Probiotics in Inflammatory Pain Relief: A Mini Review

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ABSTRACT

The commonly used therapy for treating pain is Non-steroidal anti-inflammatory drugs NSAIDs. NSAIDs work by targeting the cyclooxygenase enzyme COX1 and COX 2; however, their use comes with associated adverse side effect. Recently found are COX-2 specific inhibitors (coxibs) which were thought to have ameliorating effect and maintained anti-inflammatory efficacy including pain. Recent studies have, however, shown that coxibs contribute to cardiovascular risk and may also induce disturbance in renal function. The bane of this current review study was to search literature for alternative and effective means of arresting inflammatory pain through current innovation that originates from nutrition and have health benefit if administered appropriately. From our search probiotics came out handy as a form of nutraceutical in the treating pain; probiotics are live organisms that confer health benefit on its host when administered in sufficient amounts.

Some researchers have shown that some probiotic strain can arrest inflammatory pain by regulating pro-inflammatory cytokines and COX-2 expression. The prowess of probiotic in pain relief has been observed in Irritable bowel syndrome (IBS) and in molar extraction where administered probiotic strain relieved pain after seven days of extraction. Development of pain relieving probiotic strain may help to circumvent negative side-effect observed in using coxibs and NSAIDs. For Probiotics, studies on which strain to be used, mode of administration and required dosage to be effective are crucial.

Keywords: Drug, Inflammatory, Pain, Pain relief, Probiotics

INTRODUCTION

Probiotics are a live organisms that confer benefit to recipient’s health when administered in sufficient amounts.1 In the Gastrointestinal tract (GIT), probiotics have been applied to a lot of health issues; most prevalent is treating irritable bowel syndrome (IBS) and functional abdominal pain.

There are indications that probiotics could be used in the specific treatment of pain for patients with IBS and functional abdominal pain.2-5 Despite the positive reporting by some authors, a recent study revealed that it may also not be as beneficial as thought, when it was reported that it could prevent the return of native microbiome once colonization was achieved 6; another maintained that it did not impact any benefit on healthy individual 7 hence, no consensus has been reached. However, there is an underlying fact that probiotics could be used at inflammatory site as an alternative to conventional NSAID but this is yet to be explored. The successes reported in the dietary use of probiotics in the GIT could be a spotlight of hope for pain relief in other body parts if the pathways could be elucidated. The bane of this current review study is to search literature for alternative and effective means of arresting inflammatory pain through current innovation that originates from nutrition and have health benefit if administered appropriately which probiotics fit in perfectly.

MATERIALS AND METHOD

Relevant literature search was carried out on multiple electronic databases and libraries such as Scopus, PubMed,
Inflammatory pain

Nociceptors are nerve endings that are free and found in all body parts except the brain and parenchyma. Pain is a vital function of the nervous system that provides the body with a warning of potential or an actual injury, in fact most ailments in the body causes pain. The detection of harmful stimuli and transformation of these into electric signals for conduction to the central nervous system is the responsibility of these specialized sensory receptors. The activation and sensitization of nociceptors by inflammatory mediators leads to inflammatory pain, inflammatory responses accompany the development and persistence of pain; it is characterized by redness, swelling, pain, heat and functionality loss. Cytokines and inflammatory mediators are small intracellular polypeptides and are of two types: pro-inflammatory or anti-inflammatory. According to Botting macrophages at a site of infection or tissue damage primary sets off the mobilization of TNFα which leads to the formation of IL-8 and thereafter leads to the liberation of hyperalgesic sympathomimetic amines which are capable of sensitizing dormant nociceptors. There is also a simultaneous release of IL-6, which in turn prompts IL-1β to be produced. IL-6 and IL-1β stimulates the synthesis of prostaglandin through arachidonic acid and induces the expression of the cyclooxygenase 2 and phospholipase A2 gene. Apart from this cascade, inflammatory mediators may ultimately sensitize nociceptors, an example is IL-8, which has been connected with the sensitization of the sympathetic neuron. The process stipulated above is shown in a diagram adapted from botting and botting.

Mechanism of inflammatory pain relief

Prostaglandins play a crucial role in the development of inflammation, the enzyme cyclooxygenase (COX) catalyzes the production of prostaglandins and thromboxane from arachidonic acid.

