

# *Zingiber officinale* (ginger): A systematic review and meta-analysis on antimicrobial activities

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## ABSTRACT

The available synthetic drugs to treat infectious diseases have many side effects on the consumer. *Zingiber officinale* which is known as ginger or “halia” in Malaysia has a good prospect as an alternative for safer treatment and has a low risk of side effects. It is because this herb is used as a traditional medicine in the community to treat several ailments, including infectious diseases. Several studies have shown that crude extracts and bioactive components of *Z. officinale* possessed diverse pharmacological properties such as anticancer, anti-inflammatory, antimicrobial, antioxidant, and immunomodulatory. The goal of this research is to find out the effects of *Z. officinale* on the antimicrobial activities from the selected previous studies (years 2000–2020). Briefly, this study involves 10 randomized controlled trials (RCTs) that determined the antimicrobial activities of *Z. officinale*. The results of the systematic analysis showed that *Z. officinale* exhibits antimicrobial activities for both *in vitro* and *in vivo* evaluations. The meta-analysis of appropriate data from four sources presented a substantial distinction between this plant and controls. The results present no significant difference between *Z. officinale* and positive controls for the antimicrobial analysis related to the overall outcome and inhibition zone [overall outcome standardized mean difference (SMD): -0.6003 (95% CI: -0.7092 to -0.4913),  $P = 100\%$ , inhibition zone SMD: 0.8771 (CI: -8.1288 to 9.8829),  $P = 99\%$ ]. In conclusion, the results presented the antimicrobial activities of *Z. officinale* to be similar to the activity of the positive control. However, one should be aware of some limitations with the detailed reporting on the controls used in the included studies. Future well-designed RCTs with detailed reporting on the controls are required to provide additional data to prove the consequences of *Z. officinale* on the antimicrobial activities as well as safety data of consuming this plant.

## INTRODUCTION

Antimicrobial activity is the process of killing or preventing the growth of the microbes that cause infectious diseases (Wang *et al.*, 2017). Nowadays, there are various antimicrobial agents available to treat these diseases. These antimicrobial agents are divided into groups based on the mechanisms of the antimicrobial activity such as agents that prevent cell wall synthesis, those that depolarize the cell membrane, and those that inhibit protein and nucleic acid synthesis as well as metabolic pathways

in bacteria (Reygaert, 2018). There are many available synthetic drugs that are used to treat infectious diseases but also have many side effects on the consumer. For example, chloramphenicol, an antimicrobial agent, is used to treat meningitis. This drug works by passing through the blood-brain barrier and is able to cause aplastic anemia (Mohsen *et al.*, 2020). Besides, treatment with ribavirin has been shown to reduce the ribonucleic acid of the virus but is able to cause hemolytic anemia in the patient (McFee, 2020).

This medicinal plant has been used by humans for a long time to treat many ailments as well as other essential roles. Also, medicinal plants have been important medicines in all cultures and are a source of many traditional medicines that also contribute to modern medicines (Dar *et al.*, 2017). In pursuit of new drug candidates, plant extracts and natural molecules from plants are being extensively analyzed (Harun *et al.*, 2018, 2019,

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2021). Plants have been used for more than 5,000 years as agents of vaccines, antimicrobials, analgesics, cardioprotective agents, and other medicines. Human beings have used natural substances in ancient history to combat pathogens. Currently, almost 70% to 90% peoples in developing countries applied herbs to treat various diseases. The strongest and most promising components of plants are secondary metabolites. More than half of the drugs authorized by the Food and Drug Administration use natural products and their derivatives (Anand *et al.*, 2019). As an alternative for safer treatment and low risk of side effects, *Zingiber officinale* or ginger is famous in the community and is traditionally used to treat many diseases including infectious diseases and fever and also was used to boost immunity.

*Zingiber officinale*, a member of the family Zingiberaceae and a species of the genus *Zingiber*, has been well known as a medicinal herbal and spice product for a long time. This herb is abundantly cultivated for commercial purposes in India, Indochina, West Indies, Mexico, Southeast Asia, and other countries as well (Banerjee *et al.*, 2011). Ginger has been traditionally used to reduce the symptoms of headaches, colds, nausea, pain, and emesis (Mao *et al.*, 2019; Mohamad *et al.*, 2019). In India, the preparation of fresh ginger juice mixed with fresh garlic juice and honey is a common practice for cough and asthma (Awang, 1992). In Southeast Asian countries such as Malaysia and Indonesia, women consume ginger soup after birth to make them hot and sweat (Mohammad and Hamed, 2012). Also, *Z. officinale* is a common component of traditional Chinese treatments for respiratory infections (Chang *et al.*, 2013) and also remedies for atonic dyspepsia and colic (Keys, 1985). Based on a study by Safa *et al.* (2020), *Z. officinale*-based tablets increased the recovery rate of clinical symptoms as well as the improvement of clinical and preclinical features in patients admitted with severe acute respiratory syndrome due to COVID-19 infection. *Zingiber officinale* and its bioactive compounds showed a variety of biological activities including antimicrobial (Aaisha *et al.*, 2020; Elmowalid *et al.*, 2019), antioxidant, antiarthritic (Murugesan *et al.*, 2020), antitumor (Liao *et al.*, 2020), anti-inflammatory, antithrombotic (Thomson *et al.*, 2002), and hypoglycemic (Ojewole, 2006) effects. *Zingiber officinale* also contains many natural organic materials such as 6-gingerol, 6-shogaol, and 6-paradol that promote its biological activities.

There are numerous previous studies related to the structure–activity relationship of bioactive compounds who isolated from *Z. officinale* and their effects on biological activity. The study by Yamauchi *et al.* (2019) who isolated 13 bioactive compounds from the methanol extract of the *Z. officinale* rhizomes and further assessed their effects on the extracellular melanogenesis inhibitory activity. The findings showed that gingerols promoted the highest inhibitory activity of extracellular melanogenesis as compared to other vanilloid compounds. They suggest that elongation of the carbon chain as well as the carbonyl and hydroxyl groups on the carbon chain played an important role in this effect. Another study by Masuda *et al.* (2004) who investigated the antioxidant properties of the gingerol-related compounds and diarylheptanoid isolated from the rhizomes of ginger. The results suggested that the alkyl chain substitution of dehydrogingerdiones is able to contribute to the radical scavenging effects of autoxidation of oils as compared with gingerol-related compounds.

