APPENDIX 7B

GUIDELINE ON NATURAL PRODUCTS WITH MODERN CLAIM

PREAMBLE

This document serves as a guide on the requirements for the registration of natural products with modern claims. This document shall be read in conjunction with the relevant sections of the latest edition of the main guidance document i.e. **Drug Registration Guidance Document (DRGD)**.

This guideline shall also be read in conjunction with the current laws and regulations together with other relevant legislations, where applicable, governing pharmaceutical and natural products for human use in Malaysia, which include but are not limited to the following:

a) Sale of Drugs Act 1952;
b) Control of Drugs and Cosmetics Regulations 1984;
c) Dangerous Drugs Act 1952;
d) Poisons Act 1952;
e) Medicines (Advertisement & Sale) Act 1956;
f) Wildlife Conservation Act 2010 (Laws of Malaysia Act 716); and
g) International Trade in Endangered Species Act 2008 (Act 686)

The written laws shall take precedence over this guidance document in any event of discrepancy.

Applicants for product registration are also requested to refer to the latest edition of the Guidelines on Good Manufacturing Practice for Traditional Medicines and Health Supplements, Malaysian Guideline for Good Clinical Practice (GCP), as well as relevant sections of any other applicable guidance documents.

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GLOSSARY

Active ingredient - The therapeutically active component in a medicine's final formulation that is responsible for its physiological action.

Active markers - Constituents or groups of constituents which are generally accepted to contribute to the therapeutic activity.

Adverse event - Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Finished product - A product that has undergone all stages of production and quality control, including packaging in its final container and labelling.

Genuine herbal preparation - Refers to the preparation without excipients, even if for technological reasons the genuine herbal preparation is not available. However, for soft and liquid herbal preparations the genuine herbal preparation may contain variable amounts of (extraction) solvent.

Health effect - Changes in health resulting from exposure to a source.

Herbal substances - All mainly whole, fragmented or cut plants, plant parts, algae, fungi, lichen in an unprocessed, usually dried form but sometimes fresh. Certain exudates that have not been subjected to a specific treatment are also considered to be herbal substances. Herbal substances

are precisely defined by the plant part used and the botanical name according to the binomial system (genus, species, variety and author).

Herbal preparations - Are obtained by subjecting herbal substances to treatments such as extraction, distillation, expression, fractionation, purification, concentration or fermentation. These include comminuted or powdered herbal substances, tinctures, extracts, essential oils, expressed juices and processed exudates.

Natural product - Product in which the drug consists solely of one or more naturally occurring substances of a plant, animal or mineral, of parts thereof. Natural product may contain excipients in addition to active ingredients. However, it shall not include any sterile preparation, vaccine, any substance derived from human parts, any chemically defined active substance, including synthetic compounds and/ isolated constituents from herbal materials or any ingredients listed under the Poisons Act 1952.

Product - A drug in a dosage unit or otherwise, for use wholly or mainly by being administered to one or more human beings or animals for a medicinal purpose; or a drug to be used as an ingredient of a preparation for a medicinal purpose.

Quantified extracts - Herbal substances/herbal preparations adjusted to one or more active markers, the content of which is controlled within a limited, specified range. Adjustments are made by blending batches of the herbal substance/herbal preparation.

Therapeutic activity - Refers to the successful prevention, diagnosis and treatment of physical and mental illnesses; improvement of symptoms of illnesses; as well as beneficial alteration or regulation of the physical and mental status of the body.

Therapeutic claim - A claim that must be substantiated with clinical evidence and require medical intervention for diagnosis and therapy whereby the disease is not self-limiting. The claim is not documented in established pharmacopoeia or monographs, and not the traditional use of the ingredient. It may include corroboration and verification of traditional use to relieve a symptom or help to treat a disease, disorder or medical condition.

Traditional health claim (traditional claim) - The sum total of knowledge, skills, and practices based on theories, beliefs, and experiences indigenous to a specific culture, used in the

maintenance of health and prevention, diagnosis, improvement, or treatment of physical and mental illness.

Traditional medicine - Any product used in the practice of indigenous medicine in which the drug consists solely of one or more naturally occurring substances of a plant, animal or mineral, of parts thereof, in the unextracted or crude extract form, and homoeopathic medicine. It shall not include any sterile preparation, vaccine, any substance derived from human parts, any isolated and characterized chemical substances.

