



The Effectiveness of Red Betel Leaf and Cinnamon Oil for Antibacterial and Anti-inflammatory in Perineal Tears: A Scoping Review

Ratih Devi Alfiana^{1*}, Sundari Mulyaningsih¹, Emelda Emelda², Dyah Pradnya Paramita¹, Amanah Rahma Delia¹, Shofi Salsabila²

¹Department of Midwifery, Faculty of Health Science, Universitas Alma Ata, Yogyakarta 55183, Indonesia; ²Department of Pharmacy, Faculty of Health Science, Universitas Alma Ata, Yogyakarta 55183, Indonesia

Abstract

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***Correspondence:** Ratih Devi Alfiana, Department of Midwifery, Faculty of Health Science, Universitas Alma Ata, DI. Yogyakarta, 55183, Indonesia.
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BACKGROUND: A tear in the perineum experienced by postpartum women can occur due to an episiotomy process or a spontaneous tear. This cloak, in addition to causing curiosity, can also cause infection if not treated or treated appropriately. Based on several research results, the current treatment for perineal tears is the administration of antiseptic, anti-pain, and antibiotics orally or topically. Several Indonesian herbal plants can be used to accelerate the healing of torn wounds in the perineum due to the ability of these plants as antibacterial and anti-inflammatory. These plants include red betel leaf and cinnamon oil.

AIM: The objective of the study was to review the literature from research results that discuss the activity of red betel leaf and cinnamon oil as antibacterial and anti-inflammatory both orally and topically.

SEARCH METHOD: Searching for articles through databases on Google Scholar, in the past years, that is, 2008–2021.

INCLUSION: Review articles involving research on experimental animals with *in vitro* and *in vivo* activity tests using the Completely Randomized Design method.

RESULTS: As well as, 12 relevant articles showed that both red betel leaf and cinnamon oil were tested *in vitro* and *in vivo*, showing that these two plants effectively act as antibacterial and anti-inflammatory.

CONCLUSION: Two herbal plants red betel leaf and cinnamon oil have the potential to treat and accelerate the healing of perineal tears through their antibacterial and anti-inflammatory activities.

Introduction

The female perineum has structures that are at risk for birth trauma due to spontaneous perineal tears of various degrees or actions episiotomy. This injury can lead to complications directly and long term in women. The risks can be best separated into the following subgroups: Maternal, fetal, and intrapartum risk factors [1], [2]. Broad-spectrum antibiotics are recommended in the immediate post-operative period to reduce the risk of infections and wounds. Paracetamol and nonsteroidal anti-inflammatory drugs (NSAIDs) can be used. However, the use of opioids is limited to reduce the risk of constipation. Therefore, it is necessary to review the literature from research results that discuss the activity of red betel leaf and cinnamon oil as antibacterial and anti-inflammatory both orally and topically so that they can help the wound healing process [3], [4], [5].

Methods

Study design

This study used a scoping review design. This design was chosen because it provides a broad coverage for a particular field. This scoping review procedure goes through several stages. The first is formulating clear research questions and objectives, then identifying appropriate research, then sorting research articles, then extracting and charting data, and then concluding and analyzing the results of the research [6].

Literature search strategy

Literature searches were carried out on several databases. The search was carried out by two researchers, who conducted separate searches on Google Scholar. The keywords used are a combination

of Medical Subheading (MESH) using Boolean's Logic to find the right article and specifics. The combination of MESH terms we use is: ("Red Betel Leaf as Anti-inflammatory," "Red Betel Leaf as Antibacterial," and "Cinnamon Oil as Anti-inflammatory") and "Cinnamon Oil as Antibacterial."

Identification and selection relevant articles

The search results of the two researchers then compared with the team and then discuss if there were any differences which were then discussed and made a decision to get the same number of searches. Articles that meet the criteria are entered into a chart (PRISMA) to report search progress (Figure 1).

