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ANTIMICROBIAL ACTIVITY OF KERSEN (*Muntingia calabura* L.) LEAVES: A SYSTEMATIC REVIEW

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ABSTRACT

Background: Many kinds of antibiotics are being used for treating the infections, but bacterial resistance is a main therapeutic problem. Medicinal plants are one of sources of therapeutic aid for relieve human illness.

Muntingia Calabura is a medicinal plant that might have pharmacological value. *Muntingia Calabura*, is called throughout the world as "Jamaican cherry" and in Indonesia, it is known as "Kersen" or "Talok". This study aims to analyze the antimicrobial activity of *Muntingia calabura* leaves.

Methodology: This systematic review was conducted from December 2018 to February 2019 using PRISMA reporting guidelines. Literature has been retrieved from MEDLINE, Science Direct, Google Scholar, PubMed, Springer Link, and IEEE Xplore, use key words *Muntingia calabura*, phytochemical, pharmacological, and antimicrobial. The articles written by English.

Results: From 9 studies, the antibacterial test for *Muntingia calabura* leaves was carried out on 18 types of microorganisms. *Muntingia calabura* leaves proved to be effective against *S. aureus* and *P. aeruginosa* bacteria. 4 studies showed negative results use *Muntingia calabura* in certain types of bacteria.

Conclusion: Therefore, this plant can be used for treatment of bacteria. This study is also presented to help guide researchers to plan their future studies related to this plant for preventing the bacterial infection, especially in obstetrics and gynecology.

Keywords: *Muntingia calabura*, antimicrobial activity, pharmacological activities

INTRODUCTION

Every day in 2015, about 830 women died due to complications during pregnancy and childbirth. Of that amount, 550 occurred in sub-Saharan Africa and 180 in Southern Asia. Maternal mortality rate in developing country is higher than in developed country. One of the primary causes of maternal death is infections (1).

Infections may be caused by microorganisms such as bacteri (e.g. *Staphylococcus sp*, *Pseudomonas sp*, *Bacillus sp*, *Klebsiella sp*, *Escherichia sp*, etc), fungus (e.g. *Candida sp*, *Aspergillus sp*, *Microsporum sp*, etc), and virus (e.g. *human immunodeficiency virus*, *herpes*, *human papilloma virus*, etc). Many kinds of antibiotics are being used for treating the infections, but bacterial resistance is a main therapeutic problem. Infectious diseases continues to grow and causes of death globally (2).

The increased of antibiotic resistance has led to the reevaluation of the use of antibiotic agents in treatment, and recent solutions such as the use of medicinal plants (3). About 80% of people in the worldwide depend on the traditional medicine for their basic healthcare. Most are in developing

countries, which situated in biodiversity hotspots in Southeast Asia, Africa, Central and Southern America. Medicinal plants are sources of therapeutic aid for relieve human illness (4).

There are a large number of medicinal plants have investigated for their possible pharmacological value. One of the plants that has recently obtained a medical plant status is *Muntingia Calabura*. *Muntingia Calabura*, is called throughout the world as “Jamaican cherry” and in Indonesia is known as “Kersen” or “Talok” (5). *Muntingia Calabura* has pharmacological activities such as antioxidant, antipyretic, antihypertensi, anti-inflammatory, antidiabetic, and antibacterial (4).

Botanical information

Muntingia Calabura is a fast-growing tree, often growing as roadside trees. The height is about 7.5-12 m and the branches spreading horizontally. The leaves are approximately 5-12.5 cm long, alternate lanceolate, long pointed at the peak, with dark green color and irregularly toothed. The flowers are along 1.25-2 cm wide, with white petals and yellow stamens. The fruits are round, approximately 1-1.25 cm wide, with red or yellow color and very sweet taste (4).

Phytochemical constituents

Muntingia Calabura has been reported to have antiproliferative, antioxidant, antinociceptive, cardioprotective and antipyretic activities (2). Ethanol extract of *Muntingia Calabura* leaves contain sterols, flavonoids, alkaloids, saponins, glycosides, and tannins. The bark, roots, and leaves contains many types of flavonoid. A study indicated the presence of flavonoids in the leaves is typically involved in antimicrobial activities (6).

