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## ORIGINAL ARTICLE

### Medicinal Plants for Dermatophytosis: *Senna Alata* (Linn.) Roxb., *Allium sativum* (Linn.) and *Cymbopogon citratus* (DC.) Stapf

#### ABSTRACT

Skin mycoses have been a major problem affecting millions around the globe. The threat of resistance to synthetic antifungal agents however is a major obstacle in its management. As an alternative to these, a thorough investigation of natural products is being performed to develop medicines that are effective and safe. In this review, we described three antifungal herbal plants that are available in the Philippines, namely *Senna alata* (Linn.) Roxb. (akapulko), *Allium sativum* (Linn.) (garlic) and *Cymbopogon citratus* (DC.) Stapf (lemongrass). In vitro studies showed promising results that can be used as a basis for drug formulation for community use as well as commercial products. So far, there have been no reported toxic effects from these plants. The common ground for these plants' mechanism of action was the effect of their phytochemicals in the cell membrane and cell wall organelles, inhibition of major biosynthetic pathways, and prevention of biofilm formation. Formulation and clinical studies also revealed promising results comparable to the synthetic ones.

**KEYWORDS:** *antifungal, dermatophytosis, Senna alata, Allium sativum, Cymbopogon citratus*

## INTRODUCTION

Skin mycosis, also known as dermatophytosis, is a global health problem that infects millions around the globe. An estimated one billion people have skin, nail, and hair fungal infections<sup>1</sup>. While they are generally non-lethal, they greatly impact everyday life, routine and confidence of those infected.

Fungal diseases are caused by keratinophilic pathogenic fungi known as dermatophytes that can be classified into three genera based on conidial morphology: Epidermophyton, Microsporum, and Trichophyton. Some of the dermatophytes include *Trichophyton rubrum* (causative agent of tinea pedis (toes), tinea cruris (groin and inner thighs), tinea unguium (nails) and tinea corporis (skin)), *T. interdigitale* (tinea pedis and tinea cruris), *T. tonsurans* (tinea capitis (scalp, eyebrows, and eyelashes) and tinea corporis), *Microsporum audouinii* (tinea capitis) and *M. canis*<sup>2</sup>. Fungi invade the skin's epidermal layer, hair, and nails by producing keratinase that digest the keratinized layer of these integuments<sup>3</sup> and then establish themselves by thieving available nutrients for them to survive. At a molecular level, subtilisin gene (SUB) encoding serine protease catalyzes the initial contact and adherence of the fungi to the keratinized tissues of the skin<sup>4</sup>.

In the Philippines, fungal infections were reported as the second leading cause of visits to dermatology clinics with a prevalence of 12.98%. The most frequently encountered diseases were pityriasis versicolor (25.34%), tinea corporis (22.63%), tinea cruris (16.7%), and tinea pedis (16.38%)<sup>5</sup>. At present, antifungal agents such as azoles, allylamines, and tolnaftate<sup>6</sup> are used in the treatment of dermatophytosis. These agents inhibit ergosterol synthesis, thereby altering membrane stability and permeability<sup>7,8</sup>. While there are advantages to these synthetic drugs, the development of resistance to antifungal agents make it harder to cure skin mycoses. Resistance has been reported for antifungal drugs, including griseofulvin<sup>9</sup>, azoles<sup>10</sup>, and terbinafine<sup>11</sup>. Azole resistance for dermatophytes was reported to be 19% in certain countries. Factors such as host's immune status, varying geographical location, prolonged use, and misuse of antifungal drugs, fungal factors, and drug-related factors<sup>8,12</sup> contribute to resistance. From a molecular standpoint, resistance is conferred by the upregulation or downregulation of various cis- and trans-

acting elements, chromosomal abnormalities, formation of biofilms, involvement of heat-shock protein 90 (Hsp90) and increased mRNA stability<sup>7</sup>. The reduced affinity of the azoles to its target molecules and increased expression of efflux pumps (ATP-binding cassette pump and major facilitator superfamily pumps)<sup>8</sup> contribute to azole resistance. Lastly, the appearance of superbugs such as *Candida auris*, first identified in 2009, adds to the problem as this species is generally multidrug-resistant<sup>8</sup>.

