UNIVERSITY *of the*
WESTERN CAPE

Nanoparticle Antifungal Therapy for Resolution of Oropharyngeal Candidiasis

Systematic review and meta-analysis

A mini thesis submitted to partially fulfil the degree requirements for:

MASTER OF SCIENCE IN ORAL MEDICINE

Faculty of Dentistry
Department of Oral Medicine and Periodontics

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DECLARATION

I declare that Nanoparticle Anti fungal Therapy for Resolution of Oropharyngeal Candidiasis is my own work, that it has not been submitted for any degree or examination in any other university, and that all the sources I have used or quoted have been indicated and acknowledged by complete references.

Ahmed Omar Saleem

May 2022

DEDICATION

My humble effort I dedicate to my beloved parents who have always believed in me, and with their encouragement, love, and support I was able to achieve this success.

My lovely wife the kindest soul who taught me to trust in Allah, and always encouraged me to believe in myself and that so much work could be done with little.

To my beloved Siblings for supporting me with their love and kindness.

To my family in low who kept me in their prayers all the time.

To my supervisor Haly Holmes who has been a great mentor and support throughout my master's program all those three years.

A special dedication to my supervisor Mark Angel who without his help and genuine support and guidance I would never be able to complete this work.

ABSTRACT

Oral candidiasis is an opportunistic infection caused by Candida Species that generally affects Immunocompromised individuals and Denture wearers. The side effects associated with the use of anti-fungal medicaments are increased and the therapeutic effectiveness is decreased. Nonetheless, the increase in resistance to conventional anti-fungal medicaments and the limitation of available antifungals make it difficult to manage the disease.

Objectives: This systematic review is to find if nanoparticle antifungal therapy is effective in the resolution of oropharyngeal candidiasis when compared to conventional antifungal therapy.

Methods: A comprehensive literature search was conducted and completed in March 2022 using the following search strategy in PubMed which was then modified for the other databases : ((“NANOPARTICLES"[MeSH Terms]) OR ("NANOPARTICLES"[Title/Abstract])) AND ("antifungal agents"[MeSH Terms]) AND ((“candid*"[Title/Abstract]) OR (candid*"[MeSH Terms]) OR ("MYCOSES"[MeSH Terms])) AND ("ORAL"[Title/Abstract] OR "DENTAL"[Title/Abstract] OR "oropharynx"[MeSH Terms]).
We used the following databases: Cochrane Library, Scopus and PubMed, the results of the search were documented, reported, and compared between the various database search and Mendeley was used to manage the references. All the selected articles were assessed by two reviewers independently, and we included all animal intervention studies that used animal models with oropharyngeal candidiasis with nanoparticle antifungal intervention and measured clinical or histological resolution (cure) of oropharyngeal candidiasis. While we exclude all studies that lack the control group or thus, case reports, review papers, Editorials, Letters to the editor and Monographs. The discrepancies were resolved by consensus and discussion with a third reviewer, and extracted data were gathered in a standardized template with Mendeley and Excel software. Two review authors individually extracted data in duplicate. The risk of bias assessment was conducted using the systematic review centre for laboratory animal experimentation (SYRCLE’s) risk of bias tools. Review Manager 5.4.1 (Cochrane Collaboration) was used for data analysis. Data are expressed with mean difference (MD) and accompanying 95% confidence interval (95% CI). Heterogeneity was evaluated using I-squared (I^2) and Chi-square test with a P value < 0.1 indicating significance.

Results: Three Intervention animal studies (49 participants) comparing the treatment of oropharyngeal candidiasis using nanoparticle antifungals as a comparison to conventional antifungals met our inclusion criteria. Methodological quality assessment and heterogeneity were

performed using peer-reviewed criteria. Nanoparticle Antifungal showed statistically significant mycological efficacy (mean difference (MD) = -0.28 [95% Confidence interval (Cl), -0.35; -0.20]; three studies, four populations, n=49) at day four, and (MD = -0.16 [95% Confidence interval (Cl), -0.25 to -0.08]; two studies, three populations, n=46) at day eight, as Compared with conventional antifungal therapy. Lack of standardization of treatment parameters and variability in the assessment of outcomes was observed across the studies. All included studies had a moderate to low risk of bias.

Conclusion: Nanoparticle antifungal therapy showed comparable effectiveness in treating oropharyngeal candidiasis in animals when compared with conventional antifungal therapy. This review, while only finding animal intervention studies to date, nevertheless suggests that nanoparticle antifungals, with a refinement of treatment parameters for human participants, as an alternative management modality for oral candidiasis.

