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A MINI REVIEW OF INDONESIAN MEDICINAL PLANTS FOR VULVOVAGINAL CANDIDIASIS

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ABSTRACT

Vulvovaginal candidiasis (VVC) is the second normal of vaginal mucosal infection after bacterial that influencing right around 70%-75% of women once in a lifetime. Azoles antibiotics are used in treatment for VVC but limited because cause drug resistance in patients. Therefore, today need for new antifungal agents for *Candida albicans* infection that safe and without side effect. This article reviews Indonesian medicinal plants related to the antifungal activity and mechanisms of action against *C. albicans.* The searches for this review were conducted via the databases PubMed, Google Scholar, online Science Direct, Science and Technology Index. The document relevant analyzed and included in the study. Almost 34 medicinal plants used for anti-Candida in Indonesia were reported. About 5.88% and 94.12% of Indonesian medicinal plants were significant and weak as an anti-*Candida* activity, respectively. The plants with the greatest anti-*Candida* activity were *Curcuma xanthorrhiza* and *Syzygium aromaticum*. The anti-*Candida* action involved disruption of hyphae production, membrane permeabilization, cell wall, biofilm formation, envelope, and filament formation. These results contribute to the drug discovering of the anti-*Candida* from Indonesian medicinal plants.

Keywords: Antifungal activity, Candidiasis, Candida albicans, Indonesia, medicinal plant, Vaginal infection

INTRODUCTION

Vulvovaginal candidiasis (VVC) is an infection of the vagina caused by *Candida* spesies[1] and diagnosed with clinical manifestations of hyperemia, pruritus, vaginal discomfort, leucorrhea, burning, soreness, dyspareunia, vaginal and vulvar erythema.[2] VVC is the second most common cause vaginosis in mucosal or vaginal after bacterial infections. Approximately, 70-75% of women reported to have suffered at least one episode of VVC during their life and about 40%-50% of these women experienced recurrent type, with 4 or more episodes within one year. In Indonesia, it constitutes 11.2-28.9% of all cases of vaginosis which prevalence in women with high-risk factors.[3] The antibiotics, particularly azoles drugs type, are used in treatment for VVC.[4] But in the treatment of *Candida albicans* infection, azoles antibiotics are limited because has led to the development of drug resistance in patients.[5, 6] Currently, according to the literature, many researchers are focused on finding plant-derived medicines[7-9] and related bioactive due to efficacy effects for anti-Candida[10-12] because medicinal plants had been reported to be safe and without side effect.[13-15] Indonesia, a country in southeast Asia, has a diverse flora that potential as medicinal plants for anti-Candida applications. The present review reports the Indonesian medicinal plants to be efficient against *C. albicans* by carrying out their anti-*Candida* activity and their mechanism of action.

This review was carried out using systematic literature search on the Indonesian medicinal plants in the databases PubMed, Google Scholar, online ScienceDirect, Science and Technology Index, and Portal Garuda. Articles published up to the end of July 2017 were used for the review with some inclusion and exclusion criteria. The language articles published were not considered. The search keywords included "*Candida albicans*", "*Candida albicans* and drug effects", "Candidiasis and therapy", "antifungal activities of plants", "anti-candida albicans activity of plants", "*Candida* and natural products", and "medicinal plants as sources of antifungals". Medicinal plants are selected based on information from data of Indonesian National Agency for Drug and Food Control (BPOM), Republic of Indonesia.

Anti-*Candida* of Indonesian Medicinal Plants

Currently, there were used five types antifungals for fungal infection included azoles, polyenes, echinocandins, allylamines, and fluoropyrimidines[16]. But there are limited in the application of these antifungal for *C. albicans* infection that has led to increasing drug resistance and toxicity in patients[17, 18]. The medicinal plants are shown to have safety and efficacy in pharmacological activities including as antifungal activity[19, 20]; it potential for developing new antifungal in tackling *Candida* infection.

