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In Vitro Antimicrobial Activity of Medicinal Plants against Oral *Candida albicans* Isolates

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ABSTRACT

In most countries of subtropical Africa, bacterial and fungal infections represent an increasing problem, particularly with patients suffering from severe immune deficiencies. *Candida* species are responsible for a wide range of systemic as well as superficial opportunistic infections. *Candida albicans* is a normal commensal, isolated intraorally in 17 to 75% of healthy individuals and all debilitated people. Eradication of candidiasis is complicated by the emergence of *Candida* strains that are resistant to the currently used antifungal agents. Furthermore, these antifungal agents are limited in number, are costly and in addition may be toxic. Plants as remedies are used by ~80% of the population in developing countries and their use is gaining popularity in developed countries. Although, many plants have already been investigated for their antifungal activity against *C.albicans* the search is still on to find a long-term prevention or cure for oral candidiasis. It is essential that such a product will prevent a recurrence of the condition, be inexpensive and prevent the development of antifungal resistance.

Keywords: antifungal, candidiasis, herbal remedies, inhibition

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INTRODUCTION

In most countries of subtropical Africa, bacterial and fungal infections represent an increasing problem, particularly with patients suffering from severe immune deficiencies, such as Acquired Immunodeficiency Syndrome (AIDS) (Atindehou *et al.* 2002). *Candida* species are responsible for a wide range of systemic as well as superficial opportunistic infections (candidiasis) occurring most frequently in vaginal or oral mucosa (Cannon *et al.* 1995; Williams *et al.* 1997). *Candida* species are normal oral commensals (Samaranayake 1990), and are isolated intraorally in 17 to 75% of healthy individuals (Arendorf and Walker 1980; Bastiaan and Reade 1982; Rindum *et al.* 1994) and all debilitated people.

The adhesion of microbes to the host's mucosal surfaces is a major determinant of successful microbial colonization and subsequent infection, and its critical role in the pathogenesis of many fungal infections is well recognized (King *et al.* 1980; Shibl 1985; Fukazawa and Kagaya 1997). Various *in vitro* studies (Samaranayake and MacFarlane 1981a, 1982) and animal studies (McCourtie and Douglas 1984; Calderone *et al.* 1985) provide evidence for a relationship between the proclivity of *Candida* species to adhere to mucosal surfaces and their presence in infections. Therefore, candidal adherence to human buccal epithelial cells (HBEC) is considered the critical initial step in the pathogenesis of oral candidiasis, which may eventually lead to a systemic infection, especially in immuno-compromised people (Schafer-Korting *et al.* 1996).

Plants as remedies are used by ~80% of the population in developing countries and their use is gaining popularity in developed countries (Ernst 2005). Medicinal plants have attracted considerable research attention as new sources of antimicrobial agents. A wide variety of plant extracts have antimicrobial effects and anti-inflammatory properties, and several herbal extracts have been added to some cosmetics and health-care preparations (Taweechaisupapong *et al.* 2005).

This short review describes the occurrence of *C. albicans* in the oral cavity as well as the treatment of candidiasis with conventional medication and herbal remedies.

CANDIDA ALBICANS IN THE ORAL CAVITY

C. albicans is a fungus that can grow in a number of morphological forms, ranging from yeast to hyphae (Cannon *et al.* 1995). Pseudohyphal forms are also seen, and this morphology can be assumed by several other *Candida* species (Odds 1988). Sherwood *et al*. (1992) demonstrated that hyphae are capable of contact-sensing or thigmotropism. *C. albicans* hyphae incubated on perforated filters over agar plates have been shown to grow through the pores and along grooves, possibly facilitating the penetration of some tissues. Certain *C. albicans* strains exhibit high-frequency switching of colony morphology when nutritionally stressed and this can be accompanied by chromosomal translocation allowing the asexual *C. albicans* to adapt to environmental

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change (Soll 1992). Evidence has confirmed that *C. albicans* cell surface modulation occurs *in vivo* (De Benardis *et al.* 1994). These surface changes may enable a commensal yeast strain to escape immune surveillance (Diamond 1993) or adhere to different host receptors, thereby promoting candidiasis (Cannon *et al.* 1995). Changes in surface protein glycosylation may expose hydrophobic protein structures at the cell surface (Hazen and Glee 1994), in turn affecting adherence properties. Yeast cell surface changes may be brought about by *Candida*-host interactions as adherence to human buccal epithelial cells induces the synthesis of new proteins in *C. albicans* and the expression of signal proteins (Bailey *et al.* 1995). An understanding of adherence mechanisms, the signals they generate and the processes that they induce, may therefore lead to specific preventive treatments for individuals predisposed to candidiasis (Cannon *et al.* 1995).

