text{147}\) (Figure 5).
Figure 5. Pregabalin works to reduce pain through several mechanisms.

By blocking VGCCs, reduces Ca\(^{2+}\) influx and inhibits the release of glutamate and sensory neuropeptides (substance P and CGRP) at synapses. Pregabalin also increases the activity of EAATs, which leads to a further reduction in glutamate synaptic availability.

This decreases the activation of NMDA receptors and reduces neuronal activity. Additionally, pregabalin opens KATP channels, which also helps to reduce neuronal excitability. Overall, these mechanisms provide significant pain relief in a variety of neuropathic pain conditions.

The communication between gut and the brain leads to many disorders like: psychiatric, metabolic, neurodevelopmental, age-related and neurodegenerative disorders. The nociceptive forms information for stress, injury or infection in form of heat and pain, which is initiated by vagal afferents at the site of pain or through the ascending spinal pathways to the brain\(^{[152]}\).

3. Probiotics

It is a Greek word that refers to “life”. According to expert of FAO (Food and Agriculture Organization) and WHO probiotics is a “living microorganism” which is administered in living body at specific mount to show some beneficial effects\(^{[161,162]}\). The term “probiotic” was first used in 1965, to describe substances secreted by one organism which stimulate the growth of another. Probiotics are living micro-organism which are administered in sufficient amount leading to health benefit on biological mass. There are various microorganism used as probiotics L. acidophilus, L. sporgenes, L. plantarum, L. rhamnosum, L. delbrueck, L. reuteri, L. fermentum, L. lactis, L. cellobiosus, L. brevis, L. casei, L. farciminis, L. paracasei, L. gasseri, L. crispatus, B. bifidum, B. infantis, B. adolescentis, B. longum, B. thermophilum, B. breve, B. lactis, B. animalis, S. lactis, S. cremoris, S. alivarius, S. intermedius, S. thermophilis, S. diacetylactis, Leuconostoc mesenteroides, Pediococcus Propionibacterium, Bacillus Enterococcus, Enterococcus faecium, Saccharomyces cerevisiae, Saccharomyces boulardii, Aspergillus niger, Aspergillus oryzae and Candida pintolespi\(^{[163–166]}\).

3.1. Probiotics and neuropathic pain

Probiotics regulated dietary supplements and foods, which contain yeasts or bacteria\(^{[162]}\). Probiotics also lead to restore microbial balance. Bacteria colonized and get reproduced in gut, link and stick to the intestinal epithelium, and stabilizing the gut flora. Probiotic show common treatment in case of gastrointestinal tract
because they have ability to restore gut flora. Lactic acid bacteria, *lactobacillus* and *Bifidobacterium* species are the regularly used probiotics. They stops the growth of bacteria and therefore because of formation of lactic acid, acetic acid, propionic due to its low intestinal pH. Due to the presence of antimicrobial matter probiotics shows that it has the potential to collect pathogens to kill microorganisms (Figure 5, Table 3).

Table 3. Mechanisms of action of probiotics.

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Biological effect</th>
<th>Host target</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interference with pathogens</td>
<td>SCFA production</td>
<td>Intestinal lumen</td>
</tr>
<tr>
<td>Adhesion</td>
<td>Mucus Layer</td>
<td>Gut microbiota</td>
</tr>
<tr>
<td>Bacteriocin production</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nutrient competition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Improvement of barrier function</td>
<td>Tight junction</td>
<td>Enterocytes</td>
</tr>
<tr>
<td></td>
<td>Increase in mucin production.</td>
<td>Colonocytes</td>
</tr>
<tr>
<td></td>
<td>Increase in IgA production.</td>
<td>Goblet cells</td>
</tr>
<tr>
<td></td>
<td>Increase in defensin production</td>
<td>Paneth cells</td>
</tr>
<tr>
<td>Immunomodulation</td>
<td>Cytokine production</td>
<td>M cells</td>
</tr>
<tr>
<td></td>
<td>T helper response</td>
<td>Dendritic cells</td>
</tr>
<tr>
<td></td>
<td>T reg response</td>
<td>Macrophage</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IEL and T cells</td>
</tr>
<tr>
<td>Neurotransmitter</td>
<td>GABA</td>
<td>Gut-brain axis</td>
</tr>
<tr>
<td></td>
<td>Tryptophan</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Serotonin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Acetylcholine</td>
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</tr>
</tbody>
</table>