Traditionally, Indonesian medicinal plants have been used by the humans for antifungal activities such as anti-Candida[21]. A summary of the medicinal plants used to treat *C. albicans* in Indonesia is presented in Table 1. From this table are enumerated of describing plant species and family, plant parts used, type of products, information of the main compounds or group of compounds, if any, test system and concentration or dose (MIC and MFC) used, and references.

Table-1: List of Indonesian medicinal plants with anti-*Candida* activity and its secondary metabolite compounds

Plant/Family	Local name	Part(s)	Product(s)	Major compound(s) or group of compounds	Test system (and concentration /dose)	References
Acorus calamus L./ Acoraceae	Jeringau	Rhizomes	Essential oil	Terpenoids	In vitro, MIC 1%	22
Allium ascalonicum L./ Amaryllidaceae	Bawang Merah	Bulbs	Infuse	Allicin	In vitro, MIC 50%	23
Allium sativum Linn./ Amaryllidaceae	Bawang putih	Bulbs	Petroleum ether extract	Allicin	In vitro, MIC 50%	24
Aloe vera/ Asphodelaceae	Lidah buaya	Leaves	Ethanol extract		In vitro, MIC 25-50%, MFC 12.5-100%	25
Alpinia galanga (L) Willd./ Zingiberaceae	Lengkuas putih	Rhizomes	Essential oils	Terpenoids	In vitro, MIC 1.56%, MFC 3.25%	26
Ageratum conyzoides L./ Asteraceae	Bandotan	Leaves	Acetone fraction of the ethanol extract	Coumarin	In vitro, MIC 125 µg/ mL	27

Azadirachta indica/ Meliaceae	Mimba	Leaves	Ethanol extract	Flavonoid, tannin, saponin	In vitro, MIC 0.2%	28
Anacardium occidentale L./ Anacardiaceae	Jambu Mete	Leaves	Infuse		In vitro, MIC 25%	29
Anredera cordifolia (Tenore) Steen./ Basellaceae	Binahong	Stems	Ethanol extract	Flavonoids; Polyphenols; Saponin	In vitro, MFC 86%	30
Apium graveolens L./ Umbellifers	Seledri	Herbs	Ethanol extract	Saponin	In vitro, Concentration 100%	31
Camelia sinensis/ Theaceae	Teh putih	Leaves	Ethyl acetate and ethanol extract		In vitro, MIC 22%	32
Cassia alata/ Caesalpiniaceae	Ketepeng Cina	Leaves	Hexane extract	Steroids	In vitro, MIC 10%	33
Centella asiatica Urb./ Apiaceae	Kaki kuda	Leaves	Ethanol extract		In vitro, MIC 60-70%	34
Cinnamomum burmannii/ Lauraceae	Kayu manis	Steam barks	Decoction		In vitro, MIC 1%, MFC 2%	35
Citrus limon/ Rutaceae	Jeruk Nipis	Peels	Essential oils	Terpenoids	In vitro, MIC 80%	36
Curcuma aeruginosa RoxB./ Zingiberaceae	Temu ireng	Rhizomes	Essential oils		In vitro, MIC 100%	37
			Ethanol extract	Curcuminoids, phenolic, flavonoid, tannin and terpenoids		38-41
Curcuma heyneana Val & Zijp/ Zingiberaceae	Temu giring	Rhizomes	Cream	Essential oils	In vitro, MIC 0.25%	42
Curcuma longa L./ Zingiberaceae	Kunyit	Rhizomes	Fresh rhizomes	Curcumin	In vitro, concentration 100%	43
Curcuma xanthorrhiza RoxB./ Zingiberaceae	Temulawak	Rhizomes	Xanthorrhizol isolated from the methanol extract	Xanthorrhizol	In vitro, MIC: 1.0-25.0 mg/L and MFC: 10-20 mg/L	44
Garcinia celebica L./ Guttiferae	Kandis	Leaves	Methanol and chloroform extract	Terpenoid, flavonoid, tannin	In vitro, MIC 0.5 mg/mL	45
Impatiens balsamina Linn./ Balsaminaceae	Pacar air	Leaves	Ethanol extract		In vitro, MIC 12.5%	46

