The potential of liquid smoke as an oral ulcer remedies: A proposed mechanism based on systematic review

by Ira Arundina

© 2021 Journal of Pharmacy & Pharmacognosy Research, 9 (6), 905-920, 2021
ISSN 0719-4250
http://jppres.com/jppres

Review

The potential of liquid smoke as an oral ulcer remedies: A proposed mechanism based on systematic review

[El potencial del humo líquido como remedio para las úlceras orales: Un mecanismo propuesto basado en una revisión sistemática]

Meircurius D.C. Surboyo[1*], Diah S. Ernawati[1], Ira Arundina[2], Dieni Mansur[3], Benni Iskandar[4,5], Arvind B.R. Santosh[6], Kelvin A.N. Anggrarista[7], Pamela H. Cecilia[7], Ayu A.B. Nagoro[7]

[1]Department of Oral Medicine, Faculty of Dental Medicine, Universitas Airlangga. Surabaya, Indonesia.
[2]Department of Oral Biology, Faculty of Dental Medicine, Universitas Airlangga. Surabaya, Indonesia.
[3]Research Centre for Chemistry, Indonesian Institute of Sciences, Kawasan PUSPIPTEK – Serpong, Tangerang Selatan, Banten, Indonesia.
[4]School of Pharmacy. College of Pharmacy, Taipei Medical University. Taipei, Taiwan.
[5]Sekolah Tinggi Ilmu Farmasi Riau, Pekanbaru, Riau, Indonesia.
[6]School of Dentistry. Faculty of Medical Sciences. University of The West Indies, Jamaica.
[7]Bachelor of Dental Surgery, Faculty of Dental Medicine, Universitas Airlangga. Surabaya, Indonesia.
*E-mail: meircurius-2015@fkg.unair.ac.id

Abstract

Context: The standard management of oral ulcer therapy is focused only on symptomatic therapy, such as reducing pain. To date, there is no topical drug that has the pharmacodynamics to intervene in oral ulcer pathogenicity. Liquid smoke is traditionally used as a safe natural preservative. The liquid smoke is highly phenolic and compound rich. It is presumed to have analgesic and anti-inflammatory effects with potentially promising therapeutic effects on oral ulcers.

Aims: To describe the possible pharmacodynamics or action mechanism of liquid smoke as a promising remedy for oral ulcer therapy.

Methods: A comprehensive literature review on PubMed, ScienceDirect, Scopus and Embase was performed using Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). The keywords used included 'liquid smoke', 'wood vinegar', 'liquid pyrolysis' and 'oral ulcer'. A screening process, including titles, abstracts and full texts, was performed. Eight related articles were selected to describe the possible pharmacodynamics or mechanism action of the liquid smoke originating from coconut shells and rice hulls for oral ulcer remedies.

Results: Liquid smoke from coconut shell and rice husk is highly contained phenol, guaiacol and 2-methoxy-5-methylphenol (2-EMP). These compounds are antioxidants that can bind reactive oxygen species and increase cellular responses, inhibiting nuclear factor-*kappa* B activation and pro-inflammatory cytokine production while increasing macrophage differentiation to M2. The increase of M2, with help from lymphocytes, can secrete various growth factors, which can accelerate the proliferation of fibroblasts and collagens needed in the healing process of oral ulcers.

Conclusions: Liquid smoke pharmacodynamics inhibit both inflammatory and proliferation pathway stimulation, which promises remedies for oral ulcers.

Resumen

Contexto: El humo líquido es altamente fenólico y rico en compuestos. Se presume que este tiene efectos analgésicos y antiinflamatorios con prometedores efectos terapéuticos potenciales sobre las úlceras orales.

Objetivos: Describir la posible farmacodinámica o mecanismo de acción del humo líquido como un remedio prometedor para la terapia de úlceras orales.

Métodos: Se realizó una revisión exhaustiva de la literatura sobre PubMed, ScienceDirect, Scopus y Embase utilizando elementos de informes preferidos para revisiones sistemáticas y metaanálisis (PRISMA). Las palabras clave utilizadas incluyeron "humo líquido", "vinagre de madera", "pirólisis líquida" y "úlcera oral". Se realizó un proceso de selección, que incluyó títulos, resúmenes y textos completos. Se seleccionaron ocho artículos relacionados para describir la posible farmacodinámica o mecanismo de acción del humo líquido procedente de las cáscaras de coco y de arroz para remediar las úlceras orales.

Resultados: El humo líquido de la cáscara de coco y la cáscara de arroz tiene un alto contenido de fenol, guayacol y 2-metoxi-5-metilfenol (2-EMP). Estos compuestos son antioxidantes que pueden unirse a especies reactivas de oxígeno y aumentar las respuestas celulares, inhibiendo la activación del factor nuclear kappa B y la producción de citocinas proinflamatorias al tiempo que aumentan la diferenciación de macrófagos a M2. El aumento de M2, con la ayuda de los linfocitos, puede secretar varios factores de crecimiento, que pueden acelerar la proliferación de fibroblastos y colágenos necesarios en el proceso de curación de las úlceras orales.

Conclusiones: La farmacodinamia del humo líquido inhibe la estimulación de las vías de proliferación e inflamación, lo que promete remedios para las úlceras orales.

Keywords: analgesic; anti-inflammatory; coconut shell-liquid smoke; human health; oral ulcer.

Palabras Clave: analgésico; antiinflamatorio; humo líquido de cáscara de coco; salud humana; úlcera oral.

ARTICLE INFO
Received: May 18, 2021.
Received in revised form: July 12, 2021.
Accepted: July 13, 2021.
Available Online: July 25, 2021.

AUTHOR INFO
ORCID: 0000-0002-6052-2287 (MDCS)

INTRODUCTION

Oral ulcers are a condition in which the epithelial tissue loses its continuity due to molecular necrosis, which manifests in the oral cavity (Lewis and Wilson, 2019). To date, oral ulcer treatment has only focused on symptomatic therapy, such as relieving the pain, which occurs as a symptom of the oral ulcer. In general, the conventional therapy for oral ulcers is divided into topical and systemic therapies (Tarakji et al., 2015).

Topical therapy is the first line of defense in oral ulcer management and is usually administered as a mouth spray or mouthwash with chlorhexidine, benzydamine hydrochloride (BHCl), povidone-iodine and triamcinolone acetonide as the active agents (Fani et al., 2012; Lewis and Wilson, 2019; Teixeira, 2019). However, topical therapy shows less efficiency in the absorption process, which causes inaccuracies of the dosages used (Bhattarai and Gupta, 2016). In addition, the only purpose of topical therapy is to relieve pain symptoms, and in some long-term cases, it can cause side effects, such as brownish staining of the teeth and yellowish tongue (Prasad et al., 2015; Pandya et al., 2017).

Systemic therapy may be suggested if topical therapy has not shown significant results in the healing of oral ulcers, especially in moderate to severe oral ulcers. Systemic therapy, such as amlexanox and corticosteroids, are usually administered orally (Lewis and Wilson, 2019). However, the mechanism of action of amlexanox is still unknown, and long-term use of corticosteroids has side effects on other organs, such as the liver and the digestive tract, and may increase the incidence of *Candida* infection in the oral cavity (Abbasi et al., 2016; Hernawati et al., 2019; Lewis and Wilson, 2019).