METHODS

Search Strategy

This systematic review was conducted from December 2018 to February 2019 using PRISMA reporting guidelines. According to these guidelines, there are several steps in this study: 1) defining eligibility criteria; 2) defining information sources; 3) study selection; 4) data collection process; and 5) data item selection (7). Figure 1 explains the steps of our work in conducting systematic review.

We conducted searches of online databases with large repositories of academic studies, including MEDLINE, Science Direct, Google Scholar, PubMed, Springer Link, and IEEE Xplore. We eliminated articles that could not be fully accessed by the authors.

The selected databases provided a total of 736 studies written in English from 2009 to 2019, matched with the keywords that needed to be analyzed. Next, those articles were screened on the basis of title, abstract, and keywords; the remaining 36 articles were then reviewed on the basis of their full text. A total of 700 articles were discarded due to IC2 (most of those articles discussed antioxidant, antinociceptive, antiinflammation activity of *Muntingia Calabura*). In addition, we eliminated 27 articles that could not be fully accessed by the authors. Finally, a total of 9 articles were selected in the review without additional articles resulting from the scanning of the reference lists.

Criteria for Inclusion and Exclusion

The following inclusion criteria (IC) were defined :

IC1 : The research is written in English; and

IC2 : Research aimed to identification the antimicrobial activity of *Muntingia Calabura* leaves.

And the exclusion criteria (EC) was defined :

EC : The research is systematic review.

Only articles written in English (IC1) were selected, because English is international language. IC2 was included to answer the research questions. The researches were selected is experimental, then the systematic review was excluded.

Search Result

The study selection was conducted from the search result in the following four phases:

1. The keyword search, or search string, was chosen according to our research interest in antibacterial activity of *Muntingia Calabura* leaves.
2. Exploration and selection of title, abstract, and keywords of identified articles were conducted based on eligibility criteria.
3. A complete or partial reading of the articles not eliminated in the previous phases was conducted to determine whether they should be included in the review, in accordance with the eligibility criteria.