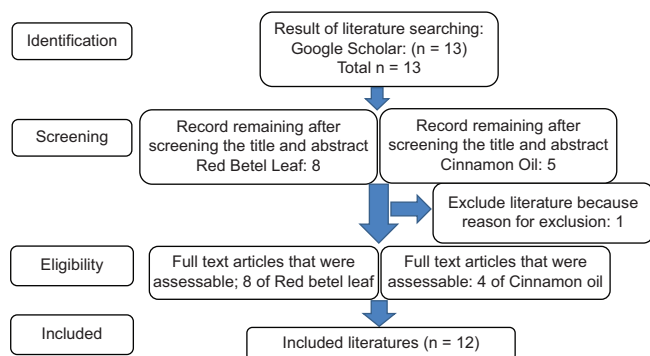


Figure 1: PRISMA flowchart for scoping review

Inclusion criteria

The following criteria were included in the study:

1. Research that aims to determine the content of red betel leaf extract as antibacterial or anti-inflammatory
2. Research samples *in vivo* and *in vitro*
3. In English
4. Full-text articles

Exclusion criteria

We exclude articles that use the literature review method.

Data extraction

Articles under the inclusion criteria are put together, then extracted on an Excel worksheet. The data extracted include title, author, date of publication, country and region, research objectives, study design, targets of study, number of samples, study settings, data collection, key findings, research domain, and subdomain.

Summarizing the findings

All articles in the inclusion criteria were then summarized taking into account the findings regarding

the content of red betel leaf and cinnamon oil and their effect on inhibiting bacterial growth in wounds. The methodological characteristics of the articles were also evaluated using an Excel spreadsheet. Each article will be rated on the research design, research target, sample, and results.

Results

Characteristic of published articles

We include 12 articles based inclusion and exclusion criteria. The articles are published from Elsevier (2), Jurnal Ilmu Dasar (1), Journal of Pharmaceutical sciences and research (1), International Research Journal of Advanced Engineering and Science (1), Journal of Natural Remedies (1), IOP Conf. Series: Earth and Environmental Science (1), Journal of International Oral Health (1), Journal of Pharmaceutical Biology (1), BMC Journal (1), Journal of microbiology and immunology WILEY (1), and Proceedings of The 2nd Annual International Conference Syiah Kuala University (1).

Data extraction of the included articles

The article data information is detailed in Table 1, all articles discuss the findings regarding the content of red betel leaf and cinnamon oil and their effect on inhibiting bacterial growth in wounds. However, some articles not describe in detail the method and number of samples. This information will be explained clearly in Table 1.

Discussion

Perineal trauma involves any type of damage to the female genitalia during labor, which can occur spontaneously or iatrogenically (through episiotomy or instrumental delivery) [7], [8]. More than 85% of females who undergo a vaginal birth will suffer from some degree of perineal tear, with 0.6–11% of all vaginal deliveries resulting in a third-degree or fourth-degree tear. Fortunately, the incidence of perineal tears decreases with subsequent births, from 90.4% in women who are nulliparous to 68.8% in women who are multiparous undergoing vaginal deliveries [9], [10]. While there is a high risk for perineal trauma following any vaginal birth, it is particularly important to note the risk factors that contribute to severe perineal tears (third degree and fourth degree). The risks can be best separated into the following subgroups: Maternal, fetal, and intrapartum risk factors [1], [2]. Perineal tears

Table 1: Data extraction of the included articles (n = 12)

