J Food Sci Nutr
Vol 10, p 95～102 (2005)

J Food Science and Nutrition

– Review –

Pharmacognosy for Korean Medical Food in the 21st Century

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Abstract

The term pharmacognosy as applied to a constituent scientific discipline of Korean Medical Food (KMF) has been in use for nearly several years, and it refers to studies on the pharmacological properties of natural products foods. During the last half of the 20th century, pharmacognosy for KMF evolved from being a descriptive botanical subject to one having a more chemical and biological focus. At the beginning of the 21st century, teaching pharmacognosy for KMF teaching in academic culinary arts and natural healing institutions has been given new relevance as a result of the explosive growth in the use of herbal foods (health foods) in modern KMF practice. In turn, pharmacognosy for KMF research areas are continuing to expand, and now include aspects of cellular and molecular biology in relation to natural products, ethnobotany and phytotherapy, in addition to the more traditional analytical method development and phytochemistry. Examples are provided in this review of promising bioactive compounds obtained in two multidisciplinary natural product KMF development and discovery projects, aimed at the elucidation of new plant-derived cancer chemotherapeutic agents and novel cancer chemopreventives, respectively. The systematic study of KMF offers pharmacognosy groups an attractive new area of research, ranging from investigating the biologically active principles of KMF and their mode of action and potential active substance interactions, to sanitary and quality control, and involvement in clinical trials.

Key words: pharmacognosy, Korean Medical Food (KMF)

INTRODUCTION

The term pharmacognosy was first used between 1811 and 1815, and originally referred to "materia medica", the knowledge of drug materials or pharmacology. It is derived from two Greek words, *pharmakon* (a drug) and *gignosko* (to acquire a knowledge of) (1). Later on, pharmacognosy became restricted to that branch of pharmacy investigating "medicinal substances from the plant, animal and mineral kingdoms in their natural, crude, or unprepared state, or in the form of such primary derivatives as oils, waxes, gums, and resins" (2)

Although this latter definition may have been appropriate for the descriptive and microscopic applications of pharmacognosy of medicated diet which were developed from the 19th century until the middle of the 20th century (3), it became necessary for the definition to be expanded and redefined as it subsequently broadened in scope to encompass the chemical components of crude medicated foods. For example, pharmacognosy was stated to be "an applied science that deals with the biologic, biochemical, and economic features of natural foods and their constituents" (4). In a further attempt to update the scope of this field in a manner consistent with scientific activities ongoing at the beginning of the 21st century, pharmacognosy for medicinal foods has recently been defined as "a molecular science that explores naturally occurring structure-activity relationships with a medicated potential" (5).

The origin of Korean Medical Food (KMF) goes back to ancient times. Probably, local foods were being used therapeutically when our ancestors settled in this land. This kind of action was like touching wounded area or vomiting the poisonous food. The result of these experiences was the belief that every illness is caused by intrusion of outside factors. Therefore, extrusion of the pathogen was believed to be the appropriate treatment of the illness. In the earliest times, the people believed in a simple naturism. Naturism gradually became animism and this animism with the concept of outer factors brought forth the idea of evil spirits. That is, people believed it was evil spirits that brings disease to people and driving out evil spirits was the way to cure diseases. Commensurate with this Shamanism driving out evil spirits in incantatory ways became the mainstream of ancient therapeutic actions. In 『Samguk-yusa · Kojosun』,

