

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}

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Abstract: New approaches to curb developmental and end-stage production expenses, whilst generating a safe and effective treatment for cancer, resulting in lower cost for the patient and healthcare system, are warranted. A bioassay-guided fractionation of a *Solanum* plant, *S. sodomaeum*, to a standardized extract can be classified as a new drug. It is shown that a specific standardized plant extract, BEC, containing a given concentration of a target efficacious and safe compound, solamargine, is an acceptable anticancer and less costly chemotherapeutic reality.

Keywords: Cancer, Solamargine, BEC, Curaderm, Solanum, Plant Extract

1. Introduction

New drug development is a complex, time consuming and expensive process. Over 12 years are required to take drug discovery of a new drug to clinical application. In today's context this involves more than 1 billion US\$ of investment [1]. Traditional anticancer drug therapies are not only costly, but most concerning, these therapies are nonselective and very toxic resulting in a lack of satisfactory results in cancer treatment. Oncologists have now recognized this and have resorted to combinational anticancer therapy utilizing multiple traditional antineoplastic agents. Still the results of these therapies are not fulfilling the needs and expectations of patients and health care professionals.

Due to the alarming lack of safe, effective treatments for cancer, considerable interests have been drawn to naturally occurring smart drugs. More than 80% of drug substances are purely natural products or were inspired by molecules derived from natural sources. Smart drugs are specific toxins that focus on a particular vulnerability of the cancer, they are specific toxins. In particular, the glycoalkaloids solasodine rhamnosides have attracted much attention. Glycoalkaloids are found in over hundreds of *Solanum* species. These

Solanum glycoalkaloids differ in their glycosidic as well as in their alkaloidal components. Different *Solanum* plants contain various amounts of percentages of such components. In nature glycoalkaloids are produced in plants as secondary metabolites and are not involved in metabolic activity. They act as defense chemicals. Their absence does not cause ill effects in the plants. However, in plants, glycoalkaloids are used to fight off pathogens such as bacteria, fungi, viruses, worms and humans, they are considered to be defensive allelo-chemicals [2-4].

Cancer is cruel to the human body and a cruel environment is cancerous to plants. Plants, which are able to comfortably survive under multiple but diverse hostile environments, may be associated with a vital source of anticancer agents.

Solanum plants, through evolution, have produced solasodine rhamnosides allelo-chemicals. This has resulted in their survival under multiple and diverse hostile environments such as being exposed to a number of detrimental pathogens. Subsequently these solasodine rhamnosides have shown to be potent anticancer agents at different stages of cancer development. They cause cancer cells to commit suicide (apoptosis) [5-31], are cytotoxic against multi drug resistant tumour cells [7, 14, 31], stimulate

lasting immunity against cancer [9, 31], are not mutagenic and even display anti mutagenic properties [7, 31].

In 1987 it was first reported that an Australian local *Solanum* species, Devil's Apple, *Solanum sodomaicum (linnaeanum)* possessed anticancer properties [5-7]. Several active ingredients, including solamargine, solasonine, monoglycosides and diglycosides of solasodine were reported to express varying degrees of anticancer activities in the *S. sodomaicum* extracts. Analyses of the extract indicated that these solasodine glycosides were present in a specific standardized mixture known as BEC [5, 8, 9]. BEC is composed of solamargine (33%), solasonine (33%) and di-

and monoglycosides of solasodine (34%) [5-9].

Solasodine glycosides in BEC have a mono or oligosaccharide chain attached to the C3 position of the nitrogenous steroid alkaloid solasodine backbone. The triglycoside solamargine contains two molecules of rhamnose, and the triglycoside solasonine contains one molecule of rhamnose. Depending on the diglycosides present in BEC, they may contain one or no rhamnose molecule, whereas the monoglycoside in BEC contains no rhamnose molecule.

Figure 1 shows the chemical structures of solasonine and solamargine.