Author (s) and date of publication	Country/region	Aim	Extract	Data collection	Key findings
Anugrahwati <i>et al.</i> , 2016	Indonesia	To investigate separation process in extraction of red betel leaves using ethanol, followed by performing cytotoxicity test on HeLa cell line from cervix tumor/cancer.	Red betel leaves	Fresh leaves of red betel were picked, thinly cut and dried in atmospheric air. First, dried leaves of red betel were taken about 25 g and were extracted with ethanol as a solvent using Soxhlet apparatus in temperature of ca. 78°C. Second, this fraction was then concentrated under reduced pressure using a rotary evaporator to afford a concentrated extract. Then, the extract was analyzed using GC–MS to identify its phytochemical contents	Bioactive compounds have the potential to inhibit the proliferation of HeLa cells.
Rinanda and Alga, November 22–24, 2012	Indonesia	This research was conducted for test the antibacterial activity of the red betel leave extract against the growth of MRSA.	Red betel leaves	The test applied the Kirby–Bauer disk diffusion method using Mueller-Hinton Agar (MHA) medium, in accordance with the procedures of European Committee on Antimicrobial Susceptibility Testing/EUCAST	Red betel leaf extract tested for concentration showed antibacterial activity against MRSA. The higher the concentration of the extract, the larger the inhibition zone formed.
Reveny, 2011	Indonesia	This study aims to test the activity of red betel (Piper betel) antimicrobial Linn.) from the n-hexane fraction ethanol extract and ethyl acetate, against <i>Staphylococcus aureus</i> , <i>Escherichia coli</i> and <i>Candida albicans</i> , MIC value testing, and content analysis chemical thin-layer chromatography (TLC) for identify the group of compounds that are suspected have antimicrobial properties. The aim of our study was to explore the effects of CEO on the composition of intestinal microbiota in the mouse model with dextran sodium sulfate (DSS)-induced colitis. These results would provide a reference for the better use of CEO as a promising therapeutic agent for IBD and other intestinal dysfunctions.	Red betel leaves	Simplicia powder was macerated with 80% ethanol, left at room temperature (28–32°C) for 2 days protected from light and stirred frequently, then separated, the pulp was macerated again with 80% ethanol solvent and carried out in the same way as above until clear maceration were obtained. Evaporation process using a rotavapor until a thick ethanol extract was obtained, then the extract was dried in a freeze dryer (–40°C) to obtain a dry extract of red betel leaf.	the ethanol extract showed a higher inhibitory effect on <i>Escherichia coli</i> , while the ethyl acetate fraction showed a higher effect on <i>Staphylococcus aureus</i> and <i>Candida albicans</i>
Li <i>et al.</i> , October 2019	China	Identified that anti-tumor effect of cinnamon extracts is also linked with their enhanced pro-apoptotic activity by inhibiting the activities of NFB and AP1 in mouse melanoma model.	Cinnamon oil	The pure cinnamon essential oil (containing approximately 68.95% cinnamaldehyde) was provided by Professor Huang Qingrong (State University of New Jersey, USA). Ceftriaxone sodium (CFT) was purchased from Xi'an Seasons Biotechnology Co., Ltd. (Xi'an, China). Dextran sodium sulfate (36–50 kDa, > 98%) was purchased from Shanghai ZZBIO Co., Ltd. (Shanghai, China).	Oral administration of CEO enriched with cinnamaldehyde effectively reduces the development of DSS-induced colitis.
Kwon <i>et al.</i> , November 14, 2019	Republic of Korea	The anti-inflammatory activity of leaf essential oils and their main compounds from seven origins of <i>C. osmophloeum</i> was investigated here for the 1 st time.	Cinnamon oil	Dried <i>Cinnamomum</i> cassia bark (Hwajin Distribution Co., Seoul, Korea) was pulverized and extracted for 3 h in a hot water extractor. The extract was filtered and the supernatant was concentrated with a rotary evaporator. The extract was then freeze dried resulting in a powder extract. The powder extract was suspended in sterilized distilled water at appropriate concentrations.	Cinnamon extract strongly inhibits tumor cell proliferation <i>in vitro</i> and induces active cell death of tumor cells by regulating pro-apoptotic molecules while inhibiting NF B and AP1 activity. Oral administration of cinnamon extract in transplanted melanoma models significantly inhibited tumor growth by the same mechanism of action observed <i>in vitro</i> .
Tung <i>et al.</i> , September 03, 2010	Taiwan	The anti-inflammatory activity of leaf essential oils and their main compounds from seven origins of <i>C. osmophloeum</i> is provided here for further testing	Cinnamon oil	The leaves of seven <i>Cinnamomum osmophloeum</i> provenances (COA–COG) were collected at the end of October 2005 from the Taiwan Sugar Company Research Center located in Nantou County in Central Taiwan. The species were confirmed by Yen-Ray Hsui of the Taiwan Forestry Research Institute and voucher specimens (CO0109, CO4407, CO1709, CO0403, CO0902, CO0502, and CO0609) were deposited at the laboratory of wood chemistry (School of Forestry and Resource Conservation, National Taiwan University).	Leaf essential oil of cinnamaldehyde and mixed types strongly inhibited the production of nitric oxide, with IC values ranging from 9.7–15.5 g/mL. Furthermore, trans-cinnamaldehyde is responsible for cinnamaldehyde-type inhibitory activity, and T-cadinol and -cadinol are responsible for mixed-type activity inhibition. Cinnamon essential oil has anti-inflammatory activity
Tung <i>et al.</i> , September 10, 2008	Taiwan	The efficacy of red betel leaf against <i>C. albicans</i> over acrylic denture surface as an herbal-based denture cleanser.	Red betel leaves	The twigs of a 13-year-old <i>C. osmophloeum</i> Kaneh. were collected at the end of July 2004 from the Taiwan Sugar Company Research Center located in Nantou County in Central Taiwan. Diameter of the twigs selected was below 1.5 cm. The species was confirmed by Dr. Yen-Ray Hsui of the Taiwan Forestry Research Institute and voucher specimens were deposited at the laboratory of wood chemistry (School of Forestry and Resource Conservation, National Taiwan University).	Red betel leaf has efficacy against <i>C. albicans</i> compared to acrylic denture surface at a concentration of 30%.
Meidarlina <i>et al.</i> , June 18, 2021	Indonesia	The extraction of red betel leaves (<i>P. crocatum</i>) was carried out by the maceration method, which was immersed in a 96% ethanol solution for 1×24 h with a 1:4 ratio of ingredients and solvents. The resulting filtrate was filtered with filter paper (Whatman no. 1). The maceration process was repeated for 6 consecutive days. The results of the filtrate from filtering with a filter paper were evaporated by a rotary vacuum evaporator at 40°C, and then, the extract was stored in a dark container at 4°C [13].	Red betel leaves		

