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Caesalpinia sappan Reduce Fever with An Anti-inflammatory and Antioxidant Mechanism: A Review

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Abstract
Caesalpinia sappan L (Sappan wood) is an herbal plant that has long been trusted by the public as an herbal medicine for tuberculosis, diarrhea, dysentery, skin infections, anemia, and other diseases by utilizing the decoction of *C.sappan*. Sappan wood is an herbal plant widely used as a raw material for traditional medicinal products. Sappan wood has been reported to have substantial pharmacological effects in analgesic, antioxidant, antibacterial, anti-inflammatory, and anti-viral. Fever is a clinical manifestation of certain conditions or diseases characterized by increased body temperature above the normal range (36.5–37.5 °C). Many studies declare that antioxidant and anti-inflammatory activity in *C.sappan* reduces oxidative stress and pro-inflammatory cytokines. This literature review shows that the antioxidant and anti-inflammatory properties of *C.sappan* are linked to fever as a sign of illness. Literature review using the last ten years' Scopus, ScienceDirect, and Pubmed databases. There are as many as 20 journals regarding sappan wood's antioxidant and anti-inflammatory effects. Sappan wood has been shown to have an antioxidant effect by lowering reactive oxygen species levels via SOD, GPx, or CAT markers. It inhibits inflammation cytokines such as IL-1, IL-6, TNF-**α**, and INF produced during fever. Sappan wood also has an anti-inflammatory effect by inhibiting PGE2 production when someone has a fever. The findings of our review state that *C.sappan* can be used to treat fever for both of these reasons. The use of *C.sappan* as a component in producing traditional health beverages has potential.

Keywords: Anti-inflammatory; Antioxidant; *Caesalpinia sappan;* Fever; Herbs

1. INTRODUCTION

Fever is an adaptive body regulatory response to the activation of the immune system (biological and chemical). Fever is a condition where the body temperature rises above the usual range (36.5-37.5 °C) due to an abnormal reaction of the immune system to infection, injury, or tissue damage (Andrews et al., 2018; Prajitha et al., 2018a). Fever is generally associated with increased hypothalamic prostaglandin E2 (PGE2) levels, which causes an increase in the body temperature set point (Mosili et al., 2020a; Mota and Madden, 2022). Fever can be controlled by using antipyretic and anti-inflammatory drugs. The mechanism of anti-inflammatory activity is by inhibiting cyclooxygenase (COX-1 and COX-2 enzymes), thereby inhibiting the formation of prostaglandins (Drożdżal et al., 2021; Ur Rashid et al., 2019)—fever induced by pyrogen chemicals that can enter the body from the outside or inside. Pyrogens are thermostable complex polysaccharide molecules containing free radicals. These antioxidants will fight free radicals that enter the human body, causing a chain reaction that can trigger inflammation, cancer, and other degenerative disorders. Some of these can cause fever (Nakamura et al., 2018; Sannasimuthu and Arockiaraj, 2019)

Caesalpinia sappan L (Sappan wood) is a Fabaceae family herbal plant found in Africa, America, and Asia, particularly India, China, and Southeast Asia, and it has various health advantages (Vardhani, 2019). Sappan wood has long been used as an herbal remedy for tuberculosis, diarrhea, dysentery, skin infections, and anemia using a sappan wood decoction. Furthermore, people are becoming more interested in drinking boiled sappan wood since it promotes blood circulation, increases energy, and reduces aging (Rajput et al., 2021). Sappan wood has analgesic, antioxidant, antibacterial, anti-inflammatory, anti-viral, anti-complementary, anti-convulsant, spasmolytic activity, hepatoprotective properties, anti-platelet concentration, antioxidative antioxidative stress, anticancer effects, and other activities (Wang et al., 2019). Brazilin ($C_{16}H_{14}O_5$), brazilein ($C_{16}H_{12}O_5$), resorcin ($C_6H_6O_2$), 3'-O-methylbrazilin, sappanon A ($C_{16}H_{12}O_5$), chalcone ($C_{15}H_{12}O$), and sappanchalcone ($C_{15}H_{12}O_5$) are among the bioactive chemicals (Vu et al., 2020). Fever treatment is still dominated by synthetic medications, which might induce adverse drug effects. The utilization of medicinal plants is one medication development technique.

No study has examined how antioxidants and anti-inflammatory affect sappan wood's fever process. Fever is a sign of almost all infections and immune system diseases, so this review is essential. Sappan wood makes health drinks and traditional medicines to give scientific knowledge.

2. MATERIAL AND METHODS

Various journals covered the period a little more than ten years ago. PubMed, Scopus, and ScienceDirect are the providers of the databases that we consult. "Sappan wood", "*Caesalpinia sappan L*", "fever", "sappan wood components", "*Caesalpinia sappan L* for human health", and "antioxidant activity" were some keywords used in this study—*Caesalpinia sappan L*, anti-inflammatory activity *Caesalpinia sappan L*. The scope of all searches was limited to publications in the English language. Journal selection criteria include things like (a) clinical studies of *C. sappan L* extract and compounds of fever, (b) anti-inflammatory and antioxidant effects on *Caesalpinia sappan L*, and (c) the effect of sappan wood on MDA (malondialdehyde), SOD parameters (superoxide dismutase), CAT (catalase), GST (glutathione S-transferase), and GSH-P (glutathione peroxidase). Twenty articles were included in the analysis (Figure 1).

