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FUNCTIONAL FOODS MONOGRAPH 2017

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FUNCTIONAL FOODS MONOGRAPH 2017

ILSI Southeast Asia Region Monograph Series

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Table of Contents

INTRODUCTION

Two main functions of food have conventionally been recognized. The primary function of food is to provide nutrients to nourish the body, to provide the energy needed for daily activities as well as for growth and development. Consuming balanced diets is vital so as to prevent nutrient deficiencies and protect from diseases. The secondary function relates to the sensory properties of the food (e.g. tastes, flavours, etc.). These are also important functions because we must enjoy what we eat. The food we eat must look good, smell great and taste delicious.

There is now thought to be an additional function of food, which pertains to regulating the physiological processes of the body, thereby promoting health. This is thought to be a new dimension in the relationship between food and health. This third function of food is not performed by nutrients in food but rather by other healthful components.

As these other components in food are able to serve physiological roles beyond meeting basic nutritional requirements, they have been known as bioactive or functional components. Many of these have yet to be fully identified and their effects characterized. Foods containing such components have been termed "functional foods". The term may have gained prominence only in recent years, but in Asia, foods with functional properties have been regarded as an integral part of some cultures for centuries. In view of their potential positive health significance, there has been a great deal of interest worldwide on functional foods and functional components in food. Many epidemiological and clinical studies have investigated the scientific basis of the health-enhancing properties. The trading and marketing of functional foods has been increasing over the years. This tremendous increase in consumer interest has been driven by the widespread prevalence of diet-related chronic diseases and the belief that functional foods are able to help reduce risk to these diseases. In response to such developments, there has been a parallel increase in regulatory activities worldwide.

Despite the great interest in foods providing additional health benefits, there is no unanimously accepted global definition of functional foods. The term "functional foods" is also currently not used in most of the relevant regulations. Nevertheless, an important development is that there is a generally accepted understanding that functional foods are foods that, by virtue of physiologically active food components, provide health benefits beyond basic nutrition. The approach by regulatory agencies towards these foods is therefore focused on the health claims permitted and their scientific substantiation.

International Life Sciences Institute Southeast Asia Region (ILSI SEA Region) has been at the forefront of scientific activities for 25 years, and has promoted a harmonized development of functional foods in the region. It organized the *First International Conference on East-West Perspectives of Functional Foods* in 1995 (Clydesdale & Chan, 1996). Following that conference, ILSI SEA Region initiated several important activities to facilitate the harmonized development of functional foods in the region, including scientific research and substantiation as well as regulatory systems.

There is much potential for the development of functional foods in Asia. A large number of food products and biologically active ingredients are unique to the region and have much potential in promoting the well-being of the population. There should thus be greater efforts in all activities related to the development of functional foods in the region, including research and development, regulatory development as well as consumer communication

ILSI SEA Region has recognized the need to continue playing an active role to facilitate, coordinate and stimulate activities in functional foods and health claims. Its series of seminars and workshops on scientific substantiation of health claims will continue to be organized, and the publication of this monograph, 13 years after the publication of the first Functional Foods Monograph, serves to update documentation of functional foods activities and relevant regulatory development in the region.

ADDRESSING FUNCTIONAL FOODS IN ASIA - ILSI SEA REGION'S INITIATIVES

ILSI SEA Region has played an active role in promoting the harmonized development of functional foods in the region, as well as stimulating research and development in this area. In September 1995, ILSI and ILSI SEA Region had co-organized the *First International Conference on East-West Perspectives on Functional Foods: Science, Innovations and Claims* that was held in Singapore (Clydesdale & Chan, 1996). This conference presented information available on functional foods and aimed to diminish the gap between Eastern and Western perspectives. A total of 41 papers presented at the conference and an additional paper on summary of the panel discussion were all published in Nutrition Reviews in 1996 (Vol. 54, No. 11). From 2000-2002, ILSI SEA Region has also partially funded a research study investigating the effect of Chinese Wolfberry (*Lycium barbarium*) on antibodies to Epstein-Barr Virus (EBV) which was headed by Prof. Soh Ha Chan at the National University of Singapore.

Subsequently, several important activities including a series of meetings, workshops, and expert consultations among representatives from the government, academe, and industry in the region and internationally, were held to promote a better understanding of functional foods, facilitate the harmonized understanding on the development of functional foods in the region, including scientific research and substantiation of the beneficial effects, health claims and safety of these foods. The series of scientific meetings include:

- 1st Asia Region Workshop on Functional Foods, held in October 2003, in Kuala Lumpur, Malaysia;
- 2nd Asia Region Workshop on Functional Foods, held in October 2004, in Bangkok, Thailand;
- ILSI SEA Region's Expert Consultation on Functional Foods, held in December 2005, in Singapore;
- 3rd Asia Region Workshop, held in July 2006, in Kuala Lumpur, Malaysia

ILSI SEA Region then organized the *2nd International Conference on East-West Perspectives on Functional Foods* with the theme on Science, Innovations and Claims, which was held in Kuala Lumpur, Malaysia, in November 2007. The conference shared information on the substantiation of health claims, as well as effective and ethical communication strategies on functional foods among other topics. It concluded with a note on the importance in harmonizing concepts and definitions to further promote the development of functional foods in the region. At the 11th Asian Congress of Nutrition held in July 2011 in Singapore, ILSI SEA Region sponsored a session on Functional Foods and Health covering various aspects of the topic including the development and status of functional foods in Asia, benefits and effects of functional foods and components on microbiota and gut health as well as cardiovascular diseases.

Since 2001, ILSI SEA Region has also facilitated a total of 10 scientific seminars and workshops on nutrition labeling and claims which were attended and participated by representatives from regulatory agencies and research scientists in the Southeast Asia and Asia Pacific region. The 9th Seminar and Workshop on Nutrition Labeling, Claims and Communication Strategies was recently held in August 2015 in Manila, Philippines. These meetings provided a platform for ILSI SEA Region's tripartite partners (government, academe and industry) to share their views and experiences related to regulatory status of nutrition labeling including health claims, scientific substantiation, future developments as well as communication strategies with consumers. A follow-up Workshop on Nutrition Labeling and Claims held in May 2016 in Hanoi, Vietnam, with the participation of representatives from the regulatory agencies of the Southeast Asia countries, discussed the possibility of harmonizing 7 potential areas related to the nutrition information panel including nutrient function claims in the Southeast Asia region.

These significant meetings resulted in the development of three documents based on a general agreement reached among key stakeholders in Asia, and were published by ILSI SEA Region:

1. Guidelines for the Scientific Substantiation of Nutrition and Health Claims for Foods/ Functional Foods (Appendix 1);

2. Guidelines for Evaluation of Safety/ Nutritional Safety of Functional Foods (Appendix 2);

3. Regulatory Framework for Nutrition Labeling and Claims for Food - Harmonization in the Southeast Asia Region (Appendix 3).

In addition, the first Monograph on Functional Foods in Asia (Tee, 2004) was published by ILSI SEA Region in 2004. It summarized the status of functional foods around the world, focusing on Asia countries. The monograph also explored the scientific substantiation of functional and health claims among international organizations and in several Asia countries. The results of an extensive survey conducted by ILSI SEA Region with the regulatory agencies in Asia on the status of functional foods were also included in the monograph together with the Asian position on functional foods.

Through spearheading and organizing activities in functional foods for more than 20 years, ILSI SEA Region acknowledges the importance of continuing its pivotal role in facilitating and coordinating the research and development of activities in functional foods and health claims. It will continue to provide a platform for its stakeholders in the region to continue the crucial discussion in these areas.

CHAPTER 1:
ESSENTIAL CHARACTERISTICS AND ATTRIBUTES OF FUNCTIONAL FOODS

A survey by ILSI SEA Region in 2002 among 11 Asian countries and region had revealed that the state of development of functional foods, as well as the direction of such development, varied between the countries. There were widely differing views among scientists and regulatory agencies on what functional foods are and the control of these foods. It was felt that if such divergence is allowed to persist, it would not be conducive to the development of functional foods in the region.

It was recognized that there should be a harmonized approach to the future development of functional foods. This may include reaching a common understanding, setting of guidelines, promotion and regulation of functional foods. This would be beneficial to the advancement of the industry and would bring about greater consumer confidence in these products.

In October 2003, ILSI SEA Region organized the 1st Asia Region Workshop on Functional Foods in Kuala Lumpur, Malaysia to discuss the development of a common position on functional foods. Workshop participants from 10 countries in Asia, comprising representatives from regulatory agencies, research organizations, academia and the food industry, deliberated on a wide range of topics pertaining to functional foods, including future developments, safety and scientific evaluation, the essential attributes or characteristics, regulatory and marketing aspects.

It was agreed that as a basic step towards a common understanding of functional foods, there should be general agreement on what functional foods are. At the conclusion of this two-day workshop, a general agreement on the following essential attributes or characteristics of functional foods was developed.

It was agreed that functional foods should:

a. Be in conventional food forms and possess sensory characteristics including appearance, color, texture, consistencies and flavors;

b. Contain nutrients and/or other substances that confer a physiological benefit over and above basic nutritional properties. These substances should not be used at levels for medicinal or therapeutic purposes;

c. Possess functional benefits that can be scientifically proven;

d. Possess functional benefits that can be derived by consuming normal amounts of the foods as part of a regular diet;

e. Contain "functional" nutrients and/or other substances that may be naturally present or be added to the food; and

f. Have been proven to be safe over long term usage for the intended target population based on existing science;

g. Not contain components that may be harmful to human health;

h. Not claim to treat diseases.

To clearly distinguish between functional foods and the functional components extracted from such foods, it was agreed that the term "functional food":

a. Should not be used for food components in isolation. The food components would be the nutrients and/or other substance conferring the functional properties and would be best referred to as "functional components". If these functional components are extracted from the food and presented in pharmaceutical dosage forms, they may be called "nutraceuticals".

b. Should not be used for dietary supplements. It was however agreed that the term "functional food":

It was however agreed that the term "functional food":

a. May be used for foods that have been fortified (or words of similar meaning) to augment a constituent normally present in a food or to add a constituent not normally present in the food in order to confer a property beyond its natural nutritional attribute.

As the term "functional foods" is not used in most regulatory systems, the approach by regulatory agencies towards these foods is thus focused on the health claims permitted and their scientific substantiation. The intention is not to curb scientific research and development of functional foods, but to ensure that only genuine beneficial effects are communicated to consumers.

To this end, there was general agreement that:

a. Functional foods would generally be regulated by food regulatory agencies.

b. Greater attention should be given to scientific substantiation of the beneficial effects of functional foods. More research needs to be carried out on appropriate methodologies for scientific substantiation of claims. Harmonization of protocols or methodologies would facilitate advancement in this area.

c. Substantiation of functional food claims should be different from drug testing. The level of scientific evidence required for substantiation of functional foods should be less stringent than that required for drugs. Studies should be done on the whole food rather than extracted ingredients whenever possible because the benefits of functional components may not be optimal when isolated and would require to be consumed as a whole to have the desired beneficial effects.

d. Experiences from other regions of the world, including experiences in the development of scientific substantiation of claims in Europe and United States of America, would be useful to the Asian region. Nevertheless, the understanding and usage of functional foods in this region should be taken into consideration when dealing with the subject.

e. Countries should preferably establish a pre-marketing approval system which reviews all products submitted for approval to ensure safety, quality and efficacy of the products. This would also ensure that the products meet all regulatory requirements.

f. For post-marketing surveillance, attention should also be given to regular inspection and monitoring of the safety of use, sale, marketing and advertising of functional foods by the relevant authorities. Information on safety of use should also be submitted to the regulatory agencies if there is any report of adverse effects.

g. Effective communications and ethical advertising to consumers are essential to maintain credibility of functional foods. Relevant authorities as well as manufacturers of functional foods should bear this in mind and work towards achieving these practices.

The general agreement reached on the characteristics and attributes of functional foods as well as the regulatory approach to health claims and their substantiation has been a significant positive development of functional foods in the region. There is now greater clarity on what these foods are and the regulatory approach to monitoring their marketing and promotional activities. It is envisaged that these will be beneficial for the research and development of these foods in Asia.

To further build on these agreements, Workshop participants also emphasized that there should be greater interaction among countries and regions in Asia to bring about greater advancement in the development of functional foods. More than a decade after that workshop in 2003, it would still be appropriate to say that enhanced networking in all aspects of functional foods development would be beneficial, including research and development as well as consumer communication. Enhanced regulatory interaction could even work towards a harmonized pre-marketing approval system which would facilitate the marketing and trade of functional foods in Asia.

A platform for regular interactions amongst key stakeholders in functional foods research and development and regulatory control in the region is necessary to realize these objectives.

The conclusions and recommendations of the Workshop were reported in the first ILSI SEA Region *Monograph on Functional Foods in Asia* (Tee, 2004).

CHAPTER 2:
CURRENT REGULATORY STATUS OF FUNCTIONAL FOODS AND HEALTH CLAIMS IN SOUTHEAST ASIA

Codex Alimentarius Approach to Functional Foods

In 1963, the 16th World Health Assembly officially approved the establishment of the Joint Food and Agriculture Organization (FAO) and World Health Organization (WHO) Programme on Food Standards and the Codex Alimentarius Commission (CAC). The main task of the CAC is to develop the Codex Alimentarius, the food code. International standards and guidelines for a wide range of food products and general standards have been formulated. These serves as guidance to governments for their respective national food control systems. The main objectives of Codex Alimentarius are to protect the health of consumers and to ensure fair practices in food trade. It aims to achieve international harmonization in food quality and safety requirements.

There are various committees under the CAC and the ones most related to functional foods are the Codex Committee on Food Labelling (CCFL), and Codex Committee on Nutrition and Foods for Special Dietary Uses (CCNFSDU).

The CCFL drafts provisions on labeling applicable to all foods; works on specific provisions on labeling prepared by the Codex Committees which are responsible for drafting standards, codes of practice and guidelines; studies specific labeling problems assigned to it by the Commission; and studies problems associated with the advertisement of food with particular reference to claims and misleading descriptions. Meanwhile, the CCNFSDU studies nutritional problems assigned to it by the CAC and advises them on general nutrition issues; drafts general provisions concerning the nutritional aspects of all foods; develops standards, guidelines or related texts for foods for special dietary uses; and works on provisions on nutritional aspects proposed for inclusion in the Codex standards, guidelines and related texts.

The topic in relation to functional foods was first brought up at the 13th session of the FAO/WHO Regional Coordinating Committee for Asia (CCAsia) meeting held in Kuala Lumpur in September 2002. It was then followed up in the 26th Session of the CAC meeting held in Rome in July 2003 where the CCAsia requested for an Expert Consultation on Functional Foods for further scientific advice to help evaluate the safety and regulatory issues related to functional foods, which is of importance to developing countries.