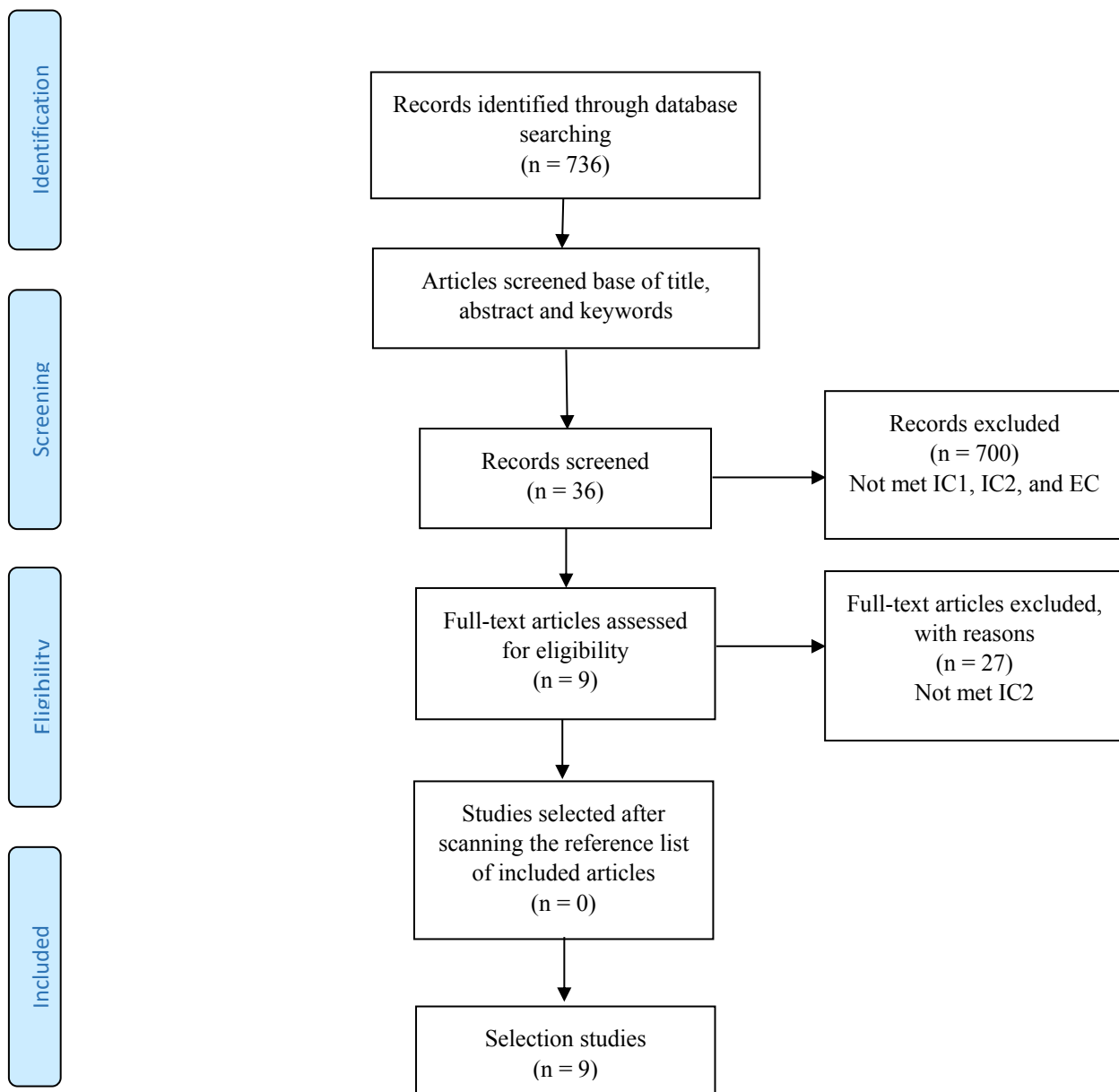


Figure 1. PRISMA Flow Diagram

RESULTS

A total of 9 articles were included in this systematic review. All articles are experimental studies and discuss the antimicrobial effects of *Muntingia Calabura* leaf extract. Leaf extract used in most articles was obtained by maceration method, but with different solvents. Only one article uses nanoparticles. Most of the antibacterial tests were carried out by the diffusion method of seven articles, while the other two articles used the dilution method. Selected articles are shown in Table 1.