The disadvantages of synthetic antifungal agents have made the search for other types of antifungals an ongoing race. Natural medicinal products have long been sought for its wide range of pharmacologic activity and safety. The main objective of this review is to highlight three herbal plants identified to have antifungal activity in vitro and in human studies. The authors did a thorough search for articles and reports for *Senna alata* (Linn.) Roxb., *Allium sativum* (Linn.) and *Cymbopogon citratus* (DC.) Stapf. and these are highlighted in this review.

### ***Senna alata* (Linn.) Roxb.**

*Senna alata* (Linn.) Roxb., more commonly known as candle bush, akapulko, ringworm bush, or calabra bush, has an average height of 10-15 feet with green leaves organized in alternate arrangement and a yellow flower<sup>13</sup>. The name ringworm bush was given because it was efficient in treating ringworm, a skin disease previously known to be caused by ringworm and other fungal diseases of the skin<sup>14</sup>.

Akapulko is pharmacologically active as a hepatoprotective, antihelminthic, anti-inflammatory, and antimicrobial agent<sup>15-18</sup>. Phytochemicals present in the plant were alkaloids, flavonoids, saponin, tannin, terpenoids<sup>19,20</sup>, anthracenosides, gallic tannins<sup>21</sup>, anthraquinone, volatile oil<sup>22</sup>, cardiac glycosides, gum, lipids, mucilage, phytosterol, quinone<sup>19</sup>, coumarin<sup>23</sup>, glycosides, phenols, steroids<sup>20</sup> and proanthocyanidin<sup>24</sup>. Some of the compounds observed in the plant and as revealed by gas chromatography – mass spectrometry (GC-MS) were aloe-emodin, cassiaindoline, and kaempferol<sup>25,26</sup>.

In a recent review<sup>27</sup>, the plant's ethanolic, aqueous, methanolic and hexane leaf, stem and root extracts have activities against *Aspergillus flavus*, *A. niger*, *A. parasiticus*, *Candida albicans*, *C. neoformans*, *Epidermophyton floccosum*, *M. canslaslomyces*, *M. canis*,

*M. gypseum*, *M. audouinii*, *T. verrucosim*, *T. megnini*, *T. mentagrophytes*, *T. rubrum*, *T. tonsurans*, and *Penicillium marneffeii*. In addition, its ethanolic extract showed excellent activity and is favorable in formulating a topical treatment for those infected with these fungi. A study also showed that soap formulated with akapulko ethanolic extract showed a higher reduction of viable cell count at  $94.78 \pm 1.82\%$  compared to an antiseptic soap ( $91.88 \pm 1.63\%$ )<sup>28</sup>.

The National Integrated Research Program (1996) developed a 50% akapulko lotion on medicinal plants, which underwent both non-clinical and clinical research, and which showed efficacy and safety against cutaneous fungal infections. In a systematic review and meta-analysis featuring seven random clinical trials for akapulko topical cream *S. alata* 50% lotion, the authors concluded that *S. alata* 50% lotion may be as efficacious as sodium thiosulfate 25% lotion and is as efficacious as ketoconazole 2% and terbinafine 1% creams<sup>29</sup>.

#### **Allium sativum (Linn.)**

*Allium sativum* of family Liliaceae, more commonly known as garlic, is a famous food seasoning and spice. The names “stinking rose,” “poor man’s treacle,” and “nectar of God” were given to this plant due to its characteristic pungent smell. It has a history of being used as a remedy for various diseases such as leprosy, scurvy, earaches, flatulence, and epidemics such as typhus, dysentery, cholera, and influenza<sup>30</sup>. Garlic bulb covered with a membranous scale has an average diameter of 4-6 cm depending on the variety and the number of bulblets or cloves present<sup>31</sup>.

