



At in

HUMAN



#### Human Journals **Review Article** September 2023 Vol.:28, Issue:2 © All rights are reserved by B. Sasidhar et al.

# Poly-Herbal Anti-Fungal Spray: A Comprehensive Review



# B. Sasidhar<sup>1</sup>, G. Raveendra Babu<sup>2</sup>, T. Jashwanth, M. Kavitha, Sk. Rabiya. I. Swathi, K. Venkata Srikanth, D. Dhachinamoorthi<sup>3</sup>

<sup>1</sup>Professor, Department of Pharmaceutical Biotechnology, QIS College of Pharmacy, Vengamukkapalem, Ongole, Andhra Pradesh, India.

<sup>2</sup>Professor, Department of Pharmaceutical Analysis, QIS College of Pharmacy, Vengamukkapalem, Ongole, Andhra Pradesh, India.

<sup>3</sup>Professor, Department of Pharmaceutics, QIS College of Pharmacy, Vengamukkapalem, Ongole, Andhra Pradesh, India.

Submitted:	21 August 2023
Accepted:	23 September 2023
Published:	30 September 2023





ijppr.humanjournals.com

**Keywords:** anti-fungal therapies, formulation, in vitro and in vivo evaluations, poly-herbal anti-fungal sprays, mechanisms of action

# ABSTRACT

Background: This review article offers a comprehensive analysis of poly-herbal anti-fungal sprays, covering their formulation, mechanisms of action, in vitro and in vivo evaluations, clinical applications, challenges, and future prospects. Main body: By synthesizing current research, the article provides valuable insights into the potential of polyherbal formulations as effective anti-fungal therapies. The prevalence of fungal infections has led to a growing demand for effective and safe treatment options. Poly-herbal formulations, combining the synergistic effects of multiple plant-derived compounds, have gained attention as promising alternatives for combating fungal infections. This review provides an in-depth analysis of the literature on poly-herbal anti-fungal sprays, highlighting their formulation, mode of action, in vitro and in vivo evaluations, potential clinical applications, and challenges. Conclusion: By synthesizing recent research findings, this article offers insights into the development and future prospects of poly-herbal anti-fungal sprays as therapeutic interventions.

## 1. BACKGROUND<sup>1-7</sup>

Fungal infections pose a significant global health burden, necessitating novel treatment strategies. Poly-herbal formulations, composed of multiple plant-derived constituents, offer a holistic approach to combat fungal pathogens. The use of poly-herbal anti-fungal sprays aligns with the growing interest in natural and traditional medicines.

#### 2. MAIN TEXT

#### 2.1 Rationale for Poly-Herbal Formulations:

2.1.1 Synergistic Effects of Plant Compounds 8-9

#### Synergy in Poly-Herbal Formulations

The concept of synergy, where the combined effect of two or more components is greater than the sum of their individual effects, forms the cornerstone of poly-herbal formulations. Plant-derived compounds contain a diverse array of bioactive molecules, each with unique modes of action against fungal pathogens. When these compounds are combined, their interactions can lead to enhanced antifungal activity, increased efficacy, and reduced risk of resistance. Synergistic interactions between plant compounds in poly-herbal formulations offer a promising approach to overcoming the limitations of conventional antifungal therapies. By harnessing the collective strength of diverse bioactive molecules, poly-herbal anti-fungal sprays have the potential to provide more effective and sustainable treatment options for fungal infections. Continued research into the mechanisms of synergy and the identification of optimal combinations will contribute to the development of innovative therapeutic solutions in the fight against fungal pathogens.

# 2.1.2 Broad-Spectrum Activity<sup>10-11</sup>

The broad-spectrum activity of poly-herbal formulations offers a compelling rationale for their development as effective antifungal therapies. By simultaneously targeting multiple fungal species and engaging diverse mechanisms of action, these formulations hold promise for overcoming the challenges posed by fungal infections, including drug resistance and limited treatment options. Continued research and exploration of synergistic plant combinations are essential for advancing the development of broad-spectrum poly-herbal anti-fungal sprays as a valuable addition to the antifungal armamentarium.

2.1.3 Reduced Risk of Resistance<sup>12</sup>

The reduced risk of resistance is a compelling rationale for the development of poly-herbal antifungal formulations. By capitalizing on the multifaceted interactions and complex synergies among various plant-derived compounds, these formulations offer a promising strategy to overcome the growing challenge of antifungal resistance. Continued research into the mechanisms underlying resistance mitigation and the identification of optimal plant combinations will contribute to the advancement of effective and sustainable antifungal therapies.

2.1.4 Enhanced Safety Profile<sup>13</sup>

The enhanced safety profile of poly-herbal formulations is a compelling rationale for their utilization in antifungal therapies. By harnessing natural plant-derived compounds and capitalizing on their complex interactions, these formulations offer the potential for effective treatment with reduced toxicity, minimal adverse effects, and modulation of host-pathogen interactions. Continued research into the safety and tolerability of poly-herbal formulations will contribute to their integration into mainstream antifungal treatment strategies, providing patients with safer and more holistic therapeutic options.

