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Goals/Objectives/Expected Outputs

The goals of the project are to develop new formulations for active pharmaceutical ingredients, functional food and beverage compounds, and new chemical entities emerging from drug discovery using a novel approach for solubilizing lipophilic compounds. Specific objectives: 1. Compile a library of water-insoluble active compounds based on chemical classes and biological mechanisms. A minimum of 100 compounds will be compiled. 2. Conduct solubility experiments for the above library compounds using newly discovered solubilizing compounds from the steviol glycoside class. 3. Characterizes the solubilized structures formed between the solubilizing compounds and bioactive compounds. 4. Perform stability experiments for the compounds that are solubilized in physiological fluids (saline, gastric and intestinal fluids). 5. Determine the permeability of water-insoluble compounds solubilized by the novel approach in Caco-2 monolayer cell culture. 6. Determine the anti-cancer activity of chemotherapeutic compounds in the solubilized formulations. Expected outputs: 1. Solubilization experiments showing solubility enhancement of selected active lipohilic compounds. 2. Patent applications on the specific composition of solubilizer-drug complexes. 3. Publications to disseminate the research results and potential utilities.

Methods

To reach the goals, general solubilizing effects will be demonstrated by a single steviol glycoside compound for a wide range of bioactive compounds, representative of various chemical classes and possibly biological mechanisms. General applicability of this approach will be proof of solving solubility problems. Stability in physiological conditions is an important aspect of formulations of medications and will be examined; and a standard cytotoxicity and permeability test will be conducted for each solubilized compound to show pharmaceutical usefulness and maintenance of activity. The novelty of the solubilization technology lies in the use of a natural food compound with possible minimal safety concern. Pharmaceutical scientists often use conventional approaches and processing methods for solubilizing and inducing drug-solubilizer interactions. The major differences from conventional approaches other investigators have attempted are as follows. First of all, never before are natural compounds used or attempted in solving the solubility problems. It is conventional to discover natural biologically active compounds from plants, because this is a proven source and will continue to be a viable source for the foreseeable future. Around the world investigators have attempted to tap into plants for the new and pharmacologically potent compounds, including our own medicinal plant laboratory. However, our visions go beyond merely a source of bioactivity-driven discovery. The functional aspents of natural compounds have been investigated as well, inspired by the historical Traditional Chinese Medicine approach to formulating herbal decoctions and a modern nano-particle drug delivery platform building approach featuring

multiple functionalities (e.g., solubility enhancement, absorption and transport enhancing, targeted and guided delivery). Our approach centers on solving the problems by using natural solubilizing compounds, not an herb, not a synthesized solubilizing unit of a single molecule, and not total synthesis from a nano-platform. The idea that plants have better strategies to solubilize water-insoluble compounds remains a trivial interest in many natural product laboratories and the pharmaceutical industry. Secondly, we use an unconventional direct interaction method between a drug and a solubilizing agent in aqueous solution. Conventional approaches often, but not always, involve the use of organic solvents in forging in the inter-molecular interaction. In general, however, pharmaceutical scientists regard formulations as art rather than pure science and technology. This realization reflects the fact that each compound is different, thus, a general methodology may not work equally effectively.

23. Non-Technical Summary

While most people are focusing their research on designing and synthesizing nano-carries for drug delivery or combining existing techniques in order to enable solubility, we have discovered a new approach for solubilizing lipophilic compounds. This approach is not duplicated in any other laboratories in the world. We are the inventor and initial patent examination has confirmed its novelty. This approach is unusual, exceptionally innovative and was discovered from an unexpected source of non-pharmaceutical formulations. Therefore, there is not only an interest from the discoverer but also an obligation to investigate further. There is no one in the world researching steviol glycoside compounds for solubilizing properties. Though rubuside, and many closely related compounds, have received intense scrutiny by food-product developers and by academic and industrial scientist, only our medicinal plant laboratory has seen and investigate the unexpected ability of steviol glycoside to solubilize other compounds by direct interaction in aqueous solution. This project will require strong commitment of time and resources, but the impact on the fields of pharmaceutical formulations could be high. Using the chemotherapeutic natural compound paclitaxel (PTX) as a good example. PTX drugs are currently prescribed to treat ovarian, breast, and non-small-cell lung, small-cell lung, and the head and neck cancers, by intravenous infusion. However, an oral drug has not been available. Approximately 85% of the pharmaceutical drugs are in oral form with tremendous advantaged and substantial benefits. Cancer patients can avoid having to be in the outpatient facility or physicians office for IV infusion, eliminate nausea often associated with the infusion procedure, and reduce the cost of chemotherapy. The problem is, converting PTX has faced obstacles of low absorption. This is because PTX is a very difficult molecule to solubilize in the first place and then not permeable to intestinal epithelia. This proposal used natural compounds recognized as foods to solubilize PTX. An oral PTX medication would be novel and could be protected by filed patents, but would add no additional safety concerns to the drug, since the solubilizing agent is foods. Our project has the potential to support oral PTX medications that could replace the current two IV infusion drugs for breast cancer therapy and expand to cover more types of cancer, bringing a safer and more efficacious anti-cancer drug to millions of cancer patients.

24. Keywords

solubilization; natural compounds; nano-particle; chemotherapy; formulation; bioactive compounds; solubility enhancement; permeability enhancement; absorption

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