COX exists in three isoforms: COX 1, COX 2 and COX 3. COX 1 is constitutively expressed in virtually all tissues and function as homeostasis regulator while COX 2, the inducible form has the function of producing prostaglandins in inflammation and in development of fever. NSAIDs act on COX enzyme by inhibiting prostaglandins production, thus reducing the sensitization of nociceptors and the overall effect of inflammatory pain. A number of negative side-effects are associated with the usage of NSAIDs and these include: Gastrointestinal complications, increase risk of renal disease and cardiovascular diseases; this prompted the search for other pain reliefs with either minimal or none adverse effects. The damaging effect seen in the use of NSAID is observed in the pain cascade initiated by COX-1. The understanding of pain mechanism spear-heads the finding of COX-2 selective inhibitors (coxibs), such as colecocixib and refernocoxibs, which have an ameliorating effect. It was thought that targeting COX-2 enzyme would by-pass the negative effect seen in the usage of NSAID which target both COX-1 and COX-2.

Recent studies have, however, shown that coxibs also contribute to cardiovascular risk and may induce disturbance in renal function. A need for an alternative therapy that is safe and has a low risk profile is thus needed; from our search probiotics came out handy as a form of nutraceutical in the management of inflammatory pain.

Probiotics

Probiotics are live organisms that confer health benefit on its host when administered in sufficient amounts. The intestinal
microbiota has in abundance species of Lactobacillus and Bifidobacterium and these constitute major probiotics; also included are species of the yeast genus Saccharomyces, others are genus of Streptococcus, Enterococcus, and Bacillus. Some clinical trials and genomic experimentation were performed to determine the appropriate strains of these genera that can be effectively applied; cocktails of different strains have also been produced to better utilize the combined benefits of identified strains. Examples of some probiotics include E. Coli strain Nissle, L. rhamnosus GG, L. acidophilus and L. delbrueckii, DR10 and DR 20 by Fonterra, VSL#3® (a combination of four strains of L. casei, L. plantarum, L. acidophilus and L. delbrueckii subsp. bulgaricus); three strains of Bifidobacteria : B. longum, B. breve and B. infantis and S. salivarius subsp. thermophilus. Some research has affirmed the usage of probiotics in the management of some pathology such as diabetics with an improvement in glucose metabolism. These benefits have heralded their importance in the development of functional foods and as therapeutics; however, this benefit are strain specific, that is the same species not imputing same effect. Strict criteria must be met before a strain is administered as a probiotic, and these include ability of being nonpathogenic and toxic, ability to resist the acid in the stomach and bile, ability to bind to the intestinal epithelium. Bacteremia, sepsis, antimicrobial resistance and general effect on host immune system are areas of concern in the application of probiotics, however, studies revealed that probiotics usage is generally safe but caution should be taken in immune-compromised and severely ill patients.

**Application of probiotics**

Probiotics have been applied to treat and curb the effect of some diseases and ailments, some beneficial effects have been observed with its use and applications.

Bottle fed infants are not as healthy as breastfed ones and infectious rate is high in the former; probiotics have been incorporated in infant formulae to mimic the microbiota profile of breastfed infants to prevent and treat diarrhea in children. Its administration reduces the incidence of illness in children and infection, particularly in the upper respiratory tract. Antibiotic resistance to antimicrobials increases with the use of antibiotics overtime, probiotics have been implied as an alternative method to reduce these resistance. Also, prevention of pouchitis and treatment of its chronic forms has been achieved with VSL#3; its promising effect is observed in ulcerative colitis, inflammatory bowel disease such as constipation, Crohn’s disease, pouchitis, Helicobacter pylori infection, irritable bowel syndrome, Antibiotic-Associated Diarrhoea and Clostridium difficile-Induced Diarrhea.

**Mechanism of action of probiotics**

The mechanism of action may not have been fully elucidated but some have been proposed as being possible ways in which they act. These mechanisms include: strengthening the intestinal barrier, antagonistic effect on pathogenic microbes, elimination of other microbes through competitive exclusion, increase rate of adhesion to epithelial cell surface and modulation of key signaling pathway.

