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# Effects of *Eurycoma longifolia Jack* standardised water extract (Physta) on well-being of perimenopausal and postmenopausal women: protocol for a randomised, double-blinded, placebo-controlled, parallel group study

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## ABSTRACT

**Introduction** *Eurycoma longifolia Jack* (EL), profoundly recognised as 'Tongkat Ali', is a medicinal herb originating from Southeast Asia. It is commonly used in traditional 'antiageing' treatments to address decreased energy, mood, libido and hormonal imbalances. While the benefits of EL have been extensively studied among the male population, less attention has been given to its effects on women. Menopause can impact the overall well-being of middle-aged women and incorporation of herbal supplements can aid them in managing the menopausal symptoms.

**Methods and analysis** This 12-week randomised double-blind, placebo-controlled, parallel-group study aims to evaluate the efficacy of the standardised water extract of EL known as Physta in increasing the quality of life of perimenopausal and postmenopausal women. The study involves 150 women aged 40–55 years who score more than 61 on the Menopause-Specific Quality of Life (MENQOL) assessment. These participants will be randomised into three groups, receiving Physta at either 50 mg or 100 mg or a placebo. The outcomes measures include mood state, quality of life, fatigue, sleep quality, sexual function and pain score assessed using Profile of Mood State, MENQOL, Chalder Fatigue Scale, Pittsburgh Sleep Quality Index, Female Sexual Function Index and the Brief Pain Inventory questionnaires, respectively. The secondary outcome of the study includes full blood analysis, urine analysis, female reproductive hormone profiling, inflammatory and oxidative stress biomarkers analysis.

**Ethics and dissemination** The research protocol of the study was reviewed and approved by the Research Ethics Committee of Universiti Kebangsaan Malaysia (UKM/PPI/111/8/JEP-2021-898). The findings will be disseminated to participants, healthcare professionals and researchers via conference presentations and peer-reviewed publications.

**Trial registration number** ACTRN12622001341718.

## STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This is a purposive sampling, randomised, double-blinded, placebo-controlled, parallel group study.
⇒ The two different dosages of Physta used in the study (50 mg and 100 mg) helps to understand and evaluate the dose-dependent relationship between the dosage of the study product and its efficacy.
⇒ The limitation of this 12 weeks study is lost to follow-up and missing data points that would challenge the validity of reported results during data analysis.
⇒ The study acknowledges the lack of nutritional intake information, which can be a limitation for a comprehensive analysis of the potential influence of dietary factors on the observed outcomes.

## INTRODUCTION

### Background and rationale

Despite the significant advances in contemporary medicine, traditional herbal medicine continues to play a vital role in healthcare industry over the past decades. According to the WHO, herbal medicines comprise plants or other plant-based materials or combinations as active ingredients in the preparation of herbs, herbal material and herbal composition related products.[1] Over 35 000 plant species have been recorded to be used for therapeutic reasons in various human cultures all over the world due to their natural origin and nutraceutical prospective.[1 2] Based on its positive past results, affordability, reliability and effectiveness, the demand for traditional medicines has escalated in today's world.[3 4] Even so, to further validate their quality, safety and efficacy, more intensive human and animal trials have been

performed globally equipped with current advancements in biological and analytical sciences.[5]

*Eurycoma longifolia Jack* (EL) is a folk medicinal herbal plant of South-East Asian origin that belongs to the Simaroubaceae family. Physiologically, it is a tall, slender, flowering shrub which grows up to 10 m in sandy soil.[6 7] This herb is known for its antipyretic, antimalarial, antibacterial, antidiabetic properties since ancient times due to the presence of numerous bioactive compounds such as alkaloids, quassinoids, peptides, eurycolactone and eurycomalactone in the plant's roots.[8] Furthermore, regular intake of EL as dietary supplement has proven to alleviate stress, eases tension, enhances physical performances, restores energy and stamina which directly improve the overall quality of life.[9] Locally recognised as 'Tongkat Ali' in Malaysia, its roots are boiled traditionally to prepare energy decoctions which predominantly used to treat impotency and decreased virility among men.[10] Nonetheless, its consumed as a power tonic to curb postpartum depression and fatigue among women after childbirth as EL possesses great antioxidative properties due to presence of high concentrations of superoxide dismutase.[3 11] Due to its various health benefits and energy enhancing capacity, there are over 200 Tongkat Ali preparations on the market in Malaysia.[12 13]

