

*Technical Report*

# Significance of Undecylenic Acid in CanXida Remove (Formula RMV)

*Undecylenic acid is a dedicated antifungal agent in Canxida remove formulation which has antifungal properties including anti-biofilm properties, fungistatic effect, and fungicidal effect. It is specifically effective against Candida albicans.*

## Contents

Executive Summary	1
1 Introduction	2
2 Antifungal Properties of Undecylenic Acid	3
2.1. Anti-Biofilm Properties	3
2.2. Fungistatic Effect	4
2.3. Fungicidal Effect	5
3. Biosafety Profile	5
4. Effective Targets	8
5. Role Undecylenic Acid in CanXida Remove (Formula RMV)	8
6. Conclusion	8
7. References	10

## Executive Summary

Undecylenic acid is a dedicated antifungal agent that is specifically effective against *Candida albicans* and *trichophyton* fungal pathogens. It is highly effective in disseminating biofilms which are necessary for virulent activity of many pathogenic fungal species. It arrests fungal growth and reproduction as a fungistatic agent by inhibiting the activity of functional proteins and enzymes. It also has a fungicidal effect (killing the fungi) by changing the plasma membrane composition and interfering with lipid metabolism. It can effectively penetrate inside the fungal cells and alter its biochemical features leading to cell death and pathogen elimination.

CaXida Remove (formula RMV) contains undecylenic acid considering its excellent antifungal profile. Its inclusion as an active ingredient in the CanXida Remove formulation is also backed by the fact that it is naturally produced in the human body as an antifungal agent. It is part of many over the counter antifungal products and food supplements which are FDA approved. It is registered as a food-grade fatty acid in the Food Database and the Food and Agriculture Organization of America. It gives CanXida formulation antifungal properties to eliminate fungal pathogens by obliterating biofilms of drug-resistant fungi. It also provides CanXida to arrest candida growth and development by countering its transformation from yeast to pathogenic filamentous hyphae.

## 1. Introduction

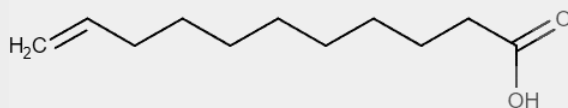
Undecylenic acid is an unsaturated fatty acid with antifungal properties. Its ability to counter fungal infections was recognized in the 1940s while treating military personnel for fungal infections. It is safe, inexpensive, and without any side effects.

Undecylenic acid is a good antifungal for treating mucosal fungal infections. The mucosa is the protective surface that covers many organs such internal lining of the gastrointestinal tract, genitals, and respiratory tract. Mucosal surfaces are the primary barrier for infectious pathogens and also provide a favorable environment for beneficial microbiota. However, a few

pathogens including candida often target mucosal surfaces and make biofilms which not only destroy the normal defensive barrier and microbiome but also increase the risk of systemic infections. Undecylenic acid has been extensively studied to counter mucosal fungal infections especially caused by different candida species (Gonçalves et al 2012).

It is also effective against a wide range of fungal infections of toenails and skin. It is generally regarded as fungistatic (stopping the growth of fungus) and arrests the spread of pathogenic colonies. It is also effective in destabilizing biofilms. Biofilms are protective coatings of pathogens against body defenses as well as medicines and play a

### Undecylenic Acid



Generic Name:	Undecylenic Acid
Drug Bank Accession Number:	DB11117
Drug Bank Status:	Approved
Drug Category:	Small Molecule, Fatty Acid
FDA UNII:	K3D86KJ24N
CAS No.	112-38-9
Other Names:	10-undecenoic acid, Undecenoic acid
Chemical Formula:	C <sub>11</sub> H <sub>20</sub> O <sub>2</sub>
Molecular Weight:	184.27 g/mol
Melting Point:	23 °C

significant role in imparting drug-resistant characteristics to the pathogens. Its ability to destabilize biofilms makes it effective against drug-resistant pathogens as well.

It can be found as over the counter (OTC) section of pharmacies as a food supplement and as an antifungal agent. It has been approved by the FDA with UNII K3D86KJ24N. It is a registered drug in the Drug Bank database with accession number DB11117.

