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Literature Review

Essential of *Graptophyllum pictum* for the medical and dental purposes

Devin Elysia Dhywinanda,[1] Sinta Nuriyah Dien,[1] Hadfi Dhaky Chairuly,[1] Gilang Ratri Sakti,[1] Renata Jasmine Ramadhanty Felisha Tandra,[1] Nadia Kartikasari,[2] Karina Mundiratri,[2] Ratri Maya Sitalaksmi[2], Mohammed Ahmed Qasim Saleh Aljunaid[3]
[1]Undergraduate Student, Faculty of Dental Medicine, Universitas Airlangga, Surabaya, Indonesia
[2]Department of Prosthodontics, Faculty of Dental Medicine, Universitas Airlangga, Surabaya, Indonesia
[3]Department of Dental Medicine, Faculty of Medicine, University of Taiz, Taiz, Yemen

ABSTRACT

Background: The use of plants for medicinal purposes continues to expand rapidly across the world. Up to 80% of the world's population is estimated to rely heavily on herbal medicines for their primary health care. *Graptophyllum pictum* leaves (GPL) have long been used as herbal medicine for several diseases or health conditions. However, until now, there have been only limited studies regarding laboratory experiments and the pharmacological effects of GPL. **Purpose:** To summarize the phytopharmacology aspect of GPL used for medical and dental purposes. **Review:** Based on the 36 articles included, GPL is widely used in medicine and dentistry, such as for treatment of hemorrhoids, periodontitis, and candidiasis, due to its anti-inflammatory, antioxidant, and antifungal properties. However, the current research study designs are still in vitro and in vivo experiments. Continuing experiments and clinical tests are needed to explore the essential use of the GPL. **Conclusion:** GPL can be used for medical and dental purposes due to its anti-inflammatory, antioxidant, antibacterial, and antifungal properties.

Keywords: dentistry; *Graptophyllum pictum*; medicine; human & health

Correspondence: Ratri Maya Sitalaksmi, Department of Prosthodontics, Faculty of Dental Medicine, Universitas Airlangga, Jl. Mayjen Prof. Dr. Moestopo 47 Surabaya, 60132 - Indonesia. E-mail: ratri.maya.s@fkg.unair.ac.id

INTRODUCTION

In recent years, the use of plants for medicinal purposes has continued to expand rapidly. High prices, side effects, and patients' dissatisfaction with allopathic medicine have become the disadvantage of modern medicine.[1] In addition, increased reports of adverse side effects and antibiotic resistance as one of the significant public health threats had made synthetic drugs less attractive.[2] Along with the development of science and technology, herbal medicine has become an alternative medicine. The increased safety, efficacy, and efficiency of herbal medicine made this type of medicine recently gained attention. The World Health Organization (WHO) estimated that up to four billion people (approximately 80% of the world's population) in developing countries rely on herbal medicines for their primary health care.[1] Approximately 50% of medicinal prescriptions were originally discovered in plants.[3]

As a country with high biodiversity, Indonesia has many plant species with the potential to be used for medicinal and dental purposes. It is estimated that 80% of the world's herbal medicine grows in Indonesia. Thirty percent of the 25,000 plant species in Indonesia are known to have pharmacological effects. However, the percentage of cultivated plants is only 4%. According to Indonesian Biodiversity Foundation, the potential value of pharmacochemical medicinal plants in Indonesia is around USD 14.6 billion or more than IDR 150 trillion.[3]

Graptophyllum pictum (G. pictum) is a species of Acanthaceae family from the tropical region. It has many common names depending on the area, including handeuleum and purple leaves (in Indonesia).[4] The leaves are the most common part of the *G. pictum* used as a herbal medicine.[5] This plant is included in the 66 biopharmaceutical plant commodities stipulated through the Decree of the Minister of Agriculture Number 511/Kpts/PD.310/9/2006.[6]

G. pictum leaves (GPL) are used as herbal medicine due to their pharmacological effects: antioxidant, anti-inflammatory, anti-implantation, antidiabetic, antibacterial, anti-hemorrhoid, nephrotoxicity, photoprotective, and immunomodulatory properties. Several secondary metabolites can also be found in GPL: alkaloids, glycosides, pectin, formic acid, steroids, saponins,

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tannins, anthraquinones, flavonoids, and alcohol.[5,7,8] Empirically, GPL is widely used as an herbal medicine in Indonesia. However, until now, studies discussing phytopharmacological aspects of GPL have been limited; therefore, we would like to summarize the studies relating to GPL's use for medicinal and dental purposes.