# 2.2. Active Ingredients in Poly-Herbal Anti-Fungal Sprays:

# 2.2.1 Commonly Used Plant Extracts<sup>14-16</sup>

Commonly used plant extracts, such as neem, turmeric, garlic, tea tree, and aloe vera, serve as potent sources of active ingredients in poly-herbal anti-fungal sprays. Their diverse array of bioactive compounds, multifaceted mechanisms of action, and established antifungal properties make them invaluable components in combating fungal infections. By synergistically harnessing the power of these plant-derived compounds, poly-herbal formulations offer promising therapeutic options for addressing fungal pathogens effectively and holistically.

# 2.2.2 Bioactive Compounds and Mechanisms of Action<sup>17-19</sup>

Bioactive compounds within commonly used plant extracts contribute to the efficacy of polyherbal anti-fungal sprays through diverse mechanisms of action. The interplay of these compounds offers multifaceted attacks on fungal pathogens, reducing the risk of resistance development. The comprehensive understanding of these mechanisms enriches the

development of potent and sustainable poly-herbal formulations for combating fungal infections.

#### 2.3. Formulation and Development of Poly-Herbal Anti-Fungal Sprays:

#### 2.3.1 Extraction Techniques and Solvents<sup>20-22</sup>

Extraction techniques and solvents play a crucial role in the formulation and development of poly-herbal anti-fungal sprays. Proper selection and optimization of these factors are essential for obtaining high-quality extracts rich in bioactive compounds, ensuring the efficacy and potency of the final formulation.

2.3.2 Excipients and Stabilizers<sup>23, 24</sup>

Excipients and stabilizers play a pivotal role in formulating poly-herbal anti-fungal sprays. Their careful selection and incorporation contribute to the overall stability, bioavailability, and therapeutic effectiveness of the formulation. By optimizing these components, developers can create poly-herbal sprays that deliver enhanced antifungal activity while maintaining the desired physical and chemical attributes.

#### 2.3.3 Nano formulations for Enhanced Efficacy<sup>25-27</sup>

Integration of nanoformulations into poly-herbal anti-fungal sprays holds great promise for enhancing their efficacy, bioavailability, and targeted delivery. While challenges exist, the potential benefits of improved treatment outcomes, reduced dosing frequency and enhanced patient compliance make nanoformulations a compelling avenue for advancing poly-herbal spray development and optimizing antifungal therapy.

#### 2.4. Mechanisms of Action:

# 2.4.1 Disruption of Fungal Cell Membranes<sup>28-30</sup>

Disruption of fungal cell membranes is a key mechanism through which poly-herbal antifungal sprays exert their antifungal activity. By targeting this essential component of fungal cells, these sprays effectively inhibit growth, prevent colonization, and contribute to the overall management of fungal infections.

# 2.4.2 Inhibition of Fungal Enzymes<sup>31-33</sup>

Inhibition of fungal enzymes is a pivotal mechanism through which poly-herbal anti-fungal sprays exert their antifungal effects. By disrupting key cellular processes and metabolic pathways, these sprays effectively target fungal growth and proliferation. The combination of enzyme inhibition with other mechanisms of action enhances their overall antifungal efficacy, offering a multifaceted approach to combatting fungal infections.

# 2.4.3 Modulation of Host Immune Response<sup>34-36</sup>

The modulation of host immune responses is a crucial mechanism through which poly-herbal anti-fungal sprays combat fungal infections. By enhancing immune cell activation, signalling pathways, and overall immune defence, these sprays contribute to a comprehensive and effective approach to managing fungal pathogens.

# 2.5. In vitro Evaluation:

# 2.5.1 Minimum Inhibitory Concentration (MIC) Assays<sup>37-39</sup>

Minimum Inhibitory Concentration (MIC) assays play a pivotal role in evaluating the antifungal activity of poly-herbal sprays. By providing quantitative data on the concentration required to inhibit fungal growth, MIC assays guide formulation optimization, clinical relevance assessment, and the development of effective antifungal therapies.

# 2.5.2 Disk Diffusion and Agar Well Diffusion Tests<sup>40-42</sup>

Disk diffusion and agar well diffusion tests are valuable tools for evaluating the antifungal activity of poly-herbal sprays. While they offer a qualitative assessment of inhibitory potential, these tests provide rapid and informative insights into the formulation's effectiveness against fungal pathogens. When combined with other in vitro and in vivo evaluations, these methods contribute to a comprehensive understanding of the antifungal properties of poly-herbal anti-fungal sprays.

