Ethnopharmaceuticals for the Treatment of Old World Cutaneous Leishmaniasis: A Systematic Review

R. Kariyawasam[1,2], M. Klowak[3,4], **S. Bhasker[3]**, J. Kwan[3], S. Igboanugo[3], A. K Boggild[3,4,5]

[1]University of Alberta, Division of Diagnostic & Applied Medicine, [2]Department of Laboratory Medicine & Pathology, Edmonton, Canada, University of Alberta, Alberta Precision Laboratories – Public Health Laboratory (ProvLab), Edmonton, Canada, [3]UHN-Toronto General Hospital, Tropical Disease Unit, Division of Infectious Diseases, Toronto, Canada, University of Toronto, [4]Institute of Medical Science, Toronto, Canada, [5]University of Toronto, Department of Medicine, Toronto, Canada

Introduction

- **Old World Cutaneous Leishmaniasis (OWCL):** neglected parasitic disease caused by members of the genus *Leishmania,* passed onto humans by the bite of sandflies[1]
- Better drugs needed due to the toxicity, accessibility limits, and expense of first-line treatment options
- **Ethnopharmaceuticals:** plant-based compounds with potential anti-leishmanial effects found in and around local endemic communities[2]
- Potential to overcome the aforementioned therapeutic challenges using ethnopharmaceuticals, are supported by anecdotal evidence of efficacy

Objective: Aim to synthesize existing evidence around available ethnopharmaceuticals to promote drug discovery for the prevention and treatment of OWCL

Methods

- A systematic review architecture was used
- PubMed (NCBI), Medline (OVID), Embase (OVID), and Web of Science (BioSIS) were searched using combinations of the search terms and related concepts of **"cutaneous leishmaniasis"** and **"ethnopharmaceuticals"**
- Inclusion criteria: CL patient from the Old World (Africa, Asia, Europe), treated with an ethnopharmaceutical, patient outcome(s) reported after treatment
- GRADE approach used to assess the quality of studies reporting therapeutic interventions[4]
- Data were grouped and summarized by *Leishmania* spp. and plant species

