BIOMEDICAL OVERVIEW OF THE AGRICULTURAL PRODUCT UTILIZATION IN THE SCABIES ERADICATION AS NEGLECTED TROPICAL DISEASE

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Abstract

Scabies is considered by WHO as a neglected tropical disease and requires large-scale control. Treatment of scabies so far has focused on chemical agents, such as Permethrin 5% which is reported to be irritating, unsafe for infants, pregnant women, toxic to the elderly, and trigger resistance to the mite *Sarcoptes scabiei*. For this reason, the development of treatment is urgently needed by using active ingredients that are safer and more effective. Indonesia is a tropical country that has many agricultural products which are useful for the treatment of scabies. The purpose of this study is to review the possibility of agricultural products that can be used as active compounds for scabies eradication in Indonesia. This study is a systematic review conducted from January-July 2022. The literature search was carried out through electronic databases, namely Science Direct, PubMed, Cochrane, Google scholar, and Springer Link using inclusion and exclusion criteria. Previously, screening was carried out using the Patient, Intervention, Comparison, Outcome, and Study (PICOS) criteria. From the search results for 1,357 articles, there were 19 articles that matched the inclusion criteria. The findings of this study indicate that various agricultural products can be extracted for their active compounds to be used in the treatment of scabies in Indonesia, such as Nimba leaves, maja, skeleton grass, reeds, tea tree, manga, betel, areca nut, galangal, beluntas, bratawali, temu hitam, temu putih. The active compounds produced from the extraction process of leaves, roots, flowers and seeds of agricultural products are proven to be able to inhibit the life cycle of *Sarcoptes scabiei* during its metamorphosis process. Irritation and toxicity caused by conventional scabies treatment, as well as potential resistance to scabicide drugs encourage the possibility of using herbal remedies from agricultural products that are more effective and without side effects.

Keyword: agricultural product, scabies, neglected tropical disease

1. Introduction

Scabies is a disease that attacks the integumentary organs due to *Sarcoptes scabiei* mite infestation and irritation by mite products. In 2019, WHO classified scabies into the list of neglected tropical diseases [1]. The total number of scabies patients in the world every year is more than 310 million with the number of cases varying in each country [2]. In Indonesia, one of the most common skin diseases in Puskesmas is scabies. In 2019, the prevalence of scabies was 5.7-13.1% and became the third most common skin disease [3]. Surveys conducted in several slum settlements in 2018 such as flats and landfills in Jakarta showed the prevalence of scabies was 6.2%, in Semarang 5.8%, in Boyolali 7.4%, in Pasuruan 8,2% [4].

One of the factors that can affect the prevalence of scabies in a community is treatment failure due to lack of patient compliance. The drug to kill *Sarcoptes scabiei* is called a scabicide, while the drug to kill *Sarcoptes scabiei* eggs is called

ovicide. Sulfur precipitate is an example of a drug that is only a scabicide. Meanwhile, permethrin and gamma benzene hexachloride are drugs that can function as both scabicides and ovicides [5]. These drugs cause many side effects and drug resistance. Sometimes scabies therapy is not optimal, it even fails so that scabies cases still cannot be eliminated [6].

Indonesia has a list of selected drugs that are needed and used as a reference for prescribing in the implementation of health services in the implementation of a health insurance program called the National Formulary. Based on the Decree of the Minister of Health of the Republic of Indonesia Number HK.01.07/MENKES/813/ 2019 regarding the National Formulary, there are two anti-scabies drugs listed, namely 5% permethrin cream and 2-4 ointment [7]. However, long-term administration of both and inappropriate doses will lead to resistance to mites. For this reason, alternative medicine is needed using natural ingredients from agricultural products which are suspected to have scabicide effects [8].

These natural materials are one of the methods for biological control of vector-borne diseases. Indonesia has a variety of agricultural products with a total of 30,000 species and recently 940 species were discovered that may have the effect of treating diseases, which are called herbal medicines. Indonesian people have long used medicinal plants for healing. The knowledge of processing medicinal plants is passed down from generation to generation. Unfortunately, there is still little research that extracts plants for scabies therapy because primary scabies infection is not a research priority because it is considered not life threatening. In fact, if ignored, scabies can lead to the appearance of a secondary infection that will be increasingly difficult to treat [9]. The purpose of writing this article is to review the possibility of agricultural products that can be used as active compounds for scabies eradication in Indonesia and to confirm plant extracts that can contribute to providing information for patients seeking alternative scabies treatment.