The pharmacological validation of the antimicrobial effect of *Z. officinale* is quite restricted, and several existing review

publications on this plant have not been focused on this activity. Therefore, this study aimed to conduct a systematic assessment of all available data (years 2000–2020) to determine the effects of *Z. officinale* on antimicrobial activities. Therefore, it is crucial to prove the community's belief in traditionally consuming this herb as a treatment for infectious diseases by conducting a systematic review and meta-analysis on *Z. officinale*'s antimicrobial activities.

## METHODOLOGY

This systematic review was carried out in accordance with the principles of the Cochrane Collaboration framework and was described following the guideline by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses declaration.

### Search strategies and study selection

From 2000 until 2020, an electronic search for original articles was done using two selected electronic databases which were PubMed and Science Direct. The selection of these two databases was based on the ability to get full access to the related articles from our institution. The strategic search terms were *Z. officinale* or ginger plus antimicrobial activities or effect of *Z. officinale* or ginger on antimicrobial activities. The papers that were included in the study are research that involved the use of the extract or bioactive compound of *Z. officinale* which contained the antimicrobial outcomes (*in vivo*, *in vitro*, or clinical studies). The papers that did not include the above criteria were excluded (Moher *et al.*, 2009). The study selection was performed by following the steps in Figure 1.

### Data extraction and quality assessment

The data were extracted using standard data extraction from the two selected databases (PubMed and Science Direct) from 2000 to 2020. The extracted data included the tested substances, antimicrobial properties, method used to test the antimicrobial properties, tested microorganism, model used, tested dose, results (using tested substances), and comparison with positive controls.

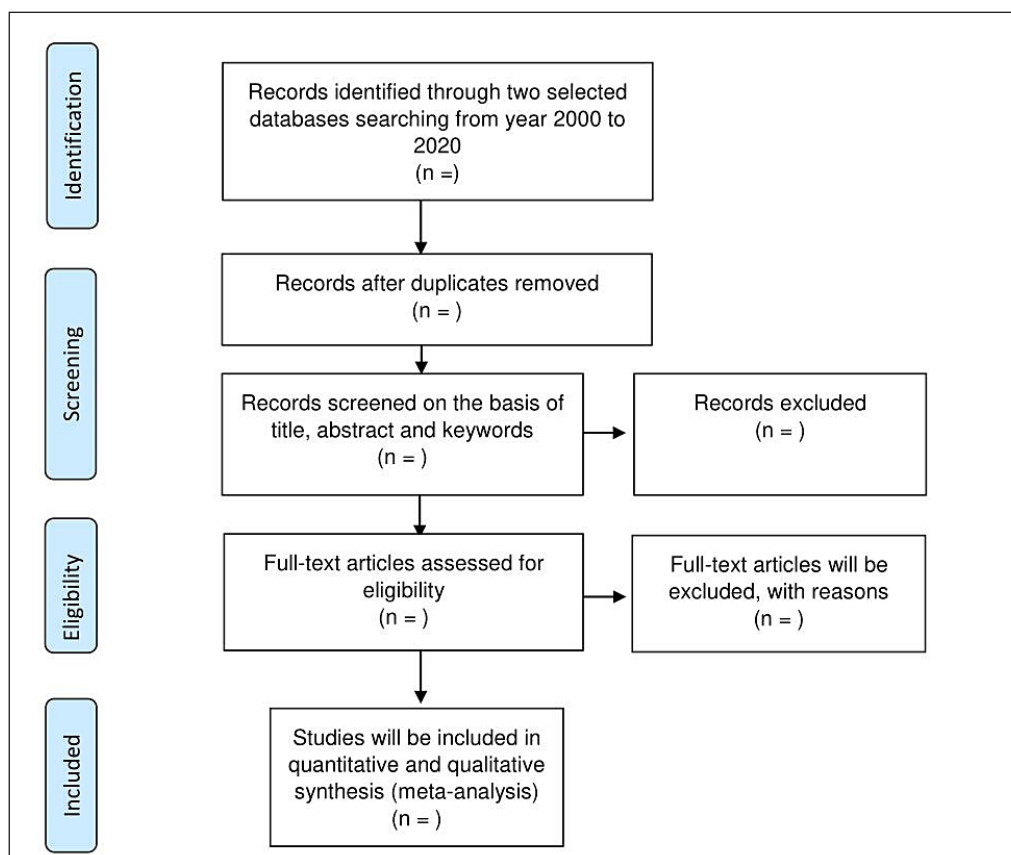
The quality of the included studies was assessed using the Cochrane risk of bias tool. Sequence generation, allocation concealment, incomplete outcome data, selective reporting, other sources of bias, and overall risk of bias were evaluated. The risk of bias assessment using the Cochrane risk of bias assessment is displayed in Table 1.

### Statistical analysis

The analysis of the antimicrobial effects of *Z. officinale* was conducted by comparing the data for the individual function test (treated with *Z. officinale*) with its comparator (positive control) [standardized mean difference (SMD) with a confidence interval (CI) at 95%]. Meanwhile, the  $I^2$ -statistic was used to assess the heterogeneity value. The direction of effects, amount, and power of heterogeneity evidence affect the value of the threshold of  $I^2$ . Substantial heterogeneity means an  $I^2$  value of more than 50%. All the statistical analyses were done using the RevMan software (edition 5.4).

