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Ethnopharmacology and Bioactive Evidence Medicinal Plants for Wound Healing in Indonesia: A Scoping Review

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SUPPLEMENTARY MATERIAL

Supplementary Table 1: Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) Checklist

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
TITLE			
Title	1	Identify the report as a scoping review.	1
ABSTRACT			
Structured summary	2	Provide a structured summary that includes (as applicable): background, objectives, eligibility criteria, sources of evidence, charting methods, results, and conclusions that relate to the review questions and objectives.	1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known. Explain why the review questions/objectives lend themselves to a scoping review approach.	3
Objectives	4	Provide an explicit statement of the questions and objectives being addressed with reference to their key elements (e.g., population or participants, concepts, and context) or other relevant key elements used to conceptualize the review questions and/or objectives.	3
METHODS			

Protocol and registration	5	Indicate whether a review protocol exists; state if and where it can be accessed (e.g., a Web address); and if available, provide registration information, including the registration number.	4
Eligibility criteria	6	Specify characteristics of the sources of evidence used as eligibility criteria (e.g., years considered, language, and publication status), and provide a rationale.	4
Information sources*	7	Describe all information sources in the search (e.g., databases with dates of coverage and contact with authors to identify additional sources), as well as the date the most recent search was executed.	4
Search	8	Present the full electronic search strategy for at least 1 database, including any limits used, such that it could be repeated.	4
Selection of sources of evidence†	9	State the process for selecting sources of evidence (i.e., screening and eligibility) included in the scoping review.	N/A
Data charting process‡	10	Describe the methods of charting data from the included sources of evidence (e.g., calibrated forms or forms that the team has tested before their use, and whether data charting was done independently or in duplicate) and any processes for obtaining and confirming data from investigators.	Figure 1
Data items	11	List and define all variables for which data were sought and any assumptions and simplifications made.	4
Critical appraisal of individual sources of evidence§	12	If done, provide a rationale for conducting a critical appraisal of included sources of evidence; describe the methods used and how this information was used in any data synthesis (if appropriate).	4-5
Synthesis of results	13	Describe the methods of handling and summarizing the data that were charted.	5
RESULTS			

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
Selection of sources of evidence	14	Give numbers of sources of evidence screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally using a flow diagram.	Figure 1
Characteristics of sources of evidence	15	For each source of evidence, present characteristics for which data were charted and provide the citations.	Suppl Table 1-2
Critical appraisal within sources of evidence	16	If done, present data on critical appraisal of included sources of evidence (see item 12).	N/A
Results of individual sources of evidence	17	For each included source of evidence, present the relevant data that were charted that relate to the review questions and objectives.	Figure 6-16

Synthesis of results	18	Summarize and/or present the charting results as they relate to the review questions and objectives.	Figure 2-16
DISCUSSION			
Summary of evidence	19	Summarize the main results (including an overview of concepts, themes, and types of evidence available), link to the review questions and objectives, and consider the relevance to key groups.	5-23
Limitations	20	Discuss the limitations of the scoping review process.	23
Conclusions	21	Provide a general interpretation of the results with respect to the review questions and objectives, as well as potential implications and/or next steps.	24
FUNDING			
Funding	22	Describe sources of funding for the included sources of evidence, as well as sources of funding for the scoping review. Describe the role of the funders of the scoping review.	24

Supplementary Table S2: The most important medicinal plants for wound healing in Indonesian and their activity studies

Species	Part of the plants	Scaffold material	Type of study	Model	Findings	Reference
Ageratum conyzoides	Leaves	Topical ethanolic extract	In vitro and in vivo	Full-thickness open excision wound	Increased hexosamine and uronic acid level, collagen synthesis at 8th day. Faster wound healing, improve ephitelization and tensile strength of the treated tissue	[69]
Allium sativum L.	Bulbs	Extract combine with Euphorbia honey	In vivo	Burn	Allium had a greater MIC compared to honey and their mixture. The mixture shown shorter epithelialization and wound contraction time compared to honey	[75]
		Ointment (30%)	In vivo	Full thickness excisional	Percentage of Wound reduction twice compared to vehicle. Ointment healed with more visually appealing scars than those treated with vehicle.	[78]