Phytochemicals extracted by using different solvents from the garlic bulb include alkaloids, flavonoids, steroids, saponin, carbohydrates, glycosides<sup>32</sup>, triterpenes, tannin<sup>33</sup>, reducing sugars<sup>34</sup>, terpenoids, anthraquinone, phenolics, cardiac glycosides, phlobotannin<sup>35</sup>, carotenoids, and phytates<sup>36</sup>. GC-MS studies revealed that specific compounds such as ajoene, thiosulfides<sup>37</sup>, allicin<sup>37,38</sup>, disulfides, trisulfides, monosulfides<sup>39</sup>, gentisic acid, chlorogenic acid, 4-hydrobenzoic acid, and p-Coumaric acid<sup>38</sup> can be derived from garlic as well. The major compound in garlic, allicin, is produced upon the action of alliinase to alliin and exists only after crushing or injuring the bulb<sup>31</sup>.

In vitro analysis of the antifungal activity of garlic is summarized in Table 1. Aqueous, ethanolic, methanolic, and petroleum ether extracts and the garlic juice extract showed antifungal activity against a wide spectrum of fungal species, comparable with the controls used. Combining the extract with the commercially available antifungal agent also showed promising results. The minimum inhibitory concentration (MIC) of fluconazole against *C. albicans*, *C. tropicalis*, and *C. glabrata* was lower suggesting a synergistic relationship between the extract and the synthetic drug in combating these fungi<sup>40</sup>. Synergism between ketoconazole and the extract was also observed against *T. mentagrophytes*, *T. rubrum*, *T. verrucosum*, *M. canis*, and *E. floccosum*<sup>41</sup>. The llocos garlic has also shown good antifungal activity against *Saccharomyces cerevisiae*, *C. albicans*, *M. canis*, *T. rubrum*, and *T. mentagrophytes*<sup>42</sup>

Table 1. In vitro analysis of the antifungal activity of *Allium sativum* against different fungal pathogens.

Organism	Extract/Media/Technique	Result	
		MIC (mg/mL)	Inhibition
<i>Alternaria alternata</i>	Aqueous, PDA, AWD	6.25	$11.7 \pm 0.3 \text{ mm}^{43}$
	Methanolic, PDA, AWD	156.2	$11.2 \pm 0.2 \text{ mm}^{43}$
<i>A. flavus</i>	Petroleum ether, SDA, CPAD	2.5	$38 \pm 1.26 \text{ mm}^{44}$
	Aqueous, SDA, CPAD	2.5	$23 \pm 0.82 \text{ mm}^{44}$
<i>A. niger</i>	Garlic Juice, SDA, ADD		$41 \pm 4.0 \text{ mm} > \text{ clotrimazole } (22.5 \pm 1.5 \text{ mm})^{45}$
	Ethanolic, PDA, PFT		93.03% mycelial growth inhibition at 200 mg/mL <sup>46</sup>
	Aqueous, PDA, AWD	3.12	$22.5 \pm 0.3 \text{ mm}^{43}$
	Methanolic, PDA, AWD	312.5	$8.4 \pm 0.1 \text{ mm}^{43}$
	Petroleum ether, SDA, CPAD	2.5	$16 \pm 1.09 \text{ mm}^{44}$