## 2. Antifungal Properties of

### Undecylenic Acid

Undecylenic acid is naturally released by the body on the skin as a defense barrier against fungal growth. It is part of many OTC antifungal products and nutraceuticals. It is a widely used antifungal due to cheaper production and relatively no side effects. Its antifungal properties are at par with many commercial antifungal agents with antifungal efficacy of up to 90%.

#### 2.1. Anti-Biofilm Properties

Microbial fungi, often called yeast, often produce biofilms and make a thriving colony which ensures growth and reproduction. In addition, these biofilms also act as a barrier against host defense mechanisms such as gastric acidic pH in the stomach, or action of corrosive bile in the intestine. It also keeps immune cells at bay as it prevents antigenic detection by mimicking some parts of the mucus layer of the gut. This allows pathogens to grow undetected for prolonged periods causing serious damage to the host. These pathogenic colonies of fungi are also hard to eliminate using anti-fungal medicine. Biofilm formation is an important virulence factor for fungal pathogens.

Undecylenic acid has extensively been studied for its activity against biofilm-forming yeasts, including candida species. It is also effective against Epidermophyton species as well as Trichophyton. *Candida albicans* are the most common fungal pathogens of healthy humans in general while it can be life-threatening for people with weakened immune systems. Drug-resistant species of Candida are also an unavoidable reality. It leads to infection relapses and intake of higher doses of anti-fungal drugs resulting in unwanted side effects such as liver damage.

Shi and colleagues from the Georgetown University Medical Center, Washington DC, USA, reported that undecylenic acid interferes with biofilm formation in the candida colonies (Shi et al 2016). It inhibits cell proliferation, hyphal development, and filament formation leading to poorly organized biofilms. A poor biofilm exposes yeast cell membranes to higher osmotic pressures producing deformed and dysfunctional cells. It also renders yeast cells with inadequate nutrient supply and fat metabolism due to rough cell surface. The poorly developed candida cells lose fundamental virulence properties and cannot maintain infectious colonies.

Another property of undecylenic acid is the inhibition of proteins called SAPs which are involved in the synthesis of biofilms. Undecylenic acid inhibits the activity of these proteins, and its efficiency is comparable to commercial antifungal agents (Mores et al 2011). SAP proteins are also involved in the degradation of host proteins such as collagen, keratin, and vimentin which allows candida to break free and enter into the circulatory system where it can cause infections anywhere in the body. SAPs also maintain

cell-to-cell adhesion and support colonies of pathogens. Inhibition of SAPs by undecylenic acid significantly reduces the virulence efficiency of candida.

## 2.2. Fungistatic Effect

*Candida albicans* is often referred to as an opportunistic pathogen. It lives as a non-pathogenic oval yeast form but turns into a filamentous infectious pathogen when conditions are favorable for pathogenesis, or the immune system has been weakened. This property of candida to change its form from yeast to filamentous form (hyphae) is called morphogenesis. Morphogenesis provides virulence during early infectious stages. Undecylenic acid is an efficient inhibitor of morphogenesis and dismantles early colonies of pathogenic candida and arrests its growth. This effect is called the fungistatic effect.

Undecylenic acid is an effective fungistatic agent even in small quantities (1 millimolar). Cell proliferation and invasiveness of candida growth often lead to pathogenic colonies during the early stages of infection. Undecylenic acid provides a fungistatic effect by checking on cell proliferation, morphogenesis, and lipid metabolism. The fungistatic effect provides enough time for the immune system to combat pathogenic colonies of candida.

*Candida* pathogenic colonies start by adhesion of fungal cells to the host cells. ALS (agglutinin-like sequence) proteins are glycoproteins that promote adhesion to the cell surfaces. Besides adhesion, these also facilitate nutrient acquisition. Undecylenic acid downregulates these proteins and hence impairs cell adhesion (Shi et al 2016). Another protein that is inhibited by undecylenic acid is hyphal wall protein

(HWP1) which is crucial for hyphae formation and adhesion to the cell surfaces for pathogenic activity. The impaired activity of these adhesion proteins leads to arrested growth and reproduction activity. More importantly, undecylenic acid inhibition of these proteins comes from reduced expression of genes involved in the synthesis of these proteins. This provides more effective control over these proteins and provides irreversible inhibition of fungal growth and reproduction.