1.0 INTRODUCTION

Traditional medicines such as traditional Chinese medicine (TCM), Ayurveda, Kampo, traditional Korean medicine (TKM), and Unani employ natural ingredients and have been practised all over the world for hundreds or even thousands of years. These traditional medicines come in various preparations such as comminuted or powdered herbs, teas (infusions), decoctions, or for addition to salves and ointments (often referred to as semi-solid preparations). Over the years, modern technology has shifted the form of traditional medicines to alcoholic or water extract, tinctures, essential oils for inhalation and freeze- or spray-dried powders and has developed into orderly regulated systems of medicine.

The evolvement of traditional medicines, especially in the development of herbal ingredients using modern technology, has enabled the discovery of medicinal properties and new uses beyond the traditional applications of various herbs. As a result, many new or modern claims have emerged for these natural/herbal ingredients, leading to a need to expand and define the different type of claims for the natural/herbal products. In European countries there are three main regulatory pathways to market herbal medicinal products namely the 'traditional use registration', 'well-established use marketing authorisation' and 'stand alone or mixed application'. The ASEAN Guidelines on Claims and Claims Substantiation for Traditional Medicine states three types of claims which are 'Traditional Health Use Claims', 'Traditional Treatment Claims' and 'Scientifically Established Treatment Claims'. Our neighbouring country, Indonesia has classified traditional or herbal products into three categories, based on formulations and level of claims; *jamu, obat herbal terstandar* and *fitofarmaka.*

In Malaysia, permissible claims for natural products are traditional and therapeutic claims. A traditional claim is based on theories, beliefs and experiences indigenous to a specific culture. It includes general health maintenance and/or relieving/alleviating mild symptoms. Traditional claim must use the words 'traditionally used'. A therapeutic claim is a claim that requires medical intervention for diagnosis and therapy whereby the disease is not self-limiting. It must be substantiated with clinical evidence and may include relieving a symptom or helping to treat a disease, disorder or medical condition. However, there remains a gap for natural products that fall under neither traditional nor therapeutic claims.

These are the products with new/modern claims based on scientific evidence available from various sources and have undergone modern processing methods. These new scientific findings would have shown the product to be beneficial towards supporting and enhancing health, reducing the risk of disease/condition as well as aiding/assisting in the management of a disease/condition or symptoms. In contrast to therapeutic claims, these are non-serious medical conditions that are expected to naturally resolve within a timely manner (i.e. self-limiting).

Hence, this guideline outlines the addition of a new category for natural products i.e. natural products with modern claim. With this addition, there will be three natural product categories according to claim which are natural products with traditional claims (traditional medicine), natural products with modern claims and natural products with therapeutic claims (**Figure 1**). The claim example between these categories are shown using active ingredient *Ginkgo biloba* L., folium as below.

Table 1: Examples of claims for each natural product category

Traditional Claim	Modern Claim	Therapeutic Claim
Herbal preparation Folium *Ginkgo biloba* powder or Folium *Ginkgo biloba* extract powder Claim : *Traditionally used to improve blood circulation*	Herbal preparation Folium *Ginkgo biloba* extract powder (24% flavanoids / 6 % terpenoid) Claim : *Herbal product used to enhance cognition*	Herbal preparation Folium *Ginkgo biloba* standardized to 24% flavonoid glycosides and 6% terpene lactones Claim : *Improve cognition for patients with Alzheimer's Disease*