A diverse array of host factors has been implicated in the pathogenesis of oral candidiasis (Samaranayake 1990). The local factors are mucosal barrier, saliva, phagocytes, and the morphogenesis of *C. albicans*. The systemic factors are: immuno-compromised individuals (patients with diseases such as diabetes mellitus, leukemia, AIDS, and cancer) and altered nutritional factors (such as iron and vitamin deficiency). Iatrogenic factors include antibiotic therapy, corticosteroid therapy, cytotoxic and radiotherapy (irradiation) and cigarette/tobacco smoking (Samaranayake 1990). These local and systemic factors act in concert and the eventual outcome of these disease processes are frequently related to the superimposition of the local factors upon systemic factors or *vice versa*.

TREATMENT OF ORAL CANDIDIASIS

Conventional therapy

Patients with oral candidiasis have painful mouths and experience difficulty with eating and swallowing. These patients are treated with the membrane-active polyenes nystatin and amphotericin B, usually administered as a suspension or lozenges, while the ergosterol biosynthesis inhibitors (imidazoles and triazoles) are administered as tablets (miconazole, ketaconazole, and fluconazole), as a gel (miconazole), or as troches (clotrimazole) (Budtz-Jörgensen 1990b; Martin 1990; Cannon *et al.* 1995). Exposure of HBEC to amphotericin B, nystatin (Macura 1988; Abu-Elteen *et al.* 1989) and ketoconazole (King *et al.* 1980; Sobel and Obedeanu 1983) have been shown to inhibit germination of *Candida* species and reduce attachment to human epithelial cells leading to a reduction in oral candidiasis. However, eradication of candidiasis is complicated by the emergence of strains of *Candida* that are resistant to the currently used antifungal agents (Perea *et al.* 2001; Khan *et al.* 2003). The currently used antifungal agents are limited in number, are costly and in addition may be toxic (Salie *et al.* 1996; Mehta *et al.* 2002; Ship *et al.* 2007). Furthermore, the social stigma associated with the HIV disease in many developing regions in Africa and Asia appears to modify the therapeutic strategies and management of fungal infections (Samaranayake *et al*. 2002). Relapse of *Candida* infections is also very common (Debruyne 1997) and this increases the burden of managing this opportunistic infection. These factors prompt the need for development of new antifungal agents in order to widen the spectrum of activities against *Candida* species and combat strains expressing resistance to the available antifungals.

Herbal remedies

Natural products have been used worldwide for medicinal purposes for thousands of years (Patel and Coogan 2008). In many developing countries, a large number of people depend on medicinal plants as their primary source of medication. Up to a quarter of all prescriptions in industrialised countries contain one or more components derived from plants (Farnsworth 1990). Medicinal plants are frequently employed in oral-health; the twigs of plants have been used as "toothbrushes" whereas leaf tinctures are used as mouthwashes (Lewis 1980).

Streblus asper Lour (Moraceae; toothbrush tree) is used for the treatment of a variety of oral complaints; the bark for relief of fever, dysentery, toothache and gingivitis (Gaitonde *et al.* 1964) and the twigs as a "toothbrush" for strengthening teeth and gums (Lewis 1980). Antibacterial activity against endodontic and periodontal pathogens has been demonstrated for the ethanolic leaf extract of *Streblus asper* (Taweechaisupapong *et al.* 2000a, 2002a). Moreover, mouthwashes containing the ethanolic extract have been shown to improve gingival health (Taweechaisupapong *et al.* 2002b). Regarding the *in vitro* adhesion of *C. albicans* to HBEC, Taweechaisupapong *et al.* (2005) found that *Streblus asper* leaf extract significantly ($p<0.05$) reduces adherence of *C. albicans* to HBEC after one hour pre-treatment exposure to the extract. The mechanism responsible for inhibition of adherence by *S. asper* extracts remains undetermined, but it could include alterations to cell surface features that in turn masts the adhesions present on the yeast or on the receptors present on the buccal cells. Other possibilities are that *S. asper* extract interferes with the synthesis of adhesins that are involved in the adhesion process, or that it causes a mechanical distortion of the adhesins already present in the outer envelopes, thereby blocking adherence (Taweechaisupapong *et al.* 2005). Exposure of HBEC to garlic extract (Ghannoum 1990) and date extract (Abu-Elteen 2000) have shown inhibition of germination of *Candida* species and reduced attachment to human epithelial cells, leading to a reduction in oral candidiasis. The inhibition of germ tube formation is important since it is well known that germ tube and mycelial forms of *C. albicans* adhere more efficiently to host cells than do yeast cells (Kimura and Pearsall 1980; Sobel *et al.* 1981; Hostetter 1994; Pendrak and Klotz 1995).