Morphogenesis (change in structure from non-pathogenic oval yeast to pathogenic filamentous hyphae) is a biochemical process regulated by enzymes and proteins. It is crucial for the pathogenic activity of candida and is triggered by changes in pH, nutrition, etc. Undecylenic acid directly affects morphological changes and reduces the hyphal cells of candida yeast. It causes direct disintegration of cell membranes in elongated cells of yeast leading to cell death. McLain and colleagues from the Medical University of South Carolina, Charleston, USA published a report demonstrating that undecylenic acid discourages morphogenesis of *Candida albicans* in the oral cavity by inhibiting lipid metabolism and changing the pH of candida cells (McLain et al 2000). Undecylenic acid is a fatty acid that makes it easy to penetrate fungal cells. When it enters the cells, it carries protons with it rendering the pH acidic. As enzymes are sensitive to pH changes, this results in cell death or slow metabolic rate not sufficient for rapid growth or cell division.

The fungistatic concentrations of undecylenic acid for *Trichophyton interdigitale*, *T. purpureum*, *T. violaceum*, *Microsporum audouini*, *Epidermophyton inguinale* [*E.floccosum*], *Torula* sp., *Candida*

*albicans*, *Aspergillus niger*, and *Penicillium notatum* were 0.004, 0.0015, 0.0025, 0.0025, 0.0025, 0.015, 0.007, 0.05, and 0.045 per cent., respectively.

### 2.3. Fungicidal Effect

The fungistatic effect refers to the direct killing of fungal cells (also known as apoptosis). The fungistatic effect is possible with minute quantities, however, the Canxida Remove formulation contains enough quantity of undecylenic acid per dose that it can induce the fungistatic and fungicidal effect. The fungicidal effect of undecylenic acid is due to its ability to alter plasma membrane fluidity and interfere with fungal metabolism along with previously mentioned fungistatic and anti-biofilm activities.

Metabolic inhibition by undecylenic acid involves a reduction in lipase activity. As the plasma membrane of fungi differs from humans in lipids and cholesterol, it effectively hinders plasma membrane synthesis in the fungi without any side effects on cells in the human body. Its inhibition is related to reducing lipase and esterase enzyme activity up to 70% so that it cannot produce new lipids necessary for cell maintenance and growth (Brito-Madurro et al 2005). The cell membrane composition is imperative for typical nutrient acquisition. Changes in the plasma membrane produce inactive cells without virulent capability.

Besides, it also inhibits the synthesis of essential lipids such as triglycerides, phospholipids, and sterols esters which play various structural and functional roles within fungal cells. These biochemical inhibitory activities combined with reduced biofilms and fungistatic effect act synergistically to create a fungicidal effect when undecylenic

acid is in slightly higher quantities. The undecylenic concentrations for fungicidal effect are 0.15% or above (Wyss et al 1945).

### 3. Biosafety Profile

Undecylenic is not a foreign substance for the human body. It is naturally present in the skin and excreted on the skin surface through apocrine sweat glands. It is part of skin defense molecules against microbes and acts as an antifungal. As it can stop fungal growth in very small quantities, it is effective against some of common pathogenic fungal species including candida and dermatophytes.

The Food and Agriculture Organization of America categorizes undecylenic acid as a flavoring agent and can be taken through oral route (JECFA No. 331). It has been approved since 1998 as a food flavoring agent and as an antifungal since 1945. It is relatively non-toxic in amounts present in supplements and nutraceuticals. It is registered as a food-grade fatty acid in the Food Database (Primary ID = FDB011844). It is safe to use in quantities at 2.5 g per kg (in rats). The human metabolome database (ID HMDB0033724) also recognizes these quantities as a reference for human use.

In addition, undecylenic acid has been used as a food supplement and as a over the counter antifungal for the past few decades. There are quite a few FDA-registered labels of supplements for undecylenic acid. Drug Bank database shows more than 250 over the counter medical products containing undecylenic acid in pure form or in combination with other compounds (Tables 1 & 2).