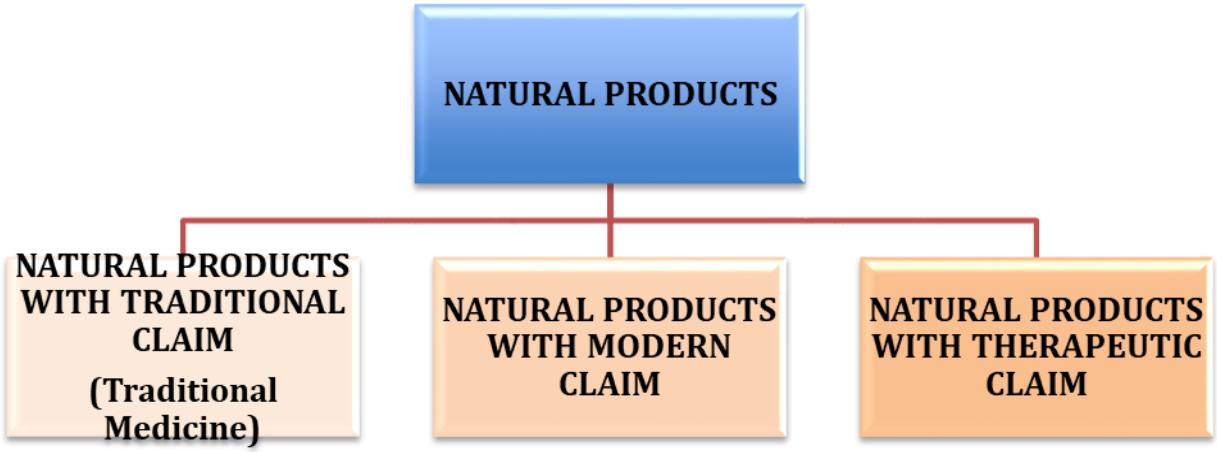

Figure 1: Category of natural products claims

This guideline aims:

i. to ensure that natural products with modern claims are supported by adequate scientific evidence to protect consumers from misleading claims.

ii. to provide a clearly defined pathway for the industry to bring new natural products into the market.

iii. to provide quality and safety data submission requirements for natural products with modern claims.

2.0 SCOPE OF THIS GUIDELINE

This guideline describes the type of evidence to support a modern claim for a natural product intended for human use. It also outlines the required quality and safety data and is applicable to products containing **herbal substances/preparations in the form of quantified extract.**

3.0 DEFINITION OF MODERN CLAIM

A modern claim is a claim based on scientific evidence, which is limited to supporting and enhancing health, risk reduction, or aiding/assisting in the management of a disease/condition or symptoms that are expected to naturally resolve within a timely manner (self-limiting)

The scientific studies considered relevant for the substantiation of the modern claim must address the relationship between the product formulation and the health effect. It is essential to ensure that the level of claims permitted for modern claims does not surpass the allowable level of claims for therapeutic claims.

4.0 REGULATORY REQUIREMENTS FOR REGISTRATION OF NATURAL PRODUCTS WITH MODERN CLAIMS

The requirements for registration shall be in accordance with the general regulatory requirement described in the Drug Registration Guidance Document (DRGD), including **Appendix 7: Guideline on Registration of Natural Products**. However, the Authority may request further information or specific conditions not described in this document that are deemed necessary to ensure the quality, safety and efficacy (claim) of the product.

Regulatory requirements that apply to natural products with modern claims are as follows:

4.1 QUALITY DOCUMENTS

In addition to the quality requirements stated in **Appendix 7: Guideline on Registration of Natural Products**, DRGD (Section 2.7 Quality Control and 2.8 Stability Data), the following are specific requirements that apply to natural products with modern claim.

4.1.1 Formulation

The product formulation must consist of herbal preparations in the form of quantified extracts. The lists of prohibited/banned ingredients in **Appendix 7: Guideline on Registration of Natural Products**, DRGD are not allowed in the formulation of natural products registered by the Authority. Below are the requirements for the formulation.

i. State the botanical source, part of plant used and type of preparation (e.g.: dry or liquid extract). The ratio of herbal substance to genuine herbal preparation must be stated.

ii. Information on the quantified extracts used in products shall be provided which include (but is not limited to);

a. active markers of the quantified extracts

b. information on the solvent system used to obtain the quantified extracts

c. method of identification of active markers in the quantified extracts

iii. Quantification of extracts

Example of calculation:

Where a herbal medicinal product contains:

Root *Eurycoma longifolia* (Tongkat Ali) freeze-dried water extract

Extraction ratio 25:1

Quantification: 0.8 – 1.5 % of eurycomanone

Other excipients: 0 %.

Quantity of the genuine herbal preparation in the herbal medicinal product:

200 mg/capsule.

The declaration in Batch Manufacturing Formula of the herbal medicinal product is:

One capsule contains 200 mg of Root *Eurycoma longifolia* (Tongkat Ali) extract, corresponding to 1.6 mg to 3 mg of total eurycomanone.

4.1.2 Control of Active Ingredients

At least one (1) batch of Certificate of Analysis (COA) of active ingredient (herbal substance/preparation/quantified extract) which consists of the following tests (as in **Table 2** and **table 3**) shall be submitted for all active ingredients in the formulation.