Table 1. Summaries of Selected Study

Authors	Title	Variables	Result
Pranay P, Siddhartha M, Thirupathaiiah. 2014.	Green Synthesis And Antibacterial Activity Of Silver Nanoparticles From Leaf Extract Of <i>Muntingia Calabura</i>	<i>S. basillus</i> , <i>S. aureus</i> , and <i>Pseudimonas aureginosa</i>	The diameter of inhibition zones around the disk containing silver nanoparticles in <i>S. basillus</i> , <i>S. aureus</i> , and <i>Pseudimonas aureginosa</i> bacterial suspension are 9 mm, 11 mm, 10 mm respectively. This test shows that silver nanoparticles are nearly 70%, 85% and 60% effective compare to Kanamycin and Arithromycin respectively
Krishnaveni M, Banu C.R, Kalaivani M, Krishnakumari G. 2015	Gc-Ms/Ms Analysis Of Phytochemicals In <i>Muntingia Calabura</i> L, Antimicrobial Assay	<i>Escherichia coli</i> , <i>Staphylococcus aureus</i> and the fungi used were <i>Aspergillus niger</i> , <i>Candida albicans</i> .	The extract of <i>Muntingia calabura</i> leaf was found to act against fungi rather than bacteria. The zone of inhibition observed was 8mm for <i>Staphylococcus aureus</i> while no zone was observed for <i>Escherichia coli</i> . The zone of inhibition observed with fungi was 15mm for <i>Aspergillus niger</i> , 12mm for <i>Candida albicans</i> .
Vasanth M, Selvaraju S, Muralidharan R, Rajarajan R. 2017	Antimicrobial Activity Of <i>Muntingia Calabura</i> L	Microorganism tested in the study was <i>Escherichia coli</i> .	<i>M. calabura</i> leaves may be a potential alternative source of antibacterial agents against <i>E. coli</i>
Zakaria Z.A, Sufian A.S, Ramasamy K, Ahmat N, Sulaiman M.R, Arifah A.K, Zuraini A, Somchit M.N. 2010	In Vitro Antimicrobial Activity Of <i>Muntingia Calabura</i> Extracts And Fractions	<i>S. aureus</i> ATCC 25923, <i>S. aureus</i> ATCC 33591 (A multi-drugs resistant <i>S. aureus</i> (MRSA) isolate), <i>Esherichia coli</i> ATCC 10536, <i>Pseudomonas aeruginosa</i> ATCC 27853, <i>Candida albicans</i> ATCC 10231 and <i>Microsporium canis</i> ATCC 36299.	Antimicrobial screening of <i>M. calabura</i> showed that the aqueous and chloroform extracts did not give significant inhibitory effects against all test microorganisms since the MIC/MBC values were > 5000 µg/ml. However, the methanol extract gave moderate inhibitory effect against <i>S. aureus</i> 25923 and <i>S. aureus</i> 33591 with the MIC/MBC value 1250 and 2500 µg/ml respectively. None of the crude extracts were effective against the test fungi tested, <i>C. albicans</i> and <i>M. canis</i> .
Boopathi T, Gopalasatheeskumar K, Parthiban S, Sangeetha G, Kokila M.T, Manimaran T. 2017	Evaluation Of Antimicrobial Activity Of Tecoma Stans And <i>Muntingia Calabura</i>	Gram-positive bacteria (<i>Staphylococcus aureus</i> , <i>Streptomyces filvissimus</i> , <i>Basillus subtilis</i>) and Gram-negative bacteria (<i>Escherichia coli</i> , <i>Pseudomonas aeruginosa</i> , <i>Klebsiella pneumonia</i> , <i>proteus mirabilis</i> , <i>shigella flexneri</i>) and two fungal	<i>Muntingia calabura</i> leaf extract also showed appreciable activity on all test bacteria (08-18mm inhibition zone) except <i>Candida albicans</i> fungal strain. It did not inhibit <i>Candida albicans</i> fungal strain

