



Liver protection: ancient empirical roots, marketing oversimplifications and novel molecular-biology-endowed compounds

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Submission Date: December 11th, 2020; **Acceptance Date:** December 18th, 2020; **Publication Date:** December 23rd, 2020

Please cite this article as: Marotta F., Sweed H., Rastmanesh R., Rasheedy D., Rasulova S., Catanzaro R. Liver protection: ancient empirical roots, marking oversimplifications and novel molecular-biology-endowed compounds. *Bioactive Compounds in Health and Disease* 2020. 3(12): 251-255. DOI: <https://www.doi.org/10.31989/bchd.v3i12.768>

EDITORIAL

Since the millenarian Traditional Chinese medicine (TCM), liver occupies a central role in health understanding and a mandatory organ to deal with whatever the disease location given that “the general of an army stores blood, and acts as a purifier of the body” [1]. The liver is indeed exposed to a storm of potentially deleterious viruses/substances bringing about a disease spectrum ranging from hepatitis and non-alcoholic fatty liver disease to liver cirrhosis and hepatocellular carcinoma (HCC) whose main cause nowadays is in fact chronic progressive initially benign

disease. TCM is culturally attracting and teaching the importance of a, now acclaimed, whole-body harmony as opposed to symptom/diseased organ-center approach. However the main understandable limitation of taking old data from TCM for granted comes not only by incomparable diagnostics and follow ups but also by the huge variety of formulations, dosages, their preparation modalities and multitude of mechanisms of action claimed. This has, on the other hand, created a blooming market in stores of “panacea” liver-TCM of often obscure

quality control, heavy metals and pesticide-free assurance and toxicity per se due to even hepatotoxic ingredients found in some. Some old TCM formulas though, once more precisely structured by advanced molecular biology analysis, have in the last decade shown to affect HCC and also receiving an FDA approval [2] , On the other hand, a lot of others interesting results in *in vitro* HCC model have been obtained with curcumin, tetrandrine and Danshen (Tan-IIA extracted from *Salvia miltiorrhiza, radix* [3-5]. But not followed by clinical studies yet. Disappointedly, despite some positive data [6, 7] coming from *in vitro* and *in vivo* studies, resveratrol and caffeine have failed to prove any benefit from prospective clinical trials, rather than inferring results from retrospective epidemiological surveys [8]. and the protective effect suggested for the latter were based only on retrospective epidemiological surveys, biased by their intrinsic limitations. Poor data also from andrographolide and Shisandra, the latter still very popular in China for liver disease but with negligible clinical studies and a recent report of potential side effects on lipid profile [9]. Also Gamboge, coming from old TCM, and with some selected moieties endowed by some proven therapeutic effects in HCC cell lines [10] and experimental fatty liver model [11], on the clinical side has not produced anything worth mentioning while raising concern about its potential detrimental effect on redox and inflammatory cytokines balance [12]. An unlike compound is represented by a rather safe profile glycyrrhizin acid-based formulation devised in Japan with valuable experimental and clinical studies [13]. During the cumbersome interferon era of HCV therapies, it did represent in Japan a valid alternative. However, besides the novel much more effective drug, a big limitation of glycyrrhizin has been represented by its mandatory

long-term, weekly intravenous administration. This natural compound had the potential to be directed to benign liver disease but all efforts to devise an effective oral or suppository formulation have failed so far. One TCM which was much deeper studied and developed in Japan is Sho-saiko-to within its long tradition of traditional (Kampo) medicine. This was the most frequently used drug (26%), as from a PubMed, Ichushi-Web-the database of the Japan Medical Abstracts Society literature review for almost ten years (1995-2015). Sho-saiko-to had robust studies in benign, viral and malignant liver disease with appreciably long follow up studies [14, 15]. However, some infrequent by very severe up to lethal side effects [16] have drastically limited its use and withdrawn from western markets. A recently popularized old TCM compound in the west is represented by Berberine. This is a natural isoquinoline alkaloid extracted from *Coptidis Rhizoma* capable of induce apoptosis and autophagic death in liver cancer cells [17]. Similarly to *Scutellaria*, Berberine can also reduce hepatic lipids accumulation in rats by epigenetic effect on SREBP-1c, pERK, TNF- α , and pJNK genes [18]. Interestingly, Berberine in TCM is also used to treat intestinal bacterial overgrowth. Silymarin (*Silybum marianum*), extracted from the fruits and seeds of milk thistle plant, is undoubtedly known as the most common and safe liver protector. and received FDA approval to treat hepatotoxicity and liver cirrhosis with a n overall good consumer reputation since several decades to date [19]. Despite all this, an extensive review taking into consideration experimental, pre-clinical and clinical data has not reached any robust conclusion so far [20]. This is likely to be the result of incomparable study methodologies to fit into a homogenous meta-analysis, different concentration of the inner moieties and delivery and erratic pharmacokinetics to define a

