Scientific Research Publishing

International Journal of Clinical Medicine, 2024, 15, 68-87
https://www.scirp.org/journal/ijcm
ISSN Online: 2158-2882
ISSN Print: 2158-284X

The Value of Excipients and the Required Understanding of the Biological System in Product Development: An Impactful Example of Curaderm, a Topical Skin Cancer Treatment

Tania Robyn Chase, Kai Elliot Cham, Bill Elliot Cham

Australasian Medical Research, Port Vila, Republic of Vanuatu
Email: bill.cham@gmail.com

How to cite this paper: Chase, T.R., Cham, K.E. and Cham, B.E. (2024) The Value of Excipients and the Required Understanding of the Biological System in Product Development: An Impactful Example of Curaderm, a Topical Skin Cancer Treatment. *International Journal of Clinical Medicine*, **15**, 68-87.
https://doi.org/10.4236/ijcm.2024.152005

Received: January 26, 2024
Accepted: February 25, 2024
Published: February 28, 2024

Abstract

The incidences of nonmelanoma skin cancer are increasing worldwide, and the ongoing war on its treatment necessitates the development of effective and non-invasive methods. Through basic and clinical research, non-invasive treatments like Curaderm have been developed, leading to improved quality of life for patients. Excipients, previously considered inactive ingredients, play a crucial role in enhancing the performance of topical formulations. The development of Curaderm emphasizes the importance of understanding the interactions between active ingredients, excipients, and the biological system to create effective and affordable pharmaceutical formulations. The systematic approach taken in the development of Curaderm, starting from the observation of the anticancer activity of natural solasodine glycosides and progressing through toxicological and efficacy studies in cell culture, animals, and humans, has provided insights into the pharmacokinetics and pharmacodynamics of solasodine glycosides. It is crucial to determine these pharmacological parameters within the skin's biological system for maximal effectiveness and cost-effectiveness of a skin cancer treatment. Curaderm, as a topical treatment for nonmelanoma skin cancer, offers benefits beyond those obtained from other topical treatments, providing hope for improved quality of life for patients.

Keywords

Curaderm, BEC, Solasodine Glycosides, Solamargine, Apoptosis, Skin Cancer, Actinic Keratosis, Keratoacanthoma, Basal Cell Carcinoma, Squamous Cell Carcinoma

1. Introduction

In 1755 Jacques Daviel, a French surgeon was the first to describe the surgical removal of a skin cancer then known as a rodent ulcer, now known as a basal cell carcinoma (BCC). Since then, surgical resection has been the mainstay course of treatment for skin neoplasms.

Initially, surgical resection of skin cancers encountered high rates of recurrences of the treated skin cancers. As time progressed, the technology of surgical resection, including Mohs surgery of skin cancers improved, resulting in lower rates of recurrences.

Similar transitional phenomena occurred with cosmetic outcomes after surgical interventions. Presently, skin grafting or flaps are often necessary to improve the cosmetic outcome resulting in costly procedures.

Nevertheless, over the decades, surgical resections have improved the morbidity and mortality of people with skin cancers. However, remaining disadvantages of surgery include the incomplete resection of the tumor growth, poor postoperative quality of life, limited cosmetic results, scarring, and costliness.

2. Rising Rates of Skin Cancer Requires New Treatment Methods

The escalating rates of nonmelanoma skin cancer (NMSC) worldwide necessitate the development of non-invasive treatment methods. Curaderm represents one such approach, offering an alternative to surgery, radiation therapy, chemotherapy, immunotherapy, and targeted therapy.

2.1. Curaderm

This communication discusses the development of Curaderm, a topical formulation used for the treatment of NMSCs. Curaderm utilizes active anticancer components called BEC derived from Solanum plant extracts.

2.1.1. BEC

BEC Denotes the Initials of the Inventor of the Glycoalkaloid Technology and is a mixture of plant glycoalkaloids from the Solanaceae family. The Solanaceae, also known as the potato or deadly nightshade family is one of humankind's most utilized and important plant families. It contains some of the worlds most important food plants, such as the potato, tomato, and eggplant. BEC glycoalkaloids, specifically solasodine glycosides, are known for their biological activity and have been studied for their potential therapeutic effects in skin cancers.

2.1.2. Aglycone Solasodine

Solasodine, the aglycone of solasodine glycosides, is employed as a hormone precursor of corticosteroids, anabolic steroids, and antifertility drugs.

Solasodine has two chemical names Spirosol-5-en-3 beta-ol and Solasod-5-en-3 beta-ol. It also goes by other synonyms such as Solancarpidine, Solanidine-s, and Purapuridine. **Figure 1** shows the chemical structure of solasodine.

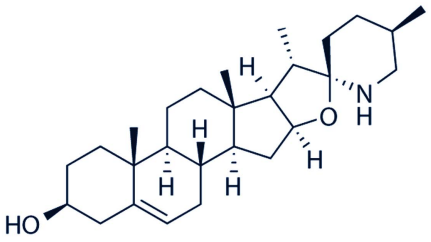


Figure 1. Chemical structure of Solasodine. Formal Name is (3beta, 22alpha, 25R)-spirosol-5-en-3-ol. Molecular Formula is C27H43NO2. Molecular mass is 414 [1].

2.1.3. Sugar Moieties of BEC Glycosides

In Solanum plants, solasodine is found as BEC, sugar(s) bound solasodine, consisting of monoglycosides, diglycosides, triglycosides, and tetraglycosides. The sugar moieties of the BEC glycosides are shown in **Table 1**.

2.2. Anticancer Effects of BEC

BEC is a natural drug that was first reported in 1987 to have remarkable anticancer effects in cell culture, animals, and humans [1] [2] [3]. The initial findings sparked interest and led to further investigations into the potential of BEC and its individual components as antineoplastic (anti-cancer) agents.

Over the years, numerous studies and experiments have been conducted to explore the efficacy and mechanisms of BEC in combating cancer. These investigations have demonstrated promising results, positioning BEC as a first-in-class natural drug with significant potential in the field of oncology [4]-[26].

The development of BEC as an antineoplastic agent has paved the way for a new family of drugs.

Figure 2 illustrates the rapid advancements and progress made in the understanding and utilization of BEC and its individual components for cancer treatment.

This communication discusses the development of Curaderm, a topical formulation used for the treatment of NMSCs. Curaderm utilizes the active anticancer BEC. The goal of this development was to create a treatment that is highly effective, safe, affordable, and provides excellent cosmetic outcomes.

When developing a pharmaceutical formulation, several factors must be considered to ensure its effectiveness, safety, reliability, and affordability. The formulation process consists of multiple stages, and the final product's quality is determined by the interactions among these stages. This includes the active pharmaceutical ingredient (API), valuable excipients (inactive ingredients), their interactions with the biological system, and the manufacturing procedure. Each component plays a crucial role in creating a beneficial medicinal product.

Curaderm's active ingredient, BEC, has been found to be effective against skin cancers at very low concentrations. However, to optimize its efficacy, it requires the cooperation of other essential ingredients present in the formulation. These ingredients work synergistically to enhance the overall effectiveness of the treatment.

