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LETTER TO THE EDITOR

Correspondence

Antiviral effects of oleandrin

We read with great interest the article entitled "Toxicity of herbal medications suggested as treatments for COVID-19: a narrative review" by M.A. DiPietro and C. Mondie that appeared in *JACEP Open* highlighting the reported use of certain herbal medications, some specifically suggested as treatments for COVID-19.[1] Although we concur with the cautionary note in the article regarding plant-derived medications that, although possibly effective, can exhibit significant toxicity, we would also note that, as the Father of Toxicology (Paracelsus) is reported to have written: "Only the dose makes the poison."

One of the plant-derived reagents discussed in the article is oleandrin, a cardiac glycoside obtained from *Nerium oleander*. At Phoenix Biotechnology, Inc., we have a long and well-documented track record over 18 years of testing extracts of *N. oleander*, including oleandrin as a purified reagent for antiviral and anti-tumor cell activities. More importantly, our published studies demonstrated the safety of the plant extract in the Food and Drug Administration (FDA)-approved Phase I and II clinical trials in cancer patients through the use of our novel drug PBI-05204.

We have recently published a review of the broad antiviral efficacy of oleandrin and extracts that contain this molecule[2] in studies conducted by us and a number of scientific colleagues around the country over the years. Our own published research has shown efficacy of oleandrin and *N. oleander* extracts against HIV and HTLV-1.[3,4] More recently, we have published a study showing efficacy both in vitro and in vivo of an oleander extract against COVID-19 without toxicity.[5]

Certainly, depending on the dosage, use of cardiac glycosides can have the potential to cause severe cardiovascular toxicities. However, the use of digoxin (Lanoxin) at appropriate doses to treat congestive heart failure has been an accepted therapeutic strategy for many years. As noted, our published studies described the use of an extract of *N. oleander* containing oleandrin (PBI-05204) for treatment of malignant disease in approved Phase I and Phase II clinical trials.[6,7] These studies did not result in any significant cardiovascular toxicities.

Our recent research with oleandrin as a proposed inhibitor of SARS-CoV-2 has demonstrated that low nanomolar concentrations of this molecule achieved near-total inhibition of the relative infectivity of this virus. The effective antiviral oleandrin concentrations were a fraction of that required for the control of cancer cell lines. This suggests that the use of oleandrin or a properly defined extract containing this molecule could be used to control COVID-19 without toxicity. We quickly point out that studies of any extract containing defined concentrations of oleandrin must be conducted in carefully designed clinical trials to seek appropriate approvals for human use. In fact, that is our current aim for PBI-05204.

Harking back to Paracelsus, "only the dose makes the poison" could easily be said to be true for hundreds of current FDA-approved medications. With respect to oleandrin and extracts containing this molecule, we point out that although toxicity can result in the use of high doses of this molecule, when used appropriately either for cancer or, as suggested, for treatment of certain viral-mediated diseases (including envelope viruses), the compound can be used with both safety and, we hope to prove, clinical efficacy.

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