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INDONESIAN HERBS WITH ANTIFERTILITY EFFECTS ON MEN: A SYSTEMATIC REVIEW

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ABSTRACT

Background: The attention and implementation of family planning programs in Indonesia tends to focus on women. Meanwhile, male contraception method has fewer types than female ones. Various herbs in Indonesia have showed potential antifertility effects on men. The objectives of this study is to identify and analyze the results of studies on the effects of Indonesian herbs on male antifertility.

Methods: This was a systematic review using several articles obtained from Science Direct, PubMed, Wiley Online Library, Google Scholar, and Garba Rujukan Digital databases. The inclusion criteria in this study were experimental research of the effects of herbs on antifertility; samples of studies included male mice, long-tailed male monkeys, and human sperm; and full-text article available.

Results: The literature search returned 1420 articles, of which 37 studies were included in the systematic review. Different Indonesian herbs were observed, such as *Carica papaya* ($n = 8$), *Momordica charantia* ($n = 7$), *Piper betle* ($n = 5$), *Hibiscus rosa* ($n = 5$), *Curcuma domestica* ($n = 4$), *Areca catechu* ($n = 4$), and *Andrographis paniculata* ($n = 4$) have been identify with different effects. Antifertility effects observed including antispermatogenic, sperm quality reduction, and the changing of the histology of reproductive organs.

Conclusions: Indonesian herbs are portentially used as new contraceptive methods for male subjects such as *Carica papaya*, *Momordica charantia*, *Piper betle*, *Hibiscus rosa*, *Curcuma domestica*, *Areca catechu*, and *Andrographic paniculata*. Further research is needed regarding the effects of herbs on human subjects, reversibility effects, and the safety of herbs on health in a long-term use.

Keywords: male antifertility, herbs, systematic review

INTRODUCTION

Based on the Ministry of Health and Information Center data in 2017, the population in Indonesia were 261,890,872 people that divided into 131,579,184 male populations and 130,311,688 female populations. Population growth in Indonesia by 2017 were 3.19 million per year [1].

High population growth will result an increase in population density lead to uneven effects of welfare, such as increasing poverty due to decreasing employment opportunities and decreasing community health status. One of the efforts made by the Government to regulate the rate of population growth in Indonesia is the establishment of a family planning program [2,3].

The Family Planning Program is an effort made to regulate the birth of children, both the number or the distance between births of children to create a good quality family and achieve physical and spiritual well-being. The target of implementing a family planning program in Indonesia is fertile age couples who are bound by a legal marriage [1]. The family planning program is also one of the strategies to reduce maternal mortality especially with 4 conditions, such as too young to giving birth, too often giving birth, too close of birth distance or space, and too old to giving birth [1].

Since the family planning program has been established until now, the attention and implementation of the program in Indonesia tends to be more focused on women. This creates a stigma

in the community that family planning is a matter and responsibility of women. In addition, compared to female contraceptive methods, male contraceptive methods have fewer types and relatively rarely used [4].

Until now, the available modern male contraceptive methods are vasectomy and condom. While the traditional male contraceptive method is interrupted intercourse. Globally, the rate of vasectomy and condom use is 8.9% of total contraceptive use. Based on a survey conducted by the National Population and Family Planning Agency in 2017, the rate of vasectomy use was 0.53%, condom use was 1.22%, and interrupted intercourse was 1.32%. This showed that men's participation in contraceptive use was still very low [1,5].

The use of condom and interrupted intercourse cause perceptions of psychological problems such as reducing sexual pleasure. The use of vasectomy cause perceptions of side effects and impotence problem make the participation of men in family planning programs to be very limited [2,4].

However, research shows that nearly 80% of men believe that contraception was a shared responsibility and 50% of men were interested in using alternative male contraceptive aside vasectomy and condoms. This survey showed that there was unmet need among men who wanted to use alternative contraceptive methods aside vasectomy and condom but no other alternative contraceptive methods that have been established [5].

The World Health Organization established a Task Force program to examine the potential of traditional herbs or plants to develop traditional herbs as an alternative and new method of contraception to control birth rates. Traditional herbs that have antifertility effects must be safe, effective, reversible, do not interfere with sexual activity, and can be accepted by the community [6,7].

Indonesia is a tropical country that has a high level of biodiversity in all its regions. This high biodiversity makes Indonesia have various types of plants that have potential as traditional herbs medicine. Herbs can be used as an alternative treatment and prevention of various diseases or certain health conditions with minimum side effects and prevent side effects from pharmacological drugs. Various herbs in Indonesia have also been shown to have the potential antifertility effects in men [7-9].

The purpose of this study is to identify and analyze the results of research on herbal plant species in Indonesia that have antifertility effects on men. This study expected to produce information that can be scientifically accountable so it can be developed and applied as a policy toward men contraceptive methods.

METHODS

Search Strategy

The source of data in this study conducted from Science Direct, PubMed, Wiley Online Library, Google Scholar, and Garba Rujukan Digital databases. Only articles that contain full text included in this study. The search was carried out by entering the first keywords, "antifertility" and "contraception", then the second keyword, "herbal" and "plant". There is no year limitation in searching articles for this study.