Towards the goal of building a healthy ageing community, the quality of life of middle-aged women is indeed a huge concern lately. Middle-aged women generally are exposed to a wide range of non-communicable symptoms and psychological challenges due to menopause. Menopause typically takes place around 45–55 years old in women's life where their ability to reproduce ceases permanently.[14] Several years prior to this vital milestone, 85% of women notably encounter at least one of the common menopausal symptoms which includes hot flushes, night sweats, sleep deprivation, memory impairments, feeling of worn out, depression, osteoporosis, bone and joint related pains.[15–17] The previous studies have found that the quality of life of menopausal women is influenced by levels of depression, self-reported health conditions, incidence of menopausal symptoms, level of education and marital status.[18]

In the efforts of managing menopausal symptoms, obstetricians and gynaecologists have agreed in recent times to recommend safe non-drug treatment options apart hormone replacement therapy (HRT). Although HRT is being the most promising treatment option in treating menopausal symptoms, suitability of it for long-term use among women above 60 has raised a concern.[19] Women's Health Initiative has reported in 2002 that long-term HRT is associated with serious adverse effects caused such as breast cancer, enhanced dementia, coronary diseases and stroke.[19] Besides, the re-emergence of menopausal symptoms on discontinuation of HRT has also triggered the alternative search for safe and efficient herbal dietary supplements in managing the complications naturally. Herbal supplements of black cohosh, evening primrose oil, maca, pollen extracts, curcumin, bitter orange, phytoestrogen rich soy and red clovers are the common herbal dietary supplements used in treating menopausal symptoms among women globally.[20] Particularly in Malaysia, local herbs such as Pucuk sendap (*Arcypteris irregularis*), Tongkat Ali (EL), Bunga pakma (*Rafflesia hasseltii*) and Kacip Fatimah (*Labisia pumila*) are generally used in rural areas to alleviate menopausal symptoms.[21]

EL has shown a great potential to be explored for menopausal symptom management as it is one of the most versatile and safe to be consumed.[3] Besides the available scientific data available, more evidence-based studies need to be conducted to establish proper clinical guidelines for safer utilisation of EL. As its exclusive benefits on enhancing sexuality and fertility mainly among male population,[10 22 23] the research studies involving women and EL to date are limited. In a randomised clinical trial (RCT) study carried out on 119 healthy women in Canada aged 41–55 years old with perimenopausal and postmenopausal symptoms, supplementation of herbal formulation consists both *Labisia pumila* and EL, has reported to be well tolerated for consumption and has potential in supporting reduction of hot flushes, improves their hormone and lipid profile.[15] Nevertheless, past studies testing intake of EL on healthy males and females with moderate stress have reported that their stress hormone profile and certain mood state parameters were improved.[24 25] Moreover, the alkaloids and triterpenes found in this root has proven to act as effective antioxidants that reduces bone loss and maintain the rate of bone formation in men.[2] A recent animal study done on ovariectomised rats has shown that intake of EL has improved hormonal levels caused by ovariectomy, an animal model resembling menopause.[26] These attributes align with our study aim of investigating the effects of Physta on menopausal symptoms in perimenopausal and postmenopausal women.

## Objectives

The primary objective of this RCT intervention study is to investigate the efficacy of Physta with placebo on quality of life, mood state, sleep quality, energy, sexual function and pain score of perimenopausal and postmenopausal women with reported menopausal symptoms. The female reproductive hormones profiles, oxidative biomarkers and inflammatory biomarkers will be assessed as the secondary objectives.

