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Unraveling current breakthroughs in *Scorodocarpus borneensis* phytochemical therapeutics: A systematic review

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A B S T R A C T

Scorodocarpus borneensis, also known as the Kulim tree or Garlic tree, has been consumed by the local communities in Southeast Asia as traditional spice using its old leaves, stem bark, and seeds. The locals also used Kulim tree parts as conventional alternative to treat many diseases such as hemorrhoids, leprosy, diabetes, and diarrhea. However, there was limited scientific evidence to support these traditional claims. Therefore, this systematic review aims to present and evaluate a detailed overview of the phytochemical constituents of *S. borneensis* from previous existing studies, shedding light on their chemical composition, bioactivity, and potential applications. In addition, current studies regarding *S. borneensis* are still on a fundamental level. Hence, we aim that this review will reveal the research gap from the previous literature and provide an insight to implement a new research approach in the future. A literature search was conducted using four databases: ScienceDirect, Scopus, Web of Science, and PubMed. The articles were screened and data were extracted based on the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guideline. 8 studies satisfied the inclusion criteria that focused on the phytochemicals from *S. borneensis*. The major phytochemical compound reported was phenolic compound. S. borneensis also exhibits several therapeutic outcomes such as antioxidant, antimicrobial, and anticancer but current studies are not enough to support the claims regarding *S. borneensis* health benefit. In conclusion, this review highlights the current understanding of *S. borneensis'* phytochemical composition and its therapeutic applications which are important in preventing human diseases especially non-communicable diseases.

1. Introduction

Scorodocarpus borneensis is a woody and wildlife plant mainly found in Southeast Asia, especially in the lowland tropical forests of Kalimantan, Sumatera, and Peninsular Malaysia. Traditionally, forest villagers used this plant as spice and medicinal plant. The locals consumed the decoctions of the roots to cure hemorrhoids while some boiled the leaves and bark and drank them to treat leprosy, diabetes, and diarrhea.[1] It is believed that *S. borneensis* holds significant promise for human health due to its rich repertoire of phytochemicals.[2] However, there was a lack of scientific evidence to support this traditional claim which includes information regarding the phytochemical compounds in *S. borneensis* and their testing in complex organisms like humans and animals. The classes of phytochemicals are numerous and include phenolic compounds (flavonoids, phenolic acids), alkaloids, carotenoids, glucosinolates, saponins, terpenes, and many others.[3]

Unfortunately, due to limited evidence regarding the characterisation and quantification of the phytochemicals of *S. borneensis*, the true compound that is responsible for offering the health benefits mentioned by the locals remains a question. The potential health benefits of phytochemicals derived from plants make them a subject of increasing interest in both traditional and modern medicine. However, current studies regarding the health benefits of *S. borneensis* were also limited, which revealed a new gap in the literature. Therefore, researchers should fill this literature gap by providing more evidence from the established methodologies regarding the potential of *S. borneensis* in treating human disease which indirectly supports the traditional claims of the locals. Without a comprehensive overview of the existing literature, new improvements that could be made in the future and the research focus will remain unclear. Therefore, this systematic review aims to present and evaluate a detailed overview of the phytochemical constituents of *S. borneensis* from previous existing studies, shedding

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light on their chemical composition, bioactivity, and potential applications. This review also aims to provide valuable insights for interested researchers to explore and prove the true potential of various phytochemicals derived from Scorodocarpus borneensis.

2. Methods

The review was performed based on the Preferred Reporting Items for Systematic Reviews (PRISMA) guideline (Page et al., 2021).

2.1. Search strategy

A systematic literature search was conducted on PubMed (Medline), Science Direct, and Scopus databases, Web of Science in September until December 2023. Search queries were as follows: ("*Scorodocarpus borneensis*") AND ("phytochemical" OR "bioactive compound"). The database search was performed by two independent investigators to avoid selection bias. The identified studies were then screened for eligibility and cross-referencing. All related articles published from 2013 to December 2023 were considered for inclusion. To avoid obsolete sources in the included data, the sources must have been published recently, which includes the last 5 up to 10 years.

2.2. Inclusion and exclusion criteria

PICOS (population, intervention, control/comparator, outcome, study type) was used to define the inclusion and exclusion criteria (Table 1). Experimental of in vitro studies related to the phytochemical properties of *S. borneensis* were eligible for inclusion along with the whole or any part of *S. borneensis* (bark, leaves, fruit, seeds). Studies using identification, isolation, and characterisation of phytochemical compounds, as well as assessments of their biological activities in vitro were also included. Our inclusion criteria encompass articles, research papers, and studies published up to December 2023. We also considered research published in English and indexed in the chosen databases. Exclusion criteria encompassed non-English language publications, reviews, conference abstracts, book chapters, notes, and articles not directly related to *Scorodocarpus borneensis* or its phytochemical analysis. Studies that lack clear in vitro experiments or fail to report phytochemical data will also be excluded. In vivo study also accepted, however there was no in vivo study regarding *Scorodocarpus borneensis* from the search conducted.

2.3. Study selection

Two investigators individually screened the titles and abstracts retrieved from the databases for eligibility. The screening process was performed using Mendeley (version 1.19.8, Mendeley, London, United Kingdom). The number of searches in each database and the number of duplicates were recorded. Duplicates were removed using the built-in function of "check for duplicates" in the Microsoft Excel 16. Abstracts that fulfilled the inclusion criteria were retrieved for further screening before obtaining the full-text articles. Full articles were reviewed based on the inclusion and exclusion criteria. Quality assessment and data extraction were carried out by the two investigators. If there was any discrepancy between the investigators, a consensus was reached by inviting another investigator. Upon confirming the included studies, the corresponding references were searched manually to ensure full inclusion of all articles that fit the pre-defined criteria. The article selection process is presented in Fig. 1.

Table 1
Eligibility criteria of the identified studies according to PICOS (Population, Intervention, Control/comparator, Outcomes, and Study type).

Properties	Eligibility Criteria
Population	Plant
Intervention	*Scorodocarpus borneensis*
Control/Comparator	Phytochemical and bioactive compound
Outcomes	- Antioxidant/free radical scavenging - Antimicrobial - Higher phenolic compound
Study type	-In vitro studies

2.4. Data extraction

The outcome variables were compiled using a standard data collection form. For each of the included studies, the first authors' surname and the study year, the origin of the study, part of the plant, type of extraction, solvent, study design, dosage, compounds, and outcome measures were extracted and synthesised in Table 4.

