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RISK-BENEFIT ASSESSMENT BETWEEN INHIBITION OF ANGIOTENSIN CONVERTING ENZYME (ACE) AND MELANOGENESIS OF MEDICINAL HERB, VIOLA MANDSHURICA

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ABSTRACT

Food substances are recognized to have the potential to exert both health benefits and health risks. The Scientific Committee of the European Food Safety Authority (EFSA) developed guidance for performing risk-benefit assessments of food. We applied chemical and biological hazard assessments of Korean Ministry of Food and Drug Safety recommends to risk-benefit aspects. A mathematical model by Tallarida's the severity of diseases and adverse drug reactions is derived from these weights and categories to calculate the observed benefit-less-risk score for an individual. For inhibition of angiotensin converting enzyme (ACE), the profit is 13.927. For melanogenesis (biochemical pathway of melanin), the profit is -11.66. Potential risks of medicinal herb, *V. mandshurica* intake must be considered in the context of potential benefits.

KEYWORDS: EFSA, mathematical model by Tallarida, risk-benefit, *Viola mandshurica*.

INTRODUCTION

Historically in food safety too much focus on risk without considering benefit. A food or food substance is recognized to have the potential to exert both health benefits and health risks.[1] Risk assessment is a process intended to calculate or estimate the risk to a given population or subpopulation, including the identification of attendant uncertainties, relating to exposure to a particular agent, taking into account the inherent characteristics of the agent of concern as well as the characteristics of the specific target system.[2] Benefit is the probability of a positive health effect and/or theprobability of a reduction of an adverse health effect in an organism, system, or (sub) population, in reaction to exposure to an agent.[3]

The Scientific Committee of the European Food Safety Authority (EFSA) developed guidance for performing risk-benefit assessments of food. The document focuses on human health risks and human health benefits, and does not address social, economic and other considerations such as "cost-effectiveness" considerations. It is important for risk-benefit managers to be able to weigh the risks against the benefits on the basis of a qualitative or quantitative risk-benefit assessment.[1]

Risk assessments also enable risk response and mitigation strategies to be expressed. Cost/benefit analysis can be used to compare risk mitigation strategies and understand how effectively the money would be spent.

Viola mandshurica W. Becker is a perennial herb and found throughout the East Asian region, China including Taiwan, Korea, Mongolia, Japan including Okinawa and the Russian Far East Korea.[4] It is native to eastern Asia, being found as far west as eastern Siberia, throughout China (including Taiwan) and Korea. Many researchers have reported that *V. mandshurica* have potential antioxidant and anti-diabetic properties[5] and can be used to treat asthma by inhibiting inflammatory response.[6] Also, *V. mandshurica* could lead to development of anti-asthma pharmaceuticals using the same principles.[7] and protect nerve cells from oxidative stress and even reduce apoptosis, which may lead to treatments for neuronal diseases.[8]

Despite the criticism of herbal medicine among mainstream medical professionals, it is wise to remember that many common drugs we use today were derived from plant-based sources. For example, scientists originally derived aspirin from willow bark; herbalists prescribe white willow for headaches and pain control. Although many scientific articles have been published on natural products and their diverse effects, each plant species has several different natural constituents, the great majority of which have not been studied.[9]

Potential risks of medicinal herb, *V. mandshurica* intake must be considered in the context of potential benefits. In this paper, we propose a method to discount the observed benefit of a treatment by the observed risk in order to facilitate the benefit-less-risk comparison of treatments in a clinical trial. The discounting, applied to each individual in a trial, utilizes a method proposed by Tallarida[10] to consolidate the safety data collected in the trial.

MATERIALS AND METHODS

For Benefit-Less-Risk Analysis (BLRA), risk and benefit relationships are presented as risks subtracted from benefits using weights assigned to one of five benefit–risk outcome categories: 1) efficacy without side effects; 2) efficacy with side effects; 3) no efficacy and no side effects; 4) no efficacy with side effects; and 5) side effects leading to withdrawal from an ongoing treatment or intolerable side effects.[10-12] The risk-adjusted benefit measure for each individual is obtained from the difference between an aggregate benefit score and an aggregate risk score.