Further comments by delegations at the 25th session of the CCNFSDU meeting in November 2003 noted that functional foods should not be considered as a separate category of foods and that it could be addressed in the framework of health claims instead. In addition, the delegations commented that there was no international definition for functional food and no work was being undertaken by the Codex in the area. They further emphasized that based on the legal perspective, functional foods could be considered as health claims for common foods or foods for special dietary uses.

ILSI SEA Region has taken on this position of discussing functional foods as foods with health claims. The essential characteristics and attributes of functional foods are elaborated in detail in this chapter under "**Codex Guidelines on Health Claims**".

Codex Guidelines on Health Claims

The Codex Alimentarius Guidelines for Use of Nutrition Claims (CAC/GL 23-1997), first adopted in 1997, was revised in 2004 to include guidelines on the use of health claims. Renamed as Codex Guidelines for Use of Nutrition and Health Claims (CAC/GL 23-1997), the document defines health claim as any representation that states, suggests or implies that a relationship exists between a food or a constituent of that food and health (FAO/WHO, 2013). The Annex on Recommendations on the Scientific Substantiation of Health Claims was adopted in 2009.

Codex document on Guidelines on Use of Nutrition and Health Claims includes three types of claims, namely nutrient function claim, other function claim and reduction of disease risk claim. Definitions of these claims are as follows.

Nutrient function claim describes the physiological role of the nutrient in growth, development and function of the body. Some examples of nutrient function claims include:

- Calcium aids in the development of strong bones and teeth.
- Vitamin D is essential for the absorption and utilization of calcium and phosphorus.

Other function claim describes specific beneficial effects of the consumption of food or food constituent in improving, modifying or preserving a physiological function or health. Some examples of other function claims include:

- Plant sterols helps in lowering blood cholesterol.

- Inulin helps increase intestinal bifidobacteria and helps maintain a good intestinal environment

Reduction of disease risk claim, also known as disease risk reduction claim, relates the consumption of a food or food constituent to the reduced risk of developing a disease or health related condition. However, the presentation of risk reduction claim must ensure that consumers do not interpret them as prevention claims. Some examples of reduction of disease risk claim include:

- Soy protein reduces risk to heart disease.

- Iron can help reduce the risk of anaemia.

In relation to functional foods, the relevant health claims are other function claim and reduction of disease risk claim. Nutrient function claims are related to nutrients and are therefore generally not relevant to functional food health claims. On the other hand, other function claim and reduction of disease risk claim refer to food or food components or constituents rather than nutrients. These claims focus on the role of food bioactive or functional components in improving or modifying a physiological function or promoting health. It should also be noted that other function claim does not relate to a disease whereas reduction of disease risk links a food or food constituent with the risk of a disease.

Status of Health Claims Pertaining to Functional Foods in Southeast Asia

Over the past 20 years, there have been greater consumer awareness on the importance of food and nutrition in the prevention and causation of diseases, including diet-related diseases which have been on the rise in all countries. There has been significant scientific progress in the understanding of the role that other food components play in health and disease, besides nutrients. These developments led to food industry innovations in providing more healthful food products to their consumers, and eventually led to major developments in the national regulations on nutrition and health claims in the Southeast Asia region. However, such regulations vary significantly throughout the region and the regulatory framework to deal with these involves various stages of development.

With the exception of Vietnam, none of the countries in the Southeast Asia region use the term "functional food" in its food regulatory system. While the use of the term is not defined, Vietnam recognized supplemented foods, health protection foods, medical foods and foods used for special dietary uses as part of functional foods. Some of the countries also recognize that functional or bioactive components can improve physiological functions. Hence these countries permit health claims related to functional components to be made although the term functional food is not used.

To assist stakeholders in their understanding, ILSI SEA Region has compiled the status of health claims in the region. Table 1 presents the compilation of the status of health claims permitted in all the ten countries in Southeast Asia, namely Brunei, Cambodia, Indonesia, Lao PDR, Malaysia, Myanmar, Philippines, Singapore, Thailand, Vietnam. Information below have been obtained through the surveys conducted by ILSI SEA Region with the regulators in the Southeast Asia region as well as from the published national regulations and guidelines.

As has been pointed out above, nutrient function claims are generally not relevant when discussing functional foods. However, this category of health claims is retained here so as to provide information for all 3 types of health claims permitted by Codex Alimentarius. However, the key claims relevant to functional ingredients and foods are other function claim and disease reduction claim.

Table 1: Status on Permitted Use of Health Claims in Southeast Asia

Country	Nutrient Function Claim	Other Function Claim	Reduction of Disease Risk Claim
Brunei	×	×	×
Cambodia	✓	✓	✓
Indonesia	✓	✓	✓
Lao PDR	✓	×	×
Malaysia	✓	✓	×
Myanmar	✓	✓	✓
Philippines	✓	✓	✓
Singapore	✓	✓	✓
Thailand	✓	✓	✓
Vietnam	✓	✓	✓

Legend: ✓ – Permitted for use; × – Not permitted for use

Currently, there are no harmonized regulations on health claims among the Southeast Asia countries and there are significant differences on the use and types of health claims permitted. Table 2 presents the status of the use of nutrient function claims in Southeast Asia region. All countries except Brunei permit the use of nutrient function claims. Brunei only allows the declaration of nutrition claims. Lao PDR, Myanmar, Philippines and Vietnam adopted the use of CAC/GL 23-1997. Meanwhile Indonesia, Malaysia, Singapore and Thailand have their own positive lists of nutrient function claims that are permitted for use which are provided in Appendix 4.

Among the 10 Southeast Asian countries, other function claims are not permitted in Brunei and Lao PDR as shown in Table 3. With the exception of Cambodia, Myanmar, Philippines, Thailand and Vietnam, the 3 other countries, namely Indonesia, Malaysia and Singapore have positive lists of permitted other function claims which are related to several bioactive components such as dietary fibers, non-digestible oligosaccharides, plant sterols, and polyunsaturated fatty acids (PUFAs) which are provided in Appendix 5. Indonesia has published a new regulation in 2016 (No. 13/2016) which has amendments to the list of its health claims. Currently, it only allows dietary fiber claims under the other function claims.

Reduction of disease risk claims are considered as higher level health claims and are permitted in 7 countries: Cambodia, Indonesia, Philippines, Myanmar, Singapore, Thailand and Vietnam. It is specifically for a selected few nutrients, bioactive compounds or food components. Table 4 presents the status of the use of reduction of disease risk claims in Southeast Asia. Only Singapore has a positive list of 5 nutrient/food-specific reduction of disease risk claims which can be found in Appendix 6.

Table 2: Status on Permitted Use of Health Claims in Southeast Asia

Country	Use of Nutrient Function Claim	Regulation
Brunei	Not permitted	Public Health Regulation – Chapter 182 (2001 and Revised 2012)
Cambodia	Permitted, adopts Codex as voluntary standards; no positive list available	Cambodian Standard CS 001-2000: Labelling of Food Product (2000)
Indonesia	Permitted, positive list consists of 19 claims (revised regulation released in 2016)	Regulation No. 13/2016 on Supervision of Claims and Advertising on Processed Food Label
Lao PDR	Permitted, adopts Codex; no positive list available	No. 519/MoH (2009) Regulation on Labeling of Prepackaged Food
Malaysia	Permitted, positive list consists of 30 claims	Food Act 1983/Food Regulation 1985 (Updated 2014); and Guide to Nutrition Labeling and Claims (2010)
Myanmar	Permitted, adopts Codex; no positive list available	-
Philippines	Permitted, adopts Codex; no positive list available	Bureau Circular No. 2007-002 on Guidelines in the Use of Nutrition and Health Claims in Food
Singapore	Permitted, positive list consists of 125 claims	AVA – A Guide to Food Labelling and Advertisements (Amendments: April 2017)
Thailand	Permitted, positive list consists of 28 nutrients and 47 claims	Notification of the Ministry of Public Health No. 182 B.E. 2541 (1998)
Vietnam	Permitted for functional foods, adopts Codex; no positive list available	Circular No: 43/2014/TT-BYT dated November 24, 2014 of the Ministry of Health regulating the management of functional foods

Table 3: Status on Use of Other Function Claims in Southeast Asia

Country	Use of Nutrient Function Claim	Regulation
Brunei	Not permitted	Public Health Regulation – Chapter 182 (2001 and Revised 2012)
Cambodia	Permitted, adopts Codex as voluntary standards; no positive list available	Cambodian Standard CS 001-2000: Labelling of Food Product (2000)
Indonesia	Permitted, revised regulation released in 2016 only allow dietary fiber claims	Regulation No. 13/2016 on Supervision of Claims and Advertising on Processed Food Label
Lao PDR	Not permitted	No. 519/MoH (2009) Regulation on Labeling of Prepackaged Food
Malaysia	Permitted, positive list consists of 22 claims	Food Act 1983/Food Regulation 1985 (Updated 2014); and Guide to Nutrition Labeling and Claims (2010)
Myanmar	Permitted, adopts Codex; no positive list available	-
Philippines	Permitted, adopts Codex; no positive list available	Bureau Circular No. 2007-002 on Guidelines in the Use of Nutrition and Health Claims in Food
Singapore	Permitted, positive list consists of 17 claims	AVA – A Guide to Food Labelling and Advertisements (Amendments: April 2017)
Thailand	Permitted	Notification of the Ministry of Public Health No. 182 B.E. 2541 (1998)
Vietnam	Permitted for functional foods, adopts Codex; no positive list available	Circular No: 43/2014/TT-BYT dated November 24, 2014 of the Ministry of Health regulating the management of functional foods

Table 4: Status on Use of Reduction of Disease Risk Claims in Southeast Asia

Country	Use of Nutrient Function Claim	Regulation
Brunei	Not permitted	Public Health Regulation – Chapter 182 (2001 and Revised 2012)
Cambodia	Permitted, adopts Codex as voluntary standards; no positive list available	Cambodian Standard CS 001-2000: Labelling of Food Product (2000)
Indonesia	Permitted; no positive list available	Regulation No. 13/2016 on Supervision of Claims and Advertising on Processed Food Label
Lao PDR	Not permitted	No. 519/MoH (2009) Regulation on Labeling of Prepackaged Food
Malaysia	Not permitted	Food Act 1983/Food Regulation 1985 (Updated 2014); and Guide to Nutrition Labeling and Claims (2010)
Myanmar	Permitted, adopts Codex; no positive list available	-
Philippines	Permitted, adopts Codex; no positive list available	Bureau Circular No. 2007-002 on Guidelines in the Use of Nutrition and Health Claims in Food
Singapore	Permitted, positive list consists of 5 nutrient/food specific claims	AVA – A Guide to Food Labelling and Advertisements (Amendments: April 2017)
Thailand	Permitted	Notification of the Ministry of Public Health No. 182 B.E. 2541 (1998)
Vietnam	Permitted for functional foods; no positive list available	Circular No: 43/2014/TT-BYT dated November 24, 2014 of the Ministry of Health Regulating the Management of Functional Foods

CHAPTER 3:
SCIENTIFIC SUBSTANTIATION OF HEALTH CLAIMS
- REGULATORY FRAMEWORK AND REVIEW PROCESS

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The previous chapter has pointed out that there are significant differences in the use and types of health claims permitted by regulatory agencies in the Southeast Asian countries. Eight countries permit the use of other function claims and three of these countries (Indonesia, Malaysia and Singapore) adopt a positive-list approach. Seven countries permit the use of reduction of disease risk claim, but only Singapore has established a positive list of the permitted claims. Claims not on these positive lists are not permitted, but industry may apply on a case-by–case basis. Regulatory framework, in various forms, exist in Southeast Asia to review applications from food industry. Although there are slight differences in approaches, one common requirement by all regulatory authorities is that applications for health claims must be supported by scientific evidence of the intended health effects.

This chapter summarizes the regulatory control of health claims amongst countries in Southeast Asia, including structure of the regulatory framework, the requirements for dossier submission, the review process and focuses on the scientific evidences required. International and regional guidelines on substantiation of health claims and regulatory framework by Codex Alimentarius and ILSI SEA Region are also summarized. The chapter also shares experiences of the review process and key learnings derived from various applications, especially from perspectives of Malaysia. Some common errors and shortcomings of some applications are discussed. Since reduction of disease risk claims are only limited to a few countries, this chapter refers more to scientific substantiation of applications for other function claims in the three countries with positive lists for such claims, namely Indonesia, Malaysia and Singapore.

Guidelines of Codex Alimentarius

Codex Alimentarius has provided guidelines to national regulatory authorities for the scientific substantiation of health claims (FAO/WHO 2013). In the context of functional foods, the relevant claims are "other function claim" and "reduction of disease risk claim". The guidelines outline the process for substantiation of health claims which includes conducting a systematic review of the scientific evidence and evaluating the quality of the available relevant scientific data. Three main criteria are outlined in the guidelines. Firstly, health claims should primarily be based on evidence provided by well-designed human intervention trials. Human observational studies and animal model studies are not generally sufficient per se to substantiate a health claim but may be submitted to support an application. The former may contribute to the totality of evidence whereas the latter may provide understanding of the relationship between the food or food component and the claimed health effect. The second criterion stipulates that the totality of the evidence should be obtained and reviewed. Publications should include those that support the claimed effect, those that contradict the claim as well as those that are neutral. Thirdly, the evidences submitted should demonstrate a consistent association between the food or food constituent and the health effect, with little or no evidence to the contrary.

Guidance Guidelines for Asian Countries

ILSI SEA Region also facilitated the development of three sets of guidelines in relation to scientific substantiation of health claims, namely

1. Guidelines for the Scientific Substantiation of Nutrition and Health Claims for Foods/ Functional Foods (Appendix 1);

2. Guidelines for Evaluation of Safety/Nutritional Safety of Functional Foods (Appendix 2);

3. Proposed Regulatory Framework for Nutrition Labeling and Claims for Food (Appendix 3)

These guidelines are aimed to serve as guidance to regulatory authorities to develop a transparent process for review of applications to cater to the needs of regulatory agencies to prevent unsubstantiated claims, the food industry to inform consumers of the health benefits of their product/ component, and giving confidence to consumers. These guidelines were published resulting from a series of Workshops and an Expert Consultation on Functional Foods involving nutrition scientists in the Asian region organized from 2003-2006. It is hoped that through these guidelines, there could be greater harmonisation of the framework and process of reviewing of applications for health claims among countries in the Southeast Asia region.