Decoctions of the leaves of *Dodonaea viscosa* var. *angustifolia* (hopbush) have been used since the 1700's and are still used today for the treatment of oral infections (Van Wyk *et al.* 2002; Patel and Coogan 2008). This plant has analgesic activity (Amabeoku *et al.* 2001), antiviral activity (against both Human immunodeficiency virus (HIV) 1 and 2) and is non-toxic (Asres *et al.* 2001). These properties suggest that the extract has the potential to be used as an effective mouthrinse for the prevention of recurrent oral candidiasis by reducing the number of *Candida* species in the mouth to an acceptable level (Patel and Coogan 2008). Furthermore, the analgesic activity contributes to reducing the pain in the mouth, a symptom of patients with oral candidiasis. Lawsone methyl ether, isolated from *Rhinacanthus nasutus* (dainty spurs) leaves possesses potent antifungal activity, making it a cost-effective mouthrinse (Blignaut *et al.* 2006).

In a study to identify a traditional remedy to treat oral candidiasis, Motsei *et al.* (2003) reported that *Allium sativum* (garlic), *Glycyrrhiza glabra* (liquorice), *Polygala myrtifolia* (August/September bush) and *Tulbaghia violacea* (wild garlic) inhibited growth of the standard strain (ATCC10231) and two clinical isolates of *C. albicans* (isolated from a 5-month-old baby and an adult). *Glycyrrhiza glabra* and *Polygala senega* (Seneca snakeroot) are also extensively used in Europe as treatment for oral candidiasis. Both plants contain saponins, compounds known to possess antifungal activity (Bruneton 1995). Thin layer chromatography (TLC)-bioautography has indicated several active compounds in *Allium sativum* and *Tulbaghia violacea* bulb extracts, one being allicin. Allicin is the active compound in garlic containing antimicrobial and antifungal properties against most Gram-positive and Gram-negative bacteria, as well as *C. albicans* (Wagner and Bladt 1996; Ankri and Mirelman 1999). Allicin's main antimicrobial effect is ascribed to its chemical reaction with the thiol groups of various enzymes (Ankri and Mirelman 1999). Furthermore, Ghannoum (1988) reported that the inhibitory effect of

Table 1 Summary of the plants identified in literature and mentioned in the text with antimicrobial activity against *C. albicans*.

