Infection - pain in oral cavity and alternative managements

PhD thesis

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List of Abbreviations

CD	Cluster of differentiation
CGRP	Calcitonin gene-related peptide
CI	Confidence interval
DRG	Dorsal root ganglia
GABA	Gamma aminobutyric acid
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
FPR	Formyl peptide receptor
HHV	Human herpes virus
HSV	Herpes simplex virus
HZI	Herpes zoster infection
HZV	Herpes zoster virus
IASP	The International Association for the Study of Pain
IL	Interleukin
LPS	Lipopolysaccharide
MAPK	Mitogen-activated protein kinase
OR	Odds Ratio
PAMP	Pathogen-associated molecular pattern
PHN	postherpetic neuralgia
PRR	Pattern recognition receptor
PICO	Population, intervention, control, outcome
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	Randomized clinical trial
SMD	Standardized mean difference
SP	Substance P
TLR	Toll-like receptor
TRP	Transient receptor potential channel
TRPA	Transient Receptor Potential Channel, Ankyrin subtype
TRPV	Transient Receptor Potential Channel, Vanilloid subtype
VZV	Varicella zoster virus

1. Introduction

1.1. Pain

Pain is a complex perception involving biological, psychological, and social factors. The International Association for the Study of Pain (IASP) has revised and defined pain as "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage" (1). Normal pain sensation or nociceptive pain is evoked by stimulus which is intense enough to trigger nociceptors (Figure 1a). Primary nociceptive afferent neurons are responsible for nociceptive pain by transmitting noxious stimuli to neurons in the spinal cord and higher center (2). The sensation felt corresponds in location, times, and quality of stimulus in expected manner (3).

Tissue injuries and/or infection cause pain through inflammatory process, serving as a warning signal to individual (4). Triggered innate immune cells secrete a various type of cytokines responsible for cell-cell interaction, immune response activation, and the maintaining of cellular function (5, 6). Chemokines, cytokines and tissue specific growth factors are upregulated in the inflammatory process (7, 8). Interleukins (ILs) are the main cytokines that play important roles on immunomodulation and the development and growth of hematopoietic tissues (9). While most ILs are pro-inflammatory mediators, some ILs such as IL-4, -10, -13 show anti-inflammatory effects (10, 11).

Secreted cytokines from activated immune cells can decrease the action potential threshold of nociceptive neurons (12, 13). The action of cytokines occurs via mitogen-activated protein kinase (MAPK) and other signaling molecules, leading to the phosphorylation and gating of ion channels such as voltage-gated sodium channels and transient receptor potential (TRP) channels (14-16). Histamine, bradykinin, prostaglandin and leukotriene secreted from immune cells also have the ability to sensitize nociceptive neurons and initiate inflammatory pain (Figure 1b). The sensitized nerve becomes more sensitive to stimulation, resulting in the secretion of neuropeptides, such as calcitonin gene-related peptide (CGRP) and substance P (SP) (Figure 1c). These secreted neuropeptides act on both immune cells and nerve endings to facilitate nerve sensitization (17).

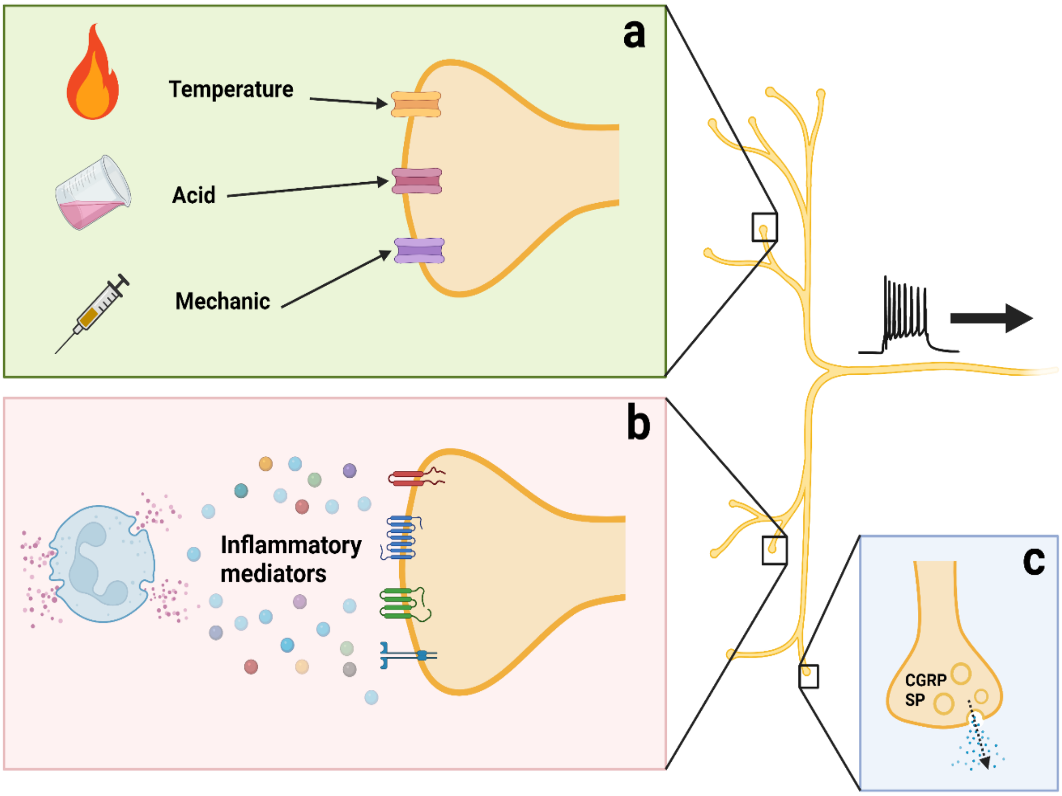

Figure 1. Nociceptive, inflammatory and neuropathic pain.
(a) Noxious stimuli are transduced into electrical activity at the peripheral terminals of unmyelinated C-fiber and thinly myelinated Aδ-fiber nociceptors by specific receptors or ion channels. The resulting input is conducted to the spinal cord and higher centers. (b) Activated immune cells release chemical mediators creating an 'inflammatory soup' that activates or modifies the stimulus response properties of nociceptor afferents. (c) The antidromic signal of the sensitized nerve fiber secretes neuropeptides at the nerve ending. Adapted from Scholz and Woolf (4), and Basbaum *et al*. (18). Created with BioRender.com.

A new aspect of pain sensation has been introduced since a discovery of pathogen recognition receptor (PRR) expression on nociceptor neurons. Nociceptive and pruriceptive neurons exhibit specific PRRs, including toll-like receptors (TLRs), formyl peptide receptors (FPRs), and signaling pathways that can sensitize transient receptor potential (TRP) channels. When microbial pathogenic ligands bind to those receptors, the nerve impulse is readily generated (Figure 2). The impulse is both orthodromically conducted to second order neurons and antidromically conducted to other axon terminals, leading to a release of neuropeptides. Consequently, the immune system is activated and modulated. This microbe-neuron-immune interplay has been implicated in host defense mechanism (19).

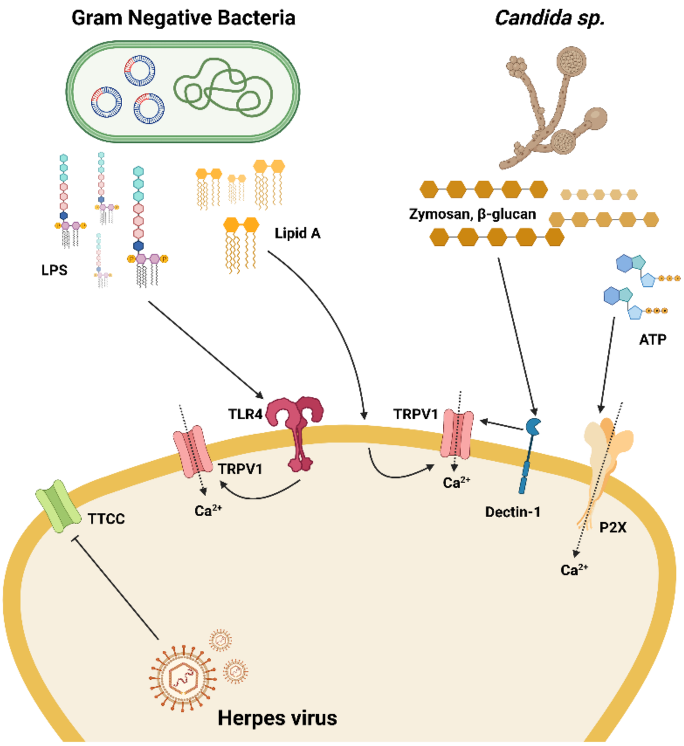

Figure 2. Molecular mechanism of microbial modulating nociception.
Bacterial, fungal and viral pathogens activate nociceptive neurons via different mechanisms. LPS: Lipopolysaccharide, ATP: Adenosine triphosphate, TTCC: T-type calcium channel, TRPV1: Transient Receptor Potential Channel, Vanilloid subtype 1, TLR4: Toll-like receptor 4. Adapted from Deng L & Chiu IM (2021) (20). Created with BioRender.com.