# 2.5.3 Time-Kill Kinetics<sup>43-45</sup>

Time-kill kinetics studies are valuable tools for understanding the temporal dynamics of fungal growth inhibition or killing by poly-herbal anti-fungal sprays. By providing a comprehensive view of the formulation's efficacy over time, these studies contribute to optimizing dosing regimens, elucidating mechanisms of action, and assessing potential

combination therapies. When combined with other in vitro and in vivo evaluations, time-kill kinetics enhance our understanding of the antifungal properties of poly-herbal sprays.

# 2.5.4 Biofilm Inhibition Assays<sup>46-48</sup>

Biofilm inhibition assays play a crucial role in assessing the effectiveness of poly-herbal antifungal sprays against biofilm-associated fungal infections. By evaluating the prevention and disruption of biofilms, these assays provide valuable insights into the formulation's potential to address a challenging aspect of fungal pathogenesis. When combined with other in vitro and in vivo evaluations, biofilm inhibition assays enhance our understanding of the antifungal properties of poly-herbal sprays and their clinical relevance.

# 2.6. In vivo Studies:

# 2.6.1 Animal Models for Fungal Infections<sup>49, 50</sup>

Animal models provide a crucial platform for evaluating the safety and efficacy of polyherbal anti-fungal sprays in a biologically relevant context. By mimicking various aspects of human fungal infections, these models contribute to our understanding of the formulation's potential clinical utility and guide further research and development efforts.

# 2.6.2 Efficacy and Safety Evaluation<sup>51-53</sup>

In vivo, efficacy and safety evaluation of poly-herbal anti-fungal sprays in animal models is crucial for determining their potential clinical utility. By assessing the formulation's impact on fungal infections and the host's health, these studies contribute to our understanding of the formulation's overall effectiveness and safety profile. When combined with in vitro and other preclinical evaluations, in vivo studies guide further development and optimization efforts of poly-herbal sprays as antifungal therapies.

# 2.6.3 Pharmacokinetic and Tissue Distribution Studies, 55

Pharmacokinetic and tissue distribution studies provide crucial insights into the behavior of poly-herbal anti-fungal sprays within the body. By understanding how the formulation is absorbed, distributed, metabolized, and excreted, researchers can optimize dosing regimens and assess the formulation's overall pharmacokinetic profile. These studies contribute to the formulation's development, safety assessment, and potential clinical translation.

# 2.7. Clinical Trials and Applications:

# 2.7.1 Case Studies and Clinical Reports<sup>56-58</sup>

Case studies and clinical reports offer valuable insights into the practical applications, efficacy, and safety of poly-herbal anti-fungal sprays in treating fungal infections. While they may not replace controlled clinical trials, these studies contribute to the growing body of evidence, inform clinical decision-making, and stimulate further research to optimize and validate the use of poly-herbal sprays in clinical practice.

# 2.7.2 Patient Adherence and Tolerability<sup>59-61</sup>

Patient adherence and tolerability are critical considerations in clinical trials and real-world applications of poly-herbal anti-fungal sprays. Ensuring that patients can consistently follow treatment regimens and tolerate the formulation is essential for maximizing therapeutic benefits and achieving positive outcomes. Effective assessment and management of patient adherence and tolerability contribute to the success and widespread use of poly-herbal sprays in treating fungal infections.

2.7.3 Combination Therapies with Conventional Anti-Fungal Agents<sup>62, 63</sup>

Combination therapies involving poly-herbal anti-fungal sprays and conventional anti-fungal agents present a promising approach to addressing the challenges of fungal infections. Clinical trials and real-world applications of these combinations provide valuable insights into their potential to enhance treatment efficacy, reduce resistance, and improve patient outcomes. While challenges exist, the benefits of combination therapies underscore their importance in advancing the field of antifungal therapy and improving the management of fungal infections.

# 2.8. Challenges and Future Directions:

# 2.8.1 Standardization of Poly-Herbal Formulations<sup>64-66</sup>

Standardization of poly-herbal anti-fungal formulations is a crucial step to ensure their consistent quality, efficacy, and safety. Overcoming the challenges posed by the complexity of these formulations requires a multidisciplinary approach involving chemical analysis, quality control methods, and adherence to regulatory guidelines. By addressing these challenges and implementing standardized practices, the field can pave the way for the

successful integration of poly-herbal formulations into antifungal therapy, benefiting patients and advancing the treatment of fungal infections.

#### 2.8.2 Regulatory Considerations and Quality Control<sup>67-69</sup>

Addressing regulatory considerations and implementing rigorous quality control measures are imperative for the successful development and utilization of poly-herbal anti-fungal formulations. By establishing standardized guidelines, conducting comprehensive safety assessments, and adhering to Good Manufacturing Practice (GMP) principles, the field can navigate the challenges posed by regulatory approval and quality control. Ensuring that these formulations meet regulatory standards enhances their credibility, safety, and potential to become effective tools in the management of fungal infections.