KEYWORDS

Oral Candidiasis

Oropharyngeal Candidiasis

Fungal Infection

Nanotechnology

Nanometre

Nanoparticles

Antifungal

Systematic Review

Animals

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Chapter 1

1.1 Introduction

Oral candidiasis is a common opportunistic infection Caused by Candida species. Candida is considered a member of the oral normal microbiome, identified as part of the oral commensal flora in 35%-80% of the normal population and It's the most commonly isolated yeast from the oral cavity. (Mun *et al*., 2016; Lewis & Williams, 2017). The most prevalent candida species is *Candida albicans* which is also recovered from the oral cavity of both healthy and infected humans. These species are estimated to be responsible for over 80% of oral fungal isolates (Mun *et al*., 2016; Lewis & Williams, 2017; Sato *et al*., 2017), The prevalence order of other non-albicans *Candida species* is *Candida glabrata*, *Candida krusei*, *Candida tropicalis*, *Candida guilliermondii*, *Candida kefyr*, and *Candida parapsilosis*, in descending order respectively. *Candida inconspicua*, *Candid lusitaniae*, *Candida norvegensis* and *Candida rugosa* are even less frequently encountered (Lewis & Williams, 2017; Mallya , 2019). The transformation of candida to a pathogenic hyphal form occurs in the presence of predisposing factors such as (AIDS, diabetes, smoking, cancer, poor oral hygiene, and denture wearers) (Lalla et al., 2010; Coronado-Castellote & Jimenez-Soriano, 2013; Patil et al., 2018; Rodrigues, Rodrigues & Henriques, 2019). Oral candidiasis is referred to as the disease of the diseased due to its opportunistic nature highlighting the primary role of reduced host defence in its development (Cannon et al., 1995). Oral candidiasis is classified into acute (pseudomembranous and erythematous variants) and chronic (nodular, hyper-plastic, erythematous, and plaque-like) variants, Common clinical variants include denture stomatitis (i.e. Erythematous candidiasis which is related to denture wearing), Angular cheilitis, Median rhomboid glossitis and linear

gingival erythema (Coronado-Castellote & Jimenez-Soriano, 2013; Singh et al., 2014; Fourie et al., 2016; Millsop & Fazel, 2016; Hellstein & Marek, 2019; Mallya & Mallya, 2019)

The diagnosis of oral candidiasis is a clinical depending on the oral manifestation, but a microbiological diagnosis is performed when the clinical diagnosis requires confirmation for establishing a differential diagnosis with other diseases and in cases characterized by resistance to antifungal drugs and in hyperplastic candidiasis (Farah, Lynch & McCullough, 2010; Fourie et al., 2016).

In general, the management of oral candidiasis involves addressing and eliminating host predisposing factors which may be local or systemic, combined with topical or systemic antifungal agents (Farah, Lynch & McCullough, 2010; Fourie et al., 2016). These may be either fungicidal or fungistatic (Farah, Lynch & McCullough, 2010; Fourie et al., 2016). The topical antifungal agent is the preferred first line of treatment as side effects and interactions with other drugs are less significant than those administered systemically (Lewis & Williams, 2017; Quindos et al., 2019).

Recently nanoparticles have been highly appreciated for their wide range of applications in various biological, pharmacy and medical fields body (Hajipour et al., 2012; Cartaxo., 2015; Maleki Dizaj et al., 2015; Amelia Piñón Castillo et al., 2019; Iqbal et al., 2019). The Nanoparticle Antifungal Therapy for the Treatment of Candida infection has shown a Promising seed which tackles the Resistance and side effects associated with topical and systematic administered antifungal drugs (Amelia Piñón Castillo et al., 2019).

Chapter 2

2.1 Literature review

2.1.1 Challenge with conventional antifungal:

There are many challenges associated with conventional antifungal agents including unpleasant taste (polyenes) and insufficient contact time for therapeutic effectiveness as individuals who take these drugs are inclined to swallow quickly or spit them out prematurely (Anil, Ellepola & Samaranayake, 2001; Lewis & Williams, 2017; Quindos et al., 2019). Antifungal resistance to conventional anti-fungal medicaments is of growing concern as it's on the increase worldwide (Kanafani & Perfect, 2008; Niimi, Firth & Cannon, 2010) as well as fundamentally limited available antifungals drugs in some clinical settings (Quindos et al., 2019).
Nanotechnology can provide a novel approach to developing a beneficial solution to improve antifungal therapy and overcome the challenges related to side effects and resistance.

2.1.2 Nanotechnology:

Nanotechnology is a recent technology that manipulates matter in a nanoscale order ($1 \times 10 \times 10^{-9}$ m) for antimicrobial, antifungal or carrier molecules. Nanoparticles range in size from 1–100 nm in any dimension, with specific physicochemical characteristics (Cartaxo, 2015; Dolez, 2015; Bhatia, 2016; Hong, 2019), these include characteristics, such as electron configuration which confers an extraordinary quantum effect, that enhances their pharmacokinetic ability/properties (Khan, Saeed & Khan, 2019).

2.1.3 The intervention:

Nanotechnology in medicine involves employing nanoparticles to deliver drugs, heat, light, or other substances to specific types of cells such as cancer cells, this technique reduces damage to healthy cells in the body (Hajipour et al., 2012; Cartaxo., 2015; Maleki Dizaj et al., 2015; Amelia Piñón Castillo et al., 2019; Iqbal et al., 2019)

There are two types of nanoparticles, namely chemical synthetic and green (Metal nanoparticles and metal oxides nanoparticles such as silver, gold, and oxide of nanoparticles like zinc, titanium, copper, and iron. Most of these nanoparticles show a wide range of antifungal activity (Bhatia, 2016; Anu Mary Ealia & Saravanakumar, 2017; Saratale et al., 2018).

While nanosized inorganic particles represent an increasingly important material in the development of novel nanodevices used in numerous physical, biological, biomedical, and pharmaceutical applications (Cartaxo., 2015), other sources of nanosized organic sources exist. These include green silver nanoparticles which are synthesized through the use of microorganisms such as *Actinobacteria Pilimelia columellifera subsp*. Pallida (Golińska et al., 2016) filamentous fungi such *as Monascus purpureus, Macromycetes* such as *Pleurotus sajorcaju*, *Bacillus species* (Castillo et al., 2018), an extract from Phoenix dactylifera (Oves et al., 2019) or Tulsi leaf plant extract (Khatoon et al., 2015), these green silver nanoparticles inhibit candida with different efficiencies (Castillo et al., 2018; Saratale et al., 2018)

2.1.4 Classification of Nanomaterials:

Nanomaterials can be classified according to their origin, dimension, and type of materials used.