Each patient's efficacy experience (benefit) of a therapy is represented by a binary response variable; "1" signifies that a therapy response is obtained, and "0" means that no response is achieved.[12] The patient's side effect experience (risk) from five different body functions is represented by a value ranging from 0.0 to 1.0, where the value of 1.0 represents the worst safety experience and 0.0 means no safety concern. Notably, these categories are primarily qualitative, but weights can be chosen by individuals to reflect the relative importance of the five categories. A mathematical model is derived from these weights and categories to calculate the observed benefit-less-risk score for an individual. If applied in a clinical trial comparing different treatments, statistical significance tests can be performed to compare treatments. The interpretation of the results remains focused on the individual. The theory underlying the analysis of physicians' prescribing practices in regard to benefit and risk is the same as that in games of chance (Table 1).[10]

In connection with drug treatments, W represents the severity of the illness being treated (removal of that illness is the prize value sought) and P is the probability of its achievement. We may apply this reasoning to drug treatments. We denote by W the severity of the illness being treated and by P the probability that the treatment will be efficacious. The expectation is the patient benefit E: $E = P \times W$

Often more than one ADR (adverse drug reactions) accompanies treatment. A second independent ADR will add to the total risk E'. If we denote the probability and severity of this second ADR by P and W, respectively, then we add its contribution, P * W, to the risk, giving
$E = P \times W + P \times W$

The "profit" of the treatment is the difference between benefit E and risk E. Table 1 illustrates the theory.

Disease states were divided into seven classes, characterized by unknown numerical severity scores W1-W7, indicating a progression of severity as described Tallarida.[10]

The weighting method used is subject to differences in interpretation between individuals. There may be a question regarding the validity of these assessments because the methods used to present the relative weights may affect the outcome. The conversion from a qualitative assessment into a quantitative value may also be subject to bias. The advantage of BLRA is that it provides a structure for combining risks and benefits into a single measure.

A number of metrics which can be used in the risk-benefit assessment are described in the document. The Korean Ministry of Food and Drug Safety[14] recommends a close collaboration between risk assessors and benefit assessors in order to ensure that data generated by one or the other can be used in a broader risk-benefit assessment context (Fig. 1).

Two examples of the approach for risk-benefit assessment are given. The first one {inhibition of angiotensin converting enzyme (ACE) by *Viola mandshurica* extraction}[15] illustrates the case where the risk and the benefit are associated with one single agent, while in the second example (inhibitory effects of methanol extract from fermented *V. mandshurica* on melanogenesis)[7], the risk is due to one selected side effects in medicinal herb (*V. mandshurica*), whilst the benefit is due to other food components. The examples highlight the complexity of risk-benefit assessment, already when entering the first steps of the assessment.

RESULTS AND DISCUSSION

Table 1: Benefit-risk model for *Viola mandshurica* extraction (analogy to games of chance)

Lottery	Drug treatment of *Viola mandshurica* extraction
Value of prize	Severity of illness treated = W
Probability of winning = P	Probability of efficacy = p
Expectation, E = W x P	Benefit, E = W x P
Risk, E' = Cost of playing	Risk: Adverse reaction of severity W' and W" with respective probabilities, P' and P" Risk, E' = W'P' + W"P"

The column headings, such as W1, W2, and W3 in Table 1, represented the numerical scores of the severities to be

considered in each case. From the entries in Table 2, we can derive for each case the benefit and risk. For hypertension of *V. Mandshurica* extracts, the benefit is E, the product of probability and severity: E = (frequency) × (severity of the blood pressure). As an example, suppose a severity of illness treated yields a value of 0.85 and that the probability of efficacy is 26.3. E = 0.85 x 26.3 = 22.355.

The risk for hypertension is E': ΣE' = (frequency) × (severity of the hypertension) = 0.11 x 1 + 0.015 x 1.2 + 0.05 x 166 = 8.428.

Thus, the profit is 13.927 (= 22.355 - 8.428).

Applying similar reasoning to Table 2, As an example, suppose a severity of illness treated yields a value of 1.0 and that the probability of efficacy is 2.36. We get from the second row elements of the completed matrix of Table 3.

For melanogenesis, the benefit is E, 1 x 2.36 = 2.36
The risk for melanogenesis is E': ΣE' = (frequency) × (severity of the melanogenesis) = 0.25 x 7.7 + 0.025 x 21.8 + 0.01 55.5 + 0.05 x 120 = 14.02
Thus, the profit is -11.66 (= 2.36 - 14.02).