## Hypothesis

We hypothesised that the efficacy of Physta potentially benefits the overall health, quality of life and well-being of perimenopausal and postmenopausal women.

## Study design

This is a randomised, double-blind (study participant and the investigator), placebo-controlled, 12 weeks parallel group study. The overall study flow is presented in figure 1. We used the The Standard Protocol Items:

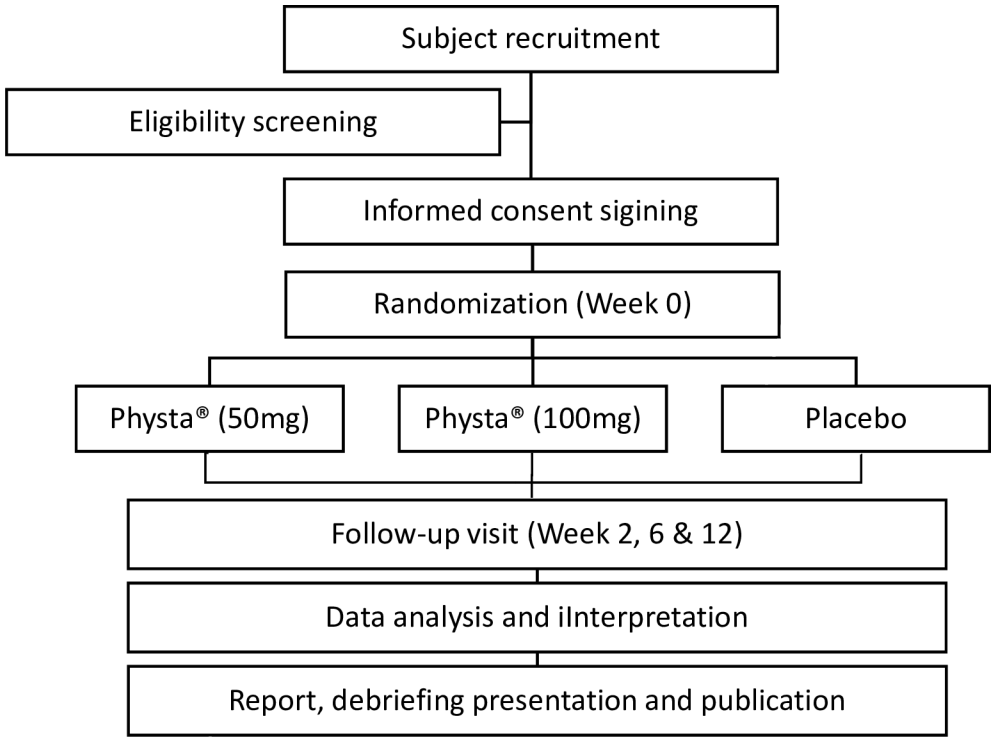


**Figure 1** Study flow chart.

Recommendation for Intervention Trials (SPIRIT) checklist as guideline while designing the study protocol.[27]

### Sample size calculation

Calculation for sample size population is determined by using G-power software (Faul *et al*, 2007). Using g-power software, under f-test, MANOVA—repeated measures—within between interaction, (effect size f(v)=0.25, alpha error prob=0.05, power=0.8. number of study groups=3, number of measures=4) total sample size calculated is 113 participants. Considering 10%–20% drop out rate, 150 participants will be recruited (50 participants per intervention group).