Therefore, other therapeutic agents, which are able to safely intervene in the pathogenicity of oral ulcers, able to improve the healing process of the ulcers and act as more than just a pain reliever are needed. A natural ingredient that has been proven to have various benefits in the wound healing process is liquid smoke. There are several studies that observe liquid smoke and its potential for human health, including liquid smoke from coconut shells (Surboyo et al., 2019a), rice hull (Budhy et al., 2021), cocoa shell (Budaraga et al., 2019), and cocoa pod shell (Desvita et al., 2021). Liquid smoke is a natural substance that has the potential to accelerate wound healing (Tarawan et al., 2017) and heal oral ulcers (Arundina et al., 2021a; Surboyo et al., 2019a); it is antibacterial (Arundina et al., 2020a), analgesic (Surboyo et al., 2012), anti-inflammatory (Kim et al., 2011) and anti-diabetes (Yang et al., 2012a). In some of the research, liquid smoke also possesses mechanisms that increase the migration and response of macrophages, thereby accelerating the inflammatory process in oral ulcers (Surboyo et al., 2019a; 2019b), increasing the number of fibroblasts (Tarawan et al., 2017) and increasing collagen formation (Surboyo et al., 2017). All the promising effects of liquid smoke are expected to stimulate oral ulcer healing. This study aims to describe the possible pharmacodynamics of liquid smoke as a promising remedy for oral ulcer treatment.

MATERIAL AND METHODS

Review methodology

A systematic review of published studies on the topic of liquid smoke for oral ulcer therapy was conducted according to the PRISMA method (Selcuk, 2019). The focus question in this review was 'How do the pharmacodynamics or mechanism action of liquid smoke promise remedies for oral ulcer therapy?'

The Population, Intervention, Comparison, Outcome (PICO) statement used for this study is the population included in all the studies investigating the potential effect of liquid smoke on oral ulcers. Intervention is defined as the topical application of liquid smoke. Any type of comparison (placebo, another topical treatment or no control) was included. All clinical outcomes were considered, including any parameter – cellular, molecular or clinical – related to oral ulcers.

Information sources

A comprehensive literature search was conducted on the following databases: PubMed (US National Library of Medicine, USA), Science Direct (Elsevier, Netherlands), Scopus, and Embase for studies published between 2010 and April 2021.

Search strategy

The terms 'liquid smoke', 'wood vinegar', 'liquid pyrolysis' and 'oral ulcer' were used as keywords in the research. Results were limited to studies published in English. Review articles were not included in this review.

Study design and selection process

All studies found on those databases and fitting the criteria below were grouped together, and any duplicates were removed. The remaining studies were then filtered according to the title, followed by the abstract. Studies that did not match were excluded at this stage. The remaining studies were screened at the final stage according to their full text, and those that did not meet the inclusion criteria were excluded. Microsoft® Excel for Mac Version 16.47.1 was used to organise the study titles and abstracts and identify duplicates. This process was conducted by four independent investigators: KNA, PHC, AABN, and MDCS. In the case of any disagreements, the investigators reached their decision through discussion.

The inclusion criteria for this review included studies about liquid smoke, studies describing the effect on or the potential of liquid smoke for oral ulcers, the dose and duration of the treatment, the marker analyzed, and the analysis methods described. This process, documented by Microsoft® Excel for Mac Version 16.47.1, was performed in the following order: the name of the first author, publication year, country, study design, and results.

The exclusion criteria were *in vitro* studies and review articles. The diagram flow for the study design and selection process is shown in (Fig. 1). The final selected articles were analyzed in detail to assess the most current and relevant information about the potential mechanism of action of liquid smoke on oral ulcers.

RESULTS

Study selection

Flow of the studies

After using a combination of keywords, 560 articles were found in the three databases. The titles were screened, and the duplicates were removed, resulting in 175 remaining articles. After reading the abstracts, only 28 articles were included in the next step of assessing the full text for eligibility. After this process, only 16 articles were included in the next step. The full texts of eight articles were included in the systematic review (Fig. 1).

Excluded studies

There were eight articles excluded from this review. Two articles assessed *in vitro* applications, three articles assessed *in vivo* applications, and three articles assessed both *in vitro* and *in vivo* applications. The excluded articles assessed the potential of liquid smoke from coconut shells (two articles) and rice hulls (six articles).

The excluded *in vitro* articles contained studies on the potential of liquid smoke from rice hulls and studies assessing its toxicity, antibacterial properties, antioxidant properties, anti-inflammatory properties, and antidiabetic properties (Table 1).

The excluded *in vivo* articles contained studies on the potential of coconut shell-liquid smoke (CS-LS), assessing its analgesic and wound healing properties. These articles also assessed the toxicity, anti-inflammatory properties, and antidiabetic properties of liquid smoke from rice hulls (Table 2).

Study characteristics

Six studies revealed the potential of CS-LS for healing oral ulcers (Table 3), and two studies examined liquid smoke from rice hulls (Table 4). All studies were *in vivo* experiments on the healing of oral ulcers conducted on animal models.

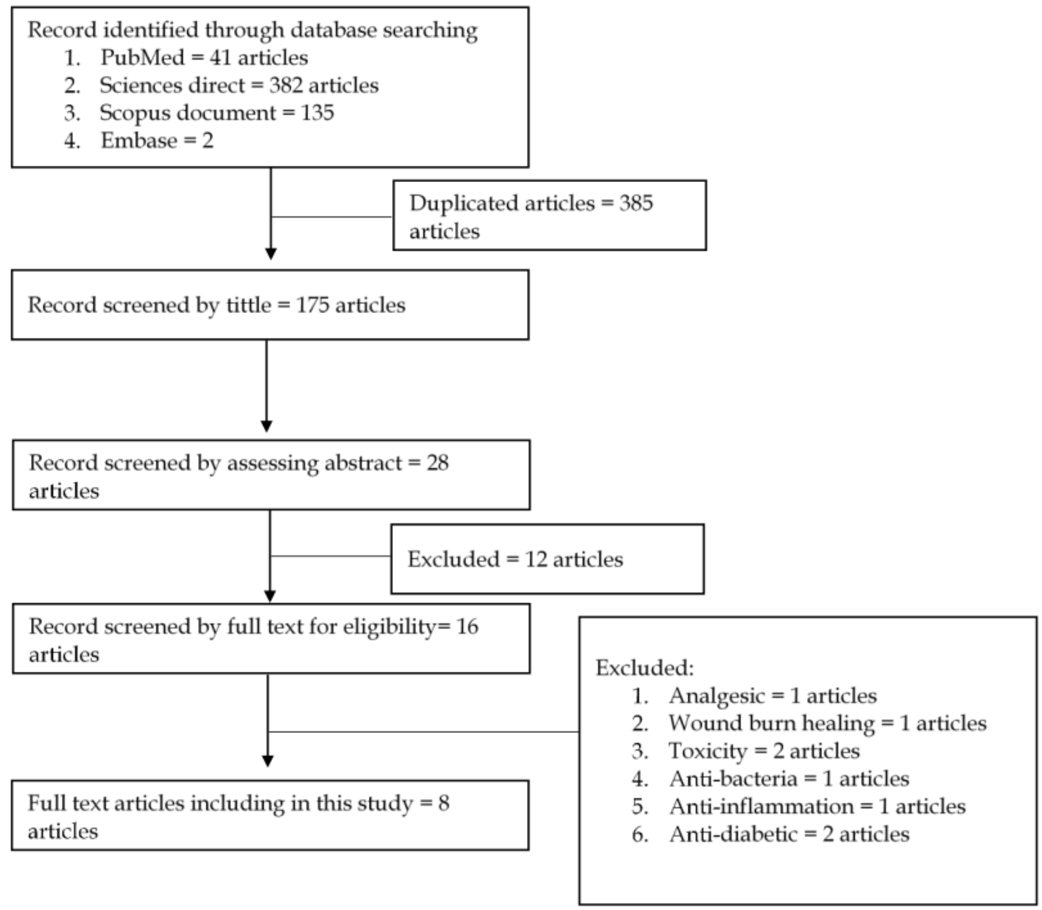

Figure 1. The study design and selection process for systematic reviews.

