Nutraceuticals of nano-betel (Piper betle L.) leaves: prevent COVID-19 and oral cavity disease

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Nutraceuticals of nano-betel (*Piper betle* L.) leaves: prevent COVID-19 and oral cavity disease

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ABSTRACT

Introduction: Betel leaf is very popular in Asia and known to have a function as traditional medicine. And is often referred to as the "Golden Heart of Nature". This is because the betel leaf has an effect such as antimicrobial, antiviral, radioprotective, antioxidant, antiseptic, bactericidal, anti-inflammatory, antiallergic, wound healing, antiplatelet, antibacterial, antifungal, and immunomodulatory activity. Nutraceutical nano-betel leaf extract contains rich in minerals, vitamins, antioxidants, phenolic compounds, and essential oils. Effectively protects the mouth from pathogens. This research aims to review the nutraceuticals of nano-betel leaf extract to prevent COVID-19 and oral cavity disease.

Methods: This systematic review study was conducted through six steps: (1) framing the questions (based on theory); (2) Run a search (on Scopus, Google Scholar, EBSCO, ProQuest, and Science Direct publishing articles from 2020 to 2022); (3) Determine the relevant research; (4) Determine the articles come from diverse backgrounds; (5) Extraction of data from individual studies; (6) Synthesis of results using the narrative method.

Results: Betel leaf contains nutrients for oral health, immunomodulators, and COVID-19, namely protein, amino acids, vitamins A, B, C, and K, as well as minerals such as Mg, K, Ca, Fe, I, P, Zn, essential oil (eugenol, hydroxylchavicol, allylpyrocatechol, quercetin, etc). Betel leaf nano extract has a significant role as antioxidants, anti-inflammatory, antimicrobial, and antivirus, which act as anti-oral cavity disease and anti-COVID-19. Betel leaf nano extract has a significant role in curing various oral cavity diseases related to COVID-19, including fungal infections, toothache, conjunctivitis, re-current HSV, oral ulcerations, xerostomia or decreased salivary flow, and gingivitis.

Conclusion: Betel leaf nano extract has a significant role in curing oral cavity disease and COVID-19. It is recommended that research into the oral disease and COVID-19 drugs combined with viable ingredients substances from betel leaf.

Keywords: *Piper betle* L., nutraceutical, oral health, COVID-19

INTRODUCTION

Nutraceutical betel leaf (*Piper betle* Linn.) is very well known for centuries in South Asia, Southeast Asia, and East Asia, and now it is known worldwide. Betel leaf is widely used as an ingredient in traditional medicine to treat various diseases, is often consumed as a mouth freshener, and is also a source of new therapeutic value. This value indicates that it is suitable for future use as a promising source for treating various conditions. Therefore, with its many biological activities, it has tremendous potential to be used as a future nutraceutical.[1,2]

Betel leaves have been studied for their effectiveness in caries control, periodontal disease, strengthening gums, preventing tooth decay, and controlling halitosis.[2,3] Several studies have stated that betel leaf extract is superior in tackling respiratory tract diseases.[4,5] The results of the study stated that the betel leaf concoction satisfactorily coped with COVID-19.[6]

COVID-19 is caused by the severe acute respiratory syndrome of coronavirus 2 (SARS-CoV-2). WHO declared the COVID-19 pandemic on March 11, 2020. The most common symptoms of COVID-19 are cough, runny nose, stuffy nose, diarrhea, and respiratory problems. COVID-19 can exacerbate oral lesions, such as candidiasis, herpes simplex, geographic tongue, ulceration, white hairy tongue, reddish macules, erythematous surface, petechiae, and pustular enanthema.[7,8]

The bioactive substances contained in betel leaf have a weakness, namely low bioavailability.[9] Betel leaf extract in the form of nanoparticles has better antimicrobial and anti-inflammatory properties by increasing its ability to penetrate cell walls. The ability to penetrate the cell wall is higher and the affinity increases due to the increase in the contact surface area by the same amount.[10] The results showed that there had been a bond between hydroxyapatite compounds and metabolites in green betel leaf extract. In testing the smallest particle size was indicated by the variation of hydroxyapatite composite and green betel leaf extract 0.3 grams, which was 690.08 nm. Antibacterial activity test of hydroxyapatite green betel leaf extract showed inhibitory activity against *Streptococcus mutans* in the strong category.[11] Based on the above background, the researcher aims to go further by analyzing how the nutraceuticals of nano betel leaf extract (*Piper betle* L.) prevent oral disease and COVID-19.