The first set of guidelines on the scientific substantiation of nutrition and health claims for foods or functional foods outlines the types of studies required for substantiation of the intended claims. Substantiation of other function claims should be based on human data (observational and/or intervention studies). Disease-risk reduction claims would require additional data from

randomized double-blind placebo controlled trials (RCT). In the event that this is not possible, data from appropriately designed intervention studies can be accepted. Notes on the proper conduct of human intervention studies are included in the guidelines, such as appropriate study and control groups, adequate length of duration of study. The compliance of consumption of food or ingredient under investigation should be closely monitored. The overall dietary intake of study subjects must also be well characterised and monitored. The claimed functional benefit should be measured directly if possible. In situations when this is not possible, appropriate biomarker(s) as intermediate endpoints, should be identified and used in the studies. The importance of adopting appropriate research design and methodology is also highlighted. The guidelines emphasise that the body of research shall convincingly demonstrate that the product will have the claimed effect at the recommended level of intake.

The types of evaluation required for safety/ nutritional safety evaluation of functional foods are summarized in the second set of guidelines. As a basic requirement, functional foods or components must fulfill the safety requirements for food as set out in the national legislations or in the absence of which, the Codex Alimentarius. Functional foods or components that meet several specified criteria do not require additional safety evaluation, including those with a history of safe food/culinary use and foods which form part of dietary guidelines or national food guidance systems. When additional safety evaluation is required, special considerations need to be given to consumption by population groups outside the target group, particularly the vulnerable groups; look out for possibility of excessive consumption and any possible resultant shifts in nutritional balance. The guidelines also emphasised the importance of measuring and monitoring of adverse events when conducting intervention trials to determine efficacy of the foods, especially when high levels are used.

The third set of guidelines proposes how a regulatory framework for nutrition labelling and health claims for food could be established by a national food control authority. As a first step an expert national committee on nutrition and health claims is recommended to be established, with members selected from appropriate research and governmental organisations, comprising experts with relevant discipline and experience. Next, it is essential to make provisions for nutrition and health claims in existing food regulations to enable new regulations to be included. The expert committee will then decide the types of nutrition and health claims to be accepted for review, the information required and the criteria needed for substantiation of claims. A clear work procedure is then established, spelling out the receipt of application, initial processing, tabling of dossiers for review by expert committee, endorsement by higher authorities , public comment and the official gazettement process.

Regulatory Framework for Application for Health Claims

Among the 10 Southeast Asia countries, other function claims are permitted in Indonesia, Malaysia, Singapore, and Thailand, but only Indonesia, Malaysia and Singapore have their own positive lists of permitted claims which are related to several bioactive components. Regulatory framework, in various forms, exist in these countries to review applications from industry, on a case-by-case basis for additional other function claims to be added to the list. Although there are differences in the work procedure in these countries, one common requirement is that each application for health claim has to be accompanied by scientific substantiation, which will be reviewed by a panel of experts appointed by the regulatory agencies in the respective country.

The National Agency for Drug and Food Control (NADFC), Indonesia has made provisions for evaluation of applications for health claims. Information required for applications and the evaluation process, including obtaining input from a team of experts, are contained in the relevant regulation (NADFC, 2016). The Food Safety & Quality Division (FSQD), Ministry of Health Malaysia has established a regulatory framework to review applications for health claims by food industry. An Expert Working Group on Nutrition, Health Claims and Advertisement meets regularly to evaluate applications. Information required for applications are clearly spelt out (MOH, 2010). Similarly, the Agri-Food and Veterinary Authority (AVA), Singapore has established the Advisory Committee for Evaluation of Health Claims (AVA, 2017).

In the other countries, for example Philippines, Thailand and Vietnam, no clear regulatory framework exists. However, manufacturers may apply for health claims on a case-by-case basis with proper scientific substantiation.

Requirements, Process for Application and Administrative Steps

Each application for a new health claim has to be submitted in a prescribed format, the requirements for which are rather similar in these three countries. Besides various basic information on the food component that is the subject of the health claim, one common requirement is that sound scientific evidences for the claim must be submitted, based on randomized, placebo-controlled double blind clinical trials and other appropriate scientific data. In view of the similarities in general principles and requirements, details of requirements and the process in place in Malaysia for applying for other function claims are summarised below.

In the case of Malaysia, for a compound to make a health claim, it must be a permitted "added nutrient" (MOH, 2018). Regulation 26 of Food Regulations 1985 defines "added nutrients" as any mineral, vitamin, amino acid, fatty acid, nucleotide or "other food components" which, when added singly or in combination to food, improves the nutritional value of the food. "Other food components" include various non-nutrients or "functional ingredients" with proven physiological effects beneficial to health. The said Regulation has a list of permitted "added nutrients", tabulated in Table IA of the Twelfth Schedule. If the intended health claim is for a component which is not in this list, an application has to be submitted for approval for use prior to application for health claim. It is to be noted that the word "nutrient" in the context of this regulation and the following paragraphs includes the classical nutrients such as minerals, vitamins, amino acids and fatty acids as well as "other food components".

Applications for must be submitted using a form prescribed by the Food Safety and Quality Division (FSQD) of the Ministry of Health Malaysia (MOH, 2010). This form is included as Appendix 1 in the Guide to Nutrition Labeling and Claims of FSQD. The Guide was published to assist industry and enforcement officers understand nutrition labeling and claims regulations. Some basic information required for new "added nutrient" application includes:

- Chemical structure and properties and physical properties of the "nutrient"
- Stability in the foods serving as vehicles
- Bioavailability
- Method of manufacture
- Analytical method
- Physiological role(s)
- Safety evaluation of the nutrient

Important information related to the use of the nutrient must be provided. The benefits of adding the nutrient to the food must be clearly explained, providing clear scientific evidence of such benefits. The name the food (s) to which the nutrient is to be added must be stated. Preferably, provide a table of the list of foods and indicate the approximate amount that will be added to each of the foods listed. The application should also provide an estimate of the daily intake of the nutrient, e.g. from various food sources containing the nutrient. Any safety concern of excessive consumption if this nutrient is added to the various foods proposed must be clearly indicated.

Upon approval for use of the intended functional/ bioactive component, an application for a new other function claim may be submitted to the FSQD using the prescribed form as indicated in Appendix 2 in the Guide to Nutrition Labeling and Claims of FSQD. The main information required for a new health claim application are similar to the basic information required for "added nutrient" application summarized above. An additional requirement for this application is to include a proposal for a minimum level that the nutrient must be present before the function claim can be made. It is also required to provide scientific justification why this level is proposed. Usually this is the level at which the nutrient is effective in bringing about the proposed physiological function (e.g. lowering blood cholesterol).

Another important requirement of this application is to provide sound scientific evidences for the intended function claim. All available literature including both positive and negative findings on the proposed claim must be provided. Findings from randomized, placebo-controlled, double-blind human trials are preferred. Epidemiological and experimental studies and reviewed papers may be included as supportive evidences. Studies submitted with the dossier should be published in refereed journals and should include those conducted by other organizations or institutions, not merely from the laboratory of the applicant. All the scientific publications cited in the dossier should be submitted with the dossier.

Each application for addition of new food

components to the "added nutrient" list or a new other function claim shall be submitted by the food company to Food Safety and Quality Division (FSQD) of the Ministry of Health Malaysia. The secretariat in FSQD does a preliminary check to make sure the application form is complete and the required documents are provided. If so, the officer requests the company to submit 20 copies of the application and all relevant documents for tabling to a meeting of the Expert Working Group on Nutrition, Health Claims and Advertisement.

This Expert Group, which meets approximately once a month, comprises about 15 nutritionists, dietitians, clinicians and food scientists from various public organisations and institutions shall examine the application. The meetings are chaired by the Deputy Director of FSQD and no industry member shall be present in this meeting. The documents submitted to this committee shall be confidential. If there are queries, the secretariat of the FSQD informs the company to provide additional information or to carry out any necessary amendments.

If this Expert group approves the application, it will be submitted to a higher committee, the Food Regulations Advisory Committee chaired by the Senior Director of FSQD, and meets about 3 times a year. If there are comments or suggestions for improvement, the application returns to the Expert Group for further action. Upon approval by this Advisory Committee, the MOH submits the proposed health claim for online public engagement with stakeholders (for about 3 months) via the website of FSQD. At the end of the public comment stage, if there are comments, the Expert Group will need to take the required action. If there are no major comments, a letter of approval may be given by the Director. Subsequently, the petition goes to the legal process for publication as a government gazette.

Examples of Some Errors/Weaknesses in Submissions – Lessons to be Learnt

Many of the other function claims permitted in the three countries mentioned above have arisen from applications by the food industry. There is significant interest among food industry players to apply for additional health claims. They are keen to understand the requirements for dossier submission, the review process, as well as the reasons some applicants have not been successful. This section provides some insights into some common errors or short comings in some applicants so that intending applicants can avoid such errors. The author shares some key learnings derived from various applications submitted and provide some pointers for improvement of quality of dossiers.

General Errors

A common reason for rejection of an application by the authority is inadequately prepared dossiers. Too brief description was provided for all the required items in the application form. Information or data provided was too scanty to enable a proper review to be undertaken. This could be because the company lacks expertise in preparing a proper dossier.

An important part of a health claim application is the section on scientific substantiation. This is also a section where applications may not be completed satisfactorily. In some applications, the scientific data was available, but they were not properly explained. The available scientific publications were merely listed with no summaries or highlights provided. Proper presentation of available data is extremely important to facilitate expert committee members in understanding the available literature when reviewing the dossier. It is imperative that the applicant explains clearly how the findings presented are able to substantiate the claims.

For some other applications, it was found that information in this section was inadequate because there was insufficient scientific data to substantiate the proposed claim. Perhaps a more thorough search of the literature must be undertaken to obtain the data. In some cases, some of the publications provided were not relevant to the subject of the claim. Applicants must bear in mind that the totality of evidence must be presented, not merely those publications with positive findings. It could also be that insufficient research has been carried out on this particular food component. In that case, the application is not ready for submission.

Specific Errors/Weaknesses

One common specific error committed by applicants is that the wordings or text of the proposed claim do not match the findings of the studies submitted to substantiate the claim. It is not uncommon to find that the proposed claim has been inappropriately extrapolated beyond the findings obtained. For example, findings from studies demonstrate a specific aspect of immune function, e.g. gut immune function. Since gut immune function is only a specific part of the immune function, it would not be appropriate

to extrapolate the findings to claim that the component helps to improve overall immune function of the body.

There are also applications where the compound used in the study does not match the compound that is the subject of the claim. For example the claim refers to a specific component x extracted from a particular plant, but the substance used in the study is an entire aqueous extract of the plant. It must be borne in mind that the plant extract contains component x as well as many other chemical compounds. Therefore any beneficial effects observed cannot be attributed only to component x.

The food vehicle for the component of interest must be appropriate for the intended claim. For example, if the claim is for a component x in milk and dairy products, the studies submitted for evaluation should be in a similar food matrix. Applications based on studies using different food matrices, e.g. soya milk will not be acceptable by the expert committee. It cannot be ascertained that the component x is still effective in other matrices. It should also be pointed out that if the application is intended for a number of foods with different matrices, studies should be performed using the component contained in of different matrices, e.g. beverages, cereals, milk products. Such studies will be able to demonstrate convincingly that the component of interest is able to effectively perform the claimed physiological function.

Several applications have been rejected because studies were carried out using "pure" compounds. In such studies, the compound is consumed with water or a beverage by the subjects, similar to ingesting a supplement. Using this approach, it cannot be ascertained that the compound is still bioavailable and effective when combined in a food matrix. Findings from such studies are therefore not acceptable to substantiate the intended claim. Studies should be carried out using the compound of interest added to food or beverage. It must be borne in mind the regulation deals with food, not supplements. One reason that applications have been received based on the "pure" compound, rather than mixed into food carriers is probably because several novel ingredients or bioactive components have started off as supplements and not yet used in the manufacture of many food products.

There have also been studies conducted that include compound of interest together with other biologically active components. For example in a study to investigate the prebiotic effect of a specific compound, other indigestible carbohydrates were also given to the subjects. In another application, to study effect of one specific polyunsaturated fatty acid (PUFA), a mixture of PUFAs were given. Findings from such studies are confounded by the other components present and the beneficial effects observed cannot be attributed solely to the specific prebiotic or PUFA of interest. For this reason, such studies are not acceptable to substantiate the claimed health benefit.

One application was not approved because the distinguishing characteristics of the compound that was the subject of the claim was not disclosed to the authorities. The company explained that for proprietary reasons, the details could not be disclosed. The expert committee felt that the application could not be approved because no distinguishing feature(s) for the compound were presented. Without clearly published unique characteristics, it is feared that another compound, without the required healthful properties may ride on this claim.

A few applications for whole foods have also been received for review by the authorities. It would be more challenging for a health claim for a whole food to be approved. This is mainly because it is not easy to characterize a whole food as compared to a food containing a specific bioactive component. For example, one application was for a milk powder, fortified or enriched with several vitamins and minerals. Since there were no clear unique characteristics for this product, the applied claims were not approved.

There have been applications where the study findings have been inappropriately extrapolated to the general population, beyond those obtained from the study subjects. For example, if the study subjects were infants, it would be inappropriate for the claim to be extrapolated to include older children and teenagers. It cannot be ascertained that the beneficial effect seen in the study subjects will be similarly observed in other age/physiological groups.

Another example of rejection of application related to scientific findings is inappropriate utilization of research data. For example, in one application, publications submitted were mostly citing usage of the compound of interest in treatment of patients. These publications are not appropriate for use to substantiate the intended claim as the application is for improving specific physiological condition in apparently healthy population. It should be noted that no food is permitted to claim prevention,

alleviation, treatment or cure of a disease, disorder or particular physiological condition

In a few applications in Malaysia, the claims were not approved because the proposed text for the claims were linked to diseases or bordering on disease reduction. For example, claims that a component is able to lower blood pressure, prevent constipation or diarrhea were not approved. In Malaysia, as well as many countries in this region, diseases risk reduction claims are not permitted.

Functional Foods and Health Claims in Southeast Asia: The Way Forward

Health claims have been in place in several Southeast Asian countries for at least a decade. In Malaysia, a regulatory framework to review applications has been in place since 2005. Applications from food manufacturers are still being reviewed by the Expert Group on Nutrition, Health Claims and Advertisement of FSQD, Ministry of Health regularly. Some companies, especially smaller establishments, have expressed concern with difficulty in preparation and submission of applications. It has been pointed out that the requirements for substantiation by the authorities are too stringent. It has been felt that since these claims are for foods and not drugs, the requirements for substantiation for "other function claims" need not be so stringent.

Many functional foods have been used for hundreds of years as part of local cultures and cuisines in many Asian countries. These foods have been recognized for various health promoting properties and the knowledge has been passed down for generations. However, there has been little proper documentation of health benefits of these foods. These documents, even if available, are not acceptable by the authorities to substantiate any intended health claims, in accordance with current regulatory requirements.