2.1.4.1 According to origin:

2.1.4.1.1 Natural or Green nanomaterials:

Nanomaterials of natural origin, for example, volcanic ash, insect wings, opals, shells, corals, spider silk. (Bhatia, 2016; Anu Mary Ealia & Saravanakumar, 2017; Saratale et al., 2018).

2.1.4.1.2 Synthetic or artificial nanomaterials:

These are synthesized using a well-defined protocol in the laboratory. Widely used nanomaterials fall under this category, for example, nanotubes, quantum dots, nanoparticles, etc. (Bhatia, 2016; Anu Mary Ealia & Saravanakumar, 2017; Saratale et al., 2018).

2.1.4.2 According to dimension:

2.1.4.2.1 Zero-dimensional:

A material whose dimensions in all three directions are in the nanometre range. They will be spherical in shape, for example, quantum dots, silver nanoparticles.

2.1.4.2.2 One-dimensional:

One dimension of these materials will be out of the nanometre range, for example, nanowires

2.1.4.2.3 Two-dimensional:

For these materials, two dimensions will be in the nanometre range. Examples are nanofilms, coatings, sheets, and walls.

2.1.4.2.4 Three-dimensional:

All dimensions will be out of the nanometre scale. These include bulk materials composed of individual blocks which are in the nanometre scale (1–100 nm).

2.1.4.3 According to the type of material involved:

2.1.4.3.1 Carbon-based nanomaterials:

In this type, carbon will be the basic component. Fullerenes, carbon nanotubes, graphene.

2.1.4.3.2 Metal-based nanomaterials:

The main component of these particles is metal, these nanomaterials include nanogold, nanosilver, and metal oxides such as titanium dioxide, silica, and alumina.

2.1.4.3.3 Dendrimers:

Dendrimers are highly branched macromolecules with dimensions on a nanometre scale.

2.1.4.3.4 Nanocomposites:

Here at least one of the components in a mixture is in the nanometre scale.

2.1.5 Mechanism of intervention:

The nanoparticles show cell wall damage, oxidative stress increase, and DNA interaction, nevertheless, the nanoparticles' toxicity mechanisms are dependent on the nanoparticle nature, size, shape, and capping nature (Amelia Piñón Castillo et al., 2019).

2.1.5.1 Silver nanoparticles:

Silver compounds have been known for their antimicrobial activity since ancient times, it has been used for several decades as a disinfectant (Leitão et al., 2018), with silver nitrate used in burn wounds to control infections. However, the discovery of penicillin showed a decline in its use. The increased resistance to antifungal agents supports the use of nanosilver as it has exhibited potent antifungal effects on fungi, through the destruction of the membrane integrity

(Kim et al., 2009; Hassan, Mansour & Mahmoud, 2012). In addition silver nanoparticles offer the possibility of using minimal doses and act in microorganisms that present antibiotic resistance or decrease the virulence factors (Amelia Piñón Castillo et al., 2019).

2.1.5.2 Zinc oxide nanoparticles:

The zinc oxide nanoparticles characteristics depend on the size, synthesis method, and superficial charge (Siddiqi et al., 2018).

Zinc oxide nanoparticles low toxicity has made them safe to use in medical devices such as antibacterial agents, drug carriers and bioimaging probes, among others. For this reason, the zinc oxide toxicity mechanism reported is ion liberation, the interaction of zinc oxide nanoparticles with the cell wall and stress oxidative generation (Sirelkhatim et al., 2015), as the silver nanoparticles.

2.1.5.3 Copper oxide nanoparticles:

Copper exhibits good characteristics such as its antimicrobial activity, chemical stability, and thermal resistance. Diverse synthesis methods have been proven to create copper oxide nanoparticles including chemical, electrochemical, and green synthesis (Goh et al., 2016). The toxicity mechanisms of copper oxide nanoparticles are still not fully understood, some authors suggest that copper oxide nanoparticles accumulate in the cell wall as well as oxidative stress increase. (Goh et al., 2016).

2.1.5.4 Gold nanoparticles:

Gold has been used for several centuries in the treatment of various disorders. Nanoparticles mostly impede the electrostatic flux across membranes, resulting in distorted membranes,

Moreover, nanoparticles also enhance the expression of genes helping in redox processes and thus leading to fungal death. (Nadeem et al., 2017).

2.1.5.5 Palladium nanoparticles:

Some studies in palladium nanoparticles show a significant growth reduction of *candida albicans* while other studies in biogenic palladium nanoparticles production with watery extract of moringa oleifera flower showed that palladium nanoparticles have no effect in *candida albicans* (Amelia Piñón Castillo et al., 2019).

2.2 Why it is important to do this systematic review:

The prevalence of infections caused by *Candida species* (candidiasis) has expanded exponentially in recent decades, due to the increase in AIDS, diabetes, smoking, cancer particularly in those undergoing chemotherapy or using dentures (Turner & Butler, 2014; Mun et al., 2016).

In addition to the problem of the increased incidence of the disease, we are facing a rapid increase in resistance to conventional anti-fungal medicaments as well as the fundamentally limited available antifungals. So new formulations of antifungal are needed, and nanomedicine and nanotechnology provide an opportunity to produce more targeted antifungal with fewer side effects, also toxicity mechanism of the nanoparticle nature, size, capping nature and shape can be tailor made to produce its desired effect (Amelia Piñón Castillo et al., 2019).

