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The combination effect of basil leaves and red betel leaves as analgesic to reduce dysmenorrhea in reproductive woman

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Abstract

Dysmenorrhea, characterized by severe lower abdominal pain during menstruation, affects a significant proportion of women of reproductive age, impairing daily activities. The pathophysiology of dysmenorrhea is primarily linked to elevated prostaglandin production (PGF2α and PGE2) and heightened uterine sensitivity, which induce myometrial contractions, hypoxia, and pain. Factors such as stress, obesity, and family history contribute to its prevalence. In recent years, medicinal plants have emerged as alternative therapies to manage dysmenorrhea symptoms. Basil (*Ocimum basilicum* L.) and red betel (*Piper crocatum*) are known for their anti-inflammatory, antioxidant, and analgesic properties due to their rich phytochemical content, including flavonoids, tannins, and essential oils. Basil leaves inhibit cyclooxygenase (COX) and lipoxygenase (LOX) pathways, reducing prostaglandin synthesis, while red betel leaves enhance antioxidant activity and modulate inflammatory responses. This study aims to investigate the combined effects of basil and red betel leaves in alleviating dysmenorrhea symptoms. Despite the lack of experimental studies on their synergistic effects, their anti-inflammatory mechanisms—targeting prostaglandin production and NF-κB pathways—present promising potential for reducing menstrual pain.

Keywords: Basil Leave Oil; Red Betel Leaves; Analgesic; Dysmenorrhea

1. Introduction

The commencement of menstruation signifies female reproductive-age which means the transition from girlhood to womanhood; hence, it is crucial to female reproductive health. These issues encompass delayed menstruation, irregular menstrual cycles, dysmenorrhea, and menorrhagia, among others. Among these, painful menstrual cycles, clinically termed dysmenorrhea, are the most significant. Dysmenorrhea is defined by mild to severe lower abdomen discomfort occurring shortly before and during the menstrual cycle. This condition is typically linked to headache, dizziness, abdominal distension, nausea, emesis, lumbar pain, and leg discomfort (Nyirenda et al., 2023). Dysmenorrhea refers to lower abdomen discomfort occurring during menstruation. Dysmenorrhea can be categorized as primary or secondary based on its underlying pathophysiology. Primary dysmenorrhea refers to menstrual discomfort occurring during menstruation without a discernible etiology. Secondary dysmenorrhea refers to menstruation discomfort with a specific underlying etiology. The discomfort begins within the initial 24–36 hours of menstruation and persists for 2–3 days following the menstrual period. Primary dysmenorrhea is typically observed in the initial years of menstruation (Belayneh et al., 2023). Dysmenorrhea is linked to a variety of factors, such as psychological and behavioral components. Symptoms of dysmenorrhea may persist for 1-3 days and begin 2-4 days before or at the commencement of menstruation (Ali et al., 2022).

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Unfortunately, the start of menstruation is typically accompanied by issues that impact between 50% and 95% of women (Nyireda et al., 2023). Approximately 10%–15% of these women have significant menstruation pain monthly, sufficiently acute to impede typical daily activities at work, home, or school (Esan et al., 2024). The pathophysiology of pain is linked to elevated prostaglandin synthesis (PGF2α and PGE2) and atypical uterine sensitivity to prostaglandins, a notion that is well acknowledged. The heightened generation of prostaglandin, along with the augmented sensitivity of uterine muscle to prostaglandin, leads to myometrial contractility, therefore subjecting the uterus to hypoxia and ischemia, finally resulting in discomfort (Belayneh et al., 2023). Factors such as nulliparity, obesity, tobacco use, positive family history, stress, familial dysmenorrhea history, dietary habits, depression, and maltreatment are significantly correlated with the occurrence of primary dysmenorrhea (Deekala et al., 2022).