Inclusion and Exclusion Criteria

The inclusion criteria in this study were articles that examined the effects of herbal plants on antifertility; samples in male mice, long-tailed male monkeys, and human sperm; and experimental research. The exclusion criteria in this study were articles that did not examine the effects of herbs on antifertility; the samples were female mice, female long-tailed monkeys; not experimental research; undergraduate or postgraduate thesis

Data Extraction

The searching of articles was carried out from January 26, 2019 to February 12, 2019. The author carried out extraction of articles that had been obtained by noting in the screening form. In the screening form, the articles were screened and analyzed by the title and abstract to classify the articles according to the type of each intervention, to find out the suitability of the research articles from inclusion and exclusion criteria, and detect of article duplication. The results of the extraction of research articles are written in the form of tables containing the article title, author's name, year, sample, and intervention.

Search Results

A total 1420 articles collected from the Science Direct, PubMed, Wiley Online Library, Google Scholar and Garba Rujukan Digital databases after entering the first and second keywords. From 1420 articles, there are 621 articles which are not full text article which leaving remaining 799 relevant articles for screening.

After a review, there were 762 research articles that did not comply with the inclusion criteria, such as the article did not examine the effect of herbal plants on antifertility (n = 4), sample did not fit the criteria (n = 529), non-experimental research (n = 82), undergraduate thesis or thesis article (n = 56), not appropriate outcome (n = 42), and duplicate articles (n = 49). After further review, 37 research articles were included in the analysis of this study.