Results

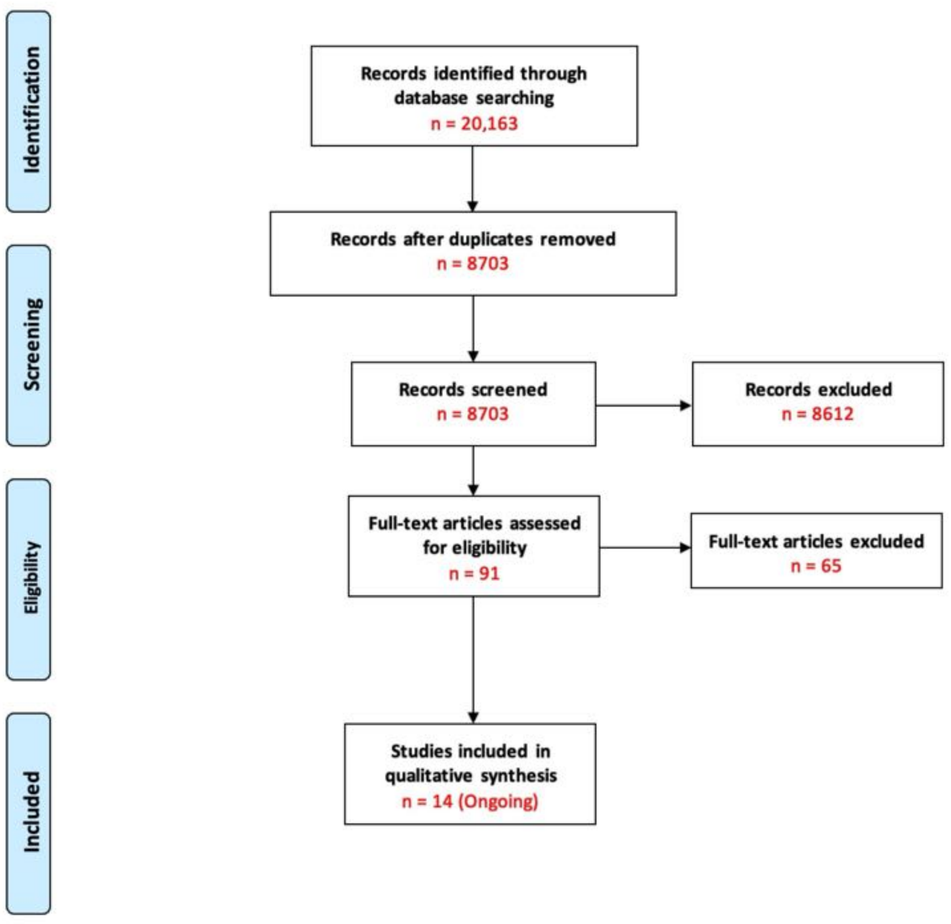

Figure 1. PRISMA Flow Diagram for studies captured in the search strategy.

Discussion & Conclusions

- 14 studies were included evaluating a number of topical applications of ethnopharmaceuticals including: *Cassia fistula*, garlic, and pepper
- *C. fistula* gel was the most studied extract, evaluated in addition to Glucantime therapy, where topical gel resulted in a complete cure
- Current data extracted does not show any forms of clinical trials for humans with NWCL using garlic as a treatment
- Toxicity, expense and accessibility limit treatment success for both Old World and New World CL
- Plant-based compounds, such as *Cassia fistula*, garlic, and pepper, have potential anti-leishmanial effects, as demonstrated in-vitro
- *Cassia fistula* has demonstrated efficacy in small human studies of OWCL, as does garlic
- Future studies evaluating compounds in in-vivo and well-conducted RCTs can identify novel therapeutics for a disease whereby drug discovery progress has been lacking for over half a century
- Increased human and vector migrations, climate change and travel, and the incidence of CL may increase in non-endemic areas
- Synthesizing current evidence surrounding ethnopharmaceuticals for the treatment of OWCL may contribute to drug discovery pipelines and potentially lead to novel therapeutics

Author	Setting	N	Age	Sex N (F:M)	Etiology	Population	Intervention	Outcome
Aghaei (2018)	Iran	30	Intervention group: mean age=35 Control group: mean age=34s	Intervent ion group: 5:10, Control group: 4:11	CL	CL patients with lesions of 30-50 mm^2	Group A: Intralesional injection of 20mg/kg Glucantime 2x/day for 20 days + topical ozonated olive oil. Group B: Intralesional injection of 20mg/kg Glucantime 2x/day for 20 days	Efficacy: Cure at 8 weeks (9.93±14.18, p,0.00) Safety: No adverse side effects Tolerability: High adherence.