Plant name (Latin binomial, common name)	Family	Active Constituent(s)	Activity Noted	Mechanism of Action	MIC Concentration mg/ml	Clinical Trial	References
Acacia nilotica Black thorn tree	Fabaceae	Tannins	Activity noted	Antimicrobial action	-	Yes	Runyoro *et al.* 2006
Allium sativum Garlic	Alliaceae	Thiol	Weak activity	Oxidation of thiol thus inactivation of enzymes and microbial growth	H_2O 6.25	Yes	Ghannoum, 1988; Motsei *et al.* 2003
Balanites aegyptiaca Simple thorned torch tree, Jericho balsam	Balanitaceae	Saponins	Weak activity	Antimicrobial action of saponins is well known	-	Yes	Runyoro *et al.* 2006
Combretum molle Velvet bush willow	Combretaceae	Tannins	Weak activity High activity	-	H_2O 6.50 M 1.00	Yes	Runyoro *et al.* 2006
Curtisia dentata Cape lancewood	Cornaceae	Flavonoids, phenolic compounds terpenoids	High activity	-	D 0.15 A 0.12 H 0.60	Yes	Shai 2007
Cussonia zuluensis Cabbage tree	Araliaceae	Saponins, tannins	High activity	-	D 1.88 A 1.25	Yes	Shai 2007
Dichrostachys cinerea Chinese lantern tree, Kalahari Chrismast tree, sicklebush	Fabaceae	Triterpenes, sterols, tannins	Activity noted	Not known, may be due to combi-nation of active ingredients	-	No	Runyoro *et al.* 2006
Dioscorea minutiflora Ivory Coast wild yam	Dioscoreaceae	Saponins, diosgenin, heterosides	High activity	-	100 µg/ml on plate for TLC	Yes	Quigley 1978; Atindehou *et al.* 2002
Dodonaea viscosa var. *Angustifolia* Hopbush	Sapindaceae	Diterpenoids, dodonic acid, hautriwaic acid	Weak to high activity	Details of its exact action are not available	H_2O >25 ETOH 2.09 ETOAc 1.04 H >8.35	Yes	Van Wyk *et al.* 2002; Motsei *et al.* 2003
Eriocephalus africanus Cape of Good Hope shrub	Asteraceae	Dehydrofalcarin, sesquiterpenoil lactones, ivangustine	-	-	-	No	Van Wk *et al.* 2002
Glycyrrhiza glabra Liquorice	Fabaceae	Saponins, chalcones, flavonoids, isoflavonoids	High activity	Not known, may be due to combi-nation of active ingredients	H_2O 12.5 ETOH 2.09 ETOAc 2.09 H >8.35	Yes	Bruneton 1995; Motsei *et al.* 2003
Helichrysum crispum Hottentots bedding	Asteraceae	Flavonoids, sesquiterpenoids, acylated phloroglucinols	-	-	-	No	Van Wyk *et al.* 2002
Kigelia africana Sausage tree	Bignoniaceae	Naphthoquinone lapachol, Dihydroisocoumarin kigelin	High activity	Beneficial effect may be due to the dihydroisocou-marins and their glycosides	H 0.45 D 0.23 A 0.23	Yes	Shai, 2007
Ozoroa insignis Tropical resin tree	Anacardiaceae	Not known	Activity noted	Not known	-	No	Runyoro *et al.* 2006
Polygala myrtifolia August/September bush	Polygalaceae	Saponins	Weak activity	Saponins are well documented for their antimicrobial activity	H_2O 6.25 ETOH 8.35 ETOAc >8.35 H >8.35	Yes	Motsei *et al.* 2003
Polygala myrtifolia August/September bush	Polygalaceae	Saponins	Weak activity	Saponins are well documented for their antimicrobial activity	H_2O 6.25 ETOH 8.35 ETOAc >8.35 H >8.35	Yes	Motsei *et al.* 2003
Salvadora persica Toothbrush tree	Salvadoraceae	-	Activity noted	-	-	Yes	Runyoro *et al.* 2006
Sclerocarya birrea Marula	Anacardiaceae	Procyanidins, gallotannins, flavonoids, catechins	Activity noted	Not known, may be due to combi-nation of active ingredients	-	No	Van Wyk *et al.* 2002; Runyoro *et al.* 2006
Securidaca longepedunculata Violet tree	Polygalaceae	Methyl salicylate, sapogenins	Activity noted	Presence of salicylate (winter green oil) may explain recorded uses	-	Yes	Van Wyk *et al.* 2002; Runyoro *et al.* 2006
Streblus asper Toothbrush tree	Moraceae	-	Weak activity	Reduce germ tube formation	ETOH 15.6	Yes	Taweechai-supapong *et al.* 2005
Terminalia phanerophlebia Lebombo cluster-leaf	Combretaceae	Tannins, saponins	High activity	Triterpenoids and saponins are well known for their antimicrobial activity	H 0.30 D 0.30 A 0.15	Yes	Shai 2007
Terminalia sambesiaca	Combretaceae	Tannins, saponins	High activity	Triterpenoids and saponins are well known for their antimicrobial activity	H 0.23 D 0.23 A 0.12	Yes	Shai 2007
Trichilia emetica Natal mahogany	Meliaceae	Limonoids, tannins	Weak activity	Exact pharmaco-logical effects appear to be unknown	H_2O >25 ETOH >8.35 ETOAc >8.35 H >8.35	Yes	Shai 2007

Table 1 (Cont.)