Chapter 3

3.1 Aim of the systematic review:

Previously published systematic reviews focussing on evidence for the effectiveness of antifungal therapeutic agents have not included nanotechnology to date. Here, we sought to use the systematic review method to evaluate the efficacy of nanoparticle-based antifungal therapy for the resolution of oropharyngeal candidiasis.

3.2 Review Question (Focus question):

Is nanoparticle antifungal therapy as effective as conventional antifungal therapy in the resolution of oropharyngeal candidiasis?

3.3 Methods:

This protocol has been registered with the PROSPERO registry of the University of York (ID: CRD42020203909).

3.3.1 Eligibility criteria (study design):

3.3.1.1 Studies included:

- Animal models with oropharyngeal candidiasis.
- Use of any nanoparticle antifungal.
- Clinical/histological resolution (cure) of oropharyngeal candidiasis.
- Animal interventions.
- cluster-randomized trials

3.3.1.2 Studies excluded:

- If control groups were lacking. Thus, case reports and review papers were automatically excluded.
- Editorials, Letter to the editor
- Monographs

3.3.2 Participants/population:

Animals.

3.3.3 Intervention(s):

The intervention includes all nanoparticles (Natural or Green nanomaterials or Synthetic or artificial nanomaterials).

3.3.4 Comparator(s)/control:

Treatment with any topical or systemic anti-fungal medicament, regardless of the dosage and duration of antifungal prescribed.

3.3.5 Outcome:

3.3.5.1 Main outcome(s):

- Clinical/mycological resolution of oral fungal infections.

3.3.5.2 Additional outcome(s):

- Effect of nanoparticles on fungal activity.

- Effect of nanoparticles on different *candida species*.
- Efficacy of different nanoparticles.
- Toxicity of nanoparticles.

3.4 Information sources and search strategy:

A comprehensive literature search was conducted and completed in March 2022 using the following search strategy in PubMed which was then modified for the other databases (Table 1): ((“NANOPARTICLES"[MeSH Terms]) OR ("NANOPARTICLES"[Title/Abstract])) AND ("antifungal agents"[MeSH Terms]) AND ((“candid*"[Title/Abstract]) OR (candid*"[MeSH Terms]) OR ("MYCOSES"[MeSH Terms])) AND ("ORAL"[Title/Abstract] OR "DENTAL"[Title/Abstract] OR "oropharynx"[MeSH Terms]).

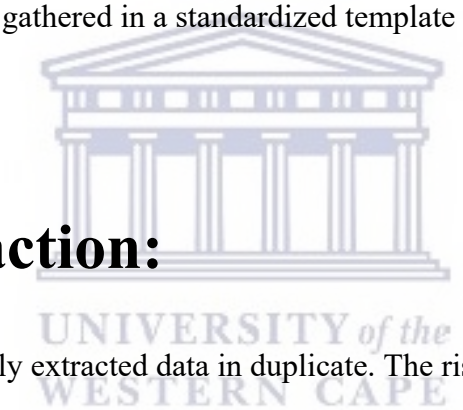
Table 1, Example of Search Strategy for nanoparticle Antifungal Therapy for Resolution of Oropharyngeal Candidiasis

Database	PubMed	
Date	22.9.2021	
Limits	None	
No	**Search**	**Result**
#1	"NANOPARTICLES"[MeSH Terms]	164,673
#2	"NANOPARTICLES"[Title/Abstract]	210,526
#3	"ANTIFUNGAL AGENTS”[MeSH Terms]	64,309
#4	#1 OR #2 AND #3	1,009
#5	"CANDID*"[Title/Abstract]	457,771
#6	"CANDID*"[MeSH Terms]	68,041
#7	“MYCOSES"[MeSH Terms]	135,850
#8	#5 OR #6 OR #7	569,701
#9	"ORAL"[Title/Abstract] OR "DENTAL"[Title/Abstract] OR "OROPHARYNX"[MeSH Terms]	885,974
#10	#8 AND #9	26,876
#11	#4 AND #10	65

We used the following databases: PubMed, Scopus and Cochrane Library, the results of the search were documented, reported, and compared between databases, the references were recorded and compared between the various database search and Mendeley was used to manage the references. There were no language restrictions.

3.5 Study management:

All the selected articles were assessed by two reviewers independently, according to the eligibility criteria, and the discrepancies were resolved by consensus and discussion with a third reviewer. Extracted data were gathered in a standardized template with Mendeley and Excel software.



3.6 Data extraction:

Two review authors individually extracted data in duplicate. The risk of bias assessment was conducted on six domains (Figure 1). We adhered to the Cochrane Collaboration statistical guidelines and fixed-effect models were used to calculate the mean difference (MD).

For each study, the following data were extracted: (1) Author name and date of the study, (2) Country where the research was conducted, (3) Sample size, (4) type of the animal model, (5) Weight of the animal model, (6) age of the animal model, (7) Classification of infection, (8) method of diagnosis, (9) Type intervention (Green or synthetic), (10) Size of Nanoparticles, (11) Type of Control.

3.7 Quality appraisal of included studies:

Two independent reviewers individually appraised methodological quality employing a risk of bias tool for animal intervention studies by using the systematic review centre for laboratory animal experimentation (SYRCLE's) risk of bias tools (figure 1) (Hooijmans *et al*., 2014). Conflicts were settled by consensus with a third reviewer.