2.5. Quality assessment

The quality assessment of the included studies was performed using the Cochrane risk of bias tool. The Cochrane tool was chosen to evaluate the quality of the research and the chosen articles. The Cochrane tool provides a standardised and transparent way to assess the risk of bias. This allows for consistency and comparability across different studies. Key aspects evaluated included randomization, allocation concealment, blinding of assessors, completeness of data, and reporting of measures of variability. Each study was assigned a risk of bias score based on its adherence to these criteria, with higher scores indicating lower risk of bias. Only studies with high methodological quality and a minimized risk of bias were included in the final analysis.

3. Results

3.1. Search result

Fig. 1 shows flow chart of the search and selection process of included studies. The initial search yielded 114. After the removal of duplicates (n = 3), 111 articles were screened based on the types of articles and out of these, 94 articles were excluded (19 review paper, 9 book chapters, 2 notes and 64 irrelevant articles). The 64 articles were excluded due to the fact that *S. borneensis* was not the subject of experimentation in the articles. Based on the 17 remaining articles reviewed in full text, additional 4 articles were excluded as they had been published for more than 10 years to avoid outdated resources and publication bias. In addition, 5 articles were excluded as they have not enough information about the phytochemical or bioactive compound of *S. borneensis* and those 5 studies only focused on the botanical part of *S. borneensis* such as the characteristics of the soil, climate changes, geographical distributions, and its herbarium.

3.2. Quality assessment and analysis of publication bias

Table 2 shows the designated questions for Cochrane tool risk of bias and the corresponding Table 3 shows an assessment of the methodological quality and potential risk of bias of the included studies. High, unclear, and low risk of bias accounted for 1 and 0 respectively. Results showed that the overall quality of the included studies was relatively high. For all included studies, the total scores of the Cochrane scale were higher than 5 points, indicating high methodological quality.

3.3. Articles included in the study

Table 4 shows the details of the eligible studies included in the final analysis. Protocols for all studies have been ethically approved by their respective institutions. All 8 studies that have been chosen encompassed in vitro studies focusing on the phenolic and bioactive compounds from different parts of *S. borneensis*. All of the studies have been conducted in Southeast Asia and the majority, (90 %, N = 7) were from Indonesia and

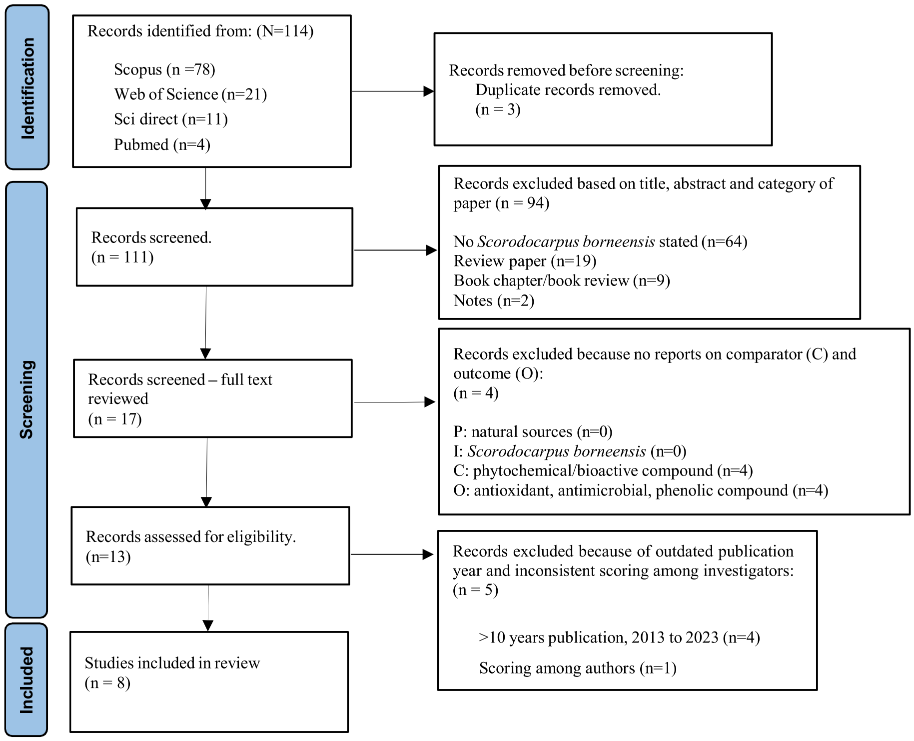

Fig. 1. Flow chart of the search and selection process based on the PRISMA guideline.

Table 2
The questions 1 to 10 from the Cochrane tool risk of bias.

No	Question
1	Was a priori design provided?
2	Was there duplicate study selection and data extraction?
3	Was a comprehensive literature search performed?
4	Was the status of publication (i.e., grew literature) used as an inclusion criteria?
5	Were the characteristics of the included studies provided?
6	Was the scientific quality of the included studies used appropriately in formulating conclusions?
7	Were the methods used to combine the findings of studies appropriate?
8	Was the conflict of interest included?
9	Was the presence of large-study effects assessed?
10	Was the study apparently free of other problems that could result in high risk of bias?

10 %, (N = 1) were conducted in Malaysia. 4 studies obtained their source of *S. borneensis* from a local forest in Sanggau Regency, Kalimantan Barat Province, Indonesia and 3 studies collected the sources from the Botanical Garden of Mulawarman University, East Kalimantan, Indonesia while one study from Malaysia collected *S. borneensis* from local forest in Sabah. The majority of the studies (N = 6) performed maceration as their type of extraction while 2 more studies involved the steam distillation method. The solvents used in the maceration were methanol, ethanol, ethyl acetate, and hexane with methanol was used in the majority of studies (N = 6), followed by ethanol (N = 4) and (N = 3) for both ethyl acetate and hexane. For steam distillation, one study was using ethyl ether to extract the volatiles. Active compound reported from the included studies were phenolic compound (N = 5), sulfur containing compound (N = 2), sesquiterpene (N = 1), and Dehydroxy scorodocarpin B and scorodocarpin B (N = 1).

