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"Weak direct" and "Strong indirect" interactions are the mode of action of food factors

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Summary

Age-dependent and lifestyle related diseases such as metabolic syndromes have become a social problem worldwide. Since these disorders are closely related to dietary lifestyle, the old saying "foods are medicine" is now being re-evaluated. Thus, dietary protection against these diseases is attracting much attention. As research into functional foods advances, a book of knowledge is being accumulated on the active ingredients, termed "food factors", present in food resources. Identifying such molecules usually follows the conventional methodology used for finding drug candidates from natural resources. The question has arisen as to whether the mode of action of food factors as molecules is the same as that of drugs. In this article, the functional properties of food factors and drugs are comparatively reviewed and the characteristic features of food factor function is discussed, based on the idea of "weak direct" and "strong indirect" actions of food factors to their receptors.

Keywords: Food factor; Functional models; Weak direct interaction; Strong indirect interaction; Ligand-receptor interaction

Introduction

Needless to say, food is essential for maintaining the structure and function of organisms. People from early historical times became aware that deficiencies of certain foods caused health disorders. For example, scurvy is caused by lack of intake of fresh vegetables or fruit [1]. Thus, a search for substances whose deficiencies cause specific disorders, and the concept of nutrition, was established [2, 3]. Therefore, modern nutritional science can be said to be a science of deficiency.

On the other hand, in the developed countries where food is available in excess, including so-called junk foods, disorders like metabolic syndromes and cancer become social concerns [4, 5]. Since complex symptoms and many pathogenic factors are associated with their pathogenesis, treatment strategies of modern medicine, such as antibiotic therapy against most viral infectious diseases, are useless. It is thus recognized that prevention is the primary strategy to combat these diseases. Since these disorders are associated with obesity caused by an excess intake of high-calorie foods and less exercise, metabolic diseases are closely related to lifestyle, especially the dietary lifestyle [6]. "Food is medicine" is an old saying in the Oriental countries and in China, Korea and Japan a medicinal "cuisine" has been developed [7]. This idea is now being revived and the health benefits of foods are now attracting much attention. Currently the search for the active ingredients in food resources or edible natural resources is actively underway, and many active ingredients have been isolated; mainly from plants as the phytochemical, and their physiological and pharmacological activities are being studied [8]. These isolated functional molecules are now termed "food factors" [9]. As the functional studies of food factors progress, a new tertiary category of food function termed pharmacological or physiological functions has been defined, in addition to the nutritional and sensory functions which are defined as the essential primary and secondary functions, respectively [10]. Therefore, food surplus has led to the formation of a new field of functional food science.

Multi-functional properties of food as a mixture

So far the search for such active ingredients in food resources has followed the same methodology used for identifying drugs or drug candidates from natural resources [11, 12 13]. The question has arisen as to whether an isolated food factor is the same as a drug. Since an isolated food ingredient is a molecule, as is a drug, both molecules may induce so-called pharmacological effects, although their magnitudes or the concentration required for the expression of their respective effects might be different. It is generally accepted that foods are a mixture of many active ingredients and thus may have multiple targets for inducing multiple functions. On the other hand, a drug is usually administered as a single molecule so that it attacks a rather specific target and has only a limited function. The extreme example of a well-designed property of food is observed in the herbal prescriptions of Oriental medicine, in which several herbs with different characteristics are combined in accordance with the Oriental medicine theory to provide beneficial health or medicinal effects [14]. For example, the formula named Shengmai San (SMS) that consists of three herbal components (*Panax Ginseng*, *Ophiopogon japonicas* and *Schisandra chinensis*) was studied as a food model. Multiple functionalities were revealed which included prevention of cerebral damage caused by ischemia/reperfusion [15] or psychological stress in rats [16], prevention of post-traumatic brain damage [17], modulation of antioxidant enzymes including HO-1, GPx and SOD in myoblasts [18], inhibition of scopolamine-induced amnesia and stimulation of acetylcholine esterase in the brain [19], stimulation of neurite outgrowth in PC12 cells through modulation of MAPKs [20], stimulation of DNA damage repair and synergistic enhancement of SOD and GPx [21], among other effects.