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where the birthmyth of Kojosun is recorded, there is a story of a tiger and a bear who wanted to reincarnate into human form took wormwood and garlic. In 『Chewang-un-gi』, which was written around the same time as 『Samguk-yusa』, wormwood and garlic are described as "eatable medicine" and this tells us that even in times when incantatory medicine was the mainstream, medicinal· herbs were applied. Moreover the fact that wormwood and garlic are not found in the Chinese herb classic 『Shinnong-boncho-kyung』 shows Korean Medicine had its own origins. Commensurate with the influence of foreign cultures, Korean Medicine underwent changes. In the period of the Three States, Chinese Medicine and Indian Medicine were adopted thereby setting up the foundation of Traditional Korean Medicine. In the period of the Unified Shilla, medicine from Tang-China and India were added to traditional medicine. During the Koryo-period), traditional medicine from Shilla and especially Buddhist Indian Medicine affected by Buddhism were incorporated into Koran traditional medicine. Merchants and Arabia and Song (a newly founded nation in China around that time) introduced various herbs from the Western and Southern tropics were introduced and new medical knowledge was also adopted. By the time the Won was established, Koryo Medicine was developing independently because there was not enough interchange of medicine between the two countries. Therefore more investigation of domestic herbs was required and the result was publication of numerous books on domestic herbs. Koryo Medicine seems very dependent on Song and Won Medicine, but that is a misperception. The theories were based on medicine of Song and Won but prescriptions were based on medicine of Unified Shilla. 『Chejung-ip-hyobang』, 『Ui-chwar-yo-bang』, 『Hyang-yak-ku-gup-bang』 are ancient medical books that attest to the independence of Korean traditional medicine. Traditional medicine was highly developed and widely used by the Chosun period and its fruit was 『Hyang-yak-chip-sung-bang』. Chinese medicine, however, was also accepted in many ways. Chinese medicine, established in the Han dynasty, was first accepted by Shilla and was accepted again by Koryo. In late Koryo, medicines of the Kim and Won dynasties were accepted but were not very influential, but has a greater affect on the medicine of the Chosun dynasty. By the time of King Sejong, a book named 『Ui-bang-yuch-wi』 was published that integrated all of the earlier books on Chinese medicine. After this, many books on specialties were published. After the Japanese invasion of Kore in 1592 『Tong-ui-bo-gam』 was written by Huh Chun that integrated the varied aspects of Korean medicine. By that time Korean medicine was based on Chinese medicine in theory, but adapted Korean (Chosun) herbal drugs (herbs produced in Korea) in practice. But 『Tong-ui-bogam』 unified these. Huh Chun gathered all the previous theories before him and developed his own system of medicine that unified Chinese (Myung) Medicine and Korean (Chosun) Medicine. Since that time, Korean medicine has spread widely throughout China, Japan and Korea and is still effectively used.

In the late Chosun dynasty, positivism was widespread. In positivism, actual proofs and experiences were highly regarded. Doctors who had turned away from politics devoted themselves to treating diseases and, as a consequence, a new educational tradition was established. Simple books on medicine for the common people were published. During those days Four Constitutional Medicine and KMF by I Che-ma was established. He typified human and matched treatments. After this, Korean medicine and KMF faced many challenges when Western medicine was introduced and Japan ruled Korea. However, KMF continued to flourish and make progress (6-15).

Today, at the beginning of the 21^{st} century, pharmacognosy for KMF teaching and research is pursued enthusiastically by its disciples in academic departments of pharmacy and culinary arts in Korea. Although the name pharmacognosy for KMF may be replaced by terms such as phytochemistry or pharmaceutical biology, the areas of research embraced by natural products may include aspects of analytical chemistry, bioactive compound discovery, bioassay method development, biocatalysis, biosynthesis, biotechnology, cell biology, chemotaxonomy, clinical studies, cultivation of medicinal plants, ethnobotany, genetics, marine chemistry, microbial biotransformation, molecular biology, organic synthesis, pharmacology, phytochemistry, phytotherapy, the standardization of traditional medicines, taxonomy, tissue culture, and zoopharmacognosy (the study of self-medication of medicinal plants by primates and other animals) (16-27).

The chemical aspects of pharmacognosy for KMF have benefited enormously from the widespread availability of powerful spectroscopic techniques, particularly mass spectrometry and nuclear magnetic resonance, coupled with effective chromatographic methods for the purification of organic molecules from crude solvent extracts (7,24,28-31). Some of the early phytochemical work in some departments tended to focus on looking for new sources bioactive components to supplement the traditional herbal prescriptions of KMF. It was quickly realized by the more research oriented-KMF institutions, however, that it was necessary to incorporate an element of biological testing with phytochemical work (15,18, 19). Incorporation of a bioassay into the process of chromatographic purification has permitted the purification of one or more bioactive substances from the crude extracts prepared from organisms by bioactivity guided fractionation. This inexpensive *in vivo* technique has become widely used in natural products chemistry and KMF. Many primary and secondary bioassays appropriate for the screening of natural product crude extracts for KMF, purified chromatographic fractions, and pure isolates have been developed, and can be varied accordingly depending on whether the desired outcome of the research is a pharmaceutically or agrochemically relevant target compound (23,27,32-34).

