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The potency of kitolod leaves (*Hipobroma longiflora*) as traditional medicine for conjunctivitis during the COVID-19 pandemic: a brief review

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ABSTRACT

During the coronavirus disease 2019 (COVID-19) pandemic, most activities have transformed into digital ones, including computer usage. The digital screen on the computer has blue light radiation which can activate inflammatory cytokines of the eye surface and cause various disorders including includes conjunctivitis. Kitolod leaves (*Hippobroma longiflora*) have been used traditionally to treat conjunctivitis. This paper aimed to describe the potency of kitolod leaves for conjunctivitis. This is a narrative literature review using publications gathering from PubMed and Google Scholar published since 2013 with exclusion criteria were the animal studies. The keywords of COVID-19 pandemic, blue light, conjunctivitis, *H. longiflora*, traditional therapy were used. Boolean logic "AND" was used to find specific international scientific publications in PubMed. Forty selected publications were gathered, summarized and then narrated. The kitolod leaves contains bioactive substances i.e. flavonoids, alkaloids, and saponins which can inhibit *S. aureus* growth as the main cause of conjunctivitis. The mechanism of antibacterial of these bioactive substances through inhibition of nucleic acid synthesis, disruption of cytoplasmic membrane function, and inhibition of energy formation process. Kitolod leaves is potential to develop as traditional medicine for conjunctivitis. However, further studies are required to obtain the best standardized extract and to evaluate its clinical efficacy and safety.

ABSTRAK

Selama pandemic COVID-19, sebagian besar aktivitas telah berubah ke digital, termasuk penggunaan komputer. Layar digital pada komputer memancarkan radiasi cahaya biru yang dapat mengaktifkan sitokin inflamasi pada permukaan mata dan menyebabkan berbagai gangguan termasuk konjungtivitis. Daun kitolod (*H. longiflora*) telah digunakan secara tradisional untuk mengobati konjungtivitis. Tulisan ini bertujuan untuk mendeskripsikan potensi daun kitolod terhadap konjungtivitis. Ini adalah tinjauan pustaka naratif melalui pengumpulan publikasi dari PubMed dan Google Scholar yang diterbitkan sejak tahun 2013 dengan kriteria eksklusi adalah studi hewan. Kata kunci pandemi COVID-19, cahaya biru, konjungtivitis, *H. longiflora*, terapi tradisional digunakan. Logika Boolean "DAN" digunakan untuk menemukan publikasi ilmiah internasional tertentu di PubMed. Empat puluh publikasi terpilih dikumpulkan, dirangkum dan kemudian dinarasikan. Daun kitolod mengandung senyawa bioaktif yaitu flavonoid, alkaloid, dan saponin yang dapat menghambat pertumbuhan *S. aureus* sebagai penyebab utama konjungtivitis. Mekanisme antibakteri senyawa bioaktif tersebut melalui penghambatan sintesis asam nukleat, gangguan fungsi membran sitoplasma, dan penghambatan proses pembentukan energi. Daun kitolod berpotensi untuk dikembangkan sebagai obat tradisional untuk konjungtivitis. Namun, penelitian lebih lanjut diperlukan untuk mendapatkan ekstrak standar terbaik dan untuk mengevaluasi efektivitas dan keamanannya secara klinik.

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INTRODUCTION

After the SARS-CoV-2 virus pandemic that caused coronavirus disease 2019 (COVID-19) entered Indonesia, the Indonesian government issued Government Regelation number 1 of 2020 concerning large-scale social restrictions which requires the Indonesian people to do work from home (WFH).[1] The Indonesian National Bureau of Statistics reported a double-digit growth of 10.58% in the information and communication technology (ICT) sector in 2020 produced by WFH as a form of rapid transition from traditional to digital solutions. Computer is one of the most commonly used products of information technology during the COVID-pandemic.[2] The increase in computer use during the COVID-19 pandemic is unavoidable. Almost all activities are carried out online in front of a computer screen or gadget so that the screen exposure time increases rapidly. An increase in screen time for a long time could harm the eyes because digital technology screens are now widely used blue light.[3]