Multi-functional properties of food factors as molecules

However, recent research developments in food factors have revealed that the food ingredient itself has some functional variability. For example, many phytochemicals such as curcumin [22], resveratrol [23], and flavonoids [24] show a wide range of functionality including antioxidant, anti-inflammation, anti-cancer, anti-cardiovascular disease, anti-aging, etc. Our studies on Schisandrin B (Sch B) as a major lignin isolated from *Shisandra chinensis*, a component herb of SMS, revealed that Sch B has multi-functional properties similar to that of SMS. It prevented oxidative stress in several systems, including cis-platin induced cerebral oxidative damage [25], liver damage [26], and paraquat-induced oxidative toxicity in PC12 [27]. Neuroprotective functions were evident against transient focal cerebral ischemia in rats [28] and also in a scopolamine-induced amnesia mice model in which Sch B prevented the functional decline of brain function through modulation of acetylcholine esterase, GSH and antioxidative enzymes [29]. It prevented anti-cancer drug-induced DNA damage and chromosomal aberrations in the brain [25]. Further, it was shown that Sch B specifically inhibited ATR (ataxia-telangiectasia mutated Rad 3-related), a PI3 kinase family that plays a central role in the DNA damage checkpoint signaling pathway [30, 31].

Therefore, the multi-functionality of SMS is in part attributable to this single ingredient of the component herb, *Schisandra chinesis*.

Ligand-receptor interactions as the basic mode of food factor function

In order to evaluate the multi-functional properties of single food factors isolated from food or herbal resources, several models can be deduced from the ligand-receptor theory that has been used for the analysis of drug action [32]. According to this theory, the magnitude and specificity of certain drug actions are related to the binding affinity of the drug to the receptor, and thus drug action is primarily governed by the plasma concentration of the drug. This is illustrated in Fig.1 as the **single component/single target model**.

Fig 1: Single component/single target model

Food factor action may be explained in the same way as drug action in that the food factor binds directly to the receptor to modulate cellular signals and thus express the food function. Based on this model, how can we explain the multi-functional properties of food factors as molecules? One plausible explanation may be attributed to the large difference in binding affinity to the receptor between the drug and the food factor. Generally, the binding affinities of drugs are significantly high, such that the effective concentrations are in the range of nM to pM.

In contrast, the binding constants or effective doses of food factors are several- or thousand- fold larger than those of drugs, as exemplified in the case of Angiotensin converting enzyme (ACE) inhibitors. Recently, the ACE inhibitory activity of food factors is attracting much attention because of its possible contribution to the dietary control of hypertension, as hypertension is a critical factor in the increasing incidence of cardiovascular diseases. Indeed, several flavonoids are known to have ACE inhibitory activity [33, 34]. However, their IC_{50} values are in the range of 10 to 100 μM, in contrast to the 20 pM to 1.8 nM range of clinical drugs like Captopril and Lisinopril [35]. A similar difference was also observed for the ATR inhibitory activity of Sch B and certain synthetic ATR inhibitors. The IC_{50} value of Sch B was approximately 7 μM [30] compared to the pM-scale activity of VE-821 [36]. It is well known that such strong receptor affinity frequently causes adverse effects since drugs may bind not only to the target receptor in diseased tissue but also in normal cells or tissues, or to other receptors. However, when the binding constant is moderate or low, as in the case of food factors, there may be a different result. The lower the binding constant for certain food factors, a higher plasma or intracellular concentration is then required to express its' function. Therefore, the probability of competitive non-specific interactions will be enhanced between the primary target and other similar low-affinity targets. This probably induces diverse effects other than the effect mediated by the primary receptor. This mechanism is illustrated in Fig. 2 for the **single component/multiple targets model**.

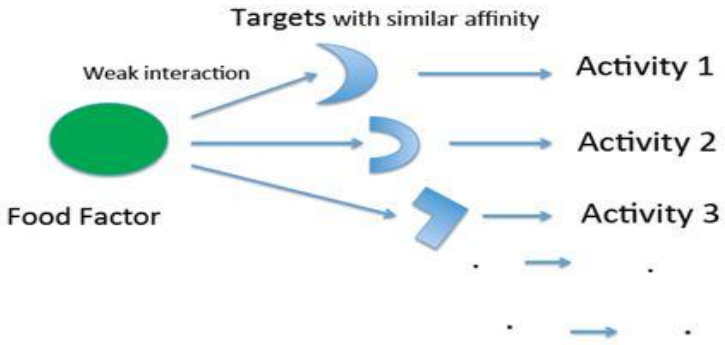

Fig 2: Single component/multi-target model

One of the examples is drown by curcumin, a typical food factor that suppresses carcinogenesis visa multifaceted molecular targets as reported by Van Erk MJ et al [37]. It showed differential gene expression profiles at its high (100 mM) and low (30 mM) doses, respectively. It was also shown that the two types of colon cancer cells used for the experiments showed diverse curucumin sensitivity.