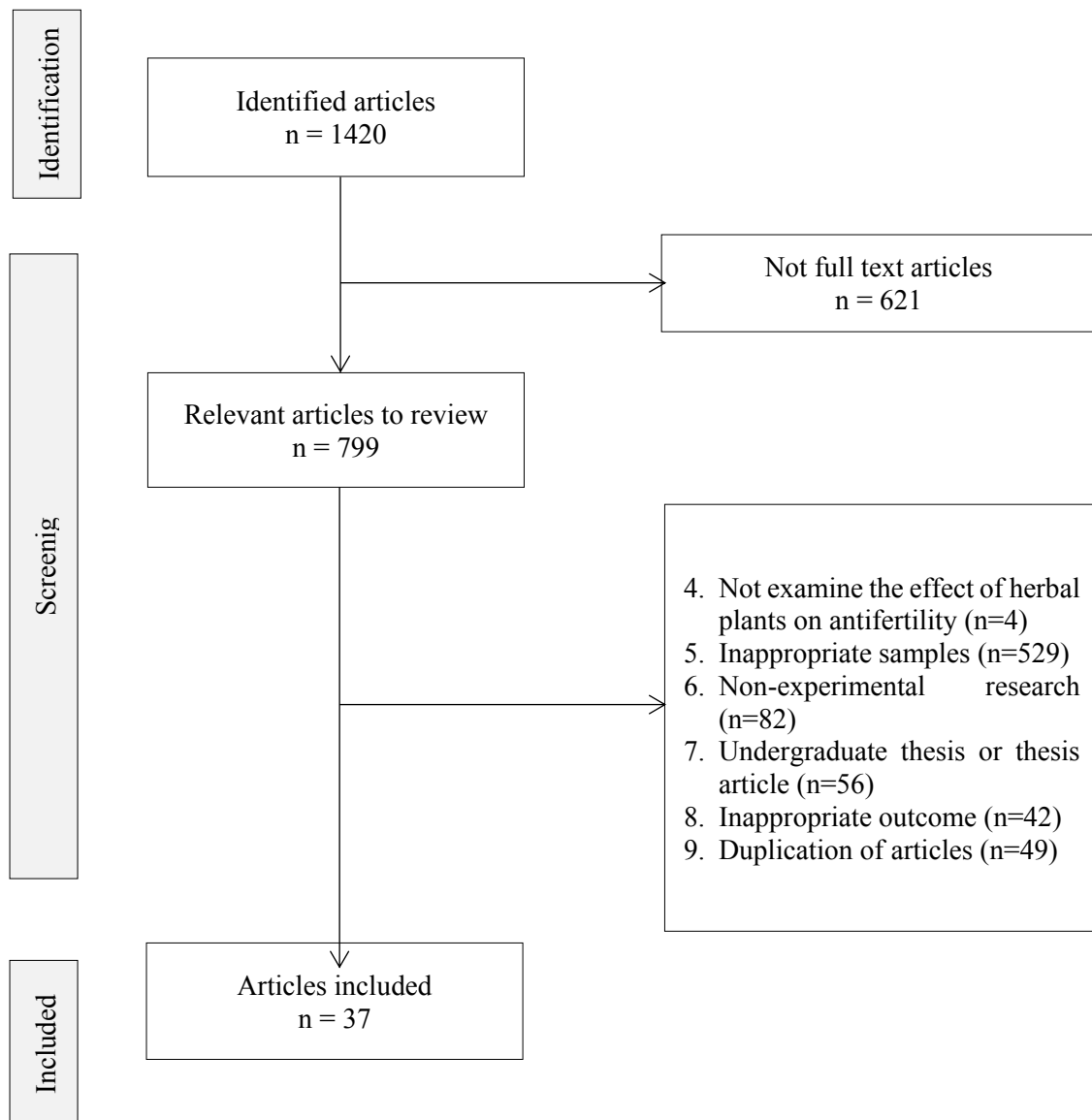


Figure 1. Search results and selection of articles

RESULTS

There are 37 articles included in the analysis of this study. The articles were divided based on specific Indonesian herbs or plants, such as papaya seeds (*Carica papaya*, $n = 8$), bitter melon (*Momordica charantia*, $n = 7$), betel leaf (*Piper betle*, $n = 5$), hibiscus (*Hibiscus rosa*, $n = 5$), turmeric (*Curcuma domestica*, $n = 4$), betel nut (*Areca catechu*, $n = 4$), and sambiloto leaf (*Andrographis paniculata*, $n = 4$).

The total sample in this research article was 946 samples which consist of 919 mice (*Mus musculus*, *Spargue Dawney*), 8 long-tailed monkeys (*Macaca fascicularis*), and 19 human sperm. The number of samples used in research articles varies from 8 to 80 samples. From 37 articles, the mice samples were found in 33 articles on papaya seeds ($n = 7$), bitter melon ($n = 7$), betel leaf ($n = 5$), hibiscus ($n = 5$), turmeric ($n = 2$), betel nut ($n = 3$), and sambiloto leaf ($n = 4$); the long-tailed monkey samples were found in 1 article about papaya seeds; and the human sperm samples were found in 3 articles about turmeric ($n = 2$) and betel nut ($n = 1$).

The intervention in the articles were given by using orally herbs extract ($n = 32$) for the administration of papaya seed, bitter melon, betel leaf, hibiscus, turmeric, betel nut, and sambiloto leaf; intra-muscular injection ($n = 2$) for the administration of papaya and betel leaf; subcutan injection ($n = 1$) for hibiscus; and extract exposure method ($n = 2$) for the administration of turmeric and betel nut with human sperm samples. From 37 articles, only 5 articles of papaya seeds ($n = 3$), bitter melon ($n = 1$), and betel leaf ($n = 1$) which evaluate the effect of reversibility.

Table 1. Journals in Review: *Carica Papaya*

No	Title	Author	Year of Publish	Sample	Intervention
1	Antifertility Compound from the Seeds of <i>Carica papaya</i>	Euis Julaela, Yunita Permatasari, Tri Mayanti, Ajeng Diantini	2015	Adult male mice (<i>R. Novergicus</i>)	Provision of ethyl acetate papaya seeds and B5C1 compounds from papaya seeds to 12.5 ng / μ L spermatozoa of mice
2	Papaya seed extract lowers sperm concentrations, motility and viability in male mice	Reryd Arindany Wiryawan, Reny I'tishom, Sri Purwaningsih	2015	28 male mice (<i>M. Musculus</i>)	Treatment of papaya seed extract once a day for 6 days orally in 20 mg/Kg BW, 40 mg / Kg BW, and 60 mg / kg BW
3	Injecting Carica Papaya Seed Extract L. Cibinong Varieties In Macaca Fascicularis L., Spermatozoa Quality, and Testosterone Hormone Levels	Tuti Nuraini, Dadang Kusmana, Efy Afifah	2012	8 long tailed monkeys (<i>Macaca fascicularis</i>)	The administration of cibinong papaya seed extract IM for 21 days at a dose of 40 mg, 80 mg, and 120 mg
4	Hexane and Methanol Fraction Young Papaya Seed Extract Inhibits Spermatogonia Male Mice	Bagus Komang Satriyasa, Wimpie I Pangkahila	2010	30 male mice	Giving a hexane fraction of unripe papaya seed extract orally for 36 days at a dose 20 mg / BW / day and methanol fraction of young papaya seed extract orally for 36 days at a dose 20 mg / BW / day
5	Sperm characteristics and ultrastructure of testes of rats after long-term treatment with the methanol subfraction of <i>Carica papaya</i> seeds	Boomi Manivannan, Ruchi Mittal, Shipra Goyal, Abdul S. Ansari, Nirmal K. Lohiya	2009	80 albino male rats	The administration of papaya seed extract orally at 50 mg / Kg BW of rats once a day for 360 days
6	Decreased Amount and Motility of Spermatozoa After Giving Papaya Seed Extract	Wulan Christijanti	2009	24 adult male rats	Giving papaya seed extract orally for 40 days at a dose of 10 mg / 200 gr BW, 20 mg / 200 gr BW, 40 mg / 200 gr BW
7	Toxicological effects of <i>Carica papaya</i> seed extract on spermatozoa of mice	R. J. Verma, Deepa Nambiar, and N. J. Chinoy	2006	70 albino male mice	The administration of papaya seed extract dose 100 mg / Kg BW, 200 mg / Kg BW, and 300 mg / Kg BW for 45 days
8	Activity of Alkaloid Extract of Carica papaya Seeds on Reproductive Functions in Wistar Rats	F.V. Udoh, P.B. Udoh, E.E. Umoh	2005	40 male mice	The administration of papaya seed extract (10, 50 and 150 mg / kg BW mice once a day for 3 days for the treatment group)