METHODS

This systematic review study was conducted through six steps: (1) framing the questions (based on theory); (2) Run a search (on Scopus, Google Scholar, EBSCO, ProQuest, and Science Direct publishing articles from 2020 to 2022); (3) Determine the relevant research; (4) Determine the articles come from diverse backgrounds; (5) Extraction of data from individual studies; (6) Synthesis of results using the narrative method.

A systematic database search used to be carried out for 2020 to 2022, with keywords *Piper betle* L. AND nutraceutical AND oral health AND COVID-19. For inclusion criteria, the researchers considered a learn about (feasible) that used to be appropriate for systematic review: (1) goals: study betel leaf for nutraceutical and COVID-19, (2) outcome: oral and COVID-19 health. While exclusion criteria are conducted by selecting published articles based on titles and abstracts that were not complete text and irrelevant.

RESULTS

Article search results in the database, namely Scopus, Google Scholar, ProQuest, and ScienceDirect have identified 81 articles, consisting of 5 review articles, and 4 experimental laboratory designs, from 3 countries, namely Indonesia, India, and Malaysia.

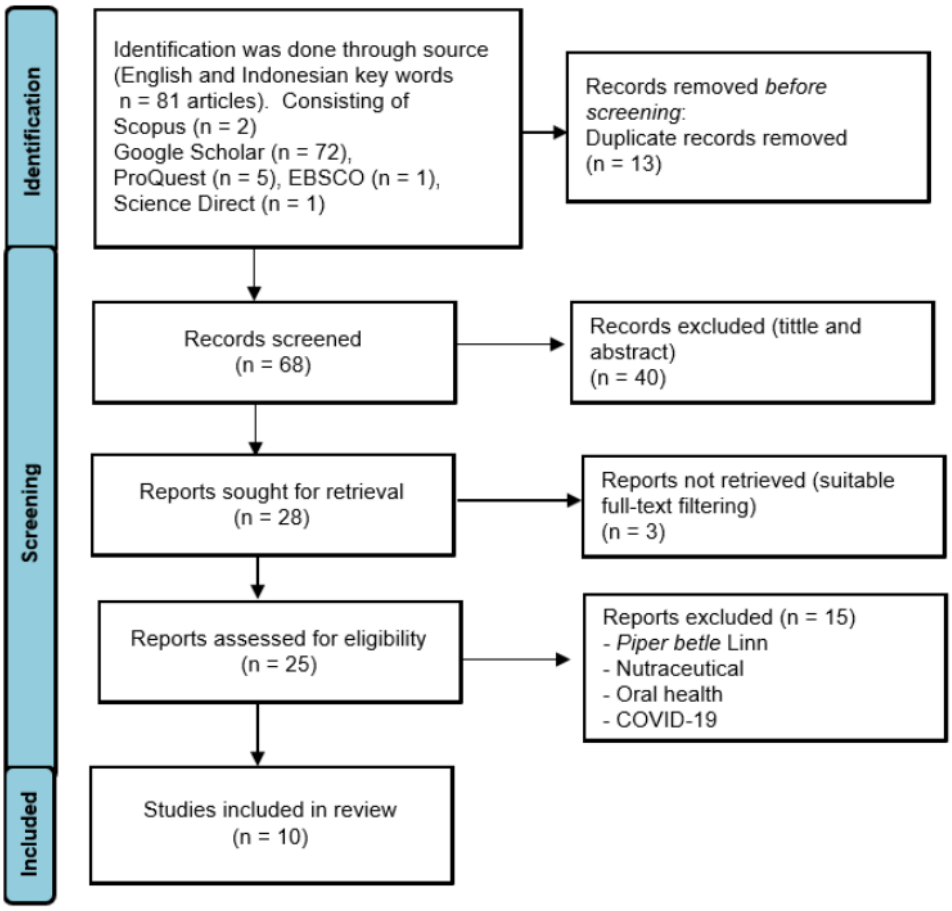

Figure 1. PRISMA Systematic Review[12]

Of the 7 articles representing that analyzing the potential of betel leaf as an antimicrobial/anti-oral disease/anti-COVID-19. The results of the selection of 10 articles are in accordance with the results of research which proves that betel leaf is high in quality nutrients/antioxidants/anti-inflammatory in 4 articles. While the results of the selection of 9 articles are in accordance with the results of research which proves that nano-betel leaf which is high in antibacterial/antimicrobial/anti-COVID-19 content is from 7 articles. Presented in Table 1, Summary of the results of nutraceuticals, oral health, and COVID-19 of nano-betel (*Piper betle* L.) leaf extract.

