

## 36<sup>th</sup> Malaysian Society of Pharmacology and Physiology Annual Scientific Meeting 2023

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Received: 1 August 2023; Revised: 4 August 2023; Accepted: 6 August 2023; Published: 6 August 2023  
DOI <https://doi.org/10.28916/lsm.7.1.2023.132>

### ABSTRACT

The 36th Malaysian Society of Pharmacology and Physiology (MSPP) Annual Scientific Meeting was hosted in collaboration with the Faculty of Medicine and Health Sciences, Universiti Putra Malaysia from the 7th to 8th of August 2023 at Bangi Resort Hotel in Bangi, Malaysia. The event focused on the theme "*Pharmacology & Physiology Post-Millennial Era: Challenges & Opportunities*". This platform is one of the suitable avenues to facilitate the exchange of scientific endeavors and enhance networking among scientists, academicians, clinicians, and postgraduate students involved in the fields of pharmacology and physiology, as well as multidisciplinary areas such as drug discovery, omics approaches, stem cells, and regenerative medicine. The primary objective of the special issue is to revitalize recent advances and breakthroughs in pharmacology and physiology to enhance opportunities and vanquish challenges in the post-millennial era, especially in the wake of the COVID-19 pandemic. In light of this, the special issue compiles the conference proceeding, to provide opportunities for knowledge integration of research and innovations.

**Keywords:** *Pharmacology; physiology; drug discovery; omics approaches; stem cells and regenerative medicine*

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**ABSTRACTS**

All presented abstracts are listed from Page 4 to 60.

# The anticancer potency of chloroform fraction of *Eleutherine bulbosa* on human lung cancer cell lines

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DOI <https://doi.org/10.28916/lsm.7.1.2023.132>

## Abstract

Lung cancer is the most common cause of cancer-related death worldwide, with most cases being detected at a very late stage. *Eleutherine bulbosa*, or “Bawang Dayak”, is a folklore medicine used among the Dayak community and was assessed as a potential anticancer remedy to inhibit the growth of human lung cancer, A549 cells. The present study aimed to determine the anticancer potency of the chloroform fraction of *E. bulbosa* and possible active compounds attributable to the cytotoxic effect on human lung cancer cell lines. Three different organic solvents, including n-hexane, ethyl acetate, and chloroform, were used in liquid-liquid fractionation. Then, the cytotoxic effect of each fraction from different solvents was evaluated using the MTT assay after the indicated treatment on A549 cells and human lung fibroblast, MRC5 cells. The GC-MS analysis was conducted to identify the possible active compounds in the chloroform fraction of *E. bulbosa*. The clonogenic survival assay was further carried out to evaluate the survival of cells and their ability to proliferate. The viability of cells was further monitored using double staining Propidium Iodide (PI) and Hoechst 33342. Chloroform fraction of *E. bulbosa* bulb has been shown to have the most cytotoxic potency to human lung cancer cell line with the IC<sub>50</sub> value 30.01 ± 2.14 µg/mL as compared to hexane and ethyl acetate 126.60 ± 4.15 µg/mL and 83.44 ± 1.31 µg/mL, respectively. The IC<sub>50</sub> value for A549 cells was 30.01 ± 2.14 µg/mL, whereas for MRC5 cells was 102.2 ± 1.78 µg/mL. GC-MS analysis identified 20 phytochemical compounds in the chloroform fraction of *E. bulbosa* and showed that eleutherine and isoeleutherine were major components. The clonogenic survival assay demonstrated that the chloroform fraction of *E. bulbosa* inhibited the survival of a single cell from forming a colony. Double staining with PI and Hoechst 33342 revealed that the chloroform fraction of the *E. bulbosa* bulb resulted in a combination of normal and apoptotic/necrotic cells. It was demonstrated that the chloroform fraction of *E. bulbosa* bulb could exhibit anticancer properties on lung cancer cells and minimal impact on normal cells that potentially be used as a chemopreventive for lung cancer treatment.

**Keywords:** *E. bulbosa*; Lung cancer; cytotoxic; anticancer

# Ascertaining the importance of rapid, colorimetric sensors in detection of hypoxia tolerance at high altitude

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DOI <https://doi.org/10.28916/lsmf.7.1.2023.132>

## Abstract

Prolonged exposure episodes to high altitudes have been demonstrated to cause acute hypoxia and lead to subsequent potential significant health consequences. In people suffering from high altitude disorders, homeostatic responses to high altitudes induce the formation of hypoxia-inducible factor (HIF) proteins which triggers a series of other physiological changes and plays a central role in hypoxia response. The activity of HIF is regulated by the oxygen-dependent degradation of the HIF-1 $\alpha$  protein (HIF-1A gene). This physiological interaction provides the opportunity of studying effects pertaining to low oxygen tensions caused by prolonged exposure in high altitudes leading to hypoxia by using rapid colorimetric sensors. The development of strip-based detection enables the use of an enzyme-linked assay in a lateral flow device to provide more sensitivity at the benefit of rapid time analysis and low sample requirements. For this purpose, parameters including reagent concentration, reagent volumes, and device dimensions were optimized to produce a calibration curve generated using rabbit IgG. Subsequently, a housing for the detection kit with a reagent storage was crafted for an autonomously operating device. There was a measurable qualitative change in colorimetric signal consequent to the presence of the HIF-1 $\alpha$  biomarker protein. In absence of the protein, no colorimetric signal was produced. The detection strip, housed in the operation device performed well to detect low volumes of the hypoxia biomarker, demonstrating potential to be further developed for use as a robust diagnostic approach with high sensitivity and specificity in hypoxia detection. This would enable point-of-care (POC) testing and individual self-administration, resulting in faster and more accurate results and enhanced health surveillance, particularly in high altitude exposure.

**Keywords:** *HIF-1 $\alpha$  (hypoxia-inducible factor 1alpha); hypoxia; high altitude; rapid colorimetric sensors; rapid test*

# Suppression of TNF- $\alpha$ , IL-6 & rheumatoid factor with anti-inflammatory and analgesic effects of two *Brassica rapa* varieties: impact on pro-inflammatory mediators

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DOI <https://doi.org/10.28916/lsmb.7.1.2023.132>

