# Extract of *Caesalpinia sappan* L. heartwood as food treatment anti-diabetic: a narrative review

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**Abstract.** Controlling blood glucose levels is the main purpose of diabetes treatment because it can reduce health complications and death. The Diabetes Commission of the World Health Organization has made recommendations for further research on the use of herbs as a treatment for diabetes. *Caesalpinia sappan* L. (CS) is a medicinal plant that has been used traditionally for diabetes management. This review aims to provide the existing literature published during the period of 2000-2020 on the potency of CS heartwood as an anti-diabetic agent. Overall, some in vitro and in vivo studies have shown that CS heartwood extract can reduce blood glucose levels, however the numbers are still limited. Interestingly, this review provides the evidence that CS heartwood has its potential to be developed and used as an anti-diabetic agent in the future.

## 1. Introduction

Diabetes is a serious threat to global health that respects neither socioeconomic status nor national boundaries. The latest data published in the International Diabetes Federation (IDF) shows that 463 million adults are currently living with diabetes. Without sufficient action to address the pandemic, 578 million people will have diabetes by 2030. That number will jump to a staggering 700 million by 2045 [1]. The World Health Organization also reported about 1.5 million people died from diabetes in 2012 and also an additional 2.2 million deaths due to the increased risk of cardiovascular diseases and others related to hyperglycemia [2]. Riset Kesehatan Dasar (Risksdas) Indonesia in 2018 explained that the prevalence of national diabetes was 8.5% which means around 20.4 million Indonesians were affected by diabetes [3].

Controlling blood glucose levels is the main goal for diabetes treatment because it can reduce the risk of health and death complications [1], in which clinically oral anti-hyperglycemia and insulin drugs are used. Several herbs have been used in the treatment of type 2 diabetes and were approved in studies involving humans and animals [4,5]. Therefore, herbs are considered to be a valuable alternative in the treatment of type 2 diabetes. The Diabetes Commission of the World Health Organization has also made recommendations for further research on the use of herbs as a treatment for diabetes [6].

*Caesalpinia sappan* L. (CS) is a traditional medicinal plant that is cultivated in India, Myanmar, Vietnam, Sri Lanka, and the Malay Peninsula, and distributed domestically in China, Fujia, and Taiwan. A CS heartwood extract has many pharmacological activities including anti-hyperuricemia, antioxidants, hypoglycemia, cytotoxic, hepatoprotective, antimicrobial, anti-inflammatory, analgesic, antifungal, immunosuppressant, acaricidal, cytoprotective and neuroprotective agents [7,8,9,10].
However, there have been no review studies in the last twenty years reporting the latest evidence of the anti-diabetic nature of CS heartwood or its relevant physiological mechanisms. Therefore, the aim of this review study is to report the latest scientific studies published in the reviewed journals on the potential of CS heartwood as anti-diabetic agent.

2. Materials and Methods

In this review, all abstracts, reports and research articles relating to the anti-diabetic activity of CS heartwood were identified and downloaded from several databases including Pubmed, Science Direct, DOAJ, MDPI, Europe PMC and Google Scholar. The keywords used were (Caesalpinia sappan, wood, and diabetes) during the period of 2000-2020. The searching activity resulted 3 articles in Pubmed, 32 articles in Science Direct, 2 articles in DOAJ, 1 article in MDPI, 19 articles in Europe PMC and 1830 articles Google Scholar.

After going through the process of screening the titles and abstracts and eliminating any duplication, the selected research articles were then searched and re-identified based on their inclusion and exclusion criteria. The inclusion criteria consisted of in vitro, in vivo, and/or clinical studies with full text publication; while the exclusion criteria consisted of review articles. The total research articles reviewed in this study were 13 (Table 1).

| Year of publication | Number of selected articles |
|---------------------|-----------------------------|
| 2005                | 1 (7.69%)                   |
| 2014                | 3 (23.08%)                  |
| 2015                | 2 (15.38%)                  |
| 2017                | 3 (23.08%)                  |
| 2019                | 3 (23.08%)                  |
| 2020                | 1 (7.69%)                   |

3. Results and Discussion

3.1. Caesalpinia sappan L.

*Caesalpinia sappan* L. (CS) was initially discovered by Kimichi – a Spanish - in Brazil. In accordance with the place of origin, this plant is called Brazil wood. However, some say that originally this plant was from India spread through Burma, Thailand, Indo China to Malaysia and to Indonesia, Philippines, Sri Lanka, Taiwan, and Hawaii. This type of plant also flourished and spread over the Europe, America and Asia. Secang (Indonesia) is named CS as a scientific name with the synonym Bianceae, which is known in various countries as 'sibukao' (Filipino), 'teingnyet' (Burma), 'sbaeng' (Cambodia), 'fang deeng' (Laos), and 'faang' (Thailand) [11].