Results of individual studies

Potential of CS-LS

Increased the neutrophils

The topical administration of liquid smoke increased the number of neutrophils compared to a seven-day administration of BHCI (Ernawati et al., 2020).

Increased the macrophages

The topical administration of liquid smoke increased the number of macrophages compared to a five-day administration of BHCI (Surboyo et al., 2020). A seven-day duration increased the number of macrophages better than five or three days (Ernawati et al., 2020).

Increased the fibroblasts

The topical administration of liquid smoke increased the number of fibroblasts compared to the five-day administration of BHCI (Ayuningtyas et al., 2020). A seven-day duration increased the number of fibroblasts compared to five days (Ernawati et al., 2020).

Increased oral ulcer healing

Topical administration of CS-LS decreased oral ulcer size by more than five- or seven-day administration of BHCI (Surboyo et al., 2019b).

Table 1. The *in vitro* experiment for assessing the potential of liquid smoke.

Authors	Liquid smoke origin	Marker	Analysis methods	Result
Arundina et al., 2020a	Rice hull	Inhibition area of *Porphyromonas gingivalis*	Standard diffusion and dilution methods	The minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) on was found in liquid smoke concentration 10% and 12.5%
		Cell viability on osteoblast	MTT assay	The highest viability of osteoblast was analysed liquid smoke concentration 1%
Arundina et al., 2021c	Rice hull	Cell viability on baby hamster kidney	MTT assay	The highest viability of osteoblast was analysed liquid smoke concentration 10%
Kim et al., 2011	Rice hull	Cell viability on RBL-2H3 and RAW264.7	MTT assay	The highest viability of osteoblast was analysed liquid smoke concentration 1%
		Antioxidant	DPPH assay	Liquid smoke exhibited strong anti-oxidative properties
		Ionophore A23187-stimulated β-hexosaminidase release from RBL-2H3	β-Hexosaminidase Secretion Assay	Liquid smoke inhibited the release of β-hexosaminidase
		NO production in RAW264.7 mouse	NO generation assay	Liquid smoke inhibited the NO production
		TNF-α, IL-1β, and IL-6 level	ELISA	Liquid smoke reduced TNF-α, IL-1β, and IL-6 level
		PGE_2 and LTB_4 level	ELISA	Liquid smoke reduced PGE2 and LTB4 level
		Myeloperoxidase assay	ELISA	Liquid smoke reduced myeloperoxidase activity
		ICAM-1, iNOS, 5-LOX, COX-2, TNF-α, IL-1β, IL-6 and β-actin	RT-PCR	Liquid smoke modulated this gene expression
		iNOS, 5-LOX, COX-2 and β-actin	Western blot	Liquid smoke modulated this protein expression

Table 1. The *in vitro* experiment for assessing the potential of liquid smoke (continued…)

Authors	Liquid smoke origin	Marker	Analysis methods	Result
Yang et al., 2012a	Rice hull	Oxidative stress	Non fluorescent probe, DCF-DA	Liquid smoke suppressed the intracellular peroxide level
		Cell viability on rat insulinoma β-cell line INS-1	MTT assay	Liquid smoke showed the highest cell viability
		NO production on INS-1 cell	Membrane-permeable fluorescent indicator DAF-2/DA	Liquid smoke decreased the NO production
		Nitric oxide (NO) generation	Pro-inflammatory cytokine genes	Liquid smoke suppressed IL-1β, IL-6, and TNF-α genes
		iNOS gene	RT-PCR	Liquid smoke modulated the iNOS gene expression
		iNOS protein	Western blot	Liquid smoke modulated the iNOS expression
		TNF-α, IL-1β, IL-6 and β-actin gene expression	RT-PCR	Liquid smoke modulated this gene expression
		Insulin release on INS-1 cell	ELISA	Liquid smoke increased insulin level
		Blood glucose	Rapid test	Liquid smoke lowered blood glucose level
		Serum insulin	ELISA kit	Liquid smoke increased serum insulin level
		Glycogen	weight	Liquid smoke restored glycogen content
		GOT and GTP	Colorimetric kit	Liquid smoke lowered the level of GOT and GTP
		C6, PEPCK and GCK gene expression	RT-PCR	Liquid smoke suppressed this gene expression
		C6, PEPCK and GCK level	ELISA	Liquid smoke suppressed these protein level
Yang et al., 2012b	Rice hull	GOT and GTP	Colorimetric assay	Liquid smoke reduced serum levels of GOT and GTP
		C6 Pase, GCK, PEPCK	Spectrophotometric	Liquid smoke lowered this enzyme
		GLUT2 and PPAR-γ	RT-PCR	Liquid smoke increased the mRNA expression in hepatic and adipose
		TNF-α, IL-1β and IL-6 level	ELISA	Liquid smoke decreased these cytokines serum and adipose tissue

Table 2. *In vivo* experiments (animal models) for assessing the potential of liquid smoke.

Authors	Liquid smoke origin	Marker	Analysis methods	Result
Tarawan et al., 2017	Coconut shell	Wound contraction Fibroblast	Histopathology	Liquid smoke promotes burn wound healing by increasing the number of fibroblasts and wound contraction
Surboyo et al., 2012	Coconut shell	Analgesic properties	Writhing reflex induced acetic acid	Liquid smoke concentration 100% has showed analgesic properties
Arundina et al., 2020b	Rice hull	Toxicity	Acute toxicity test	The toxicity dose of liquid smoke >15000mg/kg body weight and no toxicity symptoms in animals
Kim et al., 2011	Rice hull	Ear thickness	Changes in ear thickness	Liquid smoke reduced ear thickness
Yang et al., 2012a	Rice hull	Liver	Histology using HE staining	Liquid smoke ameliorated liver damaged
		Langerhans islet of the pancreas	Histology using HE staining	Liquid smoke restored the size and damage Langerhans islet
Yang et al., 2012b	Rice hull	Bodyweight		Liquid smoke suppressed body weight gain induced by a high-fat diet
		Liver weight		Liquid smoke reduced the liver weight
		White adipose tissue weight		Liquid smoke reduced the white adipose tissue
		Blood glucose	Rapid test	Liquid smoke suppressed blood glucose level
		Serum insulin	ELISA	Liquid smoke increased serum insulin level
		Oral glucose tolerance	Oral glucose tolerance test	Liquid smoke decreased oral glucose loading
		Serum lipid	commercial kit	Liquid smoke lowered serum triglycerides
		Liver tissue	Histopathology using HE staining	Liquid smoke ameliorated liver damage
		Pancreatic islets of Langerhans	Histopathology using HE staining	Liquid smoke decreased islets of Langerhans
		Pancreatic islets of Langerhans	IHC	Liquid smoke lowered insulin production

Table 3. The properties of liquid smoke from coconut shell (CS-LS) for promotes oral ulcer healing.

