OPINION

A possible involvement for the gut microbiome in the pharmaco-toxicological dilemma of oleander

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ABSTRACT

Oleander, also known as Nerium oleander L., is both a poisonous shrub and a useful plant. Heart glycosides, which inhibit Na^{+}/K^{+} ATPase and provide cardiomyocytes an inotropic effect, are abundant in all parts of the oleander plant. Numerous pre-clinical and clinical investigations suggest that purposeful, unintentional, and suicidal oleander ingestion causes acute poisoning. Contrarily, oleander is used in traditional medicine across the globe to cure a variety of illnesses, and multiple evidence-based pre-clinical investigations found that oleander extracts rich in polyphenols had positive effects on immune and metabolic health.

INTRODUCTION

The single species included under the genus *Nerium* is *Nerium oleander L.*, which is found in the family *Apocynaceae* and has the WCSP record number 135,196. It is an ornamental shrub having pharmacological and toxicological effects that is commonly referred to as oleander. Numerous clinical examples of toxicity brought on by unintentional, deliberate, or suicidal behavior have been recorded with oleander ingestion. Numerous cardiac glycosides are thought to constitute the primary mechanism of oleander poisoning. Although the toxicity of various cardiotonic steroids varies, the most frequent mechanism is the suppression of cardiac Na+/K+ ATPase. On the other hand, various oleander extracts are regularly utilized in ethnomedicinal traditions all over the world to treat a variety of illnesses. Indeed, through pre-clinical in vivo studies, these ethnopharmacological evidences have been assessed and established.

Additionally, oleander-based topical skin care products have been successfully commercialized, and oleander botanicals have demonstrated anti-viral and anti-cancer capabilities. With such significant pharmaco-toxicological contradicting results regarding oleander, it is obvious that the underlying mechanism is still severely understudied and neglected. One of the major determinants of the pharmacology, toxicity, and bioavailability of phytochemicals has been identified as the gut microbiome. Pre-clinical and clinical data indicate that changes in intestinal bacterial population, diversity, and metabolic processes are related to human health, disease pathogenesis, and drug/phytochemical biotransformation, whereas dietary phytochemicals may be preventative and/or therapeutic for chronic diseases by modifying gut microbiota. The great majority of oleander-centric pharmacological investigations have historically concentrated on in vitro anticancer activities because of the plant's severe toxicity. These cytotoxic anti-cancer studies have also been avoided since targeted cell-culture based in vitro investigations have the least physiological relevance and don't involve gut microbes. The current review thus aimed to provide gut microbiota-centric insights in unraveling the pharmaco-toxicological conundrum of the medicinal plant N. oleander and lead towards its safe and effective clinical use by focusing solely on the ethnomedicinal usage, pre-clinical and clinical oleander toxicity, and pharmacognostic reports of metabolic benefits. Different portions of the oleander have been found to contain many kinds of pharmacologically active phytochemicals, including phenolics, tannins, terpenoids, alkaloids, saponin, and anthraquinones. The anti-cancer effects and toxicological efficacies of oleander have been related to the presence of different cardiac glycosides and cytotoxic phytochemicals, despite the existence of many bioactive polyphenolic substances. The presence of cardiac glycosides in oleander, including oleandrin, adynerin, and digitoxigenin, is widely recognized. These compounds

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have strong cytotoxic effects and share structural similarities with digitoxin from *Digitalis purpurea L.* (*Foxglove; family Scrophulariaceae*). Despite the fact that lipophilic cardenolides are present in all sections of the oleander plant, the concentration is found in the following order: leaf, fruit, root, and seed. These cardenolides steroidal nuclei, in particular the 5', 14'-androstane-3', 14-diol skeleton, are thought to be the primary bioactive region and have similar binding capabilities to digitalis glycosides. The bark and twigs contained several cytotoxic pregnane chemicals, including neridienone A and B. Oleander leaves were used to isolate two coumaryloxy triterpenoids, neriucoumaric and isoneriucoumaric acid, and two cardiac glycosides, kaneroside and neriumoside. Three novel triterpenes with cytotoxic and anti-inflammatory activities, as well as ursolic acid, oleanolic acid, betulinic acid, and botulin, were discovered in oleander leaves. The methanolic extract of oleander leaves included several cardenolides, including neridiginoside, nerizoside, neritaloside, and odoroside-H, which had central nervous system depressive properties. Oleander is widely employed in ethnomedical traditions all throughout the world, despite its toxicity due to the presence of cardiac glycosides in all sections. Although the degree of toxicity varies considerably between humans and animals, various pre-clinical studies have shown that oleander at sub-lethal doses is beneficial for metabolic health. However, there is a crucial knowledge vacuum regarding the effects of oleander extracts and its cardiac glycosides at the intestine level, particularly the reciprocal interaction with the gut flora. The potential effects of oleander-microbiota reciprocal interactions in pharmaco-toxicology required thorough investigation in light of the emerging evidence of gut microbial metabolism of structurally analogous cardiac glycosides and differential effects on human health and diseases based on gut microbial populations, diversity, and metabolic functions. The clinical pharmaco-toxicological effects of oleander would probably be clarified by pre-clinical investigations focused on tailored toxicity based on individual gut flora profiles. Intestinal regiospecific effects of oleander on gut microbiota and intestinal immunometabolic balance could be investigated as next steps in solving this mystery utilizing a traditional mouse model of HF diet-induced metabolic abnormality. The assertions of gut microbial relationship with oleander effects would be supported by the use of germ-free cohort or selective elimination of glycoside-metabolizing bacteria. The clinical pharmaco-toxicological effects of oleander would probably be clarified by pre-clinical investigations focused on tailored toxicity based on individual gut flora profiles. Intestinal regiospecific effects of oleander on gut microbiota and intestinal immunometabolic balance could be investigated as next steps in solving this mystery utilizing a traditional mouse model of HF diet-induced metabolic abnormality. The assertions of gut microbial relationship with oleander effects would be supported by the use of germ-free cohort or selective elimination of glycoside-metabolizing bacteria. As a result, it is anticipated that addressing the experimental variables covered in the review in conjunction with the reciprocal interactive data from pre-clinical studies on the microbiota and oleander will improve our understanding of the therapeutic and toxicological effects of oleander and result in translational benefits.