3. RESULTS AND DISCUSSION

3.1. Fever

Fever is an adaptive body regulatory reaction that occurs in response to the activation of the immune system (biological and chemical). Fever is when the body's internal temperature rises above its normal range (36.5-37.5°C) due to an impaired immune system response to infection, injury, or tissue damage (Sasongko et al., 2019). Fever can be caused by several things, including infections, injuries, and tissue damage (Prajitha et al., 2018b). An increase in prostaglandin E2 (PGE2) levels, which then bind to prostaglandin EP3 and are produced in the hypothalamus, causing fever and an increase in body temperature set point, is what causes fever. Fever is induced by increased prostaglandin E2 (PGE2) levels (Mosili et al., 2020b). The three clinical phases that make up a fever are chills, fever, and a flush. This fever is a clinical symptom of at least one illness or disease, possibly more than one (Ohemeng et al., 2018). There are three distinct varieties of fever, each of which is designated by its underlying cause: infectious fever, non-infectious fever, and physiological fever. In 2019, the COVID-19 pandemic occurred, which was caused by the body being attacked by the coronavirus. The clinical manifestations of this illness are comparable to those of the flu and may be accompanied by a high temperature (Cann, 2021). According to the World Health Organization (WHO), a high temperature, which can induce shortness of breath, is one of the most prominent symptoms of COVID-19. Exogenous pyrogens encourage the production of pyrogenic cytokines or endogenous pyrogens, both of which work in the hypothalamus with the assistance of the cyclooxygenase 2 (COX-2) enzyme to produce prostaglandin E2, which raises the set point for the amount of fever (Wilhelms et al., 2014). As an anti-inflammatory agent, natural components or traditional medicine can be used. Sappan wood is an empirically utilized plant component to preserve health and medicine.

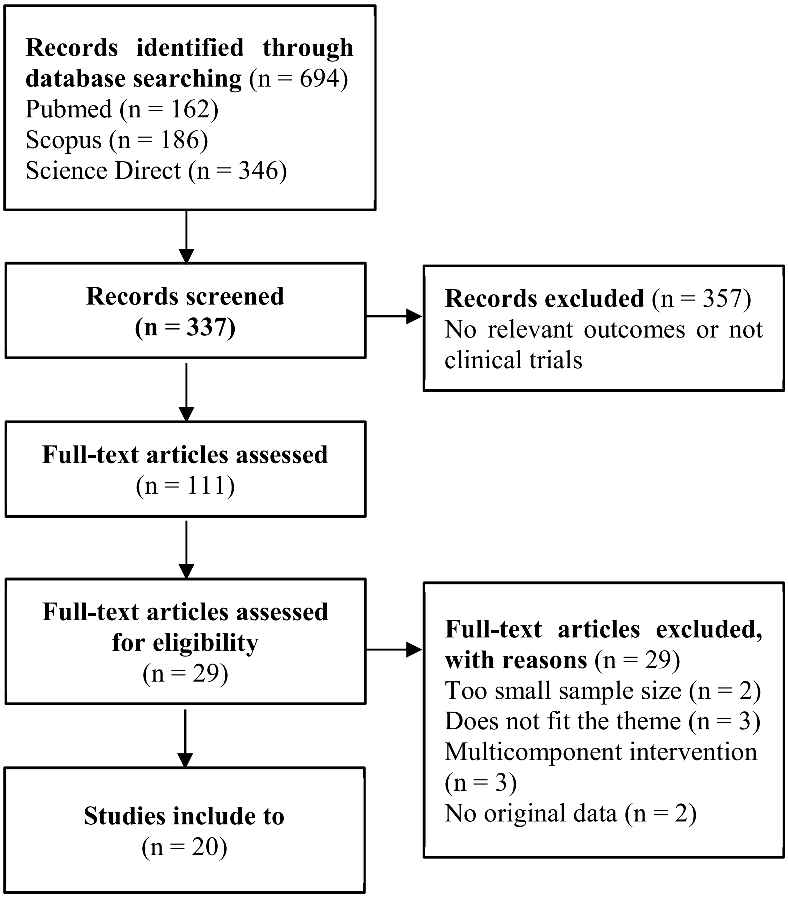


Figure 1. PRISMA flow diagram of the study selection process.

Fever can be a symptom of several conditions, including infections, inflammations, the effects of drugs, the effects of immunization, autoimmune diseases, and cancer (Figure 2). Temperature elevation, or fever, is one of the most typical signs of an infection or inflammation. Fever is caused by the binding of pro-inflammatory cytokines to receptors on brain endothelial cells, which then promotes the production of PGE2. It happens when an infection or inflammation takes place (Figure 3). The production of fever is caused by the binding of prostaglandin E2 in the preoptic hypothalamus (Pasikhova et al., 2017). Drug fever is defined as a fever that starts with administering a drug and fades after the drug is discontinued when no other cause of the fever can be determined after a thorough physical examination and adequate laboratory testing (Kurita et al., 2020).

