CURCUMA LONGA (TURMERIC) AN ANTIFUNGAL TREATMENT FOR DERMATOPHYTOSIS: A SYSTEMATIC REVIEW

RABIATUL ADAWIYAH BINTI ABDUL SHUKOR

DOCTOR OF VETERINARY MEDICINE

2023

UNIVERSITI
MALAYSIA
KELANTAN

Curcuma longa (Turmeric) an Antifungal Treatment for Dermatophytosis: A Systematic Review

By

Rabiatul Adawiyah Binti Abdul Shukor
(D19A0023)

A Research Project Submitted to the Faculty of Veterinary Medicine in Partial Fulfillment of the Requirements for the Degree of Doctor of Veterinary Medicine

Faculty of Veterinary Medicine,
UNIVERSITI MALAYSIA KELANTAN

2023

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CURCUMA LONGA (TURMERIC) AS ANTIFUNGAL TREATMENT FOR DERMATOPHYTOSIS: A SYSTEMATIC REVIEW

ABSTRACT

An abstract of the research paper presented to Faculty of Veterinary Medicine, Universiti Malaysia Kelantan, in partial requirement for the course DVT55204 Research Project, for the completion of the degree of Doctor of Veterinary Medicine. *Curcuma longa*, or turmeric, is a rhizomatous plant native to South Asia and can be grown in diverse tropical conditions. The main bioactive compounds of turmeric are curcumin, turmeric oil and methanol. Dermatophytosis is a superficial fungal infection by dermatophytes that can affect the skin, hair and nail. Dermatophytes are divided into three genera; *Trichophyton* spp., *Microsporum* spp., and *Epidermophyton* spp.. There are various home remedies regarding the use of turmeric to treat fungal infections in pets. The widespread use and turmeric accessibility to the public prompt the need for re-evaluation of the existing understanding regarding the use of turmeric in ethnoveterinary medicine. There is also limited research on the efficacy of turmeric specifically against zoonotic dermatophytes that can be used as an evidence-based guideline. This systematic review is conducted to identify the use and efficacy of turmeric bioactive compounds in treating dermatophytosis by determining its recommended preparation and the most effective type of bioactive compound. Thus, a total of 3515 publications published between the year 2012-2022 were extracted from four databases: Google Scholar, PubMed, ScienceDirect and Scopus using different search strategies. A total of nine (9) studies met the eligibility criteria after sequential screening. Ethanolic turmeric extract, curcumin and turmeric oil were found to exhibit zone of inhibition on the investigated dermatophytes, *M. canis*, *M. gypseum* and *T. mentagrophytes*, and has comparable minimum inhibitory concentration (MIC) values to common antifungal drug. Photoactivation and combination with antifungal medication were found to be beneficial due to increased antifungal activity.

Keywords: *Curcuma longa, curcumin, turmeric, antifungal, dermatophytes, Microsporum canis, Microsporum gypseum, Trichophyton mentagrophytes*

ABSTRAK

Abstrak daripada kertas penyelidikan dikemukakan kepada Fakulti Perubatan Veterinar, Universiti Malaysia Kelantan untuk memenuhi sebahagian daripada keperluan kursus DVT 55204 Projek Penyelidikan. *Curcuma longa*, atau kunyit, adalah tumbuhan berakar rizom yang berasal dari Asia Selatan dan boleh ditanam di pelbagai keadaan dan cuaca tropika. Kompaun bioaktif utama di dalam kunyit adalah kurkumin, minyak kunyit dan methanol. Dermatofitosis adalah jangkitan kulat superfisial yang boleh menjangkiti kulit, rambut dan kuku. Dermatofit terbahagi kepada tiga genera; *Trichophyton* spp., *Microsporum* spp., and *Epidermophyton* spp.. Terdapat pelbagai nasihat rawatan di rumah yang menggunakan kunyit untuk merawat jangkitan kulit di haiwan peliharaan. Penggunaan kunyit yang meluas dan kebolehcapaian kunyit dalam kalangan orang awam menyebabkan perlunya penelitian semua ke atas pemahaman sedia ada berkenaan dengan penggunaan kunyit sebagai perubatan veterinar yang berusurkan pengaruh etnik. Terdapat juga keterbatasan jumlah kajian tentang penggunaan kunyit terutamanya yang berkaitan dengan penggunaannya untuk penyakit dermatofitosis zoonotik yang boleh digunakan sebagai panduan. Kajian sistematik ini bertujuan untuk mengenal pasti kegunaan dan keberkesanan kompaun bioaktif kunyit dan menentukan penyediaan yang disyorkan. Oleh itu, sejumlah 3515 penerbitan yang diterbitkan di antara tahun 2012-2022 telah dikumpulkan daripada empat enjin carian yang merupakan sistem pangkalan data dengan menggunakan pelbagai strategi. Sejumlah sembilan (9) penerbitan telah memenuhi kriteria kelayakan setelah melalui proses saringan berturutan mengikut kriteria penerimaan dan pengecualian. Ekstrak ethanol kunyit, kurkumin dan minyak kunyit didapati mampu menunjukkan zon perencatan penumbuhan terhadap dermatofit yang dikaji, *M. canis*, *M gypseum* dan *T. mentagrophytes*, dan mempunyai nilai kepekatan perencatan minimum (MIC) yang standing dengan ubat antikulat yang biasa digunakan. Aktivasi menggunakan cahaya dan gabungan dengan ubat antikulat juga didapati dapat meningkatkan aktiviti antikulat.

Kata kunci: *Curcuma longa, kurkumin, kunyit, antikulat, dermatofit, Microsporum canis, Microsporum gypseum, Trichophyton mentagrophytes*

ACKNOWLEDGEMENTS

My profound gratitude and appreciation go out to my thesis supervisors for the guide and support. Those of which without their expertise, constructive and insightful feedback, I would have difficulty finishing this research subject.