(contd...)

Table 1: (Continued)

Author (s) and date of publication	Country/region	Aim	Extract	Data collection	Key findings
Hafizah et al., 2021	Indonesia	To identify the effects of red and green betel by applying its ethanol extract as an ingredient of soap. The use of red betel and green betel is expected to serve as a substitute of synthetic antibacterial substances which are commonly used nowadays.	Red betel leaves	A total of 10 g of 100% thick red betel leaf extract were dissolved in dimethyl sulfoxide (DMSO) 25% and then diluted with sterile distilled water to obtain concentrations of 10%, 20%, 30%, and 40% with the dilution formula $C1.V1 = C2.V2$ (C1: Initial concentration, C2: Desired concentration, V1: Initial volume, and V2: Desired volume). Fresh betel leaves were washed clean then dried using the oven at 40°C for 24 h, until the betel leaves became dry. Dried betel leaves were crushed into powder using a blender. Betel powder was soaked using 96% ethanol with a ratio of 1:5 for 72 h. The separation of filtrate and residue was carried out by filtering using filter paper. Then, the filtrate was evaporated using a rotary vacuum evaporator to separate the extract from the solvent	Transparent soap with the addition of 2.5% red betel extract has the best quality, as well as organoleptic and antibacterial activity characteristics when compared to other glycerin bar soaps.
Pradikdo et al., February 2020	Indonesia	Evaluated the effect of red betel leaf extract (RBLE) as a feed additive on gut and villi characteristics in broiler chickens.	Red betel leaves	Extraction of red betel leaf was carried out according to the previous method [4]. Red betel leaf powder was macerated for 24 hours with ethanol 70%. Ratio of red betel with ethanol was 1:6. After that, red betel leaf was extracted in the microwave oven for 10–15 min at controlled temperature 40°C and then cooled down until reach room temperature. After that, the liquid extract of red betel leaf was obtained by filtering with sterile muslin cloth.	The addition of RBLE up to 1.5% did not have a negative effect on the characteristics of the intestines and villi in broiler chickens
Kusuma et al., 2017	Indonesia	Determine the antimicrobial activity of red betel leaf ethanol extract as a natural antiseptic against several airborne pathogens as follows: <i>Staphylococcus aureus</i> , <i>Pseudomonas aeruginosa</i> , <i>Escherichia coli</i> , and <i>Candida albicans</i> .	Red betel leaves	Extraction of dried piper betel leaf was made by maceration method. The antimicrobial activity of the extract was tested using the agar diffusion method, then continued with the determination of the minimum inhibitory concentration test (MIC) carried out by the macrodilution method. While the determination of the minimum concentration of bactericide (MBC) was carried out by subculture of overnight incubation results of MIC results to Mueller-Hinton agar medium surface. The minimum inhibition time required for each test microbe was carried out by incubating the test medium at a temperature range of 1.5–6 minutes, followed by subculture to MHA using the streak plate method.	It can be concluded that the red betel ethanol extract is very effective as a natural antiseptic against airborne pathogens with a minimum effective inhibition time.
Lister et al., 2020	Indonesia	To determine the antioxidant activity of red betel leaf extract (<i>Piper crocatum</i> Ruiz and Pav.) (RBLE) compared to eugenol and Hydroxychavicol compounds.	Red betel leaves	The radical scavenger DPPH, H 2 HAI scavenging, ABTS reduction, and FRAP were tested for reduction. Results: In scavenging DPPH, RBLE showed IC 2 values of 3.98 g/mL, eugenol 2.98 g/mL, and hydroxycavikol of 18.00 g/mL. Meanwhile, H 2 HAI 2 50 scavenging activity showed IC values of RBLE, eugenol, and hydroxycavikol of 186.33 g/mL, 97.36 g/mL, and 41.06 g/mL, respectively. The ABTS reduction test showed IC 50 values of 38.43 g/mL, 181 g/mL, and 3.10 g/mL for RBLE, eugenol, and hydroxychavicol, respectively. The highest FRAP reduction activity was shown by eugenol with a concentration of 50 g/mL, which was 424.67 M Fe (II)/ μ g.	RBLE and its compounds (eugenol and hydroxychavicol) have antioxidant activity as indicated by the results of DPPH scavenging, H 2 HAI scavenging, ABTS reduction, and FRAP reduction tests. However, RBLE had the lowest antioxidant activity compared to other compounds.