Khan (2022)	Pakistan	26	Age range given: 5-20 years	Ratio was not given (but both males and females were included)	CL	CL patients with a mean of 1.2 lesions and a mean lesion size of 25.3 (SD=± 0.1 mm)	Water-in-*Linum usitatissimum* (LU) oil cream containing 10% LU crude extract (10 mg/mL).	Efficacy: 69% of patients had a complete cure for infection. Safety: No adverse side effects. Tolerability: High Adherence.
Hasan (2022)	Iraq	86	Age range: 1-44	Intervention group: 38:48 Control group: 11:15	CL	Patients diagnosed with CL caused by *Leishmania* tropica	Group 1: Flaxseed Oil (concentration of 5%) treatment. Group 2: Pentostam Drug	Efficacy: All patients had a complete cure of infection. Safety: No adverse side effects. Tolerability: High Adherence.
Azizkhani (2015)	Iran	3	-	-	Leishmaniasis	Cutaneous Leishmaniasis	Day I: injection of 0.065 cc pure garlic juice per kg (dissolved in 500 cc of saline) of the patient + Day 1-5: topical application of raw garlic 3 times a day	Leishmaniasis sores healed rapidly, no prolonged effects
Nilforoushzadeh (2006)	Iran	90	Int: 26.1; Con: 25.6	Int: 12:33; Con: 17:28	Leishmaniasis	Cutaneous Leishmaniasis	Glucantime intralesionally injected once weekly, lesions dressed with honey soaked gauze twice daily For 6 weeks or until complete healing	23 patients achieved complete cure (less than only glucantime control: 32), mean heal time was 7.04 weeks, one patient left due to contact dermatititis 12 left due to lesion progression
Khalid (2004)	Sudan	72	28.2	34:38	Leishmaniasis	Cutaneous Leishmaniasis	Garlic methanol extract (100 mg/ml) used topically twice a day for 2 months or until complete healing	Mean heal time (19.75 days), all cases showed good response to treatment, complete or partial healing of lesions