## Abstract

Anti-inflammatory and analgesic potential of polyphenol-rich extracts of root, peel and pulp of two *Brassica rapa* varieties were investigated in animal models and their impact on pro-inflammatory mediators. Methanol extracts of *Brassica rapa* yellow peel (BRYP), *Brassica rapa* white peel (BRWP), *Brassica rapa* yellow root pulp (BRYR) and *Brassica rapa* white root pulp (BRWR) were prepared using soxhlet. The polyphenols in the extracts were qualitatively and quantitatively analyzed by reversed-phase high-pressure liquid chromatography (RP-HPLC). Total phenolic contents (TPC), total flavonoid contents (TFC), DPPH radical scavenging activity and reducing potential were measured. With IACUC approval, the anti-inflammatory potential was assessed by carrageenan-induced rat paw edema, and the analgesic potential was investigated by hot plate test. A dose (200 mg/kg) of each extract was administered orally and paw diameter and inflammatory biomarkers (CRP, TNF- $\alpha$ , IL-6, and RF) were measured in all groups of rats. RP-HPLC analysis revealed the presence of 12 phenolic acids and 4 flavonoids. Gallic acid was the major phenolic acid (174.7-642.6 mg/100 g of dry plant material) while catechin was the major (29.95-365.5 mg/100 g of dry plant material) flavonoid detected in the extracts. TPC of BRYP, BRWP, BRYR and BRWR extracts were in the range of 1.21-5.01 mg/g of dry plant material, measured as GAE whereas, TFC were found in the range of 0.90-3.95 mg/g of dry plant material, measured as QE. In vivo data showed that BRYP extracts reduced paw edema and suppressed the production of inflammatory biomarkers significantly followed by BRWP, BRYR and BRWR extracts. In addition, analgesic effect as well as, histopathological evidence supported the anti-inflammatory consequence of peel extracts to be more than root pulp extracts. The BRYP extract, has higher phenolic content and showed strong antioxidant, anti-inflammatory and analgesic effects compared to other extracts.

**Keywords:** Polyphenols; carrageenan; C-reactive protein; TNF- $\alpha$ ; IL-6; rheumatoid factor

# The adverse effect of statin on erectile dysfunction among Malaysian outpatients: genetic analysis

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## Abstract

There are prominent controversial opinions about the effects of statins, where some research scholars believe that statins worsen male sexual functions. This study aims to investigate the most susceptible SNPs and variants of genotypes as statins have pharmacogenomic adverse effects on erectile dysfunction (ED). A cross-sectional design was used to determine the risk factors that affected erectile dysfunction and abnormal reduction of testosterone among users of statins. About 239 patients were on regular appointment visits to their doctors at the outpatient clinic's Hospital USM, Kubang Kerian, Kelantan. The patients were grouped into four categories which are statins with ED, statins without ED, statin and diabetes without ED, and control. A self-administered questionnaire was adopted to collect information for the patients. The information of this questionnaire involved demographic and health information (like concurrent diseases and medicines). ED was evaluated for every patient using the International Index of Erectile Function. Genotyping analysis was used in the present study to determine the SNPs using the Polymerase Chain Reaction (PCR). The testosterone level was measured from the patient's blood samples. Three primary SNPs of genes involved are rs17703883, rs4919686, and rs1799983. The outcomes of genetic SNPs found a significantly higher ED incidence for the snp1rs17703883-variant TC for those who used statin of the first group by 15 times than the patients in the control group. No significant difference in ED was obtained in the outcomes comparing the other two groups with the control group. No significant effect of the statin on the abnormal reduction of testosterone among the four groups. In conclusion, genetic results show statin use worsens ED among Malaysian patients, especially those with mutated SNPs.

**Keywords:** *Erectile dysfunction; testosterone; statin; Malaysian males; mutated SNPs*

# Spathulenol lowers blood pressure in rats possibly via inhibition of angiotensin-converting enzyme

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## Abstract

In recent years, the phytochemical profiles of most medicinal plants have been reported, with flavonoids and terpenoids being the main constituents. Among them is spathulenol (Spa), a terpenoid, derived mainly from the *Origanum* species. In the prevailing literature, Spa has been demonstrated to have apparent blood pressure (BP)-lowering properties. However, the mechanisms of action remain largely unknown. This study was therefore initiated to investigate the BP-lowering activities of Spa *in vivo* as well as to ascertain the mechanisms of action *in vitro*. Male Sprague-Dawley (SD) rats (n=6) and spontaneously hypertensive rats (SHR) (n=6) with their normotensive Wistar-Kyoto (WKY) rats (n=6) as controls, were subjected to anaesthesia and administered intravenous boluses of 0, 0.045, 0.90, 0.18, 0.36 and 0.7 mg/kg of Spa. The BP and heart rate of the rats were recorded by a computerised physiographical system (PowerLab computer system) through carotid arterial cannulation that was connected to a pressure transducer. The data were analysed using the LabChart 6 software. Spathulenol was also tested for angiotensin-converting enzyme (ACE) inhibitory activity using the ACE1 inhibitor screening kit (PromoKine). Spathulenol was found to be able to decrease the BP of the rats in a dose-dependant manner with the BP-lowering effect being significantly ( $p < 0.05$ ) higher in the SHRs than in the WKY controls. Furthermore, Spa was able to inhibit the activity ACE in a dose-dependant manner suggestive of the possibility that this could be one of the mechanisms underlying the observed BP-lowering effect.

**Keywords:** Spathulenol; blood pressure; SHR; WKY rats; ACE inhibition



# Effectiveness of a combined circuit of aerobic and resistance training on overweight and obese patients with knee osteoarthritis and type 2 diabetes mellitus: A randomized controlled trial

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**Abstract:**

Previous studies have shown that comorbidities like obesity and T2DM are linked to the onset of knee pain caused by osteoarthritis, and these comorbidities can severely impact prognosis and exercise intervention for KOA patients. However, there is currently no evidence-based exercise protocol that is optimal for treating chronic illnesses like KOA and T2DM. To date, there is no clear evidence-based protocol for exercise that is best suited for patients with chronic illnesses such as KOA and T2DM. Therefore, this study intends to examine the effectiveness of a combined circuit of aerobic and resistance training on overweight and obese individuals with KOA and T2DM. Seventy overweight or obese T2DM patients with KOA were randomly assigned to the intervention group (n=35; a combined circuit of aerobic and resistance training) or the standard care group (n=35). Following three months of the intervention, the effects of combined exercise on the Knee Injury and Osteoarthritis Outcome Score (KOOS) questionnaire, glycated haemoglobin (HbA1c), cardiovascular parameters, aerobic capacity and endurance, and renal function were assessed. Combined aerobic and resistance training significantly improved KOOS-quality of life (KOOS-QOL), KOOS-activity of daily living (KOOS-ADL), KOOS-pain, KOOS-symptom, HbA1c, potassium (K), systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), body mass index (BMI), the six-minute walking test score (6MWT), Borg Rating of Perceived Exertion (RPE), and oxygen saturation (SPO<sub>2</sub>) (P value < 0.05) compared to the control group. There were no significant differences in total bilirubin, sodium (Na), urea, heart rate (HR), and KOOS-Sport between the intervention and control groups (P value >0.05). We recommend that overweight or obese patients with T2DM and KOA combine resistance and aerobic exercise modalities as it presents practical advantages of skeletal muscle strength training and aerobic conditioning. It is recommended to conduct a larger scale randomized controlled research to examine the impact of exercise on liver functions, inflammation, and oxidative stress in obese T2DM patients with KOA.