4. Discussion

Kulim tree (*Scorodocarpus borneensis*) or also known as the Garlic tree, is one of the ancient plants that can be found in grow in tropical forests. *S. borneensis* belongs to the Oleaceae family of plants, which are known to have phytochemicals consisting of flavonoids, tannins, glycoside cyanogenetic, and polysulfide substances. The locals in Southeast Asia use the leaves, barks, and fruits as seasoning and preservation agents the Kulim tree has a similar polysulfide compound as garlic.[4] In addition, *S. borneensis* has been used in traditional practices to treat several medical problems such as kidney disease, diarrhea, hemorrhoids, leprosy, and diabetes. However, to date, there is still a lack of scientific evidence to support this traditional claim regarding the medicinal usage of *S. borneensis.* Therefore, this review aims to present a detailed overview of the phytochemical constituents within

Table 3
Risk of bias assessment for the included studies.

Cochrane scale (question based on Table 2)	1	2	3	4	5	6	7	8	9	10	Total
Kikue Kubota et al., 2014	1	1	1	0	1	1	1	0	1	1	8
Kartika et al., 2015	1	1	1	1	1	1	1	0	1	1	9
Harlinda Kuspradini et al., 2016	1	1	1	1	1	1	1	0	1	1	9
Gigante, 2019	1	1	1	1	1	1	1	0	1	1	9
Sutiknyawati and Dewi, 2020 (a)	1	1	1	1	1	1	1	1	1	1	10
Sutiknyawati and Dewi, 2020 (b)	1	1	1	1	1	1	1	0	1	1	9
Yohana Sutiknyawati Kusuma Dewi et al., 2020	1	1	1	0	1	1	1	0	1	1	9
Dewi et al., 2022	1	1	1	1	1	1	1	0	1	1	9

1 high; *0* unclear; *0* low.

Table 4
Summary of the data the included studies.

Author	Country	Part of Plant	Type of Extraction	Solvent	Study design	Dose Extract	Compound	Outcome
Dewi et al., 2022	Indonesia	Leaves	Maceration	70 % methanol, ethanol, methanol, *n*-hexane, ethyl acetate	Total phenolic content	20–140 μg/ml	Phytochemicals: • Phenolic compound • Flavonoid • Alkaloid • Tannin	• Ethyl acetate solvent extracted the highest total phenolic contents compared to other solvents. (614.86 ± 35.82 mg GAE/g)
					Total flavonoid content	20–140 μg/ml		• Ethyl acetate solvent extracted the highest flavonoid content (271.67 ± 1.30 mg QE/g)
					Total alkaloid content	20–140 μg/ml		• Ethyl acetate solvent extracted the highest alkaloid content (462.25 ± 5.12 mg BE/g)
					Antioxidant (DPPH assay)	100.24 ± 19.69 to 237.89 ± 2.66 μg/ml.		• 70 % methanol solvent showed the most powerful antioxidant activity (IC_{50}: 100.24 μg/ml)
					BSLT	25, 50, 100, 200, 500, 1000 μg/ml		• Methanol fractions were low toxic while the other fractions were considered non-toxic
Gigante, 2019	Indonesia	Leaves	Steam distillation 100 °C for 4 h or more	40 % Ethanol (for dilution of essential oil)	Antimicrobial (Well diffusion method)	1, 1:10, 1:100 (v/v)	Sulfur-containing compounds • Trisulfide dimethyl • Methyl (methylsulfinyl) methyl sulfide • 1,5-Heptadien-3-yne • 2,4,6-trithiaheptane-2,2-dioxide • Furan, tetrahydro-2,2- dimethyl-5- (1-methyl-1-propenyl) • Methane, (methylsulfinyl) methylthio	• *S. borneensis* showed significant antimicrobial activity than the commercial antibiotics, chlorhexidine, and chloramphenicol.
				Methanol (for dilution of essential oil)	Antioxidant assay (DPPH assay)	25, 50, 100, 250.500, 1000 μg/ml		• *S. borneensis* showed an inhibitory effect against radical scavenging DPPH with an IC_{50} value of 715.97 μg/ml. • The essential oil did not have good radical scavenging compared to ascorbic acid
				Helium (carrier gas)	Gas chromatography-mass spectrometry (GC/MS)	–		• GC-MS analysis revealed that the essential oil of *S. borneensis* is mainly composed of sulfur-containing compounds.
Harlinda Kuspradini et al., 2016	Indonesia	Leaves	Steam distillation 100 °C for 2 h	Methanol	Antioxidant (DPPH assay)	25, 50, and 100 ppm	Sesquiterpene	• 100 ppm of *S. borneensis* showed highest antioxidant activity (7.63 %), compared to the concentrations of 50 ppm and 25 ppm with antioxidant activity of 4.15 % and 3.28 % respectively.
				Essential oil	Antimicrobial (Well diffusion method)	25, 50, and 100 ppm		• *S. borneensis* leaves have the potential to inhibit the growth of *S. aureus* and *C. albicans.*
Kartika et al., 2015	Indonesia	Fruit	Maceration	Ethanol, *n*-hexane, water, ethyl acetate	Antioxidant (DPPH assay)	25, 50, 100 ppm	Dehydroxy scorodocarpin B and scorodocarpin B	• n- hexane had highest antioxidant activity with the lowest IC_{50}.
					Anticancer test using Leukemia cell line (L_{1210})	25, 50, 100 ppm		• Dehydroxyscorordocarpin B gave highest anticancer activity with IC_{50} value 1.1061 μg/ml (less than 20 ppm is considered as potential for anticancer).
				n-hexane, ethyl acetate	Column chromatography method	The ratio of *n*-hexane: ethyl acetate is 2:1		• Fraction 8 and fraction 9 showed the highest scavenging activity and were identified as Dehydroxy scorodocarpin B and scorodocarpin B respectively.
Kikue Kubota et al.,2014	Malaysia	Fruit	Maceration	Ethyl ether	Analytical	12.5–25 μg/ml	Sulfur-containing compound: • Methyl methylthiomethyl disulfide (I) • Bis (methylthiomethyl) disulfide (II)	• GCMS: the fresh fruit smell of *S. borneensis* was made up by methyl methylthiomethyl disulfide (I); however, bis (methylthiomethyl) disulfide (II) also significantly contributed to the smell when the fruit was used as a seasoning.

