# Review of Future Insights of Dragon's Blood in Dermatology

## Dermatology Review of Dragon's Blood

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**Abstract**

Objective: To assess the possible clinical implication of Dragon's Blood in dermatology.

Design: A pubmed search was conducted using the keyword "Dragon's Blood", "Croton lechleri", and more.

Results: Dragon's Blood from *Croton lechleri* is an Amazonian medicinal plant with a characteristic red sap. Its array of phytochemical action in preclinical studies include anti-inflammatory, anti-oxidant, antimicrobial, antifungal, and antineoplastic properties. Clinical studies reflect wound healing and antiviral properties.

Conclusion: Although its popularity is rising in western medicine, *C. lechleri* offers limited use in dermatology and further investigation is necessary to gain further insight into its potential clinical implication.

**Introduction**

Investigation of natural plant products is done through the classical and the ethnobotanical methods. The classical method is driven by phytochemical and immunopharmacological studies, taxonomy, and random screening. The ethnobotanical method uses traditional texts, interviews, and indigenous lore. (Vlietinck & Vanden Berghe, 1991) Ethnobotanical popularity in research has grown, leading to an increased probability of discovering active phytochemicals. (King & Tempesta, 1994) One medicinal plant that has increased in wound healing popularity and clinical application is Dragon's Blood.

For centuries, indigenous residents of South America have used Amazonian botanical medicine and shamanism for healing. Dragon's Blood, also known as sangre de grado and sangre de drago, is derived from *Croton lechleri* of the Euphorbiaceae family. (Jones, 2003) Although

*C. lechleri* is the most popular, other similar *Croton* spp. called Dragon's Blood includes *C. palanostigma*, *C. draconoides*, *C. perspeciosus*, *C. rimbachii*, *C. erythrochilus*, and *C. urucurana*. (Gurgel, Sidrim, Martins, Cechinel Filho, & Rao, 2005; Jones, 2003) Different genus labeled Dragon's Blood across the world includes *Dracaena* spp., *Daemonorops* spp., and *Pterocarpus* spp. (Gupta, Bleakley, & Gupta, 2008; Namjoyan, Kiashi, Moosavi, Saffari, & Makhmalzadeh, 2016)

This medium-sized tree grows in low mountainous regions of Peru, Colombia, Venezuela, Brazil, Mexico, Ecuador, and Bolivia. When sliced, *C. lechleri* bleeds a red sap, providing the namesake "Dragon's Blood". Amazonians use Dragon's Blood, either fresh or as a dry powder, in remedies for sore throat, hives, cancer, vaginal antiseptic, insect bites, hemostasis, wound healing, and diarrhea. (Brako L, 1993; Castner JL, 1998; Gupta et al., 2008; Jones, 2003; Williams, 2001) To further investigate the medicinal properties of this unusual plant, we conducted a literature review to gather insights in future dermatologic implications of *C. lechleri*.

## Methods

Scientific synonyms of plant species were searched using the plant list, an online database of all plant species. A Pubmed search was conducted on August 1, 2018, using the keywords "dragon's blood", "croton lechleri", "croton draco", "oxydectes lechleri", "sangre de drago AND dermatology", "sangre AND de AND drago", and "sangre AND de AND grado".

## Results

### Phytochemical Analysis

Phytochemical analysis of *C. lechleri* has identified proanthocyanidins, phenols, flavonols, diterpenes, essential oils, and alkaloid taspine. Steroids found in *C. lechleri* includes *β*-sitosterol-*β*-D-glucopyranoside and *β*-sitosterol. (Cai Y, 1993; Cai Y., 1991; Fayad et al., 2009; Jones, 2003; Porras-Reyes, Lewis, Roman, Simchowitz, & Mustoe, 1993; Vaisberg et al., 1989) Proanthocyanidins, catechin, epicatechin, gallocatechin, and epigallocatechin constitute 90% of Dragon's Blood dry weight (Table 1). (Chen, Cai, & Phillipson, 1994)