In recent years, medicinal plants and botanical medicines have gained prominence as a kind of complementary and alternative therapy for some gynecological problems, including dysmenorrhea (Insaniyah et al., 2023). Dysmenorrhea is managed through a combination of drug and non-drug therapies. In a variety of cultures, herbal medicine has become a popular choice for alleviating menstrual discomfort (Nurfitriyani et al., 2024). Basil (*Ocimum basilicum* L.) is a plant of the *Lamiaceae* family, which is renowned for its diverse medicinal properties (Azizah et al., 2023). As an antiproliferative, anti-inflammatory, anti-angiogenic, anti-microbial anti-oxidant, and immunomodulating agent, Basil leaves have demonstrated benefits. Along with glycosides like esculin and syringin, which help to explain the anti-inflammatory action, basil leaves include flavonoids like quercetin, isoquercitrin, kaempferol, and rutin. Basil leaf extract's anti-inflammatory action can be achieved via many mechanisms, the first of which is via the COX and lipoxygenase (LOX) pathways' suppression of arachidonic acid (Insaniyah et al., 2023; A'yuni et al., 2023).

Red betel (*Piper crocatum*) has not yet been extensively studied for its potential in managing dysmenorrhea, despite its known anti-inflammatory properties. Red betel (*Piper crocatum*), a kind of betel in Indonesia, with medical properties as an anti-inflammatory agent. It contains secondary metabolites such as flavonoids, alkaloids, tannins, saponins, triterpenoids, steroids, quinones, polyphenolics, and essential oils (Ginting et al., 2022). Exploring the function of red betel's leaves in the inflammatory pathway is crucial due to its high phenolic and flavonoid content (Maslikah et al., 2022).

According to the aforementioned background, both plants have potential anti-inflammatory benefits. Nonetheless, investigations on the synergistic effects of both remain exceedingly few. Consequently, researchers want to investigate the anti-inflammatory properties of the combination of basil leaves and red betel to alleviate discomfort associated with dysmenorrhea. This study aimed to assess the impact of combining basil leaves and red betel on alleviating dysmenorrhea symptoms in women of reproductive age.

2. Review

2.1. Pathophysiology of Dysmenorrhea

Dysmenorrhea is a disorder marked by persistent, cramp-like discomfort mostly in the lower abdomen during menstruation. The discomfort may be categorized as primary (or functional) when pelvic pathology is absent, or secondary if it is linked to an underlying pelvic pathology. Primary dysmenorrhea, often referred to as functional dysmenorrhea, is typically more prevalent than secondary dysmenorrhea in teens and young adults and is linked to regular ovulatory cycles without pelvic disease. Following ovulation and preceding menstruation, progesterone withdrawal triggers a significant release of arachidonic acid, an omega-6 fatty acid embedded within the phospholipids of cell membranes, which facilitates the activation of prostaglandins and leukotrienes in the uterus. Progesterone suppresses this process, whereas estrogens exert a stimulatory influence. Consequently, elevated estrogen synthesis following progesterone cessation enhances prostaglandin (PG) production in the endometrium via the activation of cyclooxygenase-2 (COX-2) and nuclear factor kappa B (NF-kB), a nuclear transcription factor that activates genes implicated in the inflammatory cascade. NF-kB precisely triggers the transcription of the COX-2 gene, which is responsible for a significant production of prostaglandins, hence initiating inflammation in the endometrium. The robust inflammatory response is believed to induce dysmenorrhea symptoms, including nausea, vomiting, bloating, and headache, and influences the severity of dysmenorrhea and bleeding. This recurrent inflammation in the endometrium might activate the transcription of the aromatase gene in susceptible individuals (absent in women without dysmenorrhea), leading to a localized rise in estrogens, so maintaining (Francavilla et al., 2023).

2.2. Basil Leaves Anti-inflammatory and Anti-Dysmenorrhea Effect

Basil leaf extract comprises flavonoids, tannins, steroids, and alkaloids. This aligns with recent research indicating that basil leaves contain secondary metabolites such as flavonoids, tannins, steroids, and alkaloids (Dafira et al., 2023). The