2. Methods

The review protocol was prepared using the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) method. The literature search was carried out in January-July 2022 through electronic databases, namely Science Direct, PubMed, Cochrane, Google scholar, Clinical key and Springer Link using inclusion and exclusion criteria. (Figure 1) The search keywords were “scabies and herbs”. The inclusion criteria for articles are in English and Indonesian, nationally and internationally accredited, there is information on the use of agricultural products in the treatment of scabies, and articles will be published in 2020-2021. The exclusion criteria were that there were duplications and they could not be accessed as a whole. Articles were selected based on conformity with the PICOS criteria (scabies patients, intervention with scabicide active compounds, comparison with herbal treatment extracted from medicinal plants, outcomes in the form of increased cure rates and decreased prevalence, as well as quantitative studies. The selected publications in the selection of titles and abstracts were extracted using standard format table and processed using Microsoft Excel spreadsheet. Data extracted in the form of author, year of publication, journal, and conclusion. Results are then presented qualitatively.

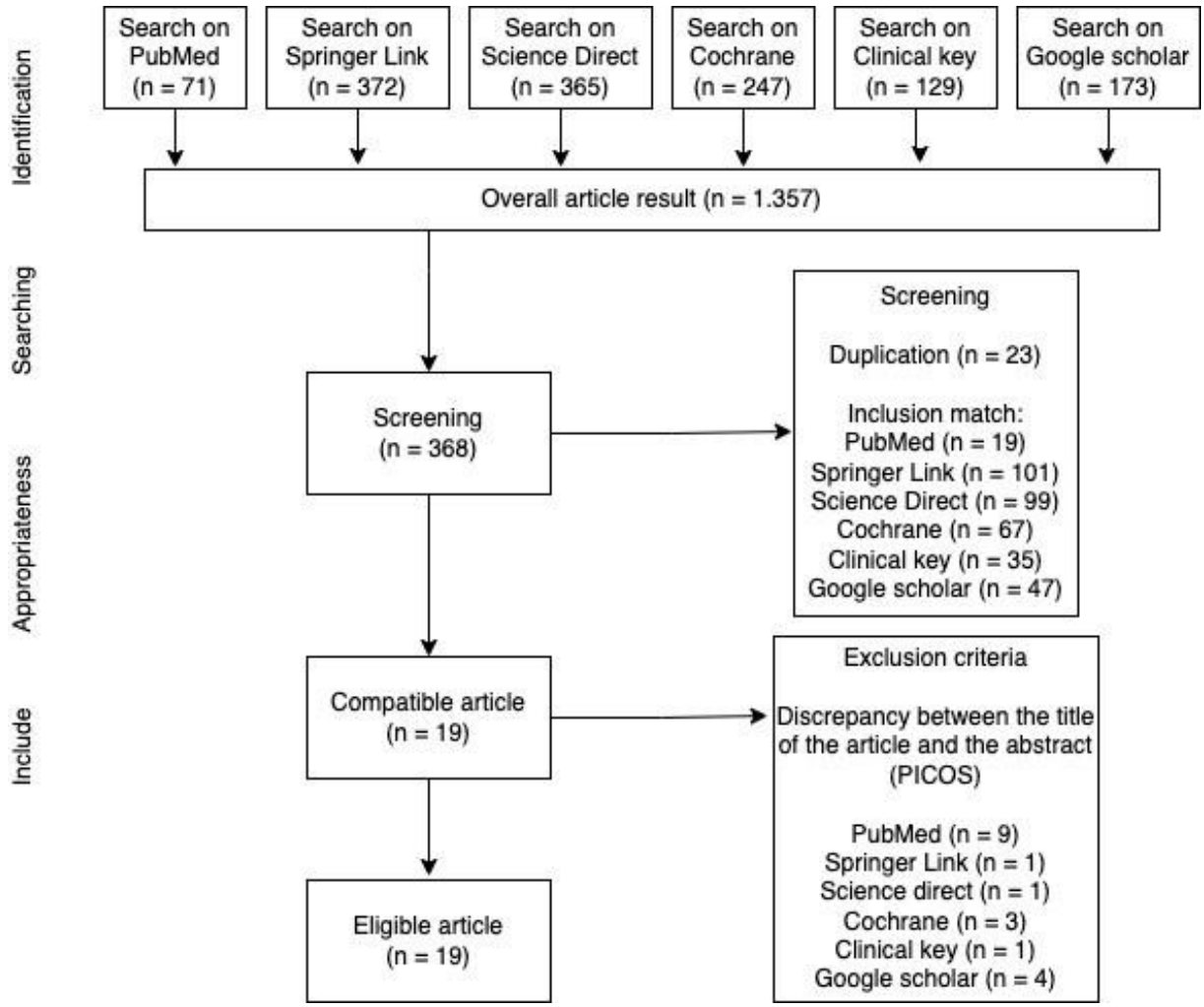

Figure 1. PRISMA Diagram

3. Result

From the search results of 1,357 articles, there were 19 articles that met the inclusion and exclusion criteria. A critical study was conducted on 19 selected articles published by accredited journals based on the Scimago Journal and Country Rank and SINTA. Journal analysis related to the use of agricultural products for the treatment of scabies is presented in Table 1.