Another model to explain how food factors show multi-functionality is **the single component/multi-functional target model (**Fig. 3). In this case, the food factor directly modulates multi-functional cellular components, such as transcription factors like NFkB or Nrf-2 which control the expression of various gene products. There have been many food factors and natural products with diverse chemical structures reported that modulate these transcription factors [38, 39] and other cellular signal molecules [40]. This mechanism is extensively discussed in chemopreventive functions of phytochemicals. The chemoprevention is an effective

anti-cancer strategy with minimized adverse effects. Kavitha K et al [41] studied Nrf2 activation potentials of several food factors such as astaxanthin, blueberry anthocyanins, ellagic acid and chlorophyllin in hamster buccal pouch carcinogeneisis model and indicated the chemopreventive function of these factors associates with an orchestral modulation of several cytoprotective responses such as anti-oxidant enzymes induction, phase I and II enzymes induction, and DNA damage repair related enzymes, which are controlled by Nrf2 signaling.

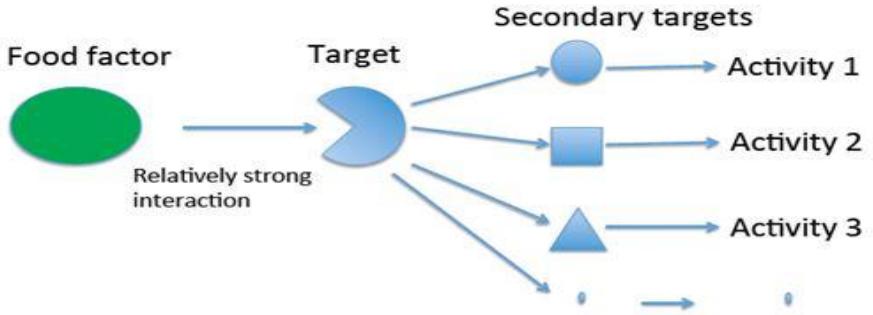

Fig 3: Single component/multi-functional target model

Antioxidant properties as another cause of the multi-functionality of food factors

An additional factor contributing to the multi-functional properties of food factors may be the antioxidant nature of food factors. It is interesting to note that food factors having multi-functionality are essentially associated with anti-oxidant properties. Typical examples are the polyphenols. When a certain food factor has antioxidant properties, the mechanism of pharmacological activity being expressed may be complex. Antioxidant food ingredients in molecular form may be processed in the body primarily by xenobiotic metabolism pathways, similar to that for drugs. They may subsequently be degraded to various metabolites, followed by excretion mainly by urine or feces. At the same time, antioxidant molecules will react readily with available oxidants or radicals, yielding degradation product(s) that have more-or-less oxidant natures [42]. This means that antioxidant ingredients may produce three different molecular species. The mole ratio of each will vary depending on physiological conditions, and may especially reflect the level of oxidative stress in the organism. If we assume that these molecules have certain pharmacological activities, it can be expected that the antioxidant ingredients may have variable functions; That is, they can be multi-functional by themselves.

Strong indirect interaction as an alternate mode of function of food factors

Besides multi-functionality, foods or food factors confer another characteristic feature: low- or non-toxicity to the organism under normal dietary conditions. Foods normally do nourish the organism but do not give rise to adverse effects. The low binding affinity of food factors to their receptors may explain this characteristic in part but not sufficiently. Therefore some other mechanism may be implicated for food factor function. The adjuvant effect is reportedly one of the characteristic functions of food factors. For example, food factors having only limited toxicity towards cancer cells by themselves can nonetheless enhance the cellular toxicity of certain genotoxic drugs or radiation [43]. Examples are known for many food ingredients,

including curucumin and resveratrol [44]. Although such an effect is frequently discussed in terms of the immune modulating effects of food factors [45], namely polysaccharides in fungi [46], alternate mechanisms may also be operative as illustrated in Fig. 4 as the **sequential action model**.