I would like to express my thanks to my friends for their shared enthusiasm, laughter, and encouragement. They have been a driving force and a foundation of support during the challenging times of my research experience. Our mutual experiences and struggles are the most memorable moments which I will not take for granted as it has forged a relationship of fun and trust.

A heartfelt acknowledgement is due to my dear Tevin for the boundless patience and never-ending fuel of encouragement. You have been my compass to help me navigate through the challenges. May our bond grow stronger, much like the plaster of Paris that you cast on your patients every day. I am hopeful for us to enjoy many more shared journeys of growth and milestones together.

To my family, my mother, father, my nine siblings, my tabby and my tiny panther, this thesis is done with all your love. I owe a debt of gratitude for the unwavering support and trust, which has been integral for my resilience and strength. I hope this small piece of academic work can positively reflect the collective triumphs and love of our family. I am truly blessed and grateful.

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

C. longa	*Curcuma longa*
FICi	Fractional inhibitory concentration index
HCl	Hydrochloric acid
ITZ-CDF/CH NPs	Itraconazole with difluorinated curcumin prepared as chitosan nanoparticles
M. canis	*Microsporum canis*
M. gypseum	*Microsporum gypseum*
MIC	Minimum inhibitory concentration
N/A	Not available
PBS	Phosphate-buffered saline
PRISMA 2020	Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020
T. mentagrophytes	*Trichophyton mentagrophytes*

LIST OF SYMBOLS

%	percentage

CHAPTER 1

INTRODUCTION

1.1 Research Background

Dermatophytosis is a superficial fungal infection by dermatophytes that may affect areas of the skin, hair, and nail. Dermatophytosis commonly manifests as a variably pruritic, erythematous, circular rash on the skin (CDC, 2020), often accompanied by alopecia and scaling. This disease is also known by other names such as ringworm and tinea. Dermatophytes are divided into three genera, *Microsporum*, *Trichophyton*, and *Epidermophyton* spp. The infection source of dermatophytes may be from the environment or through direct contact with the infected host (Panthagani, 2015). For this study, *Microsporum canis, Microsporum gypseum* and *Trichophyton mentagrophytes* will be focused on due to their zoonotic importance, whereby they have the ability to establish infection in animal and human hosts. Recent taxonomic revision of *M. gypseum* leads to a change of its nomenclature to *Nannizia gypsea* (Schoch, et al. 2020). For this study, the author will use the term interchangeably.

Examination using Wood's lamp (ultraviolet light) may help identify as some species of dermatophytes (e.g.: *Microsporum canis*) fluoresce under ultraviolet light. Nevertheless, the gold standard for diagnosing dermatophytosis is direct microscopy of the lesion and fungal culture using samples of affected skin, hair, or nail (Panthagani, 2015).

The current antifungal treatment for dermatophytosis includes preparations for topical and systemic administration of antifungal medications (Gupta, 2016), which commonly involves the use of allylamines and azole antifungal agents. However, there is an increase in the number of studies regarding antifungal resistance in dermatophytes (Ghannoum, 2016; Singh et al., 2018;

Nenoff et al., 2020; Siopi et al., 2021). Ghannoum (2016) explained that resistance towards azole is due to increased drug efflux by the overexpression of drug efflux pumps in dermatophytes. Sacheli & Hayette (2021) reported resistance issues in *T. mentagrophytes* in which it is characterized by point mutations in the squalene epoxidase (SE) gene resulting in resistance towards squalene epoxidase inhibitors such as terbinafine, from the allylamines group. The same resistance was also seen in *M. canis* isolated from a cat (Hsiao et al. 2018).

Turmeric, scientifically known as *Curcuma longa*, is a root of rhizomatous herbaceous plant belonging to the ginger family Zingiberaceae. It is native to South Asia and can be grown in diverse tropical conditions with temperature ranging from 20°C to 40°C (Prasad & Aggarwal, 2011). It has long been traditionally used as various remedies to enhance wound healing, reduce cholesterol and as an antibacterial, antiviral and antifungal agent (Lal, 2012). The main bioactive compounds curcumin, turmeric oil, and methanol are what make turmeric valuable in ethnomedicine (Prasad & Aggarwal, 2011). The antifungal activity of curcumin and turmeric oil has been studied in different preparations, including but not limited to direct application, cream (Jankasem et al., 2013), as well as dissolved in dimethylsulfoxide (DMSO) (Brasch et al., 2017) and methanol (Baltazar et al., 2015).

This study reviews the use and efficacy of turmeric (*C. longa*) in the treatment of dermatophytosis by *Microsporum canis*, *Microsporum gypseum* and *Trichophyton mentagrophytes.*

1.2 Problem Statement

There are abundant of home remedy tips suggesting the use of turmeric to treat fungal infections in pet cats. A news article written by Lee. J (2020) headlined "Thai woman ends up with brilliantly yellow cat after using turmeric remedy for its fungal infection," provides an example of the use of turmeric for fungal infection by the general population.

Turmeric is readily available to the public and thus it is commonly used by pet owners as a home remedy to treat fungal infections in their pets. These circumstances have prompted a need for re-evaluation of the existing understanding of the use of turmeric in ethnoveterinary medicine. Besides, there is limited research on the efficacy of turmeric specifically against zoonotic dermatophytes.

In this study, the use of turmeric in its bioactive form against three common zoonotic dermatophytes was reviewed to provide evidence-based information on its efficacy as dermatophytosis treatment.

1.3 Research Questions

1.3.1 What is the level of efficacy of turmeric bioactive compound; curcumin and turmeric oil against zoonotic dermatophytes?