can be a cause of increased maternal morbidity and mortality. Perineal wound care behavior in postpartum women is very important. This is related to susceptibility to the incidence of postpartum infection. According to the results of research conducted by Lestari (2016), age is more dominantly related to the behavior of perineal wound care in postpartum women than parity [11]. Based on the results of research by Fatimah, (2018), which used the Wilcoxon signed-ranks test statistical test, the significant result was 0.0001, which means that there was a relationship between pregnant women who were educated about perineal massage and the implementation of perineal massage for pregnant women [12]. Broad-spectrum antibiotics are recommended in the immediate post-operative period to reduce the risk of infections and wound. Paracetamol and nonsteroidal anti-inflammatory drugs (NSAIDs) can be used. However, the use of opioids is limited to reduce the risk of constipation. Therefore, topical herbal medicines are needed that contain antibacterial and anti-inflammatory so that they can help the wound healing process [3], [4], [5].

Analysis of red betel leaf extract and cinnamon oil in research Anugrahwati et al. (2016), Rinanda et al. (2012), Reveny et al. (2011), Li et al. (2019), Kwon et al. (2019), Tung et al. (2010), Tung et al. (2008), Meidarlina et al. (2021), Hafizah et al. (2021), Pradikdo et al. (2020), Kusuma et al. (2017), and Lister et al. (2020) overall showed that the bioactive compounds from red betel leaf and cinnamon oil have the potential to inhibit the proliferative process, antibacterial, and anti-inflammatory activity. In line with the results of the research by Emelda et al. (2021), the results showed that the combination of cinnamon oil and red betel decreased the area and percentage of the wound, decreased the inflammatory cell infiltration, and increased the vascular endothelial growth factor expression [13].

The research conducted by Anugrahwati et al. (2016) which aims to investigate the separation process in extraction of red betel leaves using ethanol, followed by performing a cytotoxicity test on HeLa cell line from cervical tumor/cancer, it was found bioactive

compounds potential to inhibit the proliferation of HeLa cells [14]. Furthermore, research conducted by Rinanda *et al.* (2012) and aimed to test the antibacterial activity of the red betel leaf extract against the growth of MRSA. The results of the red betel leaf extract that was tested for concentration showed antibacterial activity against MRSA. The higher the concentration of the extract, the larger the inhibition zone formed [15]. The results of the study Reveny (2011) aimed to test the antimicrobial activity of red betel from the ethanolic extract of the n-hexane and ethyl acetate fractions, against *Staphylococcus aureus*, *Escherichia coli*, and *Candida albicans*, MIC value testing, and content analysis, showed that the ethanol extract showed a higher inhibitory effect on *Escherichia coli*, while the ethyl acetate fraction showed a higher effect on *Staphylococcus aureus* and *Candida albicans* [16].