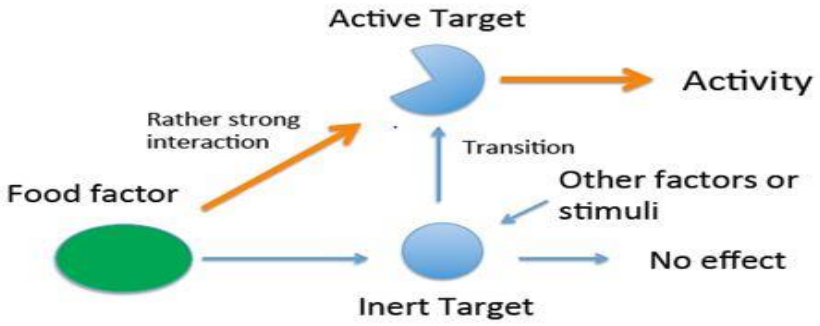

Fig 4: Sequential action (strong indirect interaction) model

In this model, the food factor does not affect cells under static conditions, even cancer cells, and therefore no significant cell toxicity is observed when the factor is incubated directly with cancer cells.

However, once the cells are transformed to another state by certain stimuli such as genotoxic reagents like anti-cancer drugs, the cells are sensitized to the food factor. In other words, the latent target is activated by the stimuli to react with the food factor to express a certain cellular effect. This type of action of food factors has been demonstrated in our studies of Sch B-mediated enhancement of doxorubicin (Dox) cytotoxicity in cancer cells [30, 31]. The DNA damage checkpoint function is a part of the DNA damage response that is the crucial mechanism for maintaining genomic stability in cells [47]. When cellular DNA is damaged, two PI3 family kinases, ATM (ataxia-telangiectasia mutated) and ATR, are recruited depending on the type of DNA damage [48]. These kinases successively phosphorylate the downstream checkpoint kinases to arrest the cell cycle at certain stages such as G1, S and G2/M and activate the DNA repair process. When the damage is too extensive to repair, the cell is led to apoptosis. We previously found that Sch B, a major lignin isolated from *Schisandra chinensis*, which is a one-component herb of traditional Oriental medicine formula SMS, specifically inhibits ATR [30]. Since ATR is not activated without DNA damage, Sch B does not give rise to any apparent effect towards cells without DNA damage. When cells are challenged by genotoxic stimuli such as Dox or radiation, ATR is recruited in response to the damaged DNA and thus the cells become reactive to Sch B. Sch B-induced ATR inhibition follows abrogation of the cellular DNA damage checkpoint function and thus the cells are forced to cycle without repairing the damaged DNA, finally leading to cell death due to mitotic failure. This kind of indirect mode of action is quite characteristic of food factor function, such that food intake or food factors under normal conditions do not induce apparent effect but become active under specified conditions. When the receptor recruited under the specified condition has high affinity to the food factor, the effect caused by the food factor becomes more specific, similar to that of a drug. Thus, this mode of

action of food factors can be defined as **strong indirect interaction** between the food factor and the receptor. Since many previously studied natural products have passed into oblivion because the activity was either low or absent when evaluated by the direct interaction model described above, a search for active ingredients based on the **sequential action model** will possibly open up innovative ways of discovering new drugs.

Conclusion and perspective

From the discussions above, it may reliably be suggested that food factors basically express their functions through "**weak direct interaction"** with their receptors. However, another mode of interaction termed "**strong indirect interaction"** may also be operative. It is reasonable to consider that both modes of interaction competitively occur in the organism and contribute to the establishment of multi-functionality and lower toxicity of foods and food factors. The strong indirect interaction mode not only explains one aspect of the characteristic features of food factor function but also provides an innovative concept for developing new screening methods to identify those candidate drugs that have escaped from the mesh of conventional screening methods. For example, direct cancer cell toxicity was evaluated as a marker for an anti-cancer effect.

In addition, we need to pay attention that the weak direct interaction model may also predict certain risk of adverse effect of food factor and the functional food in which a specific food factor is enriched, and thus control of the dose might be important for the beneficial use of functional foods and food factors.

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Abbreviations: SMS: Shengmai san; HO-1: heme oxygenase 1; GPx: glutathione peroxidase; SOD: superoxide dismutase; PC12: pheochromocytoma 12; MAPKs: mitogen-activated protein kinases; GSH: glutathione reduced form; ATR: ataxia-telangiectasia mutated Rad 3-related; ACE: angiotensin converting enzyme; IC_{50}: half maximal inhibitory concentration; PI3 kinase: phosphoinositid 3-kinase; ATM: ataxia-telangiectasia mutated

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