What would be the best approach in permitting some form of claims to inform consumers of the health benefits of these traditionally recognized functional foods? These claims, if permitted, should certainly not be misleading or over-promise. How much evidence or what type of documentation can be deemed sufficient by the authorities for such claims? Do we need to identify all beneficial or bioactive components in these foods?
A well-functioning regulatory framework for reviewing applications for health claims have been established in only three countries in Southeast Asia. Health claims are permitted in a few other countries in the region, but no clear review system is in place. There is a need for a clear transparent regulatory framework to be in place in all countries. Regular systematic review of applications from the food industry must be reviewed in a transparent manner by an established group of relevant experts. The publication of a positive list, such as that made available by authorities in Indonesia, Malaysia and Singapore is most useful. It enables all stakeholders to be clear of the permitted claims so that there is no ambiguity. Countries intending to set up a regulatory framework could utilize the Guidance Guideline for establishing a regulatory framework established at ILSI SEA Region's Workshops as well as experiences by the three countries mentioned above as references.

Since 2001, ILSI SEA Region has been conducting a series of seminars and workshops on nutrition labeling and nutrition and health claims. This platform has been provided to enable relevant stakeholders to share updates in scientific and regulatory developments. Regulatory officials in countries in the region have shared their approaches and provided regular updates on their developments. These sessions also provided opportunities for discussing possibility of harmonization of regulations in nutrition labeling and nutrition and health claims with guidelines of the Codex Alimentarius. Scientific experts have provided global developments, especially in the scientific substantiation of health claims. The usefulness of this series of scientific meetings have been well-recognised.

ILSI SEA Region will continue to provide this platform to facilitate continued discussions on basis of regulatory standards and approaches, and sharing of experience in area of nutrition labeling and claims, including sharing of process for substantiation of claims. It is also envisaged that these meetings and workshops will continue to enable sharing of progress and developments in countries in the region as well as Codex and other international standards.

Another important reason to continue with this series of meetings is that it facilitates capacity building for scientific and regulatory development in the region, especially for countries that are relatively new in the development of regulations in nutrition labeling and health claims. As has been done in the past, ILSI SEA Region can continue to organize workshops and seminars on specific topics.

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CHAPTER 4:
CASE STUDIES ON FUNCTIONAL FOODS IN SOUTHEAST ASIA

CASE STUDY 1: MUSHROOM

NATURE AND BIOACTIVITIES OF *LENTINULA EDODES*

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Lentinula edodes (Berk.) Pegler, commonly known as *Cortinellus edodes*, *Armillaria edodes*, *Cortinellus shiitake* and Xiang-gu in Chinese. It is a large and dark brown mushroom with umbrella-shaped and valuable for culinary, medicinal and pharmacology properties. *L. edodes* was first cultivated in China more than 800 years ago and is now widely cultivated in Asia, such as Japan, Vietnam and Korea (Chiu et al., 1999). Nowadays, production of *L. edodes* is more than 1.3 million tons per year in China, taking up more than 70% of world production (Rao et al., 2009).

Nutrient and Bioactive Components

Several important components have been isolated from its basidiocarp or mycelium, such as biologically active polysaccharides (lentinan), dietary fiber, ergosterol, vitamins and minerals (Choi et al., 2006). Since Japanese scientists extracted lentinan from fruit body of *L. edodes* and studied its antitumor activity first time in 1960s, lentinan gets more and more attention. Lentinan is a water-soluble, high molecular weight (from 16 kDa to more than one million) polysaccharide in a structure with mostly (1→3)-β-D-glucan linkages in the regularly branched main chain with 2(1→6)-β-D-glucopyranoside branchings for every 5(1→3)-β-glucopyranoside linear linkages (Dikeman et al., 2005). Jeff et al. (2013) isolated a novel mannogalactoglucan from the basidiocarps of *L. edodes* and named as LE-MGG. LE-MGG consists of (1→6)-, (1→4)- and (1→3)-β-D-glucopyranosyl residues, (1→6)-α-D-galactopyranosyl residues, (1→3,6)- and (1→2,4)-α-D-mannopyranosyl residues and terminal residues of α-D-glucopyranosyl.

L. edodes contains proteins composed of 18 different amino acids, including 7 kinds of essential amino acids (threonine, valine, methionine, isoleucine, leucine, phenylalanine and lysine), in a ratio similar to the ideal for humans (Borchers et al., 1999; Turlo et al., 2010).

Cheung determined the total phenolic content in *L. edodes* was 4.79±1.20 mg of GAEs/g of dry mushroom (Cheung et al., 2003). Moreover, some literatures reported 100 g dry *L. edodes* contained 160 μg cinnamic acid, 790 μg 4-hydroxybenzoic acid, 139 μg protocatechuic acid and 30 μg protocatechuic (Kim et al., 2008).

Fatty acids in the *L. edodes* were nearly 2%, of which 77% consisted of non-saturated fatty acids (8.3% oleic acid, 68.8% linoleic acid and 0.6% linoleic acid), while saturated fatty acids consisted mainly of palm acid (19.2%), stearic acid (2.7%) and peanut acid (0.4%) (Longvah and Deosthale, 1998).

L. edodes contains an abundance of vitamins and minerals. Many researchers have determined the content of vitamins and minerals by the methods of High Performance Liquid Chromatography (HPLC), Inductively Coupled Plasma Mass Spectrometer (ICP-MS) and so on.

The results are shown below:

Table 5: Amounts of vitamin and mineral contents of *L. edodes*

Vitamin (Bisen et al., 2010)		Mineral (Bisen et al., 2010; Lee et al., 2013)	
Name	**Content (μg/100 g fresh weight)**	**Name**	**Content (mg/g dry weight)**
Ergocalciferol (VD_2)	679	Calcium	1.27
Ascorbic acid (VC)	2,100	Iron	0.20
Thiamine (VB_1)	50	Magnesium	2.01
Riboflavin (VB_2)	150	Phosphorus	4.39
Niacin (VB_3)	2,600	Copper	0.01
Folic acid	30	Manganese	0.05
		Zinc	0.04

Bioactivity of *L. edodes*

L. edodes is valued as a luxury food not only for its texture and flavor, but also numerous bioactive activities. With further studies, many researchers have reported a variety of medicinal and health properties, involving depressed immune function (including AIDS), cancer, environmental allergies, fungal infection and hyperlipidemia (Takehara et al., 1979). Among its main bioactive contributors are polysaccharide lentinan, eritadenine, shiitake mushroom mycelium and culture media extracts (Bisen et al., 2010).

Health Benefits

Antioxidant Activity

Free radicals induced by oxidative stress are able to cause various diseases including cardiovascular diseases, cancer and autoimmune disease. There is an increasing focus on natural antioxidants since synthetic antioxidants have potential toxic and carcinogenic properties. *L. edodes* exhibits good antioxidant activity *in vitro*, such as DPPH radicals, superoxide radicals, hydrogen radicals and reducing power tests. Chen et al. (2012) purified three homogeneous polysaccharides from *L. edoes* and evaluated their antioxidant activities, finding they all exhibited antioxidant abilities in a concentration-dependent manner and increasing the antioxidant activity with the increase of the content of uronic acid. Turlo et al. (2010) tested the effect of enrichment in selenium on antioxidant, reducing and free radical scavenging activity of water and alcohol extracts from mycelium of *L. edodes*. Selenated extracts significantly increased antioxidant activity even when selenium is present at very low concentrations of 0.1-0.5 mg/mL.

Antimicrobial Effects

L. edodes is indicated to be effective against both gram-positive and gram-negative bacteria, even more antibacterial than ciprofloxacin. Kitzberger et al. (2007) obtained extracts of *L. edodes* by supercritical fluid extraction under different pressures and the result indicated extract obtained by high-pressure process (30 MPa) was effective against *M. luteus* and *B. cereus*, while the low-pressure (15MPa) extracts did not show antimicrobial activity. The contributors of antibacterial activity may be due to phenolic compounds by interfering with the cell membrane and cell wall of invading pathogen and subsequently leading to the death of the pathogen (Ribeiro et al., 2015). Moreover, lentiavidins, a novel avidin-like protein was discovered in *L. edodes*, but its function is still unclear (Takakura et al., 2016).

Anticancer Effect

Many reports have shown several polysaccharides and polysaccharide-protein complexes extracted from *L. edodes* have significant antitumor activities. For instance, lentinan has been demonstrated to inhibit tumor growth, anti-metastatic activity and stimulation of apoptosis. It contains β-(1→3) linkages in the main chain of the glucan and additional β-(1→6) branch. Derivatives of (1→3)-β-D-glucan has been established to be responsible for antitumor effects (Wasser, 2002). Latcripin-13, isolated from *L. edodes* and expressed in *Escherichia coli* Rosetta-gami (DE3), was able to significantly inhibit the growth of A549 cells in a time- and concentration-dependent manner (Wang et al., 2015). In Japan, there have been many of clinical trials applying lentinan to treat cancers, especially gastric and colorectal carcinoma. Lentinan makes a significant improvement in overall survival of cancer patients. Moreover, a combination of lentinan administration with hormonal therapy was quite effective for breast cancer patients, compared with hormonal therapy alone (Zhang et al., 2011).

Immune System Effects

In vitro and *in vivo* tests, lentinan and other β-glucan demonstrate good immunomodulating properties. Clinical studies report lenitan can increase human immune cells and enhance sensitivity in response to cancer cells. Pathways are postulated such as up-regulation of T-cell, cytokine, monocytes, tumor necrosis factor, natural killer cell, complement activation and other macrophage responses (Lee et al., 2008; Zhou et al., 2009). Nowadays, many nutraceuticals containing *L. edodes* have been available in the market.

Cholesterol-lowering Effects

Dietary supplementation with *L. edodes* was found to decrease the ratio of phosphatidylcholine to phosphatidylethanolamine in liver microsomes of rats. And the hypocholesterolemic action of *L. edodes* was evoked through the alteration of hepatic phospholipid composition (Sugiyama et al., 1993). Kim et al. (2009) investigated the influence of noodles made of *L. edodes* on the lipid metabolism and antioxidant system in high cholesterol fed rats. The result showed rats fed with *L. edodes* exhibited low plasma total cholesterol and triglycerides, and high high-density lipoprotein cholesterol (HDL

cholesterol) concentration. It indicates *L. edodes* can be effective in lowering atherosclerosis cardiovascular disease risk. Literature reported *L. edodes* significantly decreased total cholesterol levels due to eritadenine, which reduced plasma cholesterol in human bodies actively (Schneider et al., 2011).

Clinical Studies of *L. edodes*

The beneficial effects of *L. edodes* on human health have been studied for centuries. In the 13th century, Chinese physicians recorded the medicinal property of *L. edodes* against various forms of malignancy. The elders from Japanese Empire regarded the mushroom as the "elixir of life" (Chang et al., 1978). Oba and Kobayashi (2009) evaluated the effect of immunochemotherapy with lentinan compared to chemotherapy alone in 650 patients with advanced gastric cancer. Lentinan significantly prolonged the overall survival. Oka et al. (1992) injected lentinan into 16 patients with malignant peritoneal and/or pleural effusions. Among them 80% of lesions showed clinical responses. The average survival time in responders and non-responders was 129 days and 49 days, respectively. Moreover, amino acids in *L. edodes*, such as lysine and arginine, also inhibit tumor growth when administered orally (Shen et al., 2009).

Conclusion

L. edodes has been playing an important role in several aspects of human activity. Due to these properties, *L. edodes* has a great potential to serve as a functional food as well as for therapeutic applications. However, *L. edodes* is still needed further study in order to be accepted by the global market. Future research should focus on following directions: (1) a better understanding of *L. edodes* at the relationship of chemical structure-biological properties and mechanisms of bioactivities; (2) improve the different biological activities by means of chemical modification; (3) more double-blind and placebo-controlled clinical studies with large trial populations.

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CASE STUDY 2: TURMERIC

HEALTH BENEFITS OF TURMERIC (*CURCUMIN LONGA LINN*)

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Nutritional sciences have witnessed a plethora of scientific literature from foods/diets to, macro/micro nutrients, their recommended intakes, toxic elements, dietary ingredients and more recently phytonutrients and functional foods which impact several disease processes and health and well-being. In more recent times, consumer demand for healthy alternatives and availability of advanced technologies and tools have enlarged the scope of nutritional sciences resulting in functional foods, nutraceuticals, dietary supplements, herbal foods with claims of health benefits (Krishnaswamy 2009). Tumeric or Curcuma longa is an ancient Asian traditional plant that has been recognized to possess functional properties.

Turmeric is an herbaceous perennial plant belonging to the botanical family of Zingiberaceae, or the ginger family. The genus *Curcuma* includes 30 varieties of which *Curcuma longa* is economically the most important followed by *Curcuma aromatica*. *Curcuma longa* represents turmeric of commercial value and predominently grown in India. A number of cultivars (more than 25) are available and the popular ones are Duggirala, Tekkurpet, Sugandham, Amalapuram and Alleppey. The plant reaches up to 1 m tall, leaves are alternate and arranged in two rows. The rhizome is the valued plant part, used for cooking as well as medical aids in several disorders. The rhizome measures 2-3 inches in length, and an inch in diameter pointed or tapering at one end, yellowish brown externally, with transverse, parallel rings internally. India is the largest consumer, producer, and exporter of turmeric in the world accounting for about 80% of global turmeric production and 60% of global exports. The other main countries that export turmeric are: China, Myanmar, Nigeria and Bangladesh (Angles 2011; Lal 2012).

Traditional Uses

Traditionally turmeric from time immemorial (Vedic times) has been used as a cosmetic and spice in India and other South Asian countries, Middle East and African countries. It has a long history of use and dates back to almost 6000 years. In the culinary practice, it is commonly used for its color, flavor, and taste. It finds its place in many preparations such as rice, lentils, pulses, curry powder, and almost every dish whether it is vegetarian or non-vegetarian (Krishnaswamy 2009). While dry powder is preferred in the Indian subcontinent, in South East Asia, the fresh spice is much preferred.

In addition to culinary preparations, the golden spice as it is known has been in usage in the traditional system of medicine viz. Ayurveda, and Unani medical practice for a plethora of conditions (Table 6) (Krishnaswamy 2009). Scientific evidence suggests that the polyphenols and small peptides from turmeric exhibit therapeutic benefits such as anti-inflammatory, anti-infective, hypoglycemic, hypolipidemic, antioxidant, antimutagenic/ anti-carcinogenic, antiproliferative, anti-degenerative and vascular and cognitive effects. From antiquity, scented turmeric varieties have been in use as a cosmetic and against pimples and acne. Several skin creams with or without sandalwood paste to enhance skin glow and ointments are available commercially. It has attracted the attention of food scientists, biologists, pharmacologists, and molecular biologists. This review attempts to capture the evidence base science for the pleiotropic functional effects of turmeric/curcumin.