Activity of red betel leaf and cinnamon oil was further researched by Li *et al.* (2020) which aims to exploring the effects of CEO on the composition of intestinal microbiota in the mouse model with dextran sodium sulfate (DSS)-induced colitis. These results would provide a reference for the better use of CEO as a promising therapeutic agent for IBD and other intestinal dysfunctions. Results suggest that oral administration of CEO containing cinnamaldehyde, effectively reduces the development of DSS induced colitis. [17]. Furthermore, research from Kwon *et al.* (2019) which aims to identify that the effect of cinnamon extract as an anti-tumor shows an increase in its pro-apoptotic activity by inhibiting the activity of NFB and AP1 in mouse melanoma. Cinnamon strongly inhibits tumor cell proliferation *in vitro* and induces active cell death of tumor cells by regulating pro-apoptotic molecules while inhibiting NFB and AP1 activity. Oral administration of cinnamon extract in transplanted melanoma models significantly inhibited tumor growth by the same mechanism of action observed *in vitro* [18]. In line with the research conducted by Tung *et al.* (2010) which aimed to be investigated here for the first time of the anti-inflammatory activity of leaf essential oils and their main compounds from seven origins of *C. osmophloeum*, the results obtained leaf essential oil of cinnamaldehyde and mixed types strongly inhibited the production of nitric oxide, with IC values ranging from 9.7 to 15.5 g/mL. Furthermore, trans-cinnamaldehyde is responsible for cinnamaldehyde-type inhibitory activity, and T-cadinol is responsible for mixed-type activity inhibition [19].

A similar study conducted by Tung *et al.* (2008) with the aim of providing here for further testing of the anti-inflammatory activity of leaf essential oils and their main compounds from seven origins of *C. osmophloeum*, obtained the results that *Cinnamon* essential oil has anti-inflammatory properties-inflammatory activity [20]. Similar activity in red betel leaf extract from a study Meidarlina *et al.* (2021) which aims to assess the efficacy of red betel leaf as an herbal-based denture cleanser

on the growth of *C. albicans* on the surface of acrylic dentures got the results that red betel leaf has efficacy against *C. albicans* compared to acrylic denture surface at a concentration of 30% [21]. The effectiveness of red betel leaf is also proven from research by Hafizah *et al.* (2021) which aims to identify the effects of red betel leaf and green betel leaf by applying its ethanol extract as an ingredient of soap. The use of red betel and green betel is expected to serve as a substitute of synthetic antibacterial substances which are commonly used nowadays. That, transparent soap with the addition of 2.5% red betel extract has the best quality, as well as organoleptic and antibacterial activity characteristics when compared to other glycerin bar soaps [22].

The effectiveness of red betel leaf extract (RBLE) as a feed additive on gut and villi characteristics in broiler chickens was also investigated. The results showed that the addition of RBLE up to 1.5% did not have a negative effect on the characteristics of the intestines and villi in broiler chickens [23]. The effectiveness of the same red betel leaf is proven by research Kusuma *et al.* (2017) which aims to determine the antimicrobial activity of red betel leaf ethanol extract as a natural antiseptic against several airborne pathogens as follows: *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Escherichia coli*, and *Candida albicans*. Showing the result, it can be concluded that the red betel ethanol extract is very effective as a natural antiseptic against airborne pathogens with a minimum effective inhibition time [24]. The last article from Lister *et al.* (2020) aimed to determine the antioxidant activity of red betel leaf extract (*Piper crocatum* Ruiz and Pav.) (RBLE) compared to eugenol and hydroxycavikol compounds. RBLE and its compounds (eugenol and hydroxychavicol) were produced which have antioxidant activity, as indicated by the results of the scavenging activity test on DPPH and H₂ HAI, and reduction test on ABTS and FR. However, RBLE has the lowest antioxidant activity compared to other compounds [25].

Conclusion

Two herbal plants red betel leaf and cinnamon oil have the potential to treat and accelerate the healing of perineal tears through their antibacterial and anti-inflammatory activities.

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