1.2. Oral infection

An infection is an invasion of pathogenic bacteria, viruses, fungi or other microorganisms into the body. It initiates the body reaction called inflammation, leading to swelling, redness, heat, pain and loss of function at the inflammatory site (21).

The oral cavity harbors more than 700 species of microbes, including both non-pathogenic and pathogenic microbes (22). Different ecological conditions of oral cavity (e.g. the teeth, gingiva, buccal mucosa, tongue) are colonized by distinct microbial communities. In health, there is a commensal stage between microbe and host. However, when an imbalance between microbe-microbe or microbe-immune occurs, it can lead to oral diseases (23). For example, an overwhelming of pathogenic bacteria over non-pathogenic bacteria in oral cavity can cause periodontal diseases. The immune system intolerance contributes to oral candidiasis susceptibility, and reactivation of herpes zoster virus (HZV). Besides, interactions of pathogens with the nerve system, may result in nerve sensitization. Some pathogenic bacteria, viruses and fungi that cause diseases in the orofacial area have abilities to sensitize and activate nociceptors directly (Figure 2). Table 1 shows an example of pathogens associated with orofacial diseases that can sensitize nociceptors.

Table 1. Pathogens associated with orofacial diseases that can sensitize nociceptors.

Pathogen name	Disease	Infection site(s)	Neuronal sensitization mechanisms
Bacteria			
Porphyromonas gingivalis	Periodontal disease	Oral cavity	LPS sensitizes TRPV1
Virus			
Herpes simplex virus	Herpes labialis/ gingivostomatitis	Trigeminal ganglia	Nociceptor sensitization
Varicella zoster virus	Orofacail herpes zoster	Trigeminal ganglia	PHN
Fungus			
Candida albicans	Candidiasis	Skin, oral cavity	Zymosan sensitizes nociceptor neurons

LPS: lipopolysaccharide, PHN: postherpetic neuralgia, TRPV1: transient receptor potential channel, vanilloid subtype 1. Adapted from Chui (19) with permission.

1.3. Periodontal diseases

Periodontal diseases encompass a wide variety of chronic inflammation of gingiva, bone and tooth supporting structures, initiated by bacterial dysbiosis. It begins with a localized inflammation of the gingiva – called gingivitis. An untreated gingivitis can progressively turn into periodontitis, which is characterized by the loss of the periodontium and subsequently loss of teeth (24). Bacteria associated with periodontal diseases are dominantly Gram-negative bacteria, such as *Porphyromonas gingivalis, Treponema denticola*, *Tannerella forsythia*, *Prevotella intermedia,* and *Fusobacterium nucleatum* (25-28). In addition, *Aggregatibacter actinomycetemcomitans* is considered as a key pathogen of early-onset periodontitis (29).

The prevalence and incidence of periodontitis are globally estimated to be 10.8% and 701 cases per 100,000 person-year, respectively (30). Generally, individuals with periodontal diseases have been found in a higher proportion in developing and developed countries (31). Host and environmental factors also contribute to disease progression and inflammation (31).

Due to the chronic nature of periodontal diseases, clinical manifestations range from mild to severe inflammation. Initial symptoms are halitosis, gingival swelling and bleeding. This is followed by uncontrolled and exaggerated inflammation, leading to destruction of periodontal tissues. Consequently, gingival recession, bone resorption, tooth mobility and tooth loss can occur (25, 27). Typically, Periodontal diseases can cause mild-to-moderate, episodic or persistent dull pain due to infection and inflammation (32). A study on chief complaints of patients seeking for periodontitis treatment reported that 21.5% of patients who suffered from periodontitis complained about their painful gingiva and teeth (33).

During invasion and infection of pathogenic bacteria, the host may perceive pain from tissue damages and inflammatory processes, or from direct bacterial stimulation, or both. A recent review has suggested that nociceptor neurons can detect Gram-positive and Gram-negative bacterial infection through specific pathogen-recognition pathways including TLRs, FPR1, TRPA1, and TRPV1 ion channels (34).

Lipopolysaccharide (LPS) is a bacterial endotoxin found in all Gram-negative bacteria. It also serves as a pathogen-associated molecular pattern (PAMP) that is detected during infection via TLR4, CD14, and Myeloid differentiation factor 2. TRPV1-positive trigeminal neurons have been found to express TLR4 and CD14, allowing them to directly sense LPS (35). A study showed that application of LPS derived from *P. gingivalis*, a bacterium commonly found in periodontal diseases and endodontic infection, activated neurons and sensitized TRPV1 via TLR4 (36). Furthermore, LPS sensitizes neurons, resulting in Ca^{2+} influx and inward currents after capsaicin stimulation, via TRPA1 ion channel (37). Consequently, CGRP neuropeptide is released from nerve ending (36, 38). Therefore, LPS from oral bacteria can sensitize and produce nociceptive sensation in intraoral organs, especially dental pulp and gingiva (Figure 2).

1.4. Orofacial herpes zoster

A number of viruses have been identified in the oral cavity. Some viruses have a clear role in developing oral lesions, such as oral ulcers from herpesviruses, oral warts and tumors from papillomaviruses (39). The human herpesvirus (HHV) family is a common cause of viral disease in the orofacial region. Three members of the human herpesviruses, consisting of herpes simplex virus 1(HSV1; HHV1), herpes simplex virus 2 (HSV2; HHV2), and varicella zoster virus (VZV; HHV3), cause painful ulceration of the skin and oral mucosa. Additionally, herpesviruses can be found in periodontal pockets in associated with *P. gingivalis*, *P. intermedia*, and *T. forsythia* (40).

VZV causes varicella (chicken pox) in the primary infection. The virus then becomes latent in ganglionic neurons and glial cells (41-43). Reactivation of latent VZV infection causes herpes zoster (shingles). The viral reactivation becomes more frequent in elders who have diminished cell-mediated immunity to the virus. Moreover, immunocompromised patients are at risk for more severe diseases, such as disseminated herpes zoster (dissemination of virus in the whole body), and have a higher incidence of complications (42, 44). The infection causes damages to the infected neurons, nerve fibers, and target tissues which innervated by those infected nerves (45, 46). Consequently, the structures and functions of both peripheral and central nervous system alter, including loss of neurons and glial cells.

VZV infection frequently occurs in advanced age patients because of decreased immunity to the virus (42). The incidence of varicella ranges from 13 to 16 cases per 1,000 person-years, while the population based incidence of zoster is around 2 to 5 per 1,000 patients-years of observation (47). The varicella vaccine dramatically reduces the per year prevalence of disease (41).

Clinical manifestations of VZV infection are typically painful unilateral erythematous maculopapular rashes distributed in specific dermatomes, except for the primary infection. The rash evolves into groups of clear vesicles and subsequently ruptures, resulting in painful ulcers. Pain, hyperesthesia, and allodynia are the most common complaint of the patient (48, 49). Herpes zoster-associated pain has been categorized as follows: acute zoster pain (acute herpetic neuralgia) which occurs after the initial rash and no longer than a month; subacute zoster pain (subacute herpetic neuralgia) which occurs between 1 to 4 month; and postherpetic neuralgia (PHN) which develops beyond 4 month since the initial onset of the rash (50). Of these, PHN is complicated and intractable herpes zoster-associated pain (50).