Blue light is a light wave with the shortest wavelength, around λ of 400-500 nm, however it has the greatest energy in the visible light spectrum. Most blue light is produced by the sun. Several recent studies have revealed that other sources of blue light are digital screens such as computers, gadgets, televisions, light emitting diode (LED) lamps, and others. Exposure to blue light in high intensity and long duration can cause disturbances in the organs of the body, especially the eyes due to free radical oxidation in cells and accelerating cell death (apoptosis).[4] Exposure to blue light in the eyes can cause various eye disorders, especially in the conjunctiva (conjunctivitis).[5,6]

Conjunctivitis can be caused by various factors, such as bacteria, viruses, and allergies.[7] The most frequent and common conjunctivitis is conjunctivitis caused by bacteria, such as *Staphylococcus aureus*, *Haemophilus influenzae*, *Pseudomonas aeruginosa*, and *Streptococcus pneumoniae* with the *S. aureus* is the most dominant bacteria.[8] Several antibiotics are often used to treat the conjunctivitis such as bacitracin, chloramphenicol, erythromycin, tobramycin, neosporin, and gentamicin. However, the antibiotics have side effects and cause resistance.[9]

In 2021 in Indonesia, the conjunctivitis has reached the second position out of a total of 10 main eye diseases.[10] It is suspected that the incidence of conjunctivitis has increased during the COVID-19 pandemic due to the high intensity of the computer use or other digital media to maximize online activities. There is a positive correlation between the use of computers, laptops, and smartphones for complaints of red and dry eyes. Staring at a computer screen for a long time without taking a break has been proven to make the eyes tired, sore, and red, which has the potential to cause pink eye disease or conjunctivitis.[11] This condition is exacerbated by exposure to blue light from digital screens which can damage the conjunctiva.[4,12]

Herbal medicines have been used to treat the conjunctivitis during the COVID-19 pandemic including kitolod leaves (*H. longiflora*). Kitolod contains bioactive substances such as flavonoids, tannin, coumarin, terpenoid, alkaloids, and saponins which can act as antibacterials.[9,13–16] Kitolod leaves contain

14 polyphenols compounds, such as phenolic acids (gallic acid, ferulic acid, and caffeic acid), flavonoids (gallocatechin, catechin, epigallocatechin, epicatechin gallate, gallocatechin gallate, quercitrin, myricetin, baicalin, pelargonidin, and diosmin), and another polyphenols groups (ellagic acid).[17] These bioactive substance can inhibit the growth of *S. aureus*.[10]

Ibrahim and Rezki reported that triterpenoids compounds from *H. longiflora* might have a role in formulating the drug eyes of ordinary people.[16] In the village, people usually use the water of the kitolod flower to cure their eye problems.[18] Siska *et al.*[19] studied that kitolod leaves infusion at 60% concentration could lower the intraocular pressure in male rats that induced by 1% prednisolone acetate eye drops. The decrease in intraocular pressure is similar to the effects of the 2% pilocarpine eyedrops.[19] Previous stud revealed that kitolod flower extract could inhibit the growth of *S. aureus* and *Escherichia coli*. Meanwhile, kitolod fruit inhibited the growth of *S. aureus* bacteria but not *E. coli*.[20]

This paper focused on kitolod leaves which have many usages for the eyes, such as for conjunctivitis, cataract, myopia, and glaucoma.[13] The most common eye case in the COVID-19 pandemic in Indonesia is conjunctivitis. Therefore, this paper aims to describe the potency of *H. longiflora* (kitolod leaves) as traditional medicine for conjunctivitis during the COVID-19 pandemic. This problem is important because kitolod leaves as common weeds in Indonesia, contain many antioxidants and have many usages in traditional therapy. However, kitolod leaves are often thrown away because there is less research about these leaves, especially in conjunctivitis cases. Therefore, we need to study these leaves meticulously in obtaining the best potency in managing conjunctivitis. Besides that, conjunctiva is important as the first eye immune system.[4] It protects the eyeball and the inside of the eyelid.[21,22]