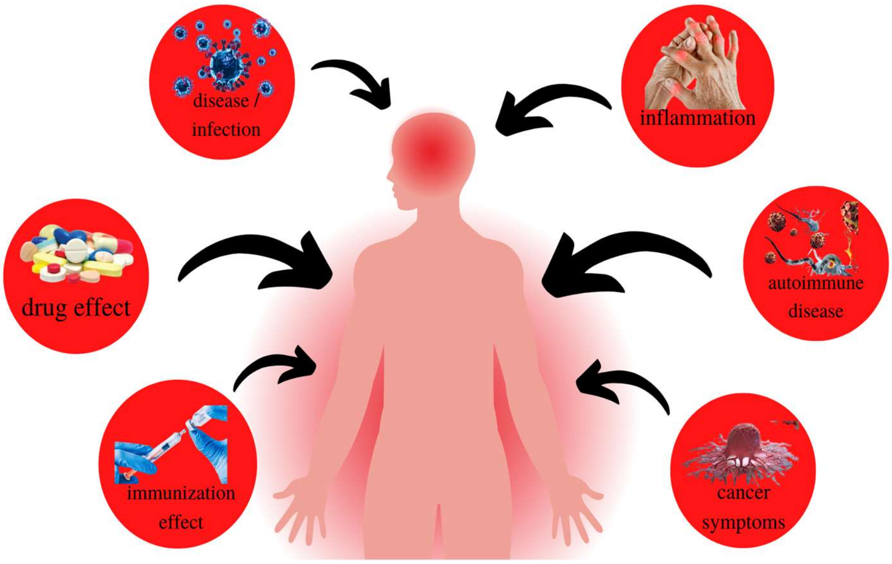


Figure 2. Several causes of fever in the body (Paquet et al., 2022; Peluso et al., 2021; Smid et al., 2018).

After receiving immunization, some people experience a well-recognized adverse effect known as fever. Some evidence suggests that infants receiving all three routine 2-month immunizations at once rather than in 2 or 3 doses have an increased risk of developing a fever after receiving the immunization (DeMeo et al., 2015). The term "non-infectious inflammatory diseases" refers to disorders that include various conditions, the most well-known being autoimmune diseases. Traditionally, it was believed that autoimmune disorders induced antigen-specific pro-inflammatory mechanisms, which could later lead to the development of fever (Kallinich et al., 2013). Fever in cancer patients can generally be connected with infectious or non-infectious, depending on the cause. Neoplastic, drug-induced, and venous thromboembolism are three significant factors that might contribute to fever in patients with hematological or solid-tumor malignancies (Pasikhova et al., 2017).

Sappan wood (*Caesalpinia sappan L*) is a herbal plant widely used and processed into traditional medicinal remedies. Existing reviews focus on the pharmacological activity of sappan wood's principal components, brazilin, and numerous additional chemicals. No studies have been published on the efficacy of sappan wood (*Caesalpinia sappan L*) as a fever therapy.

As a result, it is necessary to reread the article to learn about the benefits of sappan wood (*Caesalpinia sappan L*) in decreasing fever. Based on the research data, this article review aims to demonstrate that sappan wood has anti-inflammatory and antioxidant pharmacological activity as a fever reliever.

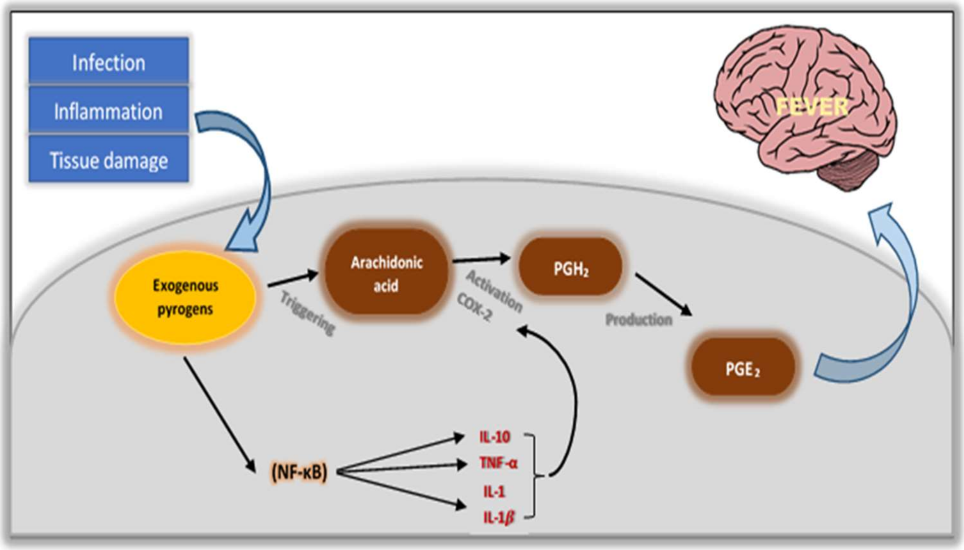


Figure 3. Mechanism of fever with expression of inflammatory markers (Prajitha et al., 2018a; Walter et al., 2016; Wrotek et al., 2020).

3.2. Sappan wood *(Caesalpinia sappan L.)*

Caesalpinia sappan is a member of the Fabaceae family and can be found in many different parts of the world, including India, China, Southeast Asia, Africa, and the Americas. Sappan can be found in various countries in the Southeast Asian region, including Indonesia, Malaysia, Thailand, Laos, and the Philippines (Vardhani, 2019). The sappan plant is harvested for the stem's heartwood, characterized by a round shape and a hue that falls between brown and green. This decoction of sappan wood shavings or pieces will create a natural red shade due to the presence of brazilin compounds; hence, sappan wood is frequently used as a natural dye (Sakti et al., 2019). By utilizing a decoction of this sappan wood, Southeast Asian people have relied on sappan wood for a very long time as a therapy for TB, diarrhea, dysentery, skin infections, and anemia. In addition, sappans have been known to treat anemia. Stomach ulcers, epilepsy, and diabetes were all treated with medicinal plants used by Indian society. In addition, the Chinese employ sappan wood to cure various illnesses, including obesity, syphilis, heart disease, ear and eye problems, and cancer (Nirmal et al., 2015).

3.3. Biochemical compounds in *Caesalpinia sappan L.* (Sappan wood)

Sappan wood has been shown to have analgesic, antioxidant, antibacterial, anti-inflammatory, anti-viral, anti-complementary, anti-convulsant, spasmolytic activity, hepatoprotective properties, anti-platelet concentration, antioxidative stress, anticancer effects, and other pharmacological effects (Wang et al., 2019).