Table 1. Sugar moiety of solasodine glycosides known as BEC

Glycosides	Sugar Moiety
γ-solamargine	Glucose $\beta(1 \rightarrow 3)$ – R
β_1-solamargine	Rhamnose $\alpha(1 \rightarrow 4)$ – Glucose $\beta(1 \rightarrow 3)$ – R
β_2-solamargine	Rhamnose $\alpha(1 \rightarrow 2)$ – Glucose $\beta(1 \rightarrow 3)$ – R
α-solamargine	Rhamnose $\alpha(1 \rightarrow 2)$ Rhamnose $\alpha(1 \rightarrow 4)$ > Glucose $\beta(1 \rightarrow 3)$ – R
γ-solasonine	Galactose $\beta(1 \rightarrow 3)$ – R
β_1-solasonine	Glucose $\beta(1 \rightarrow 3)$ – Galactose $\beta(1 \rightarrow 3)$ – R
β_2-solasonine	Rhamnose $\alpha(1 \rightarrow 2)$ – Galactose $\beta(1 \rightarrow 3)$ – R
α-solasonine	Rhamnose $\alpha(1 \rightarrow 2)$ Glucose $\beta(1 \rightarrow 3)$ > Galactose $\beta(1 \rightarrow 3)$ – R

R = Solasodine. BEC is composed of approximately 33% α-solamargine, 33% α-solasonine and 34% of β_1, β_2, γ solamargine and β_1, β_2, γ solasonine.

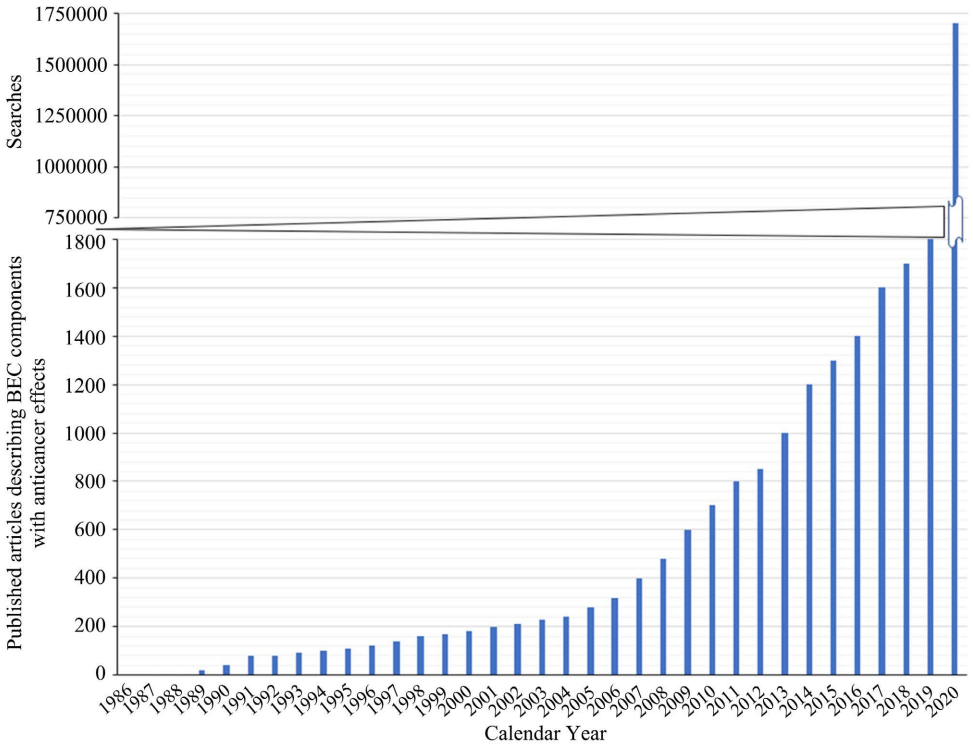


Figure 2. Importance of BEC and its components.

Since it was first reported that BEC had anticancer properties in 1987, there has been considerable interest in BEC and its components. In 2020, more than 1800 independently published articles describing the anticancer properties have been documented. In addition, there has been enormous scientific interest in BEC and its components. In the year 2020, more than 1.7 million searches of

these compounds have been reported.

In addition to efficacy, the formulation of Curaderm also focuses on safety. By carefully selecting excipients and ensuring their compatibility with the active ingredient and the biological system, the formulation aims to minimize potential adverse effects and maximize patient safety.

Cosmetic outcomes are other important considerations when treating skin cancers. Surgical interventions often require additional procedures like skin grafting or flaps to improve cosmetic results, which can be costly. Curaderm, on the other hand, aims to provide excellent cosmetic outcomes without the need for invasive procedures, thus reducing the stress and financial burden on patients.

Moreover, the escalating rates of NMSC worldwide necessitate the development of non-invasive treatment methods. Curaderm represents one such approach, offering an alternative to surgery, radiation therapy, chemotherapy, immunotherapy, and targeted therapy.

By highlighting the development of Curaderm and its unique properties, this communication emphasizes the importance of considering the biological and pharmacological systems together with the interactions between active ingredients and excipients in the formulation of pharmaceutical products. It also underscores the need for treatments that are effective, safe, affordable, and provide favourable cosmetic outcomes, ultimately improving the quality of life for individuals with skin cancer.

The mechanism of action of BEC in Curaderm involves its binding to specific mutant receptors located on the surface of cancer cells. This binding triggers a series of events within the cancer cell, leading to apoptosis or programmed cell death. The specificity of this mode of action makes it an attractive option for treating skin cancer, as it can selectively target cancer cells while minimizing damage to healthy cells.

Skin cancer is a significant global health issue, with increasing incidence, morbidity, and mortality rates. The two main types of skin cancer are melanoma, arising from dysfunctional melanocytes, and NMSC, which includes BCC and squamous cell carcinoma (SCC). In 2012, the United States reported 5.4 million new cases of NMSCs.

Skin cancer not only poses a burden on individuals' health but also has substantial psychosocial effects and requires significant investment in its treatment. The annual cost of treating nonmelanoma skin cancer in the U.S.A. is estimated at $4.8 billion. Conventional therapies for skin cancer have both advantages and drawbacks, and currently available commercial treatments do not adequately address the requirements for controlling this disease.

3. Results

The development and implementation of Curaderm as a treatment for skin cancer involves several steps. Firstly, extensive preclinical research and laboratory studies are conducted to understand the safety and efficacy of BEC in combating

skin cancer. These studies evaluate the effects of BEC on cancer cell lines and animal models.

Once preclinical studies demonstrate promising results, clinical trials are conducted to assess the effectiveness of Curaderm in human subjects. These trials involve recruiting patients with skin cancer and administering Curaderm as a topical cream according to specific protocols. The patients' response to treatment is monitored, and the safety and efficacy of Curaderm are evaluated.

If the results from clinical trials are positive, regulatory authorities review the data to determine whether Curaderm can be approved for commercial use. This involves assessing the product's safety, effectiveness, and quality. If approved, Curaderm can be made available to healthcare professionals and patients for the treatment of skin cancer.

It is important to note that the information provided here is a general overview and not a comprehensive guide to the conceptualization and implementation of Curaderm. The actual development process involves additional steps, such as formulation optimization, manufacturing scale-up, and post-marketing surveillance. Additionally, the specific regulations and requirements may vary depending on the country or region where Curaderm is being developed and marketed.

Clinical trials have been conducted to explore the use of BEC in the treatment of various types of skin cancers, including BCC and SCC. BEC exerts its effects by selectively targeting cancer cells while sparing healthy cells. It induces apoptosis (the process of programmed cell death) in cancer cells and has demonstrated anti-tumor activity in preclinical studies.