#### 2.8.3 Long-Term Safety and Toxicity<sup>70-72</sup>

Long-term safety and toxicity assessment of poly-herbal anti-fungal formulations is essential to ensure their sustained and safe use in managing fungal infections. By conducting rigorous long-term studies, employing advanced toxicology assays, and implementing comprehensive post-market surveillance, the field can address the challenges associated with long-term safety concerns. Ensuring that these formulations have a favorable long-term safety profile enhances their utility and establishes them as valuable therapeutic options for fungal infection management.

#### 2.8.4 Ethnopharmacological Knowledge Integration<sup>73-75</sup>

Ethnopharmacological knowledge integration presents an opportunity to tap into centuriesold wisdom for the development of poly-herbal anti-fungal formulations. By addressing challenges through collaborative research, modern scientific validation, and cultural sensitivity, the field can bridge the gap between traditional practices and contemporary scientific approaches. Embracing and integrating ethnopharmacological knowledge enriches the development of effective, culturally relevant, and sustainable therapeutic options for fungal infection management.

## 2.9. Comparative Analysis and Discussion:

# 2.9.1 Comparing Poly-Herbal Formulations with Single-Compound Drugs<sup>76-78</sup>

Comparing poly-herbal formulations with single-compound drugs highlights their respective strengths, limitations, and potential roles in treating fungal infections. While each approach offers unique benefits, a comprehensive understanding of their mechanisms, efficacy, and safety is crucial for optimizing antifungal therapy. Future research and clinical trials will contribute to evidence-based decision-making, guiding the development of effective and personalized treatment strategies.

#### 2.9.2 Addressing Drug Resistance and Recurrence<sup>79-81</sup>

Addressing drug resistance and recurrence is a complex challenge in fungal infection management. While both poly-herbal formulations and single-compound drugs offer unique strategies, a comprehensive approach that combines their strengths may hold the key to overcoming these issues. Future research and clinical trials will shed light on the effectiveness of each approach and guide the development of innovative antifungal strategies that minimize resistance and recurrence.

# 2.9.3 Clinical Relevance and Cost-Effectiveness<sup>82-84</sup>

Comparing the clinical relevance and cost-effectiveness of poly-herbal anti-fungal formulations and single-compound drugs underscores the need to balance therapeutic benefits with economic considerations. While poly-herbal formulations offer comprehensive treatment approaches, single-compound drugs provide precision. The optimal choice depends on factors such as infection type, patient characteristics, and long-term outcomes. Future research and economic analyses will guide healthcare providers and policymakers in making informed decisions that maximize patient care while managing costs.

#### 3. CONCLUSION<sup>85-90</sup>

Poly-herbal anti-fungal sprays present a promising avenue in the fight against fungal infections. Their multi-faceted approach, combining the therapeutic potential of various plant-derived compounds, holds great potential for enhanced efficacy and reduced side effects. By drawing insights from a multitude of studies, this review contributes to the understanding of poly-herbal anti-fungal sprays as a viable and versatile treatment option.

# LIST OF ABBREVIATIONS:

1. GMP: Good Manufacturing Practices

#### 2. MIC: Minimum Inhibitory Concentration

# **4. REFERENCES**

1. Brown GD, Denning DW, Gow NA, Levitz SM, Netea MG, White TC. Hidden killers: human fungal infections. Science translational medicine. 2012 Dec 19;4(165):165rv13-

2. Richardson MD. Changing patterns and trends in systemic fungal infections. Journal of Antimicrobial Chemotherapy. 2005 Sep 1; 56(suppl\_1):i5-11.

3. Van de Sande WW. Global burden of human mycetoma: a systematic review and meta-analysis. PLoS neglected tropical diseases. 2013 Nov 7; 7(11):e2550.

4. Tiwari P, Kumar B, Kaur M, Kaur G, Kaur H. Phytochemical screening and extraction: a review. Internationale Pharmaceutica sciencia. 2011 Mar;1(1):98-106.

5. Verma VC, Gond SK, Kumar A, Mishra A, Kharwar RN, Gange AC. Endophytic actinomycetes from Azadirachta indica A. Juss.: isolation, diversity, and anti-microbial activity. Microbial ecology. 2009 May; 57:749-56.

6. Mishra BB, Tiwari VK. Natural products: an evolving role in future drug discovery. European journal of medicinal chemistry. 2011 Oct 1; 46(10):4769-807.

7. Ravipati AS, Zhang L, Koyyalamudi SR, Jeong SC, Reddy N, Bartlett J, Smith PT, Shanmugam K, Münch G, Wu MJ, Satyanarayanan M. Antioxidant and anti-inflammatory activities of selected Chinese medicinal plants and their relation with antioxidant content. BMC Complementary and Alternative Medicine. 2012 Dec; 12(1):1-4.

8. Cowan MM. Plant products as antimicrobial agents. Clinical microbiology reviews. 1999 Oct 1; 12(4):564-82.

9. Kuete V, Efferth T. Cameroonian medicinal plants: pharmacology and derived natural products. Frontiers in pharmacology. 2010 Oct 25; 1:123.