### Participant recruitment

Purposive sampling will be conducted around Klang Valley and the official study site will be located at obstetrics and gynaecology clinic, Hospital Canselor Tuanku Muhriz, which is a teaching hospital of the National University of Malaysia. As the study aims to enrol middle-aged women between 45 and 55 years old with menopausal symptoms, the clinical diagnosis of significant menopausal symptoms will be conducted by gynaecologist supported by transabdominal sonographic findings and participant-administered Menopause-Specific Quality of Life (MENQOL) assessment.[28] To maintain the participant recruitment rate, recruitment progress will be assessed on monthly basis to troubleshoot the issues contribute to slow data collection if there is any. Community-based events, general health screenings and women's health-related awareness talks will be conducted to attract potential study participants. The results and findings of the study will be shared with enrolled participants by debriefing presentation.

### Eligibility criteria (inclusion and exclusion criteria)

Women who scores ≥61 (higher score indicates the presence of menopausal symptoms) in the MENQOL assessment will be invited to participate in the study with reportable symptoms of aches at muscles, joints, back of the neck and head (scores 'YES' for MENQOL question number 12 or/and 15), experience tiredness, worn out and lack of energy (score 'YES' for MENQOL question number 13 or/and 18). Participants must also be in a stable heterosexual relationship for at least 6 months prior to study and has a body mass index (BMI) of 20–29.9 $kg/m^2$.

The study exclusion criteria include any of the following:

1. Uncontrolled hypertension (systolic blood pressure >160 mm Hg and/or diastolic blood pressure >100 mm Hg) without any medication.
2. Familial and medical history or current diagnosis of breast cancer or breast cancer in an identical twin or any cancer (except non-melanomatous skin cancer) diagnosed less than 5 years prior to randomisation. Participants with other cancers in full remission more than 5 years after diagnosis are acceptable with the exceptions of breast cancer or genital organ cancer (eg, cervical cancer, endometrial cancer, colorectal cancer or ovarian cancer).
3. Uncontrolled diabetes which includes fasting blood sugar of >10 mM/L without any medication.
4. Uncontrolled, untreated or under medication of thyroid disorder.

5. History or current diagnosis of any major diseases of the cardiovascular, hepatic, renal, gastrointestinal, pulmonary or endocrine systems.
6. History or current diagnosis of autoimmune conditions, immunodeficiency, rheumatoid arthritis or gynaecological disease.
7. Clinically significant mental depression that is not well controlled in the opinion of the investigator.
8. Participant has undergone major surgery within the past 1 year prior to the randomisation visit, except cholecystectomy and appendectomy.
9. Participant smokes more than 15 cigarettes a day.
10. History of alcohol or drug abuse within the past year.
11. Participants with known allergic reactions to herbal supplements.
12. Participants actively consume other commercial multivitamins, dietary, traditional or herbal supplements that can affect their metabolism and disagree to stop the consumption during study period.
13. Participants on hormone replacement therapy.
14. Participants with abnormal uterine bleeding.
15. Participants with uterine fibroid and/or ovarian cyst.
16. Reported with thickened endometrium on ultrasound (ie, >5 mm (in postmenopausal) and >11 mm (perimenopausal)).

Eligible participants based on all the inclusion and exclusion criteria will be briefed about the study and written consent will be obtained prior to participating in the study (online supplemental appendix 1) equipped with participant information sheet (online supplemental appendix 2).

### Interventions and randomisation

Eligible participants will be selected and randomly allocated to one of the three intervention groups (50 mg Physta, 100 mg Physta and placebo) using computer-generated random numbers obtained through online sample randomiser software. According to their order of recruitment, each participant will be assigned a study participation ID numbered from 1 to 150 and it remains unchanged throughout the study. All the eligible participants will be randomised to receive one capsule daily with water in the morning after the first meal of the day consistently for 12 weeks.

### Preparation of Physta and placebo

The supplements capsule known as Physta is a standardised water extract of EL with high level of natural antioxidants. Finished products in form of capsule contains 50 mg of Physta extract with 300 mg maltodextrin (registration number MAL18056060T) and capsule contains 100 mg of Physta extract with 250 mg maltodextrin (registration number MAL09051452T) were developed and registered with National Pharmaceutical Regulatory Agency. Placebo capsules composed of 280 mg maltodextrin looking identical to the Physta capsules in colour, shape, size and packaging except lacking the active ingredient.

