REVIEW: MEDICINAL PLANTS WITH PHARMACOLOGICAL ACTIVITY AS ANTIPYRETIC

Nurdiani Adiningsih[1*], Dika Pramita Destiani[2]
[1]*Program Studi Profesi Apoteker, Fakultas Farmasi, Universitas Padjadjaran*
Jl. Raya Bandung Sumedang KM. 21, Hegarmanah, Jatinangor, Kabupaten Sumedang, Jawa Barat
[2]*Departemen Farmakologi dan Farmasi Klinik, Fakultas Farmasi, Universitas Padjadjaran*
Jl. Raya Bandung Sumedang KM. 21, Hegarmanah, Jatinangor, Kabupaten Sumedang, Jawa Barat
**Email Corresponding: nurdiani18001@mail.unpad.ac.id*

Submitted: 12 June 2023 ***Revised: 13 September 2023*** ***Accepted: 13 September 2023***

ABSTRACT

Fever is a medical condition characterized by an increased body temperature beyond the normal range of 36 – 37°C. If not managed appropriately, fever may lead to complications in therapy. The conventional treatment for fever involves using antipyretics such as paracetamol/acetaminophen, and ibuprofen. However, prolonged use of these synthetic medications may have adverse side effects. Consequently, more patients are turning to herbal medicine to manage fever. This review aims to identify medicinal plants with pharmacological activity as antipyretics. We conducted a systematic literature review using Google Scholar as the search engine database. Our search keywords were "tanaman herbal", "antipiretik", "penurun demam", and "uji aktivitas antipiretik". In this review, a total of 18 articles were meticulously analyzed. The collective findings from these studies demonstrated that all tested medicinal plants exhibited antipyretic activity. Flavonoids, tannins, and terpenoids were the primary constituents responsible for the observed antipyretic activity. Medicinal plants with alkaloids and steroid content were also believed to exhibit antipyretic activity.

Keywords*: fever, antipyretics, medicinal plants*

INTRODUCTION

Fever is a medical condition when the body temperature increases beyond the normal range of 36-37°C. This condition results from interference in health and is characterized by chills and redness in the skin area (Suproborini, Laksana, and Yudiantoro, 2018). Fever is generally caused by an infection induced by microorganisms such as bacteria, viruses, parasites, or even fungi. If not managed appropriately, fever can cause complications in therapy (Azis, 2019). Fever is characterized by some symptoms such as lack of oxygen, lack of appetite, weakness, headaches, muscle aches, and dehydration (Samiun, Queljoe, and Antasionasti, 2020).

Fever therapy involves the administration of antipyretic medications, such as paracetamol and ibuprofen. Patients frequently use these drugs due to their over-the-counter availability, safety, accessibility, and affordability (Samiun, Queljoe, and Antasionasti, 2020). The antipyretic effects of this medication are achieved by inhibiting the COX-2 enzyme in the Central Nervous System (CNS), thus preventing arachidonate acid conversion to prostaglandin, which is the mediator of fever or the temperature-inducing agent in the hypothalamus thermostat (Suproborini, Laksana and Yudiantoro, 2018).

Despite their relative safety, the use of synthetic drugs can lead to some adverse effects. For example, excessive use of paracetamol, which is metabolized in the liver, can lead to fulminant liver failure and acute liver failure, necessitating heart transplantation for the patient (Azis, 2019). Furthermore, cases such as ethylene glycol (EG) and diethylene glycol (DEG) in paracetamol syrup in Indonesia caused a shift towards the use of herbal medicines

as an alternative to fever therapy (BPOM RI, 2022). Medicinal plants are also considered to be safe and effective for fever treatment (Suproborini, Laksana, and Yudiantoro, 2018). This review article aims to gather information on medicinal plants that exhibit antipyretic activity as a pharmacological effect.

RESEARCH METHOD

The method of this article was a literature review. The data source for this article comes from literature obtained via the internet in the form of research journals that discuss medicinal plants with antipyretic activity. Google Scholar is used as a search engine database with keywords entered, namely "tanaman herbal" and "antipiretik" (n = 616); "tanaman herbal" and "penurun demam" (n = 85); "tanaman herbal" and "uji aktivitas antipiretik" (n = 9). The journals are then filtered based on inclusion and exclusion criteria. The inclusion criteria used were suitable for the topic reviewed, full text and open access journals, published in the last 10 years (2013 – 2023), and medicinal plants reviewed are available in Indonesia. Meanwhile, the exclusion criteria are irrelevant topics, and the journal reviewed is not original research. The complete literature review can be seen in the following image:

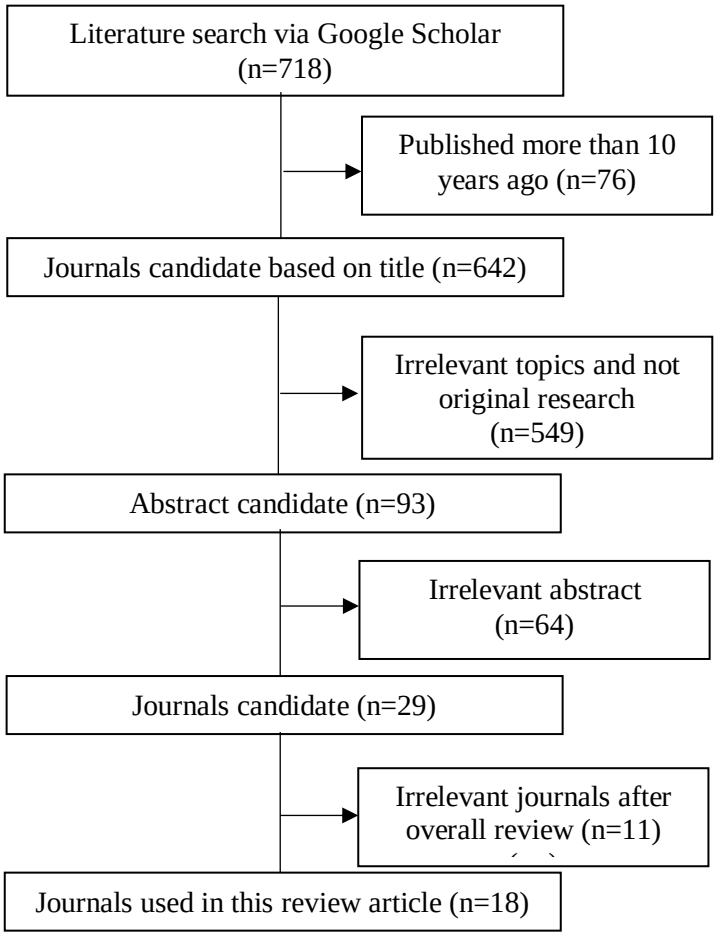

Figure 1. Literature search flowchart

RESULTS AND DISCUSSION

Fever is the body's response to disease, characterized by an increase in body temperature above normal, caused by the rise in the temperature regulation center in the hypothalamus. Fever occurs due to immunological factors that trigger mononuclear phagocyte cells to produce cytokines, which act as endogenous pyrogens. These cytokines

trigger the production of arachidonic acid, which will then be converted into prostaglandins through the cyclooxygenase enzyme, increasing temperature in the thermoregulation center in the hypothalamus (Pahmi and Ramadhan, 2022).

Fever was a symptom of diseases such as dengue fever, malaria, typhoid infection, and other infections. Fever can be considered when the armpit temperature reaches above 37,2 ℃, the oral temperature reaches above 37,8 ℃, and the rectal, forehead, or ear membrane temperature reaches above 38 ℃. It can also be considered as high fever if the body temperature reaches above 39,5 °C, and it is classified as hyperpyrexia if it reaches above 41,1 °C (Azis, 2019).

Fever can have a negative impact; it can cause dehydration, lack of oxygen, nerve damage, and discomfort, such as headaches, weakness, and muscle pain (Gosal, Queljoe, and Suoth, 2020). Therefore, action must be taken to reduce the negative impact of fever. Treatment measures can be taken to treat fever by administering antipyretic drugs such as paracetamol, aspirin, or ibuprofen. Apart from that, Indonesia is a country that has natural wealth and various kinds of plants that are spread across multiple regions. The general public has long had medicinal plants that are used to reduce fever. For example, in the Central Sulawesi area, cocor bebek leaves are empirically widely used to treat boils, loosen phlegm, tonsillitis, reduce fever, etc. (Purwitasari, Yuliet, and Ihwan, 2017). In the people of East Nusa Tenggara, the Kayu Ular plant has long been empirically known and used to treat various diseases, such as antimalarial and anti-inflammatory, and is thought to have fever-reducing properties (Yanih and Suni, 2018). Balinese people generally use the leaves of the Sembung plant as a drink from boiled leaves to treat fever, asthma, influenza, menstrual pain, rheumatism, diarrhea, diabetes, coughs, and bronchitis (Rahmi et al., 2021).

With the results from the library search within this review article, it can be concluded that many medicinal plants exhibit antipyretic activity as part of their pharmacological properties. The results of this review article are shown in Table ITable I.