**Keywords:** *Physical activity; strength training; comorbidity; chronic disease*

# Neuroprotective effect of fish oil on brain $\beta$ -amyloid deposition in a diabetic model of Alzheimer's disease

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## Abstract

Production and deposition of the  $\beta$ -amyloid have been associated with the pathological process of Alzheimer's disease (AD). One of the numerous etiological risk factors for AD is hyperglycemia, which has been shown to surge amyloid accumulation and lead to brain neurotoxicity. Meanwhile, consuming fish oil rich in omega-3 fatty acids has been linked to a lower risk of AD. However, the beneficial role of fish oil in hyperglycemia is still unclear. This study was designed to examine the effects of fish oil on brain amyloidogenesis in diabetic rats injected with lipopolysaccharides (LPS). Diabetic animals were generated using multiple doses of streptozotocin (STZ) (45 mg/kg). The fasting blood glucose (FBG) was measured one week after the STZ injection and at the end of the experiment. Only animals with FBG greater than 250mg/dL were used in the subsequent steps. Later, the animals were induced with LPS (250 $\mu$ g/kg) for one week, followed by daily fish oil treatment for three weeks. At the end of the experiment, the brain was harvested, and the cerebrum was separated by the sagittal plane. The left hemisphere was analyzed for  $\beta$ -amyloid peptide (e.g 1-42) occurrence using immunofluorescence methods. At the same time, the right hemisphere was extracted for amyloid precursor protein (APP) qualitative measurements using an ELISA assay. The result showed that fasting blood glucose decreased significantly ( $P < 0.05$ ) in the diabetic Alzheimer's disease model after fish oil intake.  $\beta$ -amyloid staining was positive in the hippocampus and cortex of the brain sections, indicating the presence of amyloid plaques. Furthermore, chronic fish oil supplementation significantly reduced APP levels ( $P < 0.05$ ) in both cortex and hippocampus. Thus, these findings suggest that fish oil supplementation could prevent hyperglycemia and  $\beta$ -amyloid production, which potentially protects the brain from neurotoxicity. Our findings also support the concept that there could be beneficial effects in utilizing fish oil in the treatment of Alzheimer's disease associated with diabetes mellitus.

**Keywords:** *Alzheimer's disease; brain; diabetes mellitus;  $\beta$ -amyloid ; fish oil; omega-3*

# Antihyperlipidemic, hepatoprotective and nephroprotective effects of functional beverages containing soybean (*Glycine max* L.), sweet potato leaves (*Ipomoea batatas* L.), and red yeast rice on a high-fat diet rats

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## Abstract

A high-fat diet is one of the main risk factors for hyperlipidemia. Soybeans (*Glycine max*), sweet potato (*Ipomoea batatas*) leaves and red yeast rice are known to have potential as sources of antihyperlipidemic compounds and antioxidants due to their phytochemical content and biological activity. This study aims to determine the effects of functional beverages containing soybeans, sweet potato leaves and red yeast rice on antihyperlipidemic, hepatoprotective and nephroprotective properties in rats fed a high-fat diet. The test animals were divided into 5 groups: normal control, positive control with Nutrive Benecol at a dose of 3.6 ml/day, negative control and treatment groups with doses of 1250 mg/kg BW and 2500 mg/kg BW, respectively. The animals were fed a high fat diet throughout the study period of 28 days, and the treatment with the functional beverage was given for 14 days starting from day 15 after the induction of the high-fat diet. The results showed that the administration of the functional beverage at a dose of 2500 mg/kg BW significantly ( $p < 0.05$ ) reduced levels of total cholesterol, triglycerides, blood urea nitrogen (BUN), creatinine, serum glutamic pyruvic transaminase (SGPT) and serum glutamic oxaloacetic transaminase (SGOT) in rats fed a high-fat diet. Histological observations of the liver organ showed a repair of the liver damage caused by the induction of the high-fat diet. In conclusion, the study suggests that functional beverages could be used for the protection against hyperlipidemia, liver damage and kidney damage caused by a high fat-diet.

**Keywords:** Functional beverages; high fat diet; red yeast rice; sweet potato leaves; soybeans

# Bioactivity-guided isolation of polyphenols from *Citrullus colocynthis* for antihypertensive effect in spontaneous hypertensive rat model

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**DOI** <https://doi.org/10.28916/lsm.7.1.2023.132>

## Abstract

The aim of the present study was to investigate the antihypertensive effect of polyphenol-rich *Citrullus colocynthis* (CC) fractions against spontaneous hypertensive rats (SHR) model. Crude CC extract was fractionated in hexane, chloroform, ethyl acetate, butanol and aqueous ethanol to get HEF, CHF, EAF, BUF and AEF fractions, respectively. The AEF represented the maximum yield (58.6 g/100g) followed by BUF (16.5 g/100g), HEF (3.7 g/100g), EAF (2.9 g/100g) and CHF (2.3 g/100g). The EAF contained the highest total phenolic contents (289.4 mg/g), total flavonoid contents (7.60 mg/g) and flavanol contents (35.7 mg/g). Among all the CC fractions, EAF showed highest DPPH radical scavenging activity (SC<sub>50</sub>, 6.2 µg/mL) followed by CHF (SC<sub>50</sub>, 17.3 µg/mL), BUF (SC<sub>50</sub>, 22.4 µg/mL), AEF (SC<sub>50</sub>, 53.7 µg/mL) and HEF (SC<sub>50</sub>, 115.9 µg/mL). Among all the CC fractions, best reducing potential was also observed from EAF. The RP-HPLC analysis of CC fraction revealed the presence of ferulic acid, vanillic acid, *p*-coumaric acid, gallic acid, *p*-hydroxy benzoic acid and chlorogenic acid, catechin, rutin, quercetin, myricetin and kaempferol. CC fraction dose of 250 and 500 mg kg<sup>-1</sup> body weight were given to male SHR and WKY rats daily for 21 days through oral gavage. Rats body weight, heart rate, blood pressure were monitored twice a week. The oxidative status of the animals was determined by conducting a series of tests from collected plasma including measurements of malondialdehyde (MDA), superoxide dismutase (SOD), reduced glutathione (GSH), nitric oxide (NO) and total antioxidant capacity (TAC) levels. Best antihypertensive effect was observed in EA-500 group that significantly decreased ( $p \leq 0.05$ ) the systolic blood, diastolic and mean arterial pressure. Surgery was performed at the end of the study and blood pressure, pulse wave velocity (PWV) and echocardiogram (ECG) were recorded. It was concluded that EAF of CC possessed significant antihypertensive and antioxidant activity in the SHR group.