(*continued on next page*)

Table 4 (*continued*)

Author	Country	Part of Plant	Type of Extraction	Solvent	Study design	Dose Extract	Compound	Outcome
					Antimirobial (Agar dilution method)	100 μg/ml		• *S. borneensis* showed considerably strong activity with MIC of 12.5–25 μg/ml against *C. albicans*, *S. cerevidiae*, *M. racemosus*, and *A. niger*.
Sutiknyawati and Dewi, 2020	Indonesia	Fruit	Fractionation	Hexane, ethyl acetate, ethanol, methanol, 70 % methanol	Total phenolic content	52.01–927.36 mg/GAE	Phenolic compounds (flavonoids, tannins, phenols, and terpenoids)	• Methanol extract showed the highest content of phenolic compound (927.36 mg/GAE) compared to ethanol, ethyl acetate, 70 % methanol, and hexane.
					Antioxidant (DPPH assay)	14.54–888.60 ppm		• Methanol extract showed the highest antioxidant activity with IC_{50} of 14.54 ppm • Methanol is the best solvent for preparing herbal infusion.
Sutiknyawati Kusuma Dewi et al., 2020	Indonesia	Bark	Maceration and fractionation	70 % Methanol, *N*-hexane, ethyl acetate, ethanol, methanol,	Total phenolic content	183.33–2332.64 mg GAE/g	Phenolic compound	• The highest total phenolic content was obtained from the methanol fraction, and the lowest was obtained from the *n*-hexane fraction
					Total flavonoid content	79.58–273.13 mg QAE/g	Phenolic compound (flavonoid)	• Highest flavonoid content was obtained from the ethyl acetate fraction, and the lowest was obtained from the ethanol fraction, while flavonoid content in the *n*-hexane fraction was undetected
					Total alkaloid content	13.00 to 19.67 (mg BE/g)	Nitrogen-containing compounds (Alkaloid)	• Total alkaloid decreasing order were methanol > ethanol>70%methanol > ethyl acetate > n-hexane
					Antioxidant (DPPH assay)	57.88–1288.19 ppm.	Phenolic compound (flavonoid)	• The highest antioxidant activity was shown by ethyl acetate fraction, and the lowest was obtained from 70 % methanol fraction.
Dewi et al., 2020	Indonesia	Stem bark, leaf, and fruit	Maceration	70 % methanol	Total phenolic content	100–400 ppm	Phenolic compound	• *S. borneensis* leaf showed the highest TPC (252.77 ppm) followed by stem bark (251.75 ppm) and fruit (238.48 ppm)
					Antioxidant (DPPH assay)	15–90 ppm		• *S. borneensis* leaf showed the highest antioxidant activities (IC_{50}: 36.88 ppm) followed by stem bark (IC_{50} 52.45 ppm) and seed/fruit (IC_{50} 86.20 ppm)
		Leaf			Antibacterial (Red Tilapia Fillets)	5 %–50 %		• The highest inhibitory percentage obtained at concentration of 50 % • The increase of extract concentrations showed a higher ability to inhibit the proteolytic bacteria.
		Leaf			Antimicrobial (Well diffusion method)	5 %–50 %		• Only leaf is being used in antimicrobial activity test due to high antioxidant activity. • *S. borneensis* leaf showed high very strong antimicrobial activity at 50 % concentrations against *Salmonella typhii*

Abbreviations: TPC, total phenolic content; DPPH, 2,2-diphenyl-1-picrylhydrazyl; BSLT, brine shrimp lethality test; ppm, parts per million; IC_{50}, half maximal inhibitory concentration; mg GAE/g, milligrams Gallic acid equivalent per gram; mg QAE/g, milligrams Quercetin equivalent per gram; mg BE/g, milligrams Berberin equivalent per gram.

Scorodocarpus borneensis, shedding light on their chemical composition, bioactivity, and potential applications. Besides, this review is conducted to appraise the data from current researchers into comprehensive insights as well as to suggest potential future studies that can be conducted to support or dispute traditional claims of *S. borneensis*.

4.1. Source

Based on the 114 records identified from 4 databases, eight studies meet the eligibility and inclusion criteria with the majority of the study from Indonesia. This is not surprising as *S. borneensis* known locally as "buah kulim," prospers in Indonesia due to its adaptability to the tropical climate, diverse soil types, and abundant rainfall. Rich biodiversity and traditional agricultural practices in Kalimantan also support its cultivation. The plant's resistance to pests and diseases enhances its suitability. Notably, the *Scorodocarpus borneensis* tree thrives in humid conditions (51.35 %–73.06 %). Indonesia's equatorial climate and extensive rainforests, as highlighted by[5] contribute to its diverse flora, emphasizing the country's abundant natural resources.

4.2. Traditional claims

Traditionally, all parts of Kulim trees have been used for various purposes. Therefore, researchers from the eight studies performed extraction from the leaves fruit, bark, and seeds. Majority of studies utilised leaves and fruit with limited studies about stem bark and seeds. This is because stem bark is known to have a low concentration of active compounds such as secondary metabolites compared to other plant parts like leaves and fruits.[6] Other than that, traditional and cultural practices often influence the choice of plant parts for extraction. In many cases, traditional medicine or local knowledge may specify certain plant parts, and researchers might follow these practices. For example, the locals used the leaves of *S. borneensis* to treat diarrhea,[7] causing the researchers prone to use leaves in their investigation. While seeds may offer chemical composition variation which causes the desired bioactive compounds to be present in lower concentrations compared to other plant parts. Besides, researchers may avoid using seeds due to germination considerations since harvesting seeds may hinder the natural germination and regeneration of the plant.

4.3. Type of extraction

Two types of extraction can be found from the studies recorded, which are maceration and steam distillation with six studies and two studies respectively. Both studies that performed steam distillation used leaves to obtain the essential oil. Fewer studies applied steam distillation compared to maceration might be due to the suitability of maceration to extract heat-sensitive compounds since it involves soaking the plant material in a solvent at room temperature. Plus, maceration is a simple process with low installation and maintenance costs. However, maceration is not suitable for extracting volatile compounds from plant material compared to steam distillation.[8] On the other hand, steam distillation still offers another advantage which is a shorter extraction time compared to maceration.[9] Moreover, it produces a product free of organic solvents, a larger yield, and inexpensive equipment. Therefore, researchers should carefully decide between these methods which depends on the specific goals of the extraction, emphasizing volatile compounds and efficiency for steam distillation, while maceration greats in providing a comprehensive spectrum of bioactive compounds, making the selection contingent on the nature of the plant material and the intended application of the extracts.