1.3.2 What is the recommended form of turmeric bioactive compound preparation as treatment against dermatophytes?

1.3.3 Which turmeric bioactive compounds show the highest efficacy against dermatophytes?

1.4 Research Hypothesis

1.4.1 Turmeric bioactive compounds (curcumin and turmeric oil) have different antifungal effect on *M. canis*, *M. sporum* and *T. mentagrophytes* depending on its concentration.

1.4.2 Turmeric oil is the best form of turmeric preparation for treatment of dermatophytosis

1.5 Research Objectives

1.5.1 To identify the use and efficacy of turmeric bioactive compounds in treating dermatophytosis.

1.5.2 To identify the recommended form of turmeric bioactive compound preparations.

1.5.3 To determine the most effective form of turmeric preparation for treatment of dermatophytosis.

1.6 Significance of the Study

This study aims to produce evidence-based information on the efficacy of turmeric bioactive compounds against the three most common zoonotic dermatophytosis. Future researchers may use the data analyzed, to provide a direction in future research, and potentially incorporate turmeric as

an integrative approach to combat dermatophytosis. The incorporation of turmeric in veterinary medicine may help to provide a treatment alternative that is more accessible and cheaper as it is a natural ingredient that can be locally sourced in Malaysia. The data collected may also be used among small animal practitioners as a guideline to advise future clients to increase awareness among pet owners. This helps to promote responsible use of herbal alternatives for their pets.

1.7 Scope of the Study

This review aimed to identify the efficacy of turmeric bioactive compounds against dermatophytosis, the recommended preparations of turmeric bioactive compounds and the most effective form of turmeric bioactive compounds for the treatment of dermatophytosis.

The publications reviewed will be related to the investigation of antifungal activity of turmeric bioactive compounds against common dermatophytes. Articles published between the year 2012 and 2022, a 10-year period, were included in the data collection process.

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 (PRISMA 2020) were used as a guideline for the sampling.

CHAPTER 2

LITERATURE REVIEW

2.1 Role of *Microsporum canis*, *Microsporum gypseum* and *Trichophyton mentagrophytes* as Dermatophytes

Dermatophytes have different host preferences which are influenced by the predilected environment of the fungus, namely in human (anthropophilic), animals (zoophilic), or environment (geophilic) (Segal & Elad, 2021). *M. canis* and *T. mentagrophytes* are categorized as zoophilic, while *M. gypseum* is categorized as geophilic dermatophytes. However, these fungi are opportunists and will establish infection in any susceptible hosts.

Zoophilic dermatophytes commonly isolated from humans include *M. canis* and *T. mentagrophytes*, whose prevalence was influenced by the demographic area studied. For example, *M. canis* was the most common dermatophyte isolated in Serbia (Otašević et al., 2019), but low in Malaysia (Ng et al. 2003) due to the majority of the population being Muslims, who do not keep pets as frequently. The geophilic dermatophytes focused on in this study, *M. gypseum*, is the most commonly isolated geophilic species in animals as concluded by Mattei et al. (2014) and also been isolated from humans (Ng et al. 2003, Mattei et al, 2014).

The zoo-anthropophilic potential, and vice versa is the most important issue as it may be the reason pet owners are opting for home remedies as a solution. In which it is to prevent the spreading of skin fungal infection in their household.

2.2 Turmeric: Characteristic & Value

According to Prasad and Aggrawal (2011), turmeric is a rhizomatous herbaceous perennial plant that can grow between 60-90 cm, until up to 1 meter high. The flower of this plant is grouped together in a dense spike and is yellow in colour. The leaves are long and oblong in shape. The turmeric rhizome is the most commonly used part of the plant. It is a tuber with rough segmented skin and has dull orange interior when halved.

Turmeric is commonly used as a cooking spice which is not only in South Asia, but also extends to Middle Eastern and South African countries. Turmeric is the main ingredient in curry and is used to give yellow colouring to various foods such as butter, rice and cheese (Prasad & Aggrawal, 2011). The rich yellowish-orange colour of turmeric also allows clothes to be dyed using it, such an example can be seen among Buddhist monks' bright orange robes (Lal, 2012). Traditionally, turmeric is believed to help with various ailments including fever, skin disease and constipation (Lal, 2012). Turmeric is also used by commoners to help with digestive disorders including to reduce gas, colic and inflammatory bowel disease. It is also believed to have anticancer properties by the traditional holistic Indian medicine known as "Ayurveda" (Prasad & Aggrawal, 2011).

2.3 Antifungal Properties of Turmeric Bioactive Compounds: Curcumin and Turmeric Oil

Turmeric has more than 100 components that can be isolated. The main components are the volatile oil, or turmeric oil, and the colouring pigment curcuminoids which contain curcumin (Prasad & Aggarwal, 2011).

A study conducted by Jankasem et al. (2013) revealed that turmeric oil possesses inhibitory activity on dermatophytes, including *M. gypseum* and *T. mentagrophytes*. Recent studies show that curcumin shows an antifungal effect by exerting a zone of inhibition for dermatophytes (Wuthi-udomlert et al., 2000, Zarrinfar et al., 2021) and up to 38.88% growth inhibitory activity on *M. canis* (Khattak et al., 2005).

CHAPTER 3

RESEARCH METHODOLOGY

This systematic review was performed using the Preferred Reporting Items for Systematic Review and Meta-Analyses 2020 (PRISMA 2020) guidelines.

3.1 Literature search

Four electronic search engine databases, Google Scholar, Pubmed, ScienceDirect and Scopus were used for literature searching. The search setting was fixed from the year 2012 to 2022 to identify all the published literature within the specified period. Specific search phrases include keywords of "curcumin" OR "turmeric" OR "curcurma" AND "antifungal" OR "antidermatophytic" AND "dermatophytes" OR "dermatophytosis" OR "*Microsporum"* OR "*Trichophyton"*. Various combinations of the above terms were included in the searches across the four previously listed databases. All search results were recorded and summarized in Table 3.0.