Table 2. Journals in Review : *Momordica charantia*

No	Title	Author	Year of Publish	Sample	Intervention
1	The Effect of Pare Extract (Momordica Charantia) on Histological Structure of Testes and Epididymis of Male Rats	Siti Cholifah, Arsyad, Salmi	2014	24 male rats	The administration of bitter melon extract orally for 56 days at a dose of 15 mg /100 g BW, 25 mg / 100 g BW, and 50 mg / 100 g BW
2	Histomorphological Alterations in the Prostate Gland and Epithelium of Seminiferous Tubule of Sprague-Dawley Rats Treated with Methanolic Extract of <i>Momordica charantia</i> Seeds	Yama Oshiozokhai Eboetse, Duru Francis Ikechukwu, Okanlawon Abayomi Olugbenga, Oremosu Ademola Ayodele, Noronha Cressie Caramel	2011	40 male rats	The administration of pare seed extract orally for 56 days once a day at a dose of 15 mg / 100 g BW, 25 mg / 100 g BW, and 50 mg / 100 g BW
3	Reproductive toxicity of <i>Momordica charantia</i> ethanol seed extracts in male rats	PanasTumkiratiwon, Ravicha Ploypatta,, Urai Pongchairerk, Wachiryah Thong-asa	2014	42 male rats	The administration of pare extract for 42 days orally at a dose of 400 mg / kg BW and a dose of 800 mg / kg BW
4	Sperm quotient in Sprague–Dawley rats fed graded doses of seed extract of <i>Momordica charantia</i>	Oshiozokhai Eboetse Y, Francis Ikechukwu D, Ademola Ayodele O, Abraham Adepoju O, Cressie Carmel N, Abayomi Olugbenga O	2011	20 male rats	The administration of bitter seed extract for 56 days orally at a dose of 15 mg / 100 g BW, dose of 25 mg / 100 g BW, and a dose of 50 mg / 100 g BW
5	Temporal adaptation in the testes of rat administered single dose <i>Momordica charantia</i> for three interrupted spermatogenic cycles: Cytometric quantification	Oshiozokhai Eboetse Yama, Francis Ikechukwu Duru	2011	50 male rats	The administration of bitter seed extract 50 mg / 100 g BW for 6 weeks, 8 weeks, 16 weeks, 24 weeks, and 32 weeks
6	The Effect of Pare Extract (M. charantia L) on Sperm Motility and Morphology of Mice	Yoni Astuti, Selly Fitriana, Nunuk Siti Rahayu	2009	20 male mice	The administration of bitter melon extract at a dose of 500, 600, 700, 800 mg of bitter melon extract / kg BW / day for 4 weeks and 6 weeks

7	Antispermatic and androgenic activities of <i>Momordica charantia</i> (Karela) in albino rats	Mulla Zehera N, Srinivas Reddy P, Somnath RP, Ravindra, Saraswati Patil	1997	48 male albino rats	The administration of ether pare extract, benzene pare extract, and alcoholic pare extract orally for 35 days at a dose of 25 mg / 100 g body weight.
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Table 3. Journals in Review : *Piper Betle*

No	Title	Author	Year of Publish	Sample	Intervention
1	Betel Leaf Extract (Piper Betle L) And Spermatozoa Quality In Mice (Mus Musculus)	Sri Mudayatiningsih, Endang Sri Dewi Hastuti Suryandari, Isnaeni	2015	24 male mice	The administration of betel leaf extract every 2 days for 24 days by intra-muscular injection at a dose of 5 mg / Kg/ BW, dose 10 mg / Kg/BW, and a dose of 20 mg /Kg/BW
2	The Quality of Spermatozoa of Albino Male Rats (<i>Rattus Norvegicus</i> L.) strain After Giving Ethanol Extract of Betel Leaves (Piper Betle L.)	Cynthia Wuwungan, Edwin de Queljoe, Defny S. Wewengkang	2017	24 male rats	Administration of betel leaf ethanol extract once a day for 50 days orally at a dose of 200 mg, 400 mg and 800 mg
3	The Effect of Piper Betle L. Extract on Spermatogenesis of Albino Rats (<i>Rattus Norvegicus</i>)	Jofter Julian Longdong, Edwin De Queljoe, Adithya Yudistira	2017	24 albino rats	Administration of betel leaf ethanol extract once a day for 50 days orally at a dose of 200 mg, 400 mg and 800 mg
4	Enzymatic Studies with Reference to Antifertility Potential of <i>Piper betle</i> Linn. Leaf Stalk Extract in Male Albino Rats	A. Govardhan Naik, C. Changamma	2015	12 albino rats	The administration of betel leaf extract once a day for 15 days orally at a dose of 150 mg / kg BW rats
5	The reversible antifertility effect of <i>Piper betle</i> Linn. on Swiss albino male mice	Madhumita Sarkar, Paramita Gangopadhyay, Bidyut Basak, Kausiki Chakrabarty, Julie Banerji, Purnima Adhikary, Asima Chatterjee	2000	40 albino rats	The administration of betel leaf extract for 30 days orally once a day in a dose of 500 mg / kg BW rats

