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Herbal Antimycotics and Their Prospects in Therapeutics

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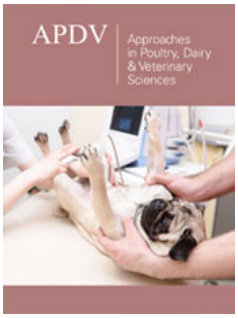

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Summary

Herbal antimycotics are being researched as antimicrobials to treat antibiotic-resistant fungal infections and as food preservatives (against food spoilage and mycotoxigenic fungi). Several antimycotic herbal compounds including cinnamaldehyde (in cinnamon, camphor, and cassia oils), carvacrol (in oregano, thyme, thymus and ajowan oils) and citral (in lemongrass, verbena, and citronella oils) inhibit yeasts and molds in microgram concentration. Their therapeutic use is still limited because of several biological, chemical, and pharmaceutical reasons. The dearth of long-term toxicity studies, pharmacodynamics and pharmacokinetics data, verifiable clinical trials data (at various stages of drug development), quality control, standard testing and preparation protocols, reference values and pharmacopoeia. Thus, proclaiming herbal antimycotics as future drugs either as an alternative or as a complementary therapeutic agent is still farfetched dream to come true.

Keywords: Herbs; Anti-mold; Anti-*Candida*; Drug-standards

Introduction

Herbal antimicrobials are considered as the future drugs to fight against multi-drug-resistant (MDR) microbes [1]. However, reports of resistance in microbes to herbal antimicrobials [2] are common. Probably lack of systematic data leads to the misconception about unbeatable efficacy of herbal antimicrobials to counter MDR pathogens. Literature shows that many bacteria, yeasts and molds are resistant to antibiosis induced by herbal antimicrobials [3,4]. Although, scientific investigations claim efficacy of herbal antimycotics, they are not effective on all fungi (similar to antimycotic antibiotics) and thus, can only be used as an alternate or complementary to antibiotics as proposed for MDR bacteria [5].

Herbal antimycotics are classified based on their utility:

1) Inhibiting the environmental, plant pathogenic and food degrading fungi,

2) Inhibiting growth of potentially pathogenic fungi affecting human, animal and birds, and

3) Broad-spectrum ones inhibiting all different types of yeasts and molds. Another classification may be based on their activity as anti-yeasts, anti-molds, and broad-spectrum affecting both yeasts and molds.

Anti-mold herbal antimicrobials

Molds are the source of many antibiotics and show resistance to a wide range of antibiotics as well as herbal antimicrobials. However, the molds that cause infections (invasive aspergillosis and mucormycosis) are also susceptible to selective antifungal drugs [6]. Several herbal antimicrobials are found to be effective in *in-vitro* studies against molds causing infections. Essential oils of lemongrass (*Cymbopogon citrates*) [3,4], ajowan (*Trachyspermum ammi*) and African basil (*Ocimum gratissimum*) [7] inhibit 70-100% of pathogenic fungi; agar-wood (*Aquilaria malaccensis*) inhibit 65% of the pathogenic molds [4], carvacrol, an ingredient of essential oils of thyme (*Thymus vulgaris*), ajowan (*Trachyspermum ammi*) and oregano (*Origanum vulgare*) inhibit almost 80% to 100% of the pathogenic the molds

[4], and cinnamaldehyde from cinnamon oil, cinnamodial and cinnamosmolide from *Pleodendron costaricense* kill majority of the molds [8], and many more, extensively reviewed by Vengurlekar and co-workers [9]. However, essential oils of *Aegle marmelos, Artemisia vulgaris, Caesulia axillaris, Cinnamomum tamala*, *Cinnamomum camphora, Citrus medica, Corymbia citriodora, Eupatorium cannabinum, Lippia alba, Mentha arvensis, Murraya koenigii, Nepeta hindostana, Citrus sinensis, Tagetes erecta, Vetiveria zizanioides, Vitex negundo, Zanthoxylum acanthopodium, Zingiber officinale* [7], *Commiphora mukul, Santalum album*, *Zanthoxyllum rhetsa* and *Pogostemon cablin* [4] have weak anti-mold potential.