Table 1. Bioactivity compounds, benefits, and structure of sappan wood.

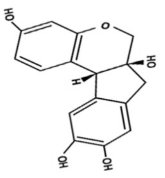
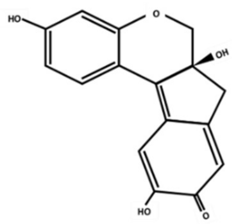
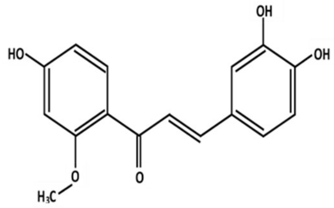
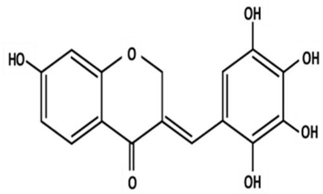
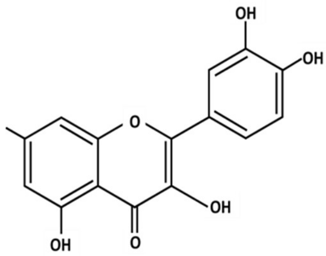
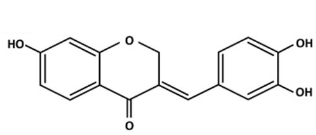
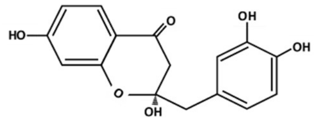
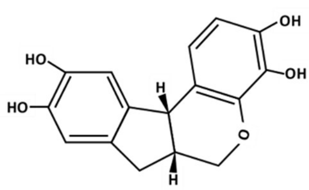
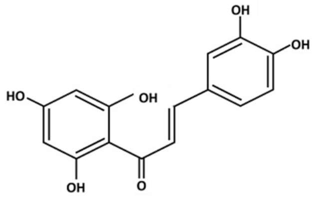
Compounds	Chemical Structure	Benefit	References
Brazilin ($C_{16}H_{14}O_5$)		Antioxidant, antibacterial, anti-inflammatory.	(Nirmal et al., 2015)
Brazilein ($C_{16}H_{12}O_5$)		Immunosuppressive agent in mice lymphocytes, cardiotonic effects in isolated rat hearts, and antioxidant properties, antitumor.	(Liang et al., 2013a; Zanin et al., 2012)
Sappanchalcone ($C_{15}H_{12}O_5$)		An anti-inflammatory, neuroprotective, inhibition of antigen-induced beta-hexosaminidase release, anti-influenza viral.	(Vu et al., 2020)
Caesalpiniaphenol		Inhibition and induction of apoptosis in human promyelocytic cancer cells.	(Vu et al., 2020)
Kuersetin ($C_{15}H_{10}O_7$)		Antioxidants, anti-inflammatory, antibacterial, anti-viral, radical scavenging, gastroprotective, and immune-modulatory activities.	(Vu et al., 2020)
Sappanone A		Anti-inflammatory, Antioxidants.	(Kang et al., 2016)
Sappanone B		Antitumor.	(Syamsunarno et al., 2021)
Hematoxylin		Antibacterial, antivirus, antitumor, inhibitor of Aβ42 fibrillogenesis.	(Tu et al., 2016)

Table 1. Bioactivity compounds, benefit, and structure of sappan wood (*Continued*).

Compounds	Chemical Structure	Benefit	References
Butein		Antioxidants, antitumor, anti-inflammatory, protein kinase inhibition	(Y.-N. Chen et al., 2012)

3.4. Antioxidants activity in *Caesalpinia sappan L.* (Sappan wood)

Including flavonoids and phenolics, have been shown to have high antioxidant activity. The antioxidant activity of timber is also regulated by age; stem extracts aged two years show higher antioxidant activity than extracts of fresh branches. A compound's antioxidant activity is mediated by numerous processes, including the prevention of chain initiation, the binding of transition metal ion catalysts, the prevention of hydrogen separation, the breakdown of peroxides, and the scavenging of free radicals that cause fever (Nirmal et al., 2015). Sappan wood contains many antioxidants, including Brazilin, Brazilein, Quercetin, Protasappanin, Sappanone A, and Butein.

3.4.1. Brazilin and brazilein

Brazilin is a homoisoflavonoid with a chemical structure that dissolves in water and causes it to turn red (Romruen et al., 2022a). When oxidized, the brazilin compound is in the form of yellow crystals and will produce the brazilein compound ($C_{16}H_{12}O_5$). Brazilein demonstrated the most potent free radical scavenging and iron reduction activities compared to other compounds such as sappanchalcone, protosappanin B, and protosappanin C. Furthermore, after the isolation of *Caesalpinia sappan L* from Indonesia, brazilin will suppress peroxide generation. The dibenzoxocin structure of this brazilin molecule allows it to effectively perform radical scavenging activities (Nirmal et al., 2015).

3.4.2. Quercetin

Quercetin is a flavonoid component that has the chemical structure of $C_{15}H_{10}O_7$. It is a compound commonly used as a supplement in food and beverages. Quercetin can be found in a variety of plants. Quercetin has been shown to have potent antioxidant activity and can efficiently scavenge free radicals and metal ions. Quercetin will produce GSH, and then superoxide dismutase will convert oxygen into H_2O_2. In addition, GSH and H_2O_2 will be catalyzed by GSH-Px, which will ultimately decrease peroxides' production. Quercetin's ability to regulate GSH levels will increase the antioxidants' therapeutic effects on the body (Kong et al., 2022).