4.4. Solvents

For maceration, there were 4 solvents that have been used in the extraction method which are ethyl acetate, methanol, hexane, and ethanol. Ethanol is polar and versatile solvent and is suitable for both polar and nonpolar compound extraction, including phenolics, flavonoids, and tannins. The ethanol concentration of the extraction solvent was the factor that had the greatest influence on the extraction of different bioactive compounds since different bioactive compounds have varying solubilities in ethanol.[10] Besides, different concentration of ethanol in extraction can selectively target different classes of bioactive compounds in which low concentration prone to extract polar compound and higher concentration enhances the extraction of less polar compounds. Ethyl acetate, possessing moderate polarity, is commonly employed for its effectiveness in extracting a diverse range of compounds, including alkaloids, fatty acids, and certain polar pigments. Ethyl acetate was chosen for the extraction because of its ability to dissolve lipophilic and hydrophilic compounds making it useful for extracting compounds from organic and aqueous matrices.[11] Majority studies utilised methanol as solvent which are six studies, followed by ethanol with four studies and three studies for both ethyl acetate and hexane. Methanol, a polar solvent, is frequently utilised for extracting polar compounds such as phenols, alkaloids, and flavonoids, making this solvent a common choice in phytochemical studies.[1212] stated that ethanol and methanol gave the highest yield for plant extraction since the plant material contains high levels of polar compounds that are soluble in solvents with high polarity. Hexane is a nonpolar solvent, which makes it effective for extracting nonpolar compounds like lipids and hydrocarbons. However, it may not be as efficient for extracting polar compounds making it less suitable to extract phenolic compound and other polar bioactive compounds. In terms of toxicity, hexane is considered more toxic than ethanol and methanol.[13] Prolonged exposure to hexane can have adverse health effects, and its use requires careful handling in a well-ventilated environment.

4.5. Beneficial activity of the phytochemicals

Scorodocarpus borneensis claimed for its traditional medicinal usage so far without any concrete evidence to support the claim. From this review, the selected studies focused on three benefits of this plant which are antioxidative effects, antimicrobial, and characterisation of phytochemical compound. The majority of the studies conducted an antioxidant activity assay which is a DPPH scavenging activity assay. Based on the result, all parts of *S. borneensis* (leaves, stem bark, fruit, and seed) tested showed high antioxidant activity which differs based on the types of solvent used. Studies that used methanol and ethanol showed better antioxidant activities with low IC_{50} value since both solvents offered better extraction of polar bioactive compounds that are responsible for the antioxidant activity of *S. borneensis.* Although DPPH scavenging activity assay is a well-established method for measuring antioxidant activity, one disadvantage is that it may not accurately reflect the antioxidant activity in complex biological systems since stable radicals cannot be produced in the normal metabolic processes of a living organism.[14] Therefore, other types of antioxidant assays should be carried out to strengthen the confirmation of the antioxidative activity of *S. borneensis* such as ABTS (2,2′-Azino-bis (3-ethylbenzothiazoline-6-sulfonic acid)) assay, FRAP (Ferric Reducing Antioxidant Power) assay, and superoxide radical scavenging assay.

For antimicrobial testing, three studies performed the test using the well diffusion method and one study performed the agar dilution method to measure the inhibition of *S. borneensis* towards microbial growth. All studies showed high antimicrobial activity of *S. borneensis* against gram-positive bacteria (*Streptococcus aureus, Streptococcus sobrinus, Streptococcus mutans, Bacillus subtilis*), gram-negative bacteria (*Salmonella typhi*), and fungi (*Candida albicans, Saccharomyces cerevisiae, Mucor racemosus, Aspergillus niger*). A notable investigation conducted an antibacterial test on proteolytic bacteria using red tilapia fillets treated with a methanolic extract of *S. borneensis*. The extract exhibited significant antibacterial activity, suggesting its potential as an effective preservative agent. However, this study stated an unstable result of inhibition activity of *S. borneensis* towards proteolytic bacteria due to no fractionation method done. Therefore, it is suggested that fractionation extraction should be done to get pure bioactive compounds and become a more stable inhibitory effect. Maceration is a good choice but it only yields a crude extract that contains many broad-spectrum compounds. Nonetheless, it is advisable to explore alternative solvents such as ethyl acetate, hexane, and ethanol in this assay to further substantiate the efficacy of *S. borneensis* against proteolytic bacteria since different solvents will produce different yields of bioactive compounds. Additionally, it is suggested to explore other antimicrobial tests, with flow cytometry emerging as a promising choice. This method enables the analysis of individual bacterial cells within a population, providing both quantitative and qualitative data,[8] thereby enhancing the reliability of assessing the antimicrobial activity of *S. borneensis*.

There was only one study focusing on the anticancer activity of *S. borneensis* fruit using L1210, a type of leukemia cell line. The data from this study suggests that dehydroxyscorodocarpin b and scorodocarpin b, which have been isolated from the fruits of *S. borneensis*, hold great potential as an anticancer agent. However, no functional study was conducted regarding the anticancer activity of *S. borneensis*. Besides, it is not conclusive as the authors stated that a sample is considered as potential for an anticancer agent if the IC_{50} of the sample is below 20 ppm. The anticancer activity of any product should be assessed further using animal studies which provide a comprehensive overview regarding its efficacy and toxicity. Furthermore, another anticancer assay should be conducted to give rigid support regarding the anticancer effect of Kulim such as the cell cycle analysis using a flow cytometer to evaluate the cell cycle using propidium iodide staining (PI).[15] Bioactive compounds from natural products like *S. borneensis* may arrest the cell cycle at the S phase and specifically induce apoptosis. Unfortunately, cell cycle analysis alone may not distinguish between cells undergoing cell cycle arrest and those undergoing apoptosis. Therefore, future researchers should be concerned about performing additional assays such as apoptosis assays or caspase activity assays to complement cell cycle analysis. Furthermore, there are numerous cancer lines derived from various tissues that can be used by other researchers to study anticancer activity such as MCF-7 (breast adenocarcinoma), HCT-116 (colorectal carcinoma), and A549 (non-small cell lung carcinoma). The use of other cancer cell lines will provide broad supporting details regarding the anticancer activities of natural products specifically on the targeted tissue. It is also worthwhile to observe the effects of *S. borneensis* on normal cell populations as well to ensure the specificity of this plant towards the disease stage.