Table I. Medicinal plants and their antipyretic activity

No	Medicinal Plants	Method	Result	Natural Compound	Reference
1	Suruhan (*Peperomia pellucida*) and Sambiloto (*Andrographis paniculata*)	Test animals: male mice Fever inducer: DPT vaccine Positive control: Paracetamol Negative control: Na-CMC 1% Sample: Suruhan herb extract and Sambiloto herb extract with dose variance	The test samples exhibit antipyretic activity with an effective dose at (80+20) mg/kg with stable antipyretic activity, and comparable effectivity with paracetamol.	Alkaloids, flavonoids, saponins, steroids, tannins.	(Pahmi and Ramadhan, 2022)
2	Cocor Bebek leaves (*Kalanchoe pinnata* L.) and Tembelekan leaves (*Lantana camara L.*)	Test animals: guinea pigs Fever inducer: Peptone 5% at 150 mg/kg Positive control: - Negative control: Na-CMC Sample: Cocor Bebek leaves extract and Tembelekan leaves extract with dose variance	The test samples exhibit an antipyretic activity with the effective dose of Cocor Bebek leaves extract at 50 mg and Tembelekan leaves extract at 720 mg (50+720).	Flavonoids, tannins.	(Purwitasari, Yuliet and Ihwan, 2017)
3	Turmeric (*Curcuma domestica* Val.)	Test animal: male mice (Swiss Webster strain) Fever inducer: peptone 10% Positive control: paracetamol	The test samples exhibit a significant effect on mice, with pressed turmeric providing the most	Flavonoids, curcumin.	(Sujana *et al.*, 2021)

		1.95 mg/30 g Negative control: Na-CMC 0,5% Sample: turmeric press, infuse, and decoction.	effective antipyretic effect compared to other samples.		
4	Bandotan leaves (*Ageratum conyzoides* L)	Test animal: male mice Fever inducer: peptone Positive control: paracetamol 1,3 mg/20 g Negative control: Na-CMC Sample: Bandotan leaves extract with dose variance	The test samples exhibit the most effective antipyretic activity in mice at 1.56 mg/20 g dose. The result showed a fever decrease rate of 3.94%, similar to positive control.	Alkaloids, amino acids, flavonoids, glycoside, coumarin, essential oils, saponins, stigmasterol, tannins, terpenes.	(Astria and Oktaviani, 2021)
5	Sungkai leaves (*Peronema canescens*)	Test animal: male mice Fever inducer: peptone 5% Positive control: paracetamol at 1,3 mg/kg dose Negative control: Na-CMC 1% Sample: Sungkai leaves infuse with dose variance	The test samples exhibit antipyretic potential with the most effective dose of 10% (0.026 g/kg).	Flavonoids.	(Brata and Wasih, 2021)
6	Bawang Hitam (*black garlic*)	Test animal: white male rat Fever inducer: Brewer's yeast Positive control: paracetamol at 45 mg/kg Negative control: Na-CMC 1% Sample: Black garlic ethanol extract with dose variance (50 mg/kg, 100 mg/kg, 200 mg/kg)	The test samples exhibit antipyretic effects on white male rats at all dose variations, with the most effective dose at 100 mg/kg.	Alkaloids, flavonoids.	(Kusuma and Anggraini, 2022)
7	Kangkung Hutan (*Ipomea carnea* Jacq)	Test animal: mice (Wistar strain) Fever inducer: peptone 0.3 ml/kg Positive control: paracetamol at 91 mg/kg Negative control: Na-CMC 1% Sample: Kangkung Hutan leaves ethanol extract with dose variance	The test samples exhibit antipyretic effects at the dose of 500 mg/kg, 250 mg/kg, and 125 mg/kg, with the percentage value of antipyretic power at 40,7%, 38,03%, and 28,4%, respectively. The antipyretic activity of the positive control is 50,73%.	Flavonoids, saponins, tannins, triterpenoids.	(Widyaningrum and Ningrum, 2021)
8	Rimpang Temu Hitam or Black rhizome (*Curcuma aeruginosa* Roxb.)	Test animal: white male rat (Wistar strain) Fever inducer: DPT-HB vaccine Positive control: paracetamol at 45 mg/kg BW mice Negative control: Na-CMC 0.5%	The test samples exhibit antipyretic activity with the most effective extract dose at 150 mg/kg BW mice.	Alkaloids, flavonoids, polyphenols, steroids, terpenoids.	(Susiloningrum and Mawarni, 2022)