			strains (<i>Aspergillus niger</i> & <i>Candida albicans</i>)	
Sekar M, Jalil N.S.A. 2017	Formulation And Evaluation Of Novel Antibacterial And Anti-Inflammatory Cream Containing <i>Muntingia Calabura</i> Leaves Extrac		Gram-positive bacteria (<i>Staphylococcus aureus</i> and <i>Bacillus cereus</i>) and Gram-negative bacteria (<i>Escherichia coli</i> and <i>Pseudomonas aeruginosa</i>)	The potential antibacterial activity of the methanolic extract of <i>M. calabura</i> leaves together with the formulated cream was determined using disc diffusion method against the pathogen of <i>S. aureus</i> , <i>B. cereus</i> , <i>E. coli</i> , and <i>P. aeruginosa</i> . From the result, the antibacterial activity of the extract shows a greater zone of inhibition toward Gram-negative bacteria compares to Gram-positive
Sufian A.S, Ramasamy K, Ahmat N, Zakaria Z.A, Izwan M, Yusof M. 2012	Isolation And Indentification Of Antebacterial And Cytotoxic Compounds From The Leaves Of <i>Muntingia Calabura</i> L		The Gram-negative bacterial strains; <i>Pseudomonas aeruginosa</i> (ATCC 27853) and <i>Esherichia coli</i> (ATCC 10536) and Gram-positive bacterial strains; methicillin-sensitive <i>Staphylococcus aureus</i> (MSSA, ATCC25923), methicillin-resistant <i>Staphylococcus aureus</i> (MRSA, ATCC33591), <i>Bacillus cereus</i> (ATCC 11778) and <i>Bacillus subtilis</i> (ATCC 6633)	Pure compounds isolated from the leaves of <i>Muntingia calabura</i> L. exhibited higher antibacterial and cytotoxic activities than the crude extract. This behavior might be due to synergism between compounds present in the extract. As a conclusion, the antibacterial activity of <i>Muntingia calabura</i> L. leaves against MSSA and MRSA is as cribable to the active compound 2 with MIC value of 50 and 100 mg/mL, respectively.
Buhian W.P.C, Rubio R.O, Valle D.L, Puzon J.J.M. 2016	Bioactive Metabolite Profiles And Antimicrobial Activity Of Ethanolic Extracts From <i>Muntingia Calabura</i> L. Leaves And Stems		<i>E. coli</i> , <i>S. typhimurium</i> , <i>P. aeruginosa</i> , <i>S. aureus</i> , <i>B. subtilis</i> (bacteria) and <i>C. albicans</i> (fungus).	<i>M. calabura</i> leaf and stem ethanol extracts are potential sources of antibacterial agents against <i>P. aeruginosa</i> and <i>S. aureus</i> . This study reports for the first time the high degree of antifungal activity of <i>M. calabura</i> ethanolic extract, especially against <i>C. albicans</i> .
Sibi G, Naveen R, Dhananjaya K, Ravikumar K.R, Mallesha H. 2012	Potential Use Of <i>Muntingia Calabura</i> L. Extracts Against Human And Plant Pathogens		<i>Bacillus cereus</i> , <i>Klebsiella pneumoniae</i> , <i>Micrococcus luteus</i> , <i>Proteus vulgaris</i> , <i>Pseudomonas aeruginosa</i> , <i>Serratia marcescens</i> , <i>Aspergillus oryzae</i> , <i>Fusarium sp</i> and <i>Penicillium sp</i>	Aqueous leaf extract has exhibited inhibitory activity against <i>M. luteus</i> and <i>P. aeruginosa</i> and bark extract with the addition of <i>B. cereus</i> . Methanolic extracts of the plant were able to control the growth of <i>B. cereus</i> and <i>M. luteus</i> . antifungal activity of methanolic extracts was recorded against <i>Fusarium</i> and <i>Penicillium</i>

Antibacterial Activity of *Muntingia Calabura* Leaves

This section describe the antibacterial activity of *Muntingia Calabura* leaves in every microorganisms that have tested in the study. Each selected study is given a number 1-9 in accordance with the order in Table 1. The sign (+) indicates that the extract of *Muntingia Calabura* shows the antimicrobial effect of the tested microorganisms. While, the sign (-) shows that *Muntingia Calabura* leaf extract does not show antimicrobial effects. The total column shows the number of bacteria that can be inhibited and bacteria that cannot be inhibited by the extract of *Muntingia Calabura* leaves. The most widely used microorganism for the antibacterial test is *S. aureus*. The most anti-bacterial activity found in *S. aureus*, then followed by *P. aureginosa*, *E. coli*, *Candida albicans*, *B. subtilis*, and other microorganisms. This

shows that *Muntingia calabura* is most effective against bacteria *S. aureus*. The antibacterial activity are shown in Table 2.

Table 2. Antibacterial Activity of *Muntingia Calabura*

Microorganisms	Study Tested									Total	
	1	2	3	4	5	6	7	8	9	+	-
<i>S. Bacillus</i>	+									1	0
<i>S. Aureus</i>	+	+		+	+	+	+	+		7	0
<i>P. Aeruginosa</i>	+				+	+	+	+	+	6	0
<i>E. Coli</i>		-	+	-	+	+		+		4	2
<i>Aspergillus Niger</i>		+			+					2	0
<i>Candida Albicans</i>		+		-	-		+	+		3	2
<i>Microsparum Canis</i>				-						0	1
<i>Streptomyces Fulvissimis</i>					+					1	0
<i>B. Subtilis</i>					+		+	+		3	0
<i>Klebsiella Pneumoniae</i>					+				-	1	1
<i>Shigella Flexnery</i>					+					1	0
<i>Proteus Mirabilis</i>					+					1	0
<i>B. Cereus</i>						+			+	2	0
<i>T. Mentagrohytes</i>							+			1	0
<i>S. Typhimurium</i>								+		1	0
<i>Micrococcus Luteus</i>									+	1	0
<i>Proteus Vulgaris</i>									-	0	1
<i>Serratia Marcescens</i>									-	0	1