### Blinding

Blinding procedure will be ensured by labelling the two different dosages of Physta supplements and placebo capsules as either A, B or C. Study participant and the investigator are blinded, only manufacturer and packager will know the coding for A, B and C labelled capsules and the allocation codes will only be disclosed at the end of the data analysis.

### Clinical assessments

All the questionnaire and clinical assessments will be conducted at the Clinical Trial Ward of Universiti Kebangsaan Malaysia Medical Centre, Kuala Lumpur, Malaysia. Participant's sociodemographic data, medical history and the concomitant medication history will be recorded at the baseline for safety purpose. Anthropometric measurements, which included the measurement of height (cm), weight (kg) and BMI calculation, will be taken at all visits alongside self-administered questionnaires. Besides that, participants vital signs such as blood pressure, pulse rate and body temperature will be recorded as well during all visits.

The primary outcomes of the study which are the participant's mood state, quality of life, fatigue, sleep quality, sexual function and pain score will be assessed using Profile of Mood State (POMS),[29] MENQOL,[28] Chalder Fatigue Scale,[30] Pittsburgh Sleep Quality Index,[31] Female Sexual Function Index[32] and Brief Pain Inventory[33] questionnaires, respectively. At all visits, participants will be required to fast for 10 hours prior to peripheral venous blood withdrawal by a trained phlebotomist. For secondary outcome measures, a total of 20 mL blood will be collected for commercial laboratory analysis assessing complete blood count, liver function, fasting glucose level, renal function, lipid profile (total cholesterol, high-density lipoprotein-cholesterol, low-density lipoprotein-cholesterol and triglycerides) and female reproductive hormonal profile (follicle-stimulating hormone), luteinising hormone, progesterone, testosterone and oestradiol). Inflammatory biomarkers (Inducible Nitric Oxide Synthase (iNOS), Cyclooxygenase (Cox2)) and oxidative stress biomarkers (Melondialdehyde (MDA), Lipid Peroxidation (LPO)) will be analysed at baseline and week 12.

### Adverse events

Participants' tolerability towards study supplement will be assessed by reviewing vital signs and adverse event (AE) reports. Frequency, intensity and severity of AEs' will be recorded in detail, based on the participants' feedbacks at all visits including week 2. To obtain comparable and standardised documentation on AEs, participants will be asked open-ended, standardise questions at each visit based on the AE form (online supplemental appendix 3).

Although not anticipated, serious AEs will immediately be reported to the principal investigator, sponsor and manufacturer of the study supplement to ensure participants' safety.

**Table 1** Summary of activities planned during the study

| Activities | | Study period | | | | |
|---|---|---|---|---|---|---|
| | | Screening | Week 0 (baseline) | Week 2 | Week 6 | Week 12 |
| Enrollment | Eligibility screen | ✓ | | | | |
| | Informed consent | ✓ | | | | |
| | Sociodemographic information | ✓ | | | | |
| | Medical history | ✓ | | | | |
| | Transvaginal ultrasound scan | ✓ | | | | ✓ |
| | Concomitant medication history | ✓ | ✓ | | ✓ | ✓ |
| | Allocation and randomisation | | ✓ | | | |
| | Study product dispensing | | ✓ | | ✓ | |
| Intervention | Physta (50 mg) capsules | | ✓ | ✓ | ✓ | ✓ |
| | Physta (100 mg) capsules | | ✓ | ✓ | ✓ | ✓ |
| | Placebo capsules | | ✓ | ✓ | ✓ | ✓ |
| | Daily dose diary checking | | | | | |
| | Compliance checking | | | | ✓ | ✓ |
| | Unused product return | | | | | |
| Assessment | Safety and tolerability assessment<br>Anthropometric measurements<br>Vital signs<br>Adverse events | ✓ | ✓ | ✓ | ✓ | ✓ |
| | Laboratory assessments<br>Urine analysis | ✓ | ✓ | | ✓ | ✓ |
| | Blood plasma/serum analysis<br>► Complete blood count<br>► Renal function test<br>► Liver function test<br>► Fasting blood sugar<br>► Lipid profile<br>Reproductive hormone profile (oestrogen, progesterone, testosterone, LH and FSH) | ✓ | ✓ | | ✓ | ✓ |
| | Inflammatory Nitric Oxide Synthase (iNOS), Cyclooxgenase-2 (Cox2)) and oxidative stress (Melondialdehyde (MDA), Lipid Peroxidation (LPO)) biomarker analysis | | ✓ | | | ✓ |
| | Questionnaires assessments<br>► Menopause-specific quality of life (MENQOL)<br>► Profile of mood state<br>► Chalder Fatigue Scale<br>► Pittsburgh Sleep Quality Index<br>► Female Sexual Function Index<br>► The Brief Pain Inventory | (Only MENQOL) | ✓ | ✓ | ✓ | ✓ |