## RESULTS

The database search resulted in the discovery of 363 articles. Because there was no duplication, none of the articles were removed. There were 96 titles, abstracts, and keywords evaluated in all. Nineteen of the full-text research articles were



**Figure 1.** The flow chart of study selection (Moher *et al.*, 2009). “n” is the number of papers.

reviewed from the screened titles, abstracts, and keywords, and all the papers were included in the systematic review. The flow of study selection for the antimicrobial activities is presented in Figure 2. After analyzing the 19 included studies, 10 studies (52.63%) had sufficient data for the comparison between *Z. officinale* and positive control while 9 other studies (47.37%) did not have sufficient data for this. All the information on the antimicrobial activities of this plant (model and method used, tested substances, tested microorganisms, results, tested dose, and comparison with control) is summarized in Table 2.

The quality assessment of the data is presented in Table 3. Fifteen studies (78.94%) showed a low possibility of bias. Four studies (21.05%) were indistinguishable. Despite the fact that all studies claimed that they were randomized controlled trials, two studies showed an unclear risk of bias for “sequence generation” due to a lack of description of the sequence generation methods. Two other studies showed an indistinguishable possibility of bias for “allocation concealment” because the explanation for the “allocation concealment” method was not present.

The antimicrobial-related outcome was categorized into overall outcomes, inhibition zone, and minimum inhibition concentration (MIC) for the meta-analysis. Qualitative analysis of heterogeneity for the “overall outcome” findings is shown in Figure 3. An analysis specifically done on the qualitative visual method of the findings suggests variability present between the studies. The individual study point evaluations of the effect of treatment (green squares) are on the same line of the upright axis, representing similar treatment amount effects between studies. The prediction of the effect on the study treatment of the population showed the difference value as presented at the

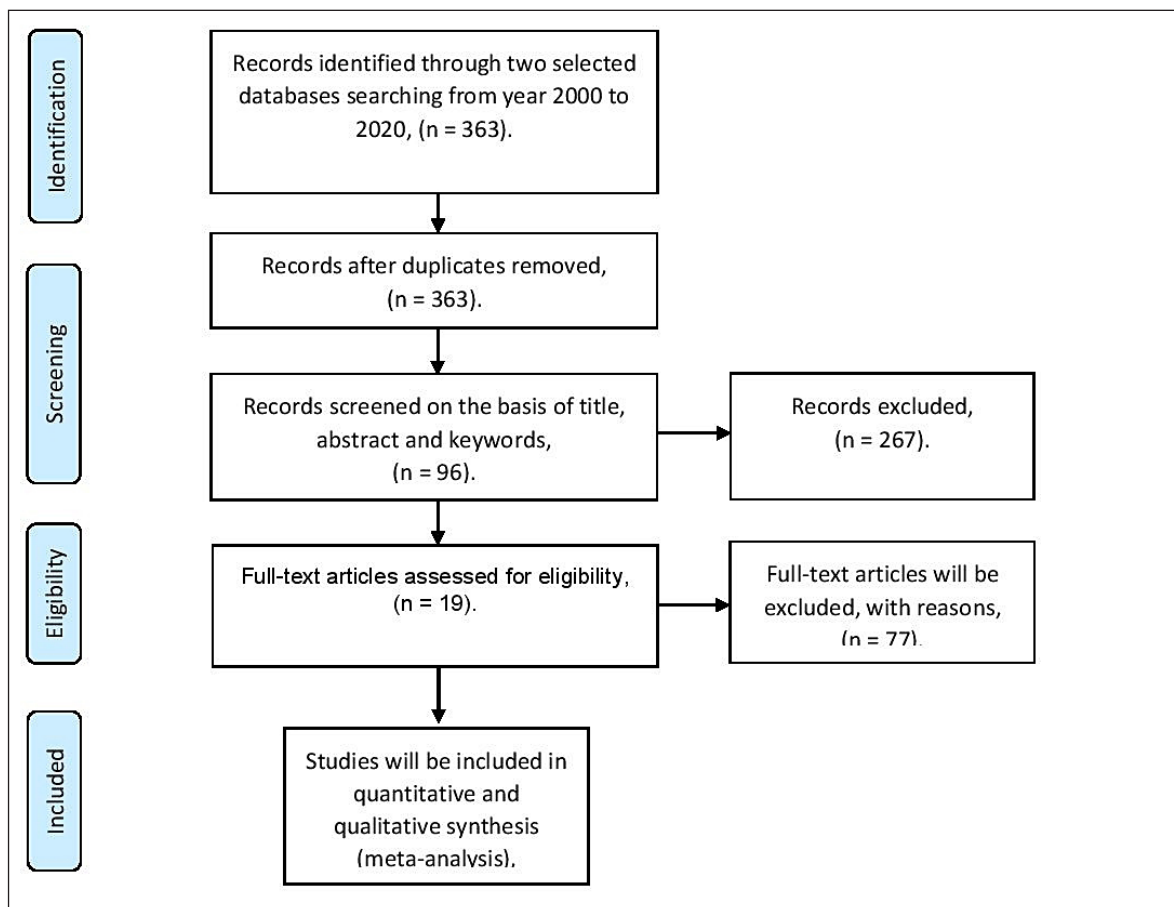
**Table 1.** The Cochrane risk of bias assessment.

Bias	Author’s judgment
Random sequence generation (selection bias)	High/low/unclear risk
Allocation concealment (selection bias)	High/low/unclear risk
Incomplete outcome data (attrition bias)	High/low/unclear risk
Selective reporting (reporting bias)	High/low/unclear risk
Other biases	High/low/unclear risk
Overall risk of bias	High/low/unclear risk

horizontal lines in the figure, and the result suggests the presence of heterogeneity. The *P*-value that presented the quantitative tests of heterogeneity was 100% and suggests there was study variability (i.e., heterogeneity).

Qualitative analysis of heterogeneity for the “inhibition zone” findings is shown in Figure 4. Observational analysis of the results suggests there is between-study variability. The individual study point evaluations of the effect of treatment (green squares) are on both sides. However, they are not located on the upright axis, representing a modification in treatment amount effect between studies. Meanwhile, the prediction of the effects of the study treatment of the population showed the difference value as presented at the horizontal lines in the figure, and the result suggests the presence of heterogeneity. The *P* value was 99% and suggests that there was study variability (i.e., heterogeneity).

