REVIEW: PHYTOCHEMICAL CONSTITUENTS AND PHARMACOLOGICAL ACTIVITY OF *Strobilanthes crispus*

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ABSTRACT

Strobilanthes crispus (S. crispus), called keji beling leaves, is a plant belonging to the genus *Strobilanthes* and family *Acanthaceae*. Keji beling (*S.crispus)* has been applied by Indonesians to cure some diseases like diabetes and dissolve kidney stones. The aim of this review article is to compile an update on the phytochemical studies and pharmacological activity of S. *crispus*. A literature review was carried out by searching for articles in the Scopus, PubMed, and Google Scholar data bases between 2014-2024. Studies have shown that *the leaves of S. crispus* contain flavonoids, phenolics, alkaloids, tannins, terpenoids, phytosterols, and fatty acids. Current pharmacological studies have revealed that the extracts, fractions, or secondary metabolites of *S. crispus possess* antimicrobial, antioxidant, antidiabetic, anti-urothelial, immunomodulatory, wound healing, cytotoxic, and anti-cancer activities. Although previous studies have provided information about *S. crispus,* pharmacological and phytochemical data are still limited. Further studies are still necessary to explore the bioactive compounds, toxicity, safety and future development of *S.crispus* as herbal medicine

Keywords: keji beling, S*trobilanthes crispus*, phytochemical constituent, pharmacological activity

INTRODUCTION

Indonesia has a variety of biodiversities, including medicinal plants. Medicinal plants have been practiced by Indonesians for centuries to maintain health and treat diseases. Although modern medicine is becoming more frequently used, the use of medicinal plants is still popular among the public (Elfahmi *et al*., 2014; Pengpid and Peltzer, 2018).

One of the medicinal plants widely used by Indonesian people is *Strobilanthes crispus*, called keji beling. The keji beling plant *(S. crispus)* is a member of the Acanthaceae family, which is in the form of a bush and flowers and is easily found in forest areas, riverbanks, and fields. In Indonesia, keji beling (S. crispus) is traditionally used to treat diabetes and to dissolve kidney stones (BPOM RI, 2011, 2006; Kasmawati *et al*., 2018).

Scientific research and literature on keji beling *(S. crispus)* are still very limited. However, *S.crispus* has the potential to be developed as a source of active medicinal ingredients or medicines, based on empirical use and existing scientific discoveries. In this review, the phytochemical content contained in the keji beling (*Strobilanthes crispus*) is explained as well as its pharmacological activity so that it can become a study material for researchers and the public regarding keji beling (*Strobilanthes crispus*).

RESEARCH METHOD

The literature review was carried out by searching articles using the Scopus, PubMed and Google Scholar databases with the keywords "*Strobilanthes crispus* phytochemical content", "*Strobilanthes crispus* isolation", "*Strobilanthes crispus* biological

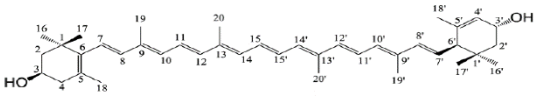
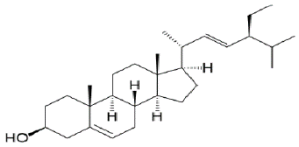
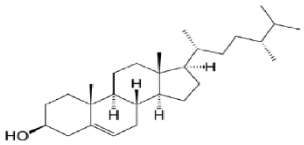
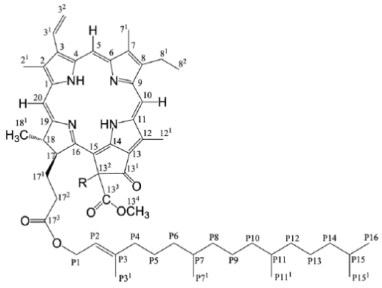
activity", "*Strobilanthes crispus* pharmacological activity", "*Strobilanthes crispus* in vitro study" and "*Strobilanthes crispus* in vivo study". The inclusion criteria in this review were original research articles published from to 2014-2024 and published national and international articles in Indonesian or English. The exclusion criteria were unpublished data, such as theses and conference publications, and articles with invalid sources. The literature collected from the database was identified, chosen based on the relevant topic, and then analyzed based on each study's sample, method, result, and conclusion.