FSH, follicle-stimulating hormone; LH, luteinising hormone.

## Prohibited concomitant medication and interventions

The following concomitant medications and interventions are not permitted while the participants are on trial:

1. Dexamethasone systemic medication.
2. Cortisone systemic medication.
3. Adrenal supplements.
4. B Complex, vitamin C, vitamin E, vitamin A, vitamin $B_6$, omega 3 fatty acids, selenium, calcium, zinc and iron supplements.
5. Herbal products that may contain androgenic/anxiolytic activity.
6. Any supplement which can influence women reproductive hormones, lipid profile, blood sugar levels, mood, sleep or other metabolic functions.
7. Any product containing EL.

At each visit, new or changes in concomitant medications will be documented.

## Assessment of compliance

Participants from all three intervention groups will receive capsule supplies at baseline and week 6 visits. Researchers will remind the participants to take study supplement through a daily WhatsApp message. Participants' compliance will be assessed by performing capsule count at week 6 and week 12 visits. Considering evidence from previous RCT studies, participants who consumed <70% of the recommended intake of study supplement will be considered non-compliance and excluded from the study.

## Follow-up visits

All participants will be followed up for a duration of 12 weeks which includes face-to-face follow-up visits at week 6 and week 12 and self-administered questionnaire assessment at week 2. Time schedule for study, intervention groups and assessments carried out at each visit are summarised in table 1.

## Amendments to the protocol

Any relevant amendments be required to be signed by the principal investigator, the sponsor and the researcher. If those amendments are substantial and are likely to have an impact on the safety of the participants or they change the interpretation of the scientific documents in support of the conduct of the trial, the changes will be notified to the Ethics Committee concerned. The approval of the amendment by the Research Ethics Committee UKM is mandatory before the changes may be implemented.

## Patient and public involvement

Patients or the public were not involved in the design, conduct, reporting or dissemination plans of our research.

## Statistical analysis

IBM SPSS Statistics V.29 will be used to run all descriptive and inferential analyses for all endpoints. To summarise the baseline characteristics, descriptive statistics will be performed. Data of participants who have consumed more than 70% of study product without any major protocol and completed all study visits will be used for primary endpoint analysis. Dependent variables will be tested for normality using Shapiro-Wilk test and non-normal variables will be analysed using non-parametric analysis. The variations between the treatment and the placebo groups will be analysed by independent Student's t-test and $\chi^2$ squared test. Data will be reported as mean, SD and 95% CI. The effects of Physta consumption over time, the effect of group and its interaction will be determined by using mixed design repeated measures Multivariate Analysis of Variance (MANOVA). Mauchly's test of sphericity will be used to analyse the assumption sphericity for each dependent variable. For the variables with $p \leq 0.05$ will be indicated as a violation of this assumption and Greenhouse-Geisser adjustment will be made to the appropriate degree of freedom. Indication of differences within and between periods of supplement consumption will be analysed using Bonferroni's post hoc test with statistical significance of $p \leq 0.05$. Subgroup analysis will be conducted if required.