Clinical trials are conducted to assess the potential benefits and risks associated with a particular intervention or treatment approach.

Phase 1: Clinical Trial

The Phase I clinical trial investigated the use of varying concentrations of BEC (BEC01) in a cetomacrogol cream formulation for the treatment of actinic keratosis (AK), keratoacanthomas (KA), BCC, and SCC. The trial aimed to determine the tolerability, safety, and dose levels of BEC and evaluate its anticancer activity.

The study found that the BEC cream formulations at dose escalation concentrations ranging from 1% to 50% were well tolerated by the patients. No significant clinical or histological reactions were observed in normal skin treated with the BEC formulation. This indicates that the cream formulation was safe for use on the skin [2] [10].

Subjective observations suggested that a concentration of 10% BEC in the cream formulation was effective in treating the skin lesions. Therefore, a controlled clinical trial was conducted using a formulation called BEC02, which contained 10% BEC and 10% dimethyl sulfoxide (DMSO) in a cetomacrogol cream base [10].

In the controlled trial, over 90% of the NMSC lesions were successfully re-

moved by BEC therapy. The diagnoses of the lesions before and after treatment were confirmed through histological studies of standard biopsy specimens. The BEC treatment induced apoptosis (programmed cell death) in the skin tumor cells, similar to the effects observed in cell culture studies with BEC-treated cancer cells.

Some patients experienced transient itching and burning around the treated lesions, but these side effects were generally mild. Importantly, there were no recurrences of the treated lesions during the follow-up period of at least three years. This suggests that the BEC cream formulation was effective in permanently removing the lesions and preventing their recurrence.

Overall, the Phase I trial demonstrated that BEC cream formulations, particularly the 10% BEC formulation (BEC02), were well-tolerated and showed anticancer activity in patients with AK, KA, BCC, and SCC. The results supported further investigation and potential use of BEC as a treatment option for these skin lesions.

Phase I studies showed that a concentration of 10% BEC (10,000 mg BEC/L cream) was highly effective in regressing skin cancers. However, this concentration was deemed too costly for practical use as a skin cancer treatment. It was also observed that the efficacy of BEC depended not only on the quantity used but also on the composition of the formulation.

Concurrently with the phase 1 clinical studies, it was established with in vitro cell culture studies that as little as 6 to 10 micrograms of BEC/mL (6 to 10 mg BEC/L) were able to kill cancer cells [22]-[28]. Similarly, experiments on mice with Sarcoma 180 showed that a concentration of 8 mg/kg body weight of BEC was able to cure the cancer [4] [9] [29] [30]. Toxicity studies at these concentrations of BEC demonstrated high safety profiles.

Considering these findings, it was hypothesized that the bioavailability of BEC played a significant role in its effectiveness against cancer cells. In an aqueous environment where BEC was in direct contact with cancer cells, such as in the peritoneal cavity or cell culture media, approximately 10 mg BEC/L was sufficient to kill cancer cells. This concentration was much lower than the concentration used to treat *in vivo* skin cancer in Phase I trials (100,000 mg BEC/L cream), indicating a stark contrast.

The difference in bioavailability was believed to be the reason for this contrast. When treating *in vivo* skin cancer, BEC had low bioavailability with anchored cancer cells, whereas in vitro cell culture studies and intraperitoneal aqueous conditions allowed for direct contact between BEC and "swimming" cancer cells, leading to higher effectiveness at lower concentrations.

Improving the bioavailability of anticancer agents in skin cancers poses several challenges due to the skin's natural barriers and the presence of tumor cells. Some strategies considered to enhance drug delivery and improve the efficacy of topical treatments were:

1) Penetration enhancers: Various penetration enhancers can be used to

overcome the barrier function of the stratum corneum. These substances can temporarily disrupt the lipid structure of the skin, allowing better penetration of drugs. Examples of penetration enhancers include surfactants, liposomes, and chemical permeation enhancers such as DMSO or ethanol. Care should be taken to ensure the safety and compatibility of these enhancers with the specific anticancer agent being used.

2) Nanocarriers: Utilizing nanotechnology-based delivery systems, such as liposomes, nanoparticles, or micelles, can enhance drug penetration into the skin and improve its bioavailability. These carriers can encapsulate the drug and facilitate its transport through the skin layers, providing controlled and targeted release at the tumor site.

3) Physical methods: Techniques like iontophoresis, sonophoresis, and microneedles can enhance drug permeation through the skin. Iontophoresis involves the use of an electric current to drive charged drug molecules across the skin. Sonophoresis uses low-frequency ultrasound to disrupt the stratum corneum and enhance drug delivery. Microneedles create temporary channels in the skin, allowing drugs to pass through more easily.

4) Chemical modifications: Modifying the drug molecule itself can improve its permeability through the skin. Pro-drug approaches involve modifying the drug structure to enhance its lipophilicity or decrease its molecular size, making it easier to penetrate the skin. This modification can be reversed by enzymatic or chemical processes at the target site, releasing the active drug.

5) Combination therapies: Using a combination of different strategies can synergistically improve drug delivery to skin cancer cells. For example, combining penetration enhancers with nanocarriers or physical methods can further enhance drug penetration and target tumor cells more effectively.

6) Targeted therapies: Developing drugs specifically designed to target the molecular characteristics of skin cancer cells can improve their bioavailability and minimize adverse effects on healthy skin. Targeting tumor-specific receptors, enzymes, or signalling pathways can enhance drug uptake by cancer cells and increase therapeutic efficacy.

It is important to note that the development and application of these strategies should be supported by rigorous scientific research and preclinical/clinical studies to ensure their safety and effectiveness in treating skin cancers.

With BEC, it was decided to concentrate on penetration enhancers and targeted therapies for the effective treatment of skin cancers.

CONCEPTUALISATION TO IMPLEMENTATION OF CURADERM WITH EMPHASIS ON MAXIMAL BIOAVAILABILITY OF BEC WITH SKIN CANCER CELLS

Challenges with skin barriers

The outermost epidermal layers of the skin, constituting the stratum corneum, are the main cutaneous barriers and influence the uptake of anticancer agents into target cells, consequently affecting the response to topical treatments. The

stratum corneum in the human skin is composed of approximately 15 - 30 corneocyte cell layers that provide a thickness of approximately 10 - 20 micrometers. Several types of lipids such as phospholipids and cholesterols together with metabolic triglycerides and non-esterified fatty acids form a complex network with corneocytes that can absorb limited amounts of water and control the penetration of various sizes and types of molecules through the skin.

In general, skin cancer has a thicker keratin layer with increased lipid content resulting in an increased barrier to the passive transport of macromolecules.

In addition, with skin cancer, tumor cells can extend throughout the epidermis and dermis. Another biological barrier is created by the tumor itself affecting deeper located skin cancer cells. The interstitial space between the tumor cells becomes dense and is composed of collagen, proteins, elastic fibres, and glycosaminoglycans resulting in increased barriers for the transport of drugs to their target.

Cohesion of epidermal cells in the skin depends on desmosomes, which contain many specialised protein complexes, including desmogleins. Desmoglein is a catherin-like adhesion molecule to maintain tissue integrity and facilitates cell-cell communication.