		In vivo Thiosulfinate enriched A. sativum extract	Invitro and In vivo	Keratinocyte cell and Acute wound healing	On day 3 following wounding, ELOVL4, HMGCoA, SPT, filaggrin, loricrin, and involucrin the expression levels of keratinocyte RNA were increased, lowered TEWEL (Transepidermal Water Loss) on day 8 compared to controls. Increased both in vivo and in vitro wound area	[79]
Aloe vera (L.) Burm. f	Leaves, *Aloe vera* gel	Aloe in a microwave plasma system	In vivo, Clinical trial	Incision	No inflammation occurs, increasing the protein concentration in the wound's site and natural epithelium at 7 min exposure	[85]
		Chitosan aloe Vera Hydrogel (CHO/aloe)	In vitro	In vitro Antibacterial activity and In vivo Full thickness excisional	CHO/Aloe showed higher MIC, had a greater wound-healing rate compared to the other groups at 3,7,14 days. After three days, the inflammatory reaction was reduced, and the epidermal thickness was higher than in the other groups.	[81,86]
		Encapsulated Bone marraw Mesenchymal stem cells (BMSCs) in Aloe vera	In vivo	In vivo Burn grade II	Highest angiogenesis and granulation tissue formation for Aloe vera/BMSCs. Increased expression of VEGF, Collagen III and I gens with the peak on day 14	[81,87]
		Aloe vera (AV) encapsulated Polycaprolactone (PCL)/Ge/AV		In vivo Full thickness excisional	PCL/Gel/AV/ and PCL/ Gel/AV/TCH group shown a highest number of micro vessel, wound healing closures compare to the single PCL /gel	[87]
Anredera cordifolia (Ten.) Steenis	Leaves	Extract	In vivo	Burn infected with *P. aeruinosa*	Increased IL-6 and VEGF on day 3 Wound healing full recover on day 5 compared to control tetrasiklin group	[93]
		Ethyl asetat fraction	In vivo	Incision	Improved % of wound healing, epithelization, and hydroxyproline level	[94]

Species	**Part of the plants**	**Scaffold material**	**Type of study**	**Model**	**Findings**	**Reference**
		Water,hexane, ethyl acetat, choloform fractination	In vivo	Diabetic excisional wound	All fraction except ethy acetat improved wound healing compared to negatif and positive control (madecassol)	[95]
Curcuma longa	Rhizome	Tumeric extract gel	In vivo	incision	Wound heal < 14 days, and 5% gel giving significant time for wound healing compared to other groups	[101]
		Curcumin	In vivo	Burn	Collagen deposition, angiogenesis and granulation tissue formation and hroxypolin levels were significantly increased on day 8	[109]

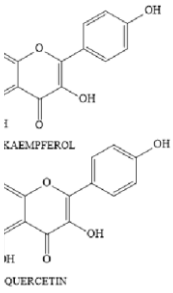
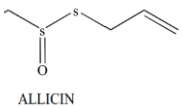
		Metallic silver nanoparticles (AgNPs) from the aqueous extract loaded in cotton fabric	In vitro	wound scratch using L929 cells	Attenuated the wound scratches through the enhanced proliferation of fibroblast cells	[106]
		Curcumin loaded tragacanth/poly (ε-caprolactone) electrospun nanofibers	In vitro	In Vitro Antibacterial activity In vivo Full thickness excisional diabet	99.9% antibacterial against MRSA and 85.14% against ESBL Significantly faster wound closure with well-formed granulation tissue dominated by fibroblast proliferation, collagen deposition, complete early regenerated epithelial layer, and sweat gland and hair follicle production.	[107]
Jatropha curcas L.	Bark	Ointment	In vivo	Incision	It increased cellular proliferation and collagen synthesis at the wound site, as evidenced by the increase in total protein and collagen content reflected by the hydroxyproline content of granulation tissues.	[124]
	Latexs	Spray formulation	In vitro	Scratch using HaCaT and the human fibroblast cell line (BJ)	improved wound healing in HaCat and BJ cells. Indeed, wound healing was faster in formula-treated HaCat cells than in proteoglycan IPC (as a positive control), but similar in BJ cells.	[127]
Jatropha multifida L.	Leaves	iota carrageenan poly (vinyl alcohol) hydrogel film	In silico and in vivo Fullthickness excision	Full-thickness excision	Significantly accelerated wound healing by 98% at day 10	[113]
Lantana camara L	Leaves	Extract	In vivo	Exicion	increased the rate of wound contraction, the rate of epithelialization, and hydroxyproline content. The extract also have antimicrobial activity against S. aureus, K. pneumoniae and E. coli.	[130]