## Trial status

The recruitment of the participants has begun in December 2022. Estimating to end the data collection by December 2023.

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**Contributors** All authors have participated in the process of in critical revision of the manuscript for optimum intellectual content. SM drafted the manuscript under supervision of HMY. SM, HMY, SS, IBKA, ZAM, NFR, AG and SMC were involved in designing the study protocol and conceptualisation. SM conducting the participant recruitment under supervision of HMY, SS and IBKA. IBKA and ZAM are the gynaecologists' who performs the transabdominal uterus scan for participant eligibility assessment. For data analysis using SPSS software, HMY, SS and NFR will guide SM with their knowledge and experience in performing statistical analysis. All authors have read, edited and approved the final draft of this manuscript.

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**Competing interests** AG and SMC are employees of Biotropics Malaysia Berhad.

**Patient and public involvement** Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

**Patient consent for publication** Not applicable.

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## REFERENCES

1 Zhang X, World Healtha Organization. *WHO Traditional Medicine Strategy 2002-2005*. 2002.
2 Mohd Effendy N, Mohamed N, Muhammad N, *et al*. Eurycoma longifolia: medicinal plant in the prevention and treatment of male osteoporosis due to androgen deficiency. *Evid Based Complement Alternat Med* 2012;2012:125761.
3 Rehman SU, Choe K, Yoo HH. Review on a traditional herbal medicine, Eurycoma Longifolia Jack (Tongkat Ali): its traditional uses, chemistry, evidence-based pharmacology and toxicology. *Molecules* 2016;21:331.