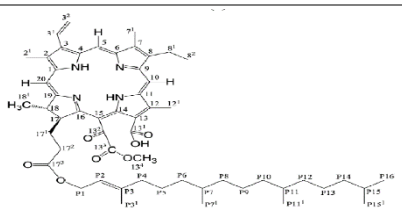
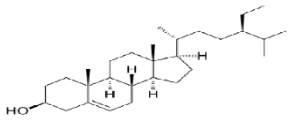
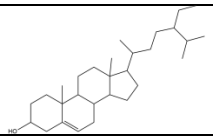
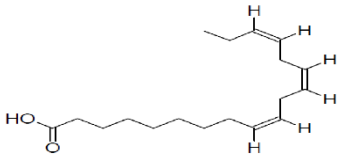
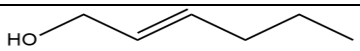
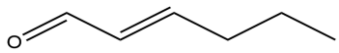
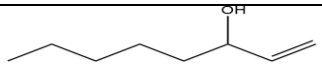
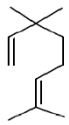
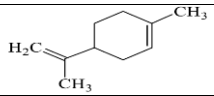
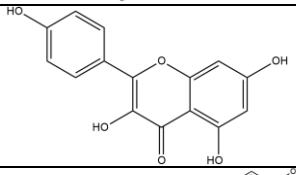
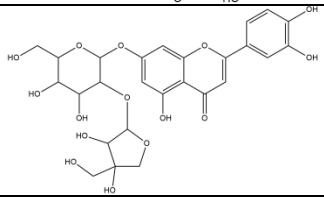
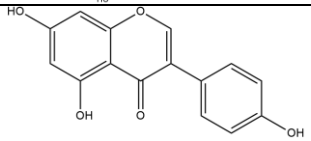
RESULTS AND DISCUSSION

Phytochemical Constituents of *Strobilanthes crispus*

Table I shows the chemical compound content in keji beling *(S.crispus)*, which has the potential for further investigation as a candidate active medicinal compound. Phytochemical screening showed that keji beling *(S.crispus)* contains phenolic compounds, flavonoids, alkaloids, and saponins, which are found in its leaves (Ghasemzadeh *et al*., 2015; Tayyab Gul *et al*., 2020). Lutein, stigmasterol, campesterol, pheophytin a, 131-hydroxy-132-oxo-pheophytin a, β-sitosterol, and 132-hydroxy-pheophytin a have been isolated from the F3 fraction of the dichloromethane extract of keji beling leaves *(S.crispus)* (Yaacob *et al*., 2015). β-Sitosterol is the main constituent of the phytosterol group in keji beling leaves, and α-linolenic acid is abundant in the fatty acids of keji beling leaves. The GC-MS analysis tests using GC-MS show that there are 33 types of essential oil compounds, with the main compounds being 2-hexen-1-ol, 2-hexenal, 1-octen-3-ol, linalool, and benzaldehyde (Chua *et al*., 2019). Another monoterpene compound, D-limonene, is thought to play a role in cytotoxicity (Sulastri *et al*., 2021).

Table I. Reported data of chemical constiuents present in Strobilanthes crispus

Compound Name	Compound Name	Part of Plant	References
Lutein		Leaf	(Yaacob *et al*., 2015)
Stigmasterol		Leaf	(Yaacob *et al*., 2015)
Campesterol		Leaf	(Yaacob *et al*., 2015)
Pheophytin-a		Leaf	(Yaacob *et al*., 2015)

132- hydroxy-pheophytin a		Leaf	(Yaacob *et al.*, 2015)
β-sitosterol		Leaf	(Chua *et al.*, 2019; Yaacob *et al.*, 2015)
γ-sitosterol		Leaf	(Endrini *et al.*, 2015)
α-linolenic acid		Leaf	(Chua *et al.*, 2019)
2-hexen-1-ol		Leaf	(Chua *et al.*, 2019)
2-hexenal		Leaf	(Chua *et al.*, 2019)
1-octen-3-ol		Leaf	(Chua *et al.*, 2019)
Linalool		Leaf	(Chua *et al.*, 2019)
D-limonen		Leaf	(Sulastri *et al.*, 2021)
Kaempferol		Leaf	(Arbianti *et al.*, 2023)
Graveobioside-A		Leaf	(Arbianti *et al.*, 2023)
Genistein		Leaf	(Arbianti *et al.*, 2023)

Pharmacological Activities of *Strobilanthes crispus*

Table II shows a recent study of *Strobilanthes crispus*, which has been carried out (in the last 10 years) both in vitro and in vivo. Extracts from the leaves and stems show various biological activities, although the flower parts have not been extensively studied. The pharmacological activities of *Strobilanthes crispus* include antimicrobial, antioxidant,

immunomodulatory, wound healing, antidiabetic, antiurothialitis, cytotoxic, and anticancer activities.