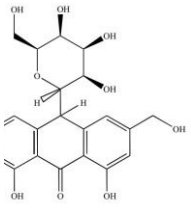
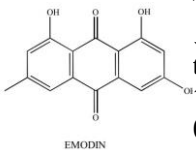
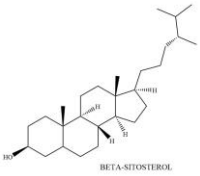
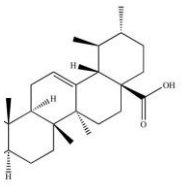
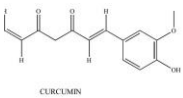
Species	**Part of the plants**	**Scaffold material**	**Type of study**	**Model**	**Findings**	**Reference**

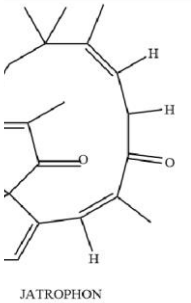
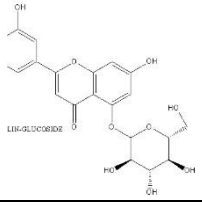
		Ointment	In vivo	Excision and incision wound	Greater wound contration, the time to wound clouser for incition was 18 ± 2 days, Excision, while excision was 10 days. Skin adrenal struture as the pilosebaceous glands, sweat glands etc were better presenter in treated extract (ointment). Inhibitef different clinical wound isolates of S. aureus and P. aeruginosa	
Melastoma malabathri-cum L	Flower and fruits	Cream	In vivo	incision wound	Flower Extract in cream has a greater wound healing activity compared to fruit due to more quercetin level compared to fruit	[138]
			In vivo			[146]
		Extract powder dissolved in the 0.9% normal saline to form a paste		Diabetic fullthickness excisional	extract showed significant increase in hydroxyproline content, superoxide dismutase (SOD) level and decreased malondialdehyde (MDA) level, 11b-HSD-1 enzyme expression	
		Sodium alginate gel	In vitro	human periodontal ligament fibroblasts	celerate the wound-healing process by reduction s in the biosynthesis of pro-inflammatory markers TNF-α, IL-1beta, IL-6, IL-8, IL-10, and IRAK1	[153]
				Fibroblast NIH3T3 cells	Increased proliferation of NIH3T3 cells and promoted wound healing in vitro and in vivo with both burn wound and excision wound models, decreased the MDA level	[145]
				Burn excision wounds		
Piper betle	Leaves					

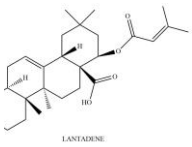
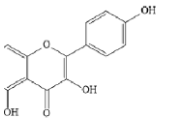
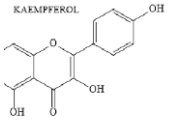
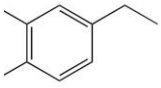
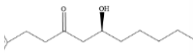
Zingiber officinale	Rhizome	Crude extract, 6-gingerol, PEGylated nanophytosomes loaded 6-gingerol	In vitro And HUVEC	Overexpression of related pro-inflammatory mediators α (TNF-α), interleukin-1β (IL1β), interleukin-6 (IL-6) and Nitric oxide (NO) was inhibited by blocking the phosphorylation pathway of TLR4/NF-κB. Enhanced the migration capacity of the HUVEC cells which exceeded cell scratch closure rate	[157]
			In vivo full-thickness	Improved wound healing and treated group were basically closed at 14 days improved epithelium, new capillaries and granulation tissue formed, and inflammatory infiltration was less.	