4 Hei CH, Latiff KA, Hassan MR, *et al*. Preferences for traditional & complementary medicine among Malaysian hospitalised patients in UKM medical Centre 2012. *Malays J Public Health Med* 2015;15:122–31.
5 Patwardhan B, Vaidya AD, Chorghade M. Ayurveda and natural products drug discovery. *Curr Sci* 2004:789–99.
6 Chua LS, Abdul-Rahman N, Rosidi B, *et al*. Plant proteins, minerals and trace elements of Eurycoma Longifolia (Tongkat Ali). *Nat Prod Res* 2013;27:314–8.
7 Tzar M. The antibacterial or antifungal effects of eurycoma longifolia root extract. Int J Herbal Plant Med 2010;2:1–6.
8 Latip MQA, Noor MHM, Ahmad H, *et al*. A systematic review on antimicrobial and antiparasitic activity of *Eurycoma Longifolia* Jack (Tongkat Ali). *Biomed Res Int* 2022;2022.
9 Annie George V. *Effects of selected Malaysian herbs on healthy ageing/Annie George VK George*. University of Malaya, 2018.
10 Udani JK, George AA, Musthapa M, *et al*. Effects of a proprietary freeze-dried water extract of Eurycoma Longifolia (Physta) and Polygonum minus on sexual performance and well-being in men: A randomized, double-blind, placebo-controlled study. *Evid Based Complement Alternat Med* 2014;2014.
11 Ahmed S, Parvezz T, Parvez M, *et al*. Dietary or nutritional supplements associated adverse effects and toxicity. Medp Nutr Food Sci 2022;1.
12 Ang HH, Lee KL, Kiyoshi M. Sexual arousal in sexually sluggish old male rats after oral administration of Eurycoma Longifolia Jack. *J Basic Clin Physiol Pharmacol* 2004;15:303–9.
13 Vejayan J, Mohamed AN, Zulkifli AA, *et al*. Marker to authenticate Eurycoma Longifolia (Tongkat Ali) containing Aphrodisiac Herbal products. *Curr Sci* 2018;115:886.
14 Ozcan H. Healthy life style behaviors and quality of life at menopause. *Int J Caring Sci* 2019;12:492–500.
15 Chinnappan SM, George A, Evans M, *et al*. Efficacy of Labisia Pumila and Eurycoma Longifolia standardised extracts on hot flushes, quality of life, hormone and lipid profile of peri-menopausal and menopausal women: a randomised, placebo-controlled study. *Food Nutr Res* 2020;64.
16 Woods NF, Mitchell ES. Symptoms during the perimenopause: prevalence, severity, trajectory, and significance in women's lives. *Am J Med* 2005;118 Suppl 12B:14–24.
17 Yahya HM, Shahar S, Ismail SNA, *et al*. Mood, cognitive function and quality of life improvements in middle aged women following supplementation with polygonum minus extract. *JSM* 2017;46:245–54.
18 Kanadys K, Wiktor-Stoma A, Lewicka M, *et al*. Predictors of the quality of life of women in peri-menopausal period. *Ann Agric Environ Med* 2016;23:641–8.
19 Moore TR, Franks RB, Fox C. Review of efficacy of complementary and alternative medicine treatments for menopausal symptoms. *J Midwifery Womens Health* 2017;62:286–97.
20 Mehrnoush V, Darsareh F, Roozbeh N, *et al*. Efficacy of the complementary and alternative therapies for the management of psychological symptoms of menopause: a systematic review of randomized controlled trials. *J Menopausal Med* 2021;27:115–31.
21 Diah NM. The knowledge of Menopause and its treatment among Orang Asli in Gombak. *Int Res J Soc Sci* 2013;2:1–4.
22 Ismail SB, Wan Mohammad WMZ, George A, *et al*. Randomized clinical trial on the use of PHYSTA freeze-dried water extract of Eurycoma Longifolia for the improvement of quality of life and sexual well-being in men. *Evid Based Complement Alternat Med* 2012;2012.
23 Tambi M, Imran MK. Eurycoma Longifolia Jack in managing idiopathic male infertility. *Asian J Androl* 2010;12:376–80.
24 Talbott SM, Talbott JA, George A, *et al*. Effect of Tongkat Ali on stress hormones and psychological mood state in moderately stressed subjects. *J Int Soc Sports Nutr* 2013;10:1–7.
25 George A, Udani J, Abidin NZ, *et al*. Efficacy and safety of *Eurycoma Longifolia* (Physta) water extract plus multivitamins on quality of life, mood and stress: a randomized placebo-controlled and parallel study. *Food Nutr Res* 2018;62.
26 M Chinnappan S, George A, Ashok G, *et al*. Effect of Herbal extract Eurycoma Longifolia (Physta®) on female reproductive hormones and bone biochemical markers: an ovariectomised rat model study. *BMC Complement Med Ther* 2020;20:1.:9.
27 Chan A-W, Tetzlaff JM, Gøtzsche PC, *et al*. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ* 2013;346:e7586.
28 Hilditch JR, Lewis J, Peter A, *et al*. A menopause-specific quality of life questionnaire: development and psychometric properties. *Maturitas* 1996;24:161–75.
29 McNair D, Lorr M, Droppleman L. *Manual for the profile of mood states (POMS) revised*. San Diego, CA: Educational and Industrial Testing Service, 1992.
30 Jackson C. The Chalder fatigue scale (CFQ 11). *Occup Med (Lond)* 2015;65:86.
31 Buysse DJ, Reynolds CF, Monk TH, *et al*. The Pittsburgh sleep quality index: a new instrument for psychiatric practice and research. *Psychiatry Res* 1989;28:193–213.
32 Rosen R, Brown C, Heiman J, *et al*. The female sexual function index (FSFI): a multidimensional self-report instrument for the assessment of female sexual function. *J Sex Marital Ther* 2000;26:191–208.
33 Cleeland CS, Ryan KM. Pain assessment: global use of the brief pain inventory. *Ann Acad Med Singap* 1994;23:129–38.