Furthermore, an observational analysis of the MIC result suggests medium between-study-group variability, as shown in Figure 5. Based on the figure, the location of the green squares



**Figure 2.** Detailed flow diagram of study selection for antimicrobial activities (Moher *et al.*, 2009).

showed similar approximation of the amount of the treatment effects for the groups. However, there was a similar prediction for the effect of population treatment groups, as illustrated by the CIs for the groups overlapping each other in the figure, suggesting there is medium heterogeneity. The  $I^2$ -value was 34%. This quantitative result suggests medium between-study variability (i.e., heterogeneity).

Based on the data of the included studies, 19 studies described the antimicrobial activities of *Z. officinale*, but only 4 had satisfactory data for further proceeding with meta-analysis. The four studies were considered in a specific area for the purpose of determining the antimicrobial effects of *Z. officinale*. The domains included: 1) overall effect outcomes, 2) inhibition zone, and 3) MIC. For the overall outcome and inhibition zone, the  $I^2$ -values were 100% and 99%, respectively. The results presented high heterogeneity between the parameters included in this study. For the MIC, the  $I^2$  value was 34%, which means there was medium heterogeneity. There was a significant difference between *Z. officinale* and positive controls on the MIC [SMD: 0.0201 (CI: 0.0166–0.0235),  $I^2 = 34\%$ ], while there was no significant difference between *Z. officinale* and positive controls for the overall outcome and inhibition zone [overall outcome SMD:  $-0.6003$  (95% CI:  $-0.7092$  to  $-0.4913$ ),  $I^2 = 100\%$ ; inhibition zone SMD: 0.8771 (CI:  $-8.1288$  to 9.8829),  $I^2 = 99\%$ ]. All the results are presented in Table 4.

## DISCUSSION

The results of preliminary research employing the disc diffusion approach reported that the methanol extract of *Z.*

*officinale* exhibited antibacterial potentials against pathogenic bacteria such as *Escherichia coli*, *Pseudomonas aeruginosa*, *Pasteurella multocida*, *Staphylococcus aureus*, *Bacillus subtilis*, *Klebsiella pneumoniae*, and *Proteus mirabilis*. In this study, the methanol extract of *Z. officinale* showed antibacterial activities with an inhibition zone of 10–15 mm (Chakraborty *et al.*, 2014). In addition, the similar extract of *Z. officinale* presented a broad range of inhibition towards *P. aeruginosa*, *Streptococcus mutans*, and *Streptococcus sobrinus*. The researcher used the agar well diffusion and agar diffusion methods to figure out these antibacterial activities, and the outcome exhibited that the methanol extract at doses of 0.2 and 2 mg/ml suppressed most major inhibitory capabilities against those microorganisms (Babaekhou and Ghane, 2020; Chakotiya *et al.*, 2017). The ethanol extract of *Z. officinale* was able to inhibit the growth of many microorganisms including *E. coli*, *P. multocida*, *B. subtilis*, and *S. aureus* on the basis of the disc diffusion method. The inhibition zone by the ethanol extract ranged from 10.6 to 15.7 mm (Abdul Qadir *et al.*, 2017; Chakraborty *et al.*, 2014). The ethanol extract also presented significant antibacterial properties by inhibiting the growth of the enterococcal species, *Enterobacter* species, *Proteus* species, and *Klebsiella* species on the basis of the agar well diffusion method and serial tube dilution technique. The ethanol extract (0.025–100 mg/ml) was able to inhibit microorganism growth with inhibition zones ranging from 4 to 20 mm (Karuppiah and Rajaram, 2012; Revati *et al.*, 2015). In addition, the acetone extract also showed promising outcomes in inhibiting the growth