Generally, pain from herpes virus infection is caused by induced peripheral and central sensitization, and abnormal reorganization of nociceptive sensation (45, 46). Interesting evidence showed that the VZV cause excitation of rat DRG sensory neurons and the DRG neurons infected with VZV became more sensitive to adrenergic stimulation (51). Nociceptive neurons have been found to express TLR3 and TLR7 which recognize the single-strand RNA of viruses (52). The study of Park *et al*. found that extracellular microRNAs can stimulate DRG to fire (52). The HSV-1 infected neuron-like cell line reducing the expression of calcium channels, thereby altering electrical excitability and affecting sensory transmission (20) (Figure 2). Although the exact mechanism on how herpes viruses affect nociceptive neurons during infection and reactivation is not well understood, herpes-associated pain is previously thought to be mediated by peripheral and central neuronal changes.

Gamma aminobutyric acid (GABA)-mediated inhibition, GABA synthesis, μ-opioid receptors are destroyed from the infection, leading to the impairment of inhibitory mechanisms. Surviving neurons also demonstrate altered protein expression and phenotypic switching (45, 46). Moreover, demyelination typically occurs and lead to ephaptic crosstalk, the non-synaptic interaction between two or more demyelinated membranes. Remodeling of membranes by alteration of transducers, receptors, and ion channels can be found in herpes infection, resulting in spontaneous ectopic discharges, and hyperexcitability electrogenesis of neurons (53).

1.5. Managements of periodontal diseases

The aims of periodontal treatments are to reduce the periodontal pathogenic bacteria and to remove infected tissues, thereby provoking periodontal tissue healing (54-56). Main conventional management of periodontal disease is removing bacterial plaque and calculus by scaling and root planning. The principle of this treatment is to mechanically remove biofilm, remove supra-and infra-gingival calculus, and infected tissue. The improvement of oral hygiene is also important to achieve and balance oral microbial symbiosis (57). However, some patients do not respond well to the conventional treatment. Therefore, several adjuvant treatments have been used, including antibiotics (24, 58), probiotics (59, 60) and photodynamic therapy (61).

Probiotics are live microorganisms, which confer a health benefit on the host when administered in adequate amounts (62). The mechanism of action of probiotics on pathogenic bacteria occurs in two modes: direct and indirect interactions (23). As the direct mechanism, probiotic microbes compete and disrupt colonization of pathogens. They can also compete for nutrients and tissue binding site, and therefore disrupt the biofilm formation. Another important and distinguished mechanism of probiotics is to produce antimicrobial substances and produce unsuitable environments for competitor species. Depending on the strain of the microbes in probiotics, different substances such as lactic acid, organic acid, peroxide, bacteriocin and anti-adhesive molecule have been reported (23, 59). The indirect mechanism of probiotics against pathogen is to modulate immune cells and alter cytokine production (23).

Since probiotics exert beneficial effects against pathogenic bacteria, some clinical trials have reported the usage of probiotics in oral health, including dental caries, halitosis, and periodontal disease (63, 64). However, the advantages of probiotics in oral health care remains unclear. One systematic review suggested that probiotics could decrease the colony forming unit of bacterial pathogens (65). On the contrary, other studies have argued that probiotic treatments do not significantly alter the pathogenic flora in the oral cavity (66-68). Recent reviews and meta-analyses on the efficacy of probiotics in periodontal diseases did not confirm the effectiveness of probiotics in decreasing the number of pathogens (69-72). Therefore, the clinical question has been addressed whether probiotics have abilities to decrease pathogenic bacteria in patients with periodontal diseases.

1.6. Management of orofacial herpes zoster

VZV are neurotropic viruses that can damage the nervous system peripherally and centrally, resulting in neuropathic pain. The goal of treatment is to control the infection and pain by using antiviral agents and analgesics (48). Antiviral agents reduce viral load by blocking viral replication, leading to a reduction in the severity and duration of infection, and reducing the intensity of zoster pain (48). An anti-inflammatory effect from corticosteroid drugs can also reduce inflammatory pain in acute herpes zoster (73-75). As the infection causes structural and functional changes of the infected neurons, management may become more difficult. Currently available medications only treat symptoms, but not the underlying cause of the pain, by acting on membranes and synapses to reduce the degree of excitation and ectopic discharge (41).

On the basis of a systematic review and meta-analysis, the Special Interest Groups on Neuropathic Pain recommended use of gabapentinoids, Tricyclic antidepressants, and Serotonin-norepinephrine reuptake inhibitors as the first line drugs for neuropathic pain (76). Lidocaine patches and capsaicin patches are the second line drugs which can be used for peripheral neuropathic pain, while botulinum and strong opioids are the third line drugs with a weak recommendation (76). In addition to pharmacotherapy, local anesthesia, neurolytic block of sympathetic nerves, acupuncture, spinal intrathecal injection, intercostal nerve block, spinal cord stimulation, and cryotherapy have been used (77-79).

Gabapentinoids (gabapentin and pregabalin) are derivatives of GABA which binds to the α2-δ sub-unit of voltage-dependent calcium channels (80). Both substances have a similar pharmacological profile (81, 82). Gabapentinoids have an ability to inhibit ectopic discharges from peripheral nerve injuries, suppress neuralgia and sensitization, and modulate GABAergic, glutaminergic and monoaminergic functions (73, 83, 84). It has been used in patients with acute zoster infection in order to effectively control acute pain and prevent developing of chronic pain (85). Gabapentinoids may be successful in preventing postherpetic neuralgia in a long run by reducing the occurrence of acute herpetic neuralgia after a healed infection. The available literature on this effective of gabapentinoids is still inhomogeneous and has low statistical power. Therefore, the clinical question has been addressed to find the conclusion and increase statistical power on the efficacy of gabapentinoids in reducing the occurrence of acute herpes zoster pain.

2. Objectives

1. To investigate the efficacy of orally administered probiotics in reducing the number of periodontal pathogenic bacteria.

2. To investigate the effectiveness of gabapentinoids in reducing the occurrence of acute herpes zoster pain after herpes zoster infection.

In order to draw a conclusion from different available results, all objectives were investigated using meta-analysis.

3. Results

3.1. The efficacy of orally-administered probiotics to reduce the quantity of pathogenic periodontal bacteria

3.1.1. Protocol and registration

The protocol of this study was registered in the International Perspective Register of Systematic Review (PROSPERO) in the registration number CRD42018094903

3.1.2. Clinical question

The PICO framework was constructed according to the interested clinical question whether the orally administered probiotics decreases the level of pathogenic periodontal bacteria in saliva and dental plaque. The population (P) consists of patients with periodontal diseases; the intervention (I) is orally administered probiotics; the control (C) is placebo treatment or no treatment; and the outcome (O) is the amount of pathogenic periodontal bacteria in saliva, supra- and sub-gingival plaque. A systemic searching for both objectives were performed in databases. The keywords used for the search was [*probiotic AND ("periodontal disease" OR periodontitis OR gingivitis or plaque or saliva)*]

3.1.3. The result of literature search and the selection of studies

The comprehensive literature search from different databases, namely PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE, and Web of Science, yielded 2,210 records. No additional record was found through the bibliographic references of review articles. After removing duplicates, there were 1,281 records remaining and they were screened for titles and abstracts. Twenty-five remaining records were assessed for eligibility. Nine articles were excluded due to non-randomized controlled trials (86-90), non-periodontal disease participants (91, 92), sub-gingivally administration (93), and non-living bacteria (94). A further two studies were excluded because they did not fit the aim of this meta-analysis from measuring total bacterial numbers and obligate anaerobes (64, 95). Finally, fourteen articles were included in the qualitative analysis, and out of these, nine were suitable for quantitative analysis (Figure 3).

From fourteen included for qualitative analysis, five studies were excluded because of no periodontal pathogen number obtained after contacting the authors (96), unspecified participants with periodontal disease (97), used combinations of probiotics and antibiotics (98, 99), and delay of probiotics administration (100). The remaining nine articles (63, 68, 101-107) were included for quantitative analysis.