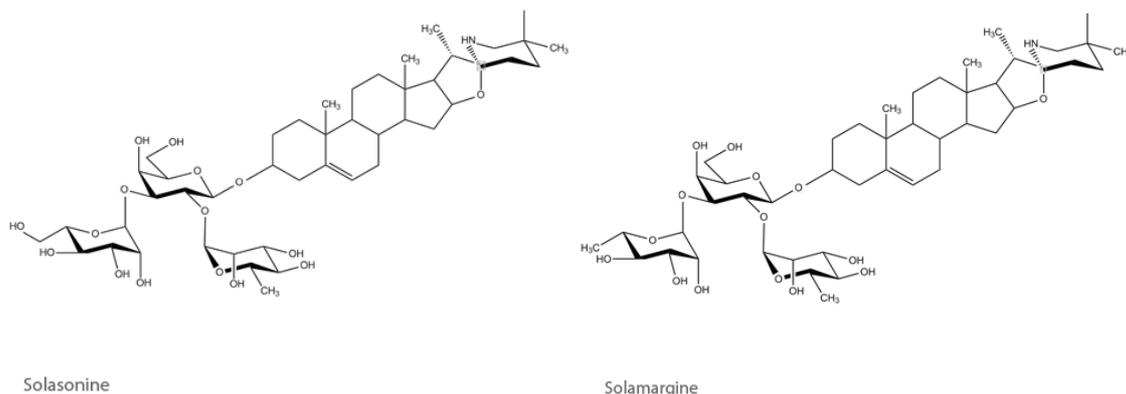


Figure 1. Chemical structures of solasonine and solamargine

The structure-activity relationship of these solasodine glycosides has been reported. The anticancer properties of solamargine, solasonine and their hydrolysis products beta 1, beta 2, and gamma solamargine and beta 2 and gamma solasonine and their aglycone solasodine revealed that solamargine and solasonine were the most active [10]. The carbohydrate side chains of these glycoalkaloids are paramount in influencing biological activity. Not only the number but also the type of carbohydrate, as well as the order of attachment affect the anticancer activity of the glycoalkaloids [10].

The two rhamnose molecules moieties of solamargine play a crucial role in triggering cancer cell death by apoptosis. The trisaccharide of solamargine, in which two rhamnose units are connected to a glucose moiety, binds more efficiently to specific cell receptor sites than the corresponding trisaccharide solasonine in which one rhamnose and one-glucose units are bridged by a galactose monosaccharide. A specific cell receptor has been identified as an endogenous endocytic lectin [8] and has been characterised as a rhamnose binding protein on the cancer cell membrane [11, 12].

Solasodine rhamnosides in BEC are now considered to be the much-sought class of targeted cancer therapy and can be classified as smart drugs. After rhamnose binding to the specific receptors, the entire solasodine rhamnosides are internalized by receptor-mediated endocytosis through "coated pit endocytosis" and a receptorsome or endosome is formed. Once internalized in the cancer cell the solasodine moiety then expresses its importance in antineoplastic activities, and, the lysosomes and mitochondria are affected.

Consequently, extrinsic and intrinsic apoptotic pathways in the cancer cell are triggered resulting in up-regulation of the expressions of external death receptors, such as tumour necrosis factor receptors (TNFR-1 and TNFR-2), Fas receptor, TNFR-1 associated death domain and Fas-associated death domain. The solasodine rhamnosides enhance the intrinsic ratio of Bax to Bcl-2 by up-regulating Bax and down-regulating Bcl-2 and Bcl-xL expressions. These effects result in activation of Caspase -8, -9 and -3 in cancer cells, a hallmark of apoptosis, which was confirmed by morphological studies [8, 13].

Apoptosis, or programmed cell death, is a naturally occurring process in the body. Healthy cells eliminate themselves by apoptosis when they become defective. Cancer cells resist apoptosis and continue to multiply uncontrollably, resulting in an increased tumour mass. Resisting apoptosis is a key process in cancer formation and proliferation. BEC specifically induces apoptosis in cancer cells making it a powerful therapeutic tool [7, 8, 14].

Studies with BEC, its individual and combinational individual components consisting of triglycosides solamargine, solasonine, diglycosides and monoglycosides of solasodine clearly show that these solasodine rhamnosides are far superior to existing chemotherapeutic agents [7, 15-17]. A topical cream formulation, Curaderm^{BEC5}, containing BEC is currently used clinically for the treatment of skin cancers [7, 18-25].

A clear distinction in terms of efficacy, safety and cost have hitherto not been reported in a clinical setting for a target potent anticancer compound when this compound is

present in a standardized extract containing other less effective antineoplastic agents.

In this report it is shown that under specified conditions, BEC, with known contents of solamargine, can be used clinically for various diseased states. This translates to reducing the costs of cancer treatment for the health system and for those affected by cancer. This is achieved by reducing the costs of producing the anticancer preparation since it is much more expensive to obtain isolated purified solamargine than it is to obtain the BEC extract.