**Keywords:** Quercetin; ferulic acid; gradient elution; pulse wave velocity; SHR

# Phytochemical analysis of seaweed *Kappaphicus striatus* extract for the treatment of hypertension and hypercholesterolemia

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DOI <https://doi.org/10.28916/lsm.7.1.2023.132>

## Abstract

Hypercholesterolemia has been identified as a substantial risk factor for cardiovascular disease, with a prevalence of more than 50% among adults in Malaysia. Food sources and components of traditional medicines play an important role in the treatment of this disease. Seaweeds are natural dietary bioresources and have drawn a lot of attention recently. *Kappaphicus striatus* (KS), a local seaweed, contains many valuable phytoconstituents that could be used in the treatment and management of hypertension and hypercholesterolemia. The aim of the study was to analyze phytoconstituents present in the seaweed KS for the treatment of hypertension and hypercholesterolemia. Extraction was carried out by a simple maceration method to prepare a methanolic extract of KS. Phytochemical analysis was carried out via GCMS and LCMS to analyze the phytoconstituents of the extract. The analysis results showed the presence of different types of compounds in the methanolic extract of KS. Some of the important compounds identified were 25-epoxycholesterol and terazosin via LCMS analysis in the methanolic extract of KS. These constituents could be used in the treatment of hypercholesterolemia and hypertension. Apart from these important constituents, many other different constituents were also detected via GCMS and LCMS analysis. KS seaweed might be used in the treatment of hypertension and hypercholesterolemia. Further *in vivo* studies are recommended and are currently under way at the faculty of pharmacy at UiTM to establish the potential role of KS phytoconstituents in the treatment of hypertension and hypercholesterolemia.

**Keywords:** *Kappaphicus striatus*; seaweed; LCMS; GCMS; hypercholesterolemia

# Excitotoxicity mediated modulation of the components of renin-angiotensin system in rat retina: Unraveling the interplay

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DOI <https://doi.org/10.28916/lsm.7.1.2023.132>

## Abstract

Renin-angiotensin system (RAS) components are expressed in neuronal tissue and play a role in neurodegenerative diseases, which involve excitotoxicity as a pathophysiological mechanism. In retina, excessive excitatory neurotransmission via N-methyl-D-aspartate (NMDA) receptors underlies neuronal apoptosis. However, it is not known if NMDA-mediated excitotoxicity alters retinal RAS expression. Hence, the aim of this study was to investigate the effect of NMDA receptor activation on the expression of RAS in rat retinas (108 rats). Sprague-Dawley rats were divided into two groups, control and experimental group which received intravitreal injection of phosphate-buffered saline (PBS) and NMDA (160 nmol), respectively. On day 7 post-treatment, the rats were euthanized, and their retinal samples were collected for analysis of RAS components including angiotensinogen, angiotensin converting enzyme (ACE), MAS receptor, angiotensin II type 1 receptor (AT1R) and ACE2 using ELISA, and PCR. It was observed that retinal expression of RAS components was altered after NMDA exposure compared to the control group. An upregulation of ACE expression was seen in both the protein (2.03 folds;  $p < 0.001$ ) and mRNA (1.86 folds;  $p < 0.01$ ). However, the mRNA expression of MAS receptor was reduced by 0.52 folds ( $p < 0.01$ ). Angiotensinogen protein and mRNA expression were increased by 2.35 and 1.99 folds, respectively ( $p < 0.05$ ). AT1R mRNA and protein expression was increased by 2.28 and 1.73 folds ( $p < 0.0001$ ), respectively. ACE2 protein and mRNA expressions were reduced by 0.66 folds ( $p < 0.05$ ) and 0.32 folds ( $p < 0.01$ ), respectively. These findings suggest that exposure to NMDA causes upregulation of the classical arm of RAS and suppression of alternate arm of RAS in rat retinas.

**Keywords:** Renin-Angiotensin-System (RAS); NMDA; retinal excitotoxicity glaucoma; ischemic retinal damage

# The anti-angiogenic and anti-metastatic effects of *Ardisia crispera* roots' hexane extract on colorectal cancer: An *in vitro* study

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## Abstract

Colorectal cancer (CRC) ranks as the world's third most prevalent cancer. In recent decades, Malaysia has shown an alarming upsurge in the incidence and mortality rate of CRC. This upward trend is often linked to the adoption of western lifestyle, diet modification and improved socio-economic status. Treatment of metastatic CRC is often limited by various adverse effects and the emergence of drug resistance. Over the past few decades, extensive research has been conducted to explore the pharmacological properties of *Ardisia crispera* roots. Among the documented potential of the hexane extract of this local medicinal plant (ACRH) include anti-inflammatory, anti-pyretic, anti-ulcer, anti-hyperalgesic, anti-arthritic, and anti-angiogenesis. Hence, this study aims to delve deeper into the potential of ACRH in hindering angiogenesis and metastasis in human CRC cell lines via various angiogenesis assays. The IC<sub>50</sub> values for HCT116 and LoVo cells was determined at 1.9±0.32 and 2.1±0.21 µg/mL, respectively via MTT assay. Subsequent experiments were then conducted with ACRH at concentrations of 0.02, 0.2, and 2.0µg/mL, respectively. ACRH significantly induced early and late apoptosis in both CRC cell lines. Additionally, ACRH at all tested concentrations significantly suppressed migration, invasion, and adhesion activities in both HCT116 and LoVo cell lines. Although the suppressive effects of ACRH on urokinase plasminogen activator (uPA) were only significant in LoVo cells, ACRH significantly hampered the concentration of membrane degradation protein, matrix metalloproteinase 2 (MMP-2) signifying ACRH's ability to inhibit CRC metastasis by preventing degradation of extracellular matrix (ECM). Furthermore, different concentrations of ACRH were able to significantly suppress the expressions of AKT, BRAF, ERK, KRAS, VEGF-A, VEGF-C, and PI3K at protein level, via ELISA assays, in both cancer cells. Therefore, these current findings suggest the auspicious potential of ACRH as an anticancer agent that acts via hampering CRC cells angiogenesis and metastasis signaling pathways.

**Keywords:** ACRH; *Ardisia crispera* roots; colorectal cancer; angiogenesis; metastasis

# Comparing the effects of self-emulsified and unformulated palm vitamin E on osteoporosis and osteoarthritis in rats with oestrogen deficiency

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DOI <https://doi.org/10.28916/lsm.7.1.2023.132>