		Sample: 96% methanol extract of black rhizome with dose variance			
9	Mengkudu or Noni leaves (*Morinda citrifolia* L.)	Test animal: white male rat (wistar strain) Fever inducer: peptone 5% Positive control: paracetamol Negative control: Na-CMC 1% Sample: ethanol extract of Noni leaves with dose variance	The test samples exhibit antipyretic effects at a dose of 72 g/kg BW with antipyretic power at 80%, equivalent to the antipyretic power of the positive control at 73%.	Flavonoids.	(Herdaningsih, Oktaviyeni and Utami, 2019)
10	Kayu Ular (*Srtychnos lucida*)	Test animal: white male rat Fever inducer: DPT vaccine Positive control: paracetamol Negative control: CMC 0.5% Sample: 70% ethanol extract of Kayu Ular stems with dose variance	The test sample at dose 8,1 mg exhibited comparable antipyretic power to the positive control.	Alkaloids, phenolics, flavonoids, glycosides, saponins, tannins, triterpenoids.	(Yanih and Suni, 2018)
11	Sungkai leaves (*Peronema canescens*)	Test animal: white male rat Fever inducer: DPT-HB vaccine Positive control: paracetamol Negative control: Na-CMC 0.5% Sample: extract of Sungkai leaves with dose variance	The test samples exhibit antipyretic effects, but the effect is still lower than the positive control.	Alkaloids, flavonoids, saponins, tannins.	(Hardiansyah and Oktriani, 2021)
12	Sembung leaves (*Blumea balsamifera*)	Test animal: white male mice Fever inducer: peptone 5% Positive control: paracetamol Negative control: Na-CMC 1% Sample: ethanol extract of Sembung leaves with dose variance	The test samples exhibit antipyretic activity, with the most effective dose at the extract dose of 200 mg/BW of mice with greater antipyretic activity compared to the positive control.	Flavonoids.	(Rahmi *et al.*, 2021)
13	Jarak Pagar leaves (*Jatropha curcas* L.)	Test animal: white male rat (wistar strain) Fever inducer: DPT vaccine Positive control: paracetamol Negative control: CMC 1% Sample: ethanol extract of Jarak Pagar leaves with dose variance	The test samples exhibit comparable antipyretic activity to the positive control.	Flavonoids, saponins, tannins.	(Gosal, Queljoe and Suoth, 2020)
14	Sisik Naga leaves (*Pyrrosia piloselloides* (L.) M. G. Price)	Test animal: white male rat (wistar strain) Fever inducer: peptone 5% Positive control: paracetamol Negative control: Na-CMC 1% Sample: extract of Sisik Naga leaves with dose variance	The test samples exhibit an antipyretic effect with the highest antipyretic power at 118% at a concentration of 0,25%. However, this effect is still lower than the antipyretic power of the positive control at 159%.	Flavonoids.	(Widyasari *et al.*, 2018)
15	Meniran	Test animal: white male mice	The test samples exhibit an	Flavonoids,	(Faizah,

	(*Phyllanthus niruri* L.) and Sambung Nyawa leaves (*Gynura procumbens* L.)	(swiss webster strain) Fever inducer: yeast dose of 20 ml/kg BW Positive control: paracetamol 1,3 mg/20g BW mice Negative control: Na-CMC Sample: single extract of Sambung Nyawa leaves, single extract of Meniran herb, and combination of ethanol extracts of Meniran herbs and Sambung Nyawa leaves with concentration variance	antipyretic effect compared to the negative control; a single dose of Sambung Nyawa leaves extract exhibit the best antipyretic effect.	tannins.	Kundarto and Sasongko , 2021)
16	Sangitan leaves (*Sambucus jabanica reinw.*EX Blume)	Test animal: white male rat Fever inducer: DPT-HB vaccine Positive control: paracetamol Negative control: CMC 0,5% Sample: ethanol extract of Daun Sangitan leaves with dose variance	The test samples exhibit an antipyretic effect with the most effective dose at a 200 mg/BW, extract dose.	Alkaloids, flavonoids, saponins, steroids, tannins.	(Sari and Mamban g, 2022)
17	White Turmeric (*Curcuma zedoaria Rosc*)	Test animal: white male rat (wistar strain) Fever inducer: brewer's yeast Positive control: paracetamol 10 mg Negative control: aquadest Sample: ethanol extract of White Turmeric with dose variance	The test sample exhibits the same antipyretic effectiveness as the positive control at a dose of 9 mg/200 g BW rats.	Flavonoids, terpenoids.	(Putra, Rahmah and Kusmiati, 2015)
18	Sawilangit leaves (*Vernonia cinereal* (L.) Less)	Test animal: white male rat (wistar strain) Fever inducer: DPT vaccine Positive control: paracetamol Negative control: CMC 1% Sample: ethanol extract of Sawilangit leaves with dose variance	The test samples exhibit antipyretic activity, comparable to the positive control, with the most effective extract dose at 7,2 mg.	Alkaloids, phenols, flavonoids, interpenoids, saponins, steroids.	(Samiun, Queljoe and Antasion asti, 2020)