Table 6: Traditional Medicinal Uses

1. General tonic

2. Gastro intestinal disorders

a. irritable bowel syndrome
b. flatulence
c. intestinal disorders.
d. ulcer
e. intestinal worms
f. jaundice and liver disorders
g. intestinal soothing agent
h. colitis
i. anorexia/dyspepsia/carminative
j. abdominal pain

3. Respiratory disorders

a. common cold
b. rhinitis
c. sore throat
d. asthma
e. bronchial hyper activity
f. allergy
g. sinusitis

4. Infections

a. measles
b. chickenpox
c. smallpox
d. insect bites
e. sore eyes

5. Inflammation

a. arthritis
b. rheumatoid arthritis
c. inflammatory bowel disease
d. obesity
e. diabetes
f. wound healing

6. Skin disorders

7. Antiseptic for cuts and burns

8. Cosmetic: depilator and to improve skin quality

Chemical and Nutrient Composition of Turmeric

The chemical analysis showed that rhizome consists of essential oils (2-4%), fatty oils (2-3%), curcumin (2-5%), ash (4-8%) and moisture (3-7%) (Srinivasan 1953). The nutrient composition is indicated in Table 7. It has many proximate principles and provides minerals and nutrients in small quantities (Pruthi 1980; Gopalan 1989). The yellow color of turmeric is due to the presence of curcuminoids. Speaking of molecules by far the most researched in turmeric are the three curcuminoids viz. curcumin I (77%), demethoxycurcumin or curcumin II (17%) and bisdemethoxycurcumin or curcumin III (3%) (Govindarajan 1980; Krishnaswamy 2008). Curcumin (1,7-bis (4-hydroxy-3-methoxyphenyl)-1,6. heptadiene-3,5-dione), possesses a number of beneficial biological and pharmacological activities. It was first discovered about two centuries ago when Vogel and Pelletier reported the isolation of a "yellow coloring matter" from rhizomes of C. *longa* and named it curcumin. It is characterized by Milobedeska et al. (Milobedeska 1910) and first synthesized by Lampe et al. (Lampe 1913). Curcumin is a yellow crystalline, odorless, solid with a melting point of 184-186°C, poorly soluble in water but easily soluble in alcohol and chloroform.

Table 7: Chemical composition of *Curcuma longa Linn*

(Pruthi 1980; Olatunde 2014; Osorio-Tobon, Carvalho et al. 2016)

Nutrients	Value/ 100 g of edible portion	Nutrients	Value/ 100 g of edible portion
Energy	349 kcal	**Minerals**	3 - 7 g
Carbohydrates	50 -70 g	Iron	15.00 mg
Proteins	6 - 10 g	Copper	0.394 mg
Fat	5 - 8 g	Manganese	8.80 mg
Fiber	3 - 7 g	Zinc	2.72 mg
Vitamins		Chromium	0.06 mg
Carotenes	0.03 mg	Selenium	0.0067 mg
Thiamine	0.03 mg	Calcium	150 mg
Riboflavin	0.19 mg	Phosphorous	280 mg
Niacin	2.30 mg	Magnesium	190 mg
Folic acid	18.00 µg	Sodium	0.03 g
Vitamin C	50.00 mg	Potassium	2.50 g
Curcuminoids	2.331 g	**Terpenes**	Traces
Steroids	Traces	**Fatty acids**	4-6 g

Medicinal and Health Properties

Research in recent years has shown significant evidence of the medicinal and health benefits of turmeric and its main active component curcumin.

Antioxidant Effect

Oxidative stress is now believed to be the primary cause for not only many degenerative diseases, such as cardiovascular diseases, inflammatory diseases, cancer, cataract, type-2 diabetes, neurodegenerative diseases, etc., but also the natural aging process. The antioxidant activity of curcumin was first reported by Sharma (1976) (Dinkova-Kostova and Talalay 2008; Srinivasan 2014). The discovery of the antioxidant properties of curcumin explains many of its wide range of pharmacological activities. Curcumin is a bifunctional antioxidant because of its properties to react directly with reactive oxygen (ROS) and nitrogen (RNS) species and also to indirectly induce an up-regulation of several cytoprotective and antioxidant proteins (Dinkova-Kostova and Talalay 2008; Trujillo, Granados-Castro et al. 2014) (Figure 1). Curcumin has been shown to be a good inhibitor of lipid peroxidation (Reddy and Lokesh 1992). Curcumin has the ability to scavenge superoxide anion, hydroxyl radical, hydrogen peroxide, singlet oxygen, nitric oxide, peroxynitrite, and peroxyl radical. Earlier studies proposed that curcumin also enhances the activity of many antioxidant enzymes such as catalase, superoxide dismutase, glutathione peroxidase and hemeoxygenase-1 (Jeong, Oh et al. 2006). The oxidant stress curtailment by curcumin was also associated with nuclear translocation of Nuclear factor erythroid-2 related factor 2 (Nrf2) and preservation of mitochondrial function (Gao, Duan et al. 2013).

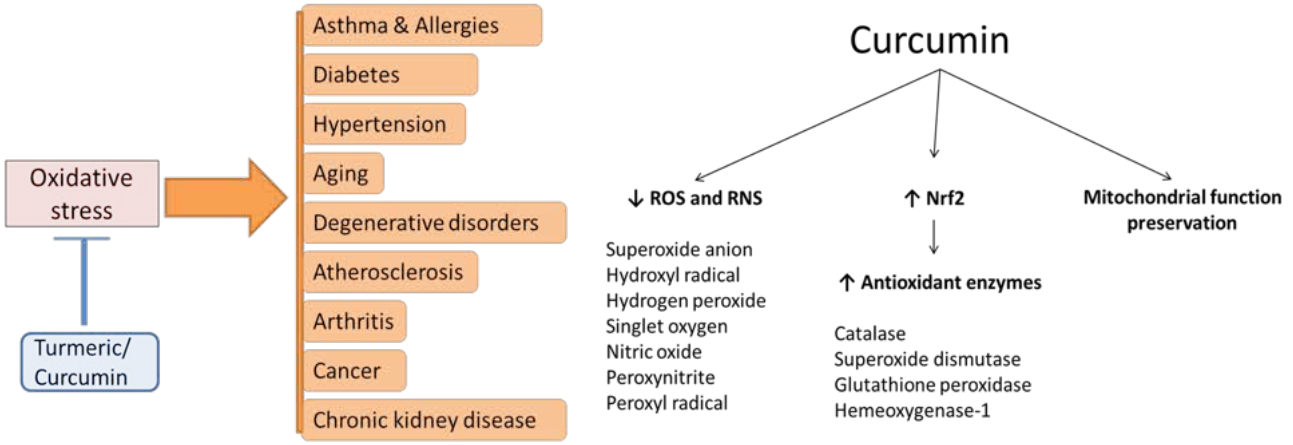

Figure 1: Oxidative stress has been associated with diverse diseases and turmeric/curcumin is shown to have a strong antioxidant activity and the possible mechanisms are depicted above. ROS: reactive oxygen species, RNS: reactive nitrogen species, Nrf2: nuclear factor E2-related factor 2.

Anti-inflammatory Effect

Inflammation is an adaptive physiological response induced by deleterious circumstances including infection and tissue injuries. It is the product of complex series of responses triggered by the immune system causing a broad range of physiological and pathological morbidities. Studies revealed that curcumin is a highly pleiotropic molecule capable of interacting with numerous molecular targets involved in inflammation. The anti-inflammatory activity of turmeric is likely accomplished via curcumin's suppression of nuclear factor kappa B (NF-κB) activation and JAK/ STAT pathway (Janus Kinases/ Signal Transducers and Activators of Transcription) (Figure 2). NF-κB, a ubiquitous eukaryotic transcription factor, is involved in the regulation of inflammation. Suppression of NF-κB activation subsequently down-regulates cyclooxygenase-2 and inducible nitric oxide synthase expression, thereby blocking expression of cytokine gene expression. Another suggested mechanism is the activation of Nrf2 which is highly related to oxidative stress in inflammation (Buhrmann 2011; Soetikno 2013) (Figure 3). Studies have shown reciprocal regulation of NF-κB and Nrf2, suggesting an anti-inflammatory role of Nrf2. A large number of studies reported that Nrf2 is associated with Mitogen-Activated Protein Kinases (MAPK), NF-κB, Phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K) and Protein kinase C (PKC) pathways (He, Yue et al. 2015). Curcumin's potent anti-inflammatory properties have led to active research on its use for a variety of inflammatory conditions, including postoperative inflammation, arthritis, allergy, asthma, bronchitis, uveitis, chronic kidney disease, psoriasis, scleroderma, diabetes, obesity, inflammatory pseudo tumors, dyspepsia, irritable bowel syndrome, inflammatory bowel disease, pancreatitis, and *Helicobacter pylori* infection.

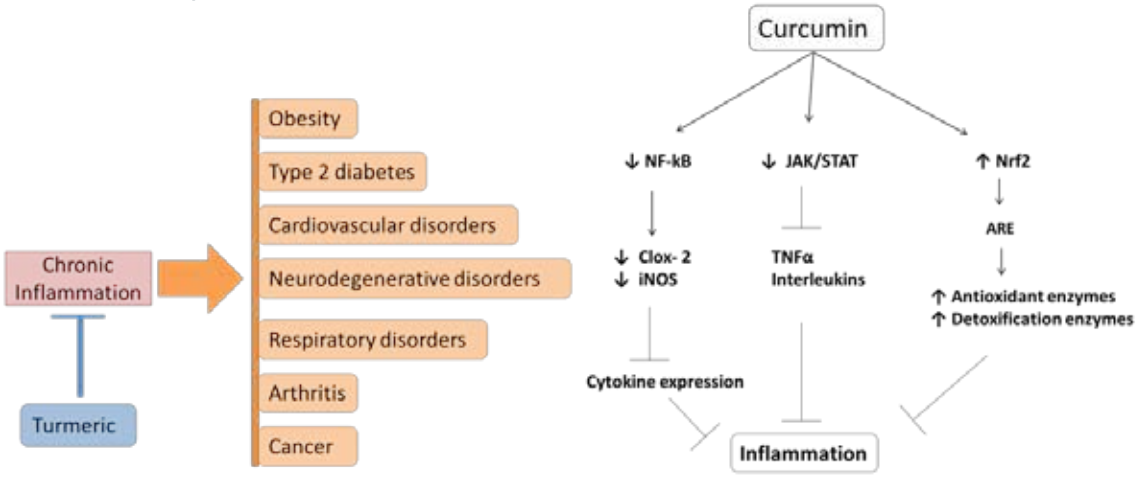

Figure 2: Chronic inflammation has been linked to several disorders and turmeric/curcumin is shown to be anti-inflammatory agent and the possible mechanisms were illustrated here. NF-kB: nuclear factor kappa- B, Clox-2: cyclooxygenase- 2, iNOS: inducible nitric oxide synthase, TNFα: Tumor necrosis factor α, Nrf2: nuclear factor E2-related factor 2, ARE: antioxidant responsive element.

Hypolipidemic Effect

An elevated level of lipids and/or lipoproteins in the blood is called as hyperlipidemia. It results in lipotoxicity leading to cellular dysfunction and cell death as observed with primary hyperlipidemias, diabetes, and obesity (Schaffer 2003). Early studies suggested that the main active component of turmeric, curcumin, is responsible for hypocholesteremic effects (Patil and Srinivasan 1971). Several molecular mechanisms have been proposed to explain the ability of curcumin to reduce plasma lipid levels in animal and human models. Curcumin influences signal transduction (e.g., Akt, AMPK) and modulates the activity of specific transcription factors (FOXO1/3a, NRF2, SREBP1/2, CREB, CREBH, PPARc, and LXRa) that regulate the expression of genes involved in lipid homeostasis (aP2/FABP4, CD36, HMG-CoA reductase, and carnitine palmitoyltransferase-I) (Srinivasan and Sambaiah 1991; Babu and Srinivasan 1997; Kim and Kim 2010; Shin 2011; Prakash and Srinivasan 2012; Zingg 2012). The reduction of plasma lipid levels by curcumin may play a major role not only in preventing lipid mediated oxidative and Endoplasmic Reticulum (ER) stress and in lowering the systemic exposure to potentially toxic and damaging lipids, but also in reducing the lipid-mediated activation and deregulation of inflammatory cells with consequent reduced risk for atherosclerosis and coronary heart disease (Zingg 2013). Long-term curcumin administration protects against atherosclerosis via hepatic regulation of lipoprotein cholesterol metabolism (Shin 2011). At the cellular level, curcumin may induce a mild lipid-metabolic stress leading to an adaptive cellular stress response by hormetic stimulation of the lipid metabolic enzymes.

Anti-obesity Effect

Experimental evidence supports the activity of curcumin in promoting weight loss and reducing the incidence of obesity. With the discovery that obesity is characterized by chronic low-grade inflammation, curcumin with its anti-inflammatory activity is being intensely investigated (Bradford 2013). Recent studies reveals that curcumin directly interacts with white adipose tissue to suppress chronic inflammation. Curcumin suppresses preadipocyte differentiation by activation of Wnt/beta-catenin signaling and thus reduce the number of adipocytes and fat content of adipose tissue (Ahn 2010). Curcumin promotes epigenetic modulations that affect target genes in obesity. These actions include global DNA hypomethylation, histone modifications, micro RNA metabolism, and specific inhibition of p300/CBP histone acetyltransferase (Fu 2010). Curcumin inhibits macrophage expansion and infiltration in white adipose tissue, to suppress inflammatory adipokine secretion (Weisberg 2008). Curcumin promotes the nuclear translocation of Nrf2 presumably through modification of Kelch-like ECH-associated protein 1 (Keap1), allowing for dissociation, nuclear translocation, and promotion of antioxidant expression, particularly the ultimate antioxidants NADPH-quinone oxidoreductase 1 (NQO1) and hemeoxygenase-1 (HO-1) (Magesh 2012).

Anti-diabetic Effect

Turmeric is claimed to possess beneficial hypoglycemic effects and to improve glucose tolerance in several studies (Srinivasan 1972; Arun and Nalini 2002; Olatunde 2014). The first report of its hypoglycemic effect was by Srinivasan (Srinivasan 1972). Daily intake of curcumin not only reduced the fasting blood sugar level but also lowered the dosage of insulin needed for normoglycemia. Suggested mechanisms for the curcumin's anti-diabetic activity are volume regulated anion channel activation (leading to increased insulin secretion), 5′ adenosine monophosphate-activated protein kinase (AMPK) activation, inhibition of α-glucosidase and α-amylase activity, antioxidant, anti-inflammatory and antilipidemic effects (Bi 2017). Although, some studies found no significant glucose-lowering effect with curcumin, it is shown to prevent diabetic complications like nephropathy (Khajehdehi 2011), retinopathy (Mrudula 2007), cataract (Suryanarayana 2005), and neuropathy (Zhao, Zhang et al. 2014) in animal models, probably through mechanisms independent of reduction in plasma glucose.