	Aqueous, SDA, CPAD	2.5	14±1.63 mm <sup>44</sup>
	Methanolic, SDA, PPT		42 mm inhibition at 100 mg/mL <sup>47</sup>
<i>A. parasiticus</i>	Aqueous, PDA, AWD	12.5	11.7±0.1mm <sup>43</sup>
	Methanolic, PDA, AWD	156.2	11.7±0.3mm <sup>43</sup>
<i>A. ustus</i>	Ethanollic, PDA, PFT		100% inhibition at 200 mg/mL <sup>46</sup>
<i>C. albicans</i>	Garlic juice CPAD		41 mm (Ilocos garlic) <sup>42</sup>
	Ethanollic CPAD		53 mm at 10% (Ilocos garlic) <sup>42</sup>
	Garlic Juice, SDA, ADD		28±1.0 mm > Clotrimazole (27.5±0.5mm) <sup>45</sup>
	Methanolic, SDA, ADD	12.5	29 mm <sup>32</sup>
	Methanolic, SDA, PPT		37 mm inhibition at 100 mg/mL <sup>47</sup>
	Petroleum ether, SDA, CPAD	2.5	23±0.05 mm <sup>44</sup>
	Aqueous, SDA, CPAD	2.5	16±1.41 mm <sup>44</sup>
	Aqueous, SBM	3.125 <sup>40</sup>	
<i>C. glabrata</i>	Aqueous, SBM	1.56 <sup>40</sup>	
<i>C. krusei</i>	Aqueous, SBM	6.25 <sup>40</sup>	
<i>C. parolopsis</i>	Methanolic, SDA, ADD	3.125	21.8 mm <sup>32</sup>
<i>C. tropicalis</i>	Methanolic, SDA, ADD	6.25	30 mm <sup>32</sup>
	Aqueous, SBM	0.78 <sup>40</sup>	
<i>Curvularia lunata</i>	Petroleum ether, SDA, CPAD	2.5	45±1.34 mm <sup>44</sup>
	Aqueous, SDA, CPAD	2.5	45±1.15 mm <sup>44</sup>
<i>E. floccosum</i>	Aqueous, SDA, AWD		6 mm < Nystatin (25mm) <sup>48</sup>
	Ethanollic, SDA, AWD		12 mm < Nystatin (25mm) <sup>48</sup>
	Methanolic, SDA, AWD		13.33 mm < Nystatin (25mm) <sup>48</sup>
<i>Fusarium</i>	Aqueous, SDA, AWD	> 20	2.4 mm at 5 mg/mL 4.2 mm at 10 mg/mL 9.5 mm at 20 mg/mL <sup>49</sup>
	Ethanollic, SDA, AWD	2.5	4.1 mm at 2.5 mg/mL 6.2 mm at 5 mg/mL 10.1 mm at 10 mg/mL 14.3 mm at 20 mg/mL <sup>49</sup>
<i>F. oxysporum</i>	Aqueous, PDA, AWD	3.12	22.6±0.1mm <sup>43</sup>
	Methanolic, PDA, AWD	156.2	10.4±0.1mm <sup>43</sup>
<i>M. canis</i>	Garlic juice CPAD		37 mm (Ilocos garlic) <sup>42</sup>
	Ethanollic CPAD		33 mm at 10% (Ilocos garlic) <sup>42</sup>
<i>Penicillium</i>	Ethanollic, PDA, PFT		92.97% mycelial growth inhibition at 200 mg/mL <sup>46</sup>
<i>Rhizopus</i>	Aqueous, SDA, AWD	> 20	4.3 mm at 5 mg/mL 5.2 mm at 10 mg/mL 10.4 mm at 20 mg/mL <sup>49</sup>
	Ethanollic, SDA, AWD	5.00	5.2 mm at 2.5 mg/mL 6.4 mm at 5 mg/mL 9.1 mm at 10 mg/mL 12.2 mm at 20 mg/mL <sup>49</sup>
<i>S. cerevisiae</i>	Garlic juice, CPAD		41 mm (Ilocos garlic) <sup>42</sup>
	Ethanollic, CPAD		53 mm at 10% (Ilocos garlic) <sup>42</sup>