Table II. Summarized data of Strobilanthes crispus pharmacological activities

Pharmacological activity	Study Design	Part of Plant	Sample	Method	Reference
Antimicrobial	In vitro	Leaf	Ethanol, acetone and chloroform extract	Disk diffusion assay on *S. pyogenes*, *S. aureus*, *MRSA*, *E. coli*, *P. aeruginosa*, *S. typhimurium*, *Shigella* sp. *K. pneumoniae*	(Ban *et al*., 2022)
	In vitro	Leaf	Aqueous extract	*Disk diffusion assay on S. aureus, E.coli, B.cereus, S.typhi, C.albicans, A.niger*	(Suboh *et al*., 2022)
Antioxidant	In vitro	Leaf	Ethanol and aqueous extract	DPPH assay and FRAP assay	(Ghasemzadeh *et al*., 2015)
	In vitro	Leaf	Ethanol extract	DPPH assay, FRAP assay, nitric oxide (NO) and ferric acid reduction assay	(Al-Henhena *et al*., 2015)
	In vitro	Leaf	Methanol extract	ABTS assay and FRAP assay	(Chua *et al*., 2019)
	In vitro	Leaf	Ethanol, acetone and chloroform extract	DPPH assay	(Ban *et al*., 2022)
Antidiabetic	In vivo	Leaf	Ethanol extract	Streptozotocin (STZ)-induced diabetic rats	(Fitri *et al*., 2022)
	In vitro	Leaf	Flavonoid isolate from ethanol extract	α-glucosidase inhibition	(Arbianti *et al*., 2023)
Anti urothialitis	In vitro	Leaf	N-hexane, ethyl acetate, methanol and aqueous extract	Inhibition of aggregation and dissolution of CaOx crystal	(Tayyab Gul *et al*., 2020)
Wound healing	In vitro	Leaf	Ethanol, acetone and chloroform extract	*Scratch assay* on OUMS-36T-4F skin fibroblasts human cell.	(Ban *et al*., 2022)

Immunomodulator	In vivo	Leaf	F3 fraction from dichloromethane extract	NMU-induced rat mammary tumor model.	(Yankuzo *et al*., 2018)
Cytotoxic and anticancer	In vitro	Leaf and stem	N-hexane, chloroform and ethyl acetate extract	MTT assay, flowcitometry, dan *Caspase activity assay* on CNE-1 cell.	(Koh *et al*., 2015)
	In vitro	Leaf and stem	N-hexane, chloroform, ethyl acetate methanol and aqueous extract	MTT assay, flowcitometry dan caspase-8 assay on HepG-2 and MDA-MB-231cell	(Koh *et al*., 2017)
	In vitro	Leaf	D-F9 subfraction from dichloromethane extract	Lactate dehydrogenase release assay MCF-7 and MDA-MB-231 cell	(Yaacob *et al*., 2014)
	In vitro	Leaf	γ-sitosterol isolate	MTT assay on Caco-2, HepG2, MCF-7 and Chang liver cell line	(Endrini *et al*., 2015)
	In vivo	Leaf	F3 subfraction from dichloromethane extract	4T1-induced mouse mammary carcinoma model	(Baraya *et al*., 2021)
	In vivo	Leaf	Methanol extract	azoxymethane (AOM)-induced colonic aberrant crypt foci (ACF) in rats	(Al-Henhena *et al*., 2015)