Anti-cancer Effect

Studies have reported the inhibitory effects of curcumin on almost all types of cancers related to the reproductive, digestive, lymphatic, immune, urinary, pulmonary, nervous, skeletal systems, and the skin. Turmeric and curcumin have also been investigated for their chemopreventive actions using several tumor models for oral cavity, skin, lung, breast, colon, liver and prostate tumors. Nitrosamines are potent carcinogens, and turmeric was shown to have antinitrosating activity both in *vivo* and in *vitro* conditions (Prasad 2003). Evidence suggests that altered inflammatory pathways play a crucial role in a multitude of chronic diseases, including cancer (Aggarwal 2003; Sethi 2012) and curcumin is a well-known anti-inflammatory agent.

Based on its distinct chemical properties, curcumin interacts with other numerous cellular molecules that are actively involved in cancer, thereby inhibiting cancer progression (Gupta 2011). The direct molecular targets include the ErbB family of receptors, protein kinase C, enzymes involved in prostaglandin synthesis, vitamin D receptor, and DNA (Heger 2014). Curcumin down regulates various transcriptional factors including NF-kB, AP-1, Notch-1, STAT-1, STAT-3, EGR-1, WT-1, beta catenin, HIF-1 and up-regulates NRF-2, PPARγ and ERE transcription factors (Figure 3) (Singh and Aggarwal 1995; Han 2002; Kinney 2015). It down-regulates the growth factors involved in cancer; FGF, HGF, EGF, PDGF, VEGF, and TGF-β1 (Korutla and Kumar 1994). Curcumin down-regulates oncogenic protein kinases including MAPKs such as p38 MAPK, JNK1/2, and extracellular signal-regulated kinase 1/2 (ERK1/2) (Seger and Krebs 1995). Curcumin was shown to down-regulate cyclin D1 which is overexpressed in a multitude of cancers (Mukhopadhyay 2002). Curcumin induces p53-dependent apoptosis and checks cancer progression (Jee 1998; Radhakrishna Pillai 2004).

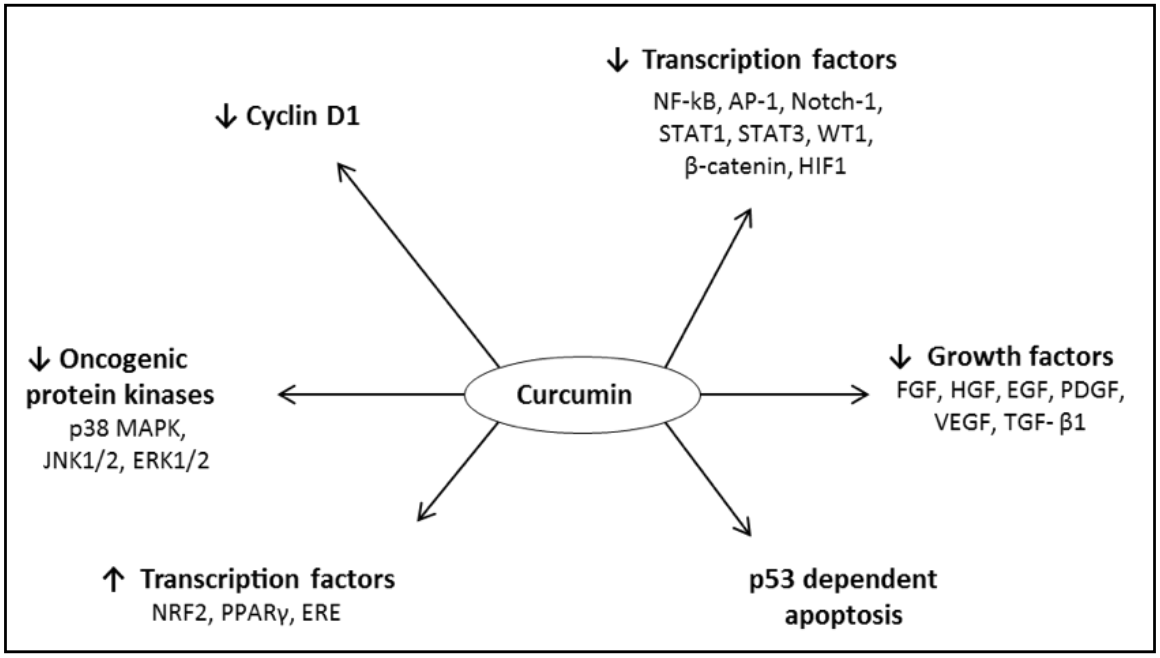

Figure 3: Possible mechanisms of curcumin's anti-cancer effect. Curcumin down regulates various transcription factors, oncogenic protein kinases, growth factors and cyclin-D1 which promote tumor growth. Curcumin up regulates transcription factors and p53 dependent apoptosis that inhibit tumor progression.

Antimutagenic Effect

Mutagenesis is a process by which the genetic material (RNA/DNA) of an animal is altered, causing a mutation. DNA damage may ultimately result in a number of diseases. Mutagenesis may occur spontaneously or by exposure to mutagens. Studies have shown that both turmeric and curcumin possess antimutagenic effects against benzo(a)pyrene, and 3-methyl cholanthrene induced mutagenesis in rats (Polasa 1991; Krishnaswamy and Raghuramulu 1998). Feeding of turmeric and curcumin was shown to inhibit DNA adduct formation in rats (Mukundan 1993), hamsters (Krishnaswamy, Goud et al. 1998), and human cells (Zhu 2014; Jain 2015). Polasa et al., observed that when turmeric is given to humans in dose of 1.5 g/day for 30 days, it significantly reduced the urinary excretion of mutagens in smokers (Polasa 1992). Another study reported the protective effect of curcumin on benzo(a) pyrene induced DNA damage in human peripheral blood lymphocyte cells (Polasa 2004).

Neurodegenerative Diseases

In addition to the age-related pathologies, curcumin may have beneficial effects on neurodegenerative diseases characterized by the formation of aggregated fibrillar protein deposits. Curcumin can cross blood brain and blood-retina barriers to exert its protective effects. Several interesting studies in rodents have investigated the neuroprotective ability of

curcumin against neurodegenerative disorders, such as Alzheimer's disease, and Parkinson's disease. In a pioneering study, Frautschy and colleagues (Frautschy 2001) showed that curcumin treatment attenuated spatial memory deficits, oxidative injury, microgliosis, synaptophysin loss, postsynaptic loss, and Aβ deposits produced by intracerebroventricular infusion of Aβ amyloid in rats. Earlier studies illustrate the potential of curcumin to reverse neurodegeneration and improve the cognitive impairments associated with Alzheimer's disease (Lim 2001; Garcia-Alloza 2007). Curcumin is also reported to reduce the oxidative damage in an Alzheimer's transgenic mouse. Direct interaction of curcumin with amyloid β and α-synuclein and inhibition of their aggregation has been demonstrated. There is data suggesting that curcumin could have a protective effect against neurodegeneration in Parkinson's disease. Curcumin was also shown to safeguard protein confirmation and prevent aggregation of transthyretin (protein involved in the transport of thyroxin and retinol in the human plasma) thereby preventing pathogenesis of familial amyloid polyneuropathy and senile systemic amyloidosis (Pullakhandam 2009). Retinitis pigmentosa is the common degenerative disease of the retina. Curcumin may serve as a possible therapeutic agent in treating retinitis pigmentosa caused by rhodopsin mutation and perhaps other degenerative diseases caused by protein trafficking defects (Vasireddy 2011).

Miscellaneous Effects

Turmeric and curcumin showed to be effective in several other illnesses such as myocardial infarction, pancreatitis, wound healing, flatulence, skin related disorders, gastric ulcer, oral ulcer, pesticide toxicity, venom toxicity, endotoxic injury, aflatoxin injury, muscle injury, spinal cord injury, bone loss, depression, heat shock stress, spermatogenic disorders, infections, myocardial fibrosis, hepatic fibrosis, renal fibrosis and cystic fibrosis.

Bioavailability (Pharmacokinetics)

In spite of its safety and efficacy, curcumin has not yet been approved as a therapeutic agent, and the relative bioavailability is a major reason for this. Studies revealed that curcumin has poor absorption, large first pass effect and rapid metabolism that severely curtails its bioavailability (Anand 2007). Studies showed that turmeric oil, present in turmeric, can enhance the bioavailability of curcumin (Aggarwal 2013). One of the important observations related to curcumin involves the observation of extremely low serum levels. The first reported study on curcumin bioavailability was by Wahlstrom and Blennow in 1978. Negligible curcumin in plasma of rats after oral administration of 1 g/kg showed that curcumin was poorly absorbed from the gut (Wahlstrom 1978). In humans, the 2g/ kg dose of curcumin resulted in either extremely low or undetectable serum levels (Shoba 1998).

The plasma concentrations of conjugated curcuminoids reach a maximum after one hour of administration. The presence of conjugative enzyme activities for glucuronidation and sulfation of curcumin in the liver, kidney, and intestinal mucosa suggested that curcumin is absorbed from the alimentary tract and present in the general blood circulation after mostly being metabolized to the form of glucuronide/sulfate conjugates (Asai 2000). Pan et al. showed that 99% of plasma curcumin was present as glucuronide conjugates (Pan 1999). A study by Wahlstrom and Blennow showed that when 1 g/kg of curcumin was fed to rats orally, 75 % of it was excreted in the feces, and insignificant amounts were observed in the urine. Intravenous and intraperitoneal administration of curcumin resulted in biliary excretion from cannulated rats (Holder 1978).

Several attempts have been made to increase the stability, solubility and bioavailability of curcumin such as designing excipient emulsions (Zou 2015), combining with piperine (Shoba, Joy et al. 1998), emu oil (Jeengar 2014), nanocarriers (Mohanty 2012), liposome encapsulation (Chaurasia 2015), silica-coated ethosome (Li 2012). Administration of piperine (20 mg/Kg) along with curcumin (2 g/Kg) increased curcumin bioavilability (2000% in humans and 154% in rats) and decreased elimination half-life and clearance of curcumin (Shoba 1998). Administration of curcumin encapsulated nanoparticles in streptozotocin induced diabetic cataract model shown to be significantly more effective than curcumin in delaying diabetic cataracts in rats due to increased bioavailability (Grama 2013). Improved bioavailability of curcumin in the near future is likely to bring this potential natural compound to the forefront of therapeutic agents for the treatment of human diseases.

Toxicity Studies

The average intake of turmeric by Asians varies from 0.5 -1.5 g/day which produces no toxic symptoms (Commandeur 1996; Eigner 1999). Human clinical trials also indicate that curcumin

has no toxicity when administered at doses of 1- 8 g/day (Chainani-Wu 2003). When rats were given turmeric in amounts normally taken by man or in amounts 1.25 to 125 times those, there was no adverse effect on growth, food efficiency ratio, erythrocyte count, leucocyte count, differential counts or on haemoglobin, total serum protein or serum albumin, globulin, aminotransferase and alkaline phosphatase (Sambaiah 1982). No apparent toxic effects were documented in rats after doses of 5 g/Kg body weight of curcumin when given orally (Wahlstrom 1978). However, a subchronic oral hepatotoxicity of turmeric in mice is reported (Kandarkar 1998).

Clinical Studies

Curcumin has been clinically tested in a wide spectrum of diseases. There are 69 completed studies and 54 active/recruiting studies as of today in U.S. National Institutes of Health (NIH) registry. Further, numerous in vitro and in *vivo* studies have shown that curcumin acts as anti-inflammatory, antiviral, antifungal, antioxidant, immunomodulatory, proapoptotic and antiangiogenic agent as well as a mediator of chemo-resistance and radio-resistance (Schaffer 2011). Turmeric and curcumin supplementation has exerted positive effects in many diseases: metabolic disorders (such as obesity, metabolic syndrome, prediabetes, and diabetes), inflammatory diseases (Rheumatoid Arthritis, Osteoarthritis, Anterior uveitis, Inflammatory Bowel Disease, Ulcerative colitis, Crohn disease, Postoperative inflammation), cancer (colon, rectal, pancreatic, breast, prostate, lung, multiple myeloma, osteosarcoma, oral mucositis), skin diseases (Vitiligo, Psoriasis), Neurodegenerative diseases (Dejerine-Sottas disease, Alzheimer's disease) cardiovascular disease, viral diseases, β-Thalassemia, Gallbladder contraction, Cholecystitis, and alcohol intoxication (Jurenka 2009; Shehzad 2010; Fan 2013; Gupta, Patchva et al. 2013; Jimenez-Osorio 2016; Saldanha 2016). Some of the completed trials with curcumin are represented in Table 8.

Table 8: Clinical Trials with Curcumin

Condition	Dose	Duration	Response	Ref.
Cancer				
Colorectal cancer	1.44 g/day	6 months	Reduced the number and size of polyps without any appreciable toxicity	(Cruz-Correa 2006)
Pancreatic cancer	1.5 g/day	6 weeks	Reduced the lipid peroxidation and increased GSH content in patients	Durgaprasad 2005)
Breast cancer	6 g/day	every 3 weeks	Safe, well-tolerated, and efficacious	(Bayet-Robert 2010)
Prostate cancer	0.1 g/day	6 months	Reduced the serum PSA content in combination with isoflavones	(Ide 2010)
Multiple myeloma	2-12 g/day	12 weeks	Safe, and efficacious	(Vadhan-Raj S 2007)
Inflammatory Diseases				
Rheumatoid arthritis	0.5 g/day	8 weeks	Improved symptoms in patients alone and in combination with diclofenac sodium	(Chandran and Goel 2012)
Osteoarthritis	1 g/day	8 months	Efficacious in the long-term management of osteoarthritis	(Belcaro 2010)
Crohn disease	1.08-1.44 g/day	3 months	Significant reduction in patients	(Holt 2005)
Metabolic Diseases				
Obesity	1 g/day	1 month	Reduction in serum levels of IL-1a, IL-4, and VEGF	(Ganjali 2014)
Prediabetes	1.5 g/day	9 months	Reduction in HbA1c, fasting glucose, and OGTT at 2 h were significantly lower	(Chuengsamarn 2012)
Metabolic syndrome	1.89 g/day	3 months	Reduction in triglycerides, total cholesterol, and LDL-Cholesterol	(Yang 2014)
Type- 2 diabetes	1.5 g/day	6 months	Reduction in HOMA-IR, triglycerides, uric acid, visceral fat and total body fat.	(Chuengsamarn 2014)

CONCLUSION

Curcuma Longa Linn (Turmeric plant) is widely cultivated in Asian countries and its rhizome is used traditionally from time immemorial as spice, coloring agent and medicine for various human ailments. Turmeric is also known as yellow root, and the color is due to the presence of curcuminoids. Curcumin is the principal curcuminoid in turmeric accounting 3-5 %. Although curcumin is assumed to account for most biological activities of turmeric, research over the past decade has indicated that curcumin-free turmeric is as effective as or even more effective than curcumin containing turmeric. Numerous components of turmeric such as turmerin, turmerone, elemene, furanodiene, curdione, bisacurone, cyclocurcumin, calebin A, and germacrone are reported to possess potent biological activities. Therefore, the future studies should be directed toward evaluating the clinical efficacy of even the noncurcumin components of turmeric. Curcumin is found to be safe at gram doses in a variety of organisms including humans. Curcumin possesses great promise as a functional food ingredient in the prevention and treatment of various human disorders. Though several attempts are made to improve the solubility and bioavailability of curcumin, it still remains a great challenge to the researchers. Interestingly, a recent comprehensive criti¬cal review on curcumin concludes that there is no evidence for any specific therapeutic benefits of curcumin, despite thousands of research papers and more than 120 clinical trials (Baker 2017; Nelson 2017). Curcumin has recently been classified as both a PAINS (pan-assay interference compounds) and an IMPS (invalid metabolic panaceas) candidate. This could be due to the drawbacks with curcumin's poor pharmacokinetic/pharmacodynamic properties, low efficacy in several disease models, and toxic effects under certain testing conditions. Although, the multicomponent activity of turmeric is known including other curcuminoids, there has been an over emphasis on curcumin instead of focusing on turmeric in totality. In addition, Phase II metabolism of curcumin such as glucuronidation and sulfation in the liver, kidney, and intestinal mucosa to the form of glucuronide/sulfate conjugates (Asai 2000), may be the reason for low or undetectable levels of curcumin. A great deal can still be expected from chemists and biologists to exploit this natural product as a therapeutic remedy for many chronic diseases. In view of the many health effects of turmeric and its main active component curcumin, it can be anticipated that this ingredient that has been widely utilized for culinary practices since ancient times, has great potential to serve as a traditional functional food.