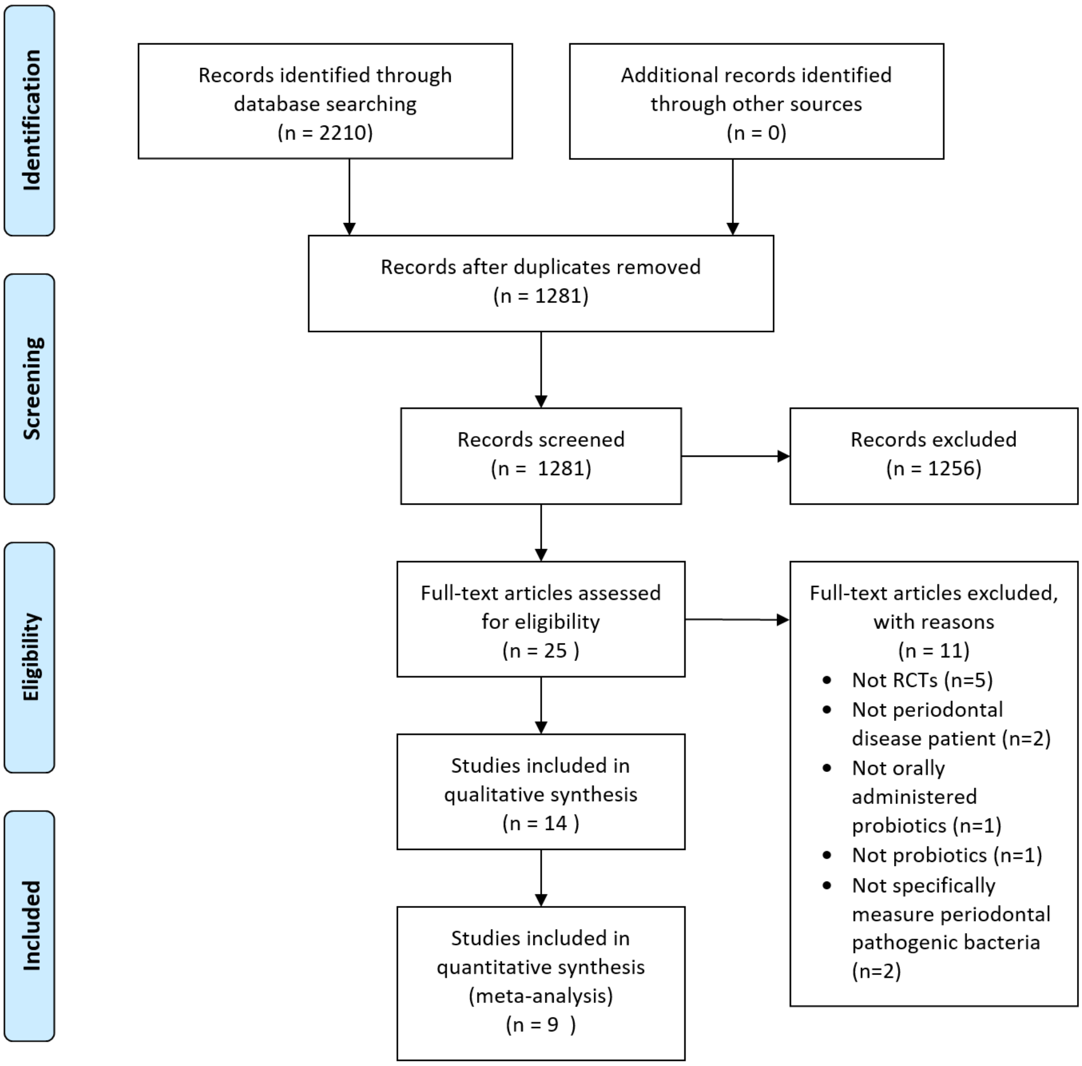

Figure 3. PRISMA 2009 flow diagram for identification of relevant studies (108).

3.1.4. Characteristics of included studies

All of the included studies are RCTs, but they differed in details. Four studies were open, controlled, parallel RCTs (97-99, 106); eight investigations were double-blinded RCTs (63, 68, 96, 101-104, 107); one study was double-blinded, crossover RCT (105), and the last one was double-blinded, split-mouth RCT (100). Each study inherited its unique in experimental design, such as different probiotic strains, forms of probiotics, instruction of use, duration of study, and the measurement of different periodontal pathogenic bacteria. The major differences among included studies for quantitative analysis are pre-treatment and microbiologic method. Majority of studies provided scaling and root planning to the participants before starting probiotics (63, 68, 101, 102, 104, 106, 107), while two studies did not provide it (103, 105). Three studies used a conventional microbiological cultivation for measuring amount of bacteria of interest (105-107), and the rest performed a molecular method using qPCR (63, 68, 101-104, 107). The summary characteristics of the included article can be found in the publication of Sang-Ngoen *et al* (108).

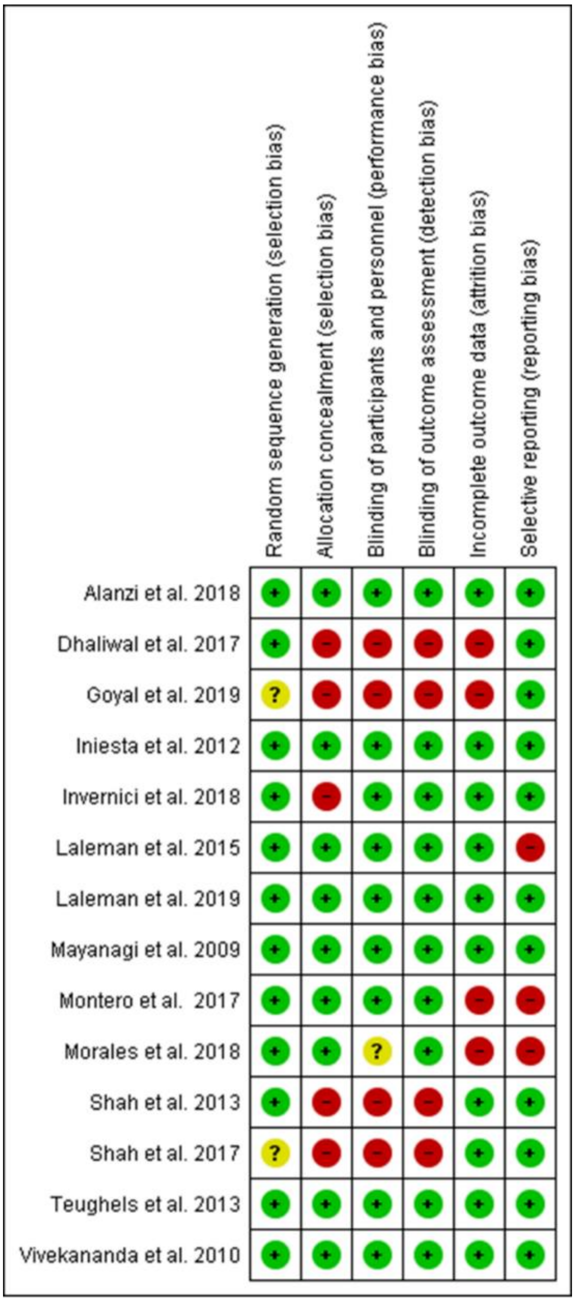

Figure 4. A summary of the risk of bias of included studies (108).

3.1.5. The risk of bias assessment

All included studies detailed the method of randomization and they were rated as a low risk of bias, except, one study that did not clearly specified the method (97). Thus, it was rated as having a questionable risk of bias. Five studies were determined as high risk of bias in the allocation of concealment domain because of no blinding of staffs (97-99, 104, 106). The performance bias domain was determined as high risk in four studies due to lack of blinding participants and involved personnel (97-99, 106), and questionable risk in one study because of a chance of unblinded personnel (107). The attrition bias domain which assesses the incomplete outcome data was rated as having a high risk for four studies due to an incomplete report without further explanation (68, 97, 106, 107). Selective reporting bias from three studies were rate as having a high risk of bias because they did not report all prespecified outcomes (68, 101, 107). The results of risk of bias assessment are summarized and detailed in Figure 4 (above).

3.1.6. The result of the meta-analysis

A. actinomycetemcomitans, *P. gingivalis*, *P. intermedia*, *F. nucleatum*, and *T. forsythia* were measured after probiotics treatment in different designated follow-up duration (four-, eight-, or twelve-week). Only the *A. actinomycetemcomitans* showed the significantly positive effect of number reduction after four week of probiotics treatment, disregarding locations of samples collected (SMD= -0.28; 95%CI= -0.56 to -0.01; p=0.045; heterogeneity: I^2=36.5%, p=0.150). However, the saliva, sub- or supra-gingival plaque of *A. actinomycetemcomitans* at four week did not show a significant difference between the probiotics treated group and control group (Figure 5). In addition, the probiotics treated group was not significantly different from the control group in overall result, saliva, sub-or supra-gingival plaque at eight week (Figure 6). With disregarding or regarding the locations of samples collected, the number of *P. gingivalis, P. intermedia, F. nucleatum*, and *T. forsythia* after treatment were not significantly different between probiotics treatment and control treatment groups at four-, and eight-week. Further forest plots representing the SMD of *P. gingivalis, P. intermedia, F. nucleatum*, and *T. forsythia* after probiotics treatment can be found in the publication of Sang-Ngoen *et al* (108).