Table 2: List of testing requirements for active ingredients (herbal substances)

Tests	Specifications	Results
Appearance/Organoleptic characteristics		
Identification: (should be specific for the herbal substance and are usually a combination of three or more of the following): Macroscopy/Microscopy/ Chromatographic procedures/ Chemical tests		
Quantitative assay		
Purity Tests: ● Foreign Matter ● Total Ash Content ● Ash insoluble in hydrochloric acid* ● Water content		
Extractive Values* ● Water Soluble extracts ● Ethanol Soluble extracts ● Extractable matter		
Microbial Contamination Tests: ● Total Aerobic Microbial Count (TAMC)		

Tests	Specifications	Results
● Total Yeast and Mould Count (TYMC) ● Bile tolerant gram-negative bacteria ● *Salmonella* ● *Escherichia coli* ● *Staphylococcus aureus* ● *Pseudomonas aeruginosa*		
Heavy metal limit: ● Arsenic ● Mercury ● Lead ● Cadmium		
Other Tests*: ● Residual solvents ● Mycotoxins (Aflatoxin, Ochratoxin A) ● Pesticides ● Particle size		

* These tests might not apply to all herbal substances and must be justified by the applicant.

Table 3: List of testing requirements for active ingredients (herbal preparations/ quantified extracts)

Tests	Specifications	Results
Appearance/Organoleptic characteristics		
Identification: Chromatographic procedure (Identification tests should be specific for the herbal preparation, and optimally should be discriminatory with regard to substitutes/adulterants that are likely to occur. Identification solely by chromatographic retention time, for example, is not regarded as being		

Tests	Specifications	Results
specific; however, a combination of chromatographic tests (e.g. HPLC and TLC-densitometry) or a combination of tests into a single procedure, such as HPLC/UV-diode array, HPLC/MS, or GC/MS may be acceptable.)		
Quantitative assay		
Purity Tests: ● Water content		
Microbial Contamination Tests: ● Total Aerobic Microbial Count (TAMC) ● Total Yeast and Mould Count (TYMC) ● Bile tolerant gram-negative bacteria ● *Salmonella* ● *Escherichia coli* ● *Staphylococcus aureus* ● *Pseudomonas aeruginosa*		
Heavy metal limit: ● Arsenic ● Mercury ● Lead ● Cadmium		
Other Tests*: ● Residual solvents ● Mycotoxins (Aflatoxin, Ochratoxin A) ● Pesticides		

* These tests might not apply to all herbal preparations and must be justified by the applicant.

4.1.3 Control of Finished Product Formulation

Documents required for finished product quality control include:

a. In-Process Quality Control (IPQC)

b. Finished Product Quality Control (FPQC)

c. Protocol of Analysis

d. At least 2 batches of COA finished product (COA FP) (Refer **Table 4**)

e. At least 2 batches of complete real-time stability data. (Refer to **Appendix 7: Guideline on Registration of Natural Products** for stability data requirements).

Table 4: List of required tests for finished product formulation

Tests	Specifications	Results
Appearance/Organoleptic characteristics		
Identification: Macroscopic and microscopic (if product contains herbal substances)/ Chemical fingerprint/ Chemical test (Identification tests should establish the specific identity of the herbal substance(s) and/or herbal preparation(s), in the herbal medicinal product and optimally should be discriminatory with regard to substitutes/adulterants that are likely to occur. Identification solely by chromatographic retention time, for example, is not regarded as being specific; however, a combination of chromatographic tests (e.g. HPLC and TLC-densitometry) or a combination of tests into a single procedure, such as HPLC/UV-diode array, HPLC/MS, or GC/MS		

Tests	Specifications	Results
may be acceptable.)		
Quantitative assay		
Microbial Contamination Test (Refer Tests for Microbial Contamination, **Appendix 7: Guideline on Registration of Natural Products**, DRGD)		
Heavy metal limit: ● Arsenic ● Mercury ● Lead ● Cadmium (Refer limit test for heavy metals, **Appendix 7: Guideline on Registration of Natural Products**, DRGD)		
Uniformity of weight (for tablets & capsules) (Refer test for uniformity of weight, **Appendix 7: Guideline on Registration of Natural Products**, DRGD)		
Disintegration (for pills, tablets & capsules) (Refer disintegration test, **Appendix 7: Guideline on Registration of Natural Products**, DRGD)		
Impurities:* ● Related / degraded substance ● Pesticide residues ● Solvent residues		
Other Tests (Any required testing)		

***** These tests might not apply to all herbal finished products and must be justified by the applicant.

4.1.4 Labelling

The applicant shall ensure that the product label complies with the labelling requirements defined in Labelling Requirements of **Appendix 7: Guideline on Registration of Natural Products**.