## Abstract

Osteoporosis (OP) and osteoarthritis (OA) are two degenerative conditions affecting postmenopausal women disproportionately. Palm vitamin E (PVE) has been suggested to prevent these conditions separately. Self-emulsified PVE (SE-PVE) has been marketed as having enhanced bioavailability, hypothetically allowing for a smaller dose to be administered to achieve similar health effects as unformulated PVE (UN-PVE). This study aimed to compare the effects of SE-PVE and UN-PVE in preventing OP and OA in ovariectomized (OVX) rats. Female Sprague-Dawley rats (three-month-old; six/group) were ovariectomized (OVX) and divided into sham-operated control, OA+OP control, OA+OP+SE-PVE, OA+OP+UN-PVE, and OA+OP+calcium+glucosamine sulfate. Monosodium iodoacetate was injected into the right knee of OA groups four weeks after OVX. Treatments of SE-PVE (p.o.; 100 mg/kg/day; 25% VE), UN-PVE (p.o.; 100 mg/kg/day; 50% VE), and calcium carbonate (ad libitum, 1% in drinking water) + glucosamine sulfate (p.o.; 250 mg/kg/day) were started for the respective groups seven days after OVX for 10 weeks. The rats were sacrificed at the end of the treatment. The results showed that SE-PVE and UN-PVE achieved similar bioavailability despite the difference in VE content. SE-PVE sustained a significant increase in BMC in OVX rats until week 10 ( $p < 0.05$ ). SE-PVE reduced single-labeled surface and increased double-labeled surface marked by calcein ( $p < 0.05$ ). Both SE-PVE and UN-PVE prevented bone micro-architectural deterioration marked by total bone volume and trabecular separation ( $p < 0.05$ ). Knee joint diameters significantly increased with OA induction but resolved earlier with SE-PVE ( $p < 0.05$ ). Grip strength was reduced with OA and significantly improved with calcium-glucosamine sulfate and SE-PVE ( $p < 0.05$ ). Mankin score for joint histology improved with all treatments compared to OP+OA control ( $p < 0.05$ ). In conclusion, SE-PVE with less VE content could achieve similar or better bone and joint protective effects compared to UN-PVE. Therefore, SE-PVE could be a more effective preventive agent for OP and OA in estrogen deficiency.

**Keywords:** Bone; joint; postmenopause; skeleton; tocotrienol



# Effect of annatto tocotrienol on experimental periodontitis in N<sup>G</sup>-nitro-L-arginine methyl ester (L-NAME)-induced hypertensive rats

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DOI <https://doi.org/10.28916/lsm.7.1.2023.132>

## Abstract

Periodontitis has been linked to blood pressure elevation in hypertensive patients. Both periodontitis and hypertension are highly prevalent among Malaysian adults and management of these diseases is costly. Recent studies have suggested that beneficial activity of annatto tocotrienol in preventing and treating diseases. This research aimed to (i) determine the role of hypertension in exacerbating periodontitis, and (ii) investigate the protective effect of annatto tocotrienol on these diseases. Adult male Wistar rats were randomly divided into seven groups: i) sham; ii) L-NAME; iii) L-NAME + annatto tocotrienol (60 mg/kg/day, oral); iv) periodontitis; v) periodontitis + annatto tocotrienol; vi) L-NAME + periodontitis; vii) L-NAME + periodontitis + annatto tocotrienol. L-NAME (40 mg/kg) was administered intraperitoneally for 14 days to induce hypertension in the rats. An orthodontic wire was ligated on the rats' left maxillary second molar to induce periodontitis. The rats were then treated with annatto tocotrienol for 28 days. The blood pressure was measured using the tail-cuff method. After 28 days, the maxilla was extracted to determine alveolar bone loss and percentage of bone remaining (%) using micro-computed tomography. There was a significant increase in blood pressure in group VI compared to group IV ( $p < 0.05$ ). Annatto tocotrienol treatment was found to reduce blood pressure in rats with hypertension and periodontitis (group VII) compared to the untreated group (VI) ( $p < 0.05$ ). It was noted that alveolar bone loss was more severe in group VI compared to group IV ( $p < 0.001$ ). Treatment with annatto tocotrienol reduced periodontitis-induced alveolar bone loss in hypertensive rats ( $p < 0.01$ ). In conclusion, the results suggest the involvement of hypertension in aggravating periodontitis. Additionally, annatto tocotrienol shows protective effects against both periodontitis and hypertension. Hence, further studies should be performed to investigate the potential mechanisms underlying the beneficial effects of annatto tocotrienol.

**Keywords:** *Annatto tocotrienol; hypertension; periodontitis; computed tomography; ligation*

# Effect of *Bouea macrophylla* yoghurt in DMH-induced colorectal cancer rat with high fat diet

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DOI <https://doi.org/10.28916/lsm.7.1.2023.132>

## Abstract

Colorectal cancer (CRC) is the third most prognoses cancer globally with high mortality and morbidity rate. Obesity is found to be one of the main factors behind CRC development. Recent discovery proves that *Bouea macrophylla* exert an anti-cancer activity as they rich in phytochemical compounds, including flavonoids, tannins, and many others. Probiotic consumption have been well known for their roles as anti-inflammatory, and anti-tumour properties. Thus, our study aimed to incorporated the ethanolic extracted *Bouea macrophylla* into yoghurt and examines the chemopreventive impact of *Bouea macrophylla* yoghurt (BMY) against a high-fat diet and 1,2-dimethylhydrazine-induced colon cancer in Sprague Dawley rats. Sprague Dawley rats were induced with 1,2-dimethylhydrazine (40 mg/kg, i.p. once a week for 10 weeks) and a high-fat diet (HFD) for 20 weeks to induce colorectal cancer. BMY was administered at 5 mg/kg, 50 mg/kg, and 250 mg/kg for 20 weeks. At the end of the experiment, blood serum and organs were collected. Our finding shows that, rats supplemented with 250 mg/kg of BMY had reduced number of aberrant crypt foci (ACF) as compared to DMH/HFD rats. Level of serum insulin and leptin also decrease in rats with 250 mg/kg of BMY as compared to DMH/HFD rats. Low level of inflammatory cytokines; TNF- $\alpha$ , IL 6, CXCL-10 and MCP-1 also detected in 250 mg/kg of BMY rats as compared to DMH/HFD rats. Expression of anti-apoptotic BCL-2 protein also reduced in 250 mg/kg of BMY as compared to DMH/HFD rats. These finding suggest that, our new formulated BMY possess anti-obesity properties as well as providing chemopreventive protection against colorectal cancer development by reducing inflammation.

**Keywords:** *Bouea macrophylla*; colorectal cancer; high fat diet; gut microbiota; crypt foci

# The impact of physical exercise on leptin-induced adverse effects on sperm parameters in Sprague-Dawley rats

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**DOI** <https://doi.org/10.28916/lsm.7.1.2023.132>

## Abstract

To investigate the effect of a 42-day treadmill running exercise regimen on leptin-induced adverse effects on sperm and testicular parameters in Sprague-Dawley (SD) rats. Twelve weeks old male SD rats were randomized into two non-exercised groups; control (C) and leptin-treated (CL), and two exercised groups; leptin-treated (LE) and control (CE) with eight rats per group. Rats in the control groups were given 0.1ml of 0.9% saline, while leptin-treated rats were given 60µg/kg body weight of leptin via intraperitoneal injections daily for 42 days. Rats in Groups LE and CE were exercised four times per week for a period of 42 days. The exercise regimen consisted of continuous running for 30 minutes on a treadmill at a speed of 0.5m/s with a 5° incline. On day 43, the rats were euthanized and total sperm count, fraction of sperm with abnormal morphology, weights of testes and epididymides were recorded. Statistical analysis was performed using ANOVA with post-hoc analysis. Data are presented as mean ± SEM. Rats in the CL group had significantly lower total sperm count and higher fraction of sperm with abnormal morphology when compared to those in groups C, LE and CE. Total sperm count was significantly higher, and the fraction of sperm with abnormal morphology was significantly lower in LE when compared to those in CL. In addition, sperm count and sperm morphology in rats in the CE group were significantly better than those in group C. No significant differences were observed in body weight and food and water intake between all four groups. The weights of the testes and epididymides were also not different between the four groups. Regular physical exercise for 42 days not only prevents the adverse effects of leptin on sperm count and sperm morphology but also improves these parameters when compared to those in normal non-exercised Sprague-Dawley rats, further confirming the importance of regular physical exercise in male reproductive health.