Table 1. Summary of the results of nutraceuticals, oral health and COVID-19 of nano-betel (*Piper betle* L.) leaf extract

Author	Title, and Study design	Results
Florent et al. (2022).[13] Indonesia	Nano-green betel leaf extracts (*Piper betle* L.) inhibits the growth of *Streptococcus mutans* and *Staphylococcus aureus.* Experimental design	In conclusion, nano-green betel leaf extract (*Piper betle* L.) showed better antibacterial effectiveness than micro-sizes in inhibiting *Streptococcus mutans* and *Staphylococcus aureus* bacteria.
Fatimawali et al. (2022).[14] Indonesia.	Immunomodulatory potential of bioactive compounds of betel leaf extracts targeting COVID-19 immunological human host proteins: An in-silico study. Experimental Design	This study states that bioactive compounds derived from betel leaf have proven to be useful in the treatment of COVID-19, especially in the context of cytokine storms.
Patra et al. (2022).[15] India	Flavored food additives on the leaves of *Piper betle* L.: A Human health perspective. Review	This study showed that the essential oil of betel leaf extract can inhibit microbial growth and damage various gram-positive and gram-negative bacteria and various fungal species. The combination of betel leaf essential oil with antibiotics has the potential to affect oral microorganisms.
Biswas et al. (2022).[16] India	Betel vine (*Piper betle* L.): A comprehensive insight into its ethnopharmacology, phytochemistry, and pharmacological, biomedical and therapeutic attributes. Review	Research shows that *Piper betle* essential oil and extract show good results as antimicrobials, have potential multi-therapeutic properties in various diseases such as inflammation, asthma, dental and oral infections.

Sahu et al. (2022).[17] India	An overview of betel vine (*Piper betle* L): Nutritional, pharmacological and economical promising natural reservoir. Review	*Piper betle* has high nutritional quality, eugenol essential oil, antimicrobial, anticancer, antioxidant, anti-apoptotic, and anti-inflammatory.
Lawarti et al. (2022).[11] Indonesia	Potential antibacterial activity of hydroxyapatite composite and green betel leaf extract (*Piper betle* Linn.) against *Streptococcus mutans* bacteria. Experimental design	This study showed that the smallest particle size was indicated by the variation of the hydroxyapatite composite and the green betel leaf extract 0.3 grams, which was 690.08 nm. Antibacterial activity test of hydroxyapatite green betel leaf extract showed inhibitory activity against *Streptococcus. mutans* in the strong category.
Rahmah et al. (2022).[18] Malaysia	Optimization of phenolic compounds and antioxidant extraction from *Piper betle* Linn. leaves using pressurized hot water. Experimental design	The results of this study indicate that Pressurized Hot Water Extraction is a potential extraction method to extract phenolic and antioxidant compounds from betel leaf.
Nayaka et al. (2021).[3] Indonesia	*Piper betle* (L.): Recent review of antibacterial and antifungal properties, safety profiles, and commercial applications. Review	This study showed that the essential oil of betel leaf extract, can inhibit microbial growth and kill various gram-negative and gram-positive bacteria and fungal species, including those that are resistant to various drugs and cause serious infectious diseases.
Soni et al. (2020).[19] India	Synergistic prophylaxis on COVID-19 by nature golden heart (*Piper betle*) & Swarna Bhasma. Review	This study showed that the water extract of fresh betel leaf showed efficient inhibition of microorganisms (antimicrobial activity) and immunomodulatory activity, so that it has the potential to overcome COVID-19.

DISCUSSION

The COVID-19 outbreak was classified as a Public Health Emergency of International Concern by WHO. The prevention and control of COVID-19 are extremely serious given the sudden rise in confirmed cases. The province with the largest number of deaths and infections from the coronavirus is recovering following therapy with a combination of Traditional Chinese Medicine and Western medicine, so Chinese health authorities are turning to centuries-old traditional medicine to treat it. For the prevention of COVID-19, betel leaf components are a crucial component.[20]

According to the findings, betel leaf extract can treat respiratory viruses that cause the flu, including influenza, respiratory syncytial virus, human metapneumovirus, etc. Influenza viruses are the most common cause of illness and mortality among respiratory viruses. Because the influenza virus is an RNA virus with a frequently changing genome, creating antiviral medications is extremely difficult. Although many antiviral medications have been created and sold to treat these viruses, the emergence of antiviral drug-resistant strains has been on the rise due to viral genome changes.[5]

