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Antidermatophytic Activity of Essential Oils from Plants

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Author's contribution

The sole author designed, analysed, interpreted and prepared the manuscript.

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ABSTRACT

Superficial mycoses are the strictly surface infections involving skin, hair, nails and mucosa. It is caused by dermatophytes that infect only keratin rich tissues without involving the living tissue and they are incapable of penetrating subcutaneous tissues. Ringworm or Dermatophytosis is found world-wide with most prevalence in hot climatic countries. Nowadays, the increasing impact of these infections, the limitations encountered in their treatment like antibiotic resistance, side-effects and high toxicity and the rising over prescription and overuse of conventional antifungals all stimulate a search for alternative natural drugs. In general, plant-derived essential oils are non-phytotoxic and potentially effective against all fungal pathogens & dermatophytes. They can be used as a natural therapy to inhibit the growth of these fungal pathogens. In recent years there has been a gradual revival of interest in the use of medicinal products such as essential oil and other botanical products in response to the ever increasing incidence of adverse side effects associated with conventional drugs, high cost medicines, long duration of treatment time and emergence of resistance to antifungal drugs especially in case of dermatophytosis.

Keywords: Dermatophytosis; essential oils; drug resistance; fungal pathogens.

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1. INTRODUCTION

Human skin can be infected by many different types of pathogenic fungi. Dermatophytes attend to infect human skin cells for their content of keratin protein. They distributed more common in the entire world, especially tropical and sub-tropical warm and humid countries. *Trichophyton, Microsporum* and *Epidermophyton* are only known genera of dermatophytes until now that responsible for human skin diseases. Hair, skin cells, and nail are the most important parts of human body that enrichment with keratin. Therefore, dermatophytosis that is caused by dermatophytes restricted only in human body content one or more of those keratinous tissues.Superficial fungal infections are caused by dermatophytes, non-dermatophytic moulds and commensal yeasts (Gupta et al, 2014). Dermatophytes, the most common causative agents, are assuming high significance in developing countries like India (Gupta et al, 2014). These organisms metabolise keratin and cause a range of pathologic clinical presentations, including *Tinea pedis, Tinea corporis, Tinea cruris,* etc. [1]. Although usually painless and superficial, these fungi can behave in an invasive manner, causing deeper and disseminated infection and should not be neglected. The lesions may become widespread and may have significant negative social, psychological, and occupational health effects, and can compromise the quality of life significantly [2]. Currently, dermatologists across India are inundated with cases of dermatophytosis presenting with unusual large lesions, ring within ring lesions, multiple site lesions (*Tinea cruris* et corporis), and corticosteroid modified lesions, making diagnosis a difficult bet [3]. This changed face of dermatophytosis has created a real panic among dermatologists. In addition, chronicity of the disease has plagued the patients unlike any other dermatological condition in the country [3]. The recent prevalence of dermatophytosis in India ranges from 36.6–78.4% [4]. Superficial Mycoses are the strictly surface infections involving skin, hair, nails and mucosa. It is caused by dermatophytes that infect only keratin rich tissues without involving the living tissue and they are incapable of penetrating subcutaneous tissues. Ringworm or Dermatophytosis is found world-wide with most prevalence in hot climatic countries [5]. These are the group of fungi that are keratin loving like to eat keratin present in outer epidermal layers of skin, hair and nails in human beings. They are very pathogenic fungi that obtain their food from keratin rich tissues from living cells. They are parasitic in nature [6]. Such type of infections spreads by contact, it may be direct or indirect, from infected humans and animals (direct) or through indirect contact such as inanimate objects and fomites (Nweze, 2010). Dermatophytes are classified into three genera, i.e. *Trichophyton, Microsporum* and *Epidermophyton.* These genera belong to Class Hyphomycetes and Division Deuteromycota. Other factors responsible for dermatophytosis is high sweating during summer, contact with animals, use of unhygienic towels, clothes and wearing of tight undergarments. Due to this major factor dermatophytosis was a very common superficial fungal infection of human beings in India [7]. Sometimesinfection may also be caused by Candida species and non-dermatophytes. Non dermatophytes belong to the genera *Fusarium, Scopulariopsis and Aspergillus* [8]. Proper diagnosis of disease was required proper laboratory diagnosis. Culture examination was the crucial step after KOH mount to identify the accurate causative agent. In some cases, on the basis of clinical symptoms, specific identification of invasive mould will be carried out. Some nail and skin infection, also reported which are caused by non dermatophytes molds which are often resistant to antidermatophytic drugs [9]. Candidiasis is the most common fungal infection mostly caused by yeast like fungus *Candida albicans* in 90% cases. Such type of infections are called Candidiasis. *C. albicans* was also normal microbial flora of healthy human body but when human body immune system is weak and suppressed due to old ages and use of immunosuppressive drugs, *Candida ablicans* was converted into pathogenic form and cause disease known as Candidiasis [10,11]. Dermatophytosis are the most common types of superficial fungal infections. Which are seen in human and animals. These are caused by group of keratinophilic fungi which are capable of invading keratinized tissues of skin and its adjunct like hair and nail. They belong to three mycelial fungal genera which are *Trichophyton, Microsporum* and *Epidermophyton*. These are collectively knownas dermatophytes. The other frequently used terms like *Tinea* (ringworm) infection are synonym of dermatophytosis. In the recent times few cases of subcutaneous and deep seated infections have been reported to be caused by dermatophytes. A review of literatures reveals that there are many essential oils which acquire antifungal activity (Ahmet et al, 2005). Essential oils and their elements are expanding