anti-inflammatory effects of the *O. basilicum* essential oil complexed with β-cyclodextrin (OBEO/β-CD) correlated with the conjugation of β-cyclodextrin with *O. basilicum* reduced the total counts of lymphocytes, leukocytes, granulocytes, and monocytes, signifying the efficacy of this complex in modulating leukocyte recruitment during an acute inflammatory response. The concentration of anthocyanins in its leaves has markedly increased following stimulation with abiotic elicitors, including jasmonic acid, arachidonic acid, and b-aminobutyric acid. Anthocyanins can inhibit lipoxygenase (LOX) activity and function as anti-inflammatory drugs. The stimulation of basil by all elicitors improved its capacity to inhibit LOX activity, shown by an IC50 value. LOX mediates the metabolism of fatty acids and their metabolites, which provoke inflammatory reactions in the body. The mucilage of this plant demonstrated enhanced protection against inflammatory mediators and oxidative stress in colitis, indicating its potential as a supplemental therapeutic agent for colitis treatment. The anti-inflammatory impact on colitis may be ascribed to terpenoids and flavonoids, which are recognized for their ability to block inflammatory signals via NF-kB inhibition. NF-kB, activated by TNF-alpha, plays a crucial role in the pathophysiology and recurrence of IBD, and its inhibition may lead to colitis remission in both experimental and clinical contexts. Furthermore, it shows that treatment with this plant reduces the wet weight of distal colon segments and the main damage score in contrast to the control, which correlates significantly with a reduction in local inflammatory scores (Kamelnia et al., 2023).

Basil leaves contain the flavonoid quercetin and rosmarinic acid, which function as mast cell stabilizers. The stabilizing mechanism of mast cells in basil leaves mitigates the suppression of IgE synthesis, hence limiting the cross-linking of the IgE-FcεRI complex and inhibiting mast cell degranulation. Mast cells can be triggered by direct interaction with antigens via the IgE-dependent route, which necessitates the release of T-helper 2 (Th2) cytokines, specifically IL-4, IL-5, and IL-13. There is an elevated expression of IL-4 in the peritoneal fluid of individuals with dysmenorrhea. The decrease in mast cell count can be attributed to the inhibitory effects of quercetin found in basil leaves. Quercetin obstructs mast cell activation by preventing calcium ion influx, diminishing the production of histamine, leukotrienes, and prostaglandins, and reducing protein kinase activity (Insaniyah et al., 2023). The anti-inflammatory properties of basil leaf extract are attributed to flavonoids that act as anti-inflammatories. Flavonoids can inhibit the release of arachidonic acid and lysosomal enzymes, as well as obstruct the cyclooxygenase and lipoxygenase pathways, which contribute to their anti-inflammatory characteristics (Dafira et al., 2023).

Basil leaves possess an array of antioxidants, including vitamin C, vitamin E, carotenoids, and flavonoids, which protect against oxidative stress and the detrimental effects of free radicals caused by hepatotoxic agents. These chemicals can damage cellular structures and induce the production of Reactive Oxygen Species (ROS). These particular chemicals were noted to impede the release of histamine and inflammatory mediators produced by mast cells. This inhibition led to the reduction of NF-kB binding, the production of pro-inflammatory cytokines (IL-6, IL-8, TNF-α, and IL-1β), and the release of histamine. The anti-inflammatory mechanism of basil leaves involves the suppression of arachidonic acid via the lipoxygenase and cyclooxygenase pathways, therefore reducing PGE2 synthesis. Basil leaves may diminish PGE2 synthesis and impede COX enzymes (COX-1 and COX-2) by attenuating macrophage activation. The presence of phytochemical substances, including euginal, euginol, sitosterol, ursolic acid, and stigmasterol in basil leaves, may function as phytoandrogens or phytoestrogens (Insaniyah et al., 2023). An investigation by Raveendran et al. in 2016 shown that basil water effectively alleviated dysmenorrhea symptoms, as evidenced by the control group's mean post-test score being higher than the experimental group's mean post-test score (Raveendran et al., 2016).