3.2 Screening, inclusion, and exclusion criteria

To ensure that the data retrieved from the literature are relevant to the scope for this review, several screenings were conducted based on the inclusion and exclusion criteria. The inclusion criteria of this review will include literature that involves the investigation of antifungal activity of turmeric/turmeric bioactive compounds against common zoonotic dermatophytes (*M. canis*, *M. gypseum* and *T. mentagrophytes*). The literature must as well include information on the antifungal effect of turmeric on dermatophytes. Articles published between the year 2012 until 2022 (10 years period) will be included in the data collection process.

For exclusion criteria, published books, case reports and non-primary research such as review articles and meta-analyses of turmeric use against dermatophytosis were excluded. Turmeric use against other types of skin ailments is irrelevant to this literature review and was not included.

After the first phase of the literature search, the first screening was done to remove unrelated and duplicated literature based on citation using EndNote 20. The second screening was done manually to remove literature based on the title. The final screening was also done manually by evaluating the title, abstract and methodology of the publications to finalize the total number of literature to be included in this literature review. The process and the result of the sequential screening were illustrated in Figure 4.0.

3.3 Result synthesis

All the literature was systematically reviewed, and the results were tabulated in Table 3.0.

Table 3.0: Search strategy across different databases and literature retrieved

Database	**Google Scholar**	**Pubmed**	**ScienceDirect**	**Scopus**
Search term	Turmeric OR curcumin OR *Curcuma* AND antifungal OR antidermatophytic AND dermatophytes OR *Microsporum* OR *Trichophyton*	*Curcuma* OR turmeric OR curcumin AND antifungal OR antidermatophytic AND dermatophyte* OR *Microsporum* OR *Trichophyton*	*Curcuma* OR turmeric OR curcumin AND antifungal OR antidermatophytic AND dermatophyte OR *Microsporum* OR *Trichophyton*	*Curcuma* OR turmeric OR curcumin AND antifungal OR antidermatophytic AND dermatophytes OR dermatophytosis OR *Microsporum* OR *Trichophyton*
Number of literatures retrieved	1550	1253	694	59
Total	3556			

CHAPTER 4

FINDINGS

4.1 Results

The first literature search using the various search strategies across four databases yielded a total of 3516 publications. Then, the screening process of the search strategy identified a total of 199 publications that were eligible to be assessed after the removal of duplicates and publications beyond the scope of interest as well as those which does not meet the eligible criteria. Based on the four sequential screenings, a total of 9 publication were identified to be eligible to be reviewed and were depicted in Figure 4.0. Among the studies included, *Microsporum canis* was included in 2 (n=2/9, 22.22%) literatures, *Microsporum* gypseum in 4/9 (44.44%) literatures, and *Trichophyton mentagrophytes* in 7/9 literatures. Each literatures have a different focus on the turmeric bioactive compound studied, except for 3 (n=3/9 33.33%) studies that suggested further research was needed to determine the active constituent or the bioactive compound responsible for the antifungal activity. The method of preparation of turmeric were included in all studies with 2 out of 9 (22.22%) of the analyzed studies involved the application of nanoparticles principle to enhance the turmeric or its active constituent for skin penetration. Additionally, 4 out of 9 (44.44%) of the studies included studied the activation and synergistic activity of turmeric with selected compound and method to increase the antifungal activity. Table 4.0 summarize the published literature with the targeted dermatophytes and the antifungal activity of the turmeric bioactive compound studied. The raw data from the selected studies were included in Appendix A and B.

Figure 4.0: Flowchart illustrating methodology and result of screening for literature review