interest because of their comparatively safe status, wide acceptance by consumers and their exploitation for potential multi-purpose functional uses. Essential oils are made up of diverse volatile compounds and the composition varies between species [12]. It appears that the antifungal and antimicrobial effects are the outcomes of many compounds acting synergistically [13]. These oils are one of the most promising groups of natural compounds for the development of safer antifungal agents [14].

2. TREATMENTS FOR DERMATOPHYTOSIS

Treatment of dermatophytosis can perform by two pharmaceutical forms of drugs: topical and systemic drugs and some time both. Most of ring worm lesions on glabrous skin that have limited size can be treated by topical creams or solution as shampoo, such as clotrimazole and miconazole, etc. (Straten et al., 2003) while nail infected of nail and hair required systemic treatment, such as griseofulvin, itraconazole, etc. [15]. All of dermatophytes infections need a long time to be cured that not less than two weeks. Some of cases needed at least six months to cure such as *Tinea capitis* and onychomycosis. Distribution of squamous epithelium cells that hold fungal elements within it are the most source to cause dermatophytosis new infection. Thus, good hygiene and limited sharing things of other people is the gold key to control and prevent the infection with dermatophytes. Moreover, decrease contact with animals is also important to get high level of protection.

Systemic antifungal drugs such as griseofulvin, terbinafine, ketoconazole, fluconazole, and itraconazole have been known to be active against dermatophytes, terbinafine being the only fungicidal drug [16]. Among these drugs, itraconazole and terbinafine are more often prescribed compared to griseofulvin and fluconazole, probably because the latter require longer duration of treatment. Most of these treatment options, however, have been found to be non effective in the therapy of the recurrent, recalcitrant, and chronic widespread dermatophytosis and steroid-modified tinea that is currently prevalent across the country. A study by Majid et al., done at Srinagar concluded that incomplete cure was very common after a 2-week course of terbinafine 250 mg (Majid et al, 2016). The need of the hour is therapeutic studies to evolve national guidelines for the management of dermatophytosis in the Indian population, as the treatment of dermatophytosis in the current scenario is mostly experience based than evidence based. Topical antifungals should be used to prevent spread but cannot supplant systemic treatment. Corticosteroids have been used in inflammatory tinea capitis (e.g., kerion) with the aim to reduce scarring. However, in comparison with oral antifungal treatment alone no definite long-term advantage has been shown and therefore are no longer recommended.