3.4.3. Protasappanin

Oxidative stress is a condition that occurs when there is an imbalance between the number of oxidants (free radicals) and antioxidants in the body, causing damage to a chain beginning with cells and progressing to a higher level. Free radicals are highly reactive and unstable entities that prefer to steal electrons from other compounds (oxidation). Nitrogen derivatives known as reactive nitrogen species (RNS) and oxygen derivatives known as reactive oxygen species (ROS) are two types of free radicals found in the body. ROS can be O2, hydroxyl radicals (OH), hypochlorous acid (HOCL), alkoxyl radicals, or peroxyl radicals. ROS can damage cells by causing lipid membrane damage through a sequence of chemical processes known as lipid peroxidation. Protosappanins have been demonstrated to have a considerable effect in suppressing the formation of ROS and NO by stimulating microglial cells in the CNS, allowing them to provide antioxidative effects on brain immunology and neuroinflammation affected by CD14 (Zeng et al., 2012).

3.4.4. Sappanone A

Sappanone A is a homoflavonoid found to have a substantial antioxidant impact in cases of ischemia or stroke, meaning it can protect brain function. This ability has been proven through scientific research. In addition, studies have shown that Sappanone A can exert antioxidant effects even in the presence of cardiomyocyte damage by inhibiting apoptosis in mitochondria. In addition, it has been proven that increased levels of the antioxidant enzyme SOD cause sappanone A to decrease the generation of ROS and MDA. Reducing ROS levels helps prevent the development of oxidative stress, which can cause cell damage (M. Wang et al., 2021).

3.4.5. Butein

Butein is a chemical that belongs to the hydroxychalcone family and can have an antioxidant impact. Butein, as an antioxidant agent, reduces lipid peroxidation and the production of superoxide anions, thereby protecting cells from free radical cytotoxicity. Additionally, this butein will suppress the generation of ROS, which is a factor that can lead to oxidative stress. Oxidative stress is the primary factor that can lead to several chronic diseases (Padmavathi et al., 2017).

3.5. Anti-inflammatory activity in *Caesalpinia sappan L.* (Sappan wood)

Flavonoids and phenolic compounds are two substances that work well as anti-inflammatory drugs (Sasongko et al., 2016); (Sasongko, 2017). Histamine, prostaglandins, kinins, and 5-HT receptors are a few of the inflammatory mediators this anti-inflammatory function inhibits. Due to excessive prostaglandin induction, the body has responded with a fever. *As demonstrated by various studies, Caesalpinia sappan* L. has a pharmacological role as an anti-inflammatory agent (Figure 4). Several substances, such as Bazilin, Sappanchalcone, Quercetin, Protosappanin, Sappanone A, and Butein, are known to have anti-inflammatory properties (Javed et al., 2020).

3.5.1. Brazilin

The anti-inflammatory impact of brazilin was the most potent, with a considerable suppression of IL-6 secretion down to 5 µg/ml-1 and a significant inhibition of TNF-α secretion down to 10 µg/ml (Mueller et al., 2016). If brazilin is administered at a low dose, such as 0.1 µg/mL, it can potentially have an anti-inflammatory effect approximately equivalent to a 50% inhibition. Additionally, brazilin inhibits the process of iNOS and Heme Oxygenase-1 gene expression, which contributes to its anti-inflammatory properties. The production of prostaglandin E2, an inflammatory mediator, can also be inhibited by brazilin, which likewise inhibits the COX-2 enzyme (Nirmal et al., 2015).

3.5.2. Sappanchalcone

Sappanchalcone is recognized to have pharmacological effects as an anti-inflammatory drug and is one of the active flavonoid compounds derived from *Caesalpinia sappan* L. Sappanchalcone is one of the flavonoid compounds that *Caesalpinia sappan* L. produce In the same way that brazilin does, sappanchalcone acts as an anti-inflammatory agent by blocking the formation of prostaglandin E2. Prostaglandin E2 is one of the inflammatory mediators that contribute to fever. Sappanchalcone does this by suppressing the activity of the COX-2 enzyme (Jeong et al., 2010).

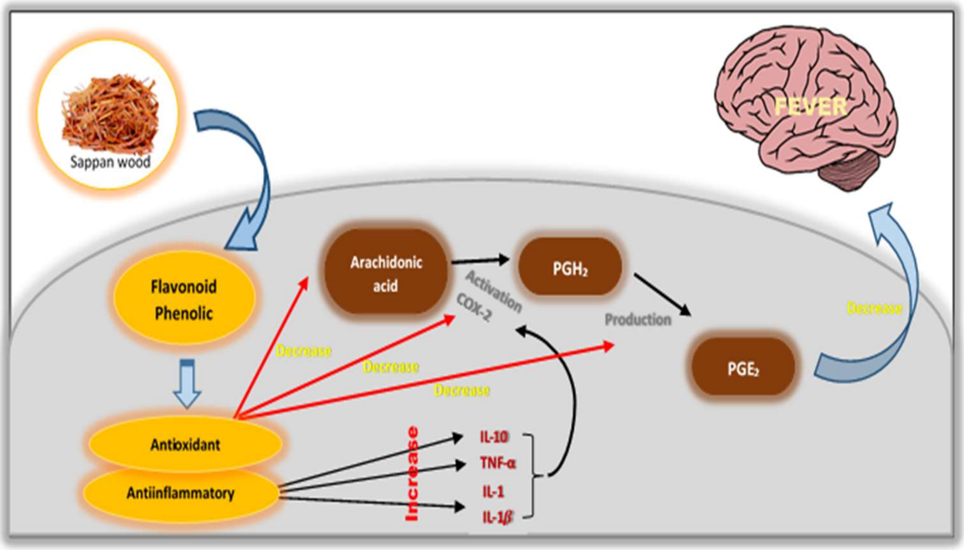


Figure 4. Mechanism of sappan wood in a fever (Azab et al., 2016; Kooti and Daraei, 2017; Xu et al., 2019).

