



International Journal of Hepatology & Gastroenterology

Editorial Article

Healthy Liver Support: A Summing Up Glance on What's Working in the Mist of Marketing Claims? -

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Submitted: 13 December 2020 **Approved:** 13 December 2020 **Published:** 15 December 2020

Cite this article: Marotta F, Kumar N, Sato Y, Taki M, Tsepkenko V. Healthy Liver Support: A Summing Up Glance on What's Working in the Mist of Marketing Claims? Int J Hepatol Gastroenterol. 2020 Dec;6(1):022-024. doi: 10.37871/ijhg.id48

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Liver is the most complex metabolic machine in our body, a crucial crossroad between the inflow of information derived from gut metabolomics signalling, internal processing and delivery to all other organs, brain included. It is not by chance then that the oldest medicine practices such as Ayurvedic, Traditional Chinese Medicine (TCM) and Japanese Kampo medicine, applying a tentative holistic understanding of human health, have clearly devoted a peculiar attention to it [1]. From around the 60s also western conventional practitioners were indeed used to prescribe a “liver protector” and in some European countries were even fully reimbursed by the health national system, giving for granted their safety and usefulness but in the lack of a truly robust scientific evidence. While institutional medicine in the past couple of decades with the advent of antiviral drugs and blooming pharma pressure have almost abandoned natural “liver protectors”, these have even increased their circulation by self-prescription and by the growing integrative medicine physicians and naturopathic communities. The widespread of sort of common sense to “protect the liver” and lack of clear-cut regulatory rules to fit in, has generated with time a rather uncontrolled promotion of herbal compounds from media to supermarkets. This has invariably raised concerns about these products for potential lack of quality control, inner toxic ingredients and interaction with concomitant drugs as discussed at the seminar “ Liver Injury from Herbal and Dietary Supplements” held in May 4–5, 2015 in Bethesda, Maryland, funded by the National Institute of Diabetes and Digestive and Kidney Diseases and National Institutes of Health and also appeared in the literature [2-4]. This is because there are worthy public and private research institutions investing in this area of “hepatoprotective” agents, by employing advanced molecular biology analysis and study designs. However, at the same time, it does exist a far bigger and expanding market undergoing at the best a minimum quality control of ingredient but poor to none safety and efficacy in vitro and in vivo testing [5-7].

Starting from the old roots of TCM a countless number of natural compounds of presumably liver protection properties have been reported in the indexed literature. However, most of these studies were based on in *in vitro* and in vivo investigations and some of the less than 100 clinically applied trials suffered by methodological limitations and relevant risk of bias [8]. Some commercially popular herbal extracts such as curcumin, resveratrol, scutellaria, *Salvia miltiorrhiza* and *garcinia cambogia* and *shisandra* have not provided significant clinical results and the latter two also reported to be potentially toxic [9,10]. Others, such as YHK, a China-made but Japan-imported blend of putative hepatoprotection properties and promoted with miraculostic benefits, such as reversing cirrhosis, failed to clinically confirm initially good experimental data and it was recently found that an antioxidant-based blend could yield better result in acute liver disease in animals [11]. Ginsenosides represent one of the most iconical TCM mirroring the millenarian Chinese culture. There are three main *Panax* spp. Compounds, i.e. *Panax ginseng* Meyer, *Panax notoginseng* and *Panax quiquifolia*. Besides the overwhelming mass of empirical reports and modern experimental studies, recently it has been shown that Korean Red Ginseng extract could remarkably curb inflammatory parameters in NALD patients [12]. To address ginsenosides there occurs a great complexity in separating out the wide variety of inner components, considering also that some may cause drug hepatotoxicity by inhibiting CYP450 [13]. On the other hand, the very promising Japanese trial-supported glycyrrhizin failed to replicate this benefit into a more feasible oral form rather than an invasive weakly intravenous injection schedule.

Sho-saiko-to, the other promising Japanese natural liver protector was drastically limited around 20 years ago, once some acute side effects erupted [14]. Silymarin (*Silybum marianum*), derived from the fruits and seeds of milk thistle plant, is one of the oldest TCM but also known in the west at the time of Greeks and Romans. The German governmental Commission E, similar to the FDA, recommends it for treatment of toxin-induced hepatotoxicity as well as supportive for chronic liver diseases [15]. Extensive reviews followed yielding a generally safe profile of silymarin [16] but conflicting results as for repeatable significant efficacy [17]. Such discrepancy may reside in the different composition of the main silymarin internal moieties, its concentration and gastrointestinal absorption, eventually often an unpredictable pharmacokinetics. Nonetheless, deeper molecular biology studies of Silymarin are likely to bring about a better designed and formulated silymarin-based liver protector. Similarly, Berberine has recently stepped on the stage of liver protectors with a couple of convincing clinical trials dealing fatty liver and associated lipid abnormalities [18,19]. By high technological analytical systems, some of our group have managed to isolate the most functionally active moieties Specific Bioactive Fractions (SBF) focussing on the some of the above compound with the best safety/efficacy profile (i.e. oleanolic acid and saponins-rich ginsenosides). We then complexed these compounds with lignans, phenolics and steroids-rich eucommiaceae extracts and Alpha-OH-ursolic triterpene derivative) so to widen the target to inflammatory and metabolic pathways. This blend protected in a glyconutrient has been tested in pilot studies. The success of which, helped launching a large multicenter investigation across different countries. The preliminary data so far obtained showed promising results with significant blood liver profile and epigenetic modulation of key genes involved in liver physiology. These data proved to be significantly better than routinely marketed liver protectors, published in a book chapter [20] and invited for presentation at major between Chinese Integrative Medicine and China Functional joint meetings and last Vitafood EU.

Aside from marketing excess and the physiological endurance of liver metabolism, the increased consumption of chemical drugs, the surging of NAFLD/NASH, now the first cause of HCC, and environmental toxins call for a wise use of “liver protectors”. This implies, more than ever, to set high standard of efficacy and safety on natural compounds prescription, especially considering the likelihood of long term use in some instances. This is now paralleled by intensive work on the often multiple mechanisms of action [21] as well as listing phytopharmaco-vigilance [22].

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