**Physiologic Studies**

*C. lechleri* sap has vasoconstrictive properties supported by rat vascular smooth muscle constriction ($P<0.01$). However, the mechanism of action is unclear with no evidence of muscarinic, L-type calcium channel, 5-$HT_{2A.}$ or α1-adrenergic modulation. (Froldi et al., 2009; Miller et al., 2001)

The phenolic components of *C. lechleri* possess antioxidant properties. The phenolic components have stronger scavenging action towards 2,2-diphenyl-1-picrylhydrazyl (DPPH) than ascorbic acid. (De Marino et al., 2008) Another *in vitro* study testing of the antioxidative properties of *C. lechleri* reported high scavenging for hydroxyl and peroxyl radicals, two agents notorious for lipid peroxidation and cell membrane damage. (Desmarchelier, Witting Schaus, Coussio, & Cicca, 1997) Pharmacologic studies on polyphenols also exhibit oxygen free radical scavenging, suggesting a possible benefit in wound healing. (Spencer C., 1988) Oxidative stress is a key component in delayed wound healing. The conversion of arachidonic acid to prostaglandins through reactive oxygen species are suppressed through scavenging or preventing free radical formation. Therefore, the antioxidative properties of *C. lechleri* may help promote wound healing. (Desmarchelier et al., 1997; Spencer C., 1988)

*C. lechleri* displayed *in vitro* inhibition of the classical and alternative complement pathway and active T-cell proliferation. *C. lechleri* suppressed the classical and alternative pathway with an inhibitory concentration ($IC_{50}$) of 5 μg/mL and 185 μg/mL, compared to control's $IC_{50}$ of 33.7 μg/mL on the classical pathway. (Risco et al., 2003)

### *In Vivo* Application for Allergic Contact Dermatitis

The antioxidative, barrier, and immunosuppressive properties of four novel formulations were evaluated in a murine model of allergic contact dermatitis (ACD). The first formulation, called mixture of antioxidant and moisturizer (MAM), was a mixture of *Rosa moschata*, *C. lechleri*, *Aloe vera*, and D-panthenol (moisturizer). The second formulation was 2% hydroglycolic solution of disodium cromoglycate (CGDS), which is an efficacious free radical scavenger and inhibitor. (Kladna et al., 2014) The final two formulations were Formulation A, a mixture of MAM and CGDS 2%, and Formulation B, a mixture of MAM and CGDS 5%.

The compound 2,4-dinitrofluorobenzene (DNFB) induced ACD on mouse ears, resulting in increased mouse ear width due to edema. Two approaches were tested: a curative approach, defined as inducing ACD then treating, and a preventative approach, defined as simultaneously treating and stimulating ACD. Efficacy was defined as a decreased width of the mouse ear, which may suggest decreased edema.

By Day 22, DNFB had increased the mouse ear's thickness from 0.20 mm to 0.48 mm. In the curative approach, MAM, CGDS 2%, and Formulation A each decreased the thickness by 64% and Formulation B decreased the thickness by 75%. All treatments had clinical effects 3 days after topical application; however, only CGDS 2% had significant improvement compared to vehicle ($P$=0.0016-0.0021). In a similar experiment, only Formulation B reduced ear thickness

($P$<0.001). The control (DNFB alone, no treatment) increased thickness 42% after Day 22. Hydrocortisone and desoximetasone decreased ear thickness comparable to control. In the preventative approach, concurrent application of DNFB with Formulation A or B resulted in only minimal thickness, with Formulation B more effectively minimizing thickness.