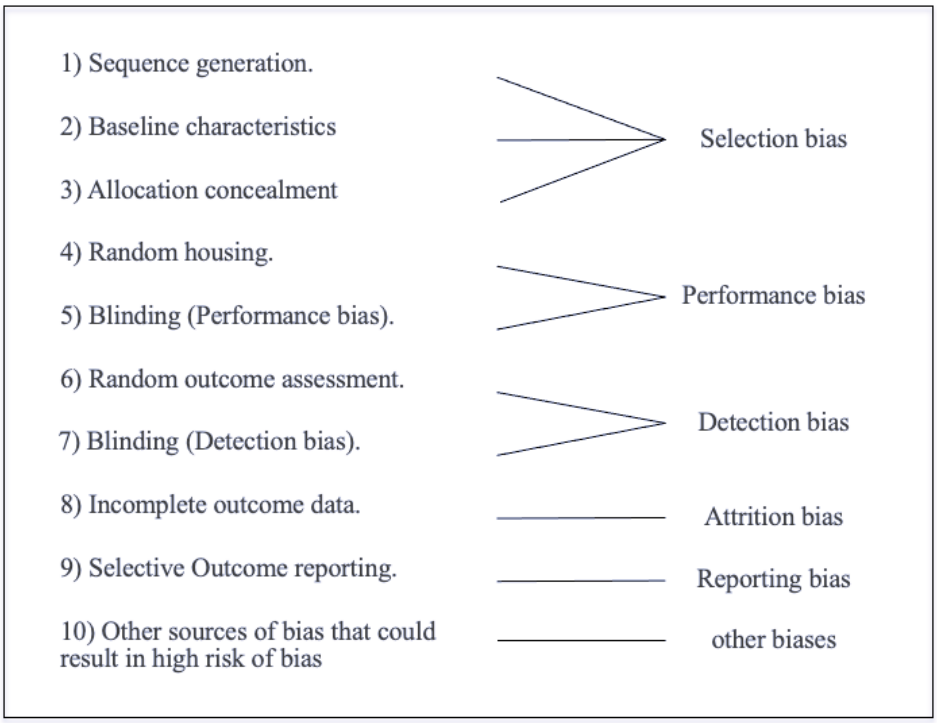


Figure 1, The domains that will be measured for each included study

3.8 Strategy for data synthesis:

Review Manager 5.4.1 (Cochrane Collaboration) was used for data analysis. Data are expressed with mean difference (MD) and accompanying 95% confidence interval (95% CI).

3.9 Assessment of heterogeneity:

Heterogeneity was evaluated using I-squared (I^2) and Chi square test with a P value < 0.1 indicating significance. To guide the type of model for meta-analysis, we considered an I^2 < 50% as having no heterogeneity to allow use of a fixed effects model, else a random effects model was to be performed.

3.10 Assessment of reporting biases:

Given the small number of studies, an assessment of reporting bias was not performed.

3.11 Confidence in cumulative evidence:

We intended to evaluate the quality of the findings by employing the Grading of Recommendations Assessment, Development and Evaluation (GRADE) method.

Chapter 4

4.1 Results:

4.1.1 Study selection:

The electronic database search resulted in the identification of 106 titles containing 19 duplicates which were excluded. The remaining titles were evaluated, and 44 titles were excluded. Subsequent abstract screening resulted in an additional 40 titles being excluded (Table 2)

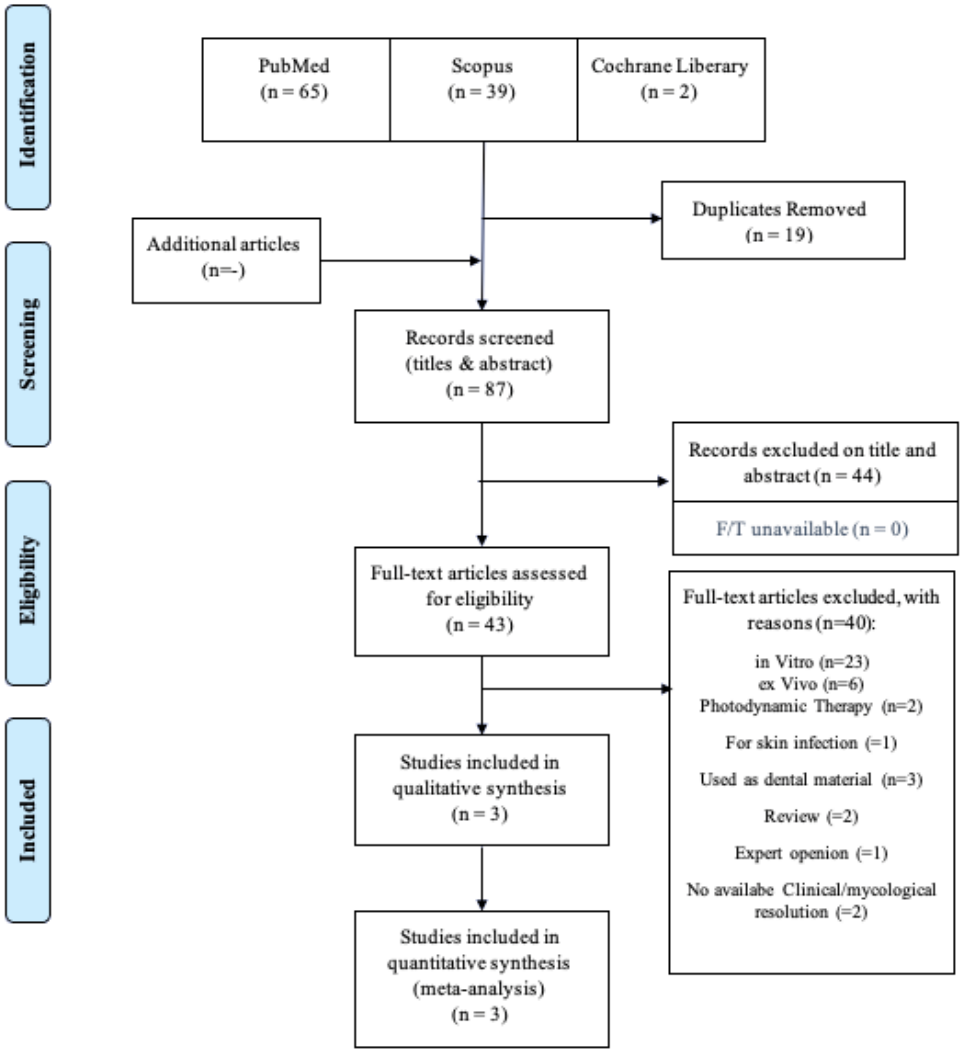


Figure 2. Schematic PRISMA flow diagram of the literature search.