<i>T. rubrum</i>	Ethanollic, CPAD	42 mm at 10% (Ilocos garlic) <sup>42</sup>
	Aqueous, SDA, AWD	18.33 mm < Nystatin (31mm) <sup>48</sup>
	Ethanollic, SDA, AWD	23.33 mm < Nystatin (31mm) <sup>48</sup>
<i>T. metagrophytes</i>	Methanollic, SDA, AWD	30.67 mm < Nystatin (31mm) <sup>48</sup>
	Ethanollic CPAD	40 mm at 10% (Ilocos garlic) <sup>42</sup>
	Aqueous, SDA, AWD	18 mm < Nystatin (30mm) <sup>48</sup>
<i>T. verrucosum</i>	Ethanollic, SDA, AWD	24 mm < Nystatin (30mm) <sup>48</sup>
	Methanollic, SDA, AWD	28.33 mm < Nystatin (30mm) <sup>48</sup>
	Aqueous, SDA, AWD	15.67 mm < Nystatin (28mm) <sup>48</sup>
<i>T. rubrum</i>	Ethanollic, SDA, AWD	23.67 mm < Nystatin (28mm) <sup>48</sup>
	Methanollic, SDA, AWD	24.67 mm < Nystatin (28mm) <sup>48</sup>

Legend: SDA – Sabouraud Dextrose Agar; PDA – Potato Dextrose Agar; AWD – Agar Well Diffusion; ADD – Agar Disk Diffusion; CPAD – Cup Plate Agar Diffusion; PPT – Pour Plate Technique; PFT – Poisoned Food Technique; SBM – Standard Broth Microdilution

The molecular mechanism of action of the garlic extract was determined using transmission electron microscopy, scanning electron microscopy, and proteomics. The extract induced several changes in the fungi such as damaged cell wall and cell membrane, formation of vacuoles, cytoplasmic granulation, cytoplasmic loss, destroyed hyphae, destroyed cellular organelles, and pseudohyphae development<sup>38,39,50,51</sup>. *In vitro*, the lag phase of the fungi was longer compared to the control, and the exponential phase was inhibited<sup>51,52</sup>. Allicin can induce cell membrane damage and impede lipid biosynthesis<sup>50</sup>. In addition, allicin, when combined with Amphotericin B and flucytosine, destroyed the fungal membrane and lowered its adhesive force<sup>53</sup>. Allyl alcohol, on the other hand, lengthened the lag phase, affected the cell wall and cell membrane, decreased cytoplasmic volume, reduced glutathione and rate of oxygen consumption, and increased cytoplasmic granulation, the concentration of reactive oxygen species and mitochondrial membrane potential<sup>51</sup>. Proteomic analyses revealed differentially expressed proteins involved in major fungal metabolic pathways, including drug metabolism, redox processes, pathogenesis, cellular response to stress, cell cycle, DNA replication, gene expression processes, protein modification, synthesis of nucleotides and certain signaling pathways<sup>52</sup>.

Clinical studies on garlic's antifungal ability have been conducted in the Philippines. In a study conducted at MCU-FDTMF Hospital, 36 patients were randomly

assigned to either garlic cream or ketoconazole treatment for superficial mycoses. They were instructed to apply the medications thinly on the affected area twice a day for one month. Weekly evaluations of microscopic clearance of fungi by KOH smear, relief of subjective complaint of itchiness, relief of objective sign of scaling, shortening of treatment duration, and adverse reactions were observed. Garlic cream was successful and equally effective as ketoconazole in terms of conversion of positive into negative KOH smears and in alleviating subjective complaints such as itchiness. Ketoconazole had no side effects while the garlic cream presented with erythema and burning sensation in the area applied, albeit tolerable<sup>54</sup>.

Another clinical study comparing garlic cream and ketoconazole, enrolled 72 patients with Tinea Versicolor, confirmed through positive KOH (potassium hydroxide) smear. After a two-week period, the smear conversion rate was similar between the two groups, and no adverse reactions were observed nor reported<sup>55</sup>.

The safety and effectiveness of 0.6% ajoene gel compared with 1% terbinafine cream for the treatment of 60 soldiers with clinical and mycological diagnosis of either tinea corporis or tinea cruris was also studied. After thirty days of treatment, the ajoene and terbinafine groups resulted in 77 and 75 percent healing rates, respectively. Sixty days after treatment, the healing rates were 73% and 71% for the groups treated with ajoene and terbinafine, respectively.