From these medicinal plants' antipyretic activity tests, it can be inferred that all tested medicinal plants exhibited antipyretic activity. In all research, antipyretic activity was carried out on male mice, guinea pigs, or rats. Male animals are used due to their inherent biological stability, and their metabolic rate is faster than that of their female counterparts. Tests on these animals were also driven by their physiological and biochemical properties similar to those of humans (Purwitasari, Yuliet, and Ihwan, 2017; Astria and Oktaviani, 2021).

DPT vaccines are used as fever inducers because of their similarity with exogenous pyrogen and stimulate antibody formation against the vaccine, thus resulting in fever (Pahmi and Ramadhan, 2022). In other research, peptone is also used as a fever inducer. Peptone is a pyrogen that could stimulate an increase in body temperature (Purwitasari, Yuliet, and Ihwan, 2017). Brewer's yeast is also used as a fever inducer due to its pyrogen content. Pyrogen inserted into the bloodstream will react with a receptor in the preoptic hypothalamus anterior and will increase prostaglandin, thus resulting in fever (Kusuma and Anggraini, 2022).

Paracetamol was used as a positive control due to its antipyretic activity, thus exhibiting a significant decrease in body temperature in the positive control group. Na-CMC was used as a negative control due to its lack of discernible pharmacological activity (Pahmi and Ramadhan, 2022). Both variances in either dose or concentration for the test sample are purposefully conducted to determine the most effective dose or concentration that exhibits antipyretic activity (Purwitasari, Yuliet, and Ihwan, 2017).

The mechanism of action of antipyretic activity is inhibiting the cyclooxygenase (COX) enzyme, preventing prostaglandin formation, which is a mediator for fever. Flavonoids, among the secondary metabolites found in plants, possess this activity due to their structural resemblance to paracetamol. Both flavonoids and paracetamol share common features, such as the presence of phenolic groups and a benzene ring (Hardiansyah and Oktriani, 2021; Widyaningrum and Ningrum, 2021).

Flavonoids are phytoconstituents that exhibit diverse physiological activities and are categorized as polyphenols. The presence of a benzopyrone structure in flavonoids contributes to their antioxidative properties (Sujana et al., 2021). Flavonoid content in plants exerts an antipyretic effect by inhibiting cyclooxygenase, an enzyme that converts arachidonic acid to prostaglandins. This inhibition leads to a reduction in prostaglandin production, subsequently lowering the body's thermostat set point in the hypothalamus and resulting in a decrease in fever (Astria and Oktaviani, 2021; Pahmi and Ramadhan, 2022). Cyclooxygenase inhibition also leads to increased cases of skin vasodilation, triggering the release of body heat accompanied by increased sweat production. This physiological response leads to a subsequent reduction in body temperature (Widyaningrum and Ningrum, 2021).

The tannin content in plants also exerts antipyretic activity by inhibiting cytokine release, which mediates fever (Faizah, Kundarto, and Sasongko, 2021). Terpenoids have three derivative chemical structures: terpenoids, sesquiterpene lactones, and triterpenoids. All three of these have different mechanisms for providing antipyretic effects. Diterpenoids have a mechanism of inhibiting LTB4, LTC4, and COX-1 in the PGE2 release pathway, sesquiterpene lactones are inhibitors of NO production and NF-κB activity, and triterpenoids are inhibitors that act on arachidonic acid (Putra, Rahmah, and Kusmiati, 2015). The antipyretic effectiveness of medicinal plants is also suspected due to the presence of other compounds, such as alkaloids and steroids (Pahmi and Ramadhan, 2022).

Medicinal plant usage as fever-reducing agents has been practiced across generations, employing diverse processing methods. Typically, administering medicinal plants involves consuming decoctions prepared from these plants (Rahmi et al., 2021; Pahmi and Ramadhan, 2022).

CONCLUSION

In this article review, 21 medicinal plants have been shown to exhibit antipyretic activity as well as their as pharmacological activity. The antipyretic activity observed in plants is attributed to specific compounds. Flavonoids, tannins, and terpenoids are compounds known to possess antipyretic properties. Additionally, alkaloids and steroids in plants are believed to contribute to their antipyretic activity.

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