Author, Year	Setting	Population	Design/Sample Size	Study Period	Species	Type of Fruit-Bearing Plant	Treatment/Intervention	Outcomes
Jaffary 2009	Iran	Inclusion: Confirmed CL on smears, lesions (<5 in quantity, <3cm). Exclusion: Lesions close to the eyelids, pregnant or feeding mothers.	RCT; 140. Group A: 70. Group B: 70.	Not report ed	Not reported	*Cassia Fistula*	Group A: 70% topical gel containing 2% DMSO from C. fistula 1x/day for 1-4 weeks + Glucantime (1-2.5mL) 2x/week up to 4 weeks. Group B: placebo gel 1x/day for 1-4 weeks + Glucantime (1-2.5mL) 2x/week up to 4 weeks.	Complete recovery at week 4: Group A (28/70) Group B (25/70) (p=0.0945). Relative recovery at week 4: Group A (28/70) Group B (22/70). Complete recovery at week 12: Group A (47/70) Group B (29/70) (p<0.001. Relative recovery at week 12: Group A (20/70) Group B (21/70). Mean complete recovery time: Group A (7.9+/-0.5) Group B (8.2+/-0.4) (p=0.005). Adverse events: Group A (9), Group B (9) - Erythema and itchiness (p=0.25).
Jaffary 2014C F	Iran	Inclusion: Confirmed CL on smears, age 6-60 years old, lesions (<5 in quantity, <3cm, <12 weeks old, not near eye)	RCT; 165. Group A: 55. Group B: 55. Group C: 55.	16 weeks	Not reported	*Cassia fistula*	Group A: boiled extract- soaked gauze applied 1x/day up to 4 weeks. Group B: hydroalcoholic extract soaked gauze applied 1x/day up to 4 weeks. Group C: intralesional Glucantime (0.5-2mL) 2x/week up to 4 weeks.	Complete cure at 16 weeks: Group A - 22 (40%), Group B - 20 (36.4%), Group C - 36 (65.5%) (p=0.02). Adverse Events: Group A - 3 (5.5%), Group B - 2 (3.6%), Group C - 2 (3.6%) due to allergic reaction.
Jaffary 2014A M	Iran	Inclusion: Severe CL for >5	RCT; 60 patients. Group	Januar y 2009-	Not reported	*Achillea millefolium*	Group A: IV Glucantime 20mg/kg/day x4 weeks + topical gel of 5% yarrow	Complete or partial cure at 12 weeks: Group A (21/30) Group B (18/30) (p=0.0351). Adverse Event at 6 weeks:
Mozafari 2019	Iran	Inclusion: Confirmed CL on smears, lesions (>14 days old). Exclusion: Pregnant women, known adverse reactions to treatment, treatment within the last month, lesions (>3 months old, near eyelids, nose, mouth, and eyes).	RCT; 110. Group A: 55. Group B: 55.	Dece mber 2017- June 2018	Not reported	*Samacucus ebulus*	Group A: 5% *S.ebulus* gel + Glucantime 2x/day up to 12 weeks. Group B: placebo gel + Glucantime 2x/day up to 12 weeks.	Duration of recovery: Group A (mean 26.64(16.24) days) Group B (mean 30.05(18.54) days) (p=0.31). Complete recovery (total epithelialization): Group A (30) Group B (29) (p=0.87). Medium recovery (>50% decrease in lesion size): Group A (8) Group B (10). Mild recovery (<50% decrease in lesion size): Group A (9) Group B (9). Failure: Group A (5) Group B (7).
Parvizi 2017	Iran	Inclusion: Confirmed CL on smears,	RCT; 62 patients. Group A: 33.	Not report ed	*Leishman ia major* and *Leishman*	*Juniperus excelsa*	Group A: Topical cream of 5% hydroalcoholic leaf extract 3x/day + Cryotherapy.	Complete cure: Group A (82%) Group B (34%). Partial cure: Group A (9%) Group B (14%). Treatment failure: Group A (9%) Group B (52%). Adverse events: Group A (85%) Group B (100%).
Sattar 2012	Paki stan	Inclusion: Patients with CL, age 6-70 years old	Cohort; 40 (30M 10F)	6 weeks	*Leishman ia donovani*	*Morinda citrifolia*	1% dry methanol leaf extract gel 3x/day then weekly up to 6 weeks	Excellent response: 20/40 (50%). Good response: 12/40 (30%. No response: 8/40 (20%). Adverse events: none.
Rahman 2012	Iran	Patients with CL	Cohort; 100 patients (35 at 2 week follow- up)	Not report ed	Not reported	*Physalis minima*	25% methanolic extract with white soft parrafin-based petroleum gel	Cure: 23/35 (65.71%) of patients showed excellent response and recovery by topical application
Zerehs az 1999	Iran	Inclusion: Confirmed CL on smears for <4 months. Exclusion: Severe CL and pregnancy.	RCT; 171. Group A: 86. Group B: 85.	Not report ed	Not reported	Z-HE herbal extract (*Althaea rosa, Althaea officinalis, Leguminosae, Faliaceae, Malvaceae*, and *Lythrace*)	Group A: topical Z-HE x5 days + 0.5mL saline injection x20 days. Group B: topical placebo x5 days + 15- 20mL/kg/day Glucantime x20 days.	Complete cure: Group A (74.4%) Group B (24.1%). Partial cure: Group A (11.6%) Group B (14.1%). Failure: Group A (14%) Group B (58.8%). Adverse Events: Group B had urticaria and generalize pruritis.