Cadherin is a transmembrane protein that binds with other cadherins to form junctions known as desmosomes between cells. Desmogleins are expressed everywhere in the skin epidermis, but mainly they are expressed in the superficial upper layers of the skin epidermis. These desmogleins play a key role in the formation of desmosomes that join cells to one another.

Overcoming the Barrier

Excipients were at one time considered to be "inactive" ingredients but now they are understood to be able to serve as "key determinants of dosage form performance". In the context of a cream composition, an excipient is a natural or synthetic substance formulated alongside the active ingredient of the medication to give a therapeutic enhancement on the active ingredient in the final dosage form, such as facilitating drug interaction with targeted diseased state, solubility and stability of the medication over the expected shelf life.

Salicylic acid is a lipid-soluble organic acid that extracts desmosomal proteins including desmogleins resulting in the loss of the cohesion of epidermal cells. Being a lipophilic agent, salicylic acid also removes intercellular lipids such as ceramides, which are linked covalently to the cornified envelope surrounding epithelial cells. Thus, salicylic acid is known to affect the skin by loosening and breaking apart desmosomes (attachments between cells in the outer layers of the skin). In this context, salicylic acid is a desmolytic agent, because its mechanism of action works by disrupting cellular junctions. Salicylic acid can lead to alterations in the underlying dermal tissue without directly wounding the skin. Depending on the concentration, salicylic acid also dissolves the keratin plugs and regulates the skin cells.

Consequently, the combined effects of salicylic acid result in loosening of skin cells, including skin cancer cells, and are akin to cells in cell culture media whe-

reby the bioavailability of BEC to such exposed skin cells are vastly improved.

Similarly, but by a different mechanism of action, urea breaks hydrogen bonds among biopolymers leading to reversible structural destabilization of epidermal proteins claudin, desmoglein, filaggrin and proteases of the intercellular matrix of the cells of the skin. Urea exerts its effect directly, by binding to the proteins, or indirectly, by altering the solvent environment. Urea binds to, and stabilizes, the denatured state, thereby favouring unfolding of the protein. This improves the bioavailability of BEC with skin cells, approaching cell culture and intraperitoneal conditions.

Salicylic acid and urea at appropriate concentrations can overcome biological barriers and can improve targeted drug delivery to the tumor sites. This enables the use of lower doses of BEC with increased treatment efficacy and decreased number and/or severity of side effects.

Salicylic acid also has another beneficial effect, its presence in the formulation results in acidic aqueous conditions with low pH that enhances the solubility of BEC. In accordance with the Quality-by-Design (QbD) approach, it was predictable that the presence of salicylic acid and urea in a topical cream formulation would pose certain challenges such as stability of the cream [31] and that this had to be addressed.

To address the challenges posed by the presence of salicylic acid and urea in a topical cream formulation, several strategies were employed:

1) Selection of appropriate excipients: Excipients play a crucial role in stabilizing the formulation and maintaining its physical and chemical properties. Careful selection of excipients that are compatible with salicylic acid and urea is essential. Excipients such as emulsifiers, thickeners, and stabilizers can help improve the stability of the cream.

2) pH adjustment: As described, salicylic acid contributes to the acidic aqueous conditions of the formulation. The pH of the cream should be carefully controlled and optimized to enhance the solubility of the active ingredient (BEC) without compromising the stability of the formulation. Buffering agents can be added to maintain the desired pH range.

3) Formulation design: The formulation was designed to ensure proper dispersion and distribution of salicylic acid, urea, and other ingredients throughout the cream. Homogeneous distribution of the active ingredients helped to ensure consistent performance and efficacy of the product.

4) Compatibility testing: Compatibility studies were conducted to assess the physical and chemical interactions between salicylic acid, urea, and other formulation components. This helped to identify any potential incompatibilities or stability issues that arose during storage or use.

5) Stability testing: The stability of the cream formulation was evaluated under various storage conditions, including temperature, light, and humidity. Accelerated stability studies provided insights into the long-term stability of the cream and helped determine its shelf life.

6) Packaging considerations: The selection of appropriate packaging materials is crucial to prevent interactions between the formulation and the container. Packaging should be resistant to moisture, light, and air to maintain the stability of the cream over its intended shelf life.

7) Manufacturing process optimization: The manufacturing process was optimized to ensure uniform mixing and dispersion of ingredients. Proper temperature control and mixing techniques were employed to minimize degradation or loss of active ingredients.

8) Quality control measures: Regular quality control testing was performed to monitor the stability and consistency of the cream formulation. This included testing for pH, viscosity, active ingredient content, and microbial testing.

By implementing these strategies, the challenges associated with the presence of salicylic acid and urea in a topical cream formulation were effectively addressed.

Natural Drug Products Limitations

Limitations with natural products include variation in preparation methods and therefore also chemical composition, dosage determination and adjustment, and the suitable route of administration. These limitations were addressed and solved by studying the anticancer contribution of the individual components of BEC.

It was previously reported that the contribution of anticancer activities in BEC is 86% for solamargine, 9% for solasonine and 5% for monoglycosides and diglycosides of solasodine. Solamargine-quantified BEC with measured IC_{50} (effective doses) values in various human cancer cell lines are identical to pure solamargine. It was subsequently reported that topical cream formulations with identical excipients containing 0.02 mg purified isolated solamargine per 1 mL cream had comparable therapeutic outcomes as 0.05 mg BEC (containing 0.02 mg solamargine) per 1 mL cream [32].

Exploration of Low Concentrations of BEC with Salicylic Acid and Urea

A wide variety of components in cream formulations were investigated to determine their suitability for improving the bioavailability of BEC with skin cancer cells. Ultimately, it was possible to prepare a cream formulation Curaderm that contained set concentrations of salicylic acid, urea and BEC to treat skin cancer effectively and safely with very low concentrations of BEC.

Phase II: Clinical Trials

Phase II clinical trials were undertaken with the designated Curaderm topical cream formulation for the treatment of premalignant and malignant skin cancers in humans. These Phase II clinical trials showed that Curaderm was effective for the treatment of AKs, KAs, BCCs and SCCs of the skin in humans [10].

However, during these clinical trials two flaws in the cream formulation were identified:

- Heath instability of the cream formulation integrity even at room temperature; and
- Degradation of the glycoalkaloids in the cream formulation.

These flaws were further explored and were eventually overcome by adding xanthan gum and lactic acid to the cream formulation. Xanthan gum stabilized the emulsion of the cream and lactic acid added to the keratolytic action and prevented the degradation of the glycoalkaloids in the cream formulation [31]. This novel topical cream formulation with appropriate excipients resulted in a substantially stable, efficacious cream formulation with a shelf life of 4 years when used clinically [3]. With this in place, embarkation on Phase III clinical trials ensued.

Phase III Clinical Trials

After addressing the flaws in the cream formulation and achieving stability, Phase III clinical trials were initiated to further evaluate the efficacy and safety of the Curaderm topical cream formulation for the treatment of premalignant and malignant skin cancers in humans. These trials involved a larger number of participants and were conducted in multiple centres to gather more comprehensive data.

The Phase III clinical trials followed rigorous protocols and included a control group for comparison. Participants with various types of skin cancers, such as AKs, KAs, BCCs, and SCCs, were recruited. The cream formulation was applied topically to the affected areas according to the specified dosage and administration instructions.