Mangifera casturi/ Anacardiaceae	Kasturi	Steam barks	Methanol extract		In vitro, MIC 25%	47
Melastoma malabathricum L./ Melastomataceae	Senggani	Leaves	Ethanol extract	Alkaloid, saponin, tanin, phenolic, flavonoids, triterpenoid, steroid, glicoside	In vitro, MIC 6%	48
Moringa oleifera Lamk./ Moringaceae	Kelor	Fruits	Aqueous, 70% ethanol, and hexane extracts	Alkaloids, flavonoids, steroids	In vitro, concentration 100%	49
Myrmecodiatuberosa Jack./ Rubiaceae	Sarang Semut		Ethanol extract	Phenolic	In vitro, MIC 0.8% and MFC 6.4%	50
Nigella sativa Linn./ Ranunculaceae	Jintan Hitam	Seeds	Infuse		In vitro, MIC 20%	51
Nephelium lappaceum L./ Sapindaceae	Rambutan	Stem barks	Ethanol extract		In vitro, MIC 20%	28
Ocimum sanctum L./ Lamiaceae	Kemangi	Leaves	Ethanol extract and fractions	Flavonoids, tanin, saponin, triterpenoid, steroid, quinon	In vitro, MIC 1024 μg/ mL	52
			Hexane and dichloromethane extracts	Tanin, phenol, essential oils, eugenol, steroid, terpenoid	In vitro, MIC 25%	53
Phaleria macrocarpa/ Thymelaeaceae	Mahkota Dewa	Leaves	Ethanol extract		In vitro, MIC 40%	54
Piper betle L./ Piperaceae	Sirih	Leaves	Essential oil from ethanol extracts	Caryophyllene	In vitro, concentration 100%	55
			Infuse		In vitro, MIC 62.5 mg/mL	56
Piper crocatum Ruiz & Pav./ Piperaceae	Sirih merah	Leaves	Ethanol extract		In vitro, MIC 10%	57
Plumeria alba/ Apocynacea	Kemboja	Stem barks	Ethyl acetate extract	Alkaloids	In vitro, MIC 10%	58

Sandoricum koetjape (Burm.f.) Merr/ Meliaceae	Kecapi	Stems	Methanol extract and fraction	α- gurjunene, trans-caryophyllene, aromadendrene, α-humulene, β-caryophyllene, δ-Cadinene, alloaromadendrene, octadecanoic acid, hexadecanoic acid metil ester, hexadecanoic acid, 9-octadecenoic acid metil ester, 9-octadecenoic acid	In vitro, MIC 7.5 mg/ mL	59
Syzygium aromaticum (L.) Merr. & Perry/ Myrtaceae	Cengkeh	Leaves	Essential oils	Eugenol	In vitro, concentration 100%	60
		Clove oil	Essential oils	Eugenol	In vitro, MIC 0.64 μg/ mL, MCF 0.64-1.25 μg/ mL	61
Zingiber officinale/ Zingiberaceae	Jahe	Rhizomes	Fresh rhizomes		In vitro, concentration 100%	62
			Hydroalcoholic extracts		In vivo, 10 mg/kg	63

MIC: minimal inhibitory concentration; MFC: minimal fungicidal concentration

A total of 34 different Indonesian medicinal plants belonging to the 25 families were reported for anti-*Candida* activity. Antifungal activity such as anti-*Candida* of extracts and compound is currently characterized in vitro by MIC and MFC. According Kuete and Efferth (2010)[64], the potency extracts of medicinal plant as antifungal, based on their MIC values, can be categorized: (1) significant (MIC < 100 μg/ mL or 0.01% w/v); (2) moderate (100<MIC≤625 μg/ mL or 0.01<MIC≤0.0625% w/v); and (3) weak (MIC > 625 μg/ mL or 0.0625% w/v). Therefore, the activity recorded with the 34 Indonesian medicinal plants reviewed could be considered as important for 2 (5.88%) and weak for 32 (94.12%). The plants which exhibited significant anti-*Candida* activity were: *Curcuma xanthorrhiza* and *Syzygium aromaticum*. These plants inhibit *C. albicans* through secondary metabolites such as xanthorrhizol for *C. xanthorrhiza* and eugenol for *S. aromaticum*.