Table 1. Agricultural Products with Scabicide Activity

No	Agricultural Product	Species	Part of Plants	Mechanism of Action
1	Lidah buaya [10]	*Aloe vera*	Leaves	Contain anthraquinone, saponin, aloemodin, anthrax zero, chrysophanic acid, anthracenesinamat, amino acid, eteraloin resistanol, catalase, oxidase enzyme, minerals, lipase, and hormones.

				Anthraquinone has mechanism of denaturing protein cell SHG, providing a damaging effect for mites. Saponin has ability as an antiseptic and spur collagen differentiation, so that it is adequate to heal open wounds. While flavonoids serve as antioxidant, antibacterial and may inhibit bleeding on the skin.
2	Mimba [11]	*Azadirachta indica*	Seed and leaves	Contain an active compound in the form of AZA, which producing a specific stimulant as chemical receptor that work together in disrupting the stimulation to eat (phagostimulant). It also acts as an ecdysone blocker or substance that may inhibit hormone work as well as it's functions in the arthropods metamorphose.
3	Bila / maja [12]	*Aegle marmelos*	Fruit meat	Contain active compound that serves as an antibacterial and scabicide. This compound interferes with microbe metabolism.
4	Pata / Rumput belulang [12]	*Eleusina indica*	Root	Contain active compound which are antihistamine and anti-inflammatory. They work in the sense of itching and pain relieve at inflammation of the skin.
5	Alang-alang [13]	*Imperata cylindrica*	Flower	It can be used to accelerate the cure of scabies lesion by mashing an old flower and applied to the skin. Its active compound has function as a scabicide that may improve the healing process by eliminating mites which play role in the inflammatory process.
6	Tea tree [14]	*Melaleuca alternifolia*	Oil	Contains anti-inflammatory, anti-pruritic and antibacterial compound. These will help accelerate curing of scabies lesion.
7	Mangga [15]	*Mangifera indica*	Leather stem	Contain active compounds of saponins and flavonoids as an anti-inflammatory to help the process of lesion healing in scabies. It also serves as an analgesic to reduce pain of scabies lesion. Saponin also has the ability as an antiseptic and can spur collagen differentiations, so that it will be useful to close the crust lesion. While flavonoid serves as antioxidant, antibacterial, and may inhibit skin bleeding.
8	Sirih [16]	*Piper bettle*	Leaves	Contain an active compound that may inhibit the expansion of scabies lesion and help the healing of the wounds.
9	Pinang [16]	*Areca catechu*	Seed	Contain flavonoids, tannins, and alkaloids

				which is serve as scabicide.
10	Temu hitam [17]	*Curcuma aeruginosa*	Rhizome	These contain anti-inflammatory active compounds which are beneficial for the treatment of scabies lesion. However, it also serves as analgesic and antipyretic, which may reduce the discomfort due to itching.
11	Temu giring [17]	*Curcuma heyneana*		
12	Temu putih [17]	*Kaempferia rotunda*		
13	Lengkuas [17]	*Languas galanga*		
14	Beluntas [17]	*Pluchea indica*	Leaves	Contain essential oils, flavonoids and alkaloids which may act as an anti-inflammatory and scabicide exhibit.
15	Bratawali [17]	*Tinospora tuberculata*	Leaves	Contain saponins, alkaloid, and flavonoid which serve as an scabicide that improve lesion healing.
16	Anting-anting [18]	*Acalypha indica*	Leaves	Contains flavonoids, triterpenoids, saponins, steroids, and alkaloids compounds that have been proven to be ovicides, larvicides, and pupisidals.
17	Sirsak [19]	*Annona muricata*	Leaves	Contains annonaceous acetogenin which has been shown to be cytotoxic in vitro. This bioactive ingredient has antifungal, antibacterial, anticancer, insecticidal, larvicidal, repellent properties, and fights various parasites.

4. Discussion

Of the 17 agricultural products that have scabicide activity, neem leaf (*Azadirachta indica*) is the most studied plant because it contains Azadirachtin (AZA) which is an active and relevant compound for the treatment of scabies. [20] The levels of AZA contained in neem leaves vary, influenced by multifactors such as geographical conditions, plant morphology, climate, tree genetic variability, procedures and collection of plant material. The presence of insect infestation, mechanical damage, plant storage time and fungal infection were also associated with decreased AZA concentrations [21].