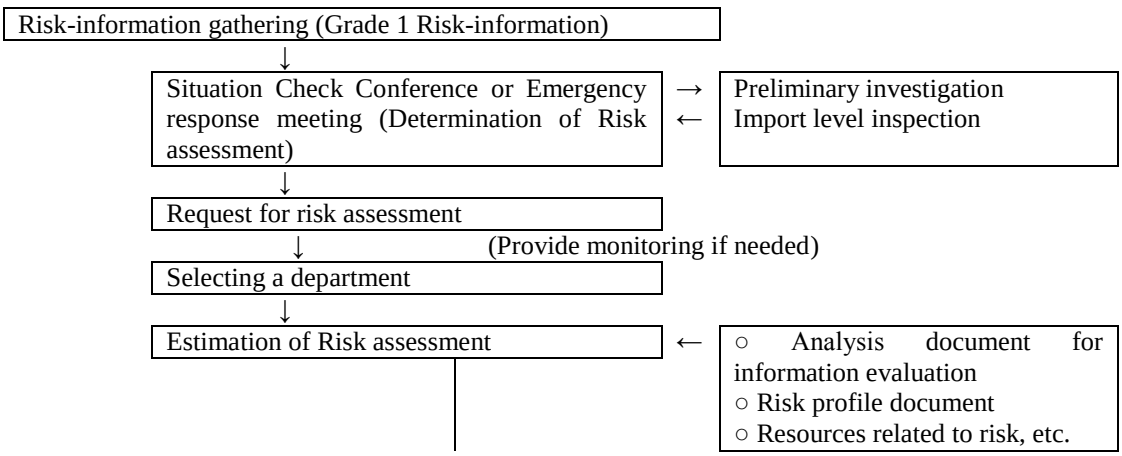
The profit is the difference of both ΣE': (profit of hypertension) – (profit of melanogenesis) = 2.267. Thus the profit for *V. mandshurica* intake is not high. Potential risks of medicinal herb, *V. mandshurica* intake must be considered in the context of potential benefits.

BLRA deals with multiple criteria decision problems using individual-level data. It organises observed adverse events into body functions for BR assessment. Benefits and risks are balanced by a defined proportionality constant f in the benefit-less-risk expression ∑benefits – f × ∑risks.[16]

Although the public and some health care professionals believe that herbal medicines are relatively safe because they are natural, there are remarkably little data to support this assumption.[9] There are many advantages and disadvantages of herbal medicine. Recent publications have highlighted the severe consequences from side effects from certain herbal products.[17-18] Many dangerous and lethal side effects have been reported from the use of herbal products. Herbal medicine remains largely an unproven, inexact science. Although the history of herbal medicine provides decades, sometimes centuries, of anecdotal information, scientific study of herbal medicine is relatively new. Expeditious collection and delivery of food and drug safety information are critical for national safety. The Ministry of Food and Drug Safety (MFDS) in Korea has been providing the collected information immediately to relevant government departments and industries to minimize risks to the public.[14] MFDS, as a national regulatory authority responsible for ensuring the safety of herbal raw materials and herbal medicinal products, is working on the improvement of standards and specifications for items listed in the herbal medicine compendium and establishment of risk management system.

The extraction of *V. mandshurica* leaves showed inhibition activity more than 39.1%.[15] The extraction of *V. mandshurica* petioles showed inhibition activity more than 28.7%. The roots of *V. mandshurica* demonstrated ACE inhibitory activity at a concentration of 20%, showing an inhibition greater than 46%. The roots extraction for ACE inhibitor was more effective than leaf and petiole extractions.

The effect of *Viola mandshurica* on hydrogen peroxide (H_2O_2)-induced DNA damage in PC12 cells was evaluated by the comet assay where the extract (100 and 250 μg/mL) was a dose-dependent inhibitor of DNA damage induced by 500 μmol/L of H_2O_2.[7] The most important transcription factor in the regulation of tyrosinase and tyrosinase-related proteins is the microphthalmia-associated transcription factor (MITF) .[19] (Slominski et al). *V. Mandshurica* extracts by chloroform significantly reduced the production of MITF and tyrosinase mRNA.[8] The violet extract helps to whiten but it inhibits pigment synthesis. *V. Mandshurica* contains at least both ingredients (benefits and risks) that help to treat hypertension and inhibits melanin synthesis.