During the Phase III trials, the efficacy of Curaderm was evaluated based on various factors, including tumor regression, reduction in lesion size, prevention of tumor recurrence, and overall patient satisfaction. Safety assessments were also conducted to monitor for any adverse effects or complications associated with the cream formulation.

The results of the Phase III clinical trials provided crucial evidence regarding the effectiveness of Curaderm for the treatment of skin cancers. The cream formulation demonstrated very high efficacy in inducing tumor regression, reducing lesion size, and preventing tumor recurrence. Additionally, the safety profile of the cream formulation was found to be acceptable, with minimal adverse effects reported.

These trials involved both uncontrolled and controlled double-blind, randomized, vehicle-controlled, parallel group, multicentre studies [33]-[42] showing highly statistical significant efficacy and safety profiles.

The studies demonstrated that Curaderm was effective against skin cancer cells while sparing normal cells. Normal cells were observed to replace the dead cancer cells during the process of killing residual cancer cells. These findings align with previous research conducted in cell cultures, animal models, and human studies, which highlighted the important specificity properties of BEC glycoalkaloids in targeting cancer cells without harming healthy cells.

The Phase III studies concluded that an 8-week treatment with Curaderm resulted in an overall efficacy rate of 78% compared to 25% in the placebo vehicle group ($P < 0.001$). The treatment was well-accepted by patients and had a low incidence of local adverse events, with no systemic side effects reported. Impor-

tantly, Curaderm was found to be effective against various types of BCCs, including superficial, nodular, and infiltrative morpheaform variants.

Researchers reported that Curaderm pharmacotherapy outperformed other treatments, including surgery, and in difficult-to-treat locations of skin cancers. Clinical studies focussing on safety, efficacy, compliance, and cosmetic outcomes in different population groups have also been conducted [43]-[49].

These investigations revealed that treatment with Curaderm for 4 weeks resulted in a success rate of approximately 40%, while over 90% of patients with BCCs were successfully treated within 12 weeks. The duration of treatment varied depending on the size and location of the skin cancer. AK required days rather than weeks of Curaderm treatment for successful outcomes. For cutaneous SCCs, the required treatment time ranged from 5 to 16 weeks. The treatment procedure was well-tolerated, with good compliance and robust efficacy, safety, and cosmetic outcomes [50]-[55].

Recurrence rates of Curaderm-treated skin cancers were found to be very low [26] [27].

In addition, amazingly, in cases where skin cancers recurred after treatment with other modalities such as radiation, photodynamic therapy, laser therapy, or cryosurgery, and were subsequently treated with Curaderm resulted in a 52% success rate. This is important because failed treatments with such modalities typically require surgical interventions, which often have poor cosmetic outcomes [50] [54] [56].

The Phase III trials demonstrated the wide-ranging efficacy of Curaderm in treating different histological types and depths of skin cancers, even in sensitive areas of the body. To this end, **Figures 3-6** show examples of Curaderm treated KA, AK, BCC, and SCC. Comparative studies with other existing treatments have established the practical use of Curaderm in dermatology. Follow-up studies conducted over five years on cases treated with Curaderm showed no recurrences.

Figures 3-6 show examples of Curaderm treated KA, AK, BCC, and SCC.

These observations with Curaderm therapy highlight the need for improved approaches in the treatment of skin cancers, specifically in enhancing the bioavailability of anti-cancer agents within cancer cells. While nanoparticle research has shown promise in *ex vivo* studies, its application *in vivo* for treating skin malignancies has been relatively unsuccessful [57] [58].

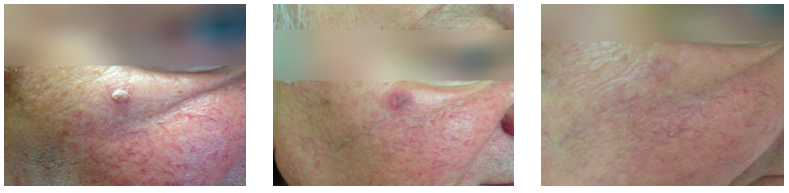
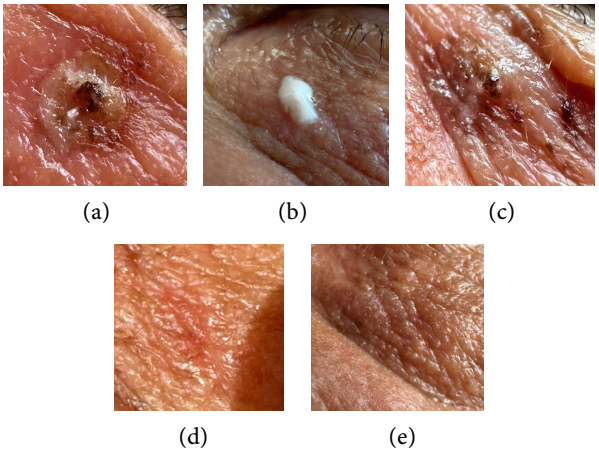


Figure 3. Keratoacanthoma of the face. The treatment was 7 days! The wound healed without the formation of scar tissue.



(a) (b) (c)

(d) (e)

Figure 4. An isolated pigmented AK (5 mm diameter) at zone 2 of the left orbital area before commencement of treatment (a), amount of Curaderm applied to AK (b), after 6 applications (end of treatment, EOT) of Curaderm, (c), 3 days after EOT (d), 14 days after EOT (e).

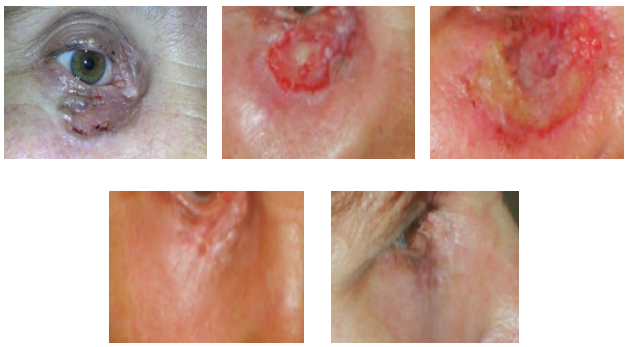
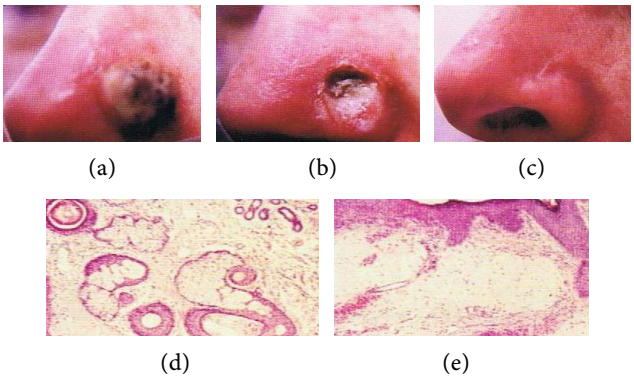


Figure 5. Scleroderma-like form of basalioma of the skin of the corner of the eye with a transition to the upper and lower eyelids. 3 weeks after the start of treatment, the true boundaries of the tumor were revealed. Curaderm treatment was 8 weeks. The tumor completely disappeared with minor tissue scarring.



(a) (b) (c)

(d) (e)

Figure 6. SCC on the nose of a patient before (a), during (b) and after Curaderm treatment (c). Curaderm was applied for 5 weeks. Note the depth of the cancer as cartilage was exposed during treatment. The clinical diagnosis was confirmed histologically by punch biopsy (d). After completion of the therapy histopathology determined that no residual cancer was present (e). Clinical assessment 5 years post treatment revealed that there was no recurrence.