Of the various AZA isomers mentioned in the literature, Azadirachtin A is the main metabolite of neem seed which is considered for commercialization of neem as a scabicide. AZA compound shows hydrophilic character, which means it has moderate solubility in water, but high solubility in polar organic solvents, which is photosensitive. The chemical structure of AZA is similar to the hormone ecdysone in insects which functions to regulate the growth process in insects [22].

AZA does not kill insects quickly, but through the mechanism of interfering with the process of reproduction, digestion, and growth. AZA significantly affects insect metamorphosis and reproduction, including fecundity, but slowly. AZA causes growth inhibition, malformation, and mortality in insect larvae. Compounds such as steroids interfere with insect development through the disrupted action of ecdysteroids (Table 2) [23].

Table 2. Effects and actions of chemical compounds in *Azadirachta indica*

Effect	Action
Primary eating disorder	Stimulates perception blocking cells to eat specifically at chemoreceptors and also blocks sugar receptor cells
Secondary eating disorder	Peristaltic inhibition Reduces enzyme production
Growth regulation	Inhibits secretion of morphogenetic peptides by ecdysteroids
Sterility	Decreased egg laying ability and egg hatchability
Cellular process	Inhibits cell division Decreased muscle tone Inhibits protein synthesis in various tissues

The primary effect of AZA on arachnids is an antifeedant through the chemoreceptor stimulation mechanism found in the mouth of the mite. These chemoreceptors along with other chemical receptors will interfere with the perception of the stimulus to eat [24]. The feeding behavior of arachnids depends on neural input from the arachnid's chemical senses (taste receptors in the tarsi and oral cavity) and the central nervous system which integrates sensory codes. AZA will stimulate specific inhibitory cells in the chemoreceptors and also block sugar receptor cells that stimulate the arachnid's perception of eating. It causes starvation and death of arachnids. The secondary effects of AZA antifeedants interfere with hormones or other physiological systems such as the movement of food through the intestines, inhibition of the production of digestive enzymes, and effects on the stomatogastric nervous system [25].

The effects of AZA on developmental and reproductive regulatory disorders of insects occur due to direct effects on somatic cells and reproductive tissues and indirect effects on neuroendocrine pathways. In the body of mites, the main hormones that regulate the growth process are ecdysone and 20-hydroxy-ecdysone hormones. These two hormones are moulting hormones and juvenile hormone (JH). Moulting hormones are produced by the prothoracic glands, while JH through stimulation of prothoracicotropic hormone (PTTH) will be produced by the corpora allata. The metamorphosis process requires synchronization of various types of hormones and physical changes, so that it works well. AZA functions as an ecdyson blocker that will inhibit the production and release of various vital hormones in the metamorphosis process. This will prevent the mites from changing their skin, so their life cycle will be disrupted. In addition, mites will be disturbed in the process of changing from eggs to larvae, or larvae to nymphs, or from nymphs to adults and sometimes causes death [26].

Disturbances in this cascade of events cause various effects such as developmental disorders and sterility effects. The effect of AZA is directly through cells and tissues, where AZA can cause inhibition of cell division and protein synthesis. Visible effects include muscle paralysis, midgut cell necrosis, loss of regenerative cells in the gut and reduced enzyme production in the midgut [25].

AZA causes effects on the reproductive process in both female and male mites. AZA inhibits ovarian ecdysteroid synthesis and oogenesis thereby preventing mites from laying eggs and decreasing egg hatchability. Reproduction in male mites is also affected by AZA, where the sex size in male mites decreases significantly. Miotic processes that play a role in the production of sperm maturation in adult male mites will be disrupted. AZA also prevents cell division at the metaphase stage [25].

Reproductive disorders of mites are also an important feature of AZA compounds because ecdysteroids are one of the hormones that regulate vitellogenesis (egg cell development). AZA can modify ecdysteroid hemolymph by inhibiting the release of PTTH and allatotropin from the brain-corpus cardiac

complex, thereby affecting the development of fecundity and fertility [25].

5. Conclusion

Irritation and toxicity caused by conventional scabies treatment, as well as potential resistance to scabicide drugs encourage the possibility of using herbal remedies from agricultural products that are more effective and without side effects. Based on the above review, it can be concluded that there are seventeen plants that contain active compounds that can inhibit the life cycle of the metamorphosis of the mite *Sarcoptes scabiei.*

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