Forty-three articles were subjected to full-text screening after which three full-text studies were included in the review (figure 2)

Table 2, Studies using Nanoparticle Antifungal which has been excluded

STUDY	PUBLICATION YEAR	REASON FOR EXCLUSION
Hosny *et al.*,	2019	Ex-vivo
Jothiprakasam *et al.*,	2017	Candida in the surface of medical devices
Araujo *et al.*,	2021	Used for skin infection
Ludwig *et al.*,	2018	Used for urinary tract infection
Fröber *et* al.,	2020	For for Peri-implantitis
Chaudhari *et* al.,	2016	Not oropharyngeal candidiasis
Aljaeid and Hosny,	2016	Not oropharyngeal candidiasis

4.1.2 Study designs:

We included all studies that used nanoparticle antifungal compared with conventional antifungal medications, all of which were animal intervention studies.

4.1.3 STUDY PARTICIPANTS: (Table 3)

Three studies provided the age of the animal models (Garg & Singh, 2011; Melkoumov et al., 2013; Chaudhari et al., 2016). Of these, one study had a sample mean age of 6 Weeks (Garg & Singh, 2011), while the remaining two studies each had a sample age range from 10 to 12 weeks (Melkoumov et al., 2013; Chaudhari et al., 2016). Two studies used rats (Garg & Singh, 2011; Chaudhari et al., 2016), two studies used rabbits (Aljaeid & Hosny, 2016; AbouSamra et al., 2020), and one study comprised mice (Melkoumov et al., 2013)).

Table 3, Characteristics of included studies

Citation	Location-country where the study done	Sample size	Type	Weight	Age (mean)	Classification of the infections
(AbouSamra et al., 2020)	National Research Centre | Cairo | Egypt	Total: 9 Control: 3 Negative control: 3 intervention: 3	albino rabbits	2.5–3 kg	-	C. albicans
(Garg and Singh, 2011)	Banaras Hindu University | India	Total: 52 Control:13 Negative control: 13 intervention: 26	Male Sprague-Dawley rats	200g	6 week	C. albicans
(Melkoumov et al., 2013)	Montreal | Canada	Total: 60 Control: 20 Negative control: 20 intervention: 20	DBA/2 mice	-	10 weeks	C. albicans

4.1.4 Treatment Parameters:

4.1.4.1 Nature of the intervention

The studies had varied treatment parameters (Table 4). All studies used Nanoparticle antifungals on *Candida albicans* except for two Studies that did not mention the type of candida. Only one study evaluated the treatment of *oral candidiasis* using synthetic Nanoparticles (Melkoumov et al., 2013). another study used fine nanoparticles (Melkoumov et al., 2013), one study used ultra-fine nanoparticles (Aljaeid & Hosny, 2016), and the rest of the studies used Coarse Nanoparticles. (According to Shah, M., 2014 who has Categorized Nanoparticle size to Coarse it is the nanoparticles it is more than 250nm, fine which it 250-100nm and Ultra-fine which is less than or equal 100nm) (Table 4).

Table 4, Nature of the intervention

Table 4, Classification of nanoparticle antifungal that used in the intervention

Citation *	Type of nanoparticles	Details of nanoparticles	Size Category	Nanoparticles Size details
(AbouSamra et al., 2020)	Green	Ciclopirox Olamine-Loaded Hybridized Vesicles (Nanovesicles)	Coarse	346.1 nm ± 10.12
(Garg and Singh, 2011)	Green	Eugenol loaded solid lipid nanoparticles (500 mg of carbopol gel (1%, w/v) containing eugenol loaded SLN)	Coarse	single lipid (332nm) and binary lipid (87.7nm)
(Melkoumov et al., 2013)	Synthetics	Yttria stabilized Zirconia (YSZ) Nanoparticles (A.K.A: Zirconium Oxide Nanoparticles)	Fine	137nm

**Shah, M., 2014. Gold nanoparticles: various methods of synthesis and antibacterial applications.*

Coarse = more than 250nm Fine = 250-100nm or equal 100nm) Ultra-fine=less than

4.1.4.2 The Antifungal medication and treatment regimen (3 studies)

Three articles measured the effect of nanoparticle antifungal where used as a topical gel form (Garg & Singh, 2011; Melkoumov *et al*., 2013; AbouSamra *et al*., 2020), the other included studies that used it systemically, via the oral route, and frequency of nanoparticles antifungal was not consistent in one article (AbouSamra *et al*., 2020), where they used free CPO-loaded gel as the comparator in the study. (Garg & Singh, 2011) used Fluconazole as gel, twice a day for 8 days. While (Melkoumov *et al*., 2013) used commercial nystatin suspension as the comparator, twice a day for a period of two weeks.