CS is known in various regions in Indonesia with different local names, such as seupeng (Aceh); sepang (Gayo); sopang (Batak); chopped (Minangkabau); secang (Sundanese); Secang wood, Javanese (Javanese) soga; kaju secang (Madura); cang (Bali); sepang (Sasak); supa, suang (Bima); sepel (Timor); hong (Alor); sema wood (Manado); dolo; Sapang (Makassar); seppang (Bugis); sefen (South Halmahera); sawala, hiniaga, sinyiang, singiang (North Halmahera); sunyiha (Ternate); and roro (Tidore) [12].

According to the taxonomy, CS is classified as follows:

Kingdom: Plantae
Division: Tracheophyta
Class: Magnoliopsida
Order: Fabales
Family: Fabaceae
Genus: Caesalpinia
Species: *Caesalpinia sappan* L. [13].
3.2. Caesalpinia sappan L. Heartwood

The important part of CS is pale red, hard, heavy wood with an even and fine structure. CS heartwood is traditionally used in Indian Ayurveda and traditional Chinese medicine. In Thailand, it is mostly used as a coloring agent in drinks, foods, garments and cosmetics [14]. Decoction of CS heartwood is used in Namya-utai solution which reduces thirst and has cardiotonic properties. In Northern Thailand, especially in the provinces of Chiang Mai, Nan and Lampang, CS heartwood decoction is used as an anti-inflammatory agent for the treatment of traumatic diseases and arthritis [15].

The Northern Thai community has a long history of using CS heartwood decoction for local consumption including a health promotion and treatment of diseases. In Ayurveda, CS heartwood is used for skin rashes, burning sensation, peptic ulcers, excessive body heat, heartburn and digestive disorders. CS heartwood is also used as a blood purifier, treatment of wounds, diarrhea, epilepsy, diabetes, pain and swelling relievers caused by external injuries and skin repairment [16]. In traditional Chinese medicine, this herb is mainly used as an emmenagog, hemostatic, analgesic, and anti-inflammatory for traumatic diseases and blood-boosting agents [17]. In addition, CS heartwood decoction is also used for the treatment of blood pressure, burning sensation, cancer, cataracts, digestion, dysmenorrhea, ear disease, gonorrhea, heart disease, jaundice, nervous disorders, obesity, eye disease, spermatorrhoea, stomach ache, syphilis, urinary tract disease and vascular disease [18].

CS heartwood contains water-soluble flavonoids namely brazilin, protosappanin and haematoxylin. Brazilin is a major homoisoflavonoid constituent found in CS heartwood, known as the natural red color for coloring [19,20]. Methanol extract of CS heartwood contained neosappanone A, naphthoquinone derivatives, phenols, sappanchalcone, caesalpin J, caesalpin P, protosappanin a, b and c, homoisoflavonoids, sterol, brazilein, Sappanol, episappanol; 3'-deoxy sappanol, 3'-O-methylsappanol, 3'-Omethylepisappanol, 3'-O-methylbrazanol, sappanon β, 3-deoxysappanone β, 3'-deoxysappanone β, dibenzoxocin derivatives, 10-0-methyl-protosan β. 4,4'-dihydroxy-2'-methoxychalcone, 8-methoxy-bonducellin, quercetin, rhamnetic, ombuin, monohydroxybrazilin, benzyl dihydrobenzofuran derivatives, brazileide A, 4-omethylepisapanol, methoxychalcone, isoliquiritin- methylsappanol, and pluchoic acids [7,8,9,10] (Figure 1).
Figure 1. Phytochemical compounds contained in CS heartwood [18].
3.3. In Vitro Studies of An Anti-diabetic Activity of Caesalpinia sappan L. Heartwood