4. Discussion

This communication introduces Curaderm, a treatment for skin cancer that has been developed by understanding the structure, mechanism of action, pharmacokinetics, pharmacodynamics, and toxicology of the medication. Curaderm contains low concentrations of naturally occurring BEC glycoalkaloids, which have demonstrated high bioavailability approaching the efficacy observed in anticancer cell culture studies. The formulation of Curaderm also incorporates desmosomal, stabilizing, and keratolytic agents to optimize the interaction and effectiveness of the low concentration of BEC.

The excipients in Curaderm reversibly denatures the epidermal proteins claudin, desmoglein, filaggrin and proteases and transiently enhance optimal bioavailability of BEC with cancer cells. To fully achieve the optimal conditions, two daily applications of Curaderm to the skin cancers are required followed by application of an occlusive dressing shown in Figure 7.

BEC in Curaderm is highly selective in targeting cancer cells and therefore has no significant side effects. However, the inclusion of desmosomal, stabilizing, and keratolytic agents in the formulation is necessary to achieve maximal effects in destroying all cancer cells. These agents, such as salicylic acid, lactic acid, and urea, have been found to cause transient side effects, including irritation, reddening, itching, pain, and burning sensations at the treatment area. These effects typically last only a few minutes after the application of Curaderm and are primarily attributed to the excipients present in the formulation [26] [27].

The economic burden of skin cancer is substantial, and in the U.S. alone, the annual costs during the period of 2016-2018 for skin cancer was $8.9 billion [59]. Controlling the cost of health care is a global concern. Attempts to avoid accelerating spending with limited outcomes should be encouraged

Curaderm is a topical treatment modality used for AK, a precancerous skin condition. Cost comparisons have indicated Curaderm's positive position in terms of affordability compared to traditional topical treatments for AKs [60]. No direct information of price structure is available for the treatments KA, BCC, and SCC for Curaderm compared with other procedures. Nevertheless, the cost benefits with Curaderm therapy compared with traditional therapies for skin cancer is expected to be even more affordable than was reported for AK.

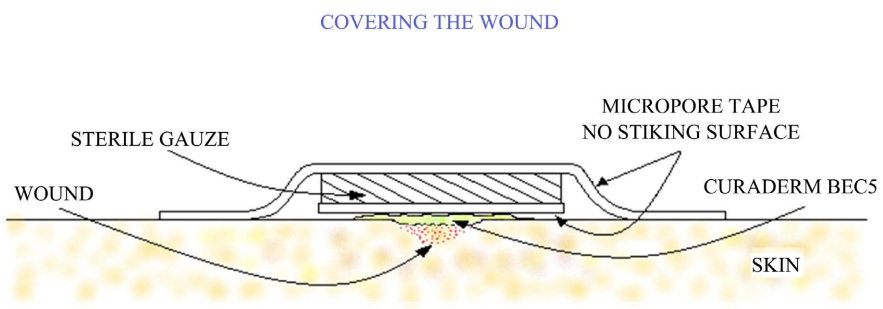


Figure 7. Occlusive dressing used after application of Curaderm to skin cancer lesions.

The historical content of the evolution of surgical removal of skin cancer, leading up to Mohs micrographic surgery, perceived to be the "gold standard" treatment of NMSC, has recently been challenged by Curaderm therapy [61]. Extensive exploration of the biochemical properties and mechanisms of BEC [26] [27] [36] [37] [38] [39] have provided a critical perspective and understanding of Curaderm's true potential and place in current medical practice [61].

5. Conclusions

In conclusion, the studies aimed to create a topical cream formulation, known as Curaderm that could address the needs of patients with skin cancer. The objectives included ensuring the safety and effectiveness of the cream, while also prioritizing factors such as excellent cosmesis, low cost, and user-friendliness.

The development of Curaderm serves as a testament to the significance of comprehending the interactions between active ingredients, excipients (additional substances added to a medication for various purposes), and the biological system. By understanding these dynamics, researchers were able to create a pharmaceutical formulation that is both effective in treating skin cancer and affordable for patients.

Author Contributions

All authors have contributed equally to this article.

Conflicts of Interest

Dr Cham holds patent rights on BEC technology.

References

[1] Cham, B.E. and Wilson, L. (1987) HPLC of Glycoalkaloids from *Solanum sodomaeum*. *Planta Medica*, **1**, 59-62. https://doi.org/10.1055/s-2006-962621

[2] Cham, B.E. (1988) Monograph BEC. *Drugs of the Future*, **13**, 714-716. https://doi.org/10.1358/dof.1988.013.08.63026

[3] Solbec Pharmaceuticals. https://en.wikipedia.org/wiki/Coramsine

[4] Cham, B.E. (2013) Inspired by Nature, Proven by Science. The New Generation Cancer Treatment That Causes Cancer Cells to Commit Suicide. 1st Edition, Colorite Graphics, Port Vila, 264 p.

[5] Cham, B.E. (2017) Solasodine, Solamargine and Mixtures of Solasodine Rhamnosides: Pathway to Expansive Clinical Anticancer Therapies. *International Journal Clinical Medicine*, **8**, 692-713. https://doi.org/10.4236/ijcm.2017.812064

[6] Millward, M., Powell, A., Tyson, S., Daly, P., Ferguson, R. and Carter, S. (2005) Phase 1 Trial of Coramsine (SBP002) in Patient with Advanced Solid Tumors. *Journal Clinical Oncology*, **23**, 3105. https://doi.org/10.1200/jco.2005.23.16_suppl.3105

[7] Chase, T., Cham, K.E. and Cham, B.E. (2020) Evaluation of Dermal Irritation and Skin Sensitization by Curaderm. *International Journal of Clinical Medicine*, **11**, 548-558. https://doi.org/10.4236/ijcm.2020.119047

[8] Daunter, B. and Cham, B.E. (1990) Solasodine Glycosides. *In Vitro* Preferential Cy-

totoxicity for Human Cancer Cells. *Cancer Letters*, **55**, 209-220. https://doi.org/10.1016/0304-3835(90)90121-D

[9] Cham, B.E., Gilliver, M. and Wilson, L. (1987) Antitumour Effects of Glycoalkaloids Isolated from *Solanum sodomaeum*. *Planta Medica*, **1**, 34-36. https://doi.org/10.1055/s-2006-962612

[10] Cham, B.E. and Meares, H.M. (1987) Glycoalkaloids from *Solanum sodomaeum L.* Are Effective in the Treatment of Skin Cancers in Man. *Cancer Letters*, **36**, 111-118. https://doi.org/10.1016/0304-3835(87)90081-4

[11] Cham, B.E., Daunter, B. and Evans, R. (1991) Topical Treatment of Malignant and Premalignant Skin Cancers by Very Low Concentrations of a Standard Mixture of Solasodine Glycosides. *Cancer Letters*, **59**, 183-192. https://doi.org/10.1016/0304-3835(91)90140-D

[12] Punjabi, S., Cook, I., Kersey, P., Marks, R., Finlay, A., Sharpe, G. and Cerio, R. (2000) A Double Blind, Multi-Centre Parallel Group Study of BEC-5 Cream in Basal Cell Carcinoma. *European Academy Dermatology Venereology*, **14**, 47-60.