3.1.7. Certainty of evidence assessment

The level of certainty of evidence was done using the GRADE approach on the efficacy of orally-administered probiotics to reduce the quantity of harmful periodontal bacteria. The outcomes from different pathogenic periodontal bacteria and duration of the measurement revealed very low grades in all assessments due to the presence of serious a risk of bias, inconsistency and imprecision. The summary of GRADE approaches be found in the publication of Sang-Ngoen *et al* (108).

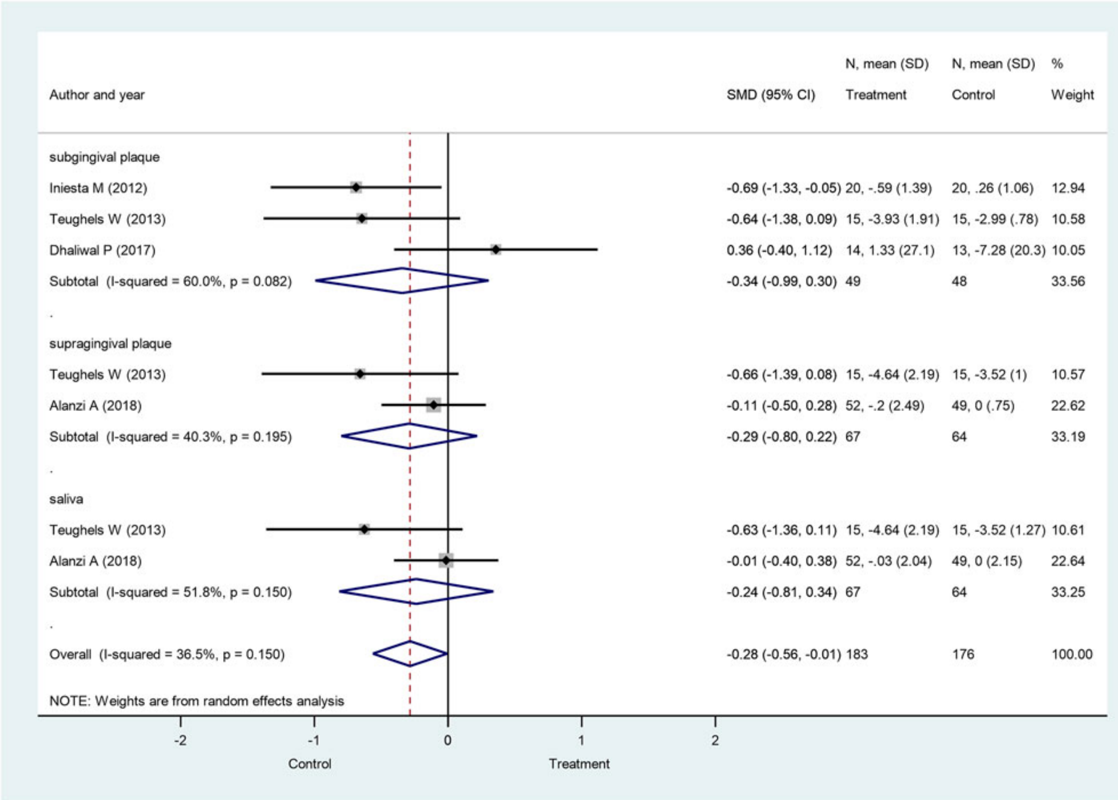

Figure 5. Forest plot analysis of the change in *A. actinomycetemcomitans* at 4 weeks (108).

The overall result of the standardized mean difference indicated a significant decrease of *A. actinomycetemcomitans* in the probiotic treatment over the control.

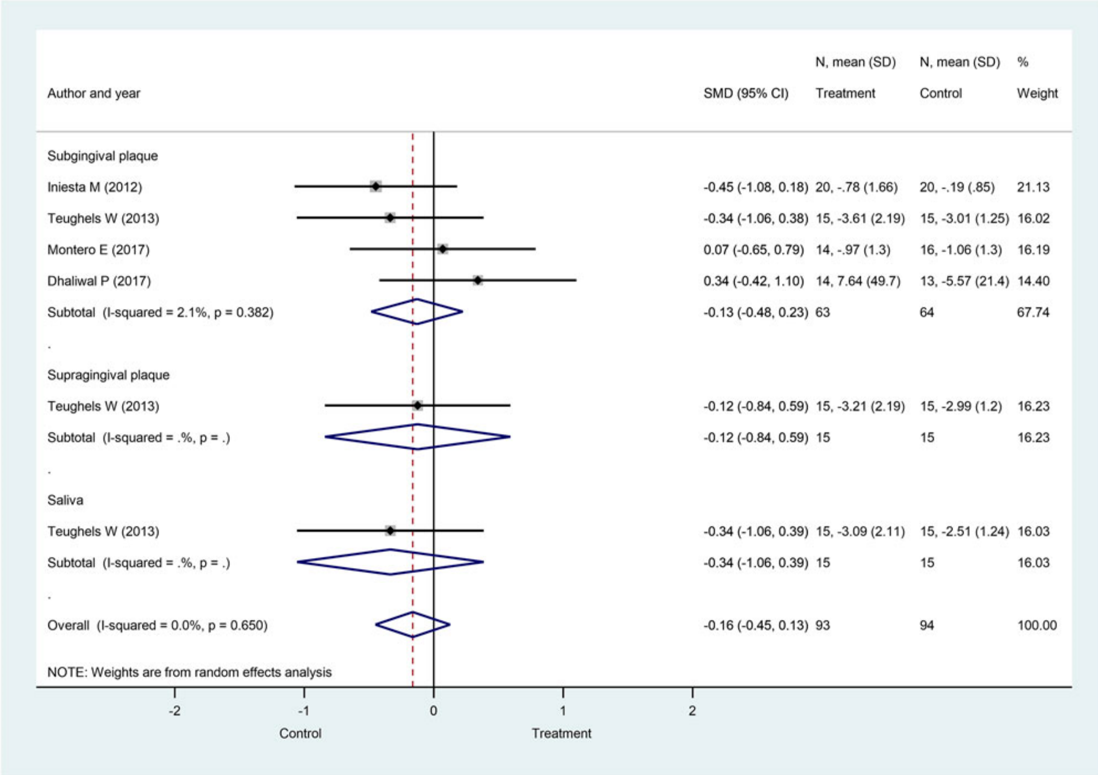

Figure 6. Forest plot analysis of the change in *A. actinomycetemcomitans* at 8 weeks (108).

The overall result of the standardized mean difference indicated a significant decrease of A. actinomycetemcomitans in the probiotic treatment over the control.

3.2. The efficacy of gabapentinoids to reduce acute herpes zoster pain occurrence

3.2.1. Protocol and registration

This meta-analysis protocol was registered in the PROSPERO; the registration number is CRD42018095758.

3.2.2. Clinical question

The PICO framework was constructed to investigate the efficacy of gabapentinoids on the reduction of the acute herpes zoster pain occurrence. The population (P) is patients with herpes zoster infection; the intervention (I) is gabapentinoids; the control (C) is placebo treatment or no treatment; and the outcome (O) is the presence of acute herpes zoster pain. The keywords used for the search was [*herpes zoster AND (gamma-aminobutyric acid OR gaba OR gabapentin OR neurontin OR pregabalin)*].

3.2.3. The result of literature search and the selection of study

The comprehensive literature search from PubMed, Web of Science, Ovid, Scopus and EMBASE databases yielded 4,888 records. No additional record was found through the bibliographic references of review articles. After removing duplicates, there were 3,130 records remaining and they were screened for titles and abstracts. Six records were relevant to the meta-analysis. Out of these, three records were excluded because one was the uncontrolled trial; another was a retrospective study (109, 110); while the third was an ongoing trial (111). The remaining three suitable records were extracted for data (112-114). See Figure 6 (below).