In this review, two major facets of current research being conducted by pharmacognosy groups for KMD will be covered, namely, KMF discovery and the scientific validation of herbal remedies. Given the broad range of such activities that are taking place around the world, it is not possible to cover all of the relevant research in this review.

KMF DEVELOPMENT AND DISCOVERY FROM NATURAL PRODUCTS

The importance of KMF from animal, microbial, and higher plants is well established, with such natural products also serving as lead compounds for semisynthetic manipulation and as templates for total synthetic modification (16-27). It has been estimated that up to 50% of the prescription medications presently dispensed in Korea may contain one or more natural food-derived products, with this term broadly defined so as to include various types of molecular modification (34). This trend is likely to continue in the future, based on the high proportion of compounds entering clinical trials that are either natural products per se, or semi-synthetic compounds based on natural product template molecules (28).

Accordingly, there remains considerable interest in the screening of organisms in KMF discovery programs, since structurally-novel chemotypes with potent and selective biological activity may be obtained, and considerable biodiversity exists (18,19,21). In a recent statistical survey, it was pointed out that when compared with libraries of synthetic substances, natural products offer the prospects of discovering a greater number of compounds with sterically more complex structures (24,30). In the next few paragraphs, Korean herbal plants will be considered specifically. Only a relatively small percentage (5 ~ 15%) of native Korean herbal plants have been systematically investigated for the presence of bioactive compounds (28,31). Plants offer the scientist searching for novel bioactive compounds the added advantage of ethnobotanical observations, since many species are used in systems of traditional KMF, mainly in developing countries (17-22,30). It has been estimated that nearly 75% of biologically active plant-derived substances used in the world were discovered by following up on leads from traditional healing sources (17,30, 35,37). However, great concern has been expressed about the prospects of indigenous knowledge of ethnomedicinal foods lasting far into this new millennium (Cox 2000). Depending on the selection of the *in vitro* and *in vivo* bioassays used to monitor the crude extracts, chromatographic fractions, and pure isolates of a plant or other organism, natural product research can be focused on a particular type of disease. Thus, the following paragraphs will summarize some of the progress made recently on the discovery of potential plant-derived anticancer agents and naturally occurring cancer chemopreventive agents in two separate multidisciplinary collaborative research projects at Seoul National University in Korea (18,19,21). Other groups in pharmaceutical education institutions have described natural product research directed toward other disease targets such as anti-fungal agents (38,39), anti-mycobacterial agents (40), and anti-viral agents (41), and hypoglycemic agents (42).

Cancer is a prevalent cause of mortality and morbidity in Korea. On a world-wide basis, the incidence of cancer is increasing at a more rapid rate than the population (42). Among the many advances in cancer therapy, cancer chemotherapeutic agents based on plant secondary metabolites have played a part, and there are now 11 such compounds based on four structural classes (bisindole alkaloids, camptothecin derivatives, epipodophyllotoxins, and the taxanes) used clinically in Korea (43).

The taxane diterpenoid, paclitaxel (Taxol; Fig. 1a), is worthy of special mention, since this was the first chemically-unmodificated plant constituent in over 25 years to have been approved by the Korean Food and Drug Administration (KFDA) in Korea, when it came onto the market as an anti-cancer agent in the early 1990s. This compound, isolated initially with the trivial name taxol from the bark of the Pacific yew (*Taxus brevifolia* Nutt.; Taxaceae), is now produced semi-synthetically from 10 deacetylbaccatin III (Fig. 1b) extracted from ornamental yew species, and has become the biggest selling anticancer agent ever in Korea. Needless to say, the clinical and commercial success of paclitaxel has played an extremely important role in stimulating further exploratory research to discover additional novel compounds from plants. In addition, several additional potential plant-derived anti-cancer agents are

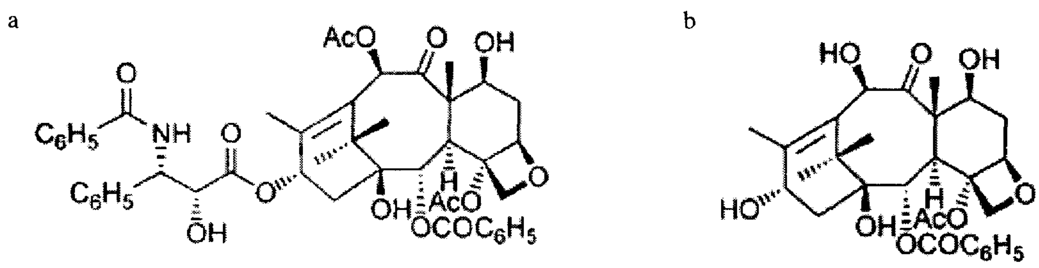


Fig. 1. Structures of paclitaxel (Taxol; a) and 10 deacetylbaccatin III (6).