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Appendices

Appendix 1: Guidelines for the Scientific Substantiation of Nutrition and Health Claims for Foods / Functional Foods

1. Types of studies required for substantiation of claims

- Studies should preferably be conducted on the whole functional foods in the form to be consumed rather than on extracted components.
- Foods containing added functional food ingredient(s) may not need individual studies to be conducted if they can show bioequivalency compared to the primary study conducted.
- Nutrient function claims* may be permitted based on authoritative statements from recognized health authorities and accepted texts.
- Scientific substantiation of other function claims* should be based on human data (observational and/or intervention studies). In vitro studies and animal studies may be submitted in support of the application.
- Disease-risk reduction* claims would require additional data from randomized double-blind placebo controlled trials (RCT). In the event that this is not possible, data from appropriately designed intervention studies can be accepted.

Definition of claims are based on definition of Codex Health Claims (FAO/WHO, 2004) :

Nutrient function claims:

- Nutrition claim that describes the physiological role of the nutrient in growth, development and normal functions of the body.

Other function claims:

- These claims concern specific beneficial effects of the consumption of foods and their constituents in the context of the total diet on normal functions or biological activities of the body. Such claims relate to a positive contribution to health or to the improvement of a function or to modifying or preserving health.

Reduction of disease claims:

- Claims relating the consumption of a food or food constituent, in the context of the total diet, to the reduced risk of developing a disease or health-related condition.

Conduct of Human Intervention Studies:

- Study group should be relevant to the intended claim and target population.
  - When the target population is different from the subjects of the original studies, the application has to justify the product is still effective and safe.
- Appropriate control is required.
- Adequate length of duration of exposure and follow-up to demonstrate the intended effect is needed.
- Dietary intake of human subjects should be characterized and monitored as part of the intervention studies and should be conducted using appropriate methodologies.
- Compliance of consumption of food or ingredient under investigation should be monitored.
- An amount of food or dose of food component used should be consistent with its intended pattern of consumption.
- The effect of the food matrix and dietary context on the functional effect of the component should be considered.

- Statistical power to test the hypothesis and clinical meaningfulness should be considered.

2. Biomarkers

- The claimed functional benefit should be measured directly if possible. In situations when this is not possible, appropriate biomarker(s) as intermediate endpoints, should be identified and used in the studies.
- A relevant biomarker is a well-defined biological, physiological, clinical or epidemiological indicator which is modulated by the ingestion of the food, food constituent or ingredient and for which there is agreement among the scientific community on the relation between the modulation of this indicator and the state of health of the population in which it is measured.
- In disease risk reduction claims, the biomarker(s) considered should be a marker(s) of that disease and recognized by the scientific community. The change of the level of such a biomarker(s) would significantly affect the risk of disease or health condition which is the substance of the claim (Guidelines from WHO Technical Report Series 916 may be referred to).
- Suitability of a given biomarker(s) within a population or between population groups should be assessed, based on variability of response.
- Methodology for measuring the biomarker(s) should be generally accepted by the international scientific community relative to that discipline.

3. Research design and methodology

- Studies should be conducted using methodologies accepted by the scientific community.
- Studies should have been approved by the appropriate ethical committee.
- Study must include adequate number of subjects to reach confident conclusions.
- Statistical analysis of the data shall be conducted with methods recognized as appropriate for such studies.
- Statistical, biological and clinical significance should be used for proper interpretation of the research.

4. Overall evaluation of submitted data

- All available positive and negative outcomes must be taken into account by a group of qualified experts, based on a clearly described search strategy.
- Studies should be peer reviewed and preferably be published in scientific journals.
- Studies conducted by independent research groups are preferred.
- Studies conducted by or funded by industry may be acceptable on condition that the research is independently peer reviewed.
- The body of research shall convincingly demonstrate that the product will have the claimed effect at the recommended level of intake.

5. Re-evaluation

- Re-evaluation will be based on the proper assessment of significant new findings.

Appendix 2: Guidelines for Evaluation of Safety / Nutritional Safety of Functional Foods

- Functional foods or components must fulfill the safety requirements for food as set out in the national legislations or in the absence of which, the Codex Alimentarius.
- Functional foods or components that meet all the following criteria do NOT require additional safety evaluation:
  - Foods with a history of safe food / culinary use in similar population, have essentially the same nature, using similar methods of processing and preparation, and with a similar consumption pattern, as established through epidemiological and retrospective surveys.
  - Foods which form part of dietary guidelines, national food guidance systems and cultural texts/ documentations for the intended population.
  - The recommended consumption levels do not cause major undesirable changes /shifts in the dietary pattern.
- Otherwise, appropriate additional safety evaluation is required with considerations given to the following:
  - Consumption by populations outside the target group particularly the vulnerable groups; excessive consumption; shifts in nutritional balance due to increased consumption of some foods and the replacement of others.
  - The interactions with nutrients and/or other food components.
- When intervention trials for efficacy testing for foods are conducted, particularly when high levels are used, researchers should include measurement of adverse effects/ monitoring of adverse events, as appropriate to the food/component in question.

Appendix 3: Regulatory Framework for Nutrition Labeling and Claims for Food - Harmonization in the Southeast Asia Region

1. Establish National Expert Committee on Nutrition and Health Claims

- Establish terms of reference
- Seek approval from appropriate authorities
- Select members based on discipline and experience – aim for multiagency, multidisciplinary

2. Make provisions for nutrition/health claims in existing food regulations

- Examine existing food regulations - determine amendments required
- Draft regulations for labeling and nutrition/health claims
- Submit for public comments and finalize regulations
- Enact as regulations

3. Make preliminary preparations

- Determine type of applications to be considered by Expert Committee (labeling amendments and types of claims)
- Decide nature of application dossier required, including developing appropriate application forms to be used
- Determine the criteria for substantiation of claims (use Guidelines for Substantiation of Claims being developed by ILSI SEA Region as reference)

4. Establish work procedure for reviewing applications

- Assign appropriate staff to serve as secretariat of Expert Committee
- Establish work flow – receipt of applications, initial processing, tabling of dossier, decisions of Expert Committee, endorsement by higher authorities, public comment, informing the applicant, etc
- Hold regular meetings to review applications

Appendix 4: Positive List of Nutrient Function Claims in Southeast Asia

INDONESIA

1. **Protein**
   a. Protein helps in the development and repair of body tissue.
   b. Protein is an essential component in children growth and development.

2. Vitamin A may help in maintaining outer linings surface integrity (eyes, digestive tract, respiratory tract, and skin).

3. **Vitamin B1 plays a role as a co-enzyme for converting carbohydrate into energy.**

4. **Vitamin B2 plays a role as a co-enzyme for converting carbohydrate into energy.**

5. **Niacin is a co-factor in formation of energy and tissue formation reactions.**

6. **Vitamin B6 is one of the factors of energy metabolism and tissue formation.**

7. **Folic acid:**
   a. Folic acid plays a role in cell growth and division.
   b. Folic acid plays a role in red blood cells formation.
   c. Folic acid plays a role in maintaining growth and development of the fetus (specifically in food products for pregnant women).

8. **Vitamin B12 acts as a coenzyme in the formation of nucleic acid such as the formation of red blood cells.**

9. **Vitamin C:**
   a. Vitamin C helps in the formation and maintenance of collagen tissues.
   b. Vitamin C helps in iron absorption.

10. **Vitamin D can help in calcium absorption.**

11. **Calcium helps in the formation and maintenance of bones and teeth density.**

12. **Iron is the hemoglobin component of red blood cells that carries oxygen all over the body.**

13. **Iodine is essential in the formation of thyroid hormone.**

14. **Magnesium helps to maintain bone density.**

15. **Soluble dietary fiber (psyllium, beta glucan from oats, inulin from chicory and pectin from fruit) can help maintain/ preserve the function of the digestive tract.**

MALAYSIA

1. **Folic acid:**
   a. Folic acid is essential for growth and division of cells.
   b. Folate plays a role in a formation of red blood cells.
   c. Folate helps to maintain the growth and developmental of the foetus.

MALAYSIA

2. **Iron:**
   a. Iron is a factor in red blood cell formation.
   b. Iron is a component of haemoglobin in red blood cell which carries oxygen to all parts of the body.

3. **Iodine is essential for the formation of thyroid hormone.**

4. **Calcium aids in the development of strong bones and teeth.**

5. **Magnesium promotes calcium absorption and retention.**

6. **Niacin is needed for the release of energy from protein, fats and carbohydrate.**

7. **Protein:**
   a. Protein helps build and repair body tissues.
   b. Protein is essential for growth and development.
   c. Protein provides amino acids necessary for protein synthesis.

8. **Vitamin A:**
   a. Vitamin A aids is maintaining the health of skin and mucous membrane.
   b. Vitamin A is essential for the functioning of the eye.

9. **Vitamin B1/Thiamine is needed for the release of energy from carbohydrate.**

10. **Vitamin B2/Riboflavin is needed for the release of energy from protein, fats and carbohydrate.**

11. **Vitamin B12/Cyanocobalamine is needed for red blood cell production.**

12. **Vitamin C:**
    a. Vitamin C enhances absorption of iron from non-meat sources.
    b. Vitamin C contributes to the absorption of iron from food.

13. **Vitamin D:**
    a. Vitamin D helps the body utilize calcium and phosphorus.
    b. Vitamin D is necessary for the absorption and utilization of calcium, and phosphorus.

14. **Vitamin E protects the fat in body tissues from oxidation.**

15. **Zinc is essential for growth.**

SINGAPORE

1. **Protein:**
   a. Protein provides the essential amino acids needed to aid in the building and maintenance of body tissues.
   b. Protein helps in tissue building and growth

2. **Lactose:**
   a. Low lactose content allows easier digestions.
   b. Low lactose content eases digestion for people who are lactose intolerant.

3. **Dietary fibre aids in digestive system.**

4. **Vitamin A:**
   a. Vitamin A is essential for the functioning of the eye.
   b. Vitamin A helps to maintain normal skin and mucous membrane.
   c. Vitamin A contributes to the normal function of the immune system.

5. **Vitamin B1 (thiamin):**
   a. Vitamin B1 helps to release energy from proteins, fats and carbohydrates.
   b. Vitamin B1 contributes to normal functioning of the nervous system.
   c. Vitamin B1 contributes to the normal functioning of the heart.

6. **Vitamin B2 (riboflavin):**
   a. Vitamin B2 helps to release energy from proteins, fats and carbohydrates.
   b. Vitamin B2 contributes to the reduction of tiredness and fatigue.
   c. Vitamin B2 contributes to the maintenance of normal skin.
   d. Vitamin B2 contributes to the maintenance of normal red blood cells.
   e. Vitamin B2 contributes to the maintenance of normal vision.
   f. Vitamin B2 contributes to normal functioning of the nervous system.
   g. Vitamin B2 contributes to the protection of cells from oxidative stress.

7. **Vitamin B3 (niacin):**
   a. Vitamin B3 helps to release energy from proteins, fats and carbohydrates.
   b. Vitamin B3 contributes to the reduction of tiredness and fatigue.
   c. Vitamin B3 contributes to the maintenance of normal skin.
   d. Vitamin B3 contributes to normal functioning of the nervous system.

8. **Vitamin B5 (pantothenic acid):**
   a. Pantothenic acid contributes to normal energy productions.
   b. Pantothenic acid contributes to the reduction of tiredness and fatigue.
   c. Pantothenic acid contributes to normal mental performance.

9. **Vitamin B6 (pyridoxine):**
   a. Vitamin B6 is important for the production of energy.
   b. Vitamin B6 contributes to the reduction of tiredness and fatigue.
   c. Vitamin B6 contributes to normal functioning of the nervous system.
   d. Vitamin B6 contributes to normal red blood cell formation.
   e. Vitamin B6 contributes to the normal function of the immune system.
   f. Vitamin B6 contributes to normal homocysteine metabolism.
   g. Vitamin B6 contributes to the regulation of hormonal activity.

10. **Vitamin B12 (cyanocobalamin):**
    a. Vitamin B12 is necessary for fat, carbohydrate and protein metabolism.
    b. Vitamin B12 is needed for/helps in the formation of red blood cells.
    c. Vitamin B12 contributes to the reduction of tiredness and fatigue.
    d. Vitamin B12 contributes to normal functioning of the nervous system.
    e. Vitamin B12 contributes to the normal function of the immune system.
    f. Vitamin B12 contributes to normal homocysteine metabolism.

11. **Folate (folic acid):**
    a. Folate contributes to normal immune system function.
    b. Folate contributes to the reduction of tiredness and fatigue.

c. Folate contributes to normal homocysteine metabolism.
d. Folate contributes to normal amino acid synthesis.

12. **Folate (folic acid) – claims for foods for pregnant women only:**
    a. Folate helps support foetus' growth and overall development.
    b. Folate plays a role in the formation of red blood cells.
    c. Folate, taken before and during early pregnancy, helps in the mental/normal and overall development of fetus.
    d. Folic acid is essential/important for growth and division of cells.