3.2.4. Characteristics of included studies

All included studies were single center RCTs (112-114). Each of studies exhibited some differences among each other such as the age of participants, the dosage and duration of treatment, and the use of antiviral agent. Only one study reported additional outcome on the quality of life (112). The summary characteristics of the included articles are presented in the publication of Sadaeng *et al* (115).

3.2.5. The risk of bias assessment

Although all studies stated that they were randomized trials, none of them detailed the method of randomization (112-114). Therefore, the selection bias in both random sequence generation and the allocation concealment were rated as a questionable risk of bias. All studies provided insufficient information on the blinding of participants and personnel, thus, they were determined as a questionable risk of bias in the domain of performance bias. A description of blinding outcome assessment method was described only in one study (112), therefore, it exhibited a low risk of bias in the domain of detection bias. Two studies were judged to have a high rate of incomplete outcome data (attrition bias domain) because of a high drop out rate and no dropout reason (112, 113). A low risk of reporting bias was determined in two studies (112, 113), while another was rated as a high risk because all pre-specified outcomes were not reported (114). To sum up, all studies exhibited a high risk of bias because there were at least one high risk of bias in the key domains. The results of risk of bias assessment are summarized and detailed in Figure 7.

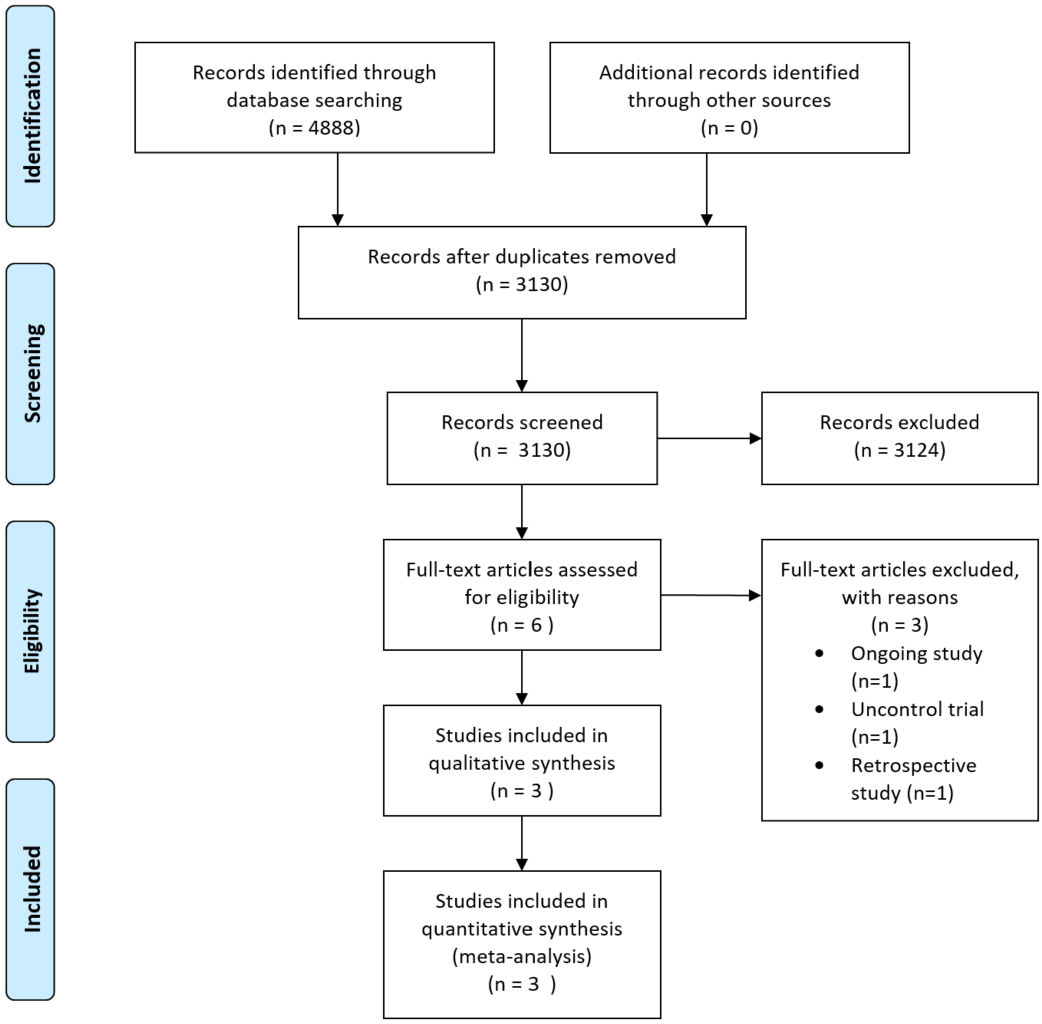

Figure 7. PRISMA 2009 flow diagram for identification of relevant studies (115).

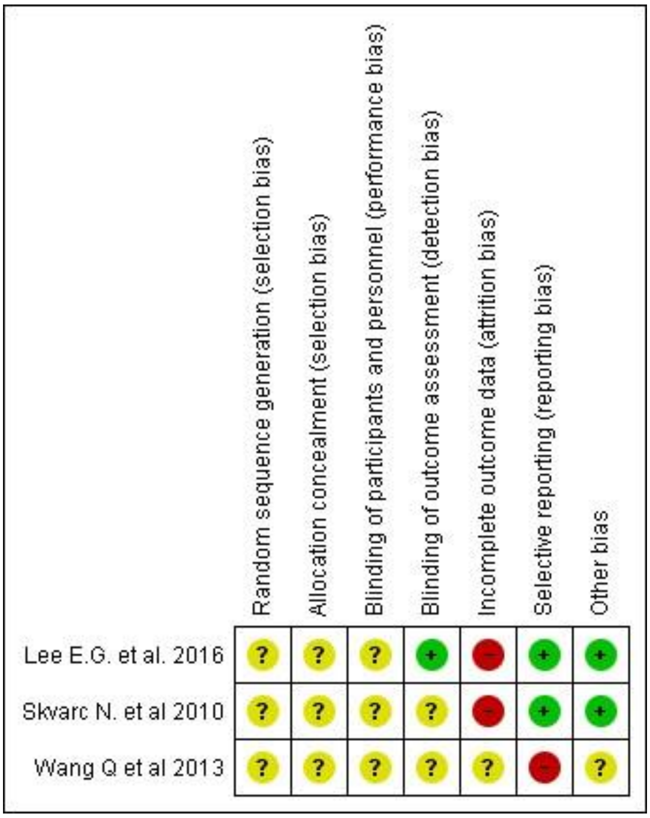

Figure 8. A summary of the risk of bias of included studies (115).

3.2.6. The result of meta-analysis

The presence of acute zoster pain after treatment

The forest plot showed the pooled odds ratios of events occurred after gabapentinoids treatment (Figure 9). The result indicated that the occurence of acute herpes zoster pain in the gabapentinoids group was significantly lower compared to the placebo group (OR=0.36; 95% CI= 0.14 to 0.93; p=0.035; heterogeneity: I^2=40.7%, p=0.186). This suggested that gabapentinoids could prevent acute zoster pain in patients after herpes zoster infection.

Presences of adverse events during treatment

The adverse events were noted in only two studies (112, 113). They reported different aspects of adverse events, but they shared some common aspect such as fatigue, constipation, and dizziness. There was no difference between the gabapentinoids group and the control group. The detail of adverse events was shown in the publication of Sadaeng *et al* (115). The meta-analysis was not performed due to insufficient data.

The quality of life

The dermatologic life quality index was assessed and reported in only one study (112). Patients suffering from HZI were asked to determine how their skin problem affects their quality of life. The quality of life between the gabapentinoids treated group and the control group was not significantly different. The meta-analysis on this basis was not performed due to insufficient data.