The first probiotic to gain clinical attention was *Lactobacillus* rhamnoses GG (LGG). It show good effect in intestinal immunity due to this, there is increase in quantity of the cells that secretes immunoglobulins in intestinal mucosa and IgA. The interactive work of microflora and probiotics support the host’s immune system and metabolic processes, preventing the colonization of the host by opportunistic and pathogenic microbes. In the case of prebiotics, it is non-digestible food ingredient which stimulate growth and activity of bacteria in colon and living health. Due to presence of good bacteria and yeast, it restores balance the GI.

3.2. Application of probiotics in neuropathic pain

Probiotic supplements have been proposed as a potential therapy for treating neuropathic pain conditions like Diabetic Neuropathy and Chemotherapy-Induced Peripheral Neuropathy (CIPN). Probiotics are a type of living bacteria that can potentially influence inflammatory responses by impacting cytokines, which are important signaling molecules involved in the body’s immune and inflammatory processes.

Probiotics can provide various health benefits by modulating the microbiota in the gut. These benefits may include improved digestion, enhanced immunity, and a reduced risk of certain diseases. By altering the balance of bacteria in the gut, probiotics can have a positive impact on overall health.

IFN-γ is a cytokine called interferon gamma (IFN), and is crucial in initiating and controlling a variety of immunological reactions. IL-12 is a heterodimeric cytokine that promotes the activation of type 1 T helper cells (Th1 cells) and enhances cell-mediated immunity. It is a necessary part of the body’s immune response against certain infections and diseases. IL-10 is an anti-inflammatory cytokine known as human.
cytokine synthesis inhibitory factor (CSIF)\textsuperscript{[173]}. LPS is a major component of the outer surface membrane found in practically all Gram-negative bacteria (Figures 6–8)\textsuperscript{[174]}.

**Figure 6.** Mechanism of gut and brain action.

**Figure 7.** The host’s normal microflora and probiotics working.

**Figure 8.** Effects of probiotics at the gut levels.
Inflammatory bowel diseases\(^{175}\), luminal gastrointestinal disorders, irritable bowel syndrome\(^{176}\), allergic diseases\(^{41,176,177}\), and even Parkinsonism\(^{178}\) have all been linked to probiotics, according to a growing body of research. Probiotics have also been shown to prevent gestational diabetes mellitus (DM) and irritable bowel syndrome\(^{175}\). It is rare to find information about probiotic therapy’s effectiveness for NP, though. Unexpectedly, there hasn’t been any research done to determine whether probiotic and Adipose-derived mesenchymal stem cells (ADMSC) therapy together would have more positive effects on NP relief. The details of probiotics in used in neuropathic pain are summarized in Table 4.