An immunoblot analysis quantified tumor necrosis factor (TNF)-α, protease-activated receptor-2 (PAR-2), and transient receptor potential vanilloids 4 (TRPV4) to grade immunomodulating properties. PAR-2, stimulated by mast cell's protease and tryptase, trigger inflammation. (Carvalho, Nilsson, & Harvima, 2010; Zhu et al., 2015) PAR-2 also stimulates TRPV4, a $Ca^{2+}$ ion channel that releases substance P and calcitonin gene-related peptide, causing pruritus and pain. (Akiyama et al., 2016; Dai et al., 2007; Grant et al., 2007; Poole et al., 2013; White et al., 2016) While Formulation B had a 50% decrease in PAR-2 levels compared to control, the levels of TRPV4 and TNFα were similar to control. Immunohistochemistry displayed diminished epidermal expression of PAR-2 in all treatment groups. (Gordon et al., 2018)

### *In Vitro* Comparison to Vinblastine and Taxol

A study compared isolated taspine and sap from *C. lechleri* to vinblastine and taxol against the cell cycle and α-tubulin frame of melanoma and human colorectal cancer cells. Outcome measurements included cell viability, flow cytometry, and microtubular immunofluorescence. *C. lechleri* sap at a concentration of 0.5 μg/mL and 10 μg/mL decreased the viability of melanoma and colorectal cells, respectively (both $P$<0.05). Tapsine at 0.6 μg/mL and 0.8 μg/mL suppressed 50% of melanoma and colorectal cancer cells. Taxol at less than 0.03

μg/mL suppressed both cancer cell lines, and vinblastine at 1 μg/mL suppressed melanoma and <0.01 μg/mL suppressed colorectal cells (all $P<0.05$).

A second study measuring viability 24 hours later also displayed a significant difference in cell suppression favoring taxol and vinblastine over taspine and *C. lechleri* sap ($P<0.05$). Using microtubular immunofluorescence, the melanoma cytoskeletal structure was disrupted by *C. lechleri's* sap 1 μg/mL, *C. lechleri*'s taspine 0.5 μg/mL, taxol 0.01 μg/mL, and vinblastine 0.1 μg/mL. Of *C. lechleri's* two components, only the sap displayed melanoma cell cycle modulation in a dose-dependent fashion ($P<0.05$). Vinblastine and taxol displayed superior efficacy in cell cycle modulation ($P<0.05$). (Montopoli et al., 2012)

**Wound Healing**

For centuries, Amazonian tribes have used *C. lechleri* for cutaneous wound healing. (Jones, 2003) Taspine and lignin 3',4-*O*-dimethylcedrusin are the two components of *C. lechleri* that stimulate wound repair mechanisms (Table 1). (Chen et al., 1994; Desmarchelier et al., 1997; Vaisberg et al., 1989)

Twice daily application of 0.05 mL of 10% *C. lechleri* sap increased the rate of wound repair in mice by 31% ($P<0.05$). The underlying active component was discovered when 0.05 mL of 10% taspine hydrochloride solution applied every 12 hours reported a 58.2% increase in wound healing ($P<0.005$). Taspine also increases fibroblast migration. (Vaisberg et al., 1989) Topical application of 250 μg taspine in 0.1 mL dimethyl sulfoxide (DMSO) on a rat incision increased wound tensile strength by 26% at Day 5 ($P<0.005$) and 30% at Day 7 ($P<0.0001$) compared to control. Histopathology displayed increased mononuclear cell infiltrates on Days 5

and 7, but no fibroblasts. Day 12 displayed no difference in tensile strength. (Porras-Reyes et al., 1993)

To assess the proliferative effects of *C. lechleri* on endothelial cells, investigators exposed different phytochemicals to tagged thymidine in DNA. Gallocatechin, epigallocatechin, and procyanidin B-4 mildly stimulated cell proliferation, while 1,3,5-trimethoxybenzene and crude sap inhibited cell proliferation. (Chen et al., 1994; Phillipson, 1995) 4,3'-*O*-dimethylcedrusin did not result in endothelial cell proliferation, but did have protective properties when cells were starved. (Pieters et al., 1993)