4.6. Toxicity

Basic toxicity study was also carried out in one of the chosen studies using Brine Shrimp Lethality test (BSLT). Based on this test, it can be concluded that *S. borneensis* is non-toxic with only methanol fractions considered as low toxic. It is known that methanol and hexane are more toxic compared to other solvents such as ethyl acetate, ethanol, and water but methanol can be less toxic when diluted into 70 % methanol. Therefore, researchers should choose the solvents by considering factors such as intended application, toxicity concerns, regulatory requirements, and environmental considerations. However, BSLT only provides general toxicity and does not provide information about the specific mechanism of toxicity whether it is cytotoxic, neurotoxic, or other specific types of toxicity. Plus, brine shrimp is a simple organism, and the results may not accurately predict toxicity in more complex mammalian systems like humans. Compounds that are toxic to brine shrimp may or may not be toxic to humans, and vice versa. Other alternative toxicity tests should be carried out to assess the potential toxicity of substances. Mammalian cell viability assay is also known to become one of the toxicity tests such as MTT assay. Besides, in vivo tests using rodents also can be conducted to evaluate acute and chronic toxicity effects by obtaining its lethal dose (LD_{50}) in animals based on the Organisation for Economic Co-operation and Development (OECD) guideline. Thus, future studies should consider conducting more toxicity assays on *S. borneensis* for human consumption.

4.7. Phytochemical compounds

Based on the eight studies recorded, there were two studies stated that the phytochemical compound from *Scorodocarpus borneensis* was sulfur-containing compound isolated using steam distillation and maceration techniques. Sulfur-containing compounds have the potential as antimicrobial agent which often exert their antimicrobial effects by disrupting cellular structures, interfering with metabolic pathways, or inducing oxidative stress. However, their effectiveness, safety, and application depend on various factors such as concentration, formulation, and the specific microorganisms involved. Meanwhile, one study recorded that *S. borneensis* also contains sesquiterpene from the essential oil of the leaves isolated by the steam distillation method. Sesquiterpene showed high antioxidant activity by DPPH scavenging activity assay. Sesquiterpenes can directly scavenge free radicals by donating electrons or hydrogen atoms, interrupting the chain reactions initiated by free radicals and preventing cellular damage.[16] The majority of the studies proved that *S. borneensis* also contains phenolic compounds such as flavonoids, tannins, and terpenoids with the use of methanol as the extracting solvent. Moreover, two studies that performed total flavonoid content assay observed that the ethyl acetate extract of *S. borneensis* showed the highest content of flavonoids due to its ability to attract polar and nonpolar chemical compounds.[17] The total alkaloid content was also performed with methanol yielding the highest content of alkaloid from *S. borneensis*. Alkaloids are one of the largest phytochemical groups that are present in natural products. It is believed that these compounds have pharmacological effects, including analgesic, antimicrobial, anticancer, and antioxidant activity.

4.8. Phenolic compound

Phenolic compounds were found to be the most abundant in *S. borneensis* and it is believed to have the potential to attenuate the risk of developing diseases caused by oxidative stress such as cancer, diabetes, and its complications. A general summary of the benefits of phenolic compounds is explained in Fig. 2.

Based on Fig. 2, the phenolic compound in *S. borneensis* offers various health benefits such as antioxidant effects and reduction of inflammatory cascade as well as reduction of redox-sensitive transcription factors. However, current studies were at a fundamental level which is not enough to prove the traditional health benefits claimed by the locals. Therefore, near future studies should focus on in vivo and clinical studies to support Kulim as an alternative medicine. The protective effects of dietary phenolic against cancer, and infectious and inflammatory diseases are explained in Fig. 3.

Traditional claims stated that *Scorodocarpus borneensis* possesses many health benefits such as antidiabetic and antimicrobial, but the scientific evidence was still limited due to fewer studies focusing on in vivo and clinical studies. Most of the chosen studies in this systematic review utilise *S. borneensis* at the analytical stage which only emphasizing its phytochemical and in vitro testing. Hence, it is suggested that future studies will apply in vivo and clinical testing to prove the antidiabetic effect of *S. borneensis* since diabetes is the leading worldwide incidence. Fig. 4 shows the protective role of dietary phenolic compounds against diabetes mellitus.

The development of cancer is a multi-stage process that involves initiation, promotion, and progression. Phenolic compounds can affect and modulate multiple diverse biochemical processes and pathways involved in carcinogenesis such as estrogenic and antiestrogenic involvement, antiproliferation, cell cycle arrest or apoptosis activation, oxidation resistance, induction of detoxification enzymes, host immune system regulation, anti-inflammatory activity, and improvements in cellular signaling.[18] This was proved by a study from,[19] that phenolic compound exhibits anticancer activity by testing the *S. borneensis* extract on the Leukemia cell lines. They recorded that *S. borneensis* possesses antioxidative activity by showing a very low value of 50 % inhibitory

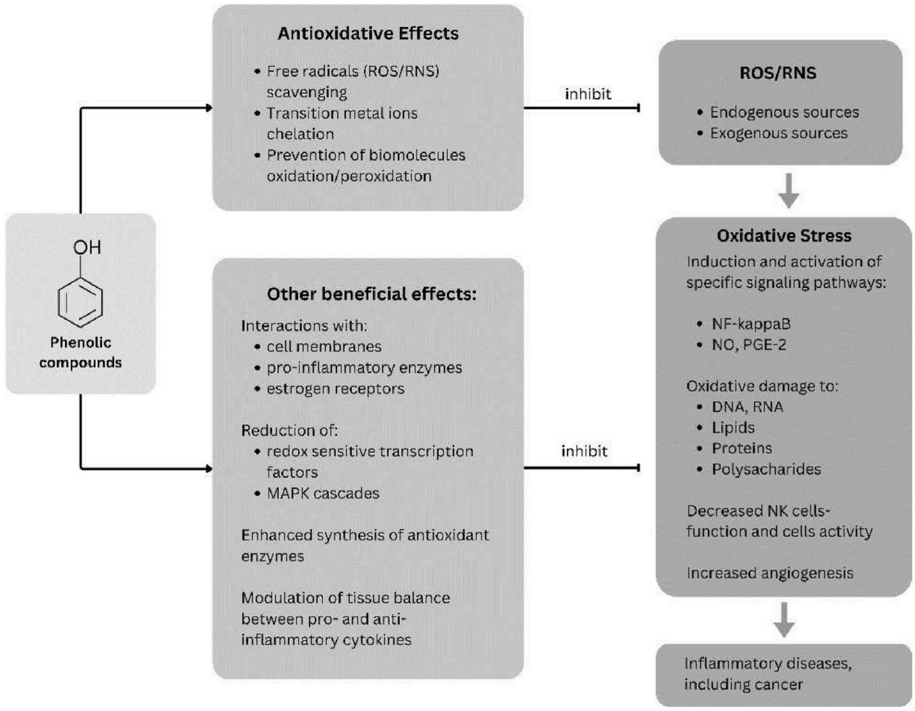

Fig. 2. Summary of oxidative stress reactions and the beneficial effects of phenolic compounds.