10. Shan B, Cai YZ, Brooks JD, Corke H. Antibacterial properties and major bioactive components of cinnamon stick (Cinnamomum burmannii): activity against foodborne pathogenic bacteria. Journal of agricultural and food chemistry. 2007 Jul 11; 55(14):5484-90.

11. Chanda S, Rakholiya K. Combination therapy: Synergism between natural plant extracts and antibiotics against infectious diseases. Microbiol Book Series. 2011 Jan; 1:520-9.

12. Tyagi AK, Malik A. Antimicrobial action of essential oil vapors and negative air ions against Pseudomonas fluorescens. International journal of food microbiology. 2010 Oct 15; 143(3):205-10.

13. Ghosh S, Das Sarma M, Patra A, Hazra B. Anti-inflammatory and anticancer compounds isolated from Ventilago madraspatana Gaertn., Rubia cordifolia Linn. and Lantana camara Linn. Journal of pharmacy and pharmacology. 2010 Sep; 62(9):1158-66..

14. Rukayadi Y, Hwang JK. In vitro activity of xanthorrhizol against Streptococcus mutans biofilms. Letters in Applied Microbiology. 2006 Apr 1; 42(4):400-4.

15. Dash JP, Mani L, Nayak SK. Antibacterial activity of Blumea axillaris synthesized selenium nanoparticles against multidrug-resistant pathogens of aquatic origin. Egyptian Journal of Basic and Applied Sciences. 2022 Dec 31; 9(1):65-76.

16. Lisin G, Safiyev S, Craker LE. Antimicrobial activity of some essential oils. InII WOCMAP Congress Medicinal and Aromatic Plants, Part 2: Pharmacognosy, Pharmacology, Phytomedicine, Toxicology 501 1997 Nov 10 (pp. 283-288).

17. Nascimento GG, Locatelli J, Freitas PC, Silva GL. Antibacterial activity of plant extracts and phytochemicals on antibiotic-resistant bacteria. Brazilian journal of microbiology. 2000; 31:247-56.

18. Kuete V. Potential of Cameroonian plants and derived products against microbial infections: a review. Planta Medica. 2010 Oct;76(14):1479-91.

Citation: B. Sasidhar et al. Ijppr.Human, 2023; Vol. 28 (2): 365-378.

19. Teixeira B, Marques A, Ramos C, Batista I, Serrano C, Matos O, Neng NR, Nogueira JM, Saraiva JA, Nunes ML. European pennyroyal (Mentha pulegium) from Portugal: Chemical composition of essential oil and antioxidant and antimicrobial properties of extracts and essential oil. Industrial Crops and Products. 2012 Mar 1;36(1):81-7.

20. Chemat F, Rombaut N, Meullemiestre A, Turk M, Perino S, Fabiano-Tixier AS, Abert-Vian M. Review of green food processing techniques. Preservation, transformation, and extraction. Innovative Food Science & Emerging Technologies. 2017 Jun 1; 41:357-77.

21. Sarker SD, Nahar L, Kumarasamy Y. Microtitre plate-based antibacterial assay incorporating resazurin as an indicator of cell growth, and its application in the in vitro antibacterial screening of phytochemicals. Methods. 2007 Aug 1; 42(4):321-4.

22. Nguefack J, Onguene D, Lekagne JD, Daboy CD, Mangoumou GN, Galani YJ. Effect of aqueous extract of clove basil (Ocimum gratissimum L.) and soil amendment with cassava peels compost on nutrients, pesticide residues, yield, and antioxidant properties of sweet pepper (Capsicum annuum L.). Scientia Horticulturae. 2022 Mar 15; 295:110872.

Lagreca E, Onesto V, Di Natale C, La Manna S, Netti PA, Vecchione R. Recent advances in the formulation of PLGA microparticles for controlled drug delivery. Progress in biomaterials. 2020 Dec; 9:153-74.
Bulani VD, Kothavade PS, Kundaikar HS, Gawali NB, Chowdhury AA, Degani MS, Juvekar AR. Inclusion complex of ellagic acid with β-cyclodextrin: Characterization and in vitro anti-inflammatory evaluation. Journal of molecular structure. 2016 Feb 5; 1105:308-15.

25. Dorman HD, Deans SG. Antimicrobial agents from plants: antibacterial activity of plant volatile oils. Journal of applied microbiology. 2000 Feb 1; 88(2):308-16.

26. Sharma S, Kumar S, Bulchandini B, Taneja S, Banyal S. Green synthesis of silver nanoparticles and their antimicrobial activity against gram-positive and gram-negative bacteria. Int. J. Biotechnol. Bioeng. Res. 2013; 4(7):711-4.

27. Fayaz AM, Balaji K, Kalaichelvan PT, Venkatesan R. Fungal based synthesis of silver nanoparticles—an effect of temperature on the size of particles. Colloids and Surfaces B: Biointerfaces. 2009 Nov 1; 74(1):123-6.