Several trials have shown good clinical evidence on the potential of garlic as an effective antifungal



agent<sup>56</sup>. As an oral rinse, garlic mouthwash was compared to nystatin mouthwash for denture stomatitis and given to patients for four weeks. The changes in the length and width of erythema were found to be significant for both treatments. Moreover, greater satisfaction with the use of garlic was seen compared with nystatin<sup>57</sup>.

### ***Cymbopogon citratus* (DC.) Stapf**

Known as lemongrass, *Cymbopogon citratus* belongs to the family of Poaceae and is characterized by a lemon-like odor. It is used as a food flavoring and is common in teas, soups, and curries<sup>58</sup>. It is a perennial herb that grows approximately two meters in height with short rhizomes that can be a means of propagation. The plant has reported antimicrobial, anti-inflammatory, and antioxidant properties and has been added to pesticides, insecticides, cosmetics, perfumes, and pharmaceuticals<sup>59</sup>. In the Philippines, it is traditionally used in the control of diabetes and for cleansing<sup>60</sup>. The phytochemical constituents observed in lemongrass include alkaloids, tannins, flavonoids<sup>60,61</sup>, saponins, phenols, carbohydrates, reducing sugars<sup>62</sup>, anthraquinones, steroids<sup>63</sup>, terpenoids<sup>64</sup>, volatile oil<sup>66</sup>,

unsaturated fats<sup>60</sup>, phlorotannins, cardiac glycosides<sup>66</sup>, triterpenoids, and phytosterols<sup>67</sup>. GC-MS analysis of essential oils extracted from lemongrass showed three major components arranged from the most to the least abundant: geraniol (37.70 - 52.80%), neral (31.52 - 36.65%) and  $\beta$ -myrcene (3.73% - 11.41%)<sup>68-70</sup>.

Majority of the in vitro antifungal analysis of lemongrass was done on the plant's essential oil. Essential oil is approximately 1-2% of the lemongrass's dry weight<sup>71</sup>. In several studies summarized in Table 2, liquid and vapor phases of the essential oil were compared for its antifungal activity. Better antifungal activities were observed in vapor phases, which might suggest that the volatile compounds present were more effective in inhibiting fungal growth. In vitro analysis of an antifungal cream containing 2.5% and 3.0% lemongrass oil had higher efficiency compared to the commercially available creams that contain clotrimazole, isoconazole, and nitrate as its active ingredient<sup>72</sup>. Silicon rubber surfaces coated with essential oil and prepared using hypromellose ointment showed a 45-76% decrease in biofilm formation. The oil inhibited biofilm formation of the two strains of *C. tropicalis* (U71 and V89)<sup>73</sup>.

Table 2. In vitro analysis of the antifungal activity of *Cymbopogon citratus* (DC.) Stapf against different fungal pathogens.

Organism	Extract, Media, Technique	Result	
		MIC	Inhibition
<i>A. flavus</i>	LGEO (liq), PDA, Plate Assay	0.9 $\mu$ L/mL	Total inhibition of fungal growth at 1.0 $\mu$ L/mL observed for 8 days <sup>74</sup>
	LGEO (liq), SDA, DDA		90 mm <sup>69</sup>
	LGEO (vap), SDA, VDT		90 mm <sup>69</sup>
	LGEO (liq), PDA, PFT	5 $\mu$ L/mL	<ul style="list-style-type: none"> <li>- Spore production reduced by 23.2% at 1 <math>\mu</math>L/mL</li> <li>- Spore germination reduced by 79.7% at 4 <math>\mu</math>L/mL</li> <li>- 100% inhibition of Aflatoxin B1 production<sup>70</sup></li> </ul>
<i>A. fumigatus</i>	LGEO (liq), SDA, DDA		90 mm <sup>69</sup>
	LGEO (vap), SDA, VDT		90 mm <sup>69</sup>
<i>A. niger</i>	LGEO (liq), SDA, DDA		An1 - 90 mm; An2 - 59 mm <sup>69</sup>
	LGEO (vap), SDA, VDT		An1 - 59 mm; An2 - 75 mm <sup>69</sup>
	LGEO (liq), PDA, PFT	5 $\mu$ L/mL	<ul style="list-style-type: none"> <li>- Spore production reduced by 38.9% at 1 <math>\mu</math>L/mL</li> <li>- Spore germination reduced by 91.3% at 4 <math>\mu</math>L/mL<sup>70</sup></li> </ul>