3.5.3. Quercetin

Quercetin is a flavonoid compound found in many plants, one of which is *Caesalpinia sappan L*. Quercetin is a compound often used in the food and pharmaceutical industry because of its pharmacological effects. Quercetin is known to provide good progress when used as a treatment for COVID-19. *In vitro* testing stated that quercetin is anti-inflammatory by inhibiting iNOS and NO production. *In vivo* testing of quercetin showed an anti-inflammatory effect in diabetes-induced rats. Tests on human cells showed that quercetin provides an anti-inflammatory effect by inhibiting the activity of the COX-2 enzyme (Septembre-Malaterre et al., 2022). Quercetin can regulate inflammation and exert potent anti-inflammatory effects. It has been tested on several animals and human cell types (Chunlian Tian et al., 2021).

3.6. Antioxidant and anti-inflammatory parameters

Antioxidants have several parameters that can be used to determine their presence. Antioxidant parameters include Superoxide Dismutase (SOD), Glutathione Peroxidase (GPx), Glutathione Reductase (GRx), Catalase (CAT), Malonyl Dialdehyde (MDA), Glutathione Peroxidase (GSH-Px), Myeloperoxidase (MPO), and also Xanthine Oxidase (XO) (Lu et al., 2021; Urfalioglu et al., 2021). Of these parameters, some of them are included in enzymatic systems such as GSH-Px, SOD, GRx, and CAT. In the enzymatic system, GSH-Px plays an essential role in antioxidants by protecting intracellular phagocytic cells. In addition to enzymatic systems, there are non-enzymatic systems such as GSH, melatonin, vitamin A, vitamin E, and ascorbic acid. GSH plays a vital role in this system by neutralizing harmful compounds and reducing oxidative stress (Derindağ et al., 2021).

The anti-inflammatory parameters used were lipooxygenase, cyclooxygenase, Interleukin-1β (IL-1β), Nitric Oxide (NO), Malondialdehyde (MDA), Tumor Necrosis Factor-α (TNF-α), Cyclooxygenase-2 (COX-2), and Nuclear Factor kappa B (NF-κB) (Xie et al., 2022). Lipooxygenase and cyclooxygenase are enzymatic pathways in arachidonic acid metabolism. In the lipooxygenase pathway, there are enzymes, including LOX-5, LOX-8, LOX-12, and LOX-15 enzymes and their products, leukotrienes (LTA4, an unstable intermediate, LTB4, LTC4, LTD4, and LTE4), lipoxins (LXA4 and LXB4 formed upon LXA4 degradation) and 8–12- 15- hydroperoxy-eicosatetraenoic acid (HPETE). In the cyclooxygenase pathway, there are several enzymes, such as COX-1 and COX-2, along with downstream enzymes that mediate the production of prostaglandins (PGH2, an unstable intermediate, PGE2, PGD2, and PGF2alpha, prostacyclins (PGI2), and thromboxanes (TXA2, TXB2) (Hanna and Hafez, 2018).

Sappan wood has pharmacological effects such as antioxidants and anti-inflammatories derived from its flavonoid compounds. Both of these effects have great potential to reduce fever. Fever occurs due to an increase in PGE2. Antioxidants in sappan wood can inhibit PGE2 production through the COX-2 pathway. These antioxidants play an essential role in the body, reducing oxidative processes and the effects of reactive oxygen species (ROS) (Gulcin, 2020). Determine the activity of this antioxidant can be done using several methods such as 2,2′-azinobis-(3- ethylbenzothiazoline- 6- sulphonate) radical (ABTS•+) scavenging, 1,1-diphenyl-2-picrylhydrazyl (DPPH•) radical scavenging, $Fe^{3+}Fe^{2+}$transformation assay, ferric reducing antioxidant power (FRAP) assay, cupric ions (Cu^{2+}) reducing power assay (Cuprac), Folin–Ciocalteu reducing capacity (FCR assay), peroxyl radical (ROO•), superoxide radical anion (O2•−), hydrogen peroxide (H_2O_2) scavenging assay, hydroxyl radical (OH•) scavenging assay, singlet oxygen (O_2) quenching assay, nitric oxide radical (NO•) scavenging assay and chemiluminescence assay (Gulcin, 2020; Csepregi et al., 2016; Mendonça et al., 2022).

Table 2. Antioxidant and anti-inflammatory activity in *Caesalpinia sappan L.* Description: ↓ = *significant decrease*, ↑ = *significant increase.*