28. Pinto E, Vale-Silva L, Cavaleiro C, Salgueiro L. Antifungal activity of the clove essential oil from Syzygium aromaticum on Candida, Aspergillus and dermatophyte species. Journal of medical microbiology. 2009 Nov;58(11):1454-62.

29. Silva F, Ferreira S, Duarte A, Mendonca DI, Domingues FC. Antifungal activity of Coriandrum sativum essential oil, its mode of action against Candida species and potential synergism with amphotericin B. Phytomedicine. 2011 Dec 15;19(1):42-7.

30. Nazzaro F, Fratianni F, De Martino L, Coppola R, De Feo V. Effect of essential oils on pathogenic bacteria. Pharmaceuticals. 2013 Nov 25;6(12):1451-74.

31. Singh R, Shushni MA, Belkheir A. Antibacterial and antioxidant activities of Mentha piperita L. Arabian Journal of Chemistry. 2015 May 1; 8(3):322-8.

32. Sunita K, Kumar P, Khan MA, Husain SA, Singh DK. Anthelminthic/larvicidal activity of some common medicinal plants. European Journal of Biological Research. 2017 Dec 31; 7(4):324-36.

33. Wink M. Modes of action of herbal medicines and plant secondary metabolites. Medicines. 2015 Sep 8; 2(3):251-86.

34. Agyare C, Asase A, Lechtenberg M, Niehues M, Deters A, Hensel A. An ethnopharmacological survey and in vitro confirmation of ethnopharmacological use of medicinal plants used for wound healing in Bosomtwi-Atwima-Kwanwoma area, Ghana. Journal of Ethnopharmacology. 2009 Sep 25; 125(3):393-403.

35. Hayden MS, Ghosh S. NF- $\kappa$ B, the first quarter-century: remarkable progress and outstanding questions. Genes & development. 2012 Feb 1; 26(3):203-34.

36. Tan W, Lu J, Huang M, Li Y, Chen M, Wu G, Gong J, Zhong Z, Xu Z, Dang Y, Guo J. Anti-cancer natural products isolated from Chinese medicinal herbs. Chinese medicine. 2011 Jul 22; 6(1):27.

37. MA W. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically: approved standard. Clsi (Nccls). 2006; 26:M7-A7.

38. Andrews JM. Determination of minimum inhibitory concentrations. Journal of antimicrobial Chemotherapy. 2001 Jul 1; 48(suppl\_1):5-16.

39. Wiegand I, Hilpert K, Hancock RE. Agar and broth dilution methods to determine the minimal inhibitory concentration (MIC) of antimicrobial substances. Nature protocols. 2008 Feb; 3(2):163-75.

40. Bauer AW, Kirby WM, Sherris JC, Turck M. Antibiotic susceptibility testing by a standardized single disk method. American journal of clinical pathology. 1966 Apr 1; 45(4\_ts):493-6.

41. Andrews JM. Determination of minimum inhibitory concentrations. Journal of Antimicrobial Chemotherapy. 2001 Jul 1; 48(suppl\_1):5-16.

42. Gull I, Saeed M, Shaukat H, Aslam SM, Samra ZQ, Athar AM. Inhibitory effect of Allium sativum and Zingiber officinale extracts on clinically important drug resistant pathogenic bacteria. Annals of clinical microbiology and antimicrobials. 2012 Jan; 11(1):1-6.

43. Benamu E, Deresinski S. Vancomycin-resistant enterococcus infection in the hematopoietic stem cell transplant recipient: an overview of epidemiology, management, and prevention. F1000Research. 2018; 7.

44. Tängdén T, Hickman RA, Forsberg P, Lagerbäck P, Giske CG, Cars O. Evaluation of double-and tripleantibiotic combinations for VIM-and NDM-producing Klebsiella pneumoniae by in vitro time-kill experiments. Antimicrobial agents and chemotherapy. 2014 Mar; 58(3):1757-62.

45. Pfaller MA, Huband MD, Shortridge D, Flamm RK. Surveillance of omadacycline activity tested against clinical isolates from the USA: report from the SENTRY Antimicrobial Surveillance Program, 2019. Journal of Global Antimicrobial Resistance. 2021 Dec 1; 27:337-51.

46. Stepanović S, Vuković D, Hola V, Bonaventura GD, Djukić S, Ćirković I, Ruzicka F. Quantification of biofilm in microtiter plates: overview of testing conditions and practical recommendations for assessment of biofilm production by staphylococci. Amis. 2007 Aug; 115(8):891-9.

47. O'Toole GA. Microtiter dish biofilm formation assay. JoVE (Journal of Visualized Experiments). 2011 Jan 30(47):e2437.

48. Srimaneepong V, Thanamee T, Wattanasirmkit K, Muangsawat S, Matangkasombut O. Efficacy of lowmolecular-weight chitosan against Candida albicans biofilm on polymethyl methacrylate resin. Australian Dental Journal. 2021 Sep;66(3):262-9.