Treatment of dermatophytosis depends upon the site and the kind of lesion. Localized dermatophytic infection is the main indication of topical application of antifungal therapy. Most patients with ringworm infections can be treated with topical antifungal drugs, such as butenafine (1%), butoconazole (1%), ciclopiroxolamine (1%), clotrimazole (1%), Eberconazole (1%), econazole (1%), itraconazole (1%), Ketoconazole (2%), luconazole (1%), oxiconazole (2%), miconazole (2%), naftifine (1%), sertaconazole (1%), sulconazole (1%), terbinafine (1%), terconazole (1%), tioconazole (1%), and tolnaftate (1%).The topical medicines should be applied as a thin layer once or twice a day depending on the therapeutic agents to the affected area for 2 to 3 weeks. Clinical efficacy of terbinafine 1% cream was studied in 16 patients of localized Tineacorporis (Pal & Patel, 2018). All the patients showed complete clinical cure at third week of its continuous topical use. The drug was well tolerated with no adverse effects in the treatment of Tinea corporis (Pratibha Dave, Personal observation). It is suggested that infants and pregnant women should preferably be treated with topical antifungal drugs. However, systemic therapy with fluconazole (150 mg orally), it raconazole (100 - 200 mg orally) and terbinafine (250 - 500 mg) is suggested in tinea capitis, Tineapedis, tinea unguium, wide spread invasive lesions, recurrent or chronic lesions, unresponsive to topical antifungal drugs, and immune compromised state. Clinical experience has shown that management of tinea barbae is better with oral medications than topical therapy as affected hair follicles do not respond well with topical drugs. It is advised that itraconazole should be taken immediately after full meals. People with a history of liver disease should not take oral terbinafine therapy. As oral antifungal drugs may cause some side effects, it is pertinent to monitor the patient during the course of therapy. The duration of treatment may vary from one month to one year depending on the type of tinea and severity of lesions. It is

experienced that ringworm infection is persistent and resistant in 10% of the patients. Effective treatment with antifungal drugs can reduce the duration of symptoms and give relief to the patients. It is advised that patient should continue the drugs until clinical cure is achieved. In case of any drug reaction, patient should immediately consult the physician. It is emphasized that early (Pal & Patel, 2018).

3. LIMITATIONS OF AVAILABLE STRATEGIES OF TREATMENT

Over the last few decades, there has been an increase in the number of serious human infections in immune compromised patients caused by fungi [17]. The range of severity of these infections is a consequence of the host reaction to the metabolic products produced by fungi, the virulence of the infecting strain, the site of infection and also environmental factors (Romani, 2007). Nowadays, the increasing impact of these infections, the limitations encountered in their treatment (e.g. resistance, side-effects and high toxicity) and the rising over prescription and overuse of conventional antifungals [18]; Ferris *et al.*, 2002) all stimulate a search for alternative natural drugs.

- The increasing resistance to antifungal compounds and the reduced number of available drugs led us to search for the new alternatives among aromatic plants and their essential oils, used for their antifungal properties. The increased use of antibacterial and antifungal agents in recent years has resulted in the development of resistance to these drugs.

- Amphotericin B is fungicidal and is the most broad spectrum antifungal available. One of the primary drawbacks of polyenes is their significant toxicity, although the development of lipid formulations of amphotericin B has reduced this problem significantly [19]; such formulations are quite expensive and not available in some regions. Amphotericin B, in combination with the adjunctive drug 5-flucytosine, is the treatment of choice for cryptococcal meningitis (Day et al. 2013)as well as for a wide range of less common invasive mycoses.
- The emergence of acquired drug resistance among prevalent fungal pathogens restricts treatment options, which alters patient management. A greater understanding of mechanism-specific resistance and the biological factors that contribute to resistance emergence is critical to develop better therapeutics, and to improve diagnostics and intervention strategies that may overcome and prevent resistance.

- Clinical resistance refers to therapeutic failure in which a patient fails to respond to an antifungal drug following administration at a standard dose. The development of antifungal resistance is complex and depends on multiple host and microbial factors (White et al. 1998).Host immune status is a critical factor, as fungi static drugs must work synergistically to control and clear an infection. Patients with severe immune dysfunction are more likely to fail therapy, as the antifungal drug must combat the infection without the benefit of an immune response (Ben-Ami et al., 2008). The presence of indwelling catheters, artificial heart valves, and other surgical devices may also contribute to refractory infections, as infecting organisms attach to these objects and establish biofilms that resist drug action (Ramage et al. 2009; Bonhomme and d'Enfert 2013)

4. ESSENTIAL OILS

For many years, plants and plant-derived metabolites have served as the starting point for the discovery and development of new antimicrobial agents. Phytochemicals have been recognized as some of the most promising compounds for the development of novel ecofriendly phyto fungicides. Indeed, the need to develop plant-based fungicides as alternatives to synthetic chemicals has become a matter of priority among scientists globally (Reddy et al, 2007).The primary advantages of using plant-derived antimicrobials in comparison to synthetic chemicals are their low mammalian toxicity, high degradability, multiple mechanisms of action, and fewer incidences of the numerous side effects often associated with synthetic chemicals (Raja et al, 2014). Numerous research reports have highlighted the bioactive properties of plant essential oil against a wide range of economically important plant pathogens (Clara et al, 2013).