<i>A. ochraceus</i>	LGEO (liq), PDA, PFT	5 $\mu$ L/mL	<ul style="list-style-type: none"> <li>- Spore production reduced by 45.6% at 1 <math>\mu</math>L/mL</li> <li>- Spore germination reduced by 84% at 4 <math>\mu</math>L/mL<sup>70</sup></li> </ul>
<i>A. parasiticus</i>	LGEO (liq), PDA, PFT	5 $\mu$ L/mL	Spore production reduced by 39.2% at 1 $\mu$ L/mL Spore germination reduced by 88.2% at 4 $\mu$ L/mL <sup>70</sup>
<i>A.s terreus</i>	LGEO (liq), SDA, DDA		90 mm <sup>69</sup>
	LGEO (vap), SDA, VDT		90 mm <sup>69</sup>
<i>C. albicans</i>	LGEO (liq), SDA, DDA		Ca1 - 80 mm; Ca2 – 90 mm; Ca3 – 90 mm; Ca4 – 45 mm <sup>69</sup>
	LGEO (vap), SDA, VDT		Ca1-Ca4 – 90 mm <sup>69</sup>
	Chloroform, SDA, DDA	Leaf – 32 $\mu$ g/mL Root – 38 $\mu$ f/mL <sup>65</sup>	
	LGEO (liq), PDA, DVA	288 mg/L	80 mm inhibition at 20 $\mu$ L LGEO liquid phase <sup>75</sup>
	LGEO (vap), PDA, DVA	32.7 mg/L	Complete inhibition at 40 $\mu$ L LGEO vapor phase <sup>75</sup>
<i>C. dubliniensis</i>	LGEO (liq), SDA, BDM	0.43 mg/mL	80% biofilm formation inhibition at MIC; Reduced adhesion to acrylic at 1.7 mg/mL concentration <sup>76</sup>
<i>C. parapsilosis</i>	LGEO (liq), SDA, DDA		Cp1 - 90 mm; Cp2 – 18 mm <sup>69</sup>
	LGEO (vap), SDA, VDT		Cp1 - 90mm; Cp2 – 25 mm <sup>69</sup>
<i>C. tropicalis</i>	LGEO (liq), SDA, DDA		Ct1 and Ct2 - 90 mm <sup>69</sup>
	LGEO (vap), SDA, VDT		Ct1 and Ct2 - 90mm <sup>69</sup>
<i>E. floccosum</i>	LGEO (liq), SDA, DDA	115 $\mu$ g/mL	90 mm <sup>72</sup>
<i>M. furfur</i>	LGEO (liq), Mycosel medium, ADT	0.62 $\mu$ L/mL <sup>68</sup>	
<i>M. globose</i>	LGEO (liq), Mycosel medium, ADT	0.31 $\mu$ L/mL <sup>68</sup>	
<i>M. obtusa</i>	LGEO (liq), Mycosel medium, ADT	0.62 $\mu$ L/mL <sup>68</sup>	
<i>M. sloofiae</i>	LGEO (liq), Mycosel medium, ADT	0.31 $\mu$ L/mL <sup>68</sup>	
<i>M. sympodialis</i>	LGEO (liq), Mycosel medium, ADT	1.52 $\mu$ L/mL <sup>68</sup>	
<i>Mi. gypseum</i>	LGEO (liq), SDA, DDA	235 $\mu$ g/mL	90 mm <sup>72</sup>
<i>Mucor</i>	LGEO (liq), SDA, DDA		42 mm <sup>69</sup>
	LGEO (vap), SDA, VDT		90mm <sup>69</sup>
	Ethanolic	Stem – 1.10 mg/mL <sup>66</sup>	
<i>Penicillium</i>	LGEO (liq), SDA, DDA		90 mm <sup>69</sup>
	LGEO (vap), SDA, VDT		90 mm <sup>69</sup>
	Ethanolic	Leaf – 0.70 mg/mL	