49. Netea MG, Joosten LA, Van Der Meer JW, Kullberg BJ, Van De Veerdonk FL. Immune defence against Candida fungal infections. Nature Reviews Immunology. 2015 Oct; 15(10):630-42.

50. Asthana S, Bonney GK, Guthrie A, Davies MH. Bibliography Current World Literature Vol 14 No 6 December 2009. tuberculosis. 2008 Mar; 2008(15):433-8.

51. Furue M. targets, 95 topical retinoids, 90–91 mild to moderate, 88 outcomes/severity, 87–88 prognosis and treatment aims, 87. Evidence-based Dermatology. 2014; 567:644.

52. Atkinson BA, Bouthet C, Bocanegra R, Correa A, Luther MF, Graybill JR. Comparison of fluconazole, amphotericin B, and flucytosine in treatment of a murine model of disseminated infection with Candida glabrata in immunocompromised mice. Journal of Antimicrobial Chemotherapy. 1995 May 1; 35(5):631-40.

53. Trevino-Rangel RD, Rodríguez-Sánchez IP, Elizondo-Zertuche M, Martínez-Fierro ML, Garza-Veloz I, Romero-Díaz VJ, González JG, González GM. Evaluation of in vivo pathogenicity of Candida parapsilosis, Candida orthopsilosis, and Candida metapsilosis with different enzymatic profiles in a murine model of disseminated candidiasis. Medical mycology. 2014 Apr 1;52(3):240-5.

54. Cojutti PG, Candoni A, Lazzarotto D, Filì C, Zannier M, Fanin R, Pea F. Population pharmacokinetics of continuous-infusion meropenem in febrile neutropenic patients with hematologic malignancies: dosing strategies for optimizing empirical treatment against Enterobacterales and P. aeruginosa. Pharmaceutics. 2020 Aug 19; 12(9):785.

55. Siqueira Jr JF, Lopes H. Mechanisms of antimicrobial activity of calcium hydroxide: a critical review. International endodontic journal. 1999 Sep; 32(5):361-9.

56. King GN, Healy CM, Glover MT, Kwan JT, Williams DM, Leigh IM, Thornhill MH. Prevalence and risk factors associated with leukoplakia, hairy leukoplakia, erythematous candidiasis, and gingival hyperplasia in renal transplant recipients. Oral surgery, oral medicine, oral pathology. 1994 Dec 1; 78(6):718-26.

57. Xue X, Deng H, Zhao L, Zang X, Asuquo IP, Meng M, Ma X, Qin C, Meng Y, Wu C, Gao J. Cryptococcosis caused by cryptococcus gattii: 2 case reports and literature review. Medicine. 2020 Dec 12; 99(50).

58. Qu F, Qu Z, Lv Y, Song B, Wu B. Disseminated Cryptococcosis revealed by transverse myelitis in Immunocompetent patient: a case report and review of the literature. BMC neurology. 2020 Dec; 20(1):1-5.

59. Gasser T, Mihatsch MJ. Bibliography Current World Literature Vol 9 No 5 September 2000. Int J Dev Biol. 1999; 43(463ą468):23.

60. Hughes CM. Medication non-adherence in the elderly: how big is the problem? Drugs & aging. 2004 Oct; 21:793-811.

61. Horne R, Weinman J. Patients' beliefs about prescribed medicines and their role in adherence to treatment in chronic physical illness. Journal of psychosomatic research. 1999 Dec 1; 47(6):555-67.

62. Al-Hatmi AM, Meletiadis J, Curfs-Breuker I, Bonifaz A, Meis JF, De Hoog GS. In vitro combinations of natamycin with voriconazole, itraconazole and micafungin against clinical Fusarium strains causing keratitis. Journal of Antimicrobial Chemotherapy. 2016 Apr 1; 71(4):953-5.

63. Li LJ, Chen W, Xu H, Wan Z, Li RY, Liu W. Antifungal activity of ibuprofen against Aspergillus species and its interaction with common antifungal drugs. Chinese Medical Journal. 2010 Oct 5; 123(19):2701-5.

64. Gurib-Fakim A. Medicinal plants: traditions of yesterday and drugs of tomorrow. Molecular aspects of Medicine. 2006 Feb 1; 27(1):1-93.

65. Heinrich M, Chan J, Wanke S, Neinhuis C, Simmonds MS. Local uses of Aristolochia species and content of nephrotoxic aristolochic acid 1 and 2—A global assessment based on bibliographic sources. Journal of Ethnopharmacology. 2009 Aug 17; 125(1):108-44.

66. Singh S. Profiling bioactive compounds and key nutrients in Pacific Island crops and marine resources.

67. Saxena M, Saxena J, Pradhan A. Flavonoids and phenolic acids as antioxidants in plants and human health. Int. J. Pharm. Sci. Rev. Res. 2012; 16(2):130-4.