Authors	Marker	Analysis methods	Duration of administration	Result	P-value
Surboyo et al., 2019a	NF-κB expression	Immunohistochemistry	3 days 5 days	Topical administration of CS-LS lowered the NF-κB expression	<0.05
	TNF-α expression	Immunohistochemistry	3 days	Topical administration of CS-LS lowered the TNF-α expression	<0.05
Surboyo et al., 2019b	Oral ulcer diameter	Ulcer diameter using digital calipers	5 days 7 days	Topical administration of CS-LS decreased the oral ulcer size	0.005 0.004
Surboyo et al., 2017	Collagen	Histology by Masson trichome staining	5 days	Topical administration of CS-LS increased the collagen numbers	0.006
Ernawati et al., 2020	Fibroblast	Histology by hematoxylin-eosin staining	7 days	Topical administration of CS-LS increased the fibroblast numbers	<0.01
	Macrophages	Histology by hematoxylin-eosin staining	7 days	Topical administration of CS-LS increased the macrophage numbers	<0.01
	Neutrophils	Histology by hematoxylin-eosin staining	7 days	Topical administration of CS-LS decreased the neutrophil numbers	<0.01
	Lymphocytes	Histology by hematoxylin-eosin staining	7 days	Topical administration of CS-LS increased the neutrophil numbers	<0.01
Surboyo et al., 2020	Macrophages	Histology by hematoxylin-eosin staining	5 days	Topical administration of CS-LS decreased the macrophage numbers	0.000
	NF-κB expression	Immunohistochemistry	5 days	Topical administration of CS-LS decreased the NF-κB expression	0.000
Ayuningtyas et al., 2020	Fibroblast	Histology by hematoxylin-eosin staining	5 days	Topical administration of CS-LS increased the fibroblast numbers	0.028
	FGF-2 expression	Immunohistochemistry	7 days	Topical administration of CS-LS increased the FGF-2 expression	0.000
	VEGF expression	Immunohistochemistry	5 days 7 days	Topical administration of CS-LS increased the VEGF expression	0.019

Table 4. The properties of liquid smoke (LS) from rice hull that promote oral ulcer healing.

Authors	Marker	Analysis methods	Duration of administration	Result	P-value
Arundina et al., 2021a	Macrophages	Histology by hematoxylin-eosin staining	3 days 5 days 7 days	Topical administration of LS increased the macrophage numbers	0.005 0.022 0.022
	Lymphocytes	Histology by hematoxylin-eosin staining	3 days 5 days	Topical administration of LS increased the lymphocyte numbers	0.001 0.000
	Fibroblast	Histology by hematoxylin-eosin staining	3 days 5 days 7 days	Topical administration of LS increased the fibroblast numbers	0.032 0.001 0.025
	IL-6 expression	Immunohistochemistry	5 days	Topical administration of LS increased the IL-6 expression	0.001
	TGF-β expression	Immunohistochemistry	3 days 7 days	Topical administration of LS increased the TGF-b expression	0.034 0.019
Arundina et al., 2021b	FGF-2 expression	Immunohistochemistry	5 days 7 days	Topical administration of LS increased the FGF-2 expression	0.000 0.009
	VEGF expression	Immunohistochemistry	7 days	Topical administration of LS increased the VEGF expression	0.002
	COL-1 expression	Immunohistochemistry	5 days 7 days	Topical administration of LS increased the COL-1 expression than control	0.001 0.000
	PDGF expression	Immunohistochemistry	3 days 5 days 7 days	Topical administration of LS increased the PDGF expression	0.002 0.003 0.003

Increased the density of collagens

The topical administration of liquid smoke increased the density of collagen compared to the five-day administration of BHCI (Surboyo et al., 2012).

Inhibited NF-κB expression

Topical administration of CS-LS showed lower NF-κB expression than three- or five-day administration of BHCI (Surboyo et al., 2019a). Five-day administration showed increased NF-κB expression (Surboyo et al., 2020).

Inhibited TNF-α expression

The topical administration of CS-LS showed lower TNF-α expression than three-day topical administration of BHCI (Surboyo et al., 2019a).

Increased FGF-2 expression

The topical administration of CS-LS increased the FGF-2 expression by more than seven-day administration of BHCI (Ayuningtyas et al., 2020).

Increased VEGF expression

The topical administration of CS-LS showed a higher expression of VEGF than five- or seven-day administration of BHCI (Ayuningtyas et al., 2020).

Potential of liquid smoke from rice hull

Increased the macrophages

The topical administration of liquid smoke increased the number of macrophages compared to three-, five- or seven-day administration of a control (Arundina et al., 2021a).

Increased the lymphocytes

The topical administration of liquid smoke increased the number of lymphocytes compared to the three- and five-day administration of a control (Arundina et al., 2021a).

Increased the fibroblasts

The topical administration of liquid smoke increased the number of fibroblasts compared to three-, five- or seven-day administration of a control (Arundina et al., 2021a).

Increased FGF-2 expression

Topical administration of liquid smoke increased the expression of FGF-2 compared to five- and seven-day administration of a control (Arundina et al., 2021b).

Increased VEGF expression

The topical administration of liquid smoke increased VEGF expression compared to the seven-day administration of a control (Arundina et al., 2021b).

Increased IL-6 expression

Topical administration of liquid smoke increased the expression of IL-6 compared to the five-day administration of a control (Arundina et al., 2021a).

Increased TGF-β expression

Topical administration of liquid smoke increased TGF-β expression compared to three- and seven-day administration of a control (Arundina et al., 2021a).

Increased PDGF expression

Topical administration of liquid smoke increased the expression of PDGF compared to three-, five- and seven-day administration of a control (Arundina et al., 2021b).

Increased COL-1 expression

The topical administration of liquid smoke increased COL-1 expression compared to the five- and seven-day administration of a control (Arundina et al., 2021b).

DISCUSSION

Oral ulcers have a complex healing process that includes the phases of inflammation, granulation, and tissue cell regeneration (Sunarjo et al., 2016). To promote the healing process of oral ulcers and act as more than just a pain reliever, a new therapy that is able to intervene in the pathogenicity of oral ulcers is needed. However, to date, there are no topical drugs that have the pharmacodynamics to intervene in the pathogenicity of oral ulcers.

Both CS-LS and liquid smoke from rice hulls are rich in phenolic components. The physical characteristics are similar: CS-LS has an acidity of 2.39 (Surboyo et al., 2019b), and liquid smoke from rice hull has an acidity of 2.296 (Arundina et al., 2021c). Liquid smoke has a pH range between 2.5 and 3.1 and is presumed to have carcinogenic properties; however, it has been shown to have non-toxic and therapeutic effects (Maryam, 2015). CS-LS is 36.6% phenolic components, 25.2% 2-methoxyphenols (guaiacol), 5.2% EMP, 3.5% 4-ethyl-2-methoxyphenols and 28 other minor components (Surboyo et al., 2019a). Liquid smoke from rice hull contains 13.45% guaiacol, 13.45% mequinol, and 10.52% phenol (Arundina et al., 2021c). In the analyzed studies, there were eight that explored the potential of liquid smoke for the topical therapy of oral ulcers, especially traumatic ulcers.

Liquid smoke has the potential to accelerate the healing of oral ulcers. The healing process requires a faster inflammatory response and a shorter inflammatory phase to provide faster tissue regeneration. The application of CS-LS is able to increase the number of fibroblasts, macrophages, and lymphocytes continuously after three days, up to seven days, except for the number of neutrophils that increase after three days, up to five days, but then decrease by the seventh day (Ernawati et al., 2020). In addition, the topical administration of liquid smoke from rice husk for three, five, and seven days showed a higher number of macrophages, lymphocytes, and fibroblasts (Arundina et al., 2021a). During the inflammatory phase, neutrophils, macrophages, fibroblasts, and endothelial cells produce ROS to compensate for the inflammatory response and protect from microorganism invasion. The overproduction of ROS can slow the healing process. Phenolic compounds contained in liquid smoke, such as EMP and guaiacol, have antioxidant abilities that can increase the cellular response, such as the recruitment of lymphocytes and macrophages. Increased ROS causes oxidative stress on the lymphocytes, which causes apoptosis; hence, with ROS inhibition, the number of lymphocytes will increase. When the inflammatory responses decrease, neutrophils cleanse bacteria and foreign materials from the ulcer area to provide a good environment for the oral ulcer healing process.