Plant name (Latin binomial, common name)	Family	Active Constituent(s)	Activity Noted	Mechanism of Action	MIC Concentration mg/ml	Clinical Trial	References
Tulbaghia violacea Wild garlic	Amaryllidaceae	Allicin	Weak activity	Oxidation of thiol thus inactivation of enzymes and microbial growth	H_2O 12.5 ETOH 2.09 ETOAc 2.09 H 8.35	Yes	Wagner and Bladt 1996; Ankri and Mirrelman 1999; Motsei *et al.* 2003
Zanha africana Velvet-fruited zanha	Sapindaceae	Not known	Activity noted	-	-	No	Runyoro *et al.* 2006
Ziziphus mucronata Buffalo thorn	Rhamnaceae	Alkaloids (peptide alkaloids), mucronine D	Activty noted	Not known	_	No	Van Wyk *et al.* 2002; Runyoro *et al.* 2006
Verpris reflexa bushveld white-ironwood	Rutaceae	Tannins, quinolone alkaloids (veprisinium salt)	High activity	Not known, may be due to combi-bination of ac-tive ingredients	H 1.25 D 1.25 A 1.25	Yes	Shai 2007

ETOH - ethanol; H_2O - water; D - dichloromethane; M - Methanol
ETOAc - ethyl acetate; H - hexane; A - acetibe; - - no data

garlic against yeast is attributed to the exidation of essential protein thiol, causing inactivation of enzymes and subsequent microbial growth inhibition.

Plants from Tanzania with antifungal activity against *C. albicans* and used to treat oral candidiasis include: dried fruits of *Acacia nilotica* (black thorn tree); saponin fraction from the mesocarp of *Balanites aegyptiaca* (simple thorned torch tree, Jericho balsam); methanolic extract of the leaf of *Cajanus cajan* (pigeon pea); fruits, roots, latex and leaves of *Carica papaya* (papaya); methanol extract of the dried bark of *Combretum molle* (velvet bush willow); dried stem of *Dichrostachys cinerea* (Chinese lantern tree, Kalahari Christmas tree (South Africa), sicklebush); methanol extract of dried root bark of *Harrisonia abyssinica*; dried stem bark of *Ozoroa insignis* (tropical resin tree); roots of *Salvadora persica* (toothbrush tree); ethanolic extract of dried stem-bark of *Sclerocarya birrea* (marula); aqueous, dichloromethane and ethanol extracts of *Securidaca longepedunculata* (violet tree); aqueous and methanol extracts of the stem-bark of *Ziziphus mucronata* (buffalo thorn) and stem-bark of *Zanha africana* (velvet-fruited zanha). Some of these plants also inhibited *Cryptococcus neoformans* growth, which is an important pathogenic fungi in HIV/AIDS (Runyoro *et al.* 2006).

Lipophilic extracts of the leaves of *Eriocephalus africanus* L. (Cape of Good Hope shrub), stems of *Helichrysum crispum* (L.) D. Don. (Hottentots bedding) and leaves of *Felicia erigeroides* DC. (Felicia) possesses in *vitro* antimicrobial activity, amongst others against the fungus *C. albicans* (Salie *et al.* 1996). The herbal remedies: *Curtisia dentata* (Cape lancewood); *Trichilia emetica* (Natal mahogany); *Kigelia africana* (sausage tree); *Terminalia sambesiaca*; *Vepris reflexa* (bushveld white-ironwood); *Terminalia phanerophlebia* (Lebombo cluster-leaf) and *Cussonia zuluensis* (cabbage tree) have shown promising inhibitory activity against *C. albicans* with minimal inhibitory concentration (MIC) values of the crude extracts between 0.08-1.0 mg/ml (Shai 2007). One-hundred and fifteen plants used as traditional medicine in the Ivory Coast were evaluated by Atindehou *et al.* (2002) for antibacterial and antifungal activity, which included *C. albicans* and *Cladosporium cucumerinum. Dioscorea minutiflora* (Ivory Coast wild yam), and *Erythrina vogelii* ('Ouossoupalie' à Fleurs rouges (French)/red flower tree), contained the best antifungal activity. Interestingly, young tubers of *D. minutiflora* displayed strong antifungal activity whereas older tubers did not show any antifungal properties. This could be due to the presence of diosgenin heterosides in the young tubers and their absence in the old tubers of *Dioscorea* species, previously reported in West Africa (Quigley 1978). The plants containing activity against *C. albicans* have been summarised in **Table 1**.

In conclusion, although many plants have been investigated to determine their antifungal activity against *C. albicans*, the search is still on to find a long-term prevention or cure for oral candidiasis. This product should prevent recurrence of the condition, be inexpensive and prevent the development of antifungal resistance. The plant compound/s isolated thus far and presented in the text and Table should be further researched as these could play a role in future drug development.

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