Pharmacological Activity	References	Animals/cells tested	Methods	Result
Antioxidant	(Masturi et al., 2021)	Comprises with phytochemical assessments	DPPH method	↑ The IC_{50} values in Extract Sappan Wood
	(Kadir et al., 2014)	Adult male healthy *Sprague Dawley* (SD) rats weighing 180–200 g	Western blot analysis and detection of endogenous antioxidant enzymes	↓ Catalase (CAT) ↓ Superoxide Dismutase (SOD) ↓ Glutathione Peroxidase (GPx)
	(Suwan et al., 2018)	Two aerobic bacterial strains, Staphylococcus aureus and Escherichia coli	Ferric Reducing Antioxidant Power (FRAP) assay, 2,20-azinobis-(3-ethylbenzothiazoline-6-sulfonic acid) diammonium salt (ABTS) and 1,1-diphenyl-2-picrylhydrazyl (DPPH)	↑ The free radical scavenging in FRAP assay ↑ The free radical scavenging in ABTS ↑ The free radical scavenging in DPPH
	(Nirmal and Panichayupakaranant, 2015)	-	DPPH radical scavenging, Reducing power, and β-carotene bleaching assays	Reducing power ↑Brazilin-Rich Extract (BRE) and brazilin β-carotene bleaching assays ↑Brazilin-Rich Extract (BRE) and brazilin
	(F.-Z. Chen et al., 2014)	Vitamin C as control positif	DPPH assay	Brazilin > Neoprotosappanin > Vitamin C
	(Hwang and Shim, 2018)	Normal human epidermal keratinocytes	DPPH assay	↓ SOD1 ↓ SOD2 ↓ CAT ↑ GPX7
	(Khristian et al., 2022)	Male and female rats	Number of Kuffer cells	↓ Kupffer cells in the female group at a dose of 100 mg/kgBW and the male group at 200 mg/kgBW
	(Arsiningtyas, 2021)	Ascorbic acid, as the control positive	DPPH radical scavenging activity	↑ IC_{50} value from sapwood and heartwood on a branch, middle, and primary *C. sappan* wood

Table 2. Antioxidant and anti-inflammatory activity in *Caesalpinia sappan L.* Description: ↓ = *significant decrease*, ↑ = *significant increase* (*Continued*).

Pharmacological Activity	References	Animals/cells tested	Methods	Result
	(Liang et al., 2013b)	Human epidermoid carcinoma, human oral squamous cell carcinoma, human skin malignant melanoma, mouse leukemic monocyte macrophage, and mouse normal embryonic liver cells	DPPH and ABTS	↑ The EC_{50} values of brazilein for the scavenging of DPPH ↑ The EC_{50} values for the scavenging of ABTS
	(Romruen et al., 2022b)	-	Total Phenolic Content (TPC), DPPH radical scavenging activity, and Ferric Reducing Antioxidant Power (FRAP)	↑ The film's TPC values with ↑ sappan heartwood extract concentration ↑ The film's DPPH values with ↑ sappan heartwood extract concentration ↑ The film's FRAP values with ↑ sappan heartwood extract concentration
	(Khristian et al., 2022)	Male and female rats	Number of Kuffer cells	↓ Kupffer cells in the female group at a dose of 100 mg/kgBW and the male group at 200 mg/kgBW
	(Widodo et al., 2022)	Lung cancer cell	DPPH radical scavenging activity	↑ IC_{50} value from *Caesalpinia sappan* ethanol extract

Table 2. Antioxidant and anti-inflammatory activity in *Caesalpinia sappan L.* Description: ↓ = *significant decrease*, ↑ = *significant increase* (*Continued*).

Pharmacological Activity	References	Animals/cells tested	Methods	Result
Anti-inflammatory	(Pattananandecha et al., 2022)	Macrophage cells	Anti-inflammatory activity through an inhibition effect on nitric oxide (NO) and inducible nitric oxide synthase (iNOS) production	↓ NO production and Regulating Nuclear Factor kappa-B (NF-κB) and activator protein-1, ↓ COX-2, and iNOS expression.
	(Tewtrakul et al., 2015)	Male and female Swiss albino mice (30–40 g)	The inhibitory activity against NO, PGE2, and TNF-α.	↓ mRNA expressions of the iNOS, COX-2, and TNF-α ↓ PGE2 and TNF-α
	(K.-J. Kim et al., 2015)	Macrophage cells	Western blotting and cytokine assay	↓ iNOS and COX-2 protein significantly with the presence of brazilein.
	(Gao et al., 2015)	Mammary gland and mammary epithelial cells	Cytokine assays	Attenuated inflammatory cell infiltration ↓ The expressions of TNF-α, IL-1β and IL-6
	(C.-L. Chen and Zhang, 2014)	Macrophage cells	Cell viability by MTT assay	↓ over 90% NO production
	(Wu et al., 2011)	Primary cells, chondrocytes, and THP-1 macrophages	Griess assay and ELISA	↓ pro-inflammatory cytokines IL-1β and TNF-α suppressed the synthesis of NO blocking iNOS mRNA expression. The inhibition of COX-2 transcription
	(Jung, Han, Kwon, et al., 2015)	Male DBA/1J mice	A mouse immunoassay kit	↓ The blood serum levels of TNF-α, IL-1β, and IL-6
	(J.-H. Kim et al., 2014)	Macrophage cells	Measurement of NO and IL-6 and cell viability assay	↓ Production NO dan IL-6

Table 2. Antioxidant and anti-inflammatory activity in *Caesalpinia sappan L.* Description: ↓ = *significant decrease*, ↑ = *significant increase* (*Continued*).

Pharmacological Activity	References	Animals/cells tested	Methods	Result
	(Jung, Han, Hwang, et al., 2015)	Male DBA/1J mice	Serum biochemical analysis	Brazilin markedly attenuated mouse CIA and ↓ the serum levels of inflammatory cytokines, including TNF-α, IL-1β, and IL-6.

Most of the compounds in sappan are flavonoid compounds. The antioxidant action mechanisms of flavonoids include (a) direct scavenging of ROS, (b) inhibition of ROS formation through the chelation of trace elements or inhibition of the enzymes that participate in the generation of free radicals, and (c) activation of antioxidant defenses in addition to upregulation of antioxidant enzymes with radical scavenging ability. Glutathione S-transferase, microsomal monooxygenase, mitochondrial succinodidase, NADH oxidase, and xanthine oxidase are some of the enzymes that can be inhibited to prevent the generation of free radicals (Dias et al., 2021). Compounds derived from sappan wood can, as antioxidants, prevent the activation of COX-2 and NF-B activation, particularly in brazilein compounds (Aldini et al., 2018; Handayani et al., 2017).