Antioxidant activity

Antioxidants are compounds that prevent excess free radicals from causing oxidative stress. Various diseases, including inflammation, autoimmunity, cancer, and aging, are initiated and progress by oxidative stress (Hayes *et al*., 2020; Liguori *et al*., 2018). Four articles reported the antioxidant activity of keji beling *(S.crispus)* leaves. Most of them used the ethanolic extract of keji beling *(S.crispus)* leaves as samples and were tested in several in vitro assays. Al-Henhena *et al*. (2015), evaluated the antioxidant activity of ethanol extract of keji beling *(S.crispus)* leaves using the DPPH, FRAP, and NO reduction methods. The results showed that the ethanolic extract had the high antioxidant activity with an IC50 value of 5.44 ± 1.76 µmol/l tested by DPPH assay and an IC50 value of 0.39 ± 0.11 µmol/l tested in nitric oxide (NO) and ferric acid reduction assay. Ghasemzadeh et al. (2015) used DPPH and FRAP assays to compare ethanolic and aqueous extracts. It was reported that the aqueous extract from keji beling *(S.crispus)* leaves has better antioxidant activity with IC50 values of 44.1 µg/mL and 52.8 µg/mL for DPPH and FRAP assay. Ban *et al*. (2022) reported that ethanolic, acetone, and chloroform leaf extracts had the same superior antioxidant activity in a DPPH scavenging assay, but there was no IC50 information. The differences in

antioxidant activity might be due to the influence of drying temperature, microwave waves, and the solvent used, which affects the content of phenolic and flavonoid compounds, which can produce the antioxidant activity of *S.crispus* (Chua *et al*., 2019).

Antimicrobial activity

The antimicrobial activity of keji beling *(S.crispus)* leaf extract evaluated using the disk diffusion assay against several bacteria: *S. pyogenes*, *S. aureus*, *E. coli*, *S. typhimurium*, *P. aeruginosa*, *Shigella* sp. *K. pneumoniae*. Potential antimicrobial activity was only observed in the ethanolic, acetone, and chloroform extracts against *P. aeruginosa*, with average inhibitory zone diameters of 14, 12, and 11 mm (Ban *et al*., 2022). In other in vitro study, the aqueous extract of *S.crispus* leaves reported to have inhibitory activity against *E. coli* at concentration fo 25 mg/mL and 50 mg/mL with the average diameter of inhibition zone was 7.3 ± 0.017 mm and 8.7 ± 0.017 mm (Suboh *et al*., 2022)

Antidiabetic activity

Diabetes is caused by endocrine system disorders. This disorder can cause an increase in blood glucose levels due to impaired insulin secretion. Long-term diabetes can lead to increased lipid peroxidation, which affects fat levels in the body and causes oxidative stress (Asmat *et al*., 2016). The ethanolic extract of *Scrispus* leaves has demonstrated antidiabetic activity in rats. It decreased the blood glucose level starting at a dose of 3.2% until 16.8% was administered for 14 days in streptozotocin (STZ)-induced diabetic rats. The 16.8% concentration of ethanolic *S. crispus* leaf extract was optimal not only for decreasing the blood glucose levels of rats but also for improving the lipid profile of rats, such as reducing the levels of triglycerides, total cholesterol, LDL, and increasing HDL levels (Fitri *et al*., 2022). Other studies have reported the inhibition of α-glucosidase using in vitro assays. The ethanolic extract and six fractions were studied, and acarbose was used as the positive control. Fractions III and IV had lower IC50 values than the crude extract, and the compounds isolated were kaempferol, graveobioside A, and genistein. Among these three compound, kaempherol showed the most antidiabetic activity with an IC50 valuo of 201.87 µg/mL (Arbianti *et al*., 2023).

Anti urolithiatis activity

Urolithiasis or urinary stones are generated by the build-up of inorganic salts (such as calcium, oxalate, phosphorus, and ammonia) or organic salts (such as uric acid) (Gupta et al., 2018). Studies on the anti-urothialitis activity of S. crispus are limited. The anti-urothialitis activity of keji (S.crispus) extracts from several solvents has been evaluated in vitro based on their ability to inhibit calcium oxalate (CaOx) using the titrimetric method based on aggregation and dissolution tests. S. crispus significantly inhibited CaOx crystal aggregation and reduced crystal density ($p < 0.05$). The methanol extract of keji beling leaves (S.crispus) had the greatest inhibitory effect on CaOx crystal aggregation (50.54 ± 2.11%), while the ethyl acetate extract of keji beling leaves (S.crispus) had the best ability to dissolve CaOx crystals (52 .50 ± 2.50%). For further studies, isolation of the responsible compounds and in vivo studies are suggested (Tayyab Gul et al., 2020).