**Table 2.** Antimicrobial activities of crude extracts, bioactive fraction, and compounds derived from *Z. officinale*.

No	Tested substances	Part	Antimicrobial properties	Method	Tested microorganism	Results (using tested substances)	Comparison with positive control	References
1.	Methanol, ethanol, and acetone extract	Not stated	Antibacterial	Disc diffusion ( $n = 3$ )	<i>E. coli</i> , <i>P. multocida</i> , <i>B. subtilis</i> , and <i>S. aureus</i>	Inhibition zone (dose: 100 mg/ml): Methanol: 11.4–15.2 mm Ethanol: 11.8–15.7 mm Acetone: 9.1–12.4 mm	Inhibition zone (dose not stated): Rifampicin: 21 to 7–28.2 mm	
2.	Essential oil	Rhizome	Antibacterial	Disc diffusion ( $n = 3$ )	<i>Aeromonas hydrophila</i> and <i>Staphylococcus</i> spp.	Inhibition zone (dose: 50 mg/ml): <i>A. hydrophila</i> : 10.33 to 22.33 ± 0.58 mm, MIC: 0.05–0.2 mg/ml <i>Staphylococcus</i> spp.: 6 to 15.33 ± 0.58 mm, MIC: 0.05–0.2 mg/ml	Inhibition zone (dose not stated): Erythromycin: 6 to 24 mm Kanamycin: 6 to 20 mm	Snuossi <i>et al.</i> , 2016
3.	Hot water extracts	Rhizome	Antiviral	Plaque reduction assay ( $n = 1$ )	HRSV	Infection rate (dose: 0.3 mg/ml): 20%, dose-dependently effective	Infection rate (dose: 0.03 mg/ml): 50%, dose-dependently effective	Chang <i>et al.</i> , 2013
4.	GNF	Rhizome	Antibacterial	Agar diffusion assay ( $n = 3$ )	<i>B. cereus</i> , <i>S. aureus</i> , <i>E. coli</i> , and <i>S. typhimurium</i>	MIC value (dose not stated): GNF: 0.013 ± 0.00012 to 0.031 ± 0.002 mg/ml	MIC value (dose not stated): Ampicillin: 0.0004 ± 0 to 0.012 ± 0.0008 mg/ml	Jacob <i>et al.</i> , 2019
5.	Mixture of methanol	Rhizome	Antibacterial	Agar well diffusion method ( $n = 1$ )	<i>P. aeruginosa</i>	Inhibition zone (dose: 0.2 mg/ml): 27.09 ± 0.003 mm, MIC: 0.01 mg/ml	Inhibition zone of amikacin (dose: 0.2 mg/ml): 30.78 ± 0.1 mm, MIC: 0.005 mg/ml	Chakotiya <i>et al.</i> , 2017
6.	Phenolic extract	Not stated	Antibacterial	Agar well diffusion method	<i>S. aureus</i> , <i>K. pneumoniae</i> , <i>P. mirabilis</i> , and <i>E. coli</i>	Inhibition zone (dose: 0.05 mg/ml): 16–25 mm, MIC: 1.59–2.2 mg/ml	Not stated	Saleh <i>et al.</i> , 2018
7.	Crude extract and methanolic extract	Rhizome	Antibacterial	Microdilution method	<i>S. mutans</i>	Dose: 5 mg/ml MIC: 0.256 mg/ml	Not stated	Hasan <i>et al.</i> , 2015
8.	Essential oil	Rhizome	Antibacterial	Agar diffusion method	<i>L. monocytogenes</i> , <i>S. aureus</i> , <i>E. coli</i> , <i>S. typhimurium</i> , and <i>P. aeruginosa</i>	Inhibition zone (dose: 300 mg/ml): 13.0–37.0 mm, MIC: 2.3–9.4 mg/ml	Not stated	Silva <i>et al.</i> , 2018
9.	n-Hexane, ethyl acetate, methanol, and water extracts	Rhizome	Antibacterial	Agar diffusion method ( $n = 3$ )	<i>S. mutans</i> and <i>S. sobrinus</i>	Inhibition zone (dose: 2 mg/ml): n-Hexane: 12 ± 4.9 to 18 ± 1.7 mm, MIC: 0.8 mg/ml Ethyl acetate: 11.3 ± 1.0 to 19.3 ± 0.6 mm, MIC: 0.8 mg/ml Methanol: 16.8 ± 0.6 to 21.8 ± 0.6 mm, MIC: 0.8 mg/ml	Inhibition zone (dose: 40 mg/ml): Penicillin: 15.8 ± 0.6 to 16.3 ± 1.1 mm	Babaeekhou and Ghane, 2020

Continued

No	Tested substances	Part	Antimicrobial properties	Method	Tested microorganism	Results (using tested substances)	Comparison with positive control	References
10.	Ethanol extract	Rhizome	Antibacterial	Agar well diffusion method	Enterococcal species	Inhibition zone (dose: 100 mg/ml): 20 mm	Not stated	Revati <i>et al.</i> , 2015
11.	Essential oil		Antibacterial	Resazurin microtiter assay plate ( $n = 3$ )	<i>M. tuberculosis</i>	Dose: 0.0004–0.25 mg/ml MIC: 0.063–0.25 mg/ml	(Dose: 0.000007–0.001 mg/ml) MIC of isoniazid: 0.00003–0.004 mg/ml	Baldin <i>et al.</i> , 2019
				Broth microdilution method ( $n = 3$ )	Nontuberculous mycobacteria	(Dose: 0.0004–0.25 mg/ml) MIC: 0.016–0.25 mg/ml	(Dose: 0.00003–0.008 mg/ml) MIC of ciprofloxacin: 0.00012–0.0005 mg/ml	Baldin <i>et al.</i> , 2019
12.	Essential oil	Rhizome	Antifungal	Broth dilution antifungal susceptibility testing	<i>Aspergillus niger</i> , <i>Aspergillus fumigatus</i> , <i>Aspergillus flavus</i> , <i>Aspergillus ochraceus</i> , <i>P. citrinum</i> , and <i>P. chrysogenum</i>	(Dose: 0.25–5 mg/ml) MIC (mg/ml): <i>A. niger</i> : 2 <i>A. fumigatus</i> : 1.5 <i>A. flavus</i> : 1.8 <i>A. ochraceus</i> : 1.3 <i>P. citrinum</i> : 2 <i>P. chrysogenum</i> : 2.5	Not stated	Sharifzadeh <i>et al.</i> , 2016
13.	Crude and aqueous extract	Rhizome	Antibacterial	Agar well diffusion method ( $n = 3$ )	<i>S. mutans</i>	Inhibition zone (dose: 2 mg/ml): Crude: 7.65 ± 0.27 mm, MIC: 0 Aqueous: 14.02 ± 0.32 mm, MIC: 50 mg/ml	Inhibition zone of 0.2% chlorhexidine: 22.57 mm	Jain <i>et al.</i> , 2015
14.	Free phenolics	Rhizome	Antibacterial	Agar diffusion and conventional broth dilution method ( $n = 3$ )	<i>H. pylori</i>	Inhibition zone (dose: 0.01 mg/ml): 20 mm, MIC: 0.049 ± 0.0041 mg/ml	Inhibition zone of amoxicillin (dose: 0.01 mg/ml): 23 mm, MIC: 0.026 ± 0.0032 mg/ml	Siddaraju and Dharmesh, 2007
15.	[6]-Dehydrogingerdione, [6]-shogaol, [10]-gingerol, and [6]-gingerol	Rhizome	Antibacterial	Broth microdilution method	Extensively drug-resistant <i>A. baumannii</i>	Dose: 0.01–0.2 mg/ml MIC: 0.132–0.347 mg/ml	Not stated	Wang <i>et al.</i> , 2010
16.	Methanol, ethanol, and acetone extract	Rhizome	Antibacterial	Disc diffusion ( $n = 3$ )	<i>S. aureus</i> , <i>P. aeruginosa</i> , <i>K. pneumoniae</i> , <i>E. coli</i> , <i>B. subtilis</i> , and <i>P. mirabilis</i>	Inhibition zone (dose: 0.03 mg/ml): Methanol: 10.3–13.6 mm, MIC: 0.008 to 0.026 ± 0.00007 mg/ml Ethanol: 10.6–12.3 mm, MIC: 0.011 to 0.034 ± 0.00027 mg/ml Acetone: 10.6–14.6 mm, MIC: 0.011 to 0.028 ± 0.000024 mg/ml	Ampicillin (dose: 0.03 mg/ml): Inhibition zone > 15 m ( <i>P. aeruginosa</i> and <i>P. mirabilis</i> ), MIC < 0.1 mg/ml Inhibition zone < 15 mm ( <i>S. aureus</i> , <i>K. pneumoniae</i> , <i>E. coli</i> , and <i>B. subtilis</i> ), MIC > 0.5 mg/ml	Chakraborty <i>et al.</i> , 2014