Another *in vitro* study using an ethanol-based *C. lechleri* extract investigated the potential for wound healing properties on endothelial cells. *C. lechleri* 25 μg/mL and 5 μg/mL extract stimulated human vein endothelial cell proliferation similar to 30% human serum (positive control) compared to 5% human serum (negative control). *C. lechleri* 250 μg/mL extract was cytotoxic, and only the ethanol extracts were effective. Further phytochemical analysis using mass spectrometry and nuclear magnetic resonance uncovered 3',4-*O*-dimethylcedrusin or 4-O-methyldihydrodehydrodiconiferyl as the chief constituents in stimulating endothelial cells. To investigate whether 3',4-*O*-dimethylcedrusin causes endothelial proliferation or inhibition of cell degradation, the same study exposed 3',4-*O*-dimethylcedrusin into DNA and measured thymidine levels. While 3',4-*O*-dimethylcedrusin stimulated human vein endothelial cells, DNA evidence suggested it was through inhibition of cell proliferation, not stimulation, in a starvation medium. (Pieters et al., 1993)

A randomized, double-blind, placebo-controlled trial with 60 subjects with removed skin tags were randomized to apply twice daily *C. lechleri* ethanol extract cream or placebo. 18 subjects had one wound, 26 subjects had two wounds, and 16 subjects had three wounds totaling

100 wounds. Wounds were measured on Day 1, 3, 5, 7, 10, 14, and 20. There was no significant difference between wound size in each group before study initiation (*P*=0.946). Patients receiving *C. lechleri* extract displayed greater complete wound healing compared to placebo on Day 3 (31.06% vs 4.74% [*P*=0.0001]), Day 5 (63.77% vs 23.50% [*P*=0.0001]), Day 7 (77.8% vs 43.9% [*P*=0.0001]), Day 10 (89.14% vs 61.95% [*P*=0.0001]), and Day 14 (95.73% vs 78.10% [*P*=0.0001]). (Namjoyan et al., 2016)

**Antibacterial Properties**

2, 4, 6-trimethoxyphenol, 1, 3, 5-trimethoxybenzene, crolechinic acid, and korberins A and B of *C. lechleri* all contain antimicrobial properties (Table 1). (Chen et al., 1994) The two phenolic and diterpene phytochemicals, 1,3,5-trimethoxybenzene and 2,4,6-trimethoxyphenol from *C. lechleri* were assessed for antibacterial properties. Both molecules possessed 30 times greater minimum inhibition amount (both $IA_{min}$= 0.0003μg) against *B. subtilis* than penicillin and chloramphenicol. 2,4,6-trimethoxyphenol and 1,3,5-trimethoxybenzene also displayed an $IA_{min}$ of 1.0 and 0.04μg against *E. coli*. The diterpenoid crolechinic acid displayed an $IA_{min}$ of 1.0 and 0.2μg against *E. coli* and *B. subtilis*. Korberins A and B reported an $IA_{min}$ of 0.04 and 0.05μg against *B. subtilis.* (Chen et al., 1994; Phillipson, 1995) Another study mixing undiluted *C. lechleri* and *C. palanostigma*'s sap reported 100% lethality against *E. coli*, while the mixed sap diluted at 1:10 reported 90% lethality against *E. coli*. (Miller et al., 2000)

A second in vitro study measured the antibacterial properties of *C. lechleri* against 36 strains of bacteria. Efficacy was defined as the minimal concentration (mg/mL) of plant extract to prevent bacterial growth in the growth medium, also known as minimal inhibitory concentration (MIC). *C. lechleri* displayed MIC in every bacterial strain (Table 2). Of the 40

Amazonian plants investigated, *C. lechleri* displayed a MIC ≤0.03 mg/mL in one or more strains. (Roumy et al., 2015)