Betel leaf contains antioxidants that can minimize the severity of disease caused by the formation of free radicals during influenza virus infection. The antioxidant activity of betel leaf extract is caused by the presence of phenolic compounds, hydroxy-chavicol, chevibetol, allylpyrocatecholare, and contains vitamin C (high nutritional quality).[17,18,20–22] The antioxidant activity of nano betel leaf extracts have the capacity to combat COVID-19-like illness.[14]

One of the conditions that trigger the fusion of COVID-19 with human cells is endosomes that are acidified on the cell surface. In other words, the virus requires a low pH environment.[23] Betel leaf with a little hydroapatite whiting can normalize the body's pH, so that the coronavirus cannot live, by chewing fresh betel leaves with a little hydroapatite whiting, can make the body condition alkaline, at a cost cheap and practical.[24] This happens because hydroxyapatite can extract nano bioactive substances from betel leaf, so that the high content of potassium in betel leaf can be extracted and can be available for the body.[25]

Nutraceutical

The scientific development of nutraceuticals has continued to grow in recent years. Natural nutrients contained in plants, turns out to have potentially beneficial effects on health. Nutraceuticals can be extracted, used for dietary supplements, or added to food. The results of the study show the nutraceutical potential of betel leaf, including the high content of vitamin C, and essential oil (which acts as an antioxidant, antimicrobial, anti-inflammatory, and antivirus). This has been proven in research on betel leaf ingredients in communities in Indonesia and India, which has succeeded satisfactorily in overcoming COVID-19.

Protein, vital fatty acids, carbohydrates, vitamins A, B, and C, as well as minerals like Mg, K, Ca, Fe, I, P, and Zn are all nutrients found in betel leaves that are beneficial for oral and dental health as well as COVID-19 prevention. Chevibetol and allylpyrocatechol, two antioxidants that work as COVID-19 inhibitors, are found in betel leaves, which also have potassium as a possible nutrient. In the context of the continuing COVID-19 pandemic, the principal nutraceuticals to which viral roles have been assigned, betel leaf nano extracts have long been intriguing in terms of their viral capabilities (either by direct action on viruses or by modulating the immune system).[9,13,15,25] An adequate balance of vitamins and micronutrients, including zinc is important for maintaining oral health and general health.[26]

The results of the study stated that betel leaf contains the mineral zinc.[27] According to studies, zinc may lessen viral replication and boost immune responses. Prophylactic treatment may offer an extra barrier against the start and spread of COVID-19 while eating zinc (within the advised upper safety limits). This appears to support the notion that preventing COVID-19 infection requires maintaining an ideal zinc balance. Higher intracellular zinc concentrations may have an impact on how the RNA viruses replicate, slowing down viral replication. The fact that COVID-19 is an RNA virus is noteworthy (Figure 2). Low zinc level may influence vaccine reactions even after vaccination.[28]

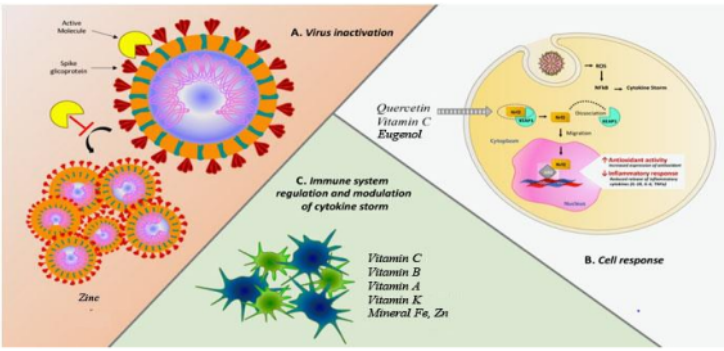

Figure 2. Summary of reaction scheme of betel leaf nutraceuticals in tackling oral disease and COVID-19[29]

Antimicrobial

Betel leaf is a good source of natural antioxidants for the pharmaceutical industry, which will achieve the desired therapeutic results and can be of great potential as a source of health care to fight various pathogens.[16,20] Inhibiting the growth of germs and harming numerous gram-positive and punnet bacteria, as well as fungus species, is possible with betel leaf extract and its essential oil. According to some studies, combining piper leaves essential oil with antibiotics may have an impact on the oral bacteria.[15]