4.1.4.3 Method of clinical and microbiological Assessment (3 studies)

All three studies took swabs from oral mucosa for the assessment of colony forming units (CFUs) (Garg & Singh, 2011; Melkoumov *et al*., 2013; AbouSamra *et al*., 2020). Quantification of CFUs was used to assess the microbiological success of treatment in these three studies.

4.2 Outcomes:

4.2.1 (CFUs at day four: 3 studies, 4 populations, n=49)

The use of nanoparticles showed a statistically significant reduction in CFUs when compared to conventional antifungals on day four. (Mean difference (MD) = -0.28 [95% Confidence interval (Cl), -0.35 to -0.20] (Figure 3)

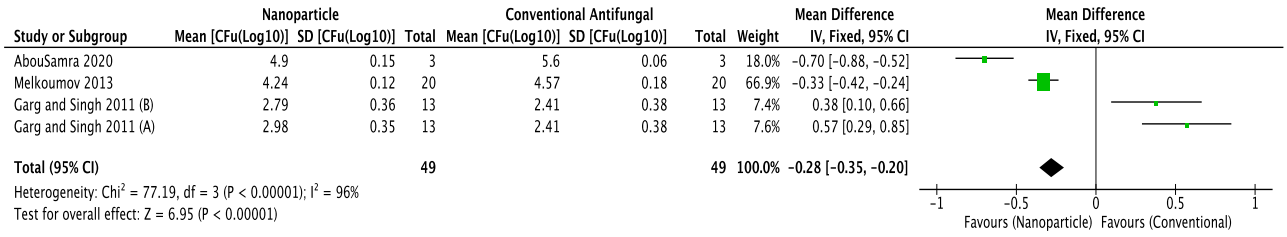


Figure 3, Forest plot of comparison: Nanoparticle VS Conventional Antifungal, outcome: Fu in 4th day [CFUs (Log10)].

4.2.2 (CFUs at day eight: 2 studies, 3 population, n=46)

On day eight the use of nanoparticles showed a statistically significant reduction in CFUs when compared to conventional antifungals. (MD = -0.16 [95% Cl, -0.25 to -0.08] (Figure 4).

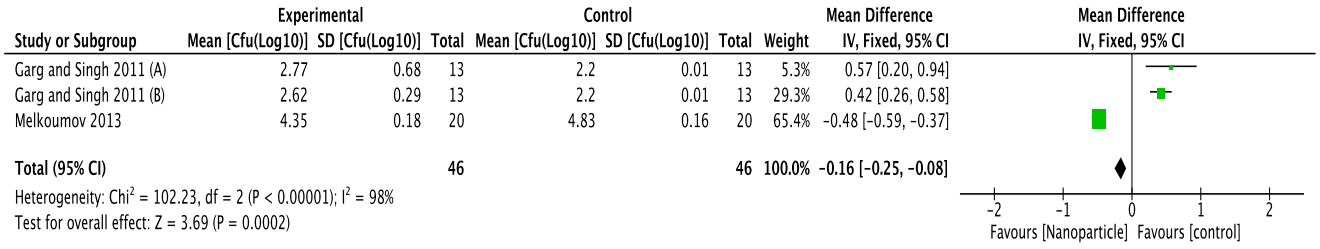


Figure 4, Forest plot of comparison: Nanoparticle VS Conventional Antifungal, outcome: Fu in 8th day [CFUs (Log10)].

histological resolution:

4.2.3 Heterogeneity

A statistically significant difference between nanoparticle antifungal and conventional antifungal medication was found at both time points 4 days: [MD = -0.28, 95% Cl= -0.35 to -0.20], and 8 days: [RR= 1.59, 95% CI= 0.44, 5.82]. Heterogeneity was found to be very high at 4 days (I^2= 96%) and at 8 days (I^2= 98%)

4.2.4 Publication bias

The researchers were unable to assess publication bias due to the sparsity of studies.

4.2.5 Quality assessment

We used the systematic review centre for laboratory animal experimentation (SYRCLE's) risk of bias tools for the evaluation of the risk of bias of the included studies (Hooijmans *et al*., 2014). Studies were largely designated as being of low risk of bias, except for one study where blinding and lost-to-follow-up data were graded as being of high bias (Figure 5).

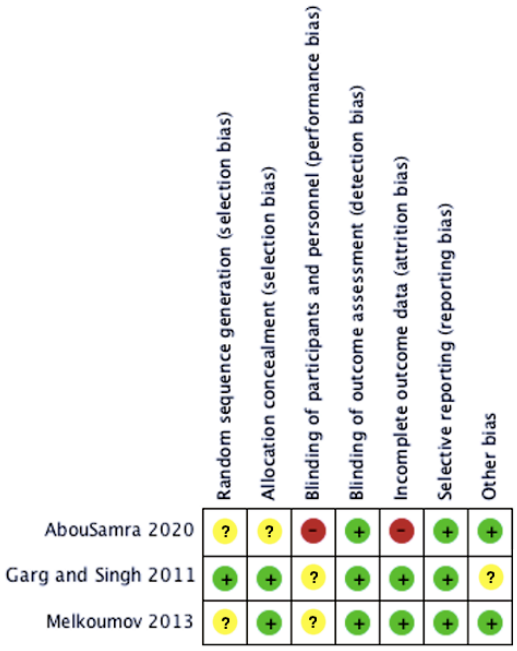


Figure 5, Risk of bias summary: review authors' judgements about each risk of bias item for each included study. (Blank space, unclear risk of bias based on study data provided)

4.3 Discussion

This first systematic review performed on nanoparticle antifungal therapy for oropharyngeal candidiasis found evidence for the effectiveness of using nanoparticle antifungals in the treatment of oral candidiasis in animals when compared with conventional antifungal therapy. This review, while only finding animal intervention studies to date, nevertheless suggests that nanoparticle antifungals, with a refinement of treatment parameters for human participants, bodes well as an alternative management modality for oral candidiasis.