Liquid smoke has been shown to increase the recruitment of macrophages in the tissue. In oral ulcer healing, the topical administration of liquid smoke is able to increase fibroblast formation through increased macrophage recruitment (Surboyo et al., 2020). An *in vivo* study by Ernawati et al. (2020) confirms that topical administration of liquid smoke on oral ulcers for seven days increases the recruitment of macrophages. Macrophages play an important role in the wound healing process through M1 polarization in the early stages, followed by M2 polarization at the final stage (Okizaki et al., 2015). M2 plays a role in the formation of new vessels, and an increase in the number of macrophages correlates with a high microvessel density. A higher number of macrophages was also proven by Arundina et al. (2020) *in vivo* study, which shows that topical administration of liquid smoke from rice husk increases macrophages and produces growth factors.

After providing faster cellular responses, liquid smoke also plays a crucial role in the control of the inflammatory phase. This mechanism begins by inhibiting the formation of ROS by phenolic compounds contained in the liquid smoke. Part of the hydroxyl group (-OH) makes up the active site of the phenolic compounds contained in an aromatic hydrocarbon ring. This free-radical resistance mechanism consists of the binding of superoxide radicals (O_2-) to the phenol hydroxyl group (-OH) so that NF-κB activation decreases, leading to inhibition of TNF-α production and other pro-inflammatory cytokines, such as IL-6 (Shahidi and Yeo, 2018). This condition has been confirmed by Surboyo et al. (2019a; 2020), who show that topical administration of liquid smoke for three, five, and seven days can reduce the expression of NF-κB. This mechanism may occur because the phenol content, such as guaiacol and EMP, in liquid smoke, affects the expression of NF-κB in macrophages through a hydroxyl group (-OH), which is able to bind superoxide (O_2-) during signaling, resulting in the production of pro-inflammatory cytokines, such as TNF-α and IL-6. Superoxide binding (O_2-) inhibits phosphorylation IκB kinase (IKK), inhibitory degradation of the IκB factor, translocation of NF-κB and phosphorylation of p65 in the cell nucleus. Therefore, the activation and expression of NF-κB are decreased, leading to a reduction in the expression of pro-inflammatory cytokines (Lopes et al., 2019).

The proliferation stage of oral ulcer healing through topical administration of liquid smoke has been shown to stimulate fibroblast formation, increase collagen density, FGF-2 expression and VEGF expression, and accelerate oral ulcer contraction. The topical application of liquid smoke for seven days increases the number of fibroblasts and the expressions of FGF-2 and VEGF in oral ulcers (Ayuningtyas et al., 2020). In addition, growth factor expression and collagen formation are also positive in the administration of liquid smoke from rice husk. The topical administration of liquid smoke from rice husk shows higher TGF-β, FGF-2, VEGF, PDGF and COL-1 expression (Arundina et al., 2021b). The mechanism that might be involved uses anti-inflammatory effects that Inhibit NF-κB and TNF-α, resulting in more dominant M2 polarisation through a switch from M1 to M2. M2 secretes growth factors, including TGF-β, FGF-2, VEGF, PDGF, and COL-1. The result of this secretion is increased fibroblast proliferation, collagen production and new vascular formation, leading to the complete healing process (Arundina et al., 2021a; Ayuningtyas et al., 2020). The complete healing process is also supported by the liquid smoke, significantly increasing collagen synthesis (Surboyo et al., 2017) and being clinically able to accelerate the contraction of oral ulcers (Surboyo et al., 2019b).

Finally, based on the literature, the role of liquid smoke in the healing of oral ulcers interferes with the cellular responses, inhibits the inflammatory phase and increases the proliferation phases. The purpose of this mechanism is shown in Fig. 2.

There is limited data on the possible mechanism or pharmacodynamics of liquid smoke in oral ulcer healing because most of the research focuses on the potential of liquid smoke as a natural preservative. The research data, excluding articles from this study, which are presented in Tables 1 and 2, also support the potential of liquid smoke in oral ulcer healing.

Liquid smoke has been confirmed as a safe material. It was confirmed that a 10% concentration of liquid smoke derived from rice hull showed the highest living cells *in vitro* (Arundina et al., 2021c). *In vivo*, it was also confirmed that liquid smoke from rice hull had a lethal dose value >15,000 mg/kg body weight, categorizing it as a relatively harmless substance (Arundina et al., 2020b). Despite its toxicity, studies have proven several potentials of liquid smoke derived from rice hulls, such as antibacterial properties and an increase in the proliferation effect (Arundina et al., 2020a).

Moreover, liquid smoke derived from rice hull also has the ability to suppress inducible nitric oxide synthase (iNOS) gene expression and pro-inflammatory cytokines, such as TNF-α, IL-1β and IL-6 (Kim et al., 2011; Yang et al., 2012a). It also has an antidiabetic potential due to decreasing blood glucose and cholesterol concentrations, increasing serum insulin and hepar glycogen, and improving glucose tolerance, which may be beneficial for the management of oral ulcers in diabetic patients (Yang et al., 2012a; 2012b).

The other benefit of liquid smoke for oral ulcer healing is its analgesic properties. *In vitro*, liquid smoke from rice hull reduces prostaglandin E_2 (PGE_2) and leukotriene B_4 (LTB_4) levels (Kim et al., 2011), and *in vivo*, CS-LS showed analgesic properties by reducing pain-induced reflexes in experimental animals (Surboyo et al., 2012). The analgesic properties in liquid smoke are produced by its phenolic components, which inhibit the cyclooxygenase enzyme in the tissue by binding to the prostaglandin G_2 (PGG_2) and the prostaglandin H_2 (PGH_2) components, causing a decrease in the synthesis of PGE_2. Decreasing PGE_2 levels can interfere with the transduction mechanism of afferent nociceptors so that the pain caused by oral ulcers is reduced (Surboyo et al., 2012). This analgesic property is needed in topical oral ulcer therapy, considering the loss of epithelial tissue is the main complaint of oral ulcer pain.

An *in vivo* study by Tarawan et al. (2017) shows that CS-LS accelerates wound healing by increasing wound contraction and the number of fibroblasts. The components of CS-LS that play a role in the healing process are flavonoids, phenols and tannins. The flavonoids and phenols have antioxidant and anti-microbial effects that mediate wound healing by increasing collagen and protein and decreasing lipid peroxidation in granulation tissue. Tannins play a role in fibroblast proliferation; by secreting fibroblast growth factors from neutrophils, fibroblasts proliferate and synthesize collagen. Fibroblasts migrate and proliferate at the wound site during wound healing. The resulting extracellular matrix strengthens the edges of the wound and causes wound contraction.

The study by Kim et al. (2011) shows that topical application of liquid smoke from rice husk has the ability to change ear thickness or swelling, i.e., the inflammatory response characterized by delayed onset and long-term inflammation associated with leukocytes. The rate of leukocyte infiltration changes in ear thickening or swelling. The liquid smoke from rice husk suppresses leukocyte infiltration in the dermis through inhibition of intracellular adhesion molecule-1 (ICAM-1) expression.

Future research needs to further elaborate on the potential of the pharmacodynamics of liquid smoke as a remedy for oral ulcers. Based on the available data, liquid smoke is a promising development in oral ulcer medicine.

Interpretation

Finally, based on the literature, the role of liquid smoke in oral ulcer healing interferes with cellular responses, inhibiting the inflammatory phase and increasing the proliferation phases. The purpose of this mechanism is provided in Fig. 2.

Limitations of evidence

The available articles are limited to *in vivo* and *in vitro* research models, so the level of evidence provided is limited. Further research on liquid smoke needs to be done to add to the data supporting the mechanisms outlined in this review.