2. Results

2.1. Cytotoxic Activities of BEC and Its Individual Solasodine Glycosides

Daunter and Cham reported that the relative cytotoxic activities of BEC against various cancer cell lines were mainly due to solamargine, whereas solasonine and the mono-and-diglycosides of solasodine had limited cytotoxic activities relative to solamargine [6-8]. Using a variety of cancer and normal cell lines it was shown that solamargine was 15 times more effective than solasonine and 13 times more effective than a mixture of diglycosides and monoglycosides of solasodine [7, 26].

Carter *et al.* reported that the cytotoxicity of purified solamargine (SBP04) against the human cell lines mesothelioma (NO36), prostate adenocarcinoma (LNCaP), colonic carcinoma (LS174T), melanoma (A2058) and renal cell carcinoma (786-0) was more than 4 times higher than that of purified solasonine (SBP05). Furthermore, solamargine-quantified BEC with measured IC₅₀ in various human cancer cell lines were similar to that of pure solamargine [27].

Table 1. Relative Percent Anticancer Activities

	Compound BEC	Compound BEC	Compound SR-T100	Compound MEP	Synthesized	SBP04, SBP05
Solamargine	100	100	100	100	100	100
Solasonine	13	7	6	42	-	25
Di, monoglycosides	10	8	<2	-	20	-
Reference	8	26	29	30	28	27

Compounds BEC, SR-T100, MEP are different extracts containing a mixture of solamargine, solasonine, diglycosides of solasodine and monoglycosides of solasodine. Synthesized denotes synthesized solamargine and other variations, including monoglycosides, of solasodine. SBP04 and SBP05 are extracted purified solamargine and solasonine respectively.

Cui *et al.* have synthesized various solasodine glycosides and evaluated and compared their cytotoxic effects with solamargine on human cancer cells. They showed that the cytotoxicity of solamargine on four human cancer cell lines, squamous cell carcinoma (KB), breast adenocarcinoma (MCF-7), myelogenous leukemia (K562) and prostate cancer (PC3) was much higher than 9 variations of synthesised solasodine glycosides, including the monoglycoside solasodine rhamnoside. The IC₅₀ of solamargine for human cancer cell lines was more efficient than other solasodine glycosides by factors ranging from 2.7 to 8.9 [28].

Wu *et al.* showed that the cytotoxicity of solamargine against squamous cell carcinoma (SCC25) was 17 times higher than that of solasonine. Furthermore, solamargine-quantified *S. incanum* extract SR-T100 (an extract which is similar to BEC) had identical efficacy compared with pure solamargine [29].

Shabana *et al.* studied the anticancer activity of an extract MEP (another extract which is similar to BEC) and its individual glycoalkaloids of the fruit peels of *S. melongena* and demonstrated that solamargine was 2.38 more potent than solasonine in antineoplastic activity in 5 human cancer cell lines – colon cancer (HCT116), larynx cancer (HEP2), breast cancer (MCF7), cervix cancer (HELA) and liver cancer (HEPG2) [30].

Table 1 shows the relative anticancer activities of various solasodine conjugates against a large range and number of cancers. Relative, and for comparison of activities, the most effective substance is rated as 100%. In all cases this was solamargine. On average solamargine is 9 and 19 times more effective against cancer than solasonine and mono-and-diglycosides of solasodine respectively.

2.2. Toxicities of Solamargine and BEC in Humans

Table 2 demonstrates concentrations of BEC and solamargine used in humans. Large concentration ranges of solamargine (0.02 – 166 mg/mL) and BEC (0.05-500 mg/mL) have been used safely in humans. Toxicity studies in animal models have been previously reported [7].

Table 2. Doses of Solamargine used in Humans

Solamargine Concentration mg/mL	Parent Compound	Administration	Phase Clinical Study	Reference
7-166	BEC	Topical	I	4, 31
33	BEC	Topical – BEC02	II	4, 31
0.02	BEC	Topical - Curaderm	III	4, 31
0.02	Solamargine	Topical	Pilot clinical	32
23	SR-T100	Topical	Pilot clinical	29
0.03	BEC	Intralesion	Pilot clinical	4, 31
2	BEC	Oral	Pilot clinical	4, 31
0.75-1.5	SBP02	Intravenous	I	4, 27, 31

A wide concentration range of solamargine in various extracts and in isolated purified form have been used clinically in human Pivotal Clinical Studies and Phases I to III Clinical Trials.