**Antifungal Properties**

The antifungal properties of *C. lechleri* were tested in vitro against common dermatophytes *Trichophyton tonsurans, Trichophyton mentagrophytes, Trichophyton rubrum, Microsporum canis,* and *Epidermophyton floccossum*. Extracts of *C. urucurana* and a griseofulvin control were tested using a disk diffusion method against the five fungal strains. Efficacy was measured by the diameter of the inhibition zone around the disk after 8 days and minimal inhibitory concentration (MIC), defined as the lowest concentration to produce no visible growth after incubation. To investigate which concentration of *C. urucurana* extract was efficacious, a measure of its growth inhibition zone (GIZ) was tested. *C. urucurana* 3mg per disk displayed a GIZ of 25.6 ± 0.4 mm against *T. rubrum*, 21.8 ± 0.5 mm against *T. mentagrophytes*, 26.9 ± 1.3 mm against *T. tonsurans*, 23.5 ± 0.3 mm against *M. canis*, and 23.4 ± 0.8 mm against *E. floccossum*. Griseofulvin 6μg per disk displayed a GIZ of 34.0 ± 1.3 mm against *T. rubrum*, 25.2 ± 1.4 mm against *T. mentagrophytes*, 28.8 ± 3.2 mm against *T. tonsurans*, 26.5 ± 2.6 mm against *M. canis*, and 27.5 ± 1.4 mm against *E. floccossum* (Table 2). The MIC of *C. lechleri* for each fungus was 2.5mg/mL except for *T. tonsurans* which reported 1.25mg/mL. (Gurgel et al., 2005)

**Antiviral Properties**

*C. lechleri'*s antiviral properties were first revealed in a screening test against cytomegalovirus and other microorganisms. (Macrae, Hudson, & Towers, 1988) Since then,

multiple *in vitro* studies reported activity against influenza, parainfluenza, herpes simplex virus (HSV) I and II, hepatitis A, and B. (Chen et al., 1994; *Desarrollando Nuestra Diversidad Biocultural: "Sangre de Grado" y el Reto de su Produccion Sustentable en el Peru.* , 1999; Sidwell, Huffman, Moscon, & Warren, 1994). SP-303 is an isolated proanthrocyanidin mixture of *C. lechleri* consisting of (-)-epigallocatechin, (+)-gallocatechin, (+)-catechin, and (-)-epicatechin. (Ubillas et al., 1994) SP-303 demonstrated *in vitro* activity against HSV-1, HSV-2, acyclovir-resistant HSV strain, and thymidine kinase deficient HSV strain. (Barnard, Smee, Huffman, Meyerson, & Sidwell, 1993; Safrin S, 1993) Evidence suggests SP-303 may act at the membrane level. (Barnard et al., 1993; Ubillas et al., 1994)

A randomized, multicenter, double-blind, placebo-controlled Phase II study in 45 subjects with acquired immune deficiency syndrome (AIDS) and recurrent genital herpes were randomized to receive topical SP-303 or placebo. At Day 21, 50% of SP-303 group and 19% of placebo group were culture negative ($P$=0.06). 41% of subjects in the SP-303 group and 14% of placebo group reported complete healing of ulcers ($P$=0.053). Due to loss to follow-up, intent-to-treat analysis was insignificant ($P$=0.077). (Orozco-Topete et al., 1997)

**Insect Bites**

Ten insect control workers received both encoded 1% *C. lechleri* balm (Zangrado Bug Bite Balm, Rainforest Phytoceuticals, LLC) and placebo balm as needed for 3 months. Fire ant bites were the most common affliction in all subjects. Subjects preferred *C. lechleri* balm over placebo to treat ($P$<0.001), edema ($P$<0.01), pain ($P$<0.05), discomfort ($P$<0.05), and erythema ($P$<0.05). Average relief time of active balm was 2 minutes. (Miller et al., 2001)