When considering the efficacy of nanoparticle antifungal therapy by the reduction in the CFUs count compared to Conventional antifungal on day four and day eight, two studies using

nanoparticle antifungal showed a significant reduction in CFUs (Melkoumov *et al*., 2013; AbouSamra *et al*., 2020), which supports the literature that reported the wide range of antifungal activity of nanoparticles (Bhatia, 2016; Anu Mary Ealia & Saravanakumar, 2017; Saratale et al., 2018). Furthermore, this review provides histological evidence of comparative efficiency to support microbial efficiency as demonstrated by damage and cellular alterations of both fungi and the oral mucosa. In addition, animals treated with nanoparticle antifungals showed diminished in candida hyphae density and few inflammatory cells within the epithelium as well as underlying lamina propria showed evidence of healed granulation tissue with hyaline tissue formation and accessory salivary serous glands were occasionally observed within the submucosa.

The histological picture was similar in the mucosa of animals treated with conventional antifungals, except in the study by (AbouSamra et al., 2020), in which additional histological findings such as oedema and the presence of elastic fibres in the connective tissue. The mucosa of animals treated with the placebo, showed extensive candida infection of the stratified squamous epithelium, with an abundant inflammatory cell infiltrate and superficial ulceration characterized by complete loss of mucosal squamous epithelium involving the basement membrane. The submucosal loose connective tissue oedema, masses of the fungal microorganisms with mild inflammatory cellular infiltration and a few fibroblasts were seen 6 days after administration of the placebo (AbouSamra et al., 2020), and 10 days (Melkoumov et al., 2013). While the antifungal effect of nanoparticles was greatly reduced, the studies included within this review only targeted its effect on *Candida Albicans* and did not investigate the effect of other *candida species* implicated in oral candidiasis, these include *Candida glabrata*, *Candida krusei*, Candida tropicalis, *Candida guilliermondii*, *Candida kefyr*, and *Candida parapsilosis*.

Analysis of the effect of nanoparticles on the various *candida species* could therefore not be conducted. Identifying the various *Candida species* implicated in the presenting oral mucosal condition is important to measure therapeutic antifungal success for any antifungal agent.

In this systematic review, no difference was seen in CFUs when comparing studies using natural versus synthetic nanoparticles, despite the varied use antifungal nanoparticles (zirconium oxide, lipids, COL, eugenol loaded solid lipid). Subgroup analysis comparing the effect of the various natural nanoparticles could not be done, due to a lack of similarity of nanoparticle type.

We made the strengths of this systematic review lie within the facts that a concerted effort was made to make the literature search as thorough and comprehensive as possible, while limiting restrictions in the search itself. Furthermore, we employed peer-reviewed tools for risk of bias appraisal. Lastly, the inclusion of only comparative studies enabled us to make robust comparisons with conventional antifungal therapy, thus presenting a higher level of evidence.

However, the biggest challenge in conducting this review was the lack of standardization of methods across studies and variability in the assessment of outcomes. Included studies employed different treatment parameters which we would expect to affect treatment outcomes. Therefore, placing these treatment procedures under a single umbrella of Nanoparticle antifungals is not the most ideal means of analysis. Unfortunately, the lack of studies did not allow us to perform the desired subgroup analysis, as only three studies measured CFUs in the oral mucosa (Garg & Singh, 2011; Melkoumov et al., 2013; AbouSamra et al., 2020). Also, there is a lack of studies that used the same animal models to measure defined outcomes of this systematic review. There was variability in the manufacturing specifications of the nanoparticles. Given that it is conceivable that outcomes may be influenced by these parameters.

The result of the efficacy of nanoparticle antifungal therapy in the management of oral candidiasis, can be attributed due to the mechanism of action of nanoparticles on Candida. It damages the cell wall, increases oxidative stress within and damage DNA. However, the toxicity mechanisms of the various nanoparticles are dependent on the characteristics of the nanoparticle. These include its nature, size, shape and capping status (Amelia Piñón Castillo et al., 2019). There are many side effects associated with conventional antifungals. In particular, those belonging to the polyene group, have an unpleasant taste and provide insufficient contact time for therapeutic effectiveness. This is because individuals who take these drugs are inclined to swallow quickly or spit them out prematurely (Anil, Ellepola & Samaranayake, 2001; Lewis & Williams, 2017; Quindos et al., 2019). The small size of the nanoparticles however, reduces the contact time needed to exert its therapeutic effect, because the nanoparticles will reach the targeted cell in less time when compared to conventional antifungals In addition, the electron configuration of nanoparticles, confers an extraordinary quantum effect on the nanoparticle, which enhances their pharmacokinetic action (Khan, Saeed & Khan, 2019).

Chapter 5

5.1 Conclusions

5.1.1 Implications for Practice:

Unfortunately, only animal studies were available; thus, this makes it difficult to extrapolate findings for human therapy.

5.1.2 Implications for Research:

This is the first systematic review to evaluate the efficacy of nanoparticle antifungal treatment of oropharyngeal Candidiasis. The result of this systematic review provides robust evidence as a basis for translation into future clinical studies, which are sorely needed, given a lack of sufficient evidence to support the clinical effectiveness of nanoparticle antifungal therapy for the treatment of oral fungal infections in humans.

5.2 Conflict of interest

None to declare.

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