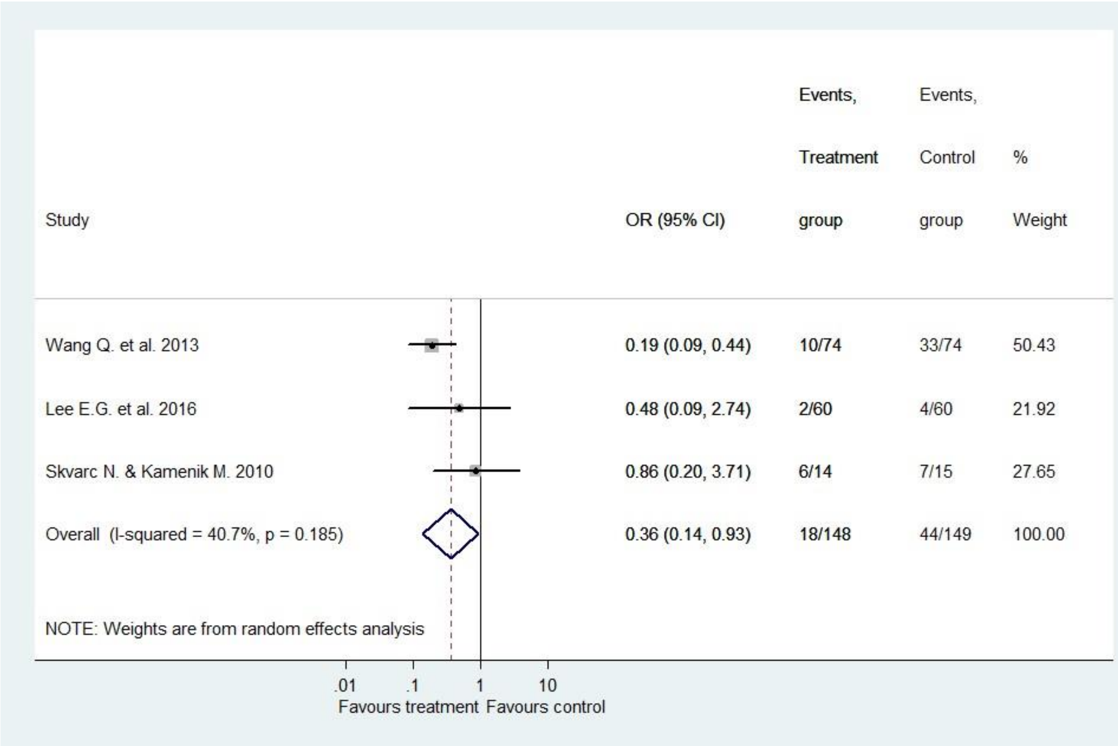

Figure 9. Forest plot analysis of the presence of acute zoster pain (115).
Overall results of odds ratio indicated a preventive effect from acute zoster pain in the gabapentinoids group over the placebo group.

3.2.7. Certainty of evidence assessment

The level of certainty of evidence was done using the GRADE approach on the efficacy of gabapentinoids to reduce the acute herpes zoster pain occurrence. The result reveled a very low grade because of the presence of a very high risk of bias and publication bias. The summary of GRADE approach is shown in the publication of Sadaeng *et al* (115).

4. Discussions

4.1. The efficacy of orally-administered probiotics to reduce the quantity of pathogenic periodontal bacteria

This meta-analysis aimed to evaluate whether orally administered probiotics decreases the level of pathogenic periodontal bacteria in patients diagnosed with periodontal diseases. The present study focused on five pathogenic bacteria which are highly related to periodontal disease progression and severity. The results from this meta-analysis suggested that the probiotics-treated group had a significant decrease of *A. actinomycetemcomitans* count when compared to the control groups at four weeks, but not at 8 weeks, after treatment initiation. Likewise, bacterial counts of *P. gingivalis, P. intermedia, F. nucleatum,* and *T. forsythia* at four weeks and eight weeks after treatment were not significantly different between probiotics and control groups.

Two studies, which included only two trials each, showed similar results to the results obtained in this study, suggesting that the use of probiotics has an insignificant effect in the reduction in the number of pathogenic periodontal bacteria count. In addition, a decreasing trend in the number of *A. actinomycetemcomitans, P. gingivalis, P. intermedia, F. nucleatum* and *T. forsythia* has been noted (116, 117). Other than the alteration of bacterial count, the clinical parameters after the probiotic used were also investigated and the results were inconsistent and diverse in each clinical parameter (70, 71, 88, 116-118). Diverse outcomes of clinical periodontal parameters have also been reported in reviews, either supporting or questioning the effectiveness of probiotics in periodontal diseases (65, 69, 72, 119-121). These controversial results may be explained by different follow-up times, various probiotic strains, and the dosage of probiotics in each trial, and different patients' characteristics.

The spectrum of periodontal diseases ranges from locally mild inflammation to generalized severe inflammation of the periodontium. In this study, all types of periodontal diseases were included for analyses. Also, all strains of probiotics were eligible for the study in order to yield the conclusive answer of the study question. Among the included studies, *Lactobacillus reuteri* has been frequently used as probiotics because it has a potency to overcome the pathogenic microorganisms by producing antimicrobial substances such as reuterin, reutericyclin, and lactic acid, and modulating the immune system (122). Additionally, *in* vivo experiments have supported the antimicrobial effect of *L. reuteri* against cariogenic and periodontogenic bacteria (123-125). In harmony with these antimicrobial activities, included studies using *L. reuterin* found a reduction of periodontal pathogens, such as *A. actinomycetemcomitans, P. gingivalis,* and *T. forsythia,* in patients with periodontal diseases (63, 97, 100, 105). In contrast, the administration of *L. reuteri* had no effect over the periodontal pathogen at 12 and 24 weeks (102). This outcome could be reversed by using a mixture of *L. reuteri* with *Lactobacillus rhamnosus, Bifidobacterium longum,* and *Bifidobacterium bifidum* (97). Therefore, it might suggest that a mixture of *L. reuteri* with other beneficial bacteria could overcome the limitation of antibacterial effect in a long-term used of *L. reuteri* alone.

The efficacy of probiotics probably relied on many factors, including bacterial strains, dosages of probiotics, durations of treatment and follow-up time (126-128). Different probiotic species may affect differently on pathogenic bacteria (128, 129), and a specific pathogenic bacteria may probably be susceptible to a specific species of probiotics (128). In periodontitis, different pathogenic bacterial species has been identified to cause different types of periodontal diseases, ranging from mild to severe and acute to chronic inflammation (130, 131). Therefore, the selection of probiotics to match the type of periodontal diseases could be considered for future studies.

Besides the species of probiotics, the amount of probiotics used can influence the outcome. The acceptable dose of probiotics used per day is at the total amount of 10^8-10^9 microorganisms (126). Included studies administered the dose of probiotics within this range.

This present meta-analysis has unavoidable limitations. A low number of included articles with relative heterogeneity is the major limitation. A major heterogeneity of included studies is microbiological assessment between conventional cultivation and molecular PCR. Since a cultivation of periodontal pathogenic bacteria is difficult to perform and has low sensitivity (132-135). This could result in a lower number of bacterial counts compared to the PCR method. Moreover, all spectrum of periodontal diseases ranging from gingivitis to severe chronic periodontitis were included in this study. Other limitations were different probiotic strains, doses and forms, specific interaction between probiotic strains and pathogenic bacterial species, different genetic background and different environment such as oral hygiene procedure or pre-treatment with scaling and root planning. These varieties across studies may have influenced the results.

4.2. The efficacy of gabapentinoids to reduce the acute herpes zoster pain occurrence

This meta-analysis aimed to investigate the effectiveness of gabapentinoids in reducing acute pain occurrence in patients who have HZV infection. By comparing the number of patients with the presence of pain between gabapentinoid-treated and placebo-treated groups, the pooled odds ratio indicated that the treatment of gabapentinoids significantly reduced the number of patients with acute zoster pain.

The pathophysiology of pain-associated with HZV infection involves both central and peripheral nervous system, resulting from the destruction of nervous system during the acute infection (136, 137). At the cellular level, the TRPV1 is upregulated and it is associated with pain (74). Furthermore, the expression of voltage-gated sodium channels and voltage-gated potassium channels is increased (138). As a consequence, peripheral nerves lose their ability to suppress nociceptive pain signals, thereby, decreasing the threshold of nociceptive sensory activation and producing spontaneous ectopic discharges. Then, peripheral and central sensitizations evoke, causing allodynia and hyperalgesia sensation (139). These pathologic outcomes cause neuropathic pain which can be controlled by GABA-like substances called gabapentinoids. A study of VZV induced neuropathic changes can be attenuated by the gabapentin or by sodium channel blockers (138).

