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Original Article

New Drug Development using Korean Herbal Formulae: A model role study

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Objectives: Traditional Korean herbal formulae are composed of multiple medicinal plants. This situation of multiple-ingredient mixtures has been considered as a major obstacle to new drug development using herbal formulae in the world market, despite the effectiveness of such mixtures. This study reviewed Liv-52 as a representative model of successful drug development using a multiple-herb mixture.
Methods: All articles for Liv-52 were collected from the PubMed database. The history, composition of Liv-52, its pharmaceutical efficacy and mechanisms, and data from clinical studies including its market size were analyzed.
Results: Liv-52 is composed of seven herbal plants and it is the best known in Ayurvedic medicine for treating liver disorders. Since its 1955 introduction, forty four international papers have been published based on pre-clinical and clinical trials. The efficacy and mechanisms of Liv-52 were intensively studied. Currently, Liv-52 is one of the top-selling products, with over 10 million dollars sales annually, in the world market.
Conclusions: These results indicate that Korean herbal formulae could be new global drugs if scientific evidence for efficacy and standardization are produced via literature researches.

Key Words : Drug development, traditional Korean medicine, formula, Liv-52

Introduction

Owing to an aging society and importance of quality of life, there is a growing need for medicines based on natural products. The scale of the global market for natural products is thought to be over 20 billion dollars[1]. Then, the world drug market demands scientific evidence of efficacy, safety, and standardization of herbal or botanical medicines[2]. This reason has leaded to a focus on mainly single compounds or fractionated extracts from one plant in the field of herbal-derived drug research[3-5].

The herbal formulae have been developed along with clinically experienced effectiveness and safe applications for thousand of years, so these formulae are very important intellectual property in Korea. However, no traditional formulae have yet gained prominence in global products, and successful drug development using multiple-herb compounds has been regarded as difficult.

On the other hand, Ayurvedic medicine in India has also prescribed traditional herbal formulae composed of multiple medicinal plants similar to Korean traditional medicine. Among them, Liv-52 is the best known, a drug modernly developed from a traditional Ayurvedic formula composed of seven herbal plants. This drug became very widely used in many countries for patients with hepatic disorders.

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Liv-52 was initially introduced by an Indian company called Himalaya Herbal Healthcare in 1955. It succeeded as a new drug after FDA approval and now has been exported for over 10 million dollars annually[6-8].

It was reported that 65% of patients with hepatic diseases in United States of America use Complimentary and Alternative Medicine (CAM), including herbal drugs[9]. However, their negative reputation is increasing, especially about herbal medicines. Accordingly, the success of Liv-52 could be a big challenge for us to try for a formula-derived new drug development.

This study aimed to review Liv-52 as a representative model, so as to provide useful information for drug development using multiple mixture herbs in Korea traditional medicine.

Method

Systematic literature searches were conducted using the electronic PubMed database (a service of the U.S. National Library of Medicine and the National Institutes of Health). Forty-four relevant papers were found in the PubMed database by limitation of default tag "Title" and key word "Live-52" from 1 January, 1996 to 31 August, 2009. According to statistics and analysis of these literatures, history, composition, efficacy, pharmacologic mechanism, current situation of clinical study and marketing of Liv-52 were presented, as follows.

Result and Discussion

1. History and composition of Liv-52

Liv-52 is one of the best-selling natural complex medicines, used since 1955 in India. Each Liv-52 contains seven kinds of herbal plant: capers (*Capparis Spinosa*), wild chicory (*Cichorium intybus*), arjuna (*Terminalia arjuna*), black nightshade (*Solanum nigrum*), coffee senna (*Cassia occidentalis*), yarrow (*Achillea millefolium*), and tamarisk (*Tamarix gallica*)[10]. These components were mixed in different combinations and after 51 repeated trials, the perfect combination was discovered on the 52nd, thereby, it was named Liv-52[11].