**Table 1:** Over the counter antifungal formulations containing only undecylenic acid as an active ingredient. Source: Drug Bank

Name	Strength	Labeler	Marketing Start
Anti-Fungal Pen CVS	25 g/100mL	CVS Health	9/15/2016
Antifungal	4.8 mg/36.97mL	Blaine Labs Inc.	4/1/2016
Athletes Foot	14.77 mg/59.148mL	Blaine Labs Inc.	4/1/2016
Botanimedix OnychoRX Antifungal Nail Gel	0.2508 kg/1kg	Cosco International, Inc.	1/1/2020
CRYSTAL FLUSH Maximum Strength Anti-Fungal Formula	25 g/100mL	Triple Point Group, LLC	9/17/2020
CVS Maximum Strength Anti-Fungal Pen 25%	25 mg/100mL	Denison Pharmaceuticals, LLC	1/9/2019
CVS Pharmacy Anti-fungal Pen Maximum Strength	250 mg/1mL	CVS Pharmacy	12/27/2012
CVS Pharmacy Maximum Strength Antifungal Liquid with Aloe and Vitamin E	0.25 g/1L	CVS Health	5/1/2010
Dermaced Maximum Strength Anti-Fungal	250 mg/1mL	Dermaced, LLC	6/29/2017
Derman	10 g/100g	Compania Internacional de Comercio, S.A. de C.V.	8/27/2012
DERMAN	20.360 g	Compania Internacional De Comercio, S.A.P.I. De C.V.	1/1/1999
Derman Antifungal	100 mg/1mL	Compania Internacional De Comercio, S.A.P.I De C.V.	10/21/2013
DESENEX	22.060 g	Dinafarma, S.A. De C.V.	1/17/2011



**Table 2:** List of FDA registered labelled supplements containing undecylenic acid.  
Source: NIH, office of dietary supplements. DSLD: dietary supplement labels database.

DSLD ID	Product Name	Brand Name	Date Entered into DSLD	Market Status
24248	NF Formulas Phytofuge	Integrative Therapeutics	2013-07-25	On Market
178166	Undecylenic Acid	Swanson Premium Brand	2018-06-25	On Market
182318	Formula SF722	Thorne	2018-10-25	On Market
183542	A.C. Formula II	Pure Encapsulations	2018-11-21	On Market
233375	Candida Cleanse	Balance One	2020-08-23	On Market
246472	Phytostan	Integrative Therapeutics	2021-03-25	On Market
248752	YeastMD Premium	Premium Certified	2021-06-23	On Market
280414	Undecylenic Acid	Thorne	2023-01-23	On Market
34001	KandidaPlex	Vitamin Research Products	2014-06-25	On Market
219854	Fungal Fighter 400 mg	Dr. Clark Store	2020-05-22	On Market
281266	Undecylex	Klaire Labs	2023-01-23	On Market

## 4. Effective Targets

Undecylenic acid is a dedicated antifungal agent which encounters most commonly found fungal pathogens including candida species and other fungal pathogens which often target mucosal surfaces. Some of the extensively studied targets of undecylenic acid are given in Table 3.

***Candida albicans***: Candida is a common yeast and an opportunistic pathogen. It changes its morphology and biochemical features into a virulent strain when conditions are favorable to do so. Damage to the outer protective layer (epidermis), nutritional deficiencies and imbalances, microbiome disturbances, and immune system malfunctions are some of the triggers that encourage candida to turn into a pathogenic form. Undecylenic acid encounters it by disintegrating biofilms, disrupting cell functions, and inhibiting its conversion to a pathogenic form.

***Trichophyton species***: Trichophyton species include *Trichophyton interdigitale* and *Trichophyton rubrum* which are common pathogens of nails and skin, respectively. These fungal species are highly drug-resistant (32% of infections) and are hard to treat. A combination therapy is often recommended. Undecylenic acid shows considerable antifungal activity for these fungal pathogens.

***Serratia marcescens***: *Serratia marcescens* is an opportunistic pathogenic bacteria found in the urinary tract and gastrointestinal tract. Recent studies have shown that undecylenic acid inhibits the growth of this bacteria (Rossie et al. 2021).

## 5. Role of Undecylenic Acid in CanXida Remove (Formula RMV).

Undecylenic acid acts as an exclusive antifungal agent in the CanXida Remove formulation. It works with other antifungal agents such as caprylic acid which is another medium-chain fatty acid.