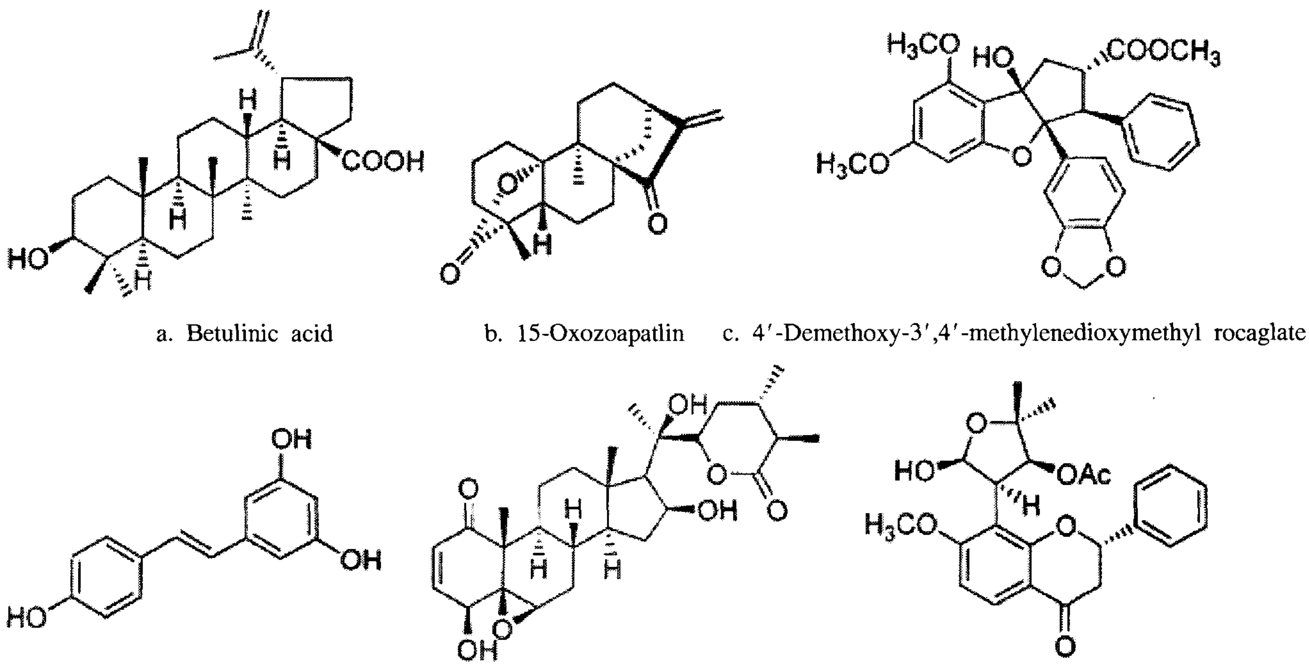
presently undergoing preclinical or clinical trials. Accordingly, there is an enduring interest in investigating the plant kingdom further, with the aim of discovering additional new classes of compounds with anti-cancer activity (43-47).

In an effort to develop and discover novel anti-cancer agents of plant origin from KMF, our team at the Catholic University of Korea is performing collaborative work with groups from a private research institute and a major pharmaceutical and food company (Samyang Co. Ltd., Seoul, Korea). Our group has developed a standard extraction scheme suitable for the screening of dried plant samples, in which the chloroform-soluble extracts are subjected to a detannification step by washing with sodium chloride solution to remove vegetable tannins, which tend to interfere with protein-based bioassays (43). The organic-solvent crude extract of each plant acquisition is screened in a panel of about 25 cell-based and enzyme-inhibitory and receptor binding mechanismbased *in vitro* bioassays housed at the three primary sites in the consortial group, including high-throughput screening procedures at our partner pharmaceutical and food company. Before performing activity-guided fractionation of a promising lead, a dereplication step is taken, in an attempt to detect active compounds with previously known structures present in the crude extract. This involves subjecting the active extract in a standard HPLC system, passage through a UV detector at 280 nm, and splitting the stream into two. The smaller portion is treated and then passes into a mass spectrometer, while the larger portion is fractionated into a 96 well plate, with each well then evaluated in the bioassay in which the initial activity was found. Several hundred biologically active compounds have been obtained in this collaborative project thus far, representing a wide range of plant secondary metabolites.