Anti-*Candida* mechanism of action of Indonesian medicinal plants

Anti-Candida or antifungal mechanism of action of secondary metabolite reviewed Indonesian medicinal plants are presented in Table-2. In the present review, mechanism action of antifungal activities against C. albicans were exhibited by metabolites of ten Indonesian medicinal plants, namely, allicin from *A. sativum*, diterpene from *A. galanga*, coumarin from *A. canyzoides*, terpenoids from *C. limon*, curcumin from *C. longa*, xanthorrhizol from *C. xanthorrhiza*, thymol from *N. sativa*, essential oils from *O. sanctum*, eugenol from S. *aromaticum*, and [6]-shogaol from *Z. officinale*. The metabolites of Indonesian medicinal plants have their antifungal mechanism well described in the literature: disruption of hyphae production by allicin[65], filament and biofilm formation by [6]-shogaol[66], curcumin[67] and xanthorrhizol[68, 69], envelope by eugenol[70], membrane permeabilization by essential oils[71], thymol[72] and diterpene[73], and cell wall by terpenoids[36], thymol[74], and coumarin[27]. Metabolite from Indonesian medicinal plants mostly exerts their antifungal effect by growth inhibition, membrane, and cell wall active mechanism. This review indicated that needed to isolation and characterization of the bioactive compounds from Indonesian medicinal plants that responsible for anti-*Candida* activity in further studies.

Table-2: Anti-*Candida* or antifungal mechanism of action of reviewed Indonesian medicinal plants

Plant/Family	Product(s) of metabolite	Investigation methods	Mechanism of action/ target	References
Allium sativum Linn./ Amaryllidaceae	Allicin	*C. albicans* fitness test	Inhibition SIR2 gene-related suppress hyphae production	65
Alpinia galanga (L) Willd./	Diterpene	*C. albicans* fitness test	Alters membrane permeability	73
Ageratum conyzoides L./ Asteraceae	Coumarin	*C. albicans* fitness test	Damages cell by pore formation in the cell wall	27
Citrus limon/ Rutaceae	Terpenoids	*C. albicans* fitness test	Inhibition ergosterol synthesis (a component of cell wall)	36
Curcuma longa L./ Zingiberaceae	Curcumin	*C. albicans* fitness test	Prevents induction of transcription of genes integrally involved in the processes related to biofilm formation by elicits anti-adhesive effects of *C. albicans*	67
Curcuma xanthorrhiza RoxB./ Zingiberaceae	Xanthorrhizol	*C. albicans, C. glabrata, C. guilliermondii,* and *C. parapsilosis* fitness test	Inhibition biofilm formation	68,69
Nigella sativa Linn./ Ranunculaceae	Thymol	*C. albicans* fitness test; Testing with sorbitol and ergosterol	Involves a direct interaction with the cell wall structure or with the ion permeability of the membrane	72,74
Ocimum sanctum L./ Lamiaceae	Essential oils: eugenol, methyl eugenol, linalool, and 1, 8-cineole,	Proton efflux measurements	Inhibition of H^+ extrusion by the proton pumps	71
Syzygium aromaticum (L.) Merr. & Perry/ Myrtaceae	Eugenol	*C. albicans* fitness test	Alters the morphogenesis of the envelope	70
Zingiber officinale/ Zingiberaceae	[6]-Shogaol	*C. albicans* fitness test	Inhibition filament formation	66

CONCLUSION

In summary, the results of the present review indicated that 34 Indonesian medicinal plants belonging to 25 families have been reported as being employed for anti-*Candida*. Ten plants have been explored for metabolite and mechanism of mode action against pathogenic *C. albicans*. These results contribute to the drug discovering of the anti-*Candida* from Indonesian medicinal plants. There is a need for the isolation and characterization of the metabolite from Indonesian medicinal plants that responsible for the anti-*Candida* properties.

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