The unique properties of undecylenic acid for candida yeast make it a compulsory ingredient in any formulation that is designed to counter candida infections. Its antifungal properties for candida species come from the natural selection of antifungal agents during the course of human evolution. As it is still being produced in human skin and sweat to counter candida and other related pathogenic fungi, its effectiveness against these pathogens is unquestionably verified by nature itself. CanXida Remove formulation contains undecylenic acid in combination with other antimicrobials to combat a wide range of pathogens including fungi. Undecylenic is also effective against genital infections of candida and can supplement natural defense mechanisms. Its ability to counter biofilms provides enhanced efficacy to the CanXida Remove formulation for optimal antifungal activity.

## 6. Conclusion

In conclusion, undecylenic acid is a natural antifungal agent produced by the skin glands to combat fungal infections, especially *Candida albicans*. CanXida Remove formulation contains undecylenic acid as an exclusive antifungal agent that works in synergy with other ingredients to combat fungal pathogens. It provides CanXida Remove with efficacy to completely remove fungal pathogens.

**Table 3:** Effectiv targets of undecylenic acid and its antifungal mechanism. Corresponding dosages are also provided. Source Rossie et al (2021).

Microorganism	Observed effect	Working doses
<i>Trichophyton rubrum</i>	Inhibited production of exocellular lipase and keratinase	27.5 µg per ml
	Inhibited phospholipid metabolism	50 µg per ml
	Affected fungal metabolism and pre-mRNA processing regulatory events	17.5 µg per ml
<i>Trichophyton interdigitale</i>	Inhibited growth in response to UDA and carbon source for both wild-type and UDAr strains	Dose-dependent
	Affected gene-expression profile	50 µg per ml
<i>Serratia marcescens</i>	Impaired biofilm formation	ranging from 20 to 160 µg/ml
<i>Candida albicans</i>		2 µg per ml
		QA (50–800 µg mL <sup>-1</sup> ) in combination with UDA (5–80 µg per ml )
<i>Aspergillus nidulans</i>	Decreased extracellular lipase activity	200 µg per ml
	Impaired conidia germination	0 to 300 µg per ml
<i>Saccharomyces cerevisiae</i>	Inhibited growth	0.5 mM, 1 mM, or 2 mM
<i>Umbelopsis isabellina</i>	Inhibited biosynthesis of long-chain fatty acids	Dose-dependent

## 7. References

- Brito-Madurro, A. G., Cuadros-Orellana, S., Madurro, J. M., Martinez-Rossi, N. M., & Rossi, A. (2005). Effect of undecanoic acid on the production of esterases and lipases by *Aspergillus nidulans*. *Annals of Microbiology*, *55*(4), 291.
- Gonçalves, L. M., Del Bel Cury, A. A., Sartoratto, A., Garcia Rehder, V. L., & Silva, W. J. (2012). Effects of undecylenic acid released from denture liner on *Candida* biofilms. *Journal of Dental Research*, *91*(10), 985-989.
- McLain, N., Ascanio, R., Baker, C., Strohaber, R. A., & Dolan, J. W. (2000). Undecylenic acid inhibits morphogenesis of *Candida albicans*. *Antimicrobial agents and chemotherapy*, *44*(10), 2873-2875.
- Mores, A. U., Souza, R. D., Cavalca, L., de Paula e Carvalho, A., Gursky, L. C., Rosa, R. T., ... & Rosa, E. A. R. (2011). Enhancement of Secretory Aspartyl Protease production in biofilms of *Candida albicans* exposed to sub-inhibitory concentrations of fluconazole. *Mycoses*, *54*(3), 195-201.
- Rossi, A., Martins, M. P., Bitencourt, T. A., Peres, N. T., Rocha, C. H., Rocha, F. M., ... & Martinez-Rossi, N. M. (2021). Reassessing the use of undecanoic acid as a therapeutic strategy for treating fungal infections. *Mycopathologia*, *186*, 327-340.
- Shi, D., Zhao, Y., Yan, H., Fu, H., Shen, Y., Lu, G., ... & Liu, W. (2016). Antifungal effects of undecylenic acid on the biofilm formation of *Candida albicans*. *International journal of clinical pharmacology and therapeutics*, *54*(5), 343.
- Wyss, O., Ludwig, B. J., & Joiner, R. R. (1945). The fungistatic and fungicidal action of fatty acids and related compounds. *Arch. Biochem.*, *7*(3).