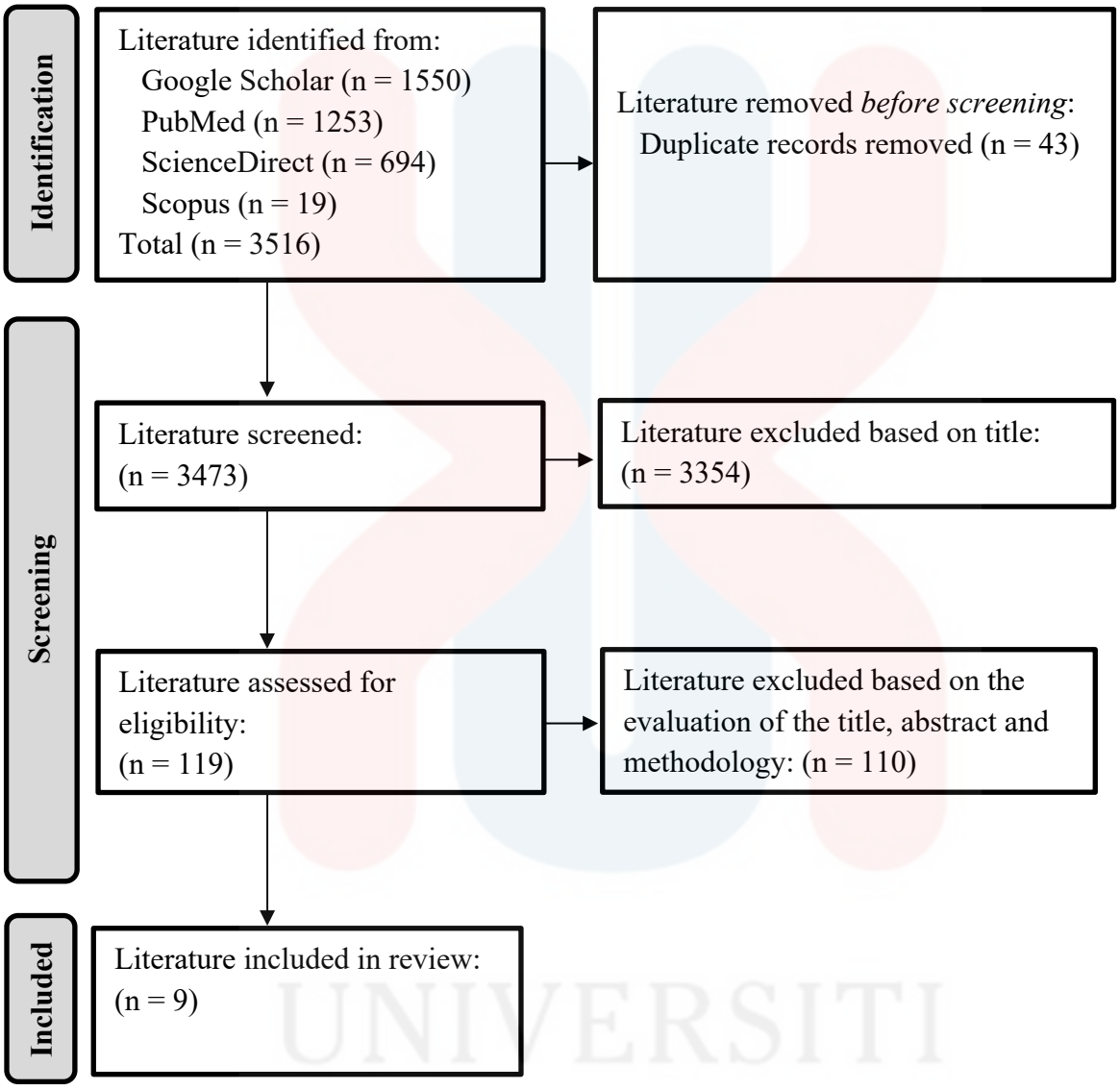

Table 4.0: Number of studies included in the analysis

First author (year)	Dermatophyte species	Main turmeric bioactive compound	Form of turmeric preparation	Activation/ Synergism	Antifungal study method
Alolofi (2022)	*M. canis*, *M. gypseum*, *T. mentagrophytes*	N/A	Dissolved in ethanol and chloroform	N/A	Disc diffusion method
Brasch (2017)	*M. canis*, *M. gypseum*	Curcumin	Dissolved in DMSO	Photoactivation	Agar well diffusion assay
Huong (2013)	*T. mentagrophytes*	turmerones (ar- turmerone and α-turmerone)	Turmeric oil	N/A	Disc diffusion method

Jankasem (2013)	*M. gypseum*, *T. mentagrophytes*	ar-turmerone, turmeric oil	Oil in water turmeric cream, turmeric oil and ar-turmerone	N/A	Broth microdilution assay
Kesharwani (2022)	*T. mentagrophytes*	Difluorinated curcumin	Dissolved in chitosan solution (nanoparticles)	Itraconazole	Cylinder plate method
Mishra (2021)	*T. mentagrophytes*	Curcumin	Dissolved in light paraffin, almond oil and sesame oil and Span 80, Tween 80, ethanol (nanoemulsion)	Fluconazole	Checkerboard experiment

Ogidi (2021)	*T. mentagrophytes*	Turmeric oil (Z-citral)	Turmeric oil	Antifungal creams (clotrimazole, fluconazole, ketoconazole, terbinafine)	Agar well diffusion method
Rath (2014)	*T. mentagrophytes*	N/A	Dissolved in water, alcohol, chloroform, ether	N/A	Poison food technique
Shivakumar Singh (2014)	*M. gypseum*	N/A	Dissolved in petroleum ether, chloroform, ethyl acetate, methanol,	N/A	Agar well diffusion method

aqueous

M. canis = *Microsporum canis*, *M. gypseum* = *Microsporum gypseum*, *T. mentagrophytes* = *Trichophyton mentagrophytes*, N/A = not available

4.2 Antifungal Activity of Turmeric on Dermatophytes

4.2.1 Turmeric Preparation

Curcumin has a poor solubility in water due to its hydrophobic property (Mishra & Gupta, 2021). In the order of solubility, curcumin was found to be very soluble in paraffin light, freely soluble in sesame oil and almond oil, and soluble in tween 80 and span 80 surfactants as demonstrated by Mishra and Gupta, 2021. Kesharwani et al. (2022) found that difluorinated curcumin was completely soluble in DMSO and methanol, but insoluble in water, HCl, and PBS.

Following that, different studies have been conducted to determine the best way to increase the penetration of turmeric bioactive compounds for topical administration for the treatment against dermatophytes. Preparation of turmeric or its bioactive compound in the form of nanoparticles enhances the penetration of the active constituent into the keratin layers. This method of preparation also allows the delivery of other antifungal medications effectively for synergistic effect, as presented by Kesharwani et al., 2022. Mishra & Gupta (2021) describes the same phenomenon of enhanced penetration and delivery of antifungal drugs and curcumin in synergism when nanoemulsion was used.

Ethanolic extract of *Curcuma longa* was found to have a 100% inhibition towards *T. mentagrophytes* (Rath & Mohanty, 2013). The report from Alolofi et al. (2022) corresponds to the data by which it was revealed that ethanolic extract of *C. longa* shows better inhibition zone against *T. mentagrophytes* than methanolic extract, at 50 and 40 mm consecutively. Rath and Mohanty (2013) demonstrated a comparable data that support the aforementioned reports, wherein the chloroform extract of *C. longa* exhibited a fourfold increase in MIC value compared to ethanolic extract.