In vitro studies of an anti-diabetic activity of CS heartwood have been carried out. Annamalai et al. (2014) evaluated the anti-diabetic activity of ethanol extracts of CS heartwood in the Wistar albino rat model (in vivo) and the α-glucosidase (in vitro) enzyme inhibition method. In the invitro studies, ethanol extracts of CS heartwood showed significant inhibition on the α-glucosidase enzyme. The inhibition of this enzyme increases along with the rise of the concentrations of ethanol extracts of CS heartwood used which vary between 25-1000 µg/mL. The IC50 of extract was 215.95±7.52 µg/mL and the standard drug of acarbose showed IC50 of 183.46±5.85 µg/mL; this shows that the ethanol extract of CS heartwood inhibits the α-glucosidase enzyme efficiently [21].

Arsiningtyas et al. (2015) identified the inhibitory activity of α-glucosidase, α-amylase and intestinal sucrase from CS heartwood. The ethyl acetate dissolved layer from the methanol extract of CS heartwood was fractionated consecutively by silica gel column chromatography and octadecylsilyl High Performance Liquid Chromatography (HPLC) to produce four phenolic compounds. The intestinal maltase inhibitors were protosappanin B (IC50=0.81 mM), sappanchalcone (0.96 mM), protosappanin C (2.59 mM), and brazilin (3.83 mM). The isolated compounds were also investigated for their inhibitory activity for intestinal sucrase and α-amylase. Although brazilin showed moderate inhibition of intestinal sucrase (IC50=1.12 mM) and PPA (IC50=1.22 mM), sappanchalcone, protosappanin B and protosappanin C compounds did not significantly inhibit sucrase and PPA at the concentrations tested [22].

In addition, Tulin et al. (2017) evaluated the α-glucosidase inhibitory activity of aqueous and ethanol extracts of CS heartwood. The result showed that water extracts (2000 ppm) and ethanol extracts (2000 ppm) inhibited α-glucosidase 100% and 59%, respectively. The IC50 values of water and ethanol extract were found to be 300.52±1.467 ppm and 1560.81±2.582 ppm respectively. The TLC fraction showed 7 peaks for water extract and 6 peaks for ethanol extract where the compounds with RF value of 0.70 had the highest inhibitory activity of 65% [23].

Young Ju et al. (2017) tested the antioxidant and anti-diabetic activities of the CS heartwood extract which was prepared using different extraction methods. The antioxidant activity test was carried out by the method of 1,1-diphenyl-2-picrylhydrazyl (DPPH) and 2,2’-azino-bis (3-ethylbenzothiazoline-6-sulphonic acid) (ABTS +); while the anti-diabetic test was carried out using the α-glucosidase enzyme inhibition method and the formation of advanced glycation end products (AGEs). The results showed that the 80% methanol extract of CS heartwood had the strongest antioxidant activity with the IC50 value of 82.3±1.7 µg/mL against the DPPH radical cleanup test. Similarly, in the ABTS + radical scavenging activity test, the 80% CS heartwood methanol extract had a higher IC50 value than the other extracts (IC50 of 12.4±2.1 µg/mL). The 80% methanol extract of CS heartwood also showed the α-glucosidase inhibitory activity and the largest AGEs formation i.e. IC50 each of 5.3±0.6 µg/mL and 12.4±2.3 µg/mL [24].

In another study, Setyaningsih et al. (2019) studied the inhibition of the dipeptidyl peptidase-IV (DPP-IV) enzyme by a spectrophotometric method with sitagliptin as a positive control of 10 ethanol extracts of Indonesian plants. The ten plant extracts included Caesalpinia sappan, Cinchona officinalis, Scaber Elephantopus, Foeniculum vulgare, Morus nigra, Muntingia calabura, Phyllanthus niruri, Psidium guajava, Rheum palmatum and Vernonia amygdalina; and the effectiveness of DPP-IV enzyme inhibition was assessed by their % inhibition. The ethanol extract of CS heartwood showed the inhibitory activity of DPP-IV enzyme at 84.25%; which was not much different from sitagliptin by 85.18%. Brazilin, the active compound from CS provided a DPP-IV enzyme inhibition of 78.30%. Analysis of HPLC showed that the brazilin in the CS extract was 91.94%. Based on these results, ethanol extract of CS heartwood has the potential to be a better anti-diabetic agent than the other extracts used in this study [25].