Immunomodulator

The immune system-enhancing activity of keji beling leaves *(S.crispus)* was evaluated using an in vivo assay. The F3 subfraction from dichloromethane extracts of *S. crispus was analyzed* by observing cellular immune parameters (CD4+ or CD8+ T cells, MHC-II, CIITA, and CD68) in mouse mammary tumor nodules induced by NMU. These results demonstrated that the F3 subfraction was able to activate the immune system in mice with NMU-induced mammary tumors. The expression of MHC-II, CD4+, CD8+ T cells, and CIITA in tumor cells in F3 subfraction-treated mice was significantly higher than that in the control group. The F3 subfraction of *S. crispus* dichloromethane extract-treated mice also showed significant reduction in the serum levels of CCL2 and CD68+ macrophages. Serum

IFN-γ levels in the F3 group increased by 1.7-fold, indicating that increased T cell infiltration and upregulation of CIITA and MHC-II expression in tumor cells might be triggered by F3-induced IFN-γ production (Yankuzo *et al*., 2018). The main compunds identified in F3 subfraction were lutein, stigmasterol, campesterol, pheophytin a, 131-hydroxy-132-oxo-pheophytin a, β-sitosterol, and 132-hydroxy-pheophytin (Yaacob *et al*., 2015) However, whether these compounds are responsible for the immunomodulatory effects is still limited. Further investigation is required to understand the contribution of bioactive compounds to the immunomodulatory effect is a suggested direction.

Wound healing

Wound healing is a process of skin repair that involves several cells and intrinsic stages, including homeostasis, inflammation, angiogenesis, growth, re-epithelialization, and remodeling. Dangerous substances and microorganisms can also inhibit wound healing. Ethanol wound healing activity Acetone and chloroform *S. crispus* leaf extracts at a concentration of 70 µg/mL were evaluated in an in vitro *scratch assay* on OUMS-36T-4F human skin fibroblasts incubated with and without MRSA. The results showed that the chloroform extract could cover up the pseudo-wound after 48 hours incubation, but both the ethanol and acetone extracts only slowed it, but did not aid the wound. However, when co-incubated with MRSA, which repressed the open wound with MRSA invasion, the healing activity of all extracts peaked after 10 h of co-incubation. The highest peak for the co-incubation assay was 76.1% for the ethanol extract after 10 h of co-incubation and 60.2% for the chloroform extract. These findings indicate that *S. crispus extracts promote* wound healing activity better in wounds infected with MRSA (Ban *et al*., 2022).

Cytotoxic and Anticancer

Keji beling *(S.crispus)* have been evaluated for its cytotoxic and anticancer activities both in vitro and in vivo. The hexane, chloroform, and ethyl acetate extracts of *S. crispus* leaves and stems were reported to have cytotoxic activity against nasopharyngeal cancer cells, CNE 1 cells. The IC50 values of the hexane, chloroform, and ethyl acetate leaf extracts were 123.5, 161.7, and 119 µg/ml, respectively, while those of the stem extracts were 49.4, 148.3, and 163.5 µg/ml, respectively. These *S. crispus* extracts also induced apoptosis by increasing the sub-G1 population, and this effect was independent of the activation of caspase-3, 7, and 9. Based on this evaluation, S. *crispus* extracts may be potential anticancer agents (Koh *et al*., 2015). The hexane, chloroform, ethyl acetate, methanol, and water extracts of S. crispus leaves and stems were evaluated for their cytotoxic activity against HepG-2 and MDA-MB-231 cells. The study showed that The hexane extract of *S. crispus stem had* the lowest IC50 values on HepG-2 and MDA-MB-231 cells, 38.81 and 42.51 µg/mL. The hexane S. crispus stem altered the cell cycle profile, significantly delayed the doubling time of the cell population, and significantly enhanced caspase-8 activity in HepG-2 cells, but not in MDA-MB-231 cells (Koh *et al*., 2017). The synergistic effect of the bioactive subfractions from dichloromethane *S. crispus leaf* extract and tamoxifen was investigated in MCF-7 and MDA-MB-231 cancer cells. The combination of the D-F9 subfraction of the dichloromethane extract showed strong synergistic inhibition of MCF-7 and MDA-MB-231 cell growth with low doses of tamoxifen. The D-F9 subfraction of the dichloromethane extract also induced apoptosis, which was related to the modulation of the mitochondrial membrane potential and activation of caspase-8 and caspase-9 through both intrinsic and extrinsic signaling pathways (Yaacob *et al*., 2014). Although previous studies have shown that S. crispus has potential as an anticancer agent, data on its bioactive compounds are still limited. Another in vitro study investigated the cytotoxic activity of a γ-sitosterol isolate from *S. crispus* chloroform leaf extract on Caco-2, HepG2, MCF-7, and Chang liver cell lines using an MTT assay. The γ-sitosterol isolate was toxic against Caco-2, HepG2, and MCF-7 cells, with IC50 values of 8.3, 21.8 and 28.8 µg/mL. This isolate also induced apoptosis and suppressed *c-Myc* gene expression in Caco-2 and HepG2 cells (Endrini *et al*., 2015).