A study by Shivakumar Singh and Vidyasagar (2014) revealed that *C. longa* at the concentration of 5 mg/ml and 2.5 mg/ml, extracted in pet ether (18.66 ± 1.52 mm, 9.33 ± 0.57 mm) has the

highest zone of inhibition value on *M. gypseum* followed by chloroform (11.33 ± 1.15 mm, 8.33 ± 1.15 mm) and methanolic (9.33 ± 1.15 mm, 5.66 ± 1.52 mm) extract. Aqueous solution (7.01 ± 0.00 mm, 5.66 ± 1.57 mm) shows the lowest zone of inhibition. Compared to the standard drug ketoconazole (1 mg/ml), it shows an inhibition zone of 18.00 ± 0.00 mm. Thus, it was concluded that *C. longa* was effective and showed maximum activity against *M. gypseum.*

The results from Alolofi et al. (2022) showed comparison of the inhibitory activity of ethanolic and chloroformic extract of *C. longa* and several antidermatophytic drugs against *M. canis*, *M. gypseum* and *T. mentagrophytes.* In this study, ethanolic and chloroformic extract of *C. longa* exhibited similar zone of inhibition of 50 mm against *M. canis* and 0 mm zone of inhibition for *M. gypseum*. For *T. mentagrophytes* the result was parallel to the previous studies, in which ethanolic extract shows better inhibitory activity with the zone of inhibition of 50 mm when compared to 40 mm of chloroformic extract. Regarding the antifungal drugs, it was observed that clotrimazole has a similar diameter of zone of inhibition of 50 mm on *M. canis* and *T. mentagrophytes,* and 40 mm on *M. gypseum*. Itraconazole exhibited 50-, 20- and 50-mm zone of inhibition on *M. canis, M gypseum* and *T. mentagrophytes* subsequently. In the same order of dermatophytes, 40-,10- and 50-mm zone of inhibition can be seen for fluconazole. From the data, Alolofi et al. (2022) concluded that *Trichophyton* species were more sensitive to plant extracts than *Microsporum* species. The data, in general, showed that *C. longa* extracts exhibited a high antidermatophytic activity against *M. canis* and *T. mentagrophytes* which was comparable to the three antidermatophytic drugs (clotrimazole, itraconazole, fluconazole) used in the study, except against *M. gypseum*.

4.2.2 Minimum Inhibitory Concentration (MIC)

A study by Rath and Mohanty (2013) revealed that the MIC value of ethanolic extract of *Curcuma longa* was 6.575 µg/ml against *T. mentagrophytes,* which was better than the chloroform extract (26.3 µg/ml).

Ogidi et al. (2021) reported that turmeric oil has a MIC of 5 mg/ml against *T. mentagrophytes*. This value is similar that of other antifungal medication used in the study including clotrimazole (5 mg/ml), ketoconazole (5 mg/ml) and terbinafine (5 mg/ml), except for fluconazole which was twice as much at 10 mg/ml. These data highlighted the potential of *C. longa* extract in comparison to conventionally available antifungal medication.

Jankasem et al. (2013) revealed that turmeric oil displayed the best antidermatophytic activity against *T. mentagrophytes* and *M. gypseum* with the MIC value of 6.25 µg/mL for both dermatophytes when compared to the MIC of ketoconazole at 12.50 and 25 µg/mL respectively.

4.2.3 Activation and Synergistic Activity of Turmeric with Selected Compounds

Jankasem et al. (2013), Rath and Mohanty (2013) and Brasch et al. (2017), mentioned that the preparation of turmeric was done carefully to avoid exposure to light to prevent the loss of active compounds. This practice was backed by data from Brasch et al. (2017), whereby significant inhibitory effect on dermatophytes growth can be observed after photodynamic inactivation with the presence of curcumin. The photoactivation status of curcumin is concentration dependent, with higher concentration having higher inhibitory activity against *M. canis* and *M. gypseum*.

Furthermore, Ogidi et al. (2021) and Mishra and Gupta (2021) defined the synergistic activity by the fractional inhibitory concentration index (FICi) in which; synergistic when FICi ≤0.5; indifferent or no interactions when FICi was 0.5–4.0 and antagonistic when FICi ≥4.0. Experimentation by Mishra and Gupta (2021) on the synergistic activity of fluconazole and

curcumin against *T. mentagrophytes* showed synergism with FICi value of 0.0196 ± 0.0126. However, for synergistic activity of turmeric oil with antifungal drugs (clotrimazole, fluconazole, ketoconazole and terbinafine) against *T. mentagrophytes*, Ogidi et al. (2021) revealed that the FICi values range from 0.60-1.20, thus indicating no interactions. Furthermore, first synergistic interaction between itraconazole with difluorinated curcumin prepared as nanoparticles (ITZ-CDF/CH NPs) against dermatophytes was reported by Kesharwani et al. (2022), by comparing the colony forming unit (CFU).

CHAPTER 5

DISCUSSION

Turmeric widespread use for dermatophyte infections brings about the importance of identifying the active constituent for optimal benefit for therapeutic use. Various studies focus on several known bioactive compounds in turmeric with the commonest ones being curcumin, and turmerones which can be found in turmeric oil. Regardless, all the publications included in this review showcased the antidermatophytic activity of turmeric extract or its bioactive compound in different medium, against *M. canis*, *M. gypseum* and *T. mentagrophytes*, which were comparable to common commercial antifungal drugs. However, one exception was demonstrated by Alolofi et al. (2022) due to absence of any zone of inhibition on *M. gypseum* growth when ethanolic and chloroform extract of *C. longa* was used. This was hypothesized due to the different concentration of *C. longa* extracts produced which were not tested prior to the experiment. It is worth noting, as mentioned by Brasch et al. (2017) and Button et al. (2013), that a small sample size may have led to inaccurate interpretations of the result. Simultaneously, Shivakumar Singh & Vidyasagar, (2014) and Jankasem et al. (2013) have proven that *M. gypseum* can be inactivated with turmeric extract in different solvents and turmeric oil, which were equivalent, if not better, than the inhibitory activity of ketoconazole.