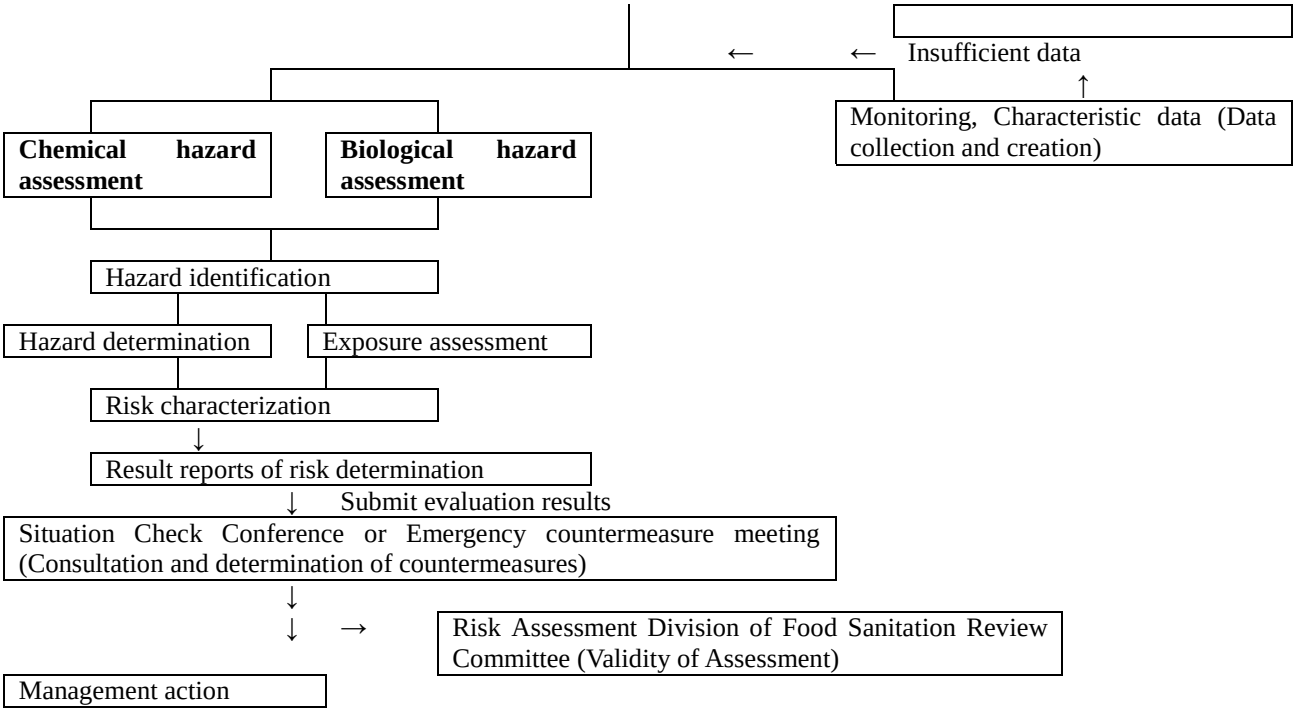


Figure. 1: Stepwise and dialogue for risk assessment and risk management in Korea (Ministry of Food and Drug Safety, 2016).

Table. 2: W3 is treated with a drug which is efficacious with probability

Case	W1	W2	W3	W4
Hypertension	1	1.2	26.3	166

Table. 3: Typical responses for W1 to W7 which were presented and in each the probability for efficacy of a drug treatment was given.

	W1	W2	W3	W4	W5	W6	W7
Melanogenesis	1	2.36	7.7	21.8	55.5	120	465

CONCLUSION

We applied chemical and biological hazard assessments of Korean Ministry of Food and Drug Safety recommends to risk benefit aspects, when designing a survey for generating data, a closer collaboration between risk assessors and benefit assessors aims at ensuring that data generated by two results or the other can be used in a broader risk benefit assessment context. Furthermore, there is a need for more hard biomarkers of effect for both risks and benefits.

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