Continued

No	Tested substances	Part	Antimicrobial properties	Method	Tested microorganism	Results (using tested substances)	Comparison with positive control	References
17.	Ethanol extract	Rhizome	Antibacterial	Serial tube dilution technique	<i>E. coli</i> , <i>Enterobacter</i> sp., <i>P. aeruginosa</i> , <i>Proteus</i> sp., <i>Klebsiella</i> sp., <i>S. aureus</i> , and <i>Bacillus</i> sp.	Inhibition zone (dose: 0.025–0.2 mg/ml): 4–16 mm, MIC: 0.075–0.186 mg/ml	Not stated	Karuppiyah and Rajaram, 2012
18.	[6]-Gingerol	Not stated	Antibacterial	alamarBlue assay	<i>M. tuberculosis</i> strain H37Rv, multidrug-resistant MDR (JAL-2261), extensively drug-resistant XDR (MYC-431), and bacilli	Dose: 0.025 mg/ml MIC: H37Rv: 0.012 mg/ml MDR: 0.003 mg/ml XDR: 0.050 mg/ml Bacilli: 0.0015 mg/ml	Not stated	Bhaskar <i>et al.</i> , 2020
19.	Essential oil	Rhizome	Antibacterial	Disc diffusion	<i>S. aureus</i> , <i>Enterococcus faecalis</i> , and <i>E. coli</i>	Inhibition zone (dose: 0.01 mg/ml): 9.7–11.5 mm, MIC: 0.15–9.85 mg/ml	Not stated	Imane <i>et al.</i> , 2020

The characteristics of the included studies for the systematic review of the antimicrobial-related outcomes. The results were presented in mean  $\pm$  standard deviation (SD).

MIC: Minimum inhibition concentration; *n*: sample size.

**Table 3.** The quality assessment of the data included in the study.

Author	Risk of bias domain					Overall risk of bias
	Random sequence generation	Allocation concealment	Incomplete outcome data	Selective reporting	Other biases	
Abdul Qadir <i>et al.</i> , 2017	L	L	L	L	L	L
Babaeekhou and Ghane, 2020	L	L	L	L	L	L
Baldin <i>et al.</i> , 2019	L	L	L	L	L	L
Bhaskar <i>et al.</i> , 2020	L	L	L	L	L	U
Chakotiya <i>et al.</i> , 2017	L	L	L	L	L	L
Chakraborty <i>et al.</i> , 2014	L	L	L	L	L	U
Chang <i>et al.</i> , 2013	L	L	L	L	L	L
Hasan <i>et al.</i> , 2015	L	L	L	L	L	L
Imane <i>et al.</i> , 2020	L	L	L	L	L	L
Jacob <i>et al.</i> , 2019	L	L	U	L	L	U
Jain <i>et al.</i> , 2015	L	L	L	L	U	U
Karuppiyah and Rajaram, 2012	L	L	L	L	L	L
Revati <i>et al.</i> , 2015	L	L	L	L	L	L
Saleh <i>et al.</i> , 2018	L	L	L	L	L	L
Sharifzadeh <i>et al.</i> , 2016	L	L	L	L	L	L
Siddaraju and Dharmesh, 2007	L	L	L	L	L	L
Silva <i>et al.</i> , 2018	L	L	L	L	L	L
Snuossi <i>et al.</i> , 2016	L	L	L	L	L	L
Wang <i>et al.</i> , 2010	L	L	L	L	L	L

L = low risk, U = unclear, and H = high risk (Higgins and Green, 2011).

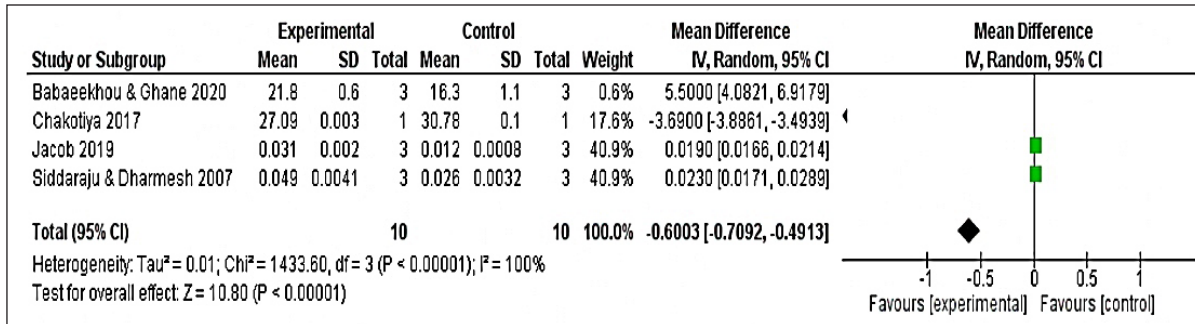


Figure 3. Qualitative and quantitative analysis of heterogeneity for “overall outcome” findings (CI: confidence interval).

