Review of: "Toxicological evaluation of aqueous extracts of Clematis hirsuta and Rhamnus prinoides"

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Potential competing interests: No potential competing interests to declare.

This study appears as an attempt to see the reactions from peers.

Study idea is good but lacks its validity with these findings by the authors !!

The purpose of this study is not clear as the selected plant extracts are already found to be effective against many health disorders including type 2 diabetic !

It lacks lot of untold and unexplained stories especially studies on molecular toxicities. The study of gene expression has become a cornerstone of **molecular toxicology** and **toxicogenomics**. From a toxicological standpoint, constitutive expression levels of a gene could be just as important in determining the outcome of toxicity as the inducible expression.. A thorough understanding of the complexity and fluidity of gene and genome structure and their regulation is an integral part in the theory and practice of molecular toxicology and toxicogenomics. Relevance of molecular toxicology to gene regulatory mechanisms needs to be emphasized in case of both the plants from several target gene analysis.

The advance in high-throughput “toxicogenomics” technologies, which allows for concurrent monitoring of cellular responses globally upon exposure to chemical toxicants including phytochemicals (if any). These experiments really proves toxicities of a plant/plant product (*Choudhuri S. Gene regulation and molecular toxicology. Toxicol Mech Methods. 2004;15(1):1-23. doi: 10.1080/15376520590890686*). Another way to find out toxicity is employing an integrated altered gene expression quantifier-TELI (transcriptional effect level index) that integrates altered gene expression magnitude over the exposure time. (*Gao C, Weisman D, Lan J, Gou N, Gu AZ. Toxicity mechanisms identification via gene set enrichment analysis of time-series toxicogenomics data: impact of time and concentration. Environ Sci Technol. 2015 Apr 7;49(7):4618-26. doi: 10.1021/es505199f*)

Genetic changes known to be associated with adverse human health effects include gene mutations, chromosomal rearrangements or deletions, and loss or gain of whole chromosomes (aneuploidy) or chromosomal segments. Genotoxicity tests are *in vitro* and *in vivo* tests are designed to detect any compound (here in case of**selected two plants extract**) that induce genetic damage. Such tests include: (1) tests that directly assess the key types of genetic alterations (gene mutations and chromosomal effects) and (2) indirect genotoxicity tests that respond to types of DNA damage known to lead to the toxic alterations. The latter category of tests may assess either DNA damage (*e.g.*, DNA adducts or DNA strand breakage) or cellular response (*FDA.Toxicological Principles for the Safety Assessment of Food Ingredients Redbook 2000.Chapter IV.C.1. Short-Term Tests for Genetic Toxicity ID: FDA-2013-S-0610*)

IMPORTANT :

1. Toxicity should be defined clearly as neurotoxicity, hematotoxicity, hepato-renal toxicity, cardio-respiratory toxicity etc. including carcinogenicity (if any report) in the introduction section.
2. Without histopathology of animal tissues no study on drug toxicity can be confirmed as valid.

1. In Vitro antioxidant study could have been done for all the doses. This is also a toxicity marker.
2. LDH, C- Reactive Protein of serum could have been assessed.
3. Before doing such study an *In Silico* Study need to be done with a) antioxidant enzymes b)target protein database & chemical database with chemicals-proteins interaction with molecular docking analysis.
4. Practically plants extracts isolated locally need to study with HPLCt to find out both known & unknown compounds.
5. Discussion section needs modification with correlation of authors' own findings with other works, It should not be speculative with not related references.
6. Authors need thorough revision and perform appropriate works to prove their hypothesis.