Table 1 & 2. Summary of findings tables for studies included in this study.

*** A sincere thank you to the University of Toronto undergraduate students in human biology named Dileesha Fernando, Eunice Aluko, and Ezra Bado who helped advance this project forward.**

References

1. Heras-Mosteiro J, Monge-Maillo B, Pinart M, Lopez Pereira P, Reveiz L, Garcia-Carrasco E, Campuzano Cuadrado P, Royuela A, Mendez Roman I, López-Vélez R. Interventions for Old World cutaneous leishmaniasis. Cochrane Database of Systematic Reviews 2017, Issue 12. Art. No.: CD005067. DOI: 10.1002/14651858.CD005067.pub5
2. American Journal of Ethnomedicine (2018).About American Journal of Ethnomedicine. Retrieved October 23, 2018.
3. Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, Norris S, Falck-Ytter Y, Glasziou P, deBeer H, Jaeschke R, Rind D, Meerpohl J, Dahm P, Schunemann HJ. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings table. J Clin Epidemiol 2011; 64(4): 380-2.
4. *What is grade?*. BMJ Best Practice. (n.d.). https://bestpractice.bmj.com/info/toolkit/learn-ebm/what-is-grade/
5. Aghaei M, Aghaei S, Sokhanvari F, Ansari N, Hosseini SM, Mohaghegh MA, Hejazi SH. Thera. The Therapeutic Effect of Ozonated Olive Oil Plus Glucantime on Human Cutaneous Leishmaniasis. Iran J Basic Med 2019; 22(1): 25-30.
6. Khan B, Faiz S, Khan MK, Menaa F, Olah NK, Almoshari Y, Alamoudi JA, Almawash S. Fabrication and Evaluation of W/O Emulsion Loaded with Linum usitatissimum Seeds Extract for Anti-Leishmaniasis Efficacy. J Antibiot 2022; 11(4): 1-11.
7. Hasan HM. Therapeutic Effect of Local Flaxseed Oil On Patients with Leishmania Tropica Compared with Pentostam. J Cardio Dis Research 2022; 13(2): 697-704.
8. Jaffary F, Nilforoushzadeh MA, Tavakoli N, Zolfaghari B, Shahbazi F. The efficacy of Achilles millefolium topical gel along with intralesional injection of glucantime in the treatment of acute cutaneous leishmaniasis major. Adv Biomed Res 2014; 3: 1111. 23.
9. Jaffary F, Nilforoushzadeh MA, Ansari N, Rahimi M. Treatment of cutaneous leishmaniasis cassia fistula fruit gel-intralesional glucantime vs. placebo gel-intralesional glucantime combination. Tehran Univ Med J 2009; 67(1): 705-711.
10. Jaffary F, Nilforoushzadeh MA, Moradi S, Derakshan R, Ansari N. Concentrated Extracts of Cassia fistula Versus Intralesional Injection of Meglumine Antimoniate in Treatment of Acute Cutaneous Leishmaniasis. J Skin Stem Cell 2014; 1(1): e16631
11. Mozafari O, Behnampour N, Pahlevanzadeh B, Saberi S, Mozafari I, Akbari J, Ebrahimzadeh MA. Effectiveness of Sambucus ebulus Leaf Extract in Treatment of Cutaneous Leishmaniasis: A Double Blind Clinical Trial. Journal of Mazandaran University of Medical Sciences 2019; 29 (181): 120-124.
12. Parvizi MM, Handjiana F, Moein M, Hatam G, Nimrouzi M, Hassanzadeh J, Namidizadeh N, Khorrami HR, Zarshenas MM. Efficacy of cryotherapy plus topical Juniperus excelsa M. Bieb cream versus cryotherapy plus placebo in the treatment of Old World cutaneous leishmaniasis: A triple-blinrad randomized controlled trial. PLoS Negl Trop Dis 2017; 11(1): e0005957.
13. Sattar FA, Ahmed F, Ahmed N, Sattar SA, Malghani MA, Choudhary MI. A double-blind, randomized, clinical trial on the antileishmanial activity of a Morinda citrifolia (Noni) stem extract and its major constituents. Nat Prod Commun 2012; 7(2): 195-6.
14. Rahman A, Choudhary MI, Yousuf S, Khan S, Soomro R, Perveen S. United States Patent Application Publication-Formulations against cutaneous leishmaniasis. Pub No. US2827921B1. 2011.
15. Zerehsaz F, Salmanpour R, Handjiana F, Ardehali S, Panjehshahi MR, Tabei SZ, Tabatabaee HR. A double-blind randomized clinical trial of a topical herbal extract (Z-HE) vs. systemic meglumine antimoniate for the treatment of cutaneous leishmaniasis in Iran. Int J Dermatol 1999; 38(8): 610-2.
16. Azizkhani, M. and Tooryan, F. (2015), Antioxidant and Antimicrobial Effects of EOs. J Food Saf, 35: 128-136. https://doi.org/10.1111/jfs.12166
17. Sadeghian G, Nilforoushzadeh MA. Effect of combination therapy with systemic glucantime and pentoxifylline in the treatment of cutaneous leishmaniasis. Int J Dermatol. 2006 Jul;45(7):819-21. doi: 10.1111/j.1365-4632.2006.02867.x. PMID: 16863518.

Contact: Dr. Andrea K. Boggild | andrea.boggild@utoronto.ca | @BoggildLab | www.boggildlab.ca