DISCUSSION

The first attempt to study the antibacterial activity of *M. calabura* was carried out by Thirupathaiyah et al. (2014) using the silver nanoparticles from leaves extract. The silver nanoparticles against *S. basillus*, *S. aureus*, and *Pseudimonas aeruginosa* bacterial suspension with diameter inhibition zone 9 mm, 11 mm, 10 mm respectively. This test shows that silver nanoparticles are nearly 70%, 85% and 60% effective compare to Kanamycin and Arithromycin respectively. It is observed that the presence of silver nanoparticles inhibited bacterial growth by more than 97% (8).

This research was followed by another antibacterial activity report by Krishnaveni et al. (2015), who studied GC-MS/MS analysis for phytochemicals and antimicrobial activities of *Muntingia calabura* leaves extract. The extract of *Muntingia calabura* leaf was found to act against fungi rather than bacteria. The zone of inhibition observed was 8mm for *Staphylococcus aureus* while no zone was observed for *Escherichia coli*. The zone of inhibition observed with fungi was 15mm for *Aspergillus niger*, 12mm for *Candida albicans*. This property might be attributed due to the presence of phytochemicals present in the *Muntingia calabura* leaf that showed the highest peak area for Propane, 1, 1-diethoxy- compared to other 11 compounds identified (8).

Another study determined the in vitro antimicrobial activity of various solvent extracts of *Muntingia calabura L.* leaves against selected microorganism. It was observed that Ethyl acetate crude extract of 30 µL showed maximum inhibitory activity against *Escherichia coli*. Similarly, the minimum inhibitory activity showed in aqueous crude extract about 10 µL concentration. Findings by Zakaria et al., have demonstrated the presence of flavonoids, triterpenes, saponins steroids and tannins in *M. calabura* leaves. The ability of tannins to form chelates with metal ions, particularly iron, which lead to the disruption of the *S. aureus* membrane, could be one of the possible factors that contribute to its antimicrobial activity (9).

Research conducted by Zakaria et al. (2010) determined the in vitro antimicrobial activity of various extracts, partitions and fractions of *Muntingia calabura* (*Elaeocarpaceae*) leaves against a selected panel of microorganisms. The methanol extract gave moderate inhibitory effect against *S. aureus* 25923 and *S. aureus* 33591 with the MIC/MBC value 1250 and 2500 µg/ml respectively. The presence of flavonoids, triterpenes, saponins steroids and tannins in *M. calabura* leaves bind the bacteria's structural membrane proteins called porines, causing changes in the tridimensional conformation exposing the hydrophilic character of the pore, which lead to an easier passage of other polar bioactive compounds via diffusion. The ability of tannins to form chelates with metal ions, particularly iron, which lead to the disruption of the *S. aureus* membrane, could be one of the possible factors that contribute to its antimicrobial activity (10).

Boopathi et al. (2017) examined the antibacterial activity of *Muntingia calabura* leaves with ethanolic extract. The antimicrobial activity of the extracts were studied in different concentrations against gram-positive (*Staphylococcus aureus*, *Streptomyces filvissimus*, *Bacillus subtilis*) and gram-negative (*Escherichia coli*, *Pseudomonas aeruginosa*, *Klebsiella pneumonia*, *Proteus mirabilis*, *Shigella flexneri*) and fungal strains (*Aspergillus niger* & *Candida albicans*). *Muntingia calabura* leaf extract also showed appreciable activity on all test bacteria (08-18mm inhibition zone) except *Candida albicans* fungal strain. The petroleum ether extract of *Muntingia calabura* contained fixed oil, steroids and tannins. While the ethanolic extract showed the presence of carbohydrates, glycosides, tannins, flavonoids, steroids, saponins and terpenoids. These compounds may isolated microorganism and fungi, as compare with standard drugs. The activities of these extracts are found to be quiet comparable with the standard antibiotics screened under similar conditions. So these extracts can be used as an external antiseptic in prevention and treatment of bacterial infections (5).