EXAMPLES OF ACTIVE COMPOUNDS WHICH HAVE COME FROM THIS PROGRAM TO DATE ARE BETULINIC

Acid (Fig. 2a) from *Ziziphus mauritiana* Lam. (Rhamnaceae), 15-oxozoapatlin (Fig. 2b) from *Parinari curatellifolia* Benth. (Chrysobalanaceae), and the novel compound 4′-demethoxy-3′,4′-methylenedioxymethyl rocaglate (Fig. 2c), from *Aglaia elliptica* Bl (Meliaceae). Betulinic acid was shown to be selectively active for a human melanoma cancer cell line, and to exhibit *in vivo* activity in a mouse xenograft model bearing human melanoma. Both 15-oxozoapatlin and 4′-demethoxy-3′, 4′-methylenedioxy-methyl rocaglate (46) have been selected for *in vivo* xenograft testing at the National Cancer Institute in Korea, following successful evaluation in a number of preliminary tests.

An alternative approach to combating cancer by intervention with natural products involves their use as potential cancer chemopreventive agents from KMF. Cancer chemoprevention has been defined as "a prevention or delay process of carcinogenesis in humans by the ingestion of medicated diet (KMF) or pharmaceutical agents" (48). There has been a considerable amount of work devoted to the cancer chemopreventive effects of extracts and purified constituents of culinary herbs, fruits, spices, teas, and vegetables, which have been shown to inhibit the development of carcinogenesis in long-term animal models (49). In our collaborative project on cancer chemopreventive agents from KMF, which has been ongoing since 2001, novel compounds have also been isolated from crude plant extracts by activity-guided fractionation, with a different panel of bioassays used than in the project described above on anti-cancer agents. As in the previously mentioned project, more than one hundred compounds have been isolated with activity in one or more bioassays, representative of a wide array of secondary metabolite structural types. Examples include resveratrol (Fig. 2d) from *Cassia quinquangulata* Rich. (Leguminosae), withaphysacarpin (Fig. 2e) from *Physalis philadelphica* Lam. (Solanaceae), and the new flavonoid, tephrorin A (Fig. 2f), from *Tephrosia purpurea* Pers. (Leguminosae), which is a flavanone containing an unusual tetrahydrofuran moiety. Resveratrol, which also occurs in grapes and red wine, was found to be active as an inhibitor of cyclo-



a. Betulinic acid b. 15-Oxozoapatlin c. 4′-Demethoxy-3′,4′-methylenedioxymethyl rocaglate

d. *trans*-Resveratrol e. Withaphysacarpin f. Tephrorin A

Fig. 2. Structures of promising bioactive natural products obtained from KMD development and discovery projects.

oxygenase 1, and then to show significant activity in the mouse mammary organ culture assay and in a full-term mouse skin carcinogenesis study (45). The above examples from two natural product projects from KMF related to cancer demonstrate that interesting new biological observations may be made in a multidisciplinary setting for even very common compounds such as betulinic acid and resveratrol. Moreover, by strict adherence to activity-guided fractionation techniques, it is still possible to obtain new active compounds of considerable structural interest, even from comparatively well investigated species such as *Tephrosia purpurea*. It can be expected that future natural product KMF development and discovery projects will involve the need to go literally to the ends of the earth, to obtain previously unstudied organisms which may be logistically quite hard to obtain. In addition to the intended development and discovery of new KMD, such programs can afford useful information concerning the protein and other cellular targets of small-molecule natural products. It is worth pointing out that natural product KMF development and discovery projects, similar to the two described above, will increasingly require that participating pharmacognosists collaborate with scientists in other disciplines, such as analytical chemists, biochemists, biostatisticians, medicinal chemists, molecular biologists, organic chemists, pharmacologists, structural biologists, taxonomists, and toxicologists. Moreover, it is necessary for academic institutions to make a considerable investment in infrastructure to support such research work. In addition to the need for properly equipped phytochemical and biological testing laboratories, it is also necessary to have access to facilities to process plants or other organisms (maintaining an inventory, taxonomic authentication, milling, small- and large-scale extraction, and storage), as well as having the appropriate means of cultivating selected species. A large amount of information is generated on the collection details of organisms, and on the biological data of extracts, chromatographic fractions and pure compounds, so it is necessary to process this information electronically. Central administrative support from the institution is also needed, as for example, the involvement of legal and international offices to help formulate agreements with authorities in the source countries of plants or other organisms of interest.