REVIEW

The method used in this article is a literature search through several databases, such as PubMed, ScienceDirect, and Google Scholar. This review's design followed the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) method. The search terms used are: "*Graptophyllum pictum*"; "*Graptophyllum pictum (L.) Griff*"; "original research"; "research article." The inclusion criteria in this study were experimental studies written in Indonesian or English that explained the utilization of GPL for medical purposes. Studies excluded from this narrative review were: (1) duplication studies; (2) studies written in other languages than Indonesian or English; (3) studies published before January 2013; (4) studies other than experimental studies (literature review, letters to editors, opinions, conference abstracts, dissertations, theses, case-control, case report, case series, cohort, cross-sectional, ecological correlation studies); (4) studies with irrelevant titles or abstracts; and (5) studies with an unclear discussion about the effect of GPL on specific diseases.

After screening, a total of 572 studies were obtained. There were only 32 studies included in this review after screening based on inclusion and exclusion criteria (Figure 1). The dataset was created and analyzed using Microsoft® Excel 2019 for Windows. Details of the data extraction were tabulated, and the data were presented as an indication, study design, pharmacological effect, application, and references, as shown in Tables 1 and 2.

DISCUSSION

The use of GPL in medical treatment is based on its pharmacological effects. Several diseases in which GPL can be used as a treatment are a hemorrhoid,[4,9–12] diabetes mellitus,[13,15,16] drug-induced toxicity,[17,18] estrogen-related conditions,[19–21] hypertension,[22] anal ulcer,[23] and the harmful effect of sunlight.[24]

GPL can be used for hemorrhoid treatment because it has anti-inflammatory and antioxidant activity.[4,9–12] Flavonoids in GPL regulate the expression of inflammatory mediators through nuclear factor-kappa B (NF-κB). NF-κB decreases the expression of TNF-α, IL-6, and COX-2.[4,9,10,12] The

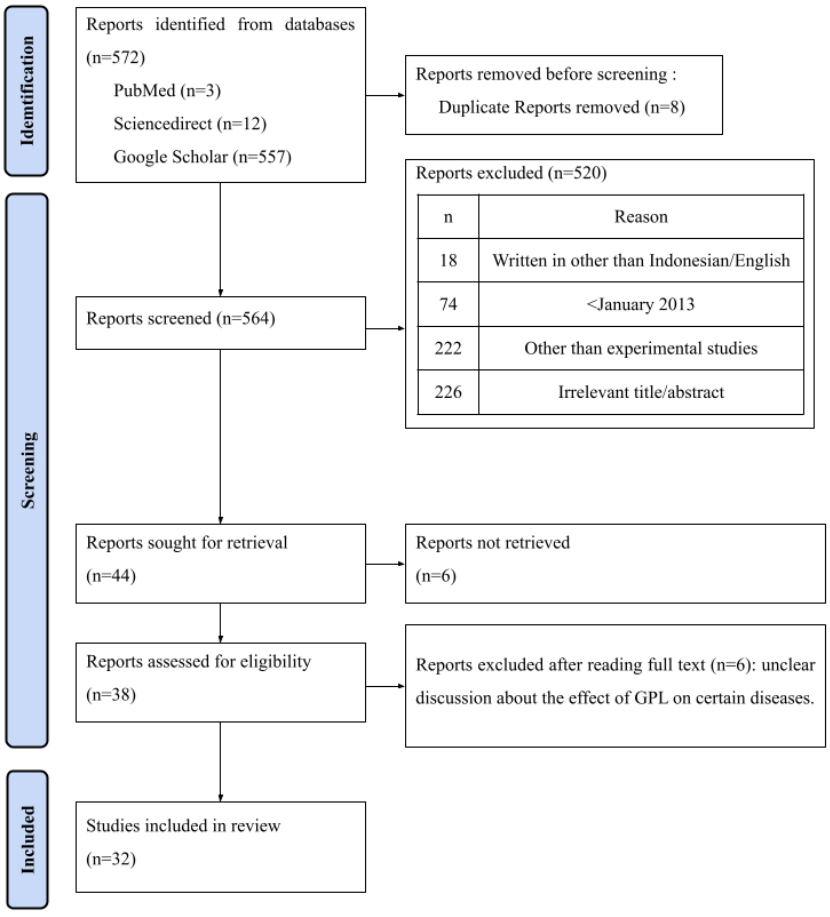

Figure 1. Flow-chart PRISMA.