A common trigger for inflammation is the presence of pathogenic microbes like bacteria, viruses, or fungi in the host body, localized tissue, and the bloodstream. Tissue damage, cell death, malignancy, ischemia, and degeneration can all trigger inflammatory responses (L. Chen et al., 2017). The B and T cells of the adaptive immune system are responsible for creating specific receptors and antibodies to destroy invading infections and cancer cells (Azab et al., 2016). Initiating an inflammatory response is dependent on several factors, including macrophage inflammatory protein-2 (MIP2), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-alpha), nitric oxide (NO), inducible nitric oxide synthase (iNOS), and cyclooxygenase-2 (COX-2) (K.-J. Kim et al., 2015)

Tumor necrosis factor (TNF)- α is a critical pro-inflammatory cytokine released by many different types of cells and has many effects on them (Abdulkhaleq et al., 2018; Zappavigna et al., 2020). IL-6 is usually a cytokine that worsens inflammation but can also help reduce inflammation. IL-10 is a strong anti-inflammatory cytokine that stops many pro-inflammatory mediators from doing their jobs. Attenuation and control of the inflammatory response: IL-10 helps keep tissue homeostasis and reduces damage from an overactive inflammatory response (Azab et al., 2016).

Prostaglandin E2 regulates body temperature, gastrointestinal mucosa integrity, renal blood flow, and female reproductive function—phospholipase A2 forms arachidonic acid from cell membrane phospholipids (PLA2). COX converts arachidonic acid to PG. The inducible COX-2 enzyme is the most active during inflammation (Azab et al., 2016). Nitric oxide synthase (NOS) is another inflammatory enzyme (NO). Inducible NOS (iNOS) is pro-inflammatory like COX-2 (Zappavigna et al., 2020). The nuclear transcription factor kappa B (NFB) is crucial in immunological and inflammatory responses and cancer pathogenesis. When NFB is not being activated, it is found in the cytoplasm. The nuclear factor kappa B (NFB) protein relocates to the nucleus after being activated by various infectious/ inflammatory/ mitogenic stimuli. Then, it stimulates the transcription of inflammation-related genes (Azab et al., 2016).

Flavonoids can play multiple roles in the inflammatory response, including (a) antioxidants scavenging reactive oxygen species (ROS) or reducing free radical accumulation, (b) inhibitors of the activity of regulatory enzymes (e.g., protein kinases and phosphodiesterase) and transcription factors related to the control of mediators involved in the inflammatory response, and (c) modulators of the activity of the immune cells (e.g., inhibition of cell activation, maturation, signaling transduction, and secretory processes) (Dias et al., 2021; Maleki et al., 2019). Sappan wood contains compounds that have been shown to limit NO production and drastically decrease iNOS and COX-2 protein expression (K.-J. Kim et al., 2015). The production of interleukin-6 (IL-6) is suppressed by several biochemical compounds, including neoprotosappanin, protosappanin E, sappanone A, and two additional compounds whose identities (Chu et al., 2013).

The glucocorticoid system is particularly important in fever. Activator protein-1 and nuclear factor-kappa B are the mediators in this system (AP-1). Both have been shown to inhibit the production of pro-inflammatory cytokines. The body's response to fever involves regulating IL-1 receptor antagonists (IL-1RA), IL-10, and TNF-binding proteins, all of which reduce fever (Young and Saxena, 2014). Antioxidants and anti-inflammatories present in secang wood components have the same effect in lowering fever. Pro-inflammatory cytokines are decreased by antioxidants and anti-inflammatories, respectively.

COVID-19 is one of the infectious diseases that has rapidly spread over the planet and turned into a pandemic after 2019 came to a close (Cann, 2021). The symptoms of the disease produced by the SARS-CoV-2 virus are almost identical to those caused by the flu. These symptoms include fever, a cough, and asthenia (Shi et al., 2020). This viral infection has the potential to stimulate the local inflammatory response, which in turn has the potential to enhance the expression of cytokines such as transforming growth factor- β1 (TGF- β1), tumor necrosis factor- α (TNF- α), interleukin-1 β (IL-1β), IL-6, interferon (IFN)- γ, IL-1, and IL-2 (Pascarella et al., 2020; Shi et al., 2020).

An increase in TNF- α, IL-1, and IL-1 β (Figure 3) can activate COX-2, leading to an increase in the production of PGE-2 (Azab et al., 2016). This, in turn, will cause the set point to rise, resulting in fever. Sappan wood's anti-inflammatory properties can inhibit cytokine synthesis, preventing COX-2 activation and allowing for cooler internal temperatures. Although this anti-inflammatory impact cannot destroy the virus, it can lower the infection's symptoms. It is necessary to have an anti-viral agent that works efficiently in order to kill the virus.

4. CONCLUSION

Sappan wood can be an alternative for reducing fevers with its anti-inflammatory and antioxidant pharmacological effects. The flavonoid compounds produce this effect in sappan wood. Antioxidants in sappan wood inhibit oxidative stress and inflammatory mediators in the form of PGE2. Inhibition of these pathways will prevent further activation of the inflammatory response. In addition, sappan wood can be used as an ingredient in traditional health drinks. Using sappan wood to reduce fever can be done by drinking sappan wood boiled water. It is possible to complete the process of boiling sappan wood in at most forty-five minutes so that the properties it contains are maintained.

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CONFLICT OF INTEREST

All authors declared that there was no conflict of interest.

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