Table 4. Journals in Review : *Hibiscus Rosa*

No	Title	Author	Year of Publish	Sample	Intervention
1	The Effect of Ethanol Extract of Flowers, Leaves and Roots of Hibiscus Rosa Sinensis Against Histology of Rats Testes	D. Febrianti, Sukarjati	2015	27 male rats	The administration of leaf extract, flower extract, and root extract of <i>H. rosa</i> orally once a day for 35 days in a dose of 150 mg / kg BW and a dose of 300 mg / kg BW
2	The Effect of Ethanol Extract of Hibiscus on the Number of Spermatozoa, Body Weight, and Weight of Testis of Wistar Male Rats (<i>Rattus Norvegicus</i>)	Nabila S. Petta, Edwin de Queljoe, Rooije R.H. Rumende	2019	24 male rats	The administration of ethanol extract of hibiscus leaves orally for 50 days once a day at a dose of 3.6 mg / ml, 7.2 mg / ml, 14.4 mg / ml
3	The activity of ethanol extract of hibiscus flower (<i>H. Rosasinensis</i> L.) on the motility of sperm mice (<i>Mus Musculus</i>)	Rani Melyandari, Abd. Halim Umar, Radhia Riski, Mirnawati Salampe	2016	12 male mice	The administration of ethanol extract of hibiscus flowers orally for 10 days once a day at a dose of 10 mg, 25 mg, and 50 mg
4	Antifertility Effect Of Benzene Extract Of Flowers Of <i>Hibiscus Rosa Sinensis</i> L. On Reproductive System In Male Albino Rats	Dinesh Kumar, P.C. Agrawal, Dhan Devi Mishra, Vikash Singh	2014	12 albino rats	Giving hibiscus extract for 30 days 1 time a day orally with a dose of 200 mg / Kg BW mice
5	The Effects Of <i>Hibiscus Rosa Sinensis</i> Flower Extracts On Spermatogenesis And Sperm Parameters Of Mice	Sherif sharawy, Nasir, A. Ibrahim	2014	20 male mice	The administration of hibiscus extract with a dose of 125 mg / kg BW for 3 days by subcutaneous injection once a day

Table 5. Journals in Review : *Curcuma Domestica*

No	Title	Author	Year of Publish	Sample	Intervention
1	Spermatozoa of Webster L. Swiss Mice (Mus Musculus) Concentration After Giving Turmeric Powder (<i>Curcuma Domestica</i>) with Chronic Dose	Muhammad Djaelani	Anwar 2010	72 male mice	The administration of turmeric extract at a dose of 1800 mg / kg BW once a day orally for 60 days
2	Can Curcumin Provide an Ideal Contraceptive?	RAJESH K. NAZ	2011	Human sperm and sperm in the epididymis of mice	The administration of turmeric extract orally, intraperitoneal, intravaginal, and intravenous.
3	Curcumin as a potential non-steroidal contraceptive with spermicidal and microbicidal properties	R.K. Naz, M.L. Lough	2014	19 human sperm sample	Sperm samples were exposed to turmeric extract with a dose of 1-1000 Mm
4	Curcumin influences semen quality parameters and 4 reverses the di(2-ethylhexyl)phthalate (DEHP)-induced 5 testicular damage in mice	Katarzyna Glombik, Agnieszka Basta-Kaim, Marta Sikora-Polaczek, Marta Kubera, Gabriela Starowicz Jozefa Styra	2014	16 male rats	The administration of turmeric extract for 21 days orally once a day with a dose of 1 µM, a dose of 30 µM, a dose of 50 µM, and a dose of 100 µM

Table 6. Journals in Review : *Areca Catechu*

No	Title	Author	Year of Publish	Sample	Intervention
1	Alkaloids from Areca (Betel) Nuts and Their Effects on Human Sperm Motility <i>In Vitro</i>	Jingsong Yuan, Dajian Yang, Yonghong Liang, Wenping Gao, Zhipeng Ren, Wei Zeng, Baorong Wang, Jian Han, and Dean Guo	2012	Voluntary male sperm samples collected after ejaculation	The administration of areca nut alkaloid extract for 3 hours at a dose of 50 µg / Ml, dose of 100 µg / mL, dose of 200 µg / mL, and a dose of 300 µg / mL
2	Antifertility Effect Of <i>Areca Catechu</i> In Male Albino Rats	Sajala Kafle, Tara Shanbhag, Smita Shenoy, Arul Amuthan2, Krishnananda Prabhu3, Sheethal Mohan4,	2011	30 albino rats	The administration areca seed ethanol extract orally for 60 days at a dose of 300 mg / kg and a dose of 600 mg / kg once a day

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Table 6. Journals in Review : *Areca Catechu*