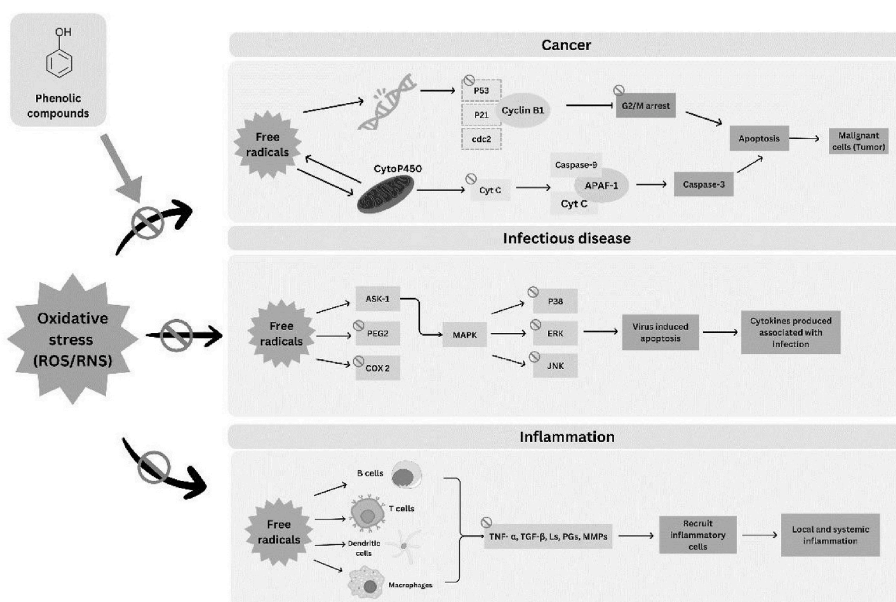

Fig. 3. Protective effects of dietary polyphenols against cancer, infectious illness, and inflammatory diseases.

concentration (IC_{50}) that promises a great anticancer potential.

Phenolic compounds exhibit a broad spectrum of antimicrobial actions through different mechanisms. Upon infection, the host's immune response initiates inflammation through the generation of reactive oxygen species (ROS), causing oxidative stress. Elevated oxidative stress can render the infection more susceptible and induce disruptions in cellular metabolism. Plus, ROS has also been proven to be beneficial to the microorganism for their signaling molecules. Phenolic compounds such as flavonoid from *S. borneensis* can modulate the effect of oxidative stress in the human body by scavenging free radicals (ROS) and chelating the metallic ions. The capability of the phenolic compound as an antimicrobial agent is also explained by,[20] in which the lipophilic character of phenolic compound causes the modification of the cell wall rigidity leading to integrity losses. In addition,[21] stated that the antimicrobial effect of phenolic compounds also occurs by inhibiting microorganism virulence factors such as enzymes and toxins, and suppression of bacterial biofilm formation. Based on the eight extracted studies, four studies had proved the capability of phenolic compound in *S. borneensis* to become a powerful antimicrobial agent that can greatly contribute to human health by inhibiting the formation of oxidative stress agents, avoiding infection, and subsequently lowering the presence of inflammation cascade.

The generation of reactive oxygen species (ROS) triggers inflammatory reactions, leading to the release of cytokines that contribute to

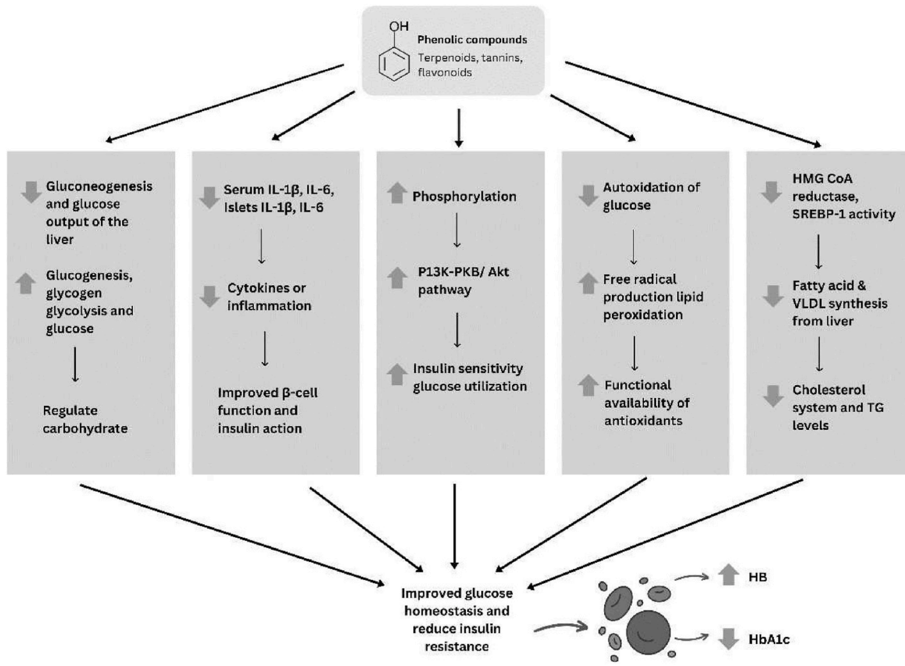

Fig. 4. Protective roles of dietary polyphenols against diabetes.