In an in vivo study, the chemopreventive effect of the ethanolic extract of S. crispus leaves in azoxymethane(AOM)-induced aberrant crypt foci (ACF) in the rat colon and its flavonoid and phenolic contents were tested. Oral administration of the ethanolic extract of *S. crispus* leaves (250 mg/kg and 500 mg/kg) was able to significantly inhibit colorectal carcinogenesis induced by AOM, as demonstrated by the reduction in the amount of ACF by approximately 71-74%. The ethanolic extract of *S. crispus* leaves reduced the expression of PCNA, Bcl2, and β-catenin. In addition, it has a stimulatory effect on glutathione peroxidase (GPx) and catalase (CAT) activity and an inhibitory effect on MDA and NO levels. The total flavonoid content was 262.86±0.0009 mg/g (quercetin), and the total phenolic content was 737.7±0.024 mg/g (gallic acid). These compounds may contribute to the chemopreventive effects of the extract.

In another in vivo study, the F3 subfraction from dichloromethane leaf extract, lutein isolate from F3, and β-sitosterol were assessed for tumor development and metastasis in a 4T1-induced mouse mammary carcinoma model. Tumor-bearing mice (n=5 per group) were treated with F3 (100 mg/kg/day), lutein (50 mg/kg/day), or Î ²-sitosterol (50 mg/kg/day) for 30 days. The results revealed that all tumor-bearing mice treated with F3, lutein, or β-sitosterol showed a significant reduction in physical tumor growth parameters compared with the untreated group. Histomorphological observation of organ tissue sections (i.e., liver and kidney) Spleen and lung) from F3-treated group showed normal features which were similar to the normal group. The total blood count values did not change significantly when F3 was administrated to normal mice. It indicated that F3 inhibited the secondary metastatic in 4T1-induced mouse mammary carcinoma (Baraya *et al*., 2021). Based on previous studiy, the main compunds identified in F3 subfraction of dichloromethane *S.crispus* leaf extract were lutein, stigmasterol, campesterol, pheophytin a, 131-hydroxy-132-oxo-pheophytin a, β-sitosterol, and 132-hydroxy-pheophytin (Yaacob *et al*., 2015). These compounds may contribute to the antitumor and antimetastatic effects of *S.crispus.* Although previous studies have shown the potential antitumor and antimetastatic effects of the F3 subfraction, further studies on F3 therapeutic development and pharmacokinetics are needed.

CONCLUSION

The data presented in this review show that keji beling *(S. crispus)* has a variety of potential pharmacological activities. Most pharmacological activity has been performed on the leaves and stems, while research on chemical constituents is only available on the leaves. Keji beling *(S.crispus)* has activity as an antioxidant, antimicrobial, antidiabetic, antiurothial, immunomodulatory, wound healing, cytotoxic and anti-cancer. Keji beling *(S. crispus)* contains various secondary metabolites, such as flavonoids, phenolics, alkaloids, tannins, terpenoids, phytosterols, and fatty acids, which may play a role in its pharmacological activity. However, studies of this plant are limited. More in-depth studies are required to identify the bioactive compounds that may be responsible for this pharmacological activity. Research on toxicity to ensure safety is a promising direction for the future development of S. crispus as an herbal medicine.

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