No	Title	Author	Year of Publish	Sample	Intervention
3	Antifertility Effect of Areca catechu Water Fraction as Apoptotic Agent in Tissue Cells Testicles of <i>Rattus norvegicus</i>	Aulanni'am, Muslim Akmal, Rosmaidar	2007	Male rats	The administration of areca seed extract for 7 days orally with a dose of 1 gram / 200 gram BW, a dose of 2 grams / 200 gram BW, 3 grams / 200 grams BW, and 4 grams / 200 grams BW once a day
4	The Effects of Exposure to Areca Catechu on Motility of Rats Spermatozoa: Efforts to Find Male Antifertility Candidates	Muslim Akmal, Aulanni'a, Rasmaidar, Dasrul, Tongku N. Siregar, Erdiansyah Rahmi	2008,	Male rats	The administration of areca seed extract for 7 days orally with a dose of 1 gram / 200 gram BW, a dose of 2 grams / 200 gram BW, 3 grams / 200 grams BW, and 4 grams / 200 grams BW

Table 7. Journals in Review : *Andrographis paniculata*

No	Title	Author	Year of Publish	Sample	Intervention
1	The Effect of Sambiloto Leaves Ethanol Extract on the Number and Motility of Spermatozoa in Male Mice	Susilo, Budhi Akbar, Ika Pratinaningsih	2018	24 male mice	The administration of sambiloto leaves ethanol extract for 15 days orally once a day at a dose of 84 mg / kg body weight, dose 140 mg / kg body weight, and dose 196 mg / kg body weight
2	In vivo test of bitter (andrographis paniculata nees.) extract to ejaculated sperm quality	R Sumarmi, NK Huda, E Yuniarti, and Violita	2018	24 male rats	The administration of sambiloto extract orally for 36 days at a dose of 0.2 grams, 0.4 gram dose, and 0.6 gram dose once a day
3	Antifertility Activity of Aqueous Leaf Extract of <i>Andrographis paniculata</i> in Male Albino Rats	K.Sathiyaraj, A.Sivaraj, T.Thirumalai, N.Baskaran, K.Vinothrasu, P.Inbasekar, B.Senthil kumar	2011	18 albino rats	The administration of sambiloto leaf extract orally for 45 days with a dose of 100 mg / kg BW and a dose of 200 mg / kg BW once a day
4	Effect of sambiloto ethanol extract toward spermatogenesis of male mice and qualitative layer chromatography	V.S. Halim, C.J. Soegihardjo, D.M. Rizal	2004	Male mice	The administration of sambiloto extract orally for 48 days at a dose of 11.25 mg / 30 g BW, dose 22.5 mg / 30 g BW, and a dose of 45 mg / 30 g BW once a day

The results of Indonesian herbs with male antifertility effects based on articles review includes:

1. *Carica papaya*

Papaya seeds (*C. papaya*) have been shown to influence the fertility of male mice by influencing sperm quality such as reducing the number of spermatozoa [10–12], spermatogonia A [13], decreasing sperm motility from 47% [14] to 100% [11], decreases sperm viability [11,14–16], and increases sperm abnormality ($P < 0.01$) [11,13]. Papaya seeds also cause changes in testicular histology such seminiferous tubular atrophy [10]. The high reversibility effect of papaya seed extract has been reported [11,13,17]. Implementation of papaya seed extract as contraceptive method in long term (370 days) does not interfere with health status, organ weight, hematology, and clinical chemistry [11].

Steroid, triterpenoids, alkaloids, estradiol (E2) and progesterone (P4) in papaya seeds are cytotoxic and anti-androgenic [13,16,18]. Cytotoxic effects will cause disruption of spermatogenic cell metabolism while the antiandrogenic effect works by press the hypothalamus and the anterior pituitary that causing gonadotropin-releasing hormone (GnRH) inhibition which results in follicle-stimulating hormone (FSH) and Luteinizing-hormone (LH). Low levels of LH will inhibit the secretion of testosterone hormone and low FSH will cause disruption in sertoli cells. Disorders of sertoli cells can cause disruption in the process of spermatogenesis including the maturation of sperm cells and transport of glucose and protein synthesis into sperm cells resulting in a decrease in the integrity of sperm cell membranes [11,13,17,18]. The glycosinolate content of papaya seeds can cause clumping or agglutination of semen which interferes with motility, viability, and morphology of spermatozoa [16].

2. *Momordica charantia*

The fruit and seeds of the bitter melon (*M. charantia*) are one of the herbs that have the effect of male antifertility [19]. Bitter melon extract can cause a decrease in the quality of spermatozoa ($p < 0.0001$) such as decreased motility, viability, and morphological disorders [19–21]. Bitter melon extract reduced the number of spermatogonia ($P < 0.01$), spermatocytes ($P < 0.01$), and spermatids ($P < 0.001$) [22]. Fruit and seeds of bitter melon extract can change the histology of the reproductive organs ($p < 0.0001$), which decreases testicular weight, epididymal weight, and seminiferous tubules diameter [23]. Bitter melon extract has a high reversibility or recovery after cessation of extraction by 8 to 32 weeks [24,25].