2.3. Red Betel Leaves Anti-inflammatory and Anti-Dysmenorrhea Effect

Red betel leaves contain various phytochemical compounds including essential oils, alkaloids, saponins, tannins and flavonoids. In addition, there are also other compounds such as hydroxychavicol, chavicol, chavibetol, carvacol, eugenol, p-cymen, cineol, caryophyllene, cadimen estragol, terpenedan phenyl propanoid. The content of compounds from the flavonoid group of red betel leaves that are thought to have anti-inflammatory activity are toxifolin, brazilin, haematoxylin, gossipin, procyanidin and nepritin. Red betel leaves contain bioactive compounds in the form of flavonoids, saponins, tannins, alkaloids, steroids/terpenoids, antarquinones and phenols. Flavonoids play a role in anti-inflammation by inhibiting capillary permeability and metabolizing arachidonic acid, as well as the secretion of lysosomal enzymes from neutrophils and endothelial cells. Anti-inflammatory potential is also found in saponin compounds through inhibiting exudate formation and increasing vascular permeability. One of the flavonoid compounds that has anti-inflammatory activity is Brazilin. Brazilin is an organic heterocyclic compound that has proapototic and anti-inflammatory potential (Asyiyah et al., 2021). The phenolic compounds in red betel leaves may enhance the endogenous antioxidant activity of glutathione peroxidase by as much as 50%. Flavonoids may serve as main antioxidants by donating hydrogen ions, therefore stabilizing ions affected by free radicals. The stable ion state results in a reduction of oxidative stress inside the tissue. Flavonoids may also serve as secondary antioxidants by enhancing the production of endogenous antioxidant enzymes, specifically superoxide dismutase (SOD) (Maslikah et al., 2019).

2.4. The Combination Effect of Basil and Red Betel Leaves to Reduce Dysmenorrhea

The combination of basil leaves and red betel has the potential to alleviate pain associated with dysmenorrhea, although experimental or clinical research to support this claim is currently lacking. Dysmenorrhea primarily results from an overproduction of prostaglandins and inflammatory mediators within the endometrium during menstruation. In primary dysmenorrhea, the withdrawal of progesterone after ovulation leads to an increase in arachidonic acid, which promotes the activation of prostaglandins through cyclooxygenase-2 (COX-2) and nuclear factor kappa B (NF-κB) pathways. Prostaglandins, particularly PGE2 and PGF2α, cause intense uterine contractions, reduced blood flow, and increased pain sensitivity. This inflammatory process is further amplified by the release of cytokines, leukotrienes, and reactive oxygen species (ROS), which contribute to symptoms such as nausea, bloating, and headache. The involvement of NF-κB in this pathway is crucial, as it regulates the expression of pro-inflammatory genes and perpetuates the inflammatory response associated with dysmenorrhea.

Given this pathophysiological mechanism, interventions that target prostaglandin synthesis, inhibit NF-κB activation, or reduce oxidative stress can effectively alleviate dysmenorrhea symptoms. Natural anti-inflammatory compounds, such as those found in basil and red betel leaves, have shown potential to mitigate these processes. Flavonoids, tannins, and essential oils in these plants inhibit pathways like cyclooxygenase (COX) and lipoxygenase (LOX), which are responsible for prostaglandin and leukotriene production. By modulating the immune response, reducing mast cell degranulation, and decreasing cytokine release, basil and red betel can theoretically reduce inflammation and associated pain in dysmenorrhea, even in the absence of clinical studies confirming these effects.

3. Conclusion

Dysmenorrhea is primarily caused by excessive production of prostaglandins and inflammatory mediators due to progesterone withdrawal and arachidonic acid metabolism, leading to severe uterine contractions and pain. The activation of pathways such as cyclooxygenase-2 (COX-2) and nuclear factor kappa B (NF-κB) perpetuates this inflammatory response, contributing to the severity of dysmenorrhea symptoms. Although no experimental or clinical research has definitively proven their efficacy, the anti-inflammatory and antioxidant properties found in basil and red betel leaves offer promising potential for alleviating dysmenorrhea. Furthermore, in the future, in basil and red betel leaves extract can be used in preclinical and clinical trials, hence it can be utilized as an alternative treatment. In addition, the development of preparations from basil leaf extract also has the potential to increase interest and compliance levels in relieving disruptive dysmenorrhea pain.

Compliance with ethical standards

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Disclosure of conflict of interest

We have no conflicts of interest to disclose. All authors declare that they have no conflicts of interest.

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