The components of Liv-52 were reported to have a wide spectrum of pharmacological properties like hepatoprotective, antioxidant, anti-inflammation, detoxification, uretic and so on. Capers and wild chicory containing esculetin and p-methoxybenzoic acid was proved antioxidative and hepatoprotective effects in animal models[12-14]. Arjunolic acid and flavonoids, isolated from arijuna, increased the glutathione contents. Black nightshade markedly protected from the DNA damage caused by free

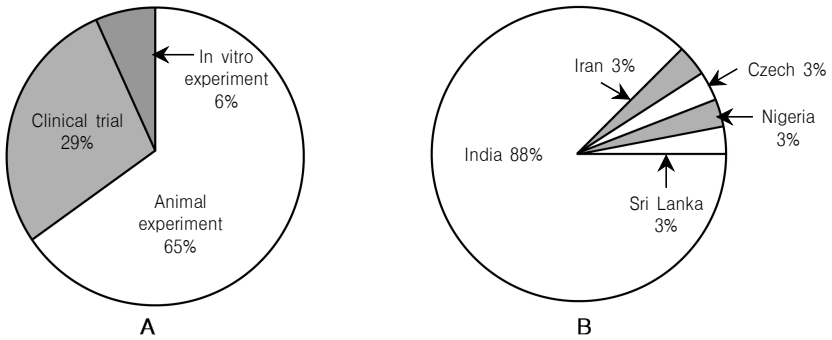

Fig. 1. Distribution of researches using Liv-52 according to objects or methods (A), and countries which studied in (B)

radicals[15,16]. Anti-oxidative and hepatoprotective effects were also found in coffee senna, yarrow and tamarisk separately[17,18].

2. Analysis on research content and process of Liv-52

Forty-four studies focusing on Liv-52 were conducted and published since 1996. Papers were increased and their number varied from seventies to nineties. Among them, clinical trails account for 29% whereas animal studies were about 64% (Fig. 1-A). It is considered that many preclinical experiments are very supportive for clinical trials in the process of drug development Liv-52. 88% of studies were done in India. The other countries include Iran, Sri Lanka, Czech, Nigeria, etc. (Fig. 1-B)

According to the efficacy-related subject of Liv-52, about 67% of papers have shown a hepatoprotective effect against various hepatotoxicity models. In addition, plenty of other beneficial efficacies have been reported, e.g. promotion of liver activity, protective effect on bone marrow failure induced by radiation, alcohol and lipid metabolism improvement and effective prophylactic role against chemical-induced carcinogenesis etc. (Fig. 2)

3. Clinical trials and pharmacological mechanisms of Liv-52

There were ten clinical trial studies using Liv-52, including four studies associated with alcoholic liver diseases and three for acute virus hepatitis[19-25]. Furthermore, improvement of appetite in fragile children and hepatoprotective effect in leprous patients were also reported[27,28]. One clinical trial in 2003 showed no positive effect, but in most of clinical trials, Liv-52 has a good effect. Especially, in 2005, efficacy on patients of liver cirrhosis was confirmed through a randomized controlled clinical trial (RCT). This result has a very important meaning because cirrhosis is the crucial step of pathological development determining clinical prognosis in chronic liver diseases[28] (Table 1).

Many studies showed the mechanisms of Liv52. This drug increases the activity of the enzymes that are distributed in mitochondria and microsomes, as well as, it seems to promote the activity of antioxidants such as glutathione, superoxide dismutase (SOD), etc.[29,30] Liv-52 can enhance hepatocyte function, cell regeneration, metabolizing activities in hepatocytes, and reduction of acetaldehyde, a highly reactive alcohol metabolic intermediate. It also inhibits the generation of tumor necrosis factor-alpha and an inflammation related-cytokine[25,31,32]. In addition, Liv-52 can inhibit lipid peroxides during alcoholic liver damage[33,34].

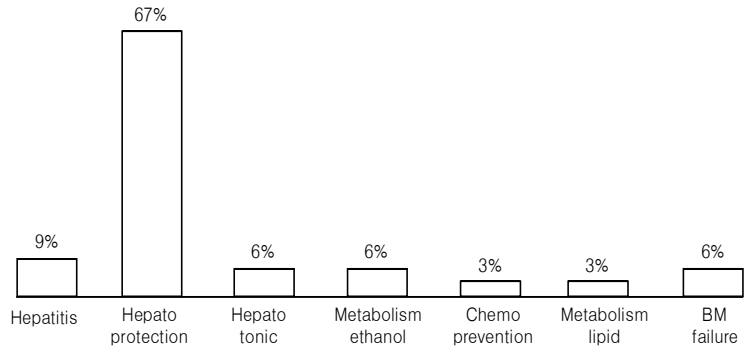

Fig. 2. Distribution of studies referencing Liv-52 according to subjects or purposes