Fruit and seeds of bitter melon extract can suppress GnRH which inhibits FSH and LH secretion that make the testosterone hormone levels drop [22–24]. Low testosterone levels cause a decrease in testicular weight and disruption to seminiferous tubular so that spermatogenic cells can not maintain their activity [23]. The decrease in testicular weight can interfere the function of the germinal epithelium to produce luminal fluid which is important for spermatogenesis process and make disruption to testicular tissue such as edema and leydig cell hypoplasia [25].

3. *Piper betle*

Betel leaf (*P. betle*) can cause interference with the process of spermatogenesis ($p < 0.0001$) by inhibiting spermatozoa formation [26] and decreasing sperm quality such as motility ($p < 0.0001$), viability ($p < 0.003$), number of spermatozoa ($p < 0.001$), and increase sperm abnormality [2,27,28]. Betel leaf extract can reduce fructose levels in seminal vesicles and decrease the weight of reproductive organs ($p < 0.01$). Reversibility or fertility recovery occurs after the cessation of betel leaf extract is stopped [28].

Flavonoids, steroids, alkaloids, terpenes and triterpenoids in betel leaves can work as antifertility compounds. The terpen compound causes clumping of sperm which decreases sperm motility and inhibits sperm transport. Flavonoids and saponins inhibit the aromatase enzyme, causing disruption of FSH and LH release. This has an impact on the decrease in testosterone levels which

causes a decrease in the weight of the reproductive organs of mice and changes in the structure of the testes, epididymis, and seminal vesicles. This will cause the process of spermatogenesis to be disrupted, for example interference with the mitosis process and proliferation of spermatogonia A [26–28].

Betel leaf extract interferes with sperm energy metabolism by reducing glucose-6-Phosphate activity ($P < 0.001$), glutamate dehydrogenase, and aldolase in the testes which causes a decrease in the energy and glucose supply available for sperm. Betel leaf extract also reduces the total activity of the phosphorylase enzyme so that enzyme phospholirase degradation as a whole can inhibit glycogenolysis [28,29].

4. *Hibiscus rosa*

H. rosa's flowers, leaves, and roots can decrease the quality of spermatozoa, which decreases sperm motility ($8.6 \pm 4.3\%$ motility), viability ($p < 0.05$), total sperm count (total count million / ml 9.26 ± 1.2), cell count spermatocytes ($p < 0.05$), and number of spermatogonia cells ($p < 0.05$) [30–34]. *H. Rosa* can cause changes in testicular histology such as a decrease in the number of leydig cells ($p < 0.05$) and a decrease in testicular weight ($p < 0.05$) [31,32,34].

Flavonoids, saponins, phenols, tannins, and alkaloids in leaves, roots, and hibiscus flowers has antifertility and antispermatogenic effects. Flavonoids can suppress the anterior pituitary to inhibit FSH and LH. Low LH levels will inhibit leydig cells in producing testosterone. Low FSH levels will reduce *tumor necrosis factor alpha* (TNF- α) expression in the testes which causes disruption in sertoli cells to produce androgen binding protein (ABP) to bind testosterone. Saponins are cytotoxic by causing disruption of the plasma membrane and inhibition of acrosine and hyaluronidase enzymes in the spermatozoa cell membrane [31,32]. Alkaloid compounds can reduce the supply of phosphate or energy sources in sperm metabolism [30].

5. *Curcuma domestica*

Turmeric (*C. domestica*) can reduce sperm quality such as decreased sperm motility ($P < 0.001$) viability, and decreased concentrations of spermatozoa in the epididymis [35,36]. Turmeric has a high reversibility effect or fertility recovery to be able to return to normal [36,37]. Turmeric also has an antibacterial effect that can provide a protective effect on sperm against reproductive organs's bacteria [37,38].

Curcumin, demethoxycurcumin, and bisdemetoksikurkumin in turmeric can interfere the process of spermatogenesis [35]. The content of turmeric can suppress the activity of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-Kb), cyclooxygenase 2 (COX-2), *5-lipoxygenase* (5-LOX) and some proteins such as thioredoxin reductase and protein kinase that contained in sperm cells to interferes with sperm metabolism. The antioxidant properties of turmeric cause high concentrations of reactive oxygen species (ROS) that have an impact on sperm membrane changes and intercellular pH affects the process of spermatogenesis thereby reducing the amount, motility and viability of sperm [36–38].

6. *Areca catechu*

Betel nut (*A. catechu*) can reduce sperm quality by reducing motility to 46.13%, decreasing the number of secondary spermatosids and the number of spermatids [39–41]. Betel nut also causes changes in testicular histology, such as disruption of sertoli cells and leydig cells, and increased diameter of seminiferous tubules due to increased fluid and necrotic tissue [39,40].

Alkaloids such as arecoline and arecaidine in betel nuts is cytotoxic by damaging the DNA of germ cells which can induce the occurrence of apoptosis or cell death in the testes [40]. Alkaloids also interfere with the activity of ATP enzymes that exist in spermatozoa cell membranes by disturbing permeability, decreasing protein content, and lipid layer resulting in an increased inflammatory response through COX-2 and ROS. This will cause disruption of sperm viability and disruption of flagellar movement in sperm thereby reducing sperm motility [41,42].