The minimum inhibitory concentration (MIC) is an important tool that can be used to determine the in vitro susceptibility or resistance of an organism to a certain drug (Leigue et al., 2016) and to monitor the antimicrobial activity of new drugs, such as turmeric in this literature review. Thus, MIC determination aids in minimizing the risk of toxicity and emergence of antifungal resistance, as it helps to identify the most effective dose to be used (Leigue et al., 2016, Libretexts, 2022).

The MIC for antifungal activity of turmeric on dermatophytes depends on the method of preparation and the form of the turmeric itself. Ethanolic extract of *C. longa* has lower MIC compared to chloroform extract (Shivakumar Singh & Vidyasagar, 2014). Turmeric in the form of turmeric oil and the active constituent *Ar*-turmerone, have better MIC (6.25, 7.81 μg/mL consecutively) against *T. mentagrophytes* and *M. gypseum* than ketoconazole (12.5, 25 μg/mL consecutively) (Jankasem et al. 2013). The MIC for turmeric oil against *T. mentagrophytes* was reported to be 5 mg/ml (5000 μg/mL) by Ogidi et al. (2021). Nevertheless, it can be concluded from Shivakumar Singh & Vidyasagar (2014), Ogidi et al. (2021) and Jankasem et al. (2013) that the MIC of turmeric and its bioactive compound against dermatophytes were comparable and better than the common azole antifungal drugs.

Turmeric bioactive compound can be activated by the presence of light (Jankasem et al., 2013, Rath & Mohanty, 2013 and Brasch et al., 2017). Brasch et al. (2017) revealed that in vitro exposure to light for 96 hours have an equivalent effect as fluconazole. In the experiment, *M. gypseum* was found to be least affected by curcumin which coincides with report by Alolofi et al. (2022). However, 5.4 mg/l of curcumin with photoactivation was found to markedly reduced its growth compared to the unexposed group and fluconazole. Given the superficial nature of dermatophytosis on the skin, topical application of curcumin is feasible and allows the exposure to light of an appropriate wavelength to the affected site.

Rath and Mohanty (2014), Brasch et al. (2017) and Shivakumar Singh and Vidyasagar (2014) studied the antifungal activity of turmeric extract in a few different solvents. Kesharwani et al. (2022), Mishra and Gupta (2021), have used curcumin as the turmeric bioactive compound against dermatophytes. Huong et al. (2013), Jankasem et al. (2013) and Ogidi et al. (2021) presented the antifungal activity of turmeric oil. The similarity of all the publications is, it was agreed that

turmeric extract and its bioactive compound were effective against *M. canis*, *M gypseum* and *T. mentagrophytes.* As previously reported by Kesharwani et al. (2022), difluorinated curcumin was insoluble in water, HCl, and PBS, but can be completely dissolved in methanol and DMSO. This drug solubility data was recognized for its importance to signify the promising potential for effective topical drug delivery (Mishra & Gupta, 2021) as well as development of optimal formulation. In addition, application of nanoparticle principle can be implemented to further enhanced the penetration of the molecules into the skin stratum layer and thus increasing efficiency. Mishra and Gupta (2021) described that increased hydration of the skin will increase penetration of molecules with hydrophobic property due to the increased interlamellar volume of the lipid bilayers in the stratum corneum. Kesharwani et al. (2022) supports this theory in their paper by using a formulation that incorporated hydrogel to increase contact time and hydration, with the goal to loosen the keratin network and disulfide bonds of the skin layer for better drug penetration.

CHAPTER 6

CONCLUSION AND RECOMMENDATIONS

In this literature review, the antifungal activity of turmeric and its bioactive compound were reviewed. A few studies have included the MICs value of the active constituents of turmeric which were comparable to antifungal drug. Turmeric oil exhibited the lowest MIC value compared to curcumin. The MIC value can be used as a reference value for the formulation process in the future. At the same time, several studies that used turmeric in different solvents without the identification of the active constituent call for further identification and purification of the bioactive compound as it may has the possibility to have a more potent antifungal activity. Moreover, turmeric and its bioactive compounds were also found to have a synergistic effect when applied together with antifungal drugs except for one study. However, a crucial point is that combinatory use of plant extract with antifungal medication were found to be effective in other studies and thus the phytomedicine value shall not be ignored. Additionally, increased antifungal activity can be achieved by photoactivation and the lipophilic molecules delivery were also described to be increased by using the formulation of nanoparticle and nanoemulsion. In essence, nine out of nine (100%) study included in this review concluded that turmeric and its bioactive compound can be used as an antifungal treatment against the three main dermatophytes investigated, *M. canis*, *M. gypseum,* and *T. mentagrophytes*.

As a recommendation for improvement of future work, aside from the antifungal activity, the safety profile of turmeric should be addressed. The long-term effect of the topical application of turmeric or its bioactive compound, toxicity, and the practicality of formulation need to be evaluated. In vivo trial using laboratory animal model that adhered to ethical standards may be valuable as it is able to provide a controlled condition and mimic the normal biology.