The following statement shall be stated on the product label:
"This is a herbal medicine/ preparation/
Ini adalah produk/persediaan herba".

4.2 SAFETY EVIDENCE

Guideline on Safety Data Requirements for Complementary Medicine Products, **Appendix 33** in DRGD may be referred to for additional information.
All products should be safe under their recommended conditions of use. Documents of safety evidence for the modern claim shall include:

4.2.1 Documented history of use for the ingredient(s).

Example: classical traditional medicine texts, pharmacopoeia, monograph, literature review, assessment of mostly bibliographic safety data.
If safety evidence is to be based on documented history or traditional use, it must be clearly shown that the ingredient under review is equivalent to that used traditionally. Knowledge of the chemical components of an ingredient will aid in safety evaluation by identifying potentially toxic constituents or constituents known to mimic or modulate endogenous reactive intermediates. Conventional extraction methods used, may in some instances produce a substance that is compositionally different from those produced using traditional methodology.
The data of any abnormalities and/or untoward adverse reaction that might occur or derive should be captured from animal and/ or human studies. Adverse events observed in clinical trials or clinical studies will be useful for safety evaluation.

Information on the extent of use in other countries may provide insight into the safety profile. The maximum amount of the ingredient that is recommended or suggested for use may be provided as proof of safe use. However, the amount in the product should not exceed the recommended level. Evidence of the product's regulatory status in other countries may also be provided as supportive evidence to justify the safe use of the product.

4.2.2 Toxicity data

If the long-term history of traditional use cannot be documented or if there are safety doubts on the use of the active ingredient(s), toxicity data shall be submitted. Toxicity data could be derived by undertaking an extensive search of the literature and evaluating performance in preclinical toxicological tests. The ingredient(s) used in the quoted literature must be the same with the intended product in terms of the species, part, form, preparation method, extraction solvent, extraction parameters, concentration method, etc. Toxicity data on each ingredient of the product shall be provided as supportive references.

Toxicity studies should be conducted in accordance with generally accepted principles, such as those described in **WHO's Research guidelines for evaluating the safety and efficacy of herbal medicines** and **ICH Guideline M3 (R2) on non-clinical safety studies for the conduct of human clinical trials and marketing authorisation for pharmaceuticals.**

The **Organisation for Economic Co-operation and Development (OECD)** Test Guideline for chemicals (OECD) shall be used as a guide to conduct toxicity studies on animals. However, it is not mandatory for non-clinical safety studies for natural products with modern claim to be conducted in a facility, which complies with OECD Good Laboratory Practice (GLP).

4.3 CLAIMS

4.3.1 Conditions

All claims made for natural products with modern claims shall:

i. be consistent with the definition of natural product with modern claim;
ii. not include 20 diseases as stipulated in Section 3 in the Medicines (Advertisement and Sale) Act 1956 (Revised 1983)**;**
iii. not be misleading or false;
iv. support the safe, beneficial, and appropriate use of the products;
v. be substantiated by good quality /reliable scientific evidence that is relevant to the claims;
vi. adhere the dosing recommendations stated in the scientific evidence or references for the claimed intended effects, unless otherwise justified,
vii. enable consumers to make an informed choice regarding products.

4.3.2 Evidence to Support Claims

The claims shall be based on evidence from a range of sources, including but not limited to clinical studies, peer-reviewed published articles, monographs, pharmacopoeias, textbooks, regulatory authority reports, animal *(in vivo)* and *in vitro* studies.

Claims must be adequately substantiated through finished product-based evidence or formulation-based evidence with a similar dosage regimen, dosage form, route of administration and target population. The study must show a consistent association between the finished product/formulation and intended claims with little or no evidence to the contrary. Where there are differences between the ingredient(s) and reported claims, a justification will be required to address the discrepancy. For products with multiple ingredients, each ingredient's intended use/function must support a logical use of the combination in question. Evidence must be provided on the product/formulation with information on individual ingredients as supportive references.