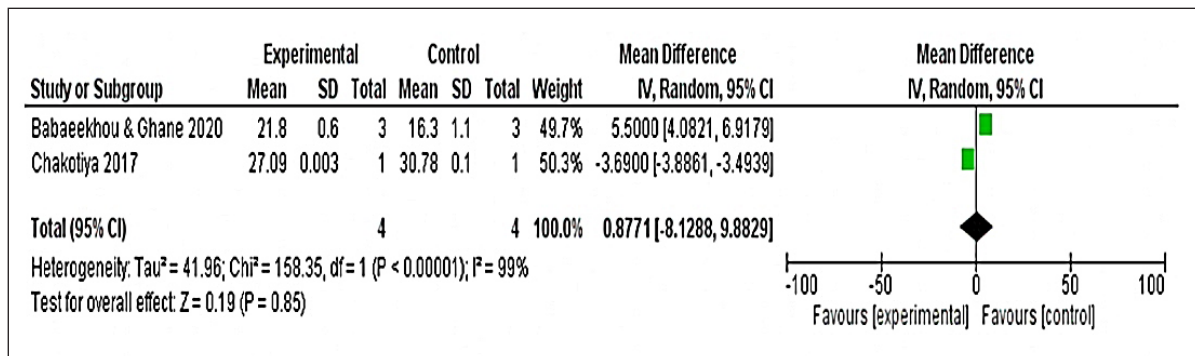


Figure 4. Qualitative and quantitative analysis of heterogeneity for “inhibition zone” findings (CI: confidence interval).

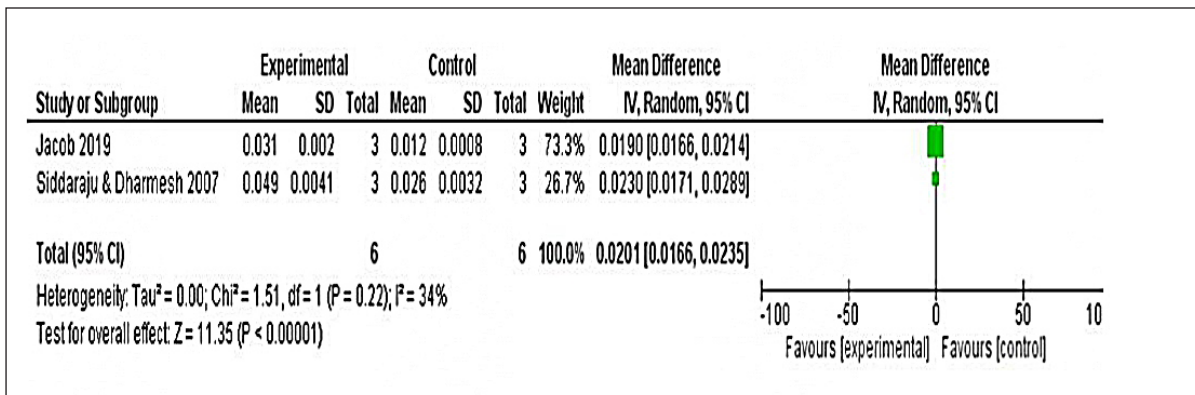


Figure 5. Qualitative and quantitative analysis of heterogeneity for “mean inhibitory concentration” findings (CI: confidence interval).

of some microorganisms such as *E. coli*, *P. multocida*, *S. aureus*, *K. pneumoniae*, *B. subtilis*, *P. aeruginosa*, and *P. mirabilis* (Abdul Qadir *et al.*, 2017; Chakraborty *et al.*, 2014).

The *Z. officinale* root essential oils exhibited effective inhibitors for pathogens (Silva *et al.*, 2018). Ginger essential oil (GEO) was effective against Gram-positive and Gram-negative bacteria. Essential oil at concentrations of 0.01 and 50 mg/ml inhibited the growth of both Gram-positive and Gram-negative bacteria with inhibition zones ranging from 6 to 22.33 mm (Imane *et al.*, 2020; Snuossi *et al.*, 2016). On the basis of the agar diffusion method, GEO (300 mg/ml) inhibited the growth of *S. aureus*, *Listeria monocytogenes*, *Salmonella typhimurium*, and *P. aeruginosa*. In addition, GEO also revealed antifungal activity by inhibiting *Penicillium citrinum*, *E. coli*, and *Penicillium chrysogenum* through broth dilution antifungal susceptibility

testing (Sharifzadeh *et al.*, 2016). Susceptibility testing of GEO against *Mycobacterium tuberculosis* and nontuberculous mycobacteria presented significant results at the concentration of 0.25 mg/ml with an MIC value of 0.25 mg/ml (Baldin *et al.*, 2019).

A finding by Chang *et al.* (2013) showed that the hot water extract of ginger was able to reduce the infection rate of the human respiratory syncytial virus (HRSV) by 50% at a dose of 0.3 mg/ml. Ginger nanofiber (GNF) is a product from the remains after ginger oil and oleoresins are extracted from the ginger. The research conducted by Jacob *et al.* (2019) stated that the bacterial susceptibility of GNF by the agar diffusion assay was 0.013 mg/ml against *Bacillus cereus*, 0.012 mg/ml against *E. coli*, 0.018 mg/ml against *S. aureus*, and 0.031 mg/ml against *S. typhimurium*. The phenolic extract also showed a significant antibacterial property against *S. aureus*, *K. pneumoniae*, *P. mirabilis*, *E. coli*,



**Table 4.** The meta-analysis of the effect of *Z. officinale* on antimicrobial activities.

Domain	Inc. trial	n	SMD (95% CI)	p value	Heterogeneity (% I <sup>2</sup> )	Pooled studies
<b>Antimicrobial outcomes</b>						
Overall outcomes	4	10	-0.6003 (-0.7092, -0.4913)	0.00001	100	Babaekhou and Ghane, 2020; Chakotiya <i>et al.</i> , 2017; Jacob <i>et al.</i> , 2019; and Siddaraju and Dharmesh, 2007.
Inhibition zone	2	4	0.8771 (-8.1288, 9.8829)	0.85	99	Babaekhou and Ghane, 2020 and Chakotiya <i>et al.</i> , 2017.
MIC	2	6	0.0201 (0.0166, 0.0235)	0.00001	34	Jacob <i>et al.</i> , 2019 and Siddaraju and Dharmesh, 2007.