Limitations of review processes

The available articles are limited to *in vivo* and *in vitro* research models, so the level of evidence provided is limited.

Implications

Further research on liquid smoke needs to be done to add to the data supporting the mechanisms outlined in this review.

CONCLUSIONS

Based on the mechanisms described, it can be concluded that liquid smoke has a mechanism of action or pharmacodynamics that inhibits the inflammatory pathway and stimulates the proliferation pathway so that it is expected to become the topical drug of choice in oral ulcer therapy. However, further research is needed regarding its application and safe dosage in humans so that liquid smoke can be used clinically for oral ulcer therapy.

CONFLICT OF INTEREST

The authors declare no conflicts of interests.

ACKNOWLEDGMENTS

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

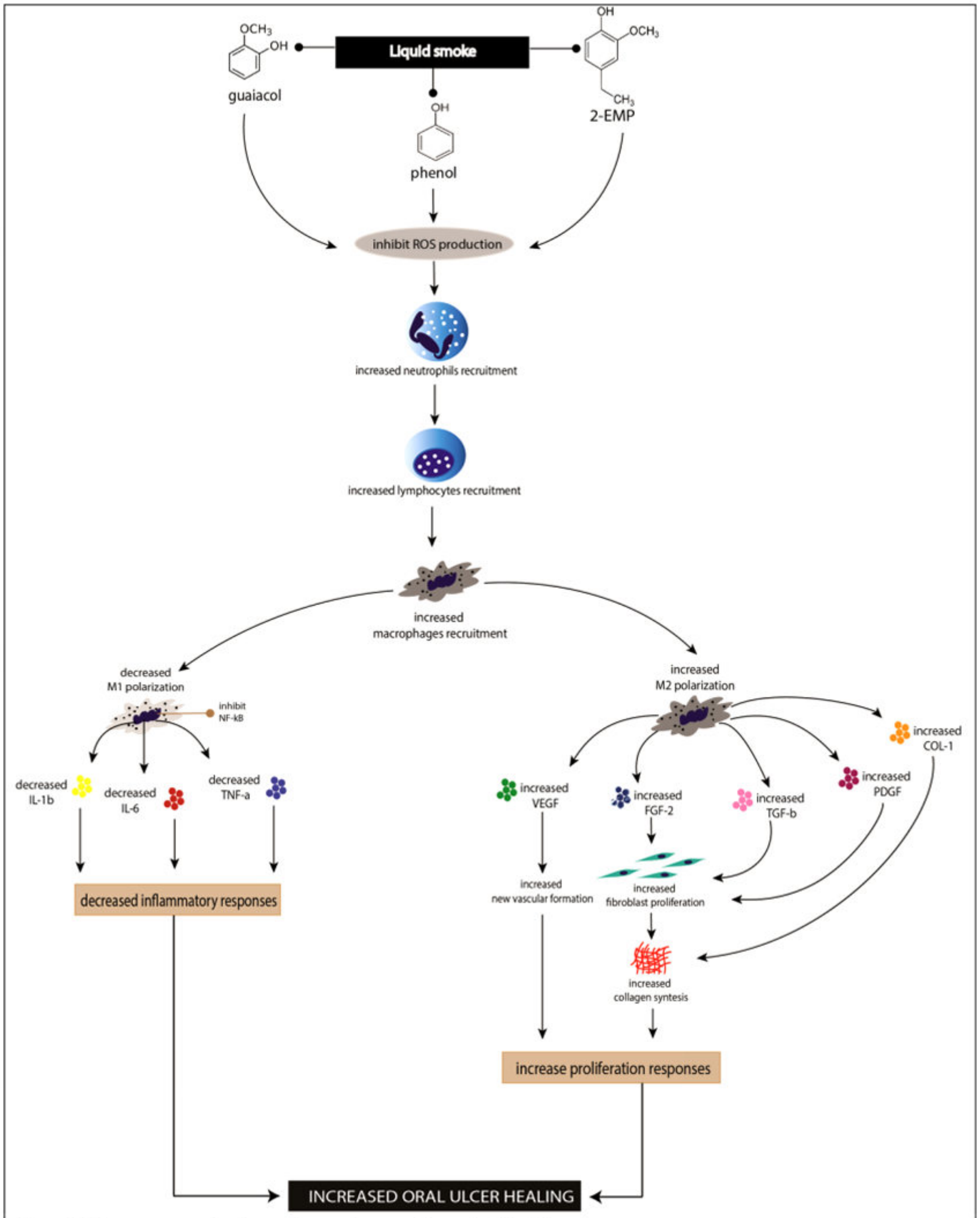

Figure 2. The purpose mechanism action or pharmacodynamic of liquid smoke.

REFERENCES

Abbasi F, Raoof M, Khatami R, Shadman N, Borjian-Boroojeni F, Nazari F (2016) Effectiveness of amlexanox and adcortyl for the treatment of recurrent aphthous ulcers. J Clin Exp Dent 18(4): 368–372.

Arundina I, Diyatri I, Kusumaningsih T, Surboyo MDC, Monica E, Afanda NM (2021a) The role of rice hull liquid smoke in the traumatic ulcer healing. Eur J Dent 15(1): 33–38.

Arundina I, Diyatri I, Surboyo MDC, Monica E, Afanda NM (2021b) Growth factor stimulation for the healing of traumatic ulcers with liquid rice hull smoke. J Taibah Univ Med Sci 16(3): 431–439.

Arundina I, Diyatri I, Surboyo MDC (2021c) The component analysis of liquid smoke from rice hulls and its toxicity test on baby hamster kidney cells. J Pharm Pharmacogn Res 9(1): 78–87.

Arundina I, Diyatri I, Surboyo MDC, Halimah AN, Chusnurrafi FI (2020a) The antibacterial effect of liquid smoke rice hull on *Porphyromonas gingivalis* and its oroliferative effects on osteoblast as periodontitis remedies: An *in vitro* study. Int J Pharm Res 12(3): 3466–3471.

Arundina I, Tantiana T, Diyatri I, Surboyo MDC, Adityasari R (2020b) Acute toxicity of liquid smoke of rice hull (*Oryza sativa*) on mice (*Mus musculus*). J Int Dent Med Res 13(1): 91–96.

Ayuningtyas NF, Surboyo MDC, Ernawati DS, Parmadiati AE, Hendarti HT, Mahdani FY, Winias S, Zakia F, Harianto IA (2020) The role of liquid dmoke coconut shell in the proliferation phase of an oral traumatic ulcer. J Pharm Pharmacogn Res 8(6): 549–557.

Bhattarai M, Gupta AK (2016) Fast dissolving oral films: A novel trend to oral drug delivery system. Sunsari Tech Coll J 2(1): 58–68.

Budaraga IK, Susanti E, Asnurita A, Nurdin E, Ramaiyulis R (2019) The antioxidant characteristics of the liquid smoke of cocoa shell (*Theobroma cacao* L) in different water content variations. J Appl Agric Sci Technol 3(2): 226–238.

Budhy TI, Arundina I, Surboyo MDC, Halimah AN (2021) The effects of rice husk liquid smoke in *Porphyromonas gingivalis*-induced periodontitis. Eur J Dent. doi: 10.1055/s-0041-1727554

Desvita H, Faisal M, Mahidin M, Suhendrayatna S (2021) Preliminary study on the antibacterial activity of liquid smoke from cacao pod shells (*Theobroma cacao* L). IOP Conf Ser Mater Sci Eng 1098(2): 022004.