Essential oils contain highly volatile substances that are isolated by a physical method or process from plants of a single botanical species. The essential oils normally bear the name of the plant species from which they are derived. Essential oils are so termed as they are believed to represent the very essence of odour and flavour. Essential oil plants and culinary herbs include a broad range of plant species that are used for their aromatic value as flavourings in foods and beverages and as fragrances in pharmaceutical and industrial products. Essential oils derive from aromatic plants of many genera distributed worldwide. Oils are used in the embalming process, in medicine and in purification rituals. There are also over 200 references to aromatics, incense and ointments in the old and new testaments. There are about three hundred essential oils in general use today by professional practitioners. Continual bombardment of viral, bacterial, parasitic and fungal contamination occurs in our body. Essential oils are a great benefit to help protect our bodies and homes from this onslaught of pathogens. Immune system needs support and these essential oils can give the required endorsement (Sumonrat et al., 2008).It is estimated that there are 250,000 to 500,000 species of plants on Earth. A relatively small percentage (1 to 10%) of these is used as foods by both humans and other animal species. It is possible that even more are used for medicinal purposes (Janssen et al, 1986). In recent years, research on aromatic plants, and particularly their essential oils, has attracted many investigators. Essential oils have traditionally been used for centuries for their antifungal properties (Ríos &Recio, 2005). More recently, several studies have confirmed the huge potential of these natural products as antifungal agents (Bakkali*et al.*, 2008; Zuzarte*et al.*, 2009). Therefore, it is not surprising that essential oils are one of the most promising groups of natural products for the development of broad-spectrum, safer and cheaper antifungal agents. Plant oils and extracts have been used for a wide variety of purposes for many thousands of years(Kommera et al, 2006).The mechanism of action of essential oils remains somewhat controversial. While some studies suggest that the compounds may penetrate the micro-organism and react with active sites of enzymes and/or interfere with cellular metabolism, most evidence supports direct disruption of cellular membranes and concentration-dependent pro-oxidant cytotoxic effects (Bakkali*et al.*, 2008). Application of essential oil has long been consideredavery promising scheme for controlling postharvest disease. The production of essential oils by plants has been considered to be principally a defence means against pathogens and pests and definitely most of the oils have been shown to possess antimicrobial and antifungal properties. There are various methods to extract essential oils but the most popular method is the steam distillation in which water is heated to produce steam that carries the most volatile chemicals of the plant materials with it. The steam is further cooled in a condenser and the resulting distillate is collected. The oil normally float on top of the Hydrosol (the distillate water component) and may be separated off (Abed, 2007).

5. ROLE OF ESSENTIAL OILS IN TREATMENT OF DERMATOPHYTE INFECTION

In general, plant-derived essential oils are non phytotoxic and potentially effective against all fungal pathogens (Chaung et al., 2007). They can be used as a natural therapy to inhibit the growth of these fungal pathogens. In recent years, several researchers have reported the mono and sesquiterpene hydrocarbons as the major components of plant essential oils with enormous potential to inhibit microbial pathogens. Essential oil of aromatic plants has been recognized for many years as a major source of pharmaceutical agents and food additives. In recent years there has been a gradual revival of interest in the use of medicinal products such as essential oil and other botanical products in response to the ever increasing incidence of adverse side effects associated with conventional drugs, high cost medicines, long duration of treatment time and emergence of resistance to antifungal drugs especially in case of dermatophytoses.

Jain et al reported the antidermatophytic activity of essential oil of *Trachyspermum ammi* and its fractions against fungi causing dermatophytoses in humans along with toxicological evaluation on mice. This study concluded that essential oil of *T. ammi* and its fractions have strong antidermatophytic properties with no side effect at low concentrations and thus could produce alternative therapeutics to current antibiotics.