The results were presented in mean  $\pm$  standard deviation (SD). The inhibition zone is in mm units, while the MICs in mg/ml units. "n" is the sample size.

and *Helicobacter pylori* on the basis of the agar well diffusion, agar diffusion, and conventional broth dilution methods. The dose of 0.05 mg/ml on the agar well produced inhibition zones ranging from 16 to 25 mm with MICs ranging from 1.59 to 2.2 mg/ml while the dose of 0.01 mg/ml in the conventional broth dilution and agar produced a 20 mm inhibition zone and an MIC value of 0.049 mg/ml (Saleh *et al.*, 2018; Siddaraju and Dharmesh, 2007).

The crude extract of ginger inhibits the growth of *S. mutans* at a dosage of 2 mg/ml with an inhibition zone of 7.65 mm. Meanwhile, the aqueous extract of ginger inhibits *S. mutans* at a similar concentration with an inhibition zone of 14.02 mm, which is higher than the crude extract. The finding showed that the aqueous extract of ginger is more effective than the crude extract in inhibiting the growth of *S. mutans* (Jain *et al.*, 2015). The ginger compounds ([6]-dehydrogingerdiol, [6]-shogaol, [10]-gingerol, and [6]-gingerol) derived from ginger display good antibacterial properties against extensively drug-resistant *Acinetobacter baumannii* when using the broth microdilution method (MIC value: 0.132–0.347 mg/ml) (Wang *et al.*, 2010). A further experiment was done on the basis of the alamarBlue assay to test gingerol against the *M. tuberculosis* drug-sensitive and drug-resistant clinical strains. Gingerol at a dose of 0.025 mg/ml inhibits the growth of the drug-sensitive and drug-resistant clinical strains of *M. tuberculosis* with MIC values ranging from 0.0015 to 0.05 mg/ml (Bhaskar *et al.*, 2020).

The concentrations of *Z. officinale* in previous papers included in this study were different with a range of 0.01 to 300 mg/ml. Variation in *Z. officinale* extract concentrations was also observed, which included four studies that used the methanol extract ranging from 0.03 to 100 mg/ml, six studies that used the ethanol extract ranging from 0.03 to 300 mg/ml, five studies that used the essential oil ranging from 0.01 to 300 mg/ml, and two studies that used acetone ranging from 0.03 to 100 mg/ml and two studies that used the crude extract ranging from 2 to 5 mg/ml. Additionally, the concentration of *Z. officinale* in some of the included studies was unclear. Hence, there is insufficient evidence to support the antimicrobial activity of *Z. officinale*. The SMD is used to measure the antimicrobial activities of *Z. officinale* across the included studies. SMD converts data from different scales to a common scale which causes the original information for each measurement of the included studies to be missing. However, the value of SMD is able to provide a significant level of the effect of *Z. officinale* when compared to the positive controls (Higgins and Green, 2011). The result of the meta-analysis for the mean

inhibitory concentration displays that the effects of the positive controls in the previous research selected in this study were more effective than the effects of the *Z. officinale* extract [SMD: 0.0201 (CI: 0.0166–0.0235),  $P = 34\%$ ]. However, the previous reports showed that *Z. officinale* were more effective than its selective positive control. These findings included in the study that used GNF showed an MIC value higher than that of ampicillin which were 0.031 and 0.012 mg/ml, respectively (Jacob *et al.*, 2019). Secondly, the study that used the methanol, n-hexane, and ethyl acetate extracts of ginger at a dose of 2 mg/ml presented higher inhibition zones than that of penicillin (40 mg/ml) (Babaekhou and Ghane, 2020). The other related study was conducted by Baldin *et al.* (2019) who demonstrated that GEO (0.25 mg/ml) has a higher MIC value than isoniazid and ciprofloxacin. The results might be because of insufficient relevant data from these studies to be included in the meta-analysis.

## CONCLUSION

In a nutshell, the overall findings revealed that the *Z. officinale* extracts and bioactive compounds have antimicrobial activities similar to the positive controls for antimicrobial analysis related to the overall outcome and inhibition zone [overall outcome SMD: -0.6003 (95% CI: -0.7092 to -0.4913),  $P = 100\%$ , inhibition zone SMD: 0.8771 (CI: -8.1288 to 9.8829),  $P = 99\%$ ]. However, the verification of the *Z. officinale* as an antimicrobial agent still needs further study with more available data from several other databases.

## LIST OF ABBREVIATIONS

*B. subtilis*: *Bacillus subtilis*; CI: Confidence interval; GEO: Ginger essential oil; GNF: Ginger nanofiber; *E. coli*: *Escherichia coli*; *K. pneumonia*: *Klebsiella pneumoniae*; *L. monocytogenes*: *Listeria monocytogenes*; MIC: Minimum inhibition concentration; *M. tuberculosis*: *Mycobacterium tuberculosis*; *P. aeruginosa*: *Pseudomonas aeruginosa*; *P. multocida*: *Pasteurella multocida*; *P. mirabilis*: *Proteus mirabilis*; *S. aureus*: *Staphylococcus aureus*; SMD: Standardized mean difference; *S. typhimurium*: *Salmonella typhimurium*; *Z. officinale*: *Zingiber officinale*

## CONFLICTS OF INTEREST

The authors declared no conflicts of interest.

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## AUTHOR CONTRIBUTIONS

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work. All the authors are eligible to be an author as per the international committee of medical journal editors (ICMJE) requirements/guidelines.

## ETHICAL APPROVALS

This study does not involve experiments on animals or human subjects.

## DATA AVAILABILITY

All data generated and analyzed are included within this research article.

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