[13] Cham, B.E. (2014) A Review of Solasodine Rhamnosides Therapy for In-Situ Squamous Cell Carcinoma on the Penis. *British Journal of Medicine and Medical Research*, **4**, 621-631. https://doi.org/10.9734/BJMMR/2014/4677

[14] Goldberg, L.H., Landau, J.M., Moody, M.N. and Vergilis-Kalner, I.J. (2011) Treatment of Bowen's Disease on the Penis with Low Concentrations of a Standard Mixture of Solasodine Glycosides and Liquid Nitrogen. *Dermatologic Surgery*, **37**, 858-861. https://doi.org/10.1111/j.1524-4725.2011.02014.x

[15] Lipscombe, R., Carter, S. and Ruane, M. (2005) Rhamnose Binding Protein. US Patent No. 6930171.

[16] Cham, B.E. (2007) Solasodine Rhamnosyl Glycosides Specifically Bind Cancer Cell Receptors and Induce Apoptosis and Necrosis. Treatment for Skin Cancer and Hope for Internal Cancers. *Research Journal Biological Sciences*, **2**, 503-514.

[17] Wang, Y., Gao. J., Gu, G., Li, G., Cui, C., Sun, B. and Long, H. (2007) *In Situ* Receptor Visualisation and Its Mediated Anticancer Activity for Solasodine Rhamnosides. *ChemBioChem*, **12**, 2418-2420. https://doi.org/10.1002/cbic.201100551

[18] An, W., Lai, H., Zhang, Y., Liu, M., Lin, X. and Cao, S. (2019) Apoptotic Pathway as the Therapeutic Target for Anticancer Traditional Chinese Medicines. *Frontiers in Pharmacology*, **10**, Article 758. https://doi.org/10.3389/fphar.2019.00758

[19] Li, X., Zhao, Y., Wu, W.K., Liu, S., Cui, M. and Lou, H. (2011) Solamargine Induces Apoptosis with p53 Transcription-Dependent and Transcription-Independent Pathways in Human Osteosarcoma U2OS Cells. *Life Sciences*, **88**, 314-321. https://doi.org/10.1016/j.lfs.2010.12.006

[20] Al Sinani, S.S., Eltayeb, E.A., Coomber, B.L. and Adham, S.A. (2016) Solamargine Triggers Cellular Necrosis Selectively in Different Types of Human Melanoma Cancer Cells through Extrinsic Lysosomal Mitochondrial Death Pathways. *Cancer Cell International*, **16**, 287-294. https://doi.org/10.1186/s12935-016-0287-4

[21] Zang, X., Yan, Z., Xu, T., An, Z., Chen, W., Wang, X., Huang, M. and Zhu, F. (2018) SM Derived from *Solanum nigrum* Induces Apoptosis of Human Cholangio Carcinoma QBC939 Cells. *Oncology Letters*, **15**, 6329-6335. https://doi.org/10.3892/ol.2018.8171

[22] Al Sinani, S.S.S. and Eltayeb, E.A. (2017) The Steroidal Glycoalkaloids Solamargine and Solasonine in Solanum Plants. *South Africa Journal Botany*, **112**, 253-269.

https://doi.org/10.1016/j.sajb.2017.06.002

[23] Kalalinia, F. and Korimi-Sani, I. (2017) Anticancer Properties of Solamargine: A Systematic Review. *Phytotherapy Research*, **31**, 858-870. https://doi.org/10.1002/ptr.5809

[24] Sani, I.K., Marashi, S.H. and Kalalinia, F. (2015) Solamargine Inhibits Migration and Invasion of Human Hepatocellular Carcinoma Cells through Down-Regulation of Matrix Metalloproteinases 2 and 9 Expression and Activity. *Toxicology in Vitro*, **29**, 893-900. https://doi.org/10.1016/j.tiv.2015.03.012

[25] Li, X., Zhao, Y., Liu, S., Cui, M. and Lou, H. (2011) Induction of Actin Disruption and Downregulation of P-Glycoprotein Expression of Solamargine in Multi-drug-Resistant K562/A02 Cells. *Clinical Medicine Journal*, **124**, 2038-2044. https://doi.org/10.3892/ol.2011.500

[26] Chase, T.R., Cham, K.E. and Cham, B.E. (2020) Curaderm, the Long-Awaited Breakthrough for Basal Cell Carcinoma. *International Journal of Clinical Medicine*, **11**, 59-604. https://doi.org/10.4236/ijcm.2020.1110050

[27] Cham, B.E. (2022) The Pharmacology of Curaderm in the Treatment of Basal Cell Carcinoma. *Clinical Medical Review and Case Reports*, **9**, Article 399. https://doi.org/10.23937/2378-3656/1410399

[28] Chang, L.C., Tsai, T.R., Wang, J.J., Lin, C.N. and Kuo, K.W. (1998) The Rhamnose Moiety of Solamargine Plays a Crucial Role in Triggering Cell Death by Apoptosis. *Biochemical and Biophysical Research Communications*, **242**, 21-25. https://doi.org/10.1006/bbrc.1997.7903

[29] Cham, B.E. (2020) Combination Treatment with BEC and Cisplatin Synergistically Augments Anticancer Activity and Results in Increased Absolute Survival. *Journal of Cancer Therapy*, **11**, 470-482. https://doi.org/10.4236/jct.2020.118040

[30] Cham, B.E. and Daunter, B. (1990) Solasodine Glycosides. Selective Cytotoxicity for Cancer Cells and Inhibition of Cytotoxicity by Rhamnose in Mice with Sarcoma 180. *Cancer Letters*, **55**, 221-225. https://doi.org/10.1016/0304-3835(90)90122-E

[31] Cham, B.E., Chase, T.R. and Cham, K.E. (2017) Glycoalkaloid Combinations and Various Uses Thereof. Patent No. WO2017147659A1.

[32] Cham, A., Cham, K., Chase, T. and Cham, B.E. (2015) A Standardized Plant Extract Containing a Target Compound Is Acceptable as a Potent Therapeutic Entity: Relevance to BEC and Solamargine, a Topical Clinical Formulation Curaderm^{BEC5}. *Journal Cancer Treatment Research*, **3**, 22-27. https://doi.org/10.11648/j.jctr.20150302.12

[33] Cham, B.E. (1994) Solasodine Glycosides as Anticancer Agents: Preclinical and Clinical Studies. *Asia Pacific Journal Pharmacology*, **9**, 113-118.

[34] Cham, B.E. and Chase, T.R. (2012) Solasodine Rhamnosyl Glycosides Cause Apoptosis in Cancer Cells. Do They Also Prime the Immune System Resulting in Long-Term Protection Against Cancer? *Planta Medica*, **78**, 349-353. https://doi.org/10.1055/s-0031-1298149

[35] Cham, B.E. (2021) The Evolution of Curaderm from the Eggplant Which Led to the Revolution of Skin Cancer Treatment. https://www.amazon.com/evolution-curaderm-eggplant-revolution-treatment-ebook/dp/b09mvp5m3l/ref=sr_1_1?keywords=the+evolution+of+curaderm&qid=1639040738&sr=8-1

[36] Cham, B.E. (2007) Solasodine Rhamnosyl Glycosides Specifically Bind Cancer Cell Receptors and Induce Apoptosis and Necrosis. Treatment for Skin Cancer and

Hope for Internal Cancers. *Research Journal Biological Sciences*, **2**, 503-5142.