13. **Vitamin C:**
    a. Vitamin C enhances absorption of iron from non-meat products.
    b. Vitamin C contributes to normal collagen formation for the normal function of blood vessels.
    c. Vitamin C contributes to normal collagen formation for the normal function of bones.
    d. Vitamin C contributes to normal collagen formation for the normal function of cartilage.
    e. Vitamin C contributes to normal collagen formation for the normal function of gums.
    f. Vitamin C contributes to normal collagen formation for the normal function of skin.
    g. Vitamin C contributes to normal collagen formation for the normal function of teeth.
    h. Vitamin C contributes to normal collagen formation for the normal function of immune system.
    i. Vitamin C contributes to normal collagen formation for the normal functioning of the nervous system.
    j. Vitamin C contributes to the reduction of tiredness and fatigue.
    k. Vitamin C contributes to the protection of cells from oxidative stress.

14. **Vitamin D:**
    a. Vitamin D helps support calcium absorption and improves bone strength.
    b. Vitamin D helps the body utilize calcium and phosphorus.
    c. Vitamin D contributes to normal blood calcium levels.
    d. Vitamin D contributes to the maintenance of normal muscle function.
    e. Vitamin D contributes to the maintenance of normal teeth.
    f. Vitamin D contributes to the normal function of the immune system.

15. **Vitamin E:**
    a. Vitamin E is an antioxidant that helps protect cells in the body.
    b. Antioxidants like Vitamin E help to protect cells from free radicals that may have escaped the natural processes of our body system.

16. **Vitamin K is necessary for normal blood coagulation.**

17. **Biotin:**
    a. Biotin contributes to normal energy-yielding metabolism.
    b. Biotin contributes to normal macronutrient metabolism.
    c. Biotin contributes to the maintenance of normal hair.

18. **Choline**
    a. Choline contributes to normal lipid metabolism.
    b. Choline contributes to the maintenance of normal live function.
    c. Choline helps support overall mental functioning (claim only for food for children up to 6 years of age).

19. **Vitamins K and D work synergistically on bone metabolism to improve bone strength/build strong bones.**

20. **Calcium:**
    a. Calcium helps build/to support development of strong bones and teeth.

b. Calcium contributes to normal energy metabolism.
c. Calcium is necessary for normal nerve and muscle function.
d. Calcium is necessary for normal blood coagulation.

21. Iodine:
a. Iodine is essential for the synthesis of thyroid hormones by the thyroid gland.
b. Iodine is necessary for normal energy metabolism.
c. Iodine contributes to normal cognitive function.
d. Iodine contributes to the maintenance of normal skin.

22. Iron:
a. Iron is an important component of red blood cells which carry oxygen to all parts of the body to help the body's production of energy.
b. Iron is needed to produce haemoglobulin, the protein in red blood cells that carries oxygen to tissues.
c. Iron is needed to produce myoglobulin, the protein that helps supply oxygen to muscle.
d. Iron contributes to normal cognitive function/development.
e. Iron contributes to normal energy production.
f. Iron contributes to the reduction of tiredness and fatigue.
g. Iron is necessary for normal immune system function.
h. Iron is necessary for normal cell division.

23. Iron – claims only for food for children up to 6 years of age:
a. Iron support the child's natural defences.

24. Phosphorus:
a. Phosphorus contributes to bone development.
b. Phosphorus contributes to normal energy metabolism.
c. Phosphorus contributes to the maintenance of normal teeth.

25. Magnesium
a. Magnesium helps in the absorption and retention of calcium.
b. Magnesium contributes to energy metabolism and the maintenance of bone and teeth.
c. Magnesium is necessary for normal nerve and muscle function.
d. Magnesium is necessary for normal electrolyte balance.
e. Magnesium contributes to a reduction of tiredness and fatigue.

26. Zinc:
a. Zinc is essential for growth.
b. Zinc contributes to normal metabolism of fatty acids.
c. Zinc contributes to the maintenance of normal bones.
d. Zinc contributes to the maintenance of normal hair.
e. Zinc contributes to the maintenance of normal nails.
f. Zinc contributes to the maintenance of normal vision.
g. Zinc contributes to normal cognitive function.
h. Zinc contributes to the normal macronutrient metabolism.
i. Zinc contributes to the normal carbohydrate metabolism.
j. Zinc contributes to the normal protein synthesis.
k. Zinc contributes to the normal metabolism of Vitamin A.
l. Zinc is necessary for cell division.
m. Zinc is necessary for normal immune system function.

27. Zinc - claims only for food for children up to 6 years of age:
a. Zinc helps in physical development.
b. Zinc support the child's natural defences.

28. Selenium:
a. Selenium contributes to the maintenance of normal hair.

SINGAPORE

b. Selenium contributes to the maintenance of normal nails.
c. Selenium contributes to the maintenance of the normal function of the immune system.
d. Selenium contributes to the protection of cells from oxidative stress.

29. **Potassium:**
    a. Potassium contributes to normal muscle function.
    b. Potassium contributes to normal functioning of the nervous system.

30. **Copper:**
    a. Copper contributes to normal energy production.
    b. Copper contributes to normal functioning of the nervous system.
    c. Copper contributes to the normal functioning of the immune system.
    d. Copper contributes to the normal hair pigment.
    e. Copper contributes to normal skin pigmentation.

THAILAND

1. **Protein:**
    a. Protein is essential for growth and repair body tissues.
    b. Protein gives essential amino acids for synthesis of varieties of protein in body.

2. **Dietary fiber increases stool bulks in digestive tract to help stimulate bowel movement.**

3. **Vitamin A:**
    a. Vitamin A aids in helping body growth.
    b. Vitamin A helps in visualization.
    c. Vitamin A aids in reinforcing mucosa in body.

4. **Vitamin B1:**
    a. Vitamin B1 helps body gain energy from carbohydrate.
    b. Vitamin B1 aids in nervous system and muscle function.

5. **Vitamin B2 helps body gain energy from carbohydrate, protein and fat.**

6. **Niacin:**
    a. Niacin helps gastrointestinal epithelium and skin stay in normal condition.
    b. Niacin helps body gain energy from carbohydrate, protein and fat.

7. **Vitamin B6:**
    a. Vitamin B6 aids in building red blood cell completely.
    b. Vitamin B6 aids in building essential substances in operation of nervous system.

8. **Folic acid/folate aids in red blood cell formation.**

9. **Biotin:**
    a. Biotin is an essential part in utilization (metabolism) of fat and carbohydrate.
    b. Biotin is an essential part in utilization of fat and carbohydrate.
    c. Biotin is an essential part in fat and carbohydrate metabolism.

10. **Pantothenic acid:**
    a. Pantothenic acid aids in utilization (metabolism) of fat and carbohydrate.
    b. Pantothenic acid aids in utilization of fat and carbohydrate.
    c. Pantothenic acid aids in fat and carbohydrate metabolism.

11. **Vitamin B12:**
    a. Vitamin B12 aids in synthesis of essential substance for red blood cell formation.
    b. Vitamin B12 helps in function of nerve and brain system.

12. **Vitamin C:**
    a. Vitamin C aids in strengthening blood vascular.
    b. Vitamin C aids in helping of anti-free radical process.
    c. Vitamin C aids in helping of collage and ligament of cartilage tissue formation.

13. **Vitamin D aids in calcium and phosphorous absorption.**

14. **Vitamin E aids in helping of anti-free radical process.**

15. **Vitamin K:**
    a. Vitamin K aids in building of substance for blood clotting.
    b. Vitamin K aids in decrease calcium disintegration, make strong bone.

16. **Calcium:**
    a. Calcium is a major component of bone and teeth.
    b. Calcium aids in helping of blood clotting.
    c. Calcium aids in formation of strong bone and teeth.

17. **Phosphorous:**
    a. Phosphorous is a major component of bone and teeth.
    b. Phosphorous aids in formation of strong bone and teeth.

18. **Iron is a major component of Hemoglobin in red blood cell.**

19. **Iodine is a major component of thyroid hormone which responsible for growth and development of body and brain.**

20. **Magnesium:**
    a. Magnesium is a component of bone and teeth.
    b. Magnesium aids in function of nerve and muscle system.

21. **Zinc aids in body growth.**

22. **Copper aids in hemoglobin formation.**

23. **Potassium works together with Sodium to maintain pH balance and body electrolyte.**

24. **Manganese aids in function of many groups of enzymes in body.**

25. **Selenium aids in helping of anti-free radical process.**

26. **Fluoride aids in strengthening strong bone and teeth.**

27. **Molybdenum aids in function of some enzymes in body.**

28. **Chromium works together with other substance to maintain pH balance in body.**

Appendix 5: Positive List of Other Function Claims in Southeast Asia

INDONESIA

1. Dietary Fiber
   a. Soluble dietary fiber (psyllium, beta glucan from oats, inulin from chicory, and pectin from fruit) can help lower blood cholesterol levels if accompanied by a diet of low saturated fat and low cholesterol.
   b. Insoluble food fiber can help facilitate bowel movements (laxative), if accompanied by drinking enough water.

MALAYSIA

1. **Sialic acid is an important component of brain tissues.**

2. **Inulin and oligofructose (fructo-oligosaccharide):**
   a. Inulin helps increase intestinal bifidobacteria and helps maintain a good intestinal environment.
   b. Oligofructose (fructo-oligosaccharide) helps increase intestinal bifidobacteria and helps maintain a good intestinal environment.
   c. Inulin is bifidogenic.
   d. Oligofructose (fructo-oligosaccharide) is bifidogenic.

3. **Oat soluble fibre (b-glucan) helps lower or reduce cholesterol.**

4. **Plant sterol or plant stanol helps lower or reduce cholesterol.**

5. **As a predominant macular pigment in the retina, lutein is able to filter blue light and may protect the eye**

6. **Beta glucan from (state the source) helps lower or reduce cholesterol**

7. **Bifidobacterium lactis:**
   a. Bifidobacterium lactis helps improve a beneficial intestinal microflora
   b. Bifidobacterium lactis may help to reduce the incidence of diarrhea

8. **DHA and ARA may contribute to the visual development of infant**

9. **High Amylose Maize Resistant Starch (HAMRS) helps improve/ promote colonic/ bowel/ intestinal function/ environment**

10. **Inulin and oligofructose (fructo-oligosaccharide):**
    a. Inulin is prebiotic
    b. Oligofructose (fructo-oligosaccharide) is prebiotic

11. **Isomaltulose:**
    a. Isomaltulose is slowly hydrolysed to glucose and fructose and therefore it provides longer lasting energy compared to sucrose
    b. Isomaltulose is a slowly release source of energy compared to sucrose
    c. Isomaltulose provides longer lasting energy compared to sucrose
    d. Isomaltulose is a slowly hydrolysed to glucose and fructose compared with sucrose

12. **Oligosaccharide mixture containing 90% (wt/wt) GOS and 10% (wt/wt) lcFOS:**
    a. Oligosaccharide mixture containing 90% (wt/wt) GOS and 10% (wt/wt) lcFOS is prebiotic
    b. Oligosaccharide mixture containing 90% (wt/wt) GOS and 10% (wt/wt) lcFOS is bifidogenic

MALAYSIA

c. Oligosaccharide mixture containing 90% (wt/wt) GOS and 10% (wt/wt) lcFOS helps increase intestinal bifidobacteria and helps maintain a good intestinal environment
d. Oligosaccharide mixture containing 90% (wt/wt) GOS and 10% (wt/wt) lcFOS helps to improve the gut/intestinal immune system of babies/ infant

13. **Oligofructose-inulin mixture containing 36-42% oligofructose (DP 2-10) and 50-56 % inulin (DP >10) helps to increase calcium absorption and increase bone mineral density when taken with calcium rich food**

14. **Patented Cooking Oil Blend helps to increase HDL Cholesterol and improve HDL/ LDL Cholesterol Ratio**

15. **Polydextrose:**
    a. Polydextrose is bifidogenic
    b. Polydextrose helps increase intestinal bifidobacteria and helps maintain a good intestinal microflora

16. **Resistant dextrin/ Resistant maltodextrin is a soluble dietary fibre that helps to regulate/ promote regular bowel movement especially of people with a tendency to constipation**

17. **Soy protein helps to reduce cholesterol**

SINGAPORE

1. **Chromium contributes to normal macronutrient metabolism.**

2. **Collagen is a protein in connective tissues found in skin, bones and muscles.**

3. **DHA and ARA are important building blocks for development of the brain and eyes in infant. (claim only for food for children up to 3 years of age).**

4. **Nucleotides:**
    a. Nucleotides support body's natural defences (claim only for infant formula less than 1 year of age).
    b. Nucleotides are essential to normal cell function and replication, which are important for the overall growth and development of infant (claim only for food for children up to 6 years of age).

5. **Taurine helps to support overall mental and physical development (claim only for food for children up to 6 years of age).**

6. **Inulin:**
    a. Inulin helps in calcium absorption.
    b. Inulin helps support growth or benefical bacteria/ good intestinal flora in gut.
    c. Inulin helps increase intestinal bifidobacteria and helps maintain a good intestinal environment.

7. **Oligofructose stimulates the bifidobacteria, resulting in a significant increase of the beneficial bifidobacteria in the intestinal tract. At the same time, the presence of less desirable bacteria is significantly reduced.**

8. **Prebiotic promotes the growth of good Bifidus bacteria to help maintain a healthy digestive system.**

9. **Prebiotic blend (galacto-oligosaccharides and long chain fructo-oligosaccharides) support the child's natural defences (claim only for food for children up to 6 years of age).**

SINGAPORE

10. **Probiotics:**
    a. Probiotics to help maintain a healthy digestive system.
    b. Probiotics helps in digestion.
    c. Probiotics helps to maintain a desirable balance of beneficial bacterial in the digestive system.
    d. Probiotics helps to suppress/ fight against harmful bacteria in the digestive system, thereby helping to maintain a healthy digestive system.

11. **Plant sterols/ stanols have been shown to lower/ reduce blood cholesterol. High blood cholesterol is a risk factor in the development of coronary heart disease.**

Appendix 6: Positive List of Reduction of Disease Risk Claims in Singapore

SINGAPORE
1. A healthy diet with adequate calcium and vitamin D, with regular exercise, helps to achieve strong bones and may reduce the risk of osteoporosis. (Name of food) is a good source of/high in/enriched in/fortified with calcium.
2. A healthy diet low in sodium may reduce the risk of high blood pressure, a risk factor for stroke and heart disease. (Name of food) is sodium free/low in/very low in/ reduced in sodium.
3. A healthy diet low in saturated fat and trans fat, may reduce the risk of heart disease. (Name of food) is free of/ low in saturated fats, trans fats.
4. A healthy diet rich in whole grains 5, fruits and vegetables that contain dietary fibre, may reduce the risk of heart disease. (Name of food) is low/free of fat and high in dietary fibre.
5. A healthy diet rich in fibre containing foods such as whole grains, fruits and vegetables may reduce the risk

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