MATERIALS AND METHODS

In the writing this narrative literature review, national and international journals were used as references. Reference searches were carried out through the Google Scholar journal database page and some used PubMed. In searching for references, the author uses the keywords COVID-19 pandemic, blue light, conjunctivitis, *H. longiflora*, traditional therapy, and uses Boolean logic "AND" to make it easier to find specific international scientific journals in PubMed. Then, the data and research results obtained have been systematically arranged according to the order of the topic of the problem raised. Problems are discussed with the data that has been obtained and arranged systematically accompanied by inclusion and exclusion criteria. There were 40 selected sources in the references, which comprised 10 review articles and 25 studies. The articles about kitolod 26 articles (4 reviews and 22 research articles). Inclusion criteria are the review and research articles that were published in 2013 and afterwards. Exclusion criteria are animal studies. The references included were shown in TABLE 1.

TABLE 1. Summary of the studies about kitolod

Author	Results
Hastuti *et al*[9]	Kitolod leaves decoction at 20, 40, 80, and 100% concentration showed inhibition zone of *S. aureus* in 6.18, 6.28, 6.68, 7.20, and 8.18 mm, respectively.
Mareintika[10]	Kitolod leaves showed inhibition power of 17.18333 mm on the growth of *S. aureus* by using a 100% concentration.
Egarani *et al.*,[14]	Based on the DPPH method, the kitolod leaves contained flavonoid (10.48 ppm), phenolic (1.46 ppm), chlorophyl (7.25 ppm), and carotenoid (56.98 ppm).
Angelina,[15]	The ethanol extract of kitolod leaves against *S. aureus* and *S. typhi* at a concentration of 75% showed a diameter of 11.3 and 12.16 mm with a strong category.
Ibrahim *et al.*,[16]	Triterpenoid was isolated from the ethyl acetate fraction of *H. longiflora*.
Dewantoro *et al.*,[17]	Kitolod leaves contain polyphenols compounds, phenolic acids, flavonoids, and ellagic acid.
Siska *et al.*,[19]	Kitolod leaves could decrease the rats' intraocular pressure which is similar to the effects of the 2% pilocarpine eyedrops
Aprilia *et al.*,[20]	Kitolod flower and fruit extract can inhibit the growth of *S. aureus*
Angganawati *et al.*,[23]	The kitolod leaves extract inhibits the growth of *S. aureus* with the optimal rate at 300mg/mL concentration with an inhibition zone of 14.3 mm.
Yulianto[24]	Decoction of kitolod flowers was effective in inhibiting the growth of *S. aureus*, but it was not better than chloramphenicol
Arsyad *et al.*,[25]	Kitolod leaves could inhibit the cornea neovascularization after 7 days in the eyes that had chemical trauma due to pesticide the Rotraz© 200EC.
Winneta *et al.*,[26]	Kitolod leaves contain the highest content of chlorophyll, carotenoid, and ascorbic acid compared to the other parts of the plants (i.e. flowers and fruits).
Gloriana *et al.*,[27]	From the encapsulation results of the kitolod leaves, the amount of flavonoids was 39.5277 mg/10 g.
Arrosyid *et al.*,[28]	The longer boiling time will decrease the flavonoid content of the kitolod leaves.
Wulandari *et al.*,[29]	The suitable solvents for kitolod leaves are n-hexane and ethyl acetate extract because those solvents give a higher content of flavonoid compared to ethanol extract.
Tanaja *et al.*,[30]	Ethanolic extract of kitolod leaves revealed antibacterial activities against *S. pyogenes* with the value of minimum bactericidal concentration (MBC) 1.75%.
Hazar *et al.*,[31]	Ethyl acetate fraction of kitolod herbs showed a better inhibition result than the fraction of n-hexane and water fraction.
Wardani *et al.*,[32]	The water fraction of kitolod leaves at a concentration of 30% showed an average inhibition zone diameter of 19.0 mm of the growth of *S. aureus*.
Haryoto *et al.*,[33]	Kitolod leaves extract showed cytotoxic activity with moderate ability on MCF-7 cells
Martiningsih *et al.*,[34]	The antioxidant activity of the ethanol extract of kitolod leaves was more potent than the n-hexane and chloroform fractions, but smaller than ascorbic acid.