**Keywords:** *Treadmill exercise; sperm count; sperm morphology; male reproductive health*

# Optimization of nanostructured lipid carrier for astaxanthin loaded

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DOI <https://doi.org/10.28916/lsm.7.1.2023.132>

## Abstract

Astaxanthin is a carotenoid belongs to the class of xanthophyll that can be found in *H. pluvialis* microalgae. This compound possesses various therapeutic properties that include potent antioxidant and anti-diabetic. Despite its excellent pharmacological activity, this highly lipid soluble carotenoid has poor oral bioavailability which hindered its clinical applications. For this reason, nanostructured lipid carrier (NLC) was design and developed to enhance the oral bioavailability of astaxanthin through hot homogenization method. In this study, response surface methodology (RSM) was employed to optimize the composition of lipid phase (palm oil and cocoa butter) and surfactant, Tween 80 to ensure small particle size with uniform shape and optimum surface charge is produced. The optimum composition of lipids and surfactant suggested by RSM was prepared accordingly and validated by using a student t-test between the theoretical prediction and the actual experimental values. The analyses showed that the optimum composition was found essential to produce NLC with size, zeta potential and polydispersity of 250 nm, -30 mV and 0.35 respectively. Data showed no significant difference between the predicted and experimental values for all three responses, indicating there were good agreement and response surface models were verified. Thus, this study exhibited the feasibility of NLCs as a good candidate for oral delivery of astaxanthin and therefore represents a new promising pharmacotherapeutic concept of astaxanthin.

**Keywords:** Astaxanthin; Optimization; Nanostructured Lipid Carrier (NLC); Response Surface Methodology (RSM)

# High-dose of vitamin C induced apoptosis on estrogen-dependent breast cancer cell spheroids

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DOI <https://doi.org/10.28916/lsm.7.1.2023.132>

## Abstract

Breast cancer is the leading malignant disease in women, with approximately 2,261,419 (11.7%) reported cases and 684,996 (6.9%) new deaths. The tumor microenvironment complex exhibits molecular and histological variations, which are associated with diverse treatment responses and clinical outcomes, posing significant risks for affected women. Therefore, it is imperative to discover a viable treatment for this lethal ailment. This study seeks to investigate the apoptotic effects of vitamin C on MCF-7 breast cancer tumor spheroids. MCF-7 cells were cultured as a monolayer until reaching 70% confluency. An agarose-coated 96-well plate was used to create a multi-cellular tumor spheroid. The spheroids were inspected using an inverted microscope after three days to evaluate their development and assure uniformity. A 200 mM stock solution of vitamin C was prepared in ddH<sub>2</sub>O. The stock solution was diluted to treat the spheroids for 72 hours at 1, 5, 10, 15, and 20 mM. CellTiter-Glo® 3D Cell Viability Assay (Promega, USA) was used to measure vitamin C's cytotoxicity. The annexin V-FITC/PI Apoptosis Detection Kit (BD, Franklin Lakes, NJ, USA) was used to examine vitamin C's apoptotic impact, and all experiments were tripled. The dose response curve and microscopic analysis indicated that a 20 mM dose of vitamin C exhibited greater cytotoxicity towards the spheroids compared to other doses. To verify the apoptotic nature of the observed cytotoxicity, flow cytometry analysis was performed using annexin V-FITC. The results demonstrated that vitamin C treatment induced apoptosis, with the 20 mM concentration exhibiting a higher efficacy compared to other concentrations. Vitamin C shows promise as an anti-cancer treatment option for breast cancer, particularly in its ability to induce apoptosis. Further investigation is warranted to explore its potential in this regard. Vitamin C's abundance, low toxicity, and cost-effectiveness make it a promising cancer therapy.

**Keywords:** *Breast cancer; vitamin C; apoptosis; anti-cancer*

# Unleashing the power of *Elateriospermum tapos* yoghurt: Exploring network pharmacology and molecular docking to combat maternal obesity

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DOI <https://doi.org/10.28916/lsm.7.1.2023.132>

## Abstract

Maternal obesity, characterized by an elevated body mass index (BMI) during pregnancy, is known to have adverse effects on the offspring. However, a recent study suggests that *Elateriospermum tapos* (*E. tapos*) yoghurt may hold potential in mitigating excessive weight retention post-pregnancy. Thus, this study aims to employ network pharmacology to explore the pharmacological effects of the bioactive compounds present in *E. tapos* yoghurt against maternal obesity. Initially, a screening process is conducted to identify the bioactive compounds in *E. tapos* yoghurt, followed by the prediction of potential gene targets for these compounds using Swiss Target Prediction and SuperPred databases. Maternal obesity-associated genes are sourced from the OMIM, DisGeNet, and GeneCards databases. The interaction between the identified compounds and maternal obesity genes is established through protein-protein interaction analysis, gene ontology examination, and KEGG pathway analysis. To validate the results, molecular docking studies are conducted using AutoDock Tools software. Among these targets, 240 are shared with maternal obesity-related genes. Further analysis demonstrates the favorable affinity of these active compounds with key targets, linking them to biological processes involving protein phosphorylation, inflammation, as well as pathways related to lipid metabolism, atherosclerosis, and other signaling pathways. In conclusion, this study provides valuable insights into the potential pharmacological effects of the bioactive compounds found in *E. tapos* yoghurt against maternal obesity. These findings open avenues for further exploration and potential therapeutic interventions targeting maternal obesity.