Table 1. Summary of GPL used for medicinal purposes

No	Indication	Study Design	Subjects	Pharmacological Effect	Application	References
1	Hemorrhoid	*In vitro*	Mice	Antioxidant, anti-inflammation, hemostatic properties	Oral, topical	Kusumawati et al., 2020[4]
		In vivo	Wistar rats			
		In vivo	Wistar rats	Anti-inflammation		Prasetyo et al., 2020[9]
		In vivo	Wistar rats	Anti-inflammation, anti-platelet aggregation	Oral	Ratnasari, Susanti & Dhiani, 2020[10]
		In vivo	Wistar rats	Anti- inflammation and antioxidant	Oral	Azhar et al., 2020[11]
		In vivo	Wistar rats	Phlebotropic	Intravenous	Hutagulung et al., 2019[12]
2	Diabetes melitus	*In vivo*	Wistar rats	Antidiabetic		Elnitiarta et al., 2021[13]
		In vivo	Wistar rats	Antidiabetic		Excelinda et al., 2021[14]
		In vivo	Wistar rats	Antidiabetic	Oral	Leonereza et al., 2020[15]
		In vivo	Mice	Antidiabetic		Rahmi et al., 2014[16]
3	Drug-induced toxicity	*In vivo*	Mice	Antioxidant	Oral	Kusumaningsih et al., 2018[17]
		In vivo	Wistar rats	Antioxidant	Oral	Srinivasan et al., 2015[18]
5	Estrogen-related conditions	*In vivo*	*Mus muculus*	Phystoregens		Rakasiwi, Suhargo & Sugiharto, 2019[19]
		In vivo	*Rattus novergicus L.*	Estrogenic properties	Oral	Pranoto, 2018[20]
		In vivo	Wistar rats	Estrogenic properties	Oral	Wanda et al., 2016[21]
		In vivo	Sprague-Dawley rats		Oral	
6	Hypertension	*In vivo*	Mice	Diuretic	Suspension	Fauziah, Irmawati & Isrul, 2022[22]
7	Anal ulcer	*In vivo*	Wistar rats	Anti-inflammation		Prasetyo et al., 2019[23]
8	Harmful effect of sunlight	*In vitro*	Isolate solution of GPL	Antioxidant		Masyita, Sayekti & Nurlina, 2022[24]

Table 2. Summary of GPL used in dentistry

No	**Indication**	**Study Design**	**Subjects**	**Pharmacological Effect**	**Application**	**References**
1	Periodontal disease	*In vitro*	*Aggregatibacter actinomycetemcomitans*	Antibacterial	Suspension	Friska et al., 2021[25]
		In vivo	Wistar rats	Anti-inflammation	-	Kusumaningsih, Putra & Aljunaid, 2021[26]
		In vivo	Wistar rats	Anti-inflammation	Gel	Rachim, Kurniawati & Astuti, 2020[27]
		In vitro	Neutrophil	Antibacterial	-	Diyatri, Kusumaningsih & Tantiana, 2020[28]
		In vivo	Wistar rats	Anti-inflammation	Topical	Kurniawati, Praharani & Handoko, 2020[29]
2	Dental caries	*In vitro*	*Streptococcus mutans*	Antibacterial	-	Kurniawati, Wahyukundari & Astuti, 2020[30]
		In vitro	*Lactobacillus acidophilus*	Antibacterial	-	Juniarti et al., 2021[31]
		In vitro	*S. mutans*	Antibacterial	Denture cleanser	Juniarti et al., 2021[32]
		Clinical test	Saliva sample subjects	Antibacterial	Mouthwash	Dewi, 2020[33]
3	Candidiasis	*In vitro*	*Candida albicans*	Antifungal	-	Kurniawati, 2018[34]
		In vitro	Monocyte	Immunomodulator	-	Kurniawati, 2018[35]
4	Pulp perforation	*In vivo*	Wistar rats	Anti-inflammation	Topical	Juniarti et al., 2020[36]

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level of COX-2 is related to thromboxane A2 (TXA2). The decrease of TXA2 level results in the decline of platelet aggregation and bleeding.[10] Moreover, flavonoids and phenolic compounds are essential to stop hemorrhoid bleeding by reducing plasma recalcification time (PRT) or the time needed for fibrin formation. Phenolic stimulates superoxide levels, and as compensation, enzyme superoxide dismutase (SOD) levels are increased. SOD enzymes repair cells and reduce the amount of superoxide damage as a defense against hemorrhoid disease.[4,11]

The β-cells are the most abundant (60%) cells in pancreatic islets, which are essential for insulin production to control blood glucose levels. The β-cells cell destruction results in insulin deficiency, disrupting blood glucose intake into the body's tissues and further increasing the blood glucose level.[13] It is essential to preserve the β-cells due to their major function in insulin production.[14]

Studies reported GPL has an antidiabetic activity through alkaloids, flavonoids, saponins, and tannins. GPL increased the pancreatic islet area and decreased blood glucose and malondialdehyde (MDA). Alkaloids play a vital role in differentiating pancreatic progenitor cells into β-cells. Flavonoids prevent the progression of β-cell apoptosis by inhibiting the pro-apoptotic gene expression process. Saponins increase the use of glucose by the liver, reduce the process of gluconeogenesis, and increase glucose oxidation resulting in a decrease in MDA level. Tannins play a role in inhibiting pro-oxidative enzymes and lipid peroxidation as well as reducing the strength of oxidation and activity of free radicals.[13–16]

Drug-induced toxicity. Paracetamol and gentamicin are reported to induce hepatotoxicity or nephrotoxicity.[17,18] Oral paracetamol metabolizes a highly reactive metabolite, N-acetyl-p-benzoquinone imine (NAPQI).[17] Oral gentamicin can increase serum creatinine and urea concentrations.[18] Hepatotoxicity and nephrotoxicity increase MDA levels. GPL has been shown to inhibit lipid peroxidation and increase glutathione in the liver and kidneys. Flavonoid compounds in GPL can inhibit enzymes that form reactive oxygen species (ROS) and neutralize free radicals by donating H ions. Tannin can inhibit pro-oxidative enzymes and lipid peroxidation.[17,18]

Estrogen-related conditions. GPL contains compounds derived from plants with similar structure and function to estradiol, called phytoestrogens. The phytoestrogens found in GPL are flavonoids and phytosterols. Therefore, GPL can be used for estrogen-related conditions such as fertility issues, osteoporosis, amenorrhea, dysmenorrhea, infertility, and birth control.[19–21] Phytoestrogens are essential for increasing osteoblast activity in bone formation and inhibiting osteoclast activity in the remineralization process in the bone.[19,20] The decrease in TNF- levels as an anti-inflammatory effect of GPL can reduce arachidonic acid secretion. thus reducing the apoptosis of osteoblast cells and preventing the osteoporosis effect after menopause.[19]

Flavonoids from GPL have estrogenic characteristics by binding to estrogen receptors (ER and ER) in the bone tissue, kidneys, endothelial cells, and blood vessels, whereas phytosterols become the precursor of estrogen hormone.[19] The binding to the estrogen receptors initiates a cascade of genomic reactions and increases uterine epithelium thickness.[21] The active compounds of GPL also act as birth control by inhibiting the steroidogenesis process; thus, testosterone formation will decrease. Decreased testosterone levels will interfere with spermatogenesis in the epididymis, resulting in sperm morphological abnormalities.[20]

Hypertension. Flavonoids have diuretic abilities through inhibition of sodium (Na^+), potassium (K^+), and chloride (Cl^-) reabsorption, resulting in increased electrolytes in the tubules and water excretion. This situation causes a reduction in blood and extracellular fluid volume, resulting in decreased cardiac output and blood pressure.[22]

Anal ulcer. GPL's anti-inflammatory and antioxidant properties can be used for anal ulcer treatment, although the mechanism is not yet known. It is hypothesized that GPL flavonoid compounds can block the formation of TLR-4/myeloid differentiation factor 2 (MD2).[23] TLR-4 recognizes lipopolysaccharide (LPS) from the cell wall of Gram-negative bacteria and initiates MyD88-dependent signaling cascades through a TLR-4/MD2 complex which promotes the production of proinflammatory cytokines such as TNF-α, IL-1β, IL-6, and IFN-γ.[37]

Harmful effects of sunlight. Flavonoid compounds in GPL were considered to have photoprotective properties. Flavonoids have a photoprotective substance called a chromophore group, a conjugated aromatic system that absorbs intense ultraviolet (UV) light.[24]

The pharmacological effects of GPL for dental purposes. GPL can be used not only for medical purposes but also for dental purposes. Several studies reported that GPL can be used for periodontal disease,[25,27–29] dental caries,[30–33] candidiasis,[34,35] and pulp perforation.[36]

Periodontal disease. The anti-inflammatory effect of GPL was reported to be used for periodontal disease. GPL extract with a concentration of 25% can inhibit the bacterial adhesion of *Porphyromonas gingivalis* by lining the neutrophil membrane and isolating neutrophil receptors. As a result, the early stages of infection can be prevented without interfering with neutrophil activity. Alkaloids in GPL can change the tertiary structure of the bacterial surface protein, resulting in bacterial attachment inhibition and bacterial death. Flavonol kaempferol can prevent the proteolytic enzymes (i.e. gingipain) in *P. gingivalis* from causing neutrophil lysis by binding to estrogen receptors on the surface of neutrophils. Thus, reactivates neutrophils. Reactivated neutrophils release antibacterial cytokines to increase phagocytosis. Flavonoids, extracts of 5% and 10% GPL in Wistar rats induced by *P. gingivalis*, can reduce TNF-α levels by decreasing the apoptosis of osteoblast cells. Osteoprortegenrin (OPG) synthesized by osteoblast cells will inhibit the binding of receptor activator of NF-κB (RANK) to its ligand (RANKL), resulting in increased apoptosis of osteoclast cells.[29,30] It was also reported that flavonoids in 10% GPL extract can inhibit the formation of prostaglandins to increase the number of fibroblast proliferation in Wistar rats gingiva induced by

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P. gingivalis.[27] However, flavonoids of GPL extract with a concentration of 30% in aggressive periodontitis were reported to reduce the infiltration of macrophages in Wistar rats induced by *A. actinomycetemcomitans*.[25,26]

Dental caries. GPL was also reported to be used for dental caries treatment.[30–33] GPL had a minimum bactericidal concentration (MBC) value of 6,25% against *S. mutans* and an MBC value of 12,5% against *L. acidophilus*.[30,31] The antibacterial activity of the secondary metabolite of GPL plays a vital role in treating dental caries. Secondary metabolites from GPL related to the antibacterial agent include flavonoids, tannins, triterpenoids, alkaloids, glycosides, saponins, and triterpenoids.[30–33] Flavonoids have the highest content in GPL (4340, 30 mg/100 wb) and are essential for protein denaturation.[32] Alkaloids deteriorate the peptidoglycan on the bacterial wall. Polyphenols also cause the lysis of bacterial cells, denaturation of proteins, and inhibition of cytoplasmic proteins, nucleic acids, and adenosine triphosphate (ATP-ase) bond formation in bacterial cell membranes. Furthermore, tannin inhibits bacterial cell wall formation through bacterial protoplasm coagulation and protein precipitation. The interaction of saponins and bacterial cell walls disrupts the surface tension of the cell walls.[30,31] In addition, triterpenoids play a role in the destruction of cell membranes by lipophilic compounds through the binding of phospholipids to the surface of the bacterial cell membrane.[33]

Candidiasis and denture stomatitis. GPL at a concentration of 40% had an antifungal effect on *C. albicans*.[34] These antifungal properties are performed by flavonoids, saponins, steroids, alkaloids, and tannins compounds. Flavonoids can denature cell memprovidedids and cause inhibition of cell wall formation, retannin in delayed hyphal growth. Saponins can damage the cytoplasmic membrane and interfere with electron transfer. Steroids can reduce the surface tension of the sterol membrane of the *C. albicans* cell wall resulting in increased permeability.[36]

GPL at a concentration of 25% can also increase the phagocytic activity of monocytes exposed to *C. albicans*. Receptors on the surface of monocyte cells (mannose and glucan receptors) bind to the constituents of the cell wall layer of *C. albicans* (mannan and mannoprotein), inducing phagocytosis activity. Flavonoids and alkaloids in GPL can increase phagocytic activity by increasing the production of pro-inflammatory cytokines. These cytokines can increase the ability of monocytes to kill bacteria by stimulating lysosomal enzymes through accelerated respiration. Phagocytic activity will produce oxidants that have the potential to cause oxidative stress and cause monocyte lysis. However, flavonoids, alkaloids, and tannins can protect monocytes from oxidation mechanisms, and the number of monocytes undergoing lysis can be reduced.[25]

Pulp perforation. GPL has anti-inflammatory activity by increasing the number of macrophage cells to stop pulp inflammation. Flavonoids in GPL extract with concentrations between 15% and 20% can inhibit the COX pathway, specifically prostaglandins. The decrease in the inflammatory process accelerates the initiation of the proliferative phase and the process of healing and tissue repair. Macrophages 2 (M2), one of the cells that play a role in tissue repair, will produce growth factors for the initiation of fibroblast cell proliferation in Wistar rats that are given a mechanical perforation of the pulp.[36]

CONCLUSION

GPL are flavonoids, phenols, alkaloids, saponins, tannins, triterpenoids, and steroids, which exert pharmacological effects such as antioxidant, anti-inflammation, antidiabetic, immunomodulator, antibacterial, antifungal, and estrogenic properties. Thus, it can be concluded that GPL can be used for medical treatment and dental purposes. However, the current published studies are limited to *in vitro* and *in vivo* studies. Future studies should conduct advanced clinical tests to legitimize the GPL as a treatment for medical and dental purposes.

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