Moreover a study reported by Sekar and Jalil (2017), who tried to formulating *Muntingia calabura* leaves extract as antimicrobial and anti-inflammatory cream. The antibacterial activity of the extract and formulated cream in different concentration was investigated against two Gram-positive bacteria (*Staphylococcus aureus* and *Bacillus cereus*) and two Gram-negative bacteria (*Escherichia coli* and *Pseudomonas aeruginosa*) through disc diffusion method. The antibacterial activity of the methanolic extract was studied in different concentrations (5, 10, and 25 mg/ml) and the formulated cream was studied in the concentration of (10, 25, 50, and 100 mg/ml). The result showed that the formulated cream can be used for bacterial infections (3).

Sufian et.al (2013) tried to isolation and identification of antimicrobial and cytotoxic compounds from the leaves of *Muntingia Calabura L.* Antimicrobial and cytotoxic activities were determined by micro-broth dilution and MIT assays, respectively. Flavones and a chalcone were isolated from the active EtOAc extract using bioassay-guided screening. The compounds were further tested for their antibacterial and cytotoxic activities. In the result, pure compounds isolated from the leaves of *Muntingia calabura L.* showed exhibited higher antibacterial and cytotoxic activities than the crude extract (11).

Other study tried to determine the bioactive phytochemicals and antimicrobial activity of leaf and stem ethanolic extracts from *Muntingia calabura L. (M. calabura)*. Phytochemical screening revealed the presence of sterols, flavonoids, alkaloids, saponins, glycosides and tannins in the leaf extract. *M. calabura* leaf and stem ethanol extracts are potential sources of antibacterial agents against *P. aeruginosa* and *S. aureus*. This study reports for the first time the high degree of antifungal activity of *M. calabura* ethanolic extract, especially against *C. albicans* (6).

The last study were carried out to determine the phytochemical and antimicrobial properties of various parts of *Muntingia calabura* Aqueous and methanol extracts of leaf, bark and fruits were prepared and phytochemical analysis of the parts revealed the presence of glycosides and flavonoids as the major biologically active compounds. The presence of glycosides, tannins and flavonoids has influenced the antimicrobial properties of the plant especially against *M. luteus* and *P. aeruginosa* (2).

From several studies that also tested the content of compounds found in *Muntingia calabura* leaves, all studies showed that *Muntingia calabura* leaves had flavonoids. Flavonoids can act as antibacterial. Each study uses several types of bacteria. The most widely used bacteria is *S. Aureus*. The results of antimicrobial tests in each study showed several similarities and differences.

The same results were obtained from testing of *S. aureus*, *P. aeruginosa*, *Aspergillus niger*, *B. subtilis*, and *B. cereus*. In each study using these bacteria, all tests showed positive antimicrobial effects. While in testing *E. coli*, *Candida albicans*, and *Klebsiella pneumoniae* showed different results in several studies. On testing *E. coli*, from 6 existing studies, 4 studies showed positive antimicrobial effects and 2 studies showed negative antimicrobial effects. In *Candida albicans* testing, out of 5 studies, 3 studies showed positive antimicrobial effects and 2 studies showed negative antimicrobial effects. Whereas in the *Klebsiella pneumoniae* test, of the two existing studies, a study showed positive antimicrobial effects and other study showed negative antimicrobial effects.