**Keywords:** *Elateriospermum tapos* yoghurt; maternal programming; obesity; network pharmacology; molecular docking

# ABO blood group association on Framingham risk score in cardiovascular disease

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DOI <https://doi.org/10.28916/lsm.7.1.2023.132>

## Abstract

Throughout the entire world, cardiovascular diseases (CVDs) are the main cause of death and it has become a global burden. It has been demonstrated that the ABO blood group system is linked to pathophysiology and particularly is CVDs. However, limited research has been conducted between ABO group system and Framingham risk score (FRS) as an assessment tool. Therefore, this study is aimed to determine the association of ABO blood group and FRS. A cross-sectional study was carried out in among 333 patients without known cardiovascular disease who aged from 30 to 75 years old. Demographic data, clinical data and smoking status were captured from patient records and by answering Performa given to patients. Blood groups were determined by antigen-antibody agglutination and FRS was calculated by using designated FRS calculation which categorized into low, moderate and high-risk group. Descriptively the median age was 55 (44-63) years and 61.6% were female. O blood group is dominant with 39.9% compared to non-O blood group as blood group A, B and AB with 20.7%, 30.9% and 8.4% respectively. Non-O blood group; A and AB represented the highest percentage in the high risk group of FRS on their own blood group versus O blood group with the increment of 0.9% and 1.8% from low risk to high risk of blood group A and AB respectively, while O blood group represented decrement of 3.6%. These data presented that A and AB blood group having higher risk in getting CVD as compared to O blood group. Thus, it indicated that there is association of ABO on FRS generally.

**Keywords:** *ABO blood group; Framingham risk score; cardiovascular diseases*

# Hypertension pre-assessment monitoring system

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**DOI** <https://doi.org/10.28916/lsm.7.1.2023.132>

## Abstract

Multiple strategies or health care measures have been developed and implemented to combat chronic disease management especially with hypertension management. Hypertension significantly increases the risk of heart, brain and kidney diseases, and is one of the top causes of death and disease throughout the world. The number of adults aged 30–79 years with hypertension has increased from 650 million to 1.28 billion in the last thirty years, according to the first comprehensive global analysis of trends in hypertension prevalence, detection, treatment and control, led by Imperial College London and WHO. Although there are many evidence-based guidelines and effective treatments for this disease, many patients with hypertension still have uncontrolled symptoms. The successful control of chronic diseases mainly depends on how well patients manage their disease conditions with the aid of healthcare providers. Recent research found that the key components to improve hypertension outcomes with the help of mobile devices are: information and self-care education, self-monitoring, feedback from devices, alerts and messages to patients, and daily use availability. The development of the Hypertension Pre-Assessment Monitoring System uses a waterfall model that consists of five phases, namely the planning phase, analysis phase, design phase, implementation phase and testing phase. The development of the Hypertension Early Assessment System can record the patient's hypertension assessment more easily and efficiently. This project is a narration of a broad overview regarding the concept to assess the user experience of a health application model in the management of adult Hypertension. The prototype will be used as a medical health application tool to assess the effectiveness of self-empowerment for patients with underlying hypertension. The effectiveness of the medical health application will be assessed through a clinical study. The study will lead to a better quality of management in managing adult hypertension patients.

**Keywords:** *Hypertension assessment; healthy living; mobile health device; hypertension management; self-care education.*



# Fucus vesiculosus as potential anti-hyperlipidemic agent: In-vitro and in-vivo findings

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DOI <https://doi.org/10.28916/lsm.7.1.2023.132>

## Abstract

*Fucus vesiculosus*, best known as bladderwrack oftentimes used in alternative medicine and homoeopathy, in treating obesity. The antioxidants activities in plants have been suggested as one of the working mechanisms against treating obesity. Hence, the antioxidative properties of *Fucus vesiculosus* was examined and established in this study. The present study explored the anti-oxidative and antihyperlipidemic potential methanolic *Fucus vesiculosus* extract in high-fat diet (HFD)-fed Sprague Dawley Rats. The antioxidant potential of the *Fucus* extract with different extractants and concentrations was determined using Total Phenolic Content (TPC) and DPPH radical-scavenging activity. In prior study, the rats were divided into 6 groups each consisting 6 rats per group. 25g of high fat diet was induced to 5 groups. The rats were acclimatized for a week prior to experiment. Plant-based and pharmacological treatment were then given for 5 weeks treatment period based on respective groups, *Fucus vesiculosus* extract at strength of 250mg/kg and 500mg/kg, *Fucus vesiculosus* mother tincture and Phentermine. Parameters that were measured throughout the study encompassed food intake, body weight, BMI, relative organ weight and average adipose fats weight. During this study continuation, all samples from previous study were subjected for biochemical evaluations, liver histopathological analysis and antioxidant study. TPC isolated from crude extract by different solvent extractions exhibited prominent antioxidant activity. Results of the present study indicated good correlation between TPC and DPPH radical scavenging activity against increasing concentration and indicated that phenolic compounds are powerful scavengers of free radical. In essence, the 70% methanolic extract exhibited superior total phenolic content and antioxidant properties in comparison to aqueous and 70% ethanolic extract ( $p < 0.05$ ). The anti-hyperlipidemic effect of *Fucus vesiculosus* methanolic extract was demonstrated by the significant reduction in lipid parameters of Total Cholesterol, Low Density Lipoprotein-c, Atherogenic Index and subsequent increase of High-Density Lipoprotein-c in rats groups receiving *Fucus vesiculosus* treatment despite being statistically insignificant. However, there are no significant differences seen in Triglyceride level. Histopathological examination reveals that animals that were treated with *Fucus* extract did not show any aggravation of histological changes and the seaweed were able to prevent and reversed obesity metabolic syndrome progression to non-alcoholic steatohepatitis (NASH) in comparison to high fat diet group ( $p < 0.05$ ). The results of the study implied *Fucus vesiculosus* methanolic extract at 250 mg/kg is the dose which bests exhibit weight reduction effect with no severe biochemical and histopathological changes in all experimental animals. This finding supported the hypothesis that *Fucus vesiculosus* supplementation successfully lowered elevated serum lipid and had potential in the prevention of obesity.

**Keywords:** *Fucus vesiculosus*, high-density lipoprotein, anti-hyperlipidemia

# Paederia foetida twigs alleviates diabetic cardiomyopathy: Antioxidative modulation through esRAGE-AGE interaction

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DOI <https://doi.org/10.28916/lsm.7.1.2023.132>