**Efficacy on Striae**

Striae distensae is a stubborn aesthetic condition typically located on the abdomen, breast, thigh and lumbosacral regions. Given the antioxidative, anti-inflammatory, and wound healing properties of *C.* lechleri, a nonrandomized control study evaluated a cream consisting of *C. lechleri* resin extract and seed oil from *Punica granatum,* which has scavenging anti-oxidant and anti-inflammatory properties. A total of 10 women with striae albae and 10 women without white striae distensae were instructed to apply the cream once daily for 6 weeks. Outcome was evaluated by dermal and epidermal changes recorded with an ultrasound machine. The striae group had a 14.85% increase in dermal thickness, 30.32% increase in hydration, and 9.75% increase in elasticity from baseline ($P$<0.0001). The non-striae distensae group had a 15.86% increase of dermal thickness, 38.40% increase in hydration, and 5.86% increase in elasticity from baseline ($P$<0.0001). Subjects in the striae distensae group subjectively felt their stretch marks were less defined and depressed. (Bogdan, Iurian, Tomuta, & Moldovan, 2017)

**Neurogenic Inflammation**

To investigate how *C. lechleri* modulates neurogenic inflammation in rats, intradermal injections of PAR2-activating peptide (PAR2-AP) and prostaglandin $E_2$ ($PGE_2$) were used to stimulate edema and a hyperalgesic state, defined as a shortened withdrawal period to heat. Application of *C. lechleri* 1% balm (Zangrado Bug Bite Balm, Rainforest Phytoceuticals, LLC) 20 minutes before intradermal injection of PAR2-AP reduced edema by 50% compared to placebo ($P$<0.01). Pretreatment with *C. lechleri* balm on PAR2-AP-injected paws maintained a baseline withdrawal period to heat, preventing hyperalgesia. *C. lechleri* balm did not increase withdrawal period to heat in rats without PAR2-AP, disputing an anesthetic effect. *C. lechleri*

balm pretreatment maintained baseline withdrawal time, while placebo withdrawal time decreased in paws injected with $PGE_2$ ($P$<0.05). (Miller et al., 2001)



**Adverse Effects**

Ingestion of crude extracts or tea (sap steeped with water) formulation of *C. lechleri* may cause mild nausea, bitter taste, or diarrhea. There are no contraindications or drug interactions reported. (Orozco-Topete et al., 1997; Williams, 2001) Phase II *C. lechleri* ointment for HSV-2 subjects reported a burning sensation in 2 subjects receiving *C. lechleri* and 1 subject receiving placebo. (Orozco-Topete et al., 1997)

**Discussion**

Dragon's Blood is a common name for multiple plant species across the world, including *Dracaena draco* in the Canary Islands, the Arabic *D. cinnabari*, *Daemonorops draco* in Malaya, and *Pterocarpus draco* in Guyana. Although they all bleed a red resin, the genus and species are different. (Emboden, 1974; Jones, 2003) This review focuses on Dragon's Blood of *C. lechleri* from South America.

The vasoconstrictive properties on rat vascular smooth muscle suggests a possible therapy in the topical treatment of erythematotelangiectatic rosacea and other vascular cutaneous pathologies. Although further investigations failed to discover an underlying mechanism of action, *C. lechleri* presents a potential option in managing vascular skin lesions. (Froldi et al., 2009)

*C. lechleri*'s clinical impact in chronic wound care may prevent prolonged wound healing by influencing the inflammatory, proliferative, and maturation phase though anti-inflammation,

anti-oxidation, increasing collagen synthesis, wound contraction, and fibroblast migration. (Chen et al., 1994; De Marino et al., 2008; Desmarchelier et al., 1997; Gordon et al., 2018; Gupta et al., 2008; Lopes, Saffi, Echeverrigaray, Henriques, & Salvador, 2004; McGibbon, 2006; Namjoyan et al., 2016; Pieters et al., 1995; Porras-Reyes et al., 1993; Vaisberg et al., 1989) Together with *C. lechleri's* antimicrobial and sap's occlusive protection, *C. lechleri* may provide an alternative therapy to chronic wound care. (McGibbon, 2006; Phillipson, 1995)