Ernawati DS, Surboyo MDC, Ayuningtyas NF, Nagoro AAB (2020) Role of inflammatory cell responses in stimulating fibroblasts in diabetic oral ulcer after treatment with liquid smoke of coconut endocarp: A histological assessment. Eur J Dent 15(1): 71–76.

Fani MM, Ebrahimi H, Pourshahidi S, Aflaki E, Sarvestani SS (2012) Comparing the effect of phenytoin syrup and triamcinolone acetonide ointment on aphthous ulcers in patients with Behcet's syndrome. Iran Red Crescent Med J 14(2): 74–77.

Hernawati S, Zikra YA, Fatmawati DWA (2019) The effects of topical application of red pomegranate (*Punica granatum* Linn) extract gel on the healing process of traumatic ulcers in Wistar rats. Dent J (Majalah Kedokt Gigi) 52(2): 90.

Kim PS, Yang YJ, Kang YM, Park CJ, Nam HS, Friedman M (2011) Composition of liquid rice hull smoke and anti-inflammatory effects in mice. J Agric Food Chem 59(9): 4570–4581.

Lewis MAO, Wilson NHF (2019) Oral ulceration: Causes and management. Pharm J 302: 7923.

Lopes K, Oliveira J, Sousa-junior FJC, Santos TF, Andrade D, Andrade SL, Pereira WL, Gomes PWP, Monteiro MC, Yoshioka CY, Nascimento M, Maia CF (2019) Chemical composition, toxicity, antinociceptive, and anti-inflammatory activity of dry aqueous extract of *Varronia multispicata* (Cham.) Borhidi (*Cordiaceae*) leaves. Front Pharmacol 10: 1376.

Maryam (2015) Applications of liquid smoke powder as flavor and food preservative (case study: Sponge cake). Int J Adv Sci Eng Inf Technol 5(2): 135–138.

Okizaki S, Ito Y, Hosono K, Oba K, Ohkubo H (2015) Suppressed recruitment of alternatively activated macrophages reduces TGF-β1 and impairs wound healing in streptozotocin-induced diabetic mice. Biomed Pharmacother 70: 317–325.

Pandya M, Kalappanavar AN, Annigeri RG, Rao DS (2017) Relative efficacy of quercetin compared with benzydamine hydrochloride in minor aphthae: A prospective, parallel, double blind, active control, preliminary study. Int J Dent 2017: 7034390.

Prasad KARV, John S, Deepika V, Dwijendra KS, Reddy BR, Chincholi S (2015) Anti-plaque efficacy of herbal and 0.2% chlorhexidine gluconate mouthwash: A comparative study. J Int Oral Heal 7(8): 98–102.

Selcuk AA (2019) A guide for systematic reviews: PRISMA. Turkish Arch Otorhinolaryngol 57(1): 57–58.

Shahidi F, Yeo JD (2018) Bioactivities of phenolics by focusing on suppression of chronic diseases: A review. Int J Mol Sci 19(6): 1573.

Sunarjo L, Hendari R, Rimbyastuti H (2016) Manfaat xanthone terhadap kesembuhan ulkus rongga mulut dilihat dari jumlah sel pmn dan fibroblast. Odonto Dent J 2(1): 14.

Surboyo MDC, Arundina I, Rahayu RP (2017) Increase of collagen in diabetes-related traumatic ulcers after the application of liquid smoke coconut shell. Dent J (Majalah Kedokt Gigi) 71(32): 71–75.

Surboyo MDC, Arundina I, Rahayu RP, Mansur D, Bramantoro T (2019a) Potential of distilled liquid smoke derived from coconut (*Cocos nucifera* L) shell for traumatic ulcer healing in diabetic rats. Eur J Dent 13(02): 271–279.

Surboyo MDC, Ernawati DS, Arundina I, Rahayu RP (2019b) Oral ulcer healing after treatment with distilled liquid smoke of coconut shell on diabetic rats. J Krishna Inst Med Sci Univ 8(2): 70–79.

Surboyo MDC, Mahdani FY, Ernawati DS, Sarasati A, Rezkita F (2020) The macrophage responses during diabetic oral ulcer healing by liquid coconut shell smoke: An immunohistochemical analysis. Eur J Dent 14(03): 410–414.

Surboyo MDC, Tantiana T, Arundina I (2012) Analgesic effect of coconut shell (*Cocos nucifera* L) liquid smoke on mice. Dent J (Majalah Kedokt Gigi) 45(3): 156–160.

Tarakji B, Gazal G, Al-Maweri SA, Azzeghaiby SN, Alaizari N, Al-Maweri SA, Azzeghaiby NS, Alaizari N (2015) Guideline for the diagnosis and treatment of recurrent aphthous stomatitis for dental practitioners. J Int Oral Heal 7(5): 74–80.

Tarawan VM, Mantilidewi KI, Dhini IM, Radhiyanti PT, Sutedja E (2017) Coconut shell liquid smoke promotes burn wound healing. J Evid Based Complementary Altern Med 22(3): 436–440.

Teixeira D (2019) The topical effect of chlorhexidine and povidone-iodine in the repair of oral wounds. A review. Stomatologija 21(2): 35–41.

Yang JY, Kang MY, Nam SH, Friedman M (2012a) Antidiabetic effects of rice hull smoke extract in alloxan-induced diabetic mice. J Agric Food Chem 60(1): 87–94.

Yang JY, Moon E, Nam SH, Friedman M (2012b) Antidiabetic effects of rice hull smoke extract on glucose-regulating mechanism in type 2 diabetic mice. J Agric Food Chem 60(30): 7442–7449.

AUTHOR CONTRIBUTION:

Contribution	Surboyo MDC	Ernawati DS	Arundina I	Mansur D	Iskandar B	Santosh ABR	Anggrarista KNA	Cecilia PH	Nagoro AAB
Concepts or ideas	x								
Design	x								
Literature search	x		x				x	x	x
Data acquisition	x								
Data analysis	x		x	x			x	x	x
Statistical analysis	x								
Manuscript preparation	x						x	x	x
Manuscript editing	x	x		x	x	x			
Manuscript review	x	x	x	x	x	x	x	x	x

Citation Format: Surboyo MDC, Ernawati DS, Arundina I, Mansur D, Iskandar B, Santosh ABR, Anggrarista KNA, Cecilia PH, Nagoro AAB (2021) The potential of liquid smoke as an oral ulcer remedies: A proposed mechanism based on systematic review. J Pharm Pharmacogn Res 9(6): 905–920.

The potential of liquid smoke as an oral ulcer remedies: A proposed mechanism based on systematic review

ORIGINALITY REPORT

16%	11%	13%	1%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	Meircurius Dwi Condro Surboyo, Ira Arundina, Retno Pudji Rahayu, Dieni Mansur, Taufan Bramantoro. "Potential of Distilled Liquid Smoke Derived from Coconut (Cocos nucifera L) Shell for Traumatic Ulcer Healing in Diabetic Rats", European Journal of Dentistry, 2019 Publication	2%
2	www.thieme-connect.com Internet Source	2%
3	mafiadoc.com Internet Source	2%
4	Ira Arundina, Indeswati Diyatri, Meircurius Dwi Condro Surboyo, Elita Monica, Novitasari Mira Afanda. "Growth factor stimulation for the healing of traumatic ulcers with liquid rice hull smoke", Journal of Taibah University Medical Sciences, 2021 Publication	1%
5	www.thieme-connect.de Internet Source	1%