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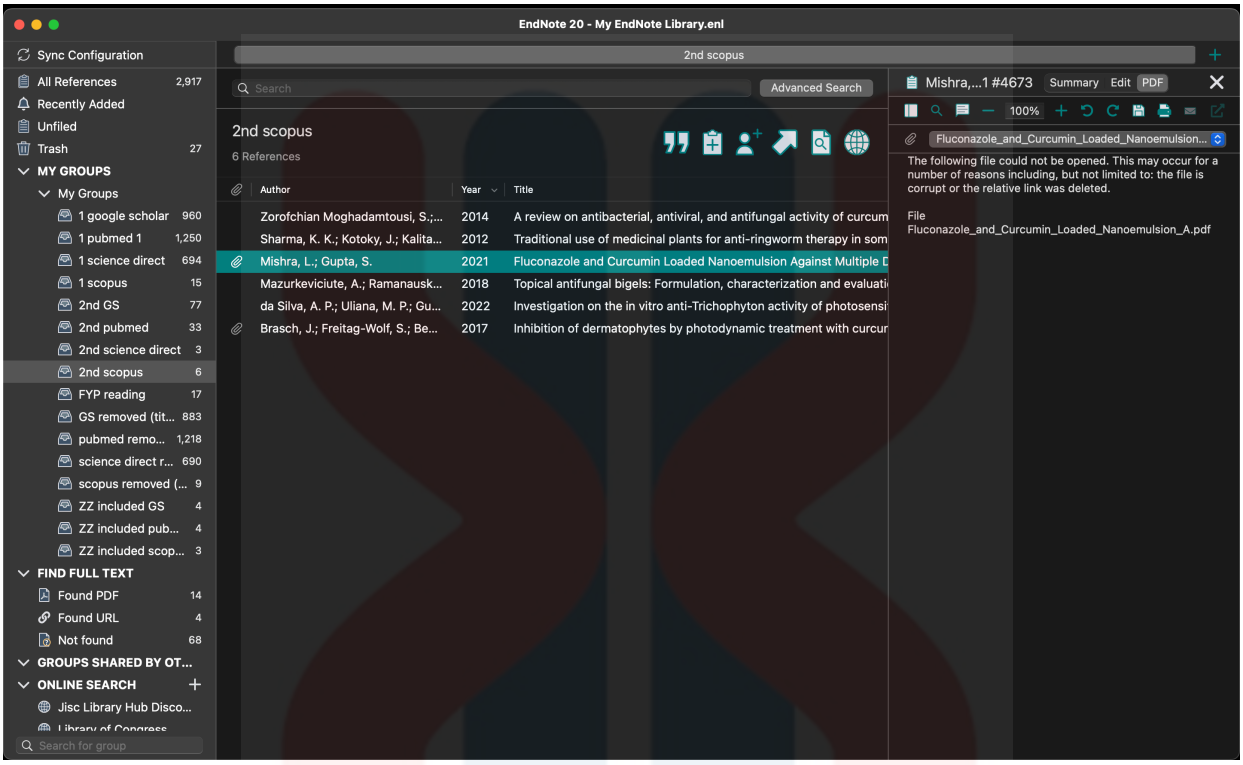
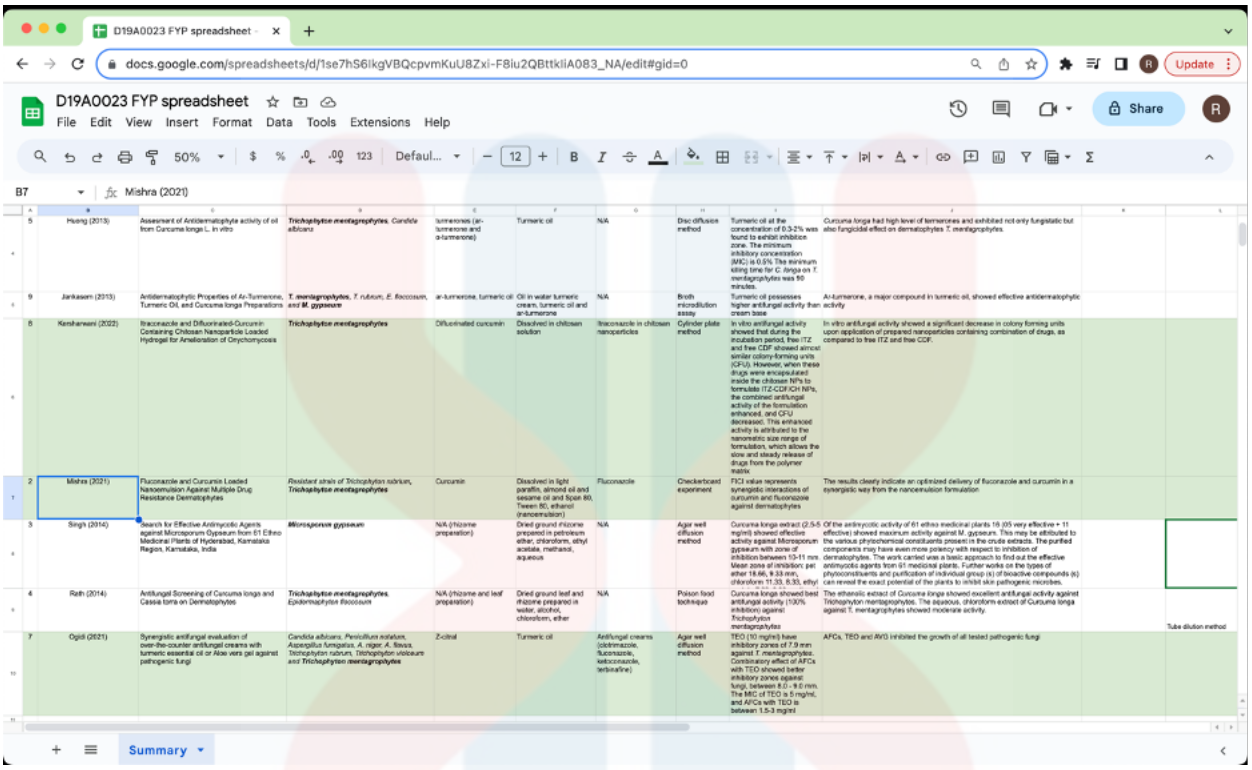


Appendix A: Print screen from EndNote 20 during the screening of the publications



Appendix B: Print screen from Google Sheets during the manual data extraction process