Similar studies were conducted by Angela et al., (2020) who compared the inhibitory activity of the Brazilian DPP-IV enzyme from CS heartwood extracts in various solvents namely Natural Deep Eutectic Solvent (NADES). The results showed that CS heartwood extract using choline chloride-lactic acid had a DPP-IV enzyme inhibitory percentage of 5.72% (2.03 ppm) and those which use
betaine-lactic acid had a DPP-IV enzyme inhibition of 7.74% (2.08 ppm). This inhibitory activity is comparable to the brazilian standard of 8.93% (2.2 ppm) [26].

Moreover, in vivo studies have been carried out on the main active compounds of CS, brazilein ((6a S-cis) -7, 11b-dihydrobenz (b) indeno (1,2-d) pyran-3,6a, 9,10 (6H)-tetrol). Brazilein has been proven in several studies as an antioxidant, antibacterial, anti-inflammatory, antiangiogenic, vasorelaxant, hepatoprotective and anti-acne agent [18]. You et al. (2005) studied the effect of brazilein on the production of fructose-2,6-bisphosphate in hepatocytes of Sprague Dawley mice. Fructose-2,6-bisphosphate (F-2,6-BP), a gluconeogenic intermediate, which plays an important role in hepatic glucose production by regulating gluconeogenesis and glycolysis in the liver. Brazilein, the active component of CS heartwood, decreased blood glucose in diabetic animals. In this study, the effect of brazilein on the production of gluconeogenic and enzyme activity was examined to investigate the hypoglycemic mechanism of brazilein. Brazilein increased the production of F-2,6-BP in hepatocytes by increasing intracellular levels of fructose-6-phosphate (F-6-P) and hexose-6-phosphate (H-6-P). Brazilein was also found to significantly increase the activity of 6-phosphofructo-2-kinase (PFK-2) and pyruvate kinase in hepatocytes treated with glucagon. However, the glucose-6-phosphatase activity was not affected by the brazilein. These data indicate that brazilein inhibits liver gluconeogenesis by increasing F-2,6-BP levels in hepatocytes, possibly by increasing cellular F-6-P/H-6-P levels and PFK-2 activity. Increased pyruvate kinase activity can also play a role in brazilein's anti-gluconeogenic action [27].

3.4. In Vivo Studies of an Antidiabetic Activity of Caesalpinia sappan L. Heartwood

Many studies have reported the antihyperglycemia activity of CS heartwood in animal experiments. Annamalai et al. (2014) evaluated the antidiabetic activity of ethanol extracts of CS heartwood in the albino Wistar rat model (in vivo) and the α-glucosidase (in vitro) enzyme inhibition method. Based on the examination of blood parameters and histopathology, the ethanol extract of CS heartwood at doses of 100 and 200 mg/kgBW significantly reduced blood glucose and HbA1c levels in alloxan-induced diabetic rats after 21 days were evaluated (p <0.001) [21].

In another study, Saefudin et al. (2014) studied the effect of the ethanol extract of the CS heartwood on blood glucose levels of white rats. This study was conducted using the glucose tolerance method measured by Refloluxs (Accutrend GC) with chloropropamide 50 mg/200 gBW as a positive control. The ethanol extracts of the CS heartwood are used in various concentrations of 10, 20, 30, 40 and 50 mg/200 gBW orally and were observed every hour, starting from 1-7 hours after the extract was introduced. The results showed that all dosage groups of the ethanol extract of the CS heartwood reduced the blood glucose levels of white rats. A treatment with a dose of 30 mg/200 gBW (103 mg/dL) has a similar effect compared to chlorpropamide as a positive control (102 mg/dL), while a dose of 50 mg/200 gBB gives a lower blood glucose level (93 mg/dL) compared to the positive control [28].

Nalla et al. (2015) conducted a study on the chloroform extract of the CS heartwood in two dosage groups: 200 and 400 mg/kgBW which were administered orally for 21 days to alloxan-induced diabetic rats. The fasting blood glucose levels of the rats while they were given the chloroform extract of the CS heartwood at the dose of 200 mg/kgBW decreased significantly from 226.53 mg/dL to 172.36 mg/dL (p <0.05); and at a dose of 400 mg/kgBW, the glucose levels decreased significantly from 225.98 mg/dL to 152.68 mg/dL (p <0.001) compared to the glibenclamide 10 mg/kgBW. In addition, the chloroform extract administration of the CS heartwood also significantly reduced the total cholesterol and triglyceride levels [29].