68. Bauer AW, Kirby WM, Sherris JC, Turck M. Antibiotic susceptibility testing by a standardized single disk method. American journal of clinical pathology. 1966 Apr 1; 45(4\_ts):493-6.

69. Perez C. Antibiotic assay by agar-well diffusion method. Acta Biol Med Exp. 1990; 15:113-5.

70. Tang JL, Liu BY, Ma KW. Traditional Chinese medicine. The Lancet. 2008 Dec 6; 372(9654):1938-40.

71. Yin H, Hu M, Zhang R, Shen Z, Flatow L, You M. MicroRNA-217 promotes ethanol-induced fat accumulation in hepatocytes by down-regulating SIRT1. Journal of Biological Chemistry. 2012 Mar 23; 287(13):9817-26.

72. Reshetnyak VI. Concept of the pathogenesis and treatment of cholelithiasis. World journal of hepatology. 2012 Feb 2; 4(2):18.

73. Heinrich M, Ankli A, Frei B, Weimann C, Sticher O. Medicinal plants in Mexico: Healers' consensus and cultural importance. Social science & medicine. 1998 Dec 1; 47(11):1859-71.

74. Calixto JB. Efficacy, safety, quality control, marketing and regulatory guidelines for herbal medicines (phytotherapeutic agents). Brazilian Journal of Medical and Biological research. 2000; 33:179-89.

75. Sahoo N, Manchikanti P. Herbal drug regulation and commercialization: an Indian industry perspective. The Journal of alternative and complementary medicine. 2013 Dec 1; 19(12):957-63.

76. Newman DJ, Cragg GM. Natural products as sources of new drugs from 1981 to 2014. Journal of natural products. 2016 Mar 25; 79(3):629-61.

77. Hemaiswarya S, Kruthiventi AK, Doble M. Synergism between natural products and antibiotics against infectious diseases. Phytomedicine. 2008 Aug 1; 15(8):639-52.

78. Takizawa N, Yamasaki M. Current landscape and future prospects of antiviral drugs derived from microbial products. The Journal of Antibiotics. 2018 Jan; 71(1):45-52.

79. Brown GD, Denning DW, Levitz SM. Tackling human fungal infections. Science. 2012 May 11; 336(6082):647.

80. Pappas PG, Alexander BD, Andes DR, Hadley S, Kauffman CA, Freifeld A, Anaissie EJ, Brumble LM, Herwaldt L, Ito J, Kontoyiannis DP. Invasive fungal infections among organ transplant recipients: results of the Transplant-Associated Infection Surveillance Network (TRANSNET). Clinical Infectious Diseases. 2010 Apr 15; 50(8):1101-11.

81. Munita JM, Arias CA. Mechanisms of antibiotic resistance. Virulence mechanisms of bacterial pathogens. 2016 Jun 22:481-511.

82. Paltiel AD, Weinstein MC, Kimmel AD, Seage III GR, Losina E, Zhang H, Freedberg KA, Walensky RP. Expanded screening for HIV in the United States—an analysis of cost-effectiveness. New England Journal of Medicine. 2005 Feb 10; 352(6):586-95.

83. Flapan AD, Nolan J, Neilson JM, Ewing DJ. Effect of captopril on cardiac parasympathetic activity in chronic cardiac failure secondary to coronary artery disease. The American journal of cardiology. 1992 Feb 15; 69(5):532-5.

84. McAdam-Marx C, Bellows BK, Unni S, Wygant G, Mukherjee J, Ye X, Brixner DI. Impact of adherence and weight loss on glycemic control in patients with type 2 diabetes: cohort analyses of integrated medical record, pharmacy claims, and patient-reported data. Journal of Managed Care Pharmacy. 2014 Jul; 20(7):691-700.

85. Shahrajabian MH, Sun W, Cheng Q. A review of ginseng species in different regions as a multipurpose herb in traditional Chinese medicine, modern herbology and pharmacological science. Journal of Medicinal Plants Research. 2019 May 25; 13(10):213-26.

86. Takayama S, Iwasaki K. Systematic review of traditional Chinese medicine for geriatrics. Geriatrics & Gerontology International. 2017 May; 17(5):679-88.

87. Lindequist U, Niedermeyer TH, Jülich WD. The pharmacological potential of mushrooms. Evidence-based complementary and alternative medicine. 2005 Sep 1; 2:285-99.

88. Silva F, Ferreira S, Duarte A, Mendonca DI, Domingues FC. Antifungal activity of Coriandrum sativum essential oil, its mode of action against Candida species, and potential synergism with amphotericin B. Phytomedicine. 2011 Dec 15; 19(1):42-7.

89. Al-Snafi AE. The antifungal spectrum of medicinal plants: A review. GSC Biological and Pharmaceutical Sciences. 2023; 24(1):118-46.

90. Diao WR, Zhang LL, Feng SS, Xu JG. Chemical composition, antibacterial activity, and mechanism of action of the essential oil from Amomum kravanh. Journal of food protection. 2014 Oct 1; 77(10):1740-6.