more adequate dose-finding [21]. This probably still leaves room to this compound but needs a thorough re-thinking and deeper molecular biology-based investigation. Definitively, a whole crude herbal extract is unlikely to be of significant help. Ginsenosides represent a very popular but wide group within the three main *Panax* spp. varieties (*Panax ginseng* Meyer, *Panax quinquefolius* and *Panax notoginseng*). The main triterpenoid glycosides and some saponins have shown to beneficially affect experimental benign liver disease models [22]. However, only recently it has been shown that Korean Red Ginseng extract could significantly improve inflammatory profile in NAFLD patients [23]. The large variety of different ginsenosides still make this field fascinating and extremely complex and unreliable when not properly analyzed by makers. Our group is intensively working on that considering also that some ginsenosides may trigger drug hepatotoxicity by inhibiting CYP450 [24]. This call is indeed one of the key commitments strongly advocated by Functional Food Center for upgrading makers' knowledge and expertise and consumers' awareness as well [25]. An adamant example of weak links is provided by the case of YHK, a Japan-based but China-imported mixture of *panax pseudo-ginseng*, *Eucommia Ulmoides*, *polygonati rhizome* and *glycyrrhiza*. While this mixture was based on popular TCM concepts and our group independently extensively tested with some success experimentally [26,27], it produced only a very few patients pilot study while boasting unrealistic commercial overclaims such as "cirrhosis reversal" [28]. This probably reflects a far too fast jump into clinical expectations without a due deepening pharma-grade analysis and quality control from the crops to seasonal collecting, storing, extracting, biochemical /functional fingerprinting of each component and encapsulation for each stock.

This compound has been indeed abandoned by publishable research work ever since.

These perplexities were enforced by a study showing the superiority of an antioxidant-based compound versus YHK in an acute experimental acute liver injury [29] as we kept moving on a meticulous and high-technology powered extraction and purification and isolating the most functionally active moieties (SBF: Specific Bioactive Fractions) of only some of the key components of YHK, as shown by in-house comparative work in vitro and discarding others of weak or interfering action. Later on, further studied SBF-isolated effective components (oleanolic acid and saponins-rich ginsenosides, lignans, phenolics and steroids-rich eucommiaceae extracts and Alpha-OH-ursolic triterpene derivative) with effective on inflammatory and metabolic pathways, were added. Finally this mixture was enhanced with a glyconutrient carrier to improve gut transit and intestinal absorption which is one of the weak and unpredictable factors of ginsenosides. Then, after a few pilot studies, we launched a large multicenter study in different countries and ethnicities, each center further deepening specific clusters. Significant benefits appeared from standard liver profile in NAFLD with/without diabetes and/or overweight, in alcohol-chronic liver disease and in epigenetic modulation of key genes for liver such as mitogen-activated protein kinase signaling, MicroRNA 122, chemerin receptor, chemokine-like receptor 1 and Cellular repressor of E1A-stimulated genes. These preliminary data have already been published [30]) and selected for presentation to a major joint meeting between Chinese Integrative Medicine and China Functional and Vitafood EU.

CONCLUSION

The nature is an unbeatable source of compounds, many of them, "isogenic" with our body as, although

with other terminology, anticipated over 2000 years ago by TCM. Several of those ancient formulas have survived till modern times and still are very much used as self-prescription (so, ruled by makers) or advised by a blurred and not homogenous range of "integrative /holistic medicine professionals". New sophisticated molecular biology applied to natural compounds is now a fast growing area but still lacks a seat into academic teaching. Thus, there is a robust call, as promoted by FFC, to guide, teach, examine and endorse new professionalism while, at the same time, to motivate makers of food supplements/functional food to maintain a fair, updated innovation in their products to the benefit of consumers. "Liver protection" after thousands of years still occupies a central concept of health and the herewith presented short analysis tackled with the lights, shadows and risks connected to an oversimplification of the matter and noxious mermaids around.

List of Abbreviations: SREBP-1c: Sterol regulatory element-binding protein 1, pERK: p-extracellular signal-regulated kinase, TNF- α : tumor necrosis factor alpha, pJNK: p-Jun N-terminal kinase, NAFLD: non-alcohol fatty liver disease, NASH: non-alcohol steathepatitis, E1A: Adenovirus early region 1°.

Authors Contributions: Francesco Marotta, Hala Sweed, Doha Rasheedy and Roberto Catanzaro equally contributed to recruit patients, run the study and analysed the data. Francesco Marotta designed the original scheme of the study and wrote this article. Roberto Catanzaro and Saida Rasulova helped studying the literature, critically selecting and comparing the relevant one.

Conflict of Interest: The authors declare that the research and the present article was conducted in the

absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Acknowledgement/Funding: The clinical study was fully supported by ReGenera R&D International which is a EU-registered not for profit research organization and by donations from Liver Support patients associations.

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