6	Ira Arundina, Indeswati Diyatri, Wisnu S. Juliastuti, Theresia I. Budhy et al. "Osteoblast Viability of Liquid Smoke Rice Hull and Nanoparticles Form as Periodontitis Treatment", European Journal of Dentistry, 2022 Publication	1%
7	www.whittington.nhs.uk Internet Source	<1%
8	www.actaitalica.it Internet Source	<1%
9	www.jkimsu.com Internet Source	<1%
10	www.jidmr.com Internet Source	<1%
11	journals.sagepub.com Internet Source	<1%
12	Sung Phil Kim, Jun Young Yang, Mi Young Kang, Jun Cheol Park, Seok Hyun Nam, Mendel Friedman. "Composition of Liquid Rice Hull Smoke and Anti-Inflammatory Effects in Mice", Journal of Agricultural and Food Chemistry, 2011 Publication	<1%
13	www.isnff-jfb.com Internet Source	<1%

14	www.accounts-commission.org.uk	Internet Source	<1 %
15	www.mdpi.com	Internet Source	<1 %
16	Meircurius Dwi Condro Surboyo, Fatma Yasmin Mahdani, Diah Savitri Ernawati, Andari Sarasati, Fianza Rezkita. "The Macrophage Responses during Diabetic Oral Ulcer Healing by Liquid Coconut Shell Smoke: An Immunohistochemical Analysis", European Journal of Dentistry, 2020	Publication	<1 %
17	www.researchgate.net	Internet Source	<1 %
18	Xuqiang Nie, Jiufeng Zhao, Hua Ling, Youcai Deng, Xiaohui Li, Yuqi He. " Exploring in diabetic chronic cutaneous ulcers: Regulatory mechanisms and therapeutic potential ", British Journal of Pharmacology, 2020	Publication	<1 %
19	Submitted to iGroup	Student Paper	<1 %
20	irep.iium.edu.my	Internet Source	<1 %
21	www.nature.com	Internet Source	<1 %

22	Meircurius Dwi Condro Surboyo, Rizky Merdietio Boedi, Ninuk Hariyani, Arvind Babu Rajendra Santosh et al. "The expression of TNF-α in recurrent aphthous stomatitis: A systematic review and meta-analysis", Cytokine, 2022 Publication	<1 %
23	journal.unwira.ac.id Internet Source	<1 %
24	Jun Young Yang, Eunpyo Moon, Seok Hyun Nam, Mendel Friedman. "Antidiabetic Effects of Rice Hull Smoke Extract on Glucose-Regulating Mechanism in Type 2 Diabetic Mice", Journal of Agricultural and Food Chemistry, 2012 Publication	<1 %
25	Vita Murniati Tarawan, Kemala Isnainiasih Mantilidewi, Ika Miqra Dhini, Putri Teesa Radhiyanti, Endang Sutedja. "Coconut Shell Liquid Smoke Promotes Burn Wound Healing", Journal of Evidence-Based Complementary & Alternative Medicine, 2016 Publication	<1 %
26	medicopublication.com Internet Source	<1 %
27	Yi Lin, Zhongjie Sun. "Thyroid hormone potentiates insulin signaling and attenuates	<1 %

hyperglycemia and insulin resistance in a mouse model of type 2 diabetes", British Journal of Pharmacology, 2011
Publication

28	journals.iau.ir Internet Source	<1 %
29	pubmed.ncbi.nlm.nih.gov Internet Source	<1 %
30	www.gssrr.org Internet Source	<1 %
31	Hera Desvita, Muhammad Faisal, Mahidin, Suhendrayatna. "Preservation of meatballs with edible coating of chitosan dissolved in rice hull-based liquid smoke", Heliyon, 2020 Publication	<1 %
32	Intan Nirwana, Elly Munadziroh, Anita Yuliati, Azalia Izzah Fadhila et al. "Ellagic acid and hydroxyapatite promote angiogenesis marker in bone defect", Journal of Oral Biology and Craniofacial Research, 2022 Publication	<1 %
33	Mendel Friedman. "Rice Brans, Rice Bran Oils, and Rice Hulls: Composition, Food and Industrial Uses, and Bioactivities in Humans, Animals, and Cells", Journal of Agricultural and Food Chemistry, 2013 Publication	<1 %

34	health.gov Internet Source	<1%
35	pubs.rsc.org Internet Source	<1%
36	www.hindawi.com Internet Source	<1%
37	www.jurnal.ugm.ac.id Internet Source	<1%
38	www.science.gov Internet Source	<1%
39	www.veterinaryworld.org Internet Source	<1%
40	Ashley Mansell. "The negative regulation of Toll-like receptor and associated pathways", Immunology and Cell Biology, 08/2007 Publication	<1%
41	Diah Savitri Ernawati, Meircurius Dwi Condro Surboyo, Nurina Febriyanti Ayuningtyas, Ayu Anggraini Broto Nagoro. "Role of Inflammatory Cell Responses in Stimulating Fibroblasts in Diabetic Oral Ulcer after Treatment with Liquid Smoke of Coconut Endocarp: A Histological Assessment", European Journal of Dentistry, 2020 Publication	<1%

42 Ira Arundina, Indeswati Diyatri, Tuti Kusumaningsih, Meircurius Dwi Condro Surboyo, Elita Monica, Novitasari Mira Afanda. "The Role of Rice Hull Liquid Smoke in the Traumatic Ulcer Healing", European Journal of Dentistry, 2020 — <1 %

Publication

---

43 Meircurius Dwi Condro Surboyo, Fatma Yasmin Mahdani, Nurina Febriyanti Ayuningtyas, Arvind Babu Rajendran Santosh et al. "The cytotoxicity, anti-inflammation, anti-nociceptive and oral ulcer healing properties of coconut shell liquid smoke", Journal of Herbmed Pharmacology, 2021 — <1 %

Publication

---

44 Sun Phil Choi, Sung Phil Kim, Mi Young Kang, Seok Hyun Nam, Mendel Friedman. "Protective Effects of Black Rice Bran against Chemically-Induced Inflammation of Mouse Skin", Journal of Agricultural and Food Chemistry, 2010 — <1 %

Publication

---

45 Tara Nazareth, Erin M Hart, Sarah M Ronnebaum, Sandhya Mehta, Dipen A Patel, Ina Kötter. "Comparability of European League Against Rheumatology-Recommended Pharmacological Treatments of Oral Ulcers Associated with Behçet's Disease: A — <1 %

Systematic Literature Review of Randomized Controlled Trials", Open Access Rheumatology: Research and Reviews, 2020
Publication

46	etheses.whiterose.ac.uk Internet Source	<1%
47	Jae In Jung, Hyun Sook Lee, Young Eun Jeon, So Mi Kim, Su Hee Hong, Joo Myung Moon, Cho Young Lim, Yoon Hee Kim, Eun Ji Kim. "Anti-inflammatory activity of palmitoylethanolamide ameliorates osteoarthritis induced by monosodium iodoacetate in Sprague–Dawley rats", Inflammopharmacology, 2021 Publication	<1%
48	T Handayani, D Xyzquolyna, Y Pranoto, A Suratman. "Reduction of Pb(II) Ion in Soybean Seeds (Glycine max) Using Corncob Liquid Smoke", IOP Conference Series: Earth and Environmental Science, 2019 Publication	<1%
49	www.ncbi.nlm.nih.gov Internet Source	<1%

Exclude quotes	Off	Exclude matches	Off
Exclude bibliography	On		

The potential of liquid smoke as an oral ulcer remedies: A proposed mechanism based on systematic review

GRADEMARK REPORT

FINAL GRADE

/0

GENERAL COMMENTS

Instructor

PAGE 1

PAGE 2

PAGE 3

PAGE 4

PAGE 5

PAGE 6

PAGE 7

PAGE 8

PAGE 9

PAGE 10

PAGE 11

PAGE 12

PAGE 13

PAGE 14

PAGE 15

PAGE 16