[37] Cham, B.E. (2013) Drug Therapy: Solamargine and Other Solasodine Rhamnosyl Glycosides as Anticancer Agents. *Modern Chemotherapy*, **2**, 33-49. https://doi.org/10.4236/mc.2013.22005

[38] Cham, B.E. (2008) Cancer Intralesion Chemotherapy with Solasodine Rhamnosyl Glycosides. *Research Journal Biological Sciences*, **3**, 1008-1017.

[39] Punjabi, S., Cook, L.J., Kersey, P., Marks, R. and Cerio, R. (2008) Solasodine Glycoalkaloids: A Novel Topical Therapy for Basal Cell Carcinoma. A Double Blind, Randomized, Placebo-Controlled, Parallel Group, Multicentre Study. *International Journal Dermatology*, **47**, 78-82. https://doi.org/10.1111/j.1365-4632.2007.03363.x

[40] Cerio, R. and Punjabi, S. (2002) Clinical Appraisal of BEC5. Dermatology Department, Barts and the London NHS.

[41] Tambuscio, A., Siliprandi, L., Dario, M., Cham, A., Cham, B. and Bordignon, M. (2016) Treatment of Cutaneous Carcinomas with a Topical Cream Containing Solasodine Rhamnosides: Focus on Efficacy, Compliance and Cosmetic Outcomes. *European Academy of Dermatology and Venereology Congress*, Athens, 19-21 May 2016, 248 p.

[42] Cham, B.E. (2007) The Eggplant Cancer Cure: A Treatment for Skin Cancers and New Hope for Other Cancers from Nature's Pharmacy. Smart Publications, Port Vila.

[43] Cham, B.E. (2007) Solasodine Rhamnosyl Glycosides in a Cream Formulation Is Effective for Treating Large and Troublesome Skin Cancers. *Research Journal of Biological Sciences*, **2**, 749-761.

[44] Cham, B.E. (2009) When Does Alternative Become Orthodox? Skin Cancer Treatment with Solasodine Rhamnosyl Glycosides in Its Transitional Stage, a Case Study. *Evidence-Based Complement Alternative Medicine*, **6**, 415-420.

[45] Cham, B.E. (2011) Topical Solasodine Rhamnosyl Glycosides Derived from the Eggplant Treats Large Skin Cancers: Two Case Reports. *International Journal Clinical Medicine*, **2**, 473-477. https://doi.org/10.4236/ijcm.2011.24080

[46] Chase, T.R. (2011) Curaderm^{BEC5} for Skin Cancers, Is It? An Overview. *Journal Cancer Therapy*, **2**, 728-745. https://doi.org/10.4236/jct.2011.25099

[47] Cham, B.E. (2012) Intralesion and Curaderm^{BEC} Topical Combination Therapies of Solasodine Rhamnosyl Glycosides Derived from the Eggplant or Devil's Apple Result in Rapid Removal of Large Skin Cancers. Methods of Treatment Compared. *International Journal Clinical Medicine*, **3**, 115-124. https://doi.org/10.4236/ijcm.2012.32024

[48] Cham, B.E. (2013) Topical Curaderm^{BEC5} Therapy for Periocular Nonmelanoma Skin Cancer: A Review of Clinical Outcomes. *International Journal Clinical Medicine*, **4**, 233-238. https://doi.org/10.4236/ijcm.2013.45041

[49] Cham, A. and Cham, B.E. (2015) Treatment of Skin Cancer with a Selective Apoptotic-Inducing Curaderm^{BEC5} Topical Cream Containing Solasodine Rhamnosides. *International Journal Clinical Medicine*, **6**, 326-333. https://doi.org/10.4236/ijcm.2015.65042

[50] Cham, B.E., Cham, K., Cham, A., Chase, T. and Zhou, V. (2015) Treatment of Non Melanoma Skin Cancers: An Intra-Comparison Study of Curaderm^{BEC5} and Various Established Modalities. *Journal Cancer Therapy*, **6**, 1045-1053. https://doi.org/10.4236/jct.2015.612114

[51] Cham, B.E. (2013) Solasodine Glycosides: A Topical Therapy for Actinic Keratosis.

A Single-Blind, Randomized, Placebo-Controlled, Parallel Group Study with Curaderm. *Journal of Cancer Therapy*, **4**, 588-596. https://doi.org/10.4236/jct.2013.42076

[52] Bordingnon, M. (2016) Efficacy and Safety of Curaderm^{BEC5} in the Treatment of Basal Cell Carcinoma: A Pilot Study in the Italian Population. *European Academy Dermatology Venereology Congress*, Athens, 19-21 May 2016, 249 p.

[53] Dobrokhotova, F.Z., Betsev, A.F. and Belysheva, T.S. (2016) The Use of Kuraderm Drug in the Treatment of Basal Cell Carcinoma of the Head and Neck. *Head and Neck Tumors*, **6**, 22-26. https://doi.org/10.17650/2222-1468-2016-6-3-22-26

[54] Batsev, A.F., Dobrokhotova, V.Z. and Cham, B.E. (2016) Topical Cream Curaderm-^{BEC5} Treats a Recalcitrant Basal Cell Carcinoma. *Clinical Medical Reviews and Case Reports*, **3**, Article 098. https://doi.org/10.23937/2378-3656/1410098

[55] Cham, B.E. (2020) First in Man Topical Treatment of Melanoma with Solasodine Glycosides in a Formulation Curaderm. *Journal of Cancer Therapy*, **11**, 617-630. https://doi.org/10.4236/jct.2020.1110052

[56] Cham, B.E. (2015) Curaderm^{BEC5}, Natural Non-Invasive Medication for Skin Cancer, Biopsy and 5 Year Cancer-Free Criteria. 2nd Edition, Curaderm Global Ltd., Vanuatu.

[57] Gupta, N., Gupta, G.D. and Singh, D. (2022) Localized Topical Drug Delivery Systems for Skin Cancer: Current Approaches and Future Prospects. *Frontier Nanotechnology*, **4**, Article 1006628. https://doi.org/10.3389/fnano.2022.1006628

[58] Inam, S.S. (2023) Topical Formulation Constituted with Transferosomes for the Treatment of Non-Melanoma Skin Cancer. *Asian Journal of Pharmaceutical and Clinical Research*, **16**, 27-32. https://doi.org/10.22159/ajpcr.2023.v16i5.47033

[59] Kao, S.Z., Ekwueme, D.U., Holman, D.M., Rim, S.H., Thomas, C.C. and Saraiya, M. (2023) Economic Burden of Skin Cancer Treatment in the USA: An Analysis of the Medical Expenditure Panel Survey Data 2012-2018. *Cancer Causes & Controls*, **34**, 205-212. https://doi.org/10.1007/s10552-022-01644-0

[60] Cham, B.E. (2023) Holistic Approach in the Treatment of Actinic Keratosis: Benefits and Disadvantages of 5-Fluorouracil, Imiquimod, Diclofenac and Curaderm. *International Journal Clinical Medicine*, **14**, 319-331. https://doi.org/10.4236/ijcm.2023.147027

[61] Cham, B.E. (2024) Gold Standard for Skin Cancer Treatment: Surgery or Micrographic Molecular-Cellular Therapy?