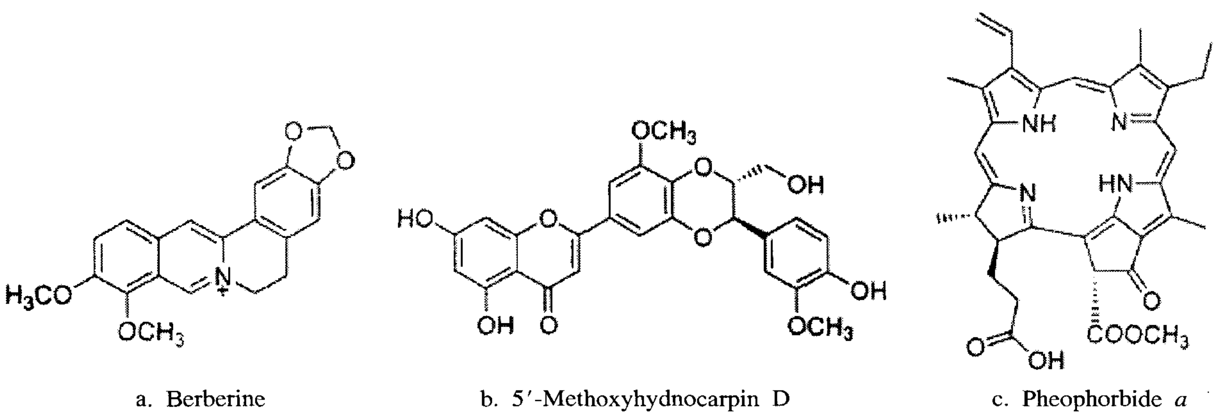
STUDIES ON HERBAL MEDICINES FOR KMF

In many developing countries, there is still a major reliance on crude preparations of plants used in traditional medicines for primary health care (48). In countries such as India, China, Japan and Korea, the systems of traditional medicine are particularly well developed, and both of these have provided interesting new drug leads for potential development in Western medicine. Moreover, a number of clinical evaluations of herbal medicinal preparations have already been conducted in certain western countries (7,29). As alluded to earlier, a major change has occurred in the interest of health professionals in Western countries concerning the use of herbal remedies over the last decade, which in large part mirrors the increasing interest held by the public in terms of self-medication with botanical products. For pharmacognosists employed in KMF educational institutions in Korea, this new awareness of natural products has come as a major "shot in the arm", and a number of useful texts on the analysis, uses and/or potential toxicities of herbal remedies have appeared recently, which not only assist with teaching in KMF professional or undergraduate curricula but also serve as useful guides in KMF practice (17,35-38).

Not only has the "herbal remedy revolution in Korea" created new opportunities for the teaching of pharmacognosy for KMF, but this phenomenon has also served to stimulate research in a new field of direct relevance to human healthcare. However, to understand the mode of action of folk herbs and related KMF is even more complex than mechanistic clarification of a single bioactive factor. This is because unfractionated or partly fractionated extracts are used, often containing complex mixtures of bioactive compounds, and in many cases synergism is most likely playing an important role. Clarification of the active constituents and their modes of action for KMF will be difficult. This is nevertheless a worthwhile subject for serious investigators. Many phytochemical and biological groups in Korea have already begun to perform laboratory work in a meaningful way on herbal remedies for KMF. For example, recent papers have appeared for common herbal remedies in terms of the development of analytical methodology (50); isolation procedures for reference compounds (51); the characterization of new chemical constituents (24); the identifcation (8,28), structure elucidation (31), biosynthesis (43) and chemical reactivity (19,20) of bioactive principles of phytomedicines; active compound mechanism of action determination (52); and the toxicological evaluation of phytomedicine components (53, 54). A potentially far-reaching observation in terms of the safety of consuming certain herbal teas from KMF was made recently, when it was realized that two hepatotoxic otosenine-type pyrrolizidine alkaloid macroester constituents of traditional KMF, *Ligularia hodgsonii* Hook. (Compositae), which is used as an antitussive, are soluble in both organic solvents and water. Although pyrrolizidine alkaloids based on otosenine are not particularly common, whenever they do occur in herbal teas used in KMF they will thus be water-soluble when in the hydrophilic ionized form, and hence potentially toxic (55).