		Stem – 1.10 mg/mL <sup>66</sup>	
<i>T. mentagrophytes</i>	LGEO (liq), SDA, DDA	122.5 µg/mL	90 mm <sup>72</sup>
<i>T. rubrum</i>	LGEO (liq), SDA, DDA	135 µg/mL	90 mm <sup>72</sup>

Legend: LGEO (liq) – Lemongrass essential oil (liquid); LGEO (vap) – Lemongrass essential oil (vapor); SDA – Sabouraud Dextrose Agar; DDA – Disk Diffusion Assay; VDT – Vapour Diffusion Technique; PFT – Poisoned Food Technique; ADT – Agar Dilution Technique; BDM – Broth Dilution Method; DVA – Disc Volatilization Assay

The mechanism of action of lemongrass essential oil (LGEO) lies in its ability to disrupt the cell membrane. In a report, both vapor and liquid phases caused disturbed fungal membranes. The most significant effect at a minute MIC, however, was observed in the vapor phase<sup>75</sup>. In another report, the citral component of LGEOs prevented the formation of pseudohyphae and chlamydoconidia in *C. albicans*<sup>77</sup>. In a review of the mechanism of action of the lemongrass essential oils, it was found that LGEO target structures such as the cell membrane, cell wall and mitochondria. Moreover, these compounds affect cell growth and morphology, block efflux pumps, increase reactive oxygen species production and prevent biofilm formation, mycotoxin synthesis, and quorum sensing<sup>78</sup>.

A study was conducted in South Africa to investigate the safety and efficacy of lemon juice and lemongrass in the treatment of oral thrush in HIV/AIDS patients versus gentian violet aqueous solution 0.5%, which is the standard of care<sup>79</sup>. Ninety patients were enrolled in the study, but only 82 had complete and acceptable data. Thirty patients were enrolled in the lemongrass arm, but only 17 completed the study. Based on the intention to treat analysis, the difference between lemongrass and gentian violet was not statistically significant. In the per-protocol analysis, lemongrass was significantly better than gentian violet aqueous solution 0.5% in treating oral thrush in an HIV-positive population.

In the Philippines, clinical trials for antifungal creams formulated with lemongrass extracts have been performed<sup>80</sup>. A double-blind, randomized controlled trial on the effectiveness of 10% lemongrass oil vs. 1% clotrimazole solution against tinea corporis and tinea cruris was conducted. Ninety-six patients with clinically and mycologically diagnosed tinea corporis and/or tinea cruris were assigned randomly to apply either 10% lemongrass oil or 1% clotrimazole solution twice daily for four weeks. There was no statistically significant

difference in terms of complete cure at four weeks between the two groups ( $p=1.0$ , Fisher's exact test). There was no recurrence two weeks post-treatment in both groups. Erythema and burning sensation from the application of lemongrass were observed in two patients.

In another randomized clinical study comparing lemongrass 10% cream versus Clotrimazole 1% cream in the treatment of superficial fungal skin infections at Quezon City General Hospital<sup>81</sup>, it was found that after two weeks, both treatments showed statistically significant improvement from baseline. The clotrimazole group showed faster resolution of lesions. No adverse reaction was observed or reported in the lemongrass group.

## CONCLUSION

Akapulko (*Senna alata*), garlic (*Allium sativum*), and lemongrass (*Cymbopogon citratus*) have demonstrated their antifungal effects both in vitro and in clinical studies. An Akapulko, 50% formulation, has undergone Phase 1 to 3 clinical trials and awaits further commercialization. Lemongrass and garlic preparations are good alternatives as topical antifungal agents and may be used in the community and further developed into commercial preparations.



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