Nedorostova et al. (2009) tested the essential oils of 27 plants species on L. monocytogenes

ATCC 7644, *S. aureus* ATCC 25923, *E. coli* ATCC 25922, *P. aeruginosa* ATCC 27853, and *S. enterica* Enteritidis ATCC 13076. Of these, 13 were active, and only the essential oils of *Allium sativum* and *Armoracia rusticana* were capable of inhibiting all of the bacteria. *Staphylococcus aureus* was inhibited by all active oils, followed by *E. coli* (8), *L. monocytogenes* (7), *S. enterica* Enteritidis (6), and *P. aeruginosa* (2).

Staphylococcus aureus and *L. monocytogenes* are Gram positive bacteria, which can facilitate the action of the oils; in other words, there is high incorporation of the additive into the cell wall (HARPAZ et al., 2003). In a study using the same test conducted *In vitro*, Dorman and Deans (2000) used essential oils of clove, oregano, geranium, and pepper to evaluate their activity on 25 species of Gram-positive and Gran-negative bacteria. Those authors observed that Gram-positive bacteria were more susceptible to the essential oils studied than the Gram-negative bacteria.Some studies demonstrated that essential oils of oregano, thyme, and rosemary are among the more active antimicrobials (DIMITRIJEVIĆ et al., 2007). However, it can be observed in the present study that the largest inhibition halos were found for *Cymbopogon citratus*. According to Moreira et al. (2005), lipophilic compounds of the oils bond the phospholipid bilayer of the cell membrane increasing its permeability and spreading out the intracellular contents or damaging the enzymatic system of the cell. Souza et al. (2010) mention that even small changes occurring in the cytoplasmic membrane structure can affect the metabolism, including the macromolecule synthesis.

The essentials oils extracts from many plants such as basil, citrus, fennel, lemon grass, oregano, rosemary, and thyme have shown considerable antifungal activity against a wide range of fungal pathogens (Fu et al, 2007). Arora and Kaur (1999) observed the antimicrobial activity of essential oils extracted from spices against fungal pathogens. They found that garlic and clove extracts inhibited the growth of *Candida acutus, C. albicans, C. apicola, C. catenulata. C. inconspicua, C. tropicalis Rhodotorula rubra, Saccharomyces cerevisiae,* and *Trigonopsis variabilis*. Similarly, Grohs and Kunz (2000) investigated mixtures of ground spices and demonstrated their efficacy against the *C. lipolytica*. According to the report of Ultee and Smid (2001) oregano and thyme essential oils were some of the best inhibitors of fungal pathogens, because of the phenolic compounds. The antifungal activity of essential oils and their derivatives on the cell viability, mycelium growth, and mycotoxin-producing ability of moulds has been studied (Juglal, 2002). It was concluded that, among all the tested essential oils, clove, cinnamon, and oregano essential oils were effective against *Aspergillus parasiticus* and *Fusarium moniliforme*. The oil of *Origanumvulgare* was efficient at inhibiting *C. albicans*, *Aspergillus Niger*, *Microsporum gypseum*, *Microsporum canis, Arthroderma cajetani, Trichophyton violaceum*, *Trichophyton mentagrophytes* ,*Epidermophyton floccosum*, *T. rubrum*, and *Trichophyton tonsurans* (Bozin et al, 2006)

Beatovic et al. (2015) have reported its antifungal potential against *Ocimumbasilicum*, *Aspergillus ochraceus, A. versicolor, A. niger, A. fumigates, Trichodermaviride,* and *P. funiculosum.* Similarly, the inhibitory potential of *Aeglemarmelos* oil against *C. albicans, A. niger,* and *F. oxysporum* was demonstrated.