The concept of several active principles acting in a synergistic manner in herbal remedies may be somewhat unusual to pharmaceutical scientists who are more accustomed to activity in a medicinal preparation being due to a single therapeutic agent (56). However, a recent example may be given of this phenomenon, with reference to constituents of the plant *Berberis freemontii* Torrey (Berberidaceae), a plant once used in traditional KMD. It has been found that the anti-bacterial activity of berberine (Fig. 3a) from *B. freemontii* against a resistant strain of *Staphylococcus aureus* was potentiated by the addition of two additional constituents of the plant, the flavonolignan, 5′-methoxyhydrocarpin D (Fig. 3b), and the porphyrin, pheophorbide *a* (Fig. 3c). Although either compound 10 or 11 potentiated the effects of a sub-threshold concentration of the alkaloid, neither possessed antibiotic activity when tested alone. Berberine is also present in high concentrations in the widely used herbal remedy Goldenseal (the rhizomes of *Hydrastis canadensis* L.; Ranunculaceae) (57,58), so it is possible that synergistic biological effects occur between this protoberberine alkaloid and other known or as-yet unidentified constituents of this KMD.

In a recent review article, we outlined some of the scientific challenges that ensuring the safe and effective



a. Berberine b. 5′-Methoxyhydnocarpin D c. Pheophorbide *a*

Fig. 3. Structures of compounds showing synergistic antibacterial activity.

use of herbal remedies will present the manufacturers of these KMF, in terms of bioavailability, phytoequivalence, standardization and other sanitary/quality control issues, and the performance of properly designed clinical trials leading to the introduction of new KMF. In Korea, the passage of the Dietary Supplement Health and Education Act in 1994 led to the categorization of herbal medicines as "dietary supplements" for "health maintenance", and has resulted in the influx of hundreds of new plant products onto the shelves of pharmacies and health food stores (26,27,30,34-36,38,59,60). Many of these products have not been studied comprehensively, and their chemical compositions and/or pharmacodynamic activity are largely unknown. Sometimes there are also concerns about their sanitation and quality or potential interactions when co administered with prescription KMF. This is in sharp contrast to the thoroughness in which KMF must be evaluated before receiving approval by the KFDA. Perhaps the present state of affairs with regard to these new botanical dietary supplements from KMF is more in keeping with the situation which might have been expected at the turn of the 20th century than at the present time (61,62).

CONCLUSION

As we enter the 21st century and the new millennium, it may be argued that interest in pharmacognosy for KMF in general is at an all time high. The last decade has seen a greater use of botanical products among members of the general public through self-selection than ever before. This phenomenon has been mirrored by an increasing attention to herbal remedies from KMF as a form of alternative therapy by the health professions. The major new addition of herbal remedies from KMF to culinary practice has greatly increased the relevance of pharmacognosy for KMF as a didactic subject, and has augmented interest in this topic among culinary students. While pharmacognosy for KMF has always been a strong core discipline in the professional culinary curriculum in Korea, it is not unreasonable to suggest that every school or department of culinary arts in the future should have at least one faculty member who is thoroughly knowledgeable in the subject of herbal remedies. The various topics and scientific approaches to research in pharmacognosy for KMF and natural products continue to expand. As interest in the scientific components of natural foods increases in both the scientific community and the general public, there will be increased funding opportunities, but there will also be increased competition from those in disciplines outside of academic culinary institutions to perform this sort of research. Though pharmacognosists for KMF have valuable knowledge that can be extremely useful in natural products for little question that pharmacognosy for KMF as a discipline will have a role to play for many more years, and that pharmacognosists for KMF can look to the future with a great deal of anticipation.

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(Received October 18, 2004; Accepted December 8, 2004)