Holidash et al. (2019) reported that all doses of the ethanol extract of the CS heartwood (50, 100, 400 mg/kgBW) could reduce the blood glucose levels of alloxan-induced mice. The biggest decrease occurred in the extract dose of 100 mg/kgBW with a decrease of 63.51%. The activity of decreasing glucose levels by the ethanol extract of the CS heartwood was not directly proportional to the increasing doses [30]. This shows that the higher dose of the extract does not guarantee the increase in
the compound activity because the higher the dose of the extract, the antagonistic effect of the various compounds in the extract will also appear [31].

Sakir et al. (2019) in their study reported that the ethanol extract of the CS heartwood can reduce blood glucose levels in alloxan-induced diabetes mice at doses of 0.25, 0.50 and 0.75 g/kgBW (p<0.001). The ethanol extract of the CS heartwood with a dose of 0.50 g/kgBW showed the most effective reduction in blood glucose levels in hyperglycemia mice [32]. Yusuf and Rusli (2019) used 15 mice divided into five treatment groups namely group I metformin (positive control), group II, III, and IV infusion of CS 10% w/v, 15% w/v, and 20% w/v and group V aquadest (negative control). In this study, the measurements of fasting blood glucose levels (initial levels) were conducted after the induction of alloxan 120 mg/kgBW and an administration of therapy for 15 days. The data obtained were processed statistically using oneway ANOVA. Based on the analysis of the statistical data, it showed that the aquadest group was significantly different (p<0.05) against all groups of the CS and metformin infusion test wood. All CS heartwood infusion test groups showed no significant difference (p>0.05) to the metformin group. Based on that result, it was concluded that the infusion of CS 10% w/v; 15% w/v and 20% w/v had an anti-hyperglycemic effect and showed results that were not significantly different (p>0.05) on metformin [33].

Li et al. (2017) explored the role of brazilin, the main flavonoid compound contained in the CS heartwood, in reducing pathological development, inflammation, and accumulation of extracellular matrix in diabetic nephropathy rats. The results indicated that brazilin decreased the worsening of the biochemical index in cases of diabetic nephropathy (proteinuria and serum glucose levels) and renal hypertrophy. Brazilin also improved renal morphology and inhibited the macrophage infiltration, as manifested by different pathological staining methods. Brazilin reduced pro-inflammatory cytokine and CD68 levels, a marker of macrophages, in the renal cortex, as seen in the Reverse Transcription PCR (RT-PCR) and western blotting experiments. In addition, brazilin significantly decreased serum levels of pro-inflammatory cytokines and chemokines. Interestingly, brazilin significantly increased levels of IL-10 anti-inflammatory factors, and prevented the accumulation of extracellular matrix. Brazilin reduced the translocation of nuclei of NF-κB p65 subunits both in vitro and in vivo. Thus, brazilin may be a useful treatment for diabetic nephropathy through mitigation of hypoglycemia, inflammation, and accumulation of extracellular matrix [34].

4. Conclusion

This review aims to fill the gap by providing comprehensive and up-to-date information on the potential of the CS heartwood as an antidiabetic agent. From this study, it is clear that an increasing number of studies on the CS antidiabetic activity have been reported in the past 20 years.

Overall, some in vitro studies carried out have shown that the CS heartwood extract can reduce blood glucose levels. The mechanisms involved include inhibition of α-glucosidase enzyme, the advanced glycation end products (AGEs) formation, and the enzyme dipeptidyl peptidase-IV (DPP-IV). In this review, we summarized studies that reported the hypoglycemic potential of the CS heartwood in animals. CS heartwood extracts used in the in vivo studies were concentrated on a 50-750 mg/kgBW dose range and varied in the ethanol, methanol, and chloroform extract and in the infusion. Among the six in vivo studies above, the duration of the study was varied, starting from 7 hours, 14 days, 21 days to 12 weeks.

However, in vitro and in vivo studies of the antidiabetic activity of the CS heartwood are still limited in number. Interestingly, this review provides the evidence that CS heartwood has its potential to be developed and used as an antidiabetic agent in the future.

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