3. Discussion

The cost for bringing a new cancer drug to market is reported to be about US\$1 billion [1]. The cost includes development of the new (successful) drug and all other drugs that failed during development, conducting the clinical trials required for approval, bonuses, salaries, infrastructures, and advertising amongst others.

However, the justification of the claim that about US\$1 billion in costs to bring a new cancer drug to market and consequently the high price of the drug charged to the patient are hotly disputed [33]. Anticancer drugs rank first of global spending by therapeutic class. New anticancer drugs are more expensive than older products. The cost of the new generation of drugs is getting out of all proportion to the added benefit and is becoming unsustainable. For example, the newly approved melanoma drug ipilimumab costs US\$120,000 for a course of therapy. The drug was shown to be associated with an incremental increase in life expectancy of four months! This suggests that increases in prices of anticancer drugs are unrelated to real health improvements. Of the 12 anticancer drugs approved by the FDA in 2012, 11 were priced above US\$100,000 per year. This represents a doubling of prices from a decade ago. This level of expense is simply unacceptable since 1/3 of people will get cancer in their lifetime. Dealing with burgeoning costs of cancer treatment is a major challenge for the health system and for those affected by cancer.

Multiple factors are involved in cancer drug pricing and impact on individual patients and healthcare policies. The need to lower the prices of cancer drugs to allow more patients to afford them and to maintain sound long-term healthcare policies are warranted.

One such factor is the production cost of the anticancer drug for its use in clinical settings.

Solamargine is a suitable glycoalkaloid with excellent antineoplastic properties both in terms of specificity and safety [7]. Solamargine is found in a large number of plant *Solanum* species. However, to date no *Solanum* plants have been found to contain solamargine on its own. In nature, solamargine is found in plant extracts, which also contain solamargine-related biomolecules such as solasonine, mono- and diglycosides of solasodine and unbound solasodine.

The compound BEC is an extract that contains the above glycosylated solasodines. In particular, BEC consists of a constant mixture of solamargine, solasonine and di- and mono-glycosides of solasodine. The triglycosides solamargine and solasonine as well as the mono- and diglycosides of solasodine possess antineoplastic properties with differing activities.

At equimolar concentrations, on average, solamargine is 9

times more efficacious than solasonine and 19 times more efficacious than the mono- and diglycosides of solasodine. BEC consists of 1/3 solamargine, 1/3 solasonine and 1/3 mono- and diglycosides of solasodine [5]. When calculated, the contribution of anticancer activities in BEC is 86% for solamargine, 9% for solasonine and 5% for mono- and diglycosides of solasodine. Solamargine-quantified BEC with measured IC₅₀ values in various human cancer cell lines are similar to that of pure solamargine. This suggests that there are no synergistic effects of solamargine with the other solasodine glycosides found in BEC and that solamargine is the most effective anticancer component in BEC.

These observations have been elaborated in a clinical setting when treating human basal cell carcinomas. It was shown that topical cream formulations with identical excipients containing 0.02mg purified isolated solamargine per 1mL cream had comparable therapeutic outcomes as 0.05mg BEC (containing 0.02mg solamargine) per 1mL cream [32]. The concentrations of BEC and solamargine for effective skin cancer treatment are similar to those reported in cell culture studies for a wide variety of cancer cells.

The extraction of BEC from a wide variety of *Solanum* species is relatively not very costly nor time consuming. However, the isolation of the individual solasodine rhamnosides including solamargine from plant material or from BEC is very time consuming and costly.

There are challenges that have to be overcome when seeking ways of reducing the costs of cancer treatment for the health system and for those affected by cancer. A particular expense that contributes to the pricing of such treatments is the cost of producing the anticancer preparations.

In assessing such a challenge, there are many factors to consider. Two such main factors are safety and efficacy. Both these factors for BEC have been addressed in this article.

Reducing the production cost of an anticancer drug consequently should result in a significant cost lowering in the final product for treating this disease. In the United States alone treatment of skin cancer amounts to US\$1.8 billion each year [34]. Any modality that can reduce such a financial burden to the Health Care System and to patients should be considered seriously.

In the case of Curaderm, a clinically available topical treatment for skin cancer, it has been established that BEC with a quantifiable known amount of solamargine is an acceptable preparation for its indications [6-9, 16-27, 29, 31, 32, 35-43].

This paper shows that it is possible to reduce the costs associated with the production of treatment preparations by using well-characterized extracts containing known amounts of the principal anticancer ingredient.

Currently, further work is being undertaken to establish the clinical relevance of BEC for other more serious cancers.

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