immunoregulation and tissue damage. Given the defective natural antioxidant defense mechanism in humans, the utilisation of exogenous antioxidants becomes crucial to combat excessive ROS. In the context of *S. borneensis*, phenolic compounds extracted from this natural resource emerge as a promising avenue for regulating inflammatory pathways associated with common inflammatory diseases like gout, osteoarthritis, and rheumatoid arthritis. Phenolic compounds function analogously to non-steroidal anti-inflammatory drugs, believed to inhibit pro-inflammatory mediators such as cyclooxygenase (COX) by blocking their activity or gene expression.[22] Furthermore, certain phenolic compounds exhibit the ability to modulate transcription factors like nuclear factor-kB or Nrf2 in both inflammatory and antioxidant pathways. Notably, phenolic compounds can effectively inhibit activated immune cells by suppressing inflammatory mediators, including IL-6, IL-1β, and TNF-α. With their multifaceted inhibitory effects, phenolic compounds from *S. borneensis* play a pivotal role in preventing vascular inflammation, oxidative stress, elevated nitric oxide levels, and platelet aggregation, ultimately reducing the risk of disease development.

4.9. Antidiabetic activity of phenolic compounds

Based on the eight papers, only analytical and in vitro studies were performed by the researchers regarding *S. borneensis* so far. Analytical studies such as GCMS already proved that *S. borneensis* is rich in phenolic compounds such as flavonoids, terpenoids, and tannins. However, only few studies provided the information about the specific compounds in *S. borneensis*. Therefore, further analytical studies should be conducted by the researchers by considering to apply other established methods such as high-performance liquid chromatography (HPLC), high-performace thin layer chromatography (HPTLC), and nuclear magnetic resonance (NMR) to determine and explore more compounds from *S. borneensis*. The in vitro studies conducted also showed the medicinal benefits of *S. borneensis* such as antimicrobial, antioxidative, and anticancer activity. Based on the characterisation study, the phenolic compound from *S. borneensis* is also known to act as antidiabetic which correlates with the traditional claim. However, no current scientific evidence showing the antidiabetic effect of *S. borneensis*. Therefore, future studies must consider conducting either in vitro antidiabetic assays such as alpha-amylase and alpha-glucosidase inhibition assay, or in vivo studies to strengthen the information about the antidiabetic potential of *S. borneensis*. As shown in Fig. 4, phenolic compounds found in *S. borneensis* are believed to possess antidiabetic effects and at the same time bring less adverse health effects. The phenolic compound can maintain the survival and function of pancreatic β-cells, reduce oxidative stress, translocation of pro-inflammatory cytokines in β-cells, increase expression of anti-apoptotic genes, and decrease expression of pro-apoptotic genes. Previous study done by[23,24] also showed that phenolic compounds had greatly contribute as a protective agent for high glucose toxicity induced endothelial cells and reduced fasting blood glucose levels in diabetic rats Moreover, phenolic compounds can protect the deoxyribonucleic acid (DNA) from damage caused by free radicals, protecting cells against autophagy and necrosis in hyperglycemia conditions. Phenolic compounds like flavonoids can also block protein glycation and inhibit key enzymes related to carbohydrate metabolism, increase glucose transporter (GLUT4) expression, and reduce glucose uptake.[25] Hence, *S. borneensis* has a promising therapeutic potential to prevent and reduce diabetes mellitus based on the phenolic content reported.

5. Study strengths and limitations

This study exhibits strengths in its systematic and comprehensive approach to reviewing the literature on *S. borneensis*. By focusing specifically on the therapeutic potential of its phytochemical compounds, the research addresses a critical gap in the literature. The inclusion of diverse data sources enhances the reliability and depth of the findings. However, the study faces challenges such as potential data heterogeneity due to varied methodologies and geographic influences of raw materials. Limited clinical evidence and the possibility of publication bias may restrict the direct translation of phytochemicals to clinical outcomes. Thus, only papers being published within 10 years had been chosen to avoid outdated data and publication bias. Additionally, the in vivo study of *Scorodocarpus borneensis* is limited and non-existent. Despite these limitations, the methodology and the focus on therapeutic potential contribute valuable insights to the current understanding of *S. borneensis,* its phytochemical compounds, and the potential therapeutic values.

6. Recommendations for future research

The research about *S. borneensis* is still scarce and introductory. So far, most of the studies are focussed on the phytochemical compounds and lack fundamental and translational research. In order to achieve a comprehensive finding and support traditional claimed, future studies should focus on the mechanistic elucidation to understand the pathways underlying their therapeutic effects. Animal studies should be conducted first followed by human studies and clinical trials to assess the efficacy and safety of these compounds in human populations, strengthening translational applications. Exploring potential geographic influences on phytochemical composition and conducting longitudinal studies can provide a more comprehensive understanding of *S. borneensis* bioactivity and sustained therapeutic effects. These recommendations aim to guide future research, building upon the current foundation and advancing our understanding of *S. borneensis* for potential healthcare applications.

7. Conclusion

In conclusion, based on the previous selected studies, this review concludes that *S. borneensis* contains several types of phytochemicals such as phenolic compounds (flavonoid, terpenoid, tannins), sulfur-containing compounds, sesquiterpene and nitrogen-containing compounds which possess several health benefits such as antioxidant, antimicrobial and anticancer. Different phytochemical compounds can be obtained by different types of extraction methods using different types of solvents with different polarity. Future researchers who want to dig deeper into the potential of phytochemicals from natural products like *S. borneensis* or other traditional plants are encouraged to carefully consider the best methodologies to be applied in their studies. Besides, this review also provides the research gap regarding the application of *S. borneensis* in previous studies. Existing studies only focused on the in vitro studies which were not enough to provide rigid support for the traditional claims for *S. borneensis*. No in vivo or human studies were involved before, hence next researchers should initiate a new study to evaluate the true activity of *S. borneensis* in complex organisms through its efficacy dose and toxicity. With a comprehensive literature from this review and new insights for new research will surely contribute to the development of innovative and effective health interventions.

Author contributions

Muhammad Hamizan performed database search identified relevant articles and contributed to the writing of the manuscript. Siti Azhani performed extraction and analysis of data assessed articles for methodological quality and risk of bias. Sabreena Safuan and Zuraidah Abdullah provides guidance and feedback on the manuscript.

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Data availability statement

The dataset generated during and analysed for the present review is available from the corresponding author on request.

Declaration of competing interest

The authors declare that the systematic review was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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