Betel leaves, which have valuable medicinal and nutritional qualities, are traditionally chewed after meals. It creates an enzyme that aids in digestion and acts as a breath

freshener in addition to containing some vitamins and minerals. The leaf has high antibacterial efficacy against a variety of microbes, according to published research.[30] Previous research has shown that green betel leaf contains alkaloids, flavonoids, tannins, saponins, phenolics, and terpenoid compounds that inhibit bacterial growth.[31] The betel leaves have essential constituents namely Eugenol and Quercetin, has been verified to exhibit antioxidant, antiinflammation, and antiviral properties.[19,22] In vitro effects of Quercetin is inhibition of JNK pathway, antagonized HIV-Luc/SARS pseudotyped virus entry (Figure 2).[32]

Nano-green betel leaf extract (*Piper betle* L.) showed better antibacterial effectiveness than micro-sizes in inhibiting *Streptococcus mutans* and *Staphylococcus aureus* bacteria.[13] This is in accordance with the results of research that betel leaf boiled water contains Hydroxychavicol, which has strong and good antibacterial activity. Along with oral cavity infections, piper betel leaves exhibit inhibitory effects. The biofilm created by anaerobes and the biofilm created in pooled saliva were both reduced by 0.5 percent Hydroxychavicol. the application of hydroxychavicol as a dental care product.[24,33]

Immunomodulatory activity

Piper betle leaf is a potential herbal medicine to grow the human body's self-defense mechanism against either the reception of such pathogens or in viral load reduction of affected patients. Betel leaf contains vitamins (A, B, and C), as well as minerals (Fe and Zn), which have been demonstrated to have key roles in supporting the human immune system, and reducing the risk of infections oral disease, and COVID-19, the reaction scheme is depicted in Figure 2.[25,33] Studies have shown that the immune-stimulating vitamin zinc may lower viral multiplication and promote immunological responses. Prophylactic may offer an additional defense while eating zinc (within the advised upper safety limits).[28]

Diosgenin, eugenol, allylpyrocatechol, Methyl eugenol, chavibetol, hydroxychavicol, triterpenes, and beta-sitosterol are all present in piper betle. The pharmacological profile of this drug has been demonstrated to have antiplatelet, anti-inflammatory, immunomodulatory, gastroprotective, and anti-diabetic properties. Important chemical components found in betel leaf include chavibetol, allylpyrocatechol, eugenol etc.[21,22,24] These components are valued as stimulants for their medicinal properties like antiplatelet, anti-inflammatory effects as well as immunomodulatory, and gastroprotective activity, reducing the risk of infections oral disease and COVID-19.[22,24]

Betel leaves contain vitamin A, B, C, K, and mineral-like Mg, K, Ca, Fe, I, P, and Zn, which act as immunomodulatory activity.[25,27,30] Vitamin C modulates the immune system in vitro (lower levels of inflammatory cytokines IFN, IL-6, and TNF are released). Vitamin C aids in the phagocytosis of infections by neutrophils. The control of NK cells, macrophages, and neutrophils is aided by vitamin A. Vitamin K aids in controlling the immunological response brought on by vascular injury.[29] Iron deficiency induces thymus atrophy, reducing

the output of naive T lymphocytes, and has multiple effects on immune function in humans.[33] A summary of the reaction scheme is depicted in Figure 2.

This Systematic review research has several limitations. First, only one study was found that discussed the nano betel leaves extract associated with COVID-19. Second, only one study was found that discussed the nano betel leaves extract related to oral cavity disease. Third, there were no studies that discussed betel nano extracts related to COVID-19, and oral cavity diseases. Fourth, so that we cannot review in more detail how the nano betel leaf extract controls COVID-19 and oral disease. The advantage of this research is that it can inform the importance of knowledge of betel leaf nano extract, for the success of COVID-19 and oral cavity disease therapy.

CONCLUSIONS

Nanobetel leaf extracts have a strong ability to fight COVID-19 and oral cavity illness. Commercially available anti-oral disease and anti-COVID-19 medications may exhibit synergistic action when evaluated in combination with betel leaf components. The effective dose of antivirals may be decreased, lowering drug pressure and preventing the emergence of viral strains that are resistant to treatment-induced drug exposure.

AUTHOR CONTRIBUTION

I G.A.A.A. conceived of the presented idea, carry out data collection, data analysis and interpretation, and be responsible for final approval of the version to be published; S.W. develop theory; D.M.W. verify the method of analysis; IW.W analyzed data and interpretation; A.A.W.L. analyzed data and interpretation. All authors discuss the results and contribute to the final manuscript

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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ETHICAL CONSIDERATION

This research was approved by the Ethical Committee of Faculty of Dentistry, Mahasaraswati Denpasar University. Letter of exemption Ref. No. K547/A.06.01/FKG-Unmas/VII/2022.

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