<table>
<thead>
<tr>
<th>Condition of pain</th>
<th>Probiotic used</th>
<th>Outcomes</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paclitaxel (PTX) induced neuropathic pain</td>
<td>DSF, 450 billion bacteria per sachet</td>
<td>Used as adjuvant therapy for counteracting chemotherapy induced peripheral neuropathy (CIPN).</td>
<td>[179–181]</td>
</tr>
<tr>
<td>Neurodegeneration</td>
<td>SLAB51 (high concentrated probiotic formulation sold as Agimixx(^5), Ormendes, Jouxtens-Mézery, Switzerland)</td>
<td>neuroprotective effects in neurodegenerative disorders.</td>
<td>[179,182]</td>
</tr>
<tr>
<td>Chronic constriction injury (CCI)</td>
<td>1 ml probiotics mixture (CP) (Lactobacillus plantarum, Lactobacillus delbrueckii, Lactobacillus acidophilus, Lactobacillus rhamnosus, and Bifidobacterium bifidum) ((10^9) CFU of each) daily.</td>
<td>Probiotics decreased cold and mechanic alldynia and thermal hyperalgesia.</td>
<td>[183]</td>
</tr>
<tr>
<td>Chronic constriction injury (CCI)</td>
<td>probiotics (PNTb-to-RAY(^{\text{TM}}) containing (L.\ paracasei; Kao A Biomedical Co., Ltd., Kaohsiung, Taiwan))</td>
<td>Enhanced the therapeutic effect of adipose-derived mesenchymal stem cells (ADMSCs) in neuropathic pain</td>
<td>[184]</td>
</tr>
<tr>
<td>Right L5 spinal nerve transection (SNT)</td>
<td>Probiotic mixture VSL# 3 (Alfasigma, Covington, LA, USA) of (450 \times 10^9) (CFU) probiotic</td>
<td>Inhibit the expression of TNF-(\alpha) through the TLR4-NF-(\kappa)B signaling pathway. Ameliorated nerve injury-induced neuropathic pain</td>
<td>[185,186]</td>
</tr>
<tr>
<td>Paclitaxel induced neuropathic pain</td>
<td>A bacterial extract of nine probiotics</td>
<td>Relieving chemotherapy-induced neuropathic pain.</td>
<td>[180]</td>
</tr>
<tr>
<td>Paclitaxel induced neuropathic pain</td>
<td>Probiotic formulation SLAB51</td>
<td>Allieving peripheral neuropathy by increasing the expression of opioid and cannabinoid receptors in the spinal cord, preventing the reduction of nerve fiber damage in the paw, and modulating serum pro-inflammatory cytokine concentrations</td>
<td>[181]</td>
</tr>
</tbody>
</table>

In addition to the results mentioned above, Xie et al.\(^{187}\) demonstrated that a probiotic mixture shielded dopamine neurons and further slowed the progression of motor dysfunctions in mice with Parkinson’s disease. A \(Drosophila melanogaster\) Alzheimer’s disease model’s gut microbiota profile was modified, and \(Lactobacillus plantarum\) DR7 reduced neurodegeneration in the eye\(^{163,187}\).

Recent reports demonstrated that the modern lifestyle and western diet cause significant alterations in the composition of microbiota of the gut. This causes drastic disturbances in a decrease in bacterial diversity and respective flora. Such conditions of dysbiosis cause dysfunction in the immune system and provide low-grade systemic inflammation\(^{188–190}\). Plant obtained products can be a good source to protect against gut brain axis and cardiovascular diseases\(^{191}\). An excessive amount of sitting and a sedentary lifestyle can worsen inflammation, oxidative stress, and hyperglycemia, which can further cause neuropathic pain and neuronal problems\(^{192,193}\).
4. Conclusion

Probiotics are increasingly being used to treat gastrointestinal diseases due to their beneficial effects, but it’s important to analyze their impact on the population and activity of gut bacteria. While several publications suggest that probiotics are linked to a lower incidence of colon cancer, it’s still unknown whether these treatments increase the risk of cancer recurrence. This review emphasizes the importance of a healthy microbiome, especially the gut microbiota, for individuals with anxiety and depression, as dysbiosis and CNS inflammation may contribute to the development of these mental illnesses. The medical research community is increasingly interested in the bidirectional connection between the brain, gut, and microbiota, with clinical observations and psychiatric co-morbidity in chronic intestinal conditions supporting the role of the intestinal microbiota in gut-brain axis communication. However, the review highlights several flaws in existing studies, including a lack of knowledge about the relationship between cytokines, TNF, and other stressors and the development of mental illness. Future research should explore the relationship between levels of intestinal flora in neuropathic pain.

Conflict of interest

The authors declare no conflict of interest.

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