4. Drug development strategies for traditional Korean formulae

Liv-52 is exported to 50 countries around the world, with over ten million dollars (US) sales, annually. It is one of the best natural medicines for liver disease in the world and every year its usage seems to be increasing steadily by 7-8%[34]. Herbal drugs like silymarin, ursodeoxycholic acid, diphenyl dimethyl dicarboxylate and glycyrrhizin originate from a single medicinal plant. However, Liv-52 is a complex formula composed of seven medical plants, and succeeded in the world market as a new drug.

In traditional Korean medicine (TKM), the available herbal formulations are composed of complex herbal mixtures. TKM has progressed systematically according to the Oriental pharmacological theory. Although plenty of clinical evidence substantiates the validity of the medicines, none of the traditional Korean medicines exist in the global market as a valid drug. One major reason for this may be the deficiency of scientific evidence. Recently, evidence-based medicine (EBM) or evidence-based complementary and alternative medicine is critically important in the medical community[35,36]. So, the importance of clinical study, especially RCT, should be highlighted for drug development using TKMs. In the case of Liv-52, more than 40 international papers provide scientific evidence for its efficacy, in particular, through 10 clinical trials. Plenty of Korean traditional formulae have been used in preclinical and clinical trials so far; however, such amount of research data has not been accumulated about one single formula, like for

Table 1. Summary of clinical trials using Liv-52 for treating various diseases

Study	Study design (N. of Patients)	Jadad* score	Etiology	Duration	Results
1[28]	randomized, double-blind, placebo-controlled (36)	5	liver cirrhosis	6 months, 6 months FU**	significantly better Child-Pugh score, ascites, serum ALT, AST
2[19]	randomized, double-blind, placebo-controlled (80)	5	alcoholic liver disease	6 months, No FU	no effect on clinical outcome and liver chemistry
3[20]	retrospective (19)	0	alcoholic liver disease	1 year No FU	improvement in subjective symptom, hepatomegaly, aminotransferases
4[21]	placebo-controlled (25)	2	alcoholic liver disease	15 days No FU	rapid absorption of ethanol and reduction of acetaldehyde levels
5[22]	placebo-controlled (9)	2	alcoholic liver disease	12 hour No FU	rapid reduction of ethanol and acetaldehyde levels
6[26]	open-label, comparative (42)	0	lepromatous leprosy	12 weeks 9 months FU	restores normal liver functions, improves appetite
7[23]	prospective, historical-controlled (70)	0	infective hepatitis	2 weeks No FU	rapid reduction of symptoms, jaundice and restored appetite
8[24]	randomized, double-blind, placebo-controlled (34)	3	viral a type hepatitis	till recovery No FU	took shorter times for symptomatic recovery and fall in bilirubin level
9[28]	open-label, comparative (unknown)	0	marasmus	20~105 days	revive lost appetite and to promote growth
10[25]	open-label, comparative (250)	0	acute hepatitis	3 months 9 months FU	restore liver function than prednisone and vitamin group

*Jadad score: Scale method to quantify the quality of clinical study according to randomization, double-blinding, placebo-control, and their proper applications(37).
**FU: Following up to observe the efficacy of drug treatment for certain period.

Liv-52.

Beside evidence for drug efficacy, standardization and safety data of complex formulae of TKM according to international standards are the most important factors. Multiple herb-derived formulae are generally considered to be more difficult in standardization and toxicity evaluation. However, in order to enter the huge global medicine market, a complete standardization and safety database is essential in the process of new drug research and development. Furthermore, it needs a strategy that accumulates research data intensively and stably by using constant recipes proved to be functionally effective. Especially, lots of genuine scientific evidence should be generated using well-designed clinical trials for traditional Korean medicine formulae in future.

Conclusion

This study reviewed the process of research and success of Liv-52 as new drug in the world, which is originated from an Indian traditional Ayurvedic herbal formula of multiple medicinal plants. TKM formulae are expected to gain world-wide attention as part of the Korean traditional heritage based on centuries-old clinical practice. The authors hope that this study may play a role on new drug development using formulae of TKM.

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