



# **Ionic Contraviral Topical Therapy in Multiple Resistant to Treatment Verruca Vulgaris**

*Thesis*

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بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

قَالَ

لَسْبَحَانَكَ لَا يَعْلَمُ لَنَا  
إِلَّا مَا عَلَّمْتَنَا إِنَّكَ أَنْتَ  
الْعَلِيمُ الْعَظِيمُ

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## Dedication

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## *List of Abbreviations*

Abb.	Full term
5-FU .....	5-flurouracil
AK.....	Actinic keratosis
ALA.....	Aminolaevulinic acid
APCs .....	Antigen presenting cells
BCG .....	Bacillus Calmette-Guérin
BIP .....	Bleomycin –induced pneumonitis
BP .....	Bowenoid papulosis
CIN .....	Cervical intraepithelial neoplasia
CIS .....	Carcinoma in situ
CO2 .....	Carbon Dioxide
DC .....	Dendritic Cell
DCP.....	Diphenocyprone
DNA .....	Deoxyribonucleic acid
DNCB .....	Dinitrochlorobenzene
DPCP .....	Diphenylcyclopropenone
E.....	Early region
EBV.....	Epstein Barr virus
ECT.....	Electrochemotherapy
Er:YAG .....	Erbium: Yttrium/Aluminum/Garnet
EV .....	Epidermodysplasia verruciformis
FEH .....	Focal epithelial hyperplasia
HIV .....	Human immunodeficiency virus
HPV .....	Human papilloma virus
IFNS .....	Interferons
IL.....	Interleukin
KS .....	Kaposi sarcoma

## *List of Abbreviations Cont...*

Abb.	Full term
LCR.....	Long control region
LCs.....	Langerhans Cells
LN2 .....	Liquid nitrogen
MC .....	Molluscum contagiosum
MRNA.....	Messenger Ribonucleic acid
Nd:YAG.....	Neodymium: Yttrium/ Aluminum/ Garnet
NEH.....	Neutrophilic Eccrine Hidradenitis
OHL .....	Oral hairy leukoplakia
PDL.....	Pulsed Dye Laser
PDT.....	Photodynamic Therapy
PIN.....	penile intraepithelial neoplasia
PPD.....	purified protein derivative
PPECs.....	Palmoplantar epidermal cysts
RRP .....	Recurrent respiratory papillomatosis
SA.....	Salicylic Acid
SADBE.....	Squaric acid dibutyl ester
SCC .....	Squamous cell carcinoma
TB .....	Tuberculosis
TCA.....	Trichloroacetic acid
TNF- $\alpha$ .....	Tumor necrosis factor alpha
VAIN.....	Vaginal intraepithelial neoplasia
VIN .....	Vulvar intraepithelial neoplasia
WHIM .....	Warts, Hypogammaglobulinemia, Infections and Myelokathxis

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## INTRODUCTION

Common warts are small, rough skin growths that occur most often on fingers or hands. Common warts often feature a pattern of tiny black dots, which are small clotted blood vessels (*Goldstein et al., 2015*).

Children and young adults are more likely to develop common warts. Common warts usually disappear on their own, but many people choose to remove them because they find them bothersome or embarrassing (*Ferri et al., 2015*).

The virus usually spreads through breaks in the skin such as a hangnail or a scrape. Biting nails also can cause warts to spread on fingertips and around nails. Each person's immune system responds to the HPV virus differently, so not everyone who comes in contact with HPV develops warts (*Kwok et al., 2015*).

Viral warts are caused by the human papilloma virus (HPV), with the most prevalent HPV genotypes being HPV 1, HPV 2, HPV 27 and HPV 57 (*Bruggink et al., 2012*).

Efficacy rates of current treatment options, for example cryotherapy, salicylic acid and monochloroacetic acid, are low (cryotherapy 39%; salicylic acid 24%; monochloroacetic acid 46%), and cure rates are dependent on HPV type (*Berger et al., 2010*).

As efficacy rates of current treatment options are not optimal, side-effects are common, and recurrences often occur. There is an unmet need to develop new therapeutics for common warts. It has been shown that DNA viruses such as HPV rely on  $K^+$  influx for replication, this could provide a therapeutic option (*Hartley et al., 2013*).

Both digoxin and furosemide inhibit the  $K^+$  influx by interacting with cell membrane ion co-transporters ( $Na^+/K^+$ -ATPase and  $Na^+-K^+-2Cl^-$  co-transporter-1, respectively). It can therefore be hypothesized that these two compounds in a topical formulation may be valuable in the treatment of HPV-induced warts. This new approach, called Ionic Contra-Viral Therapy (ICVT), has already shown inhibitory effects on DNA replication *in vitro*, with the strongest effect when digoxin and furosemide were combined and an observed response in common warts *in vivo* (*Arch Virol et al., 2010*).

A study was done to evaluate systemic exposure, safety and tolerability of a combination of furosemide and digoxin after repeated topical application in subjects with common warts that were otherwise healthy (*Gussekloo et al., 2015*).

In addition, exploratory pharmacodynamic effects on wart morphology and HPV load were included (*Assen et al., 2017*).

## **AIM OF THE WORK**

**T**o verify the efficacy, safety and tolerability of a topical formula composed of furosemide and digoxin in the treatment of multiple resistant common warts.

## REVIEW OF LITERATURE

### Warts

Warts are benign proliferations of the skin and mucosa that result from infection with HPV (*Vali and Ferdowsi, 2007*). They are usually classified according to their clinical location and morphology into three categories: cutaneous, anogenital, and extracutaneous papillomaviruses infections (*Filippone, 2014*).

Warts have their own blood and nerve supply. Commonly, pinpoint black areas are visible on the warts surface. These black dots are the wart's superficial network of capillaries, but may only be visible after the top layer of callus tissue is removed (*Laube, 2014*).

### Prevalence of warts

Although the prevalence of common warts in general population is unknown, warts occur in approximately 5% to 20% of children and young adults (*Wiley et al., 2012*).

Approximately 23% of warts regress spontaneously within 2 months, 30% within 3 months and 65% to 78% within 2 years (*Sterling et al., 2011*). Previously infected patients have a higher risk for development of new warts than those never infected (*Allen and Siegfried, 2009*).