DISCUSSION

Increased conjunctival infection on exposure to blue light

Exposure to blue light radiation on the surface of the eye can activate inflammatory cytokines. The increased formation of oxidation products due to exposure to blue light radiation will activate the NLRP3 inflammasome which will hydrolyze the IL-1 precursor to become active IL-1.[4]

A series of inflammatory responses on the surface of the eye due to exposure to blue light radiation and the release of inflammatory factors can result in reduced secretion of tears and mucin, disrupt the stability of the tear film, and cause the eye surface to become hyperosmotic.[12] In addition, blue light can also induce the formation of superoxide dismutase (SOD1). The conjunctiva is very susceptible to an increase in SOD1 because it will cause a decrease in glutathione peroxidase (GPx1) levels which play a role in protecting conjunctival epithelial cells from oxidative damage.[4]

Increased damage from blue light radiation can interfere with the function of the lacrimal glands or tear glands. The tear glands act as a storage place for vitamins in the form of retinol which will then be secreted along with the tears. Impaired function of the tear glands will lead to decreased production of retinoic acid (RA), which is a biologically active form of vitamin A due to decreased retinol secretion, which will have an effect on decreasing the number of goblet cells in the conjunctival bulbar epithelium.[14] The effect of exposure to blue light radiation can increase oxidative damage and activate inflammatory factors in the conjunctiva which worsens the immune system of the conjunctiva so that it can be susceptible to disease and infection from bacteria such as *S. aureus* which can cause conjunctivitis.[10]

The possible role of kitolod plant (*H. longiflora*) against bacterial conjunctivitis

Kitolod (*H. longiflora*) is a type of plant that is believed to have potential as a traditional medicine (FIGURE 1). It is also called *Isotoma longiflora* Presi. The kitolod plant originates from the West Indies area, but this plant has spread and is found widely in the tropics. Kitolod plants have characteristics, which are easy to grow among rocks in moist conditions, around the edges of ditches, and are even found around the yards of houses so these plants are generally known as wild plants.[13]

FIGURE 1. Kitolod plants (*H. longiflora*)[13,35]

The classification of *H. longiflora* plants is as follows:

Kingdom : Plantae
Subkingdom : Tracheobionta
Superdivision : Spermatophyta
Division : Magnoliophyta
Class : Magnoliopsida
Subclass : Asteridae
Order : Asterales
Family : Campanulaceae
Genus : Hippobroma
Species : Hippobroma longiflora (L.)
Synonym : *Isotoma longiflora* (L.)
Isotoma longiflora var. runcinata (Hassk)
Isotoma runcinata (Hassk)
Laurantia longiflora (L.)
Laurantia longiflora var. runcinata (Hassk)
Lobelia longiflora (L.)
Rapuntium longiflora (L.)
Solenopsis longiflora (L.)