Besides essential oils, fixed oils of mustard with seeds of trigonella, ajwoin, mustard and garlic bulbs completely inhibited growth of *Aspergillus niger, A. flavus, Absidia corymbifera, Penicilium nigricans* and *Candida albicans.* On the other hand, coconut oil with ajowan seeds was less fungitoxic [10]. Mycotoxin producing molds were inhibited with powdered herbs as cloves (*Eugenia caryophyllus*), cinnamon (*Cinnamomum zeylanicum* B.), allspice (*Pimenta dioica*), mustard *(Sina.pis alba*), garlic (*Allium satiuum*), and oregano (*Oreganum vulgare*) inhibited growth of myco-toxigenic molds at the 2% level in potato dextrose agar while thyme (*Thymus vulgaris*), turmeric (*Curcuma longa*), anise (*Pimpinella onisum*), paprika (*Capsicum annum*), red pepper (Red Cayenne, *Capsicum annuum*), black pepper *(Piper nigrum*), white pepper (*Piper nigrum*), leaves of sage (*Salvia officinalis*) and rosemary (*Salvia rossmarinus*) and onion *(Allium cepa*) had only little effect on the growth of mycotoxin producing fungi [11]. Among the 56 Chinese herbs tested, decoctum (containing 10% of herbal extract by weight) from *Carthamus tinctorius* and *Rheum palmatum* effectively controlled the growth of *A. flavus* [12]. *In-vitro* studies revealed the potential of herbal compounds as anti-mold. They have limited pharmaceutical value because most of the compounds may be toxic in therapeutic doses or their *in vivo* therapeutic concentration may be unachievable. Their utility as anti-mold is limited in food preservation due to unacceptable concentration required as preservative.

Anti-yeast herbal antimicrobials

Comparatively yeasts are more sensitive to antibiotics as well as herbal antimycotics than molds [4,13-15]. A variety of herbal compounds including essential oils of ajowan (*Trachyspermum ammi*), betel (*Piper betle*), guggul (*Commiphora mukul*), thyme (*Thymus vulgaris*), cinnamon (*Cinnamomum verum* and *Cinnamomum zeylanicum*), marjoram (*Origanum majorana*), holy basil (*Ocimum sanctum*), lemongrass (*Cymbopogon citrates*), sandalwood (*Santalum album*), *Zanthoxyllum rhetsa,* patchouli (*Pogostemon cablin*), thymus (*Thymus villosus*), peppermint (*Mentha piperita***)**, eucalyptus (*Eucalyptus globulus*), ginger grass (*Cymbopogon martinii*), coriander (*Coriandrum sativum*), agarwood (*Aquilaria malaccensis*), *Eupatorium odoratum* and *Ageratum conizoides* can restrict the growth or kill the yeasts [4,9,12,15,16]. The most potent anti-candida activity is reported in carvacrol (present in ajowan, oregano, thyme and thymus oils) and cinnamaldehyde (in cinnamon, camphor and cassia plant oils) that can inhibit almost all strains of yeasts in microgram concentration [4,15].

Besides essential oils, herbal extracts are also effective in controlling the growth of *Candida albicans*. Among effective herbal extracts, alcoholic extracts *of Lawsonia inermis, Limonia acidissima, Tamarindus indica, Swertia chirata, Psidium guajana, Annona reticulate, Euphorbia hirta, Pogostemon parviflorus, Adenocalymma alliacum, Echinophora platybola, Cuminum cyminum, Withania somnifer, Curcuma longa, Cymbopogon citrates,* and *Zingiber officinale* inhibited *C. albicans* at ≥5mg/mL concentration [17]. Aloholic extracts of leaves of *Ageratum conizoides* and *Eupatorium odoratum* inhibited 20-40% *Candida* strains at ≥ 1mg/mL concentration [4]. Although, the minimum inhibitory concentration (MIC) of alcoholic extracts for *Candida albicans* appears low, not low enough for therapeutic treatments [4]. Testing 56 Chinese herbal drugs against *Candida albicans; Scutellaria baicalensis* and *Rheum palmatum* had the highest activity while against *Geotrichum candidum* extracts of *Agastache rugosa* and *Pogostemon cablin* were the best, but an extract of *Mentha haplocalyx* was only moderately effective but against all i.e., *C. albicans, G. candidum* and *A. flavus* [12].

Prospects

Herbal compounds though promising as antimycotics, suffer from several deficiencies being included as mainstream antimycotic therapy. Herbal compounds like antibiotics vary in their efficacy and spectrum of activity as antimycotics. Some of the herbal compounds like cinnamaldehyde (in oils of cinnamon, camphor, and cassia), carvacrol (in oils of oregano, thyme, thymus and ajowan) and citral (in oils of lemongrass, verbena, and citronella) are considered broad spectrum antimycotics.

However, the biggest hurdle in use of herbal antimycotics in therapeutics are unavailability of verified and verifiable data on their toxicity in pharmaceutical doses, long term clinical safety and efficacy data and lack of pharmacodynamics and pharmacokinetics studies on herbal compounds. Besides, variability in the concentration of active ingredient and purity of active ingredient from batch to batch in herbs (as it depends on age, stage and season of harvesting herbs, and also on geographical location of their cultivation), variability even in *in-vitro* testing protocols and inconsistency in their reported efficacies, lack of pharmacopoeia standards for herbal antimicrobials, and problems in quality testing including lack of quality control standards and facilities are still bigger problems. Therefore, only through mending deficiencies mentioned herein herbal antimicrobials can be seen as future drugs either as an alternative or as a complementary therapeutic agent.

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