Examples of acceptable evidence to support modern claims are as below:

i. Evidence obtained from well-designed controlled clinical trials with or without randomization.
ii. Evidence obtained from at least one properly designed randomized controlled clinical (preferably multi-centre) double blind trial. It is preferable to have data from at least two trials independent of each other, but in some cases, one large well conducted trial may suffice
iii. Systematic reviews of the clinical research relating to particular subject areas. These must be published in peer-reviewed journals
iv. Peer-reviewed scientific data or meta-analysis - these must be published in peer-reviewed journals

The acceptable principles for human studies can be referenced from accepted guidelines such as **Malaysian Guideline for Good Clinical Practice** and **International Conference on Harmonization - Good Clinical Practice Guideline (ICH-GCP).**

Animal and *in vitro* studies alone cannot be the sole source of evidence for efficacy/claim. While these data can provide plausible explanations of how an active ingredient will work, it is not considered as sufficient evidence on their own to support the claimed benefit in humans. **Evidence from human use must be provided.** Animal or *in vitro* experimental evidence may be considered as additional, supporting information but may not be used as the only basis for product registration.

4.3.3 Claims Substantiation

Evidence of use available for the indication/claim (including relevant scientific evidence), **shall** be summarized as part of the substantiation document for the claim. **Table 5** outlines the format (with example) for the summary of evidence used to substantiate the claim.

Table 5: Substantiation summary of the claim

(Disclaimer: Examples provided are solely for the purpose of guiding applicants on how to fill in the table)

No.	Indication/ claim	Product/ Formulation studied	Dosage and administration route	Duration of treatment	Type of evidence	Study design*	Study population	Summary of findings	Limitations of the study	Source of evidence i) Author ii) Title iii) Publication details iv) Year v) Type (text,…)
EXAMPLE 1.	Reduce stress	Lippia citriodora (Lemon Verbena) leaf extract standardized to xxxx % verbascoside	xxxx mg, oral (capsule form)	x weeks	Clinical study	Double-blind, Placebo-controlled, randomized clinical study	Xx Healthy adults with moderate levels of stress and quality of sleep	Reduced levels of stress as assessed by … cortisol levels in plasma	Low number of participants	i. John xxx et al. ii. Study on improved … stress level upon taking lemon verbena iii. XXXX Journal iv 20xx v. Clinical study
EXAMPLE 2.	Relief of mild symptoms of stress.	Lippia citriodora folium	5 g of the comminuted herbal substance in 100 ml of boiling water as a decoction, 3 times daily.	-	Monograph	-	-	-	-	i. European Medicine Agency ii. European Union herbal monograph on Aloysia citrodora Paláu (syn. Aloysia triphylla (L'Hér.) Kuntze; Verbena triphylla L'Hér.; Lippia citriodora Kunth), folium (13th January 2021) iii. Committee on Herbal Medicinal Products (HMPC) iv. 2020 v. Monograph

***** Study should include primary endpoints/outcomes with statistical and clinical significance
Note: *Evidence not summarised and presented in the above format will not be further evaluated*

4.3.4 Examples of Indications /Claims

General note: *The indications listed below will serve as a guide for the applicant. Other indications with the same level of claim may be considered if supported with scientific evidence.*

Claims may start with "Herbal Product used…./Natural product used…. "

a) Supporting and enhancing health

i. to maintain/support liver health
ii. to maintain/ support reproductive health
iii. to maintain/support prostate health
iv. to maintain/support urinary tract health
v. to maintain/support healthy digestive system
vi. to maintain/support eye health
vii. to enhance physical endurance/ capacity/ stamina
viii. to enhance/improve cognition
ix. to maintain/support immune system

b) Support reduction of the risk of a disease/disorder

i. to help in the maintenance of a healthy body weight
ii. to help maintain/support healthy blood sugar/glucose level
iii. to help maintain/support healthy cholesterol level
iv. to help maintain healthy blood pressure levels
v. to help improve/promote intestinal transit time

c) Aid/assist in the management of a named symptom/disease/disorder

i. to relieve symptoms of premenstrual tension such as irritability, mood changes and breast tenderness.
ii. to relieve symptoms of stress such as fatigue and sensation of weakness.
iii. for improving bowel movement
iv. to relieve eye strain
v. to help relieve symptoms of menopause such as hot flushes, irritability and mood swings
vi. to support wound healing such as cuts, scratches and abrasions
vii. to improve sleep quality
viii. to help reduce occurrence of symptoms of mild allergies

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