7. *Andrographis paniculata* Ness

Sambiloto leaves (*A. paniculata* Ness.) can reduce sperm quality by reducing motility ($P < 0.001$), sperm count by 79%, and increasing sperm abnormalities by up to 50% [43–45]. Sambiloto leaves are proven to cause disruption in the process of spermatogenesis in seminiferous tubules, such as degradation, damage to sertoli cells, and lysis of the lamina basalis [46].

Andrographolide compounds (penetrated-noid ketone compounds, triterpenoids) and flavonoids in sambiloto leaf have antiandrogenic effects which can inhibit aromatase enzymes, thus disrupting FSH and LH secretion. Low FSH levels will reduce stimulation to sertoli cells which are important for sperm protein metabolism by ABP in spermatogenic maturation in seminiferous tubules. This will cause lysis of the sertoli cells and resulting in the absence of protective spermatogenic cells and disruption of spermatogenesis [44,46]. Andrographolide is also an antimetosis which interferes with spermatogonia to get to the metaphase stage so that no sperm chromosome separation occurs [45,46].

DISCUSSION

Medicinal herbs or medicinal plants are plants that have been identified having an useful content for preventing or curing a disease, carrying out certain biological functions, and prevent attacks of insects and fungi [47]. The World Health Organization established a Task Force program to examine the potential of traditional herbs or plants in an effort to develop traditional herbs as an alternative new method of contraception [6,7].

The use of herbs around the world as an alternative contraceptive method for men is due to the limited types of medical contraceptive methods such as vasectomy, condoms, and the unavailability of medical contraception in some areas especially in remote areas. In Nigeria, several hereditary herbs are used as male contraceptives such as *Xylopiya aethipica* or Ethiopian pepper by decoction or making incisions involving 7 wounds on the legs and applying dry powder to fresh wounds. In China, *Tripterygium wilfordii* extract is also often used as an alternative to male contraception which has been shown to reduce fertility in mice and humans. In India, *Azariidactha indica* is also used as an alternative to male contraception which taken daily [48–50].

Indonesian plants or herbs have male antifertility effect, such as papaya seeds (*C. papaya*); fruit and seeds of bitter melon (*M. charantia*); betel leaf (*P. betle*); flowers, leaves and roots of hibiscus (*H. rosa*); turmeric (*C. domestica*), betel nut (*A. catechu*); and sambiloto leaf (*A. paniculata*). These herbs contain several phytochemical substances such as flavonoids, saponins, tannins, steroids, triterpenoids, alkaloids, terpenes, estradiol (E2) and progesterone (P4) which cause disorders in both the anatomy and physiology of the male reproductive organs such as GnRH suppressant and make the testosterone drop level hormones. Low testosterone levels and disruption to seminiferous tubular so that spermatogenic cells can not maintain their activity. This will cause lysis of the sertoli cells and the absence of protective spermatogenic cells, causing disruption of spermatogenesis. Disruption of spermatogenesis results in decreased viability, motility, and morphology of sperm [13,25–27,37].

Papaya seeds (*C. papaya*), bitter melon (*M. charantia*), and betel leaf (*P. betle*) have high effects of reversibility or fertility recovery after intervention discontinuity [11,24]. Provision of papaya seed extract as an contraceptive method in the long term, 370 days proved to not interfere with health status, organ weight, hematology, and clinical chemistry so that it is safe to use in the long period of time [11].

Research articles on Indonesian plants or herbs with male antifertility effects still have many limitations, such as most research articles tested using samples of animals with DNA or structures and functions of reproductive organs that similar to humans like mice or long-tailed monkeys compared to research with human samples. In addition, there are still limited studies that examine the effects of reversibility or fertility recovery of the plants or herbs and the limited research that examines the effects of long-term use of herbs on health status.



However, research articles on herbs with male antifertility effects can be used as development material for further research to establish an herb or plant as an alternative new contraceptive method for men that is safe, effective, reversible, does not interfere with libido or sexual activity, and can be accepted by the community.

CONCLUSION

Alternative new methods of contraception for men can be obtained through herbs such as papaya seeds (*C. papaya*), bitter melon (*M. charantia*), betel leaf (*P. betle*), hibiscus (*H. rosa*), turmeric (*C. domestica*), betel nut (*A. catechu*), and sambiloto leaf (*A. paniculata*).

Antifertility effects possessed by these herbs include antispermatogenic, reduce sperm quality (motility, morphology, and viability), and change the histology of reproductive organs such as decreasing testicular weight, epididymic weight, seminiferous tubule diameter, and the number of leydig cells.

Further research is needed regarding the effects of herbs that have male antifertility effects on human subjects, reversibility effects, and the safety of herbs on health when used for a long period of time.

CONFLICT OF INTEREST

There is no conflict of interest in this study. The author is fully responsible for the content of this research article.

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