CONCLUSION

From 9 studies, antibacterial test for *Muntingia calabura* leaves was carried out on 18 types of microorganisms. This study shows that *Muntingia calabura* leaves proved to be effective against *S. aureus* and *P. aeruginosa* bacteria. The broad antimicrobial activity suggest the use of *Muntingia calabura* as a source of new bioactive principles for the development of drugs against human and plant pathogens. Therefore, this review paper is presented to help guide researchers to plan their future studies related to this plant for preventing the infectious diseases especially in obstetric and gynecology.

DECLARATION OF INTEREST

The authors declare that they have no potential conflicts of interest.

REFERENCES

1. Engin-Üstün Y, Sanisoğlu S, Keskin HL, Karaahmetoğlu S, Özcan A, Çelen Ş, et al. Changing trends in the Turkish maternal deaths, with a focus on direct and indirect causes. *Eur J Obstet Gynecol Reprod Biol.* 2019;234:21–5.
2. Mallesha H, Sibi G, Naveen R, Dhananjaya K, Ravikumar KR. Potential use of *Muntingia calabura* L. extracts against human and plant pathogens. *Pharmacogn J.* 2013;4(34):44–7. Available from: <http://dx.doi.org/10.5530/pj.2012.34.8>
3. Sekar M, Abdul Jalil NS. Formulation and Evaluation of Novel Antibacterial and Anti-Inflammatory Cream Containing *Muntingia Calabura* Leaves Extract. *Asian J Pharm Clin Res.* 2017;10(12):376.
4. Nasir NLM, Mahmood ND, Rofiee MS, Teh LK, Zakaria ZA, Tohid SFM, et al. *Muntingia calabura* : A review of its traditional uses, chemical properties, and pharmacological observations . *Pharm Biol.* 2014;52(12):1598–623.
5. Boopathi T, Gopalasatheeskumar K, Parthiban S, Sangeetha G, Thanga Kokila M, Manimaran T. Evaluation of Antimicrobial Activity of *Tecoma Stans* and *Muntingia Calabura*. *World J Pharm Res World J Pharm Res SJIF Impact Factor Res Artic ISSN.* 2017;6523(3):617–27.
6. Buhian WPC, Rubio RO, Valle DL, Martin-Puzon JJ. Bioactive metabolite profiles and antimicrobial activity of ethanolic extracts from *Muntingia calabura* L. leaves and stems. *Asian Pac J Trop Biomed [Internet].* 2016;6(8):682–5. Available from: <http://dx.doi.org/10.1016/j.apjtb.2016.06.006>
7. Penelitian dan Pengembangan Sistem dan Kebijakan Kesehatan P, Litbang Kesehatan B, Kesehatan Pusat Penelitian dan Pengembangan Sistem dan Kebijakan Kesehatan K, Kesehatan Korespondensi K. Systematic Review Sebagai Metode Penelitian Untuk Mensintesis Hasil-Hasil Penelitian (Sebuah Pengantar) Siswanto I. (II) (Research and Development of P Health Systems and Policy, Health Research and Development B, Health Center for Research and Development of Health Systems and Policy K, Health Correspondence K. Systematic Review as a Research Method for Synthesizing Research Results (An Introduction) Siswanto I. (II))
8. Jose B, Jesy EJ, Nedumpara RJ. World Journal of Pharmaceutical ReseaRch SEED EXTRACTS. *World J Pharm Res.* 2014;3(3):5041–8.
9. Vasanth M. Antimicrobial Activity of *Muntingia Calabura* L. *World J Pharm Res.* 2017;6(11):663–7.
10. Z. A. Zakaria1*, A. S. Sufian2, K. Ramasamy2, N. Ahmat3, M. R. Sulaiman1, A. K. Arifah4 a. Z and MNS. In vitro antimicrobial activity of *Muntingia calabura* extracts and fractions. *African J Microbiol Res.* 2010;4(4):304–8.
11. Sufian AS, Ramasamy K, Ahmat N, Zakaria ZA, Yusof MIM. Isolation and identification of antibacterial and cytotoxic compounds from the leaves of *Muntingia calabura* L. *J Ethnopharmacol [Internet].* 2013;146(1):198–204. Available from: <http://dx.doi.org/10.1016/j.jep.2012.12.032>