PAR-A2 stimulates edema and hyperalgesia by sensory afferent nerves and $PGE_2$ stimulates hyperalgesia by raising sensitivity to pain in sensory afferent nerves. *C. lechleri* suppresses sensory afferent nerves by preventing hyperalgesia induced by PAR-A2 and $PGE_2$. Its swift action in minutes postulates a lipophilic aspect that penetrates the skin barrier. *C. lechleri* may be an alternative to capsaicin in diseases such as zoster. *C. lechleri* may alleviate post-herpetic neuralgia caused by neural inflammation and TRPV1 activation by PAR-A2 suppression and sensory nerve inhibition. (Baron, Binder, & Wasner, 2010; Hadley et al., 2016; Woolf & Max, 2001)

Although *C. lechleri* displayed antimicrobial, antifungal, and antiviral activity, existing efficacious agents limit Dragon Blood's clinical implication in dermatology. (Gurgel et al., 2005; Orozco-Topete et al., 1997; Roumy et al., 2015) Its spectrum of phytochemicals offers further exploration for its future implications. The Amazonian rainforest is a biodiverse garden of medicinal plants with a promising influence in future treatments.

**Conclusion**

Dragon's Blood from *C. lechleri* is a red sap that possesses antimicrobial, antifungal, anti-inflammatory, and anti-oxidant properties in preclinical studies and wound healing and

antiviral qualities in clinical studies. Increased research in medicinal plants offers insights for future therapeutic options in dermatology.



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**Table 1.** Phytochemicals in *C. lechleri*

| **Phytochemical** | **Medicinal Activity** |
|---|---|

| | |
|---|---|
| Alkaloid Taspine | Classical complement inhibition<br>Cancer cell suppression<br>Wound healing |
| Catechin | Antiviral |
| Crolechinic acid | Antimicrobial |
| Epicatechin | Antiviral |
| Epigallocatechin | Stimulated endothelial cell proliferation<br>Antifungal<br>Antiviral |
| Flavonoids | Classical complement inhibition |
| Gallocatechin | Stimulated endothelial cell proliferation<br>Antifungal<br>Antiviral |
| Korberins A and B | Antimicrobial |
| Lignin 3',4-*O*-dimethylcedrusin | Wound healing<br>Protect endothelial cell death |
| Procyanidin B-4 | Stimulated endothelial cell proliferation |
| Quercitrin | Classical complement inhibition |
| Phenols | Anti-oxidant |
| 1,3,5-trimethoxybenzene | Inhibit endothelial cell proliferation<br>Antimicrobial |
| 2, 4, 6-trimethoxyphenol | Antimicrobial |

(16, 22, 25-28, 40-43, 62)

**Table 2**: Minimal Inhibitory Concentration of Bacterial Strains in *C. lechleri*

| Bacterial Strain | Minimal Inhibitory Concentration<br><br>Present |
|---|---|
| *Citrobacter freundii* | + |
| *C. freundii*; Cephalosporin Resistant | + |
| *C. freundii*; TEM3 | + |
| *E. coli* | + |
| *E. coli*; Penicillin Resistant | + |
| *E. coli*; Penicillin and Fluoroquinolone Resistant | + |
| *Klebsiella pneumonia*; Penicillin Resistant | + |
| *Salmonella* spp. Penicillin Resistant | + |
| *Pseudomonas aeruginosa* | + |
| *Acinetobacter baumanii*; multi-resistant | + |
| *Staphylococcus aureus* | + |
| *S. aureus*; methicillin and kanamycin resistant | + |
| *S. epidermidis* | + |
| Enterococcus spp.; aminoglycoside resistant | + |
| Enterococcus spp.; erythromycin and clindamycin resistant | + |
| Enterococcus faecalis; vancomycin susceptible | + |
| *Corynebacterium striatum* | + |
| *Candida albicans* | + |
| *Mycobacterium smegmatis* | + |

(44)