Suplementary Table 3. Natural compounds and molecular mechanisms of herbal extracts in wound healing process

Plants	Metabolite	Active compound	Structure	Mechanism	Reference
Ageratum conyzoides	Terpenoid, sterol, flavonoid, chromene, pyrrolizidine alkaloid, coumarin, pyrrole, and lignan	Kaemferol and Quercetin		Inhibited TNF-α, stimulates the secretion of growth factors : Tgf α and Tgf β	[70]
Allium sativum L.	Polyphenols, amino acids, benzenoids, sulfur-containing compounds, indoles, phenol lipids, pyrrolizines, quinolines, steroid derivatives, tetrahydrofurans	Allicin		Inhibit nuclear factor-kB (NFkB), nitric oxide (NO), matrix metalloproteinase (MMP)-2, and Interleukin-6 (IL-6)	[73,76,77]

Aloe vera (L.) Burm.f.	Lupeol, salicylic acid, urea nitrogen, cinnamonic acid, phenols, sulfur, vitamins, enzymes, minerals, lignin and amino acids	Aloin, Emodin, b-sitosterol	 ALOIN  EMODIN  BETA-SITOSTEROL	↓TNF-α and IL6; TGF-β bFGF ↑, ↑ CD4+; ↓CD8+ lymphocytes ratio in the wound area ↑ Integrin α1, β1 and PECAM1 (CD31) genes.	[84,88,89, 160]
Anredera cordifolia (Ten.) Steenis	Saponin, tannin, triterpenoid, alkaloid, flavonoid, phenolic, steroid, glycoside, oleanolic acid, protein, β-sitosterol, ursolic acid, and ascorbic acid	Ursolic acid	 URSOLIC ACID	↓IL-6 dan Il-1b, TNF-a, NO, ↑ VEGF, ↑ TGF-β1, ↑ TGF—β2, ↑ NIH-3T3 fibroblast cells proliferation, ↑ myofibroblast differentiation, ↑ type I collagen, ↑ epithelialization, ↓ lipid peroxidation, ↓ ROS, ↑ vascularization, ↓ cellular necrosis.	[93,96,138]
Curcuma longa	Curcumin, turmeron, zingiberen felandren, sabinen, borneol and sineil	Curcumin	 CURCUMIN	↑ SOD, CAT and GSH ↑ VEGF, TGF-β1, and HIF-1α ↓ NF-κB ↓ ROS production ↑ Wnt signaling pathway ↓ MCP-1 ↓ TNF-α and IL-6	[105,111]

Plants	**Metabolite**	**Active compound**	**Structure**	**Mechanism**	**Reference**
Jatropha curcas L.	Flavonoid, saponin, tannin, polyphenol	Jatrophone	 JATROPHON	↑IL-8, ↑ a-chemokine, ↑ collagen concentration, ↑ stabilization of fibers, ↑ reepithelialization	[122,124, 127]
Jatropha multifida L.	Flavonoids, saponins, alkaloids, tannins, and polyphenols	Luteolinglucoside		↓ cytokines, ↑acidic fibroblast growth factor (aFGF), epidermal fibroblast growth factor (eFGF), bFGF and TGF-α and TGF-β, ↓ PMN leukocytes	[115–118]

Lantana camara L.	Alkaloids, glycosides, steroids, saponins, flavonoids, coumarins, tannins, anthraquinones, glycosides, triterpenoids	Lantadene	 LANTADENE	↓COX 1 and ↓COX 2, ↓ ROS, ↑ protease	[130,133,134]
Melastoma malabathricum L	Alkaloid, flavonoid, terpenoid, steroid, and tannin.	Kaempferol, Quercetin	 KAEMPFEROL  QUERCETIN	↓β (GSK3-β), ↓NF-kβ, ↓COX2) and lipoxygenases, ↓PAP-1 ↓ TNF-α	[135, 141142]
Piper betle	Alkaloids, flavonoids, tannins, saponins, glycosides, steroids, triterpenes, phenolic	Eugenol	 EUGENOL	↑ fibroblast proliferalion, ↓ 11β hydroxysteroid dehydrogenase-1, ↑ collagen, ↓ ROS, ↑ NIH3T3 cell proliferation ↑cPGS, VEGF	[145,146]
Zingiber officinale	Terpenoid and phenolic	Gingerols	 GINGEROL	↓ TNF-α, IL-1β, IL-6, and NO, ↓ TLR4/NF-κB ↑ VEGF, PDGF, TGF- β	[157]