6. FUTURE PROSPECTIVE OF ESSENTIAL OILS AGAINST DERMATOPHYTIC INFECTIONS

A wide range of medicinal and aromatic plants (MAPs) have been explored for their essential oils in the past few decades. Essential oils are complex volatile compounds, synthesized naturally in different plant parts during the process of pharmaceutical, flavor and fragrance, perfumery, and cosmetic industries (Swamy & Sinniah, 2015).At present, more than 80% of the global population depends on traditional plant-based medications for treating various human health problems (Akhtar et al, 2014, Mariri &Safi, 2014). According to an estimate, the worth of herbal products on the global market is approximately 62 billion USD, and it is predicted to grow up to 5 trillion USD by the year 2050 (Bhattacharya et al, 2014).More than 9000 native plants have been identified and recorded for their curative properties, and about 1500 species are known for their aroma and flavour. Essential-oil–based products or natural aroma chemicals are in higher demand in the cosmetic, food, perfume, and pharmaceutical industries, and more than 250 types of essential oils, at a value of 1.2 billion USD, are traded annually on the international market (Swamy et al, 2016).Essential oils have great potential in the field of biomedicine as they effectively

destroy several bacterial, fungal, and viral pathogens. The presence of different types of aldehydes, phenolics, terpenes, and other antimicrobial compounds means that the essential oils are effective against a diverse range of pathogens. The reactivity of essential oil depends upon the nature, composition, and orientation of its functional groups. The aim of this article is to review the antimicrobial potential of essential oils secreted from MAPs and their possible mechanisms of action against human pathogens. This comprehensive review will benefit researchers who wish to explore the potential of essential oils in the development of novel broad-spectrum key molecules against a broad range of drug-resistant pathogenic microbes More recently, the prevalence of antimicrobial drug resistance has prompted researchers to discover novel antimicrobial lead molecules to treat various human pathogens (Rudramurthy et al., 2016).Some of the presently available synthetic drugs fail to inhibit many pathogenic microbes. In addition, the use of synthetic chemicals for the control of pathogenic microorganisms is limited because of their carcinogenic effects, acute toxicity, and environmental hazard potential. In this regard, the exploitation of essential oils to control epidemic multidrug-resistant pathogenic microorganisms can be useful to combat various infectious diseases.(Swamy et al., 2015).Essential oils are employed in aromatherapy and for the treatment of several diseases including cardiovascular disease, diabetes, Alzheimer's, cancer (Ali et al., 2015).The antimicrobial impacts of essential oils and their chemical components have been recognized by several researchers in the past (Akhtar et al., 2014, Duschatzky, et al., 2005). Furthermore, studies have shown the synergistic effect of any two or more ingredients of essential oils against various human pathogens (Koroch et al., 2007, Nazzaro et al., 2013). More recently, the prevalence of antimicrobial drug resistance has prompted researchers to discover novel antimicrobial lead molecules to treat various human pathogens (Rudramurthy et al., 2016). Some of the presently available synthetic drugs fail to inhibit many pathogenic microbes. In addition, the use of synthetic chemicals for the control of pathogenic microorganisms is limited because of their carcinogenic effects, acute toxicity, and environmental hazard potential. In this regard, the exploitation of essential oils to control epidemic multidrug-resistant pathogenic microorganisms can be useful to combat various infectious diseases (Mulyaningsih et al., 2010).Therefore, the present chapter details the antidermatophytic potentials of essential oils extracted from Medicinal aromatic plants as well as their therapeutic relevance and possible mechanisms involved in the reticence of human pathogenic microorganisms.Furthermore, studies have shown the synergistic effect of any two or more ingredients of essential oils against various human pathogens (Koroch et al, 2007., Nazzaro et al., 2013).

7. CONCLUSIONS

The essential oils extracted from various Medicinal Aromatic plants possess strong antimicrobial activity against various bacterial and fungal pathogens. The reactivity of essential oils depends upon the nature of their functional groups and orientation. Essential oils are considered to be potent against a diverse range of pathogens. Essential oils may disrupt the cell membrane of the targeted pathogens by increasing membrane permeability, inducing leakage of vital intracellular constituents, and interrupting the cellular metabolism and enzyme kinetics of the targeted pathogens. The present study reveals more information on *In vitro* research studies of essential oils; however, more efforts are required to conduct clinical trials in the future. Biopharmaceutical industries are in need of ecofriendly alternative drug molecules to treat diseases associated with microbial pathogens and body metabolism. Thus, essential oils of Medicinal Aromatic plants might be a prospective source of alternative antimicrobial agents and may play an important role in the discovery of new drugs for the treatment of a wide range of pathogenic microorganisms in the near future.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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