- **a.** The integrity of the intestinal barrier is strengthened by promoting the gene expression that is involved in tight junction signaling. Studies have shown that not only do probiotics prevent breach in the epithelia, they also sustain epithelia function; they could also repair damaged epithelia function through the reconstruction of tight junction complex by the redistribution of tight junction proteins.

  - **b.** Antagonistic effect on pathogenic microbes is another mechanism that has been proposed for the action of probiotics. Antimicrobial effect on pathogenic bacteria through the production of antibacterial substance such as bacteriocins, lactic acid, hydrogen peroxide and conjugated bile acid. Studies by Goudarzi et al. and Donkor reveals that the ability to produce proteolytic enzymes which dissolve and digest approaching bacteria may be the reason for anti-pathogenic property observed in them. They have also been found to possess antifungal properties, studies have shown that viral particles can be inactivated by probiotic substance, lactobacillus rhamnosus GR-1 and L. fermentum RC-14 inactivated adenovirus by study performed by Cadieux et al.; animal study has also indicated a great reduction of poliovirus infection by the marine bacterium Moraxella.

  - **c.** Probiotics may also eliminate the colonization and proliferation of other microbes through competitive exclusion. Several means are used by probiotics to prevent colonization of the GIT, one of such means is the
Probiotics in inflammatory pain relief

Efficient pain management remains a significant challenge in health care and basic research. COX II mediates inflammatory symptoms including fever and hyperalgesia, its level which is high at site of inflammation is subject to regulation.

Probiotics have been shown to be able to regulate COX II in study by Otte et al. which reveals that specific probiotic strains can be considered as therapeutic alternative in the regulation and expression of COX II in the intestinal epithelium to curb its inflammatory effect. This ability can be channeled in inflammatory pain relief by expounding the mechanism and pathways involved and applying to site of inflammation where there is need to regulate COX II expression.

Pain with no physiological protective function or that, which has outlived its usefulness as an acute warning system is pathological; through different mechanism, cytokines play a vital role in pain at some sites of pain transmission. Pathological pain is triggered and perjured by proinflammatory cytokines such as IL-1β, IL-6, and TNF-α. Oliveira et al. stipulated that the influence of pain and the immune system on each other cannot be easily determined and pondered on the possibility of whether the blockage of the activity of one or the other would contribute to the reduction of pro-inflammatory cytokines. However, it may not be incorrect to suggest that pain could be reduced and possibly prevented if the production of these cytokines produced are regulated and inhibited respectively; this standpoint has been confirmed by study performed by Hart et al. in their investigation it was revealed that some probiotic bacteria inhibited the synthesis of pro-inflammatory cytokines, up regulated the synthesis of anti-inflammatory cytokine IL-10 by dendritic cells. Moreover, some probiotic strains can suppress inflammation by preventing the activation of NFkB signalling through the inhibition of IκBα phosphorylation.

Furthermore, pain, if not controlled adequately during immediate postoperative periods could prompt greater pain during recovery thus, optimal analgesic therapy should not lead to the development of chronic pain and must have negligible or absolutely no side effect. Paracetamol and ibuprofen were concluded as being efficacious for the management of inflammatory complications after third molar surgery in a study performed by Cho et al. ; since an ideal pain relief should have no unwanted effects, the findings by
Osunde et al.\textsuperscript{86} which maintains that no single modality of management, effectively prevents the occurrence of complications without undesirable side effects in their review. A Study by Calabuig et al.\textsuperscript{87} reveals that after third molar extraction, oral probiotics helped achieve a larger reduction in pain towards the end of the first week. This novel area could be explored for the development of alternative option of pain not only in molar extractions but in other postoperative pain.

**CONCLUSION AND FUTURE DIRECTIONS**

Probiotics have been demonstrated to be effective in inflammatory conditions and a variety of IBS related conditions including functional abdominal pain. A careful review of literature has provided some proof that probiotics can be used in pain relief especially at sites of inflammation, its use in resolving pain would be a great breakthrough, considering that the use of NSAID in the treatment of pain comes with associated side effects.

Future directions include clinical studies of the effect of these probiotics strains on nociceptors and the general nervous and immune system, design of customized strains to suite inflammatory pains at different sites in the body and for different individuals most effective mode of usage.

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