Few well-designed studies investigating gabapentinoids were found in our preliminary literature search. Therefore, our PICO was planned to pool all types of gabapentinoids and compare them to the placebo by ignoring their differences. However, different derivatives diversely characterize in potency, adverse events, pharmacokinetics and pharmacodynamics (80). Two of included studies administered gabapentin (112, 114), while the remaining used pregabalin (113). The dosage used in included studies for gabapentin was 900 mg/day, and for pregabalin was 150 mg/day. All dosage included in this study were in a range of other trials using for PHN: 900 – 3,600 mg/day for gabapentin (84, 140-147), 150 – 600 mg/day for pregabalin (81, 148-155).

Two meta-analyses on adverse events of gabapentin and pregabalin indicated that the risk of adverse reactions significantly increased when the dosage increased (156, 157).

The common complaint of adverse events are somnolence, dizziness, ataxia, fatigue and peripheral edema which persuade patients to withdraw from the treatment (158, 159). These events usually occurred at the beginning of the treatment and at higher dosages. Therefore, a slow dose escalation was suggested to reduce the occurrence or adverse events. Included studies showed no serious adverse events of gabapentinoids. Only the study of Krčevski Škvarč *et al.* noted a significant difference in dizziness and somnolence between the pregabalin treated group and placebo groups (113).

The ability to control pain during herpes zoster infection may reduce the magnitude of the initiation phase of nociceptor evoked peripheral and central sensitivity. It was recommended to use an antiviral with effective pain control to better decrease the risk of persistent pain development than administering antiviral drugs alone (45). A published RCT protocol suggests starting the administration of gabapentin at the same time as starting antiviral therapy (160). However, the study of Bulilete *et al.* indicated that the antiviral agent with the additional gabapentin administration within 72 hours of rash onsets provided no significant relief from acute herpes zoster pain or prevent the further chronical pain (161). In the included trials, the administration of gabapentin or pregabalin was not started at the same time as the onset of the disease. We have to note that the initiation time of treatment might affect the results of individual studies and the following meta-analyses.

There are significant limitations to the present study. This study included a low number of studies with a high risk of bias, and a low number of participants. The studies have no clear randomization method and allocation concealment. This may result in imbalanced known and unknown risk factors and covariates in test and control group and selection bias. Heterogeneity of the included studies is high due to different methodologies between each study. For example, one study included participants older than 50 years old (112), while another study included participants age range from 30 – 80 years old (113). Furthermore, participants from one study received antiviral agents with the study drug within 72 hour after the onset of zoster rash (112), whereas participants in another study received treatment in a delay period (7-14 days after the onset of rash) (113). Accordingly, the results should be interpreted considering described limitations.

5. Conclusion

5.1. Meta-analysis of the efficacy of orally-administered probiotics to reduce the quantity of pathogenic periodontal bacteria

The results from our meta-analysis suggested that orally administered probiotics have an ability to reduce numbers of pathogenic periodontal bacteria – *A. actinomycetemcomitans* at 4 week, but not at 8 week, after the initiation of treatment in a pooled analysis. The amount of *A. actinomycetemcomitans* count in subgroup analyses from sub-gingiva, supra-gingiva and saliva tends to decrease after probiotics treatment. However, probiotics have no beneficial effect in reducing *P. gingivalis, P. intermedia, F. nucleatum*, and *T. forsythia*. The use of orally administered probiotics as an adjunct to the conventional scaling and root planning could reduce a specific strain of periodontal pathogenic bacteria in healthy periodontal patients. However, due to distinct heterogeneity among the available RCTs, standardized clinical protocol is needed to further evaluate the effect of various probiotics on periodontal pathogens.

5.2. Meta-analysis of the efficacy of gabapentinoids to reduce the acute herpes zoster pain occurrence

The results from our meta-analysis indicated that administration of gabapentinoids reduce the occurrence of acute herpes zoster pain after the healing of rash. Gabapentinoids also help improving the quality of life in patients who have suffered from pain during and after herpes zoster infection. However, patients could experience some adverse events, such as dizziness, which may be reasons for refusing treatment. This study provides preliminary evidence in the prevention of the development of PHN from the anti-sensitization aspect as the use of gabapentinoids can control pain which leads to the prevention of pain sensation. However, currently available evidence on this matter is weak. Therefore, additional, well designed randomized clinical trials are needed, as well as a long-term study with a higher dosage of gabapentinoids.

6. Summary

Pain is an unpleasant sensation and emotional experience of individuals. Generally, pain is perceived after tissue damage and infection, which stimulate immune cells to secrete cytokines. As a consequence, the inflammation is initiated and pain signal is generated from activated and sensitized nociceptors. Furthermore, nociceptive neurons can be activated and sensitized directly from microbes.

P. gingivalis, an anaerobic Gram-negative bacterium typically found in the oral cavity, is a causative agent for periodontitis. Its lipopolysaccharide can stimulate and sensitize nociceptors, resulting in pain. Thus, the first aim of our study was to investigate the ability of probiotics to reduce the presence of periodontal pathogenic microbial in periodontal diseases in order to decrease infection and pain levels.

Varicella-zoster virus(VZV), one of the herpes viruses found in the oral cavity, causes sever pain due to nerve damage, structural and functional alterations in the peripheral and central nervous system. Neuropathic pain caused by VZV infection can be controlled by the use of gabapentinoids. These agents block calcium channels which probably intercept the neuronal sensitization. Therefore, the second aim was to investigate the effect of gabapentinoids in reducing the occurrence of herpes zoster pain after the condition has healed.

To perform these studies, meta-analysis was used to evaluate the available evidence. Databases were searched for eligible studies. Then, the data were collected and analyzed to address each aim.

The results from the first meta-analysis showed that probiotics can significantly reduce the number of A. actinomycetemcomitans in patients with periodontal disease at 4 weeks, while other periodontal pathogens – P. gingivalis, P. intermedia, F. nucleatum, and T. forsythia – were not changed after the used of probiotics. The different response of pathogens and probiotics may probably arise from the specificity of probiotics-pathogens. The second meta-analysis on gabapentinoids and herpes zoster pain indicated that gabapentinoids can reduce the observed rate of recurring herpes zoster pain after the healing of acute VZV infection. However, limitations from inhomogeneity of study design, low number of included studies and participants, publication bias, and small study effects may influence the outcomes of meta-analyses. Therefore, additional, well-designed randomized clinical trials with large number of participants are needed to overcome those limitations.

In conclusion, periodontal disease-associated pain may be controlled by using specific probiotic. While, herpes zoster-associated pain can be managed with gabapentinoids, which could be beneficial in preventing the development of postherpetic neuralgia.

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8. Bibliography of the candidate's publications

The publications related to the PhD thesis

1. **Sadaeng W**, Marta K, Matrai P, Hegyi P, Toth B, Nemeth B, Czumbel LM, Sang-Ngoen T, Gyongyi Z, Varga G, Revesz P, Szanyi I, Karadi K, Gerber G. (2020) gamma-Aminobutyric Acid and Derivatives Reduce the Incidence of Acute Pain after Herpes Zoster - A Systematic Review and Meta-analysis. Curr Pharm Des, 26: 3026-3038. **IF: 3.116**

2. Sang-Ngoen T, Czumbel LM, **Sadaeng W**, Miko A, Nemeth DI, Matrai P, Hegyi P, Toth B, Csupor D, Kiss I, Szabo A, Gerber G, Varga G, Keremi B. (2021) Orally Administered Probiotics Decrease Aggregatibacter actinomycetemcomitans but Not Other Periodontal Pathogenic Bacteria Counts in the Oral Cavity: A Systematic Review and Meta-Analysis. Front Pharmacol, 12: 682656: 1-14. **IF: 5.811**

The publication non-related to the PhD thesis

1. Ruksakiet K, Hanak L, Farkas N, Hegyi P, **Sadaeng W**, Czumbel LM, Sang-Ngoen T, Garami A, Miko A, Varga G, Lohinai Z. (2020) Antimicrobial Efficacy of Chlorhexidine and Sodium Hypochlorite in Root Canal Disinfection: A Systematic Review and Meta-analysis of Randomized Controlled Trials. J Endod, 46: 1032-1041. **IF: 4.171**

2. Lukács A, Máté Z, Farkas N, Mikó A, Tenk J, Hegyi P, Németh B, Czumbel LM, **Wuttapon S**, Kiss I, Gyöngyi Z, Varga G, Rumbus Z, Szabó A. (2020) The quadrivalent HPV vaccine is protective against genital warts: a meta-analysis. BMC Public Health, 20: 691: 1-16. **IF: 3.295**

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