## Abstract

Diabetes mellitus, a state of hyperglycemia, triggers production of oxidative stress and advanced glycation end-products (AGE), leading to features of diabetic cardiomyopathy such as cardiac hypertrophy and fibrosis, independent of known cardiovascular risk factors. esRAGE scavenges excess AGE and reduced interaction of AGE and oxidative stress. Paederia foetida (PF) is an edible plant that has antioxidant and antidiabetic activities in an in vitro evaluation. This study aims to determine the histopathological and biochemical outcomes of PF supplementation on rat heart and its mechanism of action. The diabetic model was established in Sprague Dawley rats by intraperitoneal injection of streptozotocin (STZ, 40 mg/kg). After 4 weeks of treatment, the rats were sacrificed, and heart was harvested. Left ventricle was processed, stained using Haematoxylin & Eosin and Masson Trichrome, visualised and quantified for cardiomyocyte size and collagen volume fraction (CVF). Right ventricle was homogenised for quantification of pro-oxidative parameters (AGE and protein carbonyl content) and antioxidative parameters (esRAGE, SOD and CAT) using commercially available kit. All data was analyzed using one-way ANOVA with post-hoc Bonferroni correction to identify differences between groups and reported as mean (standard deviation). The parameters quantified for groups are as follows: Cardiomyocyte size ( $\mu\text{m}^2$ ) for are 582(119), 856(193), 744(208), 598(216); Collagen volume fraction (CVF), % are 3.4(1.9), 12.8(2.0), 5.4(1.9) and 4.2(1.0); AGE level ( $\mu\text{g}/\text{mg}$ ) are 1.31(0.19), 1.44(0.26), 1.44(0.42) and 1.39(0.16); esRAGE level (ng/mg) are 0.75(0.32), 0.20(0.18), 0.53(0.26) and 0.66(0.33); PCO concentration ( $\mu\text{g}/\text{mg}$ ) are 0.56(0.08), 0.87(0.25), 0.95(0.24) and 0.76(0.22); GPx-1 level ( $\mu\text{g}/\text{mg}$ ) are 1.18(0.25), 0.68(0.24), 0.98(0.19) and 1.12(0.23); SOD activity (U/mg) are 2.4(0.4), 1.3(0.5), 2.4(0.7) and 2.3 (0.1); CAT activity (U/mg) are 0.072(0.004), 0.096(0.015), 0.087(0.015) and 0.085(0.021). Histologically, PF ameliorated cardiac hypertrophy and fibrosis. In biochemical parameters, PF reduces pro-oxidative parameters (PCO and AGE), improves antioxidative parameters (esRAGE, GPx-1, SOD, CAT). PF exerts cardioprotective effect on diabetic cardiomyopathy through antioxidative activity involving the modulation of AGE-RAGE signalling pathway.

**Keywords:** Paederia foetida; diabetic cardiomyopathy; esRAGE; AGE; antioxidant

# Anti-hyperlipidemic potential of a combination of *Zingiber officinale* Roscoe, *Allium sativum* L., *Citrus lemon* (L.) Osbeck, Honey and *Malus domestica* Borkh. cider vinegar

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DOI <https://doi.org/10.28916/lsm.7.1.2023.132>

## Abstract

Intervention of herbal combination is widely used to decrease the risk of metabolic disorders such as cardiovascular diseases, hyperlipidemia, diabetes, and obesity. Hyperlipidemia is known as an abnormal lipid metabolism presents in the bloodstream which associated with comorbidities and mortalities that grossly rising worldwide. The study aims to investigate the anti-hyperlipidemia activities of a combination of ZACAH mixture (*Zingiber officinale* Roscoe (ginger), *Allium sativum* L. (garlic), *Citrus lemon* (L.) Osbeck, Honey, and *Malus domestica* Borkh. Cider Vinegar in hyperlipidemic rats. High-performance liquid chromatography (HPLC) was performed to identify the phytochemical component that presents in the ZACAH mixture. 36 Sprague dawley (SD) rats were divided into 6 groups. ZACAH mixture (1ml/kg, 3 ml/kg, 5 ml/kg) was administered along with a high cholesterol diet (HCD) via oral gavage, daily for 18 weeks. Simvastatin 10 mg/kg was used as a standard drug. At end of week 18, the rats were sacrificed, and blood and organs were collected for further experiments. The blood collection was performed for lipid profile (TC, TG, LDL), blood toxicity (Creatinine, AST, ALT), and enzymatic activity (HMG-CoA reductase, LCAT, ACAT2). Besides, liver, kidney and adipose tissue were performed for histological examination by using hematoxylin & eosin (H&E) stain. The phytochemical component found in the ZACAH mixture is hesperidin. Bodyweight, total cholesterol (TC), triglyceride (TG), low-density lipoprotein (LDL) reduced and an increase in high density lipoprotein (HDL) was observed in ZACAH mixture treated groups compared to the positive control (PC). ZACAH mixture treated groups reduced HMG-CoA reductase and ACAT2 activity led to a reduction of TC, TG, LDL and an increase in HDL. Histological examinations revealed that lipid accumulation was reduced in the liver tissue and the size of adipocytes was suppressed in the ZACAH mixture treated group as compared to the PC group. The findings demonstrate that the ZACAH mixture at 5ml/kg BW significantly ( $p < 0.05$ ) has a strong hyperlipidemia activity that can be an alternative approach to combat hyperlipidemia treatment.

**Keywords:** ZACAH mixture; hyperlipidemia; high cholesterol diet

# Ability of polyphenol-rich marigold petal tea to reduce oxidative stress and plasma cholesterol level: An *in vivo* study on rats fed with a high-fat-sugar diet

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DOI <https://doi.org/10.28916/lsm.7.1.2023.132>

## Abstract

The study was aimed to appraise the application of polyphenol-rich marigold petal tea (MPT) against obesity, oxidative stress and cholesterol contents in rat model. MPT, prepared using the conventional method in warm water, was subjected to reverse-phase high performance liquid chromatography analysis for determination of polyphenols. Doses of 250 and 500 mg/kg body weight of marigold petal tea (MPT-250 and MPT-500) were selected to investigate the anti-obesity potential of MPT using high-fat-sugar-diet (HFSD) -induced obese rat model. Major (> 10 mg/100 mL of tea) phenolic acid and flavonoids detected in MPT were catechin, rutin, salicylic acid, gallic acid, sinapic acid, chlorogenic acid, cinnamic acid and ellagic acid. 5.53 mg/g total phenolic contents (TPC) and 7.73 mg/g total flavonoid contents (TFC) were determined from the MPT. Furthermore, MPT exhibited 57.2% DPPH radical scavenging activity. *In vivo* study showed that MPT (500 mg/kg body weight) significantly reduced the body weight increase (51.24%) and BMI (0.49) in rats as compared to HFDC group. Significant decreases in the levels of serum total cholesterol (TC), triglyceride (TG), low density lipoprotein (LDL) and very low-density lipoprotein (VLDL) were observed in the treatment groups in comparison to the HFSD group. Furthermore, MPT prevented the alterations in malondialdehyde (MDA), superoxide dismutase (SOD) and reduced glutathione (GSH) levels of experimental groups thus showed the potential against oxidative stress. The MPT-500 group showed significant decrease in the elevated kidney and liver weights and atherogenic index in comparison to the HFDC group. It is evident from the results that a high dose of MPT exhibited protective effects against obesity, comparable to that of conventional drug orlistat.

**Keywords:** *Anti-obesity; oxidative stress; high density lipoprotein; body mass index; kidney index; liver index; malondialdehyde; DPPH radical scavenging activity; rutin*

# Modulating effect of *Abelmoschus esculentus* extracts on adenosine receptors and cAMP expression

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DOI <https://doi.org/10.28916/lsm.7.1.2023.132>

## Abstract

*Abelmoschus esculentus* (*A. esculentus*), a vegetable crop widely known as okra, demonstrates medicinal properties, such as antioxidant and anti-inflammatory effects, in inflammatory-induced