Content of kitolod leaves (*H. longiflora*)

Kitolod (*H. longiflora*) contains several bioactive compounds that act as antibacterials, anti-inflammation, analgesic, and antifungal.[25,36,37] All parts of this plant contain the same bioactive substances, but the most frequently found bioactive substances are in the leaves of the kitolod plant.[9] Bioactive substances are secondary metabolites that have biologically active characteristics. Based on the results of the phytochemical screening study, the bioactive substances contained in kitolod plants are flavonoids, alkaloids, and saponins as shown in TABLE 2.[10] Flavonoids might become alternative choices for tackling antibiotic resistance in certain cases.[38] Another study also showed that flavonoidsin the kitolod leaves might be used against *Candida albicans*.[36]

Flavonoids are one of the phytochemical compounds that are mostly found in plants with a characteristic green color. Flavonoids are a group of natural compounds that have a variety of pharmacological properties with their main activity as an antibacterial. Flavonoids belong to the largest group of phenol groups with the C6-C3-C6 framework. Flavonoid compounds have a basic structure characterized by 2-phenyl-benzo[α] pyrene or a flavan core which includes two benzene rings, namely rings A and B (FIGURE 2). The structure of this benzene ring is connected by a pyran ring heterocyclic bond. This structure can increase the work activity of flavonoids as antibacterial. Flavonoid compounds can be classified into several classes based on their biosynthetic processes, whereas the flavanone class has the highest activity characterized by the presence of bioactive activities such as antibacterial.[38]

TABLE 2. Results of phytochemical screening on *H. longiflora*[23]

Testing	Result	Description
Alkaloid	Orange-red precipitate	+
Flavonoid	Red-orange color	+
Saponin	There is foam	+

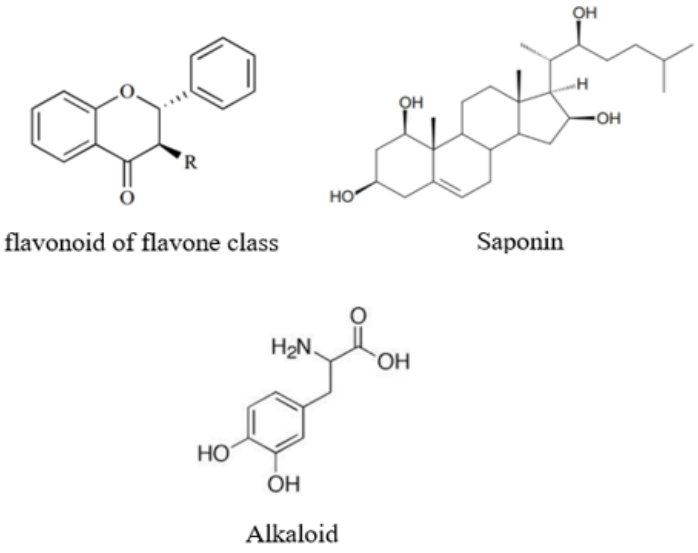

FIGURE 2. Chemical structure of phytochemical compounds[38]

Saponins are phytochemical compounds that are amphipathic glycosides. If this compound undergoes hydrolysis, a glycosidic bond will be seen in the form of a CO sugar bond which includes the aglycone and sugar chain. The chemical structure of saponin compounds can be seen in **(**FIGURE 2**).** Saponin compounds have a similar mechanism to flavonoid compounds, namely as bioactive substances with antibacterial activity *in S. aureus*.[39]

Alkaloids are phytochemical compounds that contain nitrogen, have basic properties, and have pharmacological activity. The alkaloid compounds form a heterocyclic ring structure (FIGURE 2). Alkaloids are found in all parts of the plant, starting from the stems, leaves, and seeds, so these compounds are widely used in traditional medicine.[40]

Mechanism of kitolod leaves (*H. longiflora*) against conjunctivitis

Kitolod plant (*H. longiflora*), especially the leaves of kitolod contain bioactive substances of flavonoids, saponins, and alkaloids. These three substances can be used as an alternative treatment for diseases caused by the main cause of conjunctivitis i.e. *S. aureus.* Kitolod also contains ascorbic acid and carotenoid. Carotenoid plays an important role in reducing free radicals in eyes problem.[26]

The mechanism of action of flavonoids and saponins in inhibiting the growth of *S. aureus* can be classified into three main mechanisms, including inhibiting nucleic acid synthesis, the function of the cytoplasmic membrane, and the process of energy formation.[38] Flavonoids provide bacteriolytic effects, inhibit protein synthesis, DNA synthesis, RNA, and damage cell membrane permeability.[21] Flavonoids have antibacterial activity because of the ability of flavonoids to interact with cell membranes and affect cell membrane bioactivity and it has been reported that flavonoids are able to reduce the fluidity of bacterial cell membranes that is directly related to damage to cytoplasmic membranes or indirect damage through autolysis/weakening of the cell wall and consequently osmotic lysis.[22] Flavonoids can denature proteins in *S. aureus*. The function of the cytoplasmic membrane and the formation of energy are inhibited. Therefore, the *S. aureus* will lack the energy supply to reproduce so that it can reduce the activity of the bacteria that cause conjunctivitis.[38,39]

The mechanism of action of alkaloids as an antibacterial is by inhibiting the synthesis of nucleic acids, because it can inhibit the enzymes dihydrofolate reductase and topoisomerase I.[10] Alkaloids can also disrupt the constituent components of peptidoglycan on bacterial cells so that the cell wall layers are not formed intact and cause cell death. Another mechanism of antibacterial alkaloids is that the alkaloid component is known as a DNA accelerator and inhibits bacterial cell topoisomerase enzymes.[11]

The mechanism of action of saponin as an antibacterial through the lysis of the bacterial cell wall and leakage of AKP (alkaline phosphate), an increase in saponin concentration causes the protein to dissolve, causing intercellular compounds to diffuse through the outer membrane and cell wall. This causes the cytoplasm to leak out of the cell resulting in cell death.[15]

Traditional therapy of kitolod leaves in conjunctivitis

Research about *H. longiflora* inhibits *S. aureus*

There are various *in vitro* studies that have proven the activities of kitolod leaves to inhibit the growth of *S. aureus.* This is because the content in kitolod leaves is able to act as a bioactive substance as well as an antibacterial. This content will form a radical zone so that it can inhibit the growth of *S. aureus*. This

potential makes kitolod leaves can be used as a traditional therapy for treating eyes with conjunctivitis.[9] This traditional kitolod leaf therapy is an innovation during the COVID-19 pandemic with a simple way of using it, the ingredients are easy to get, and there are no dangerous side effects.

Anjelina[15] revealed that the ethanolic extract of kitolod leaves showed inhibition against *S. aureus* and *S. typhi* at a concentration of 75% with a diameter range of 11.3 - 12.16 mm which it was within a strong category.[15] However, Wulandari *et al.*[29] reported that the ethanolic extract of kitolod leaves showed a lower concentration of total flavonoid content compared to n-hexane and ethyl acetate extract.[29]

Traditional administration of kitolod leaves for eye therapy

For the best treatment result, kitolod leaves should be green and not attacked by pests. Kitolod leaves could not be used for treating viral bacterial nor conjunctivitis caused by bacteria other than *S. aureus*. The kitolod leaves are cut into small pieces and soaked in clean water overnight and then the soaking water is put into an eye drop container. Furthermore, it can be used as eye drop therapy as much as 2-3 drops with use 2 times a week.[10]

When the kitolod leaves are boiled longer time, the total flavonoid content will decrease.[28] Flavonoid is easily degraded at high temperatures. Based on the study result, the best extraction and encapsulation use a temperature of 70℃ with 90% ethanol solvent. The amount of flavonoids obtained from encapsulation results was 39.5277 mg/10 gr.[27]

CONCLUSION

Exposure to blue radiation light from digital screens increases the production of free radicals in the conjunctival epithelium of the eye. The conjunctiva acts as a defense system for the eye from bacteria that cause conjunctivitis such as *S. aureus*. Kitolod leaves (*H. longiflora*) has been used traditionally to treat conjunctivitis. The kitolod leaves contain bioactive substance such as flavonoids, alkaloids, and saponins which can inhibit bacterial growth including *S. aureus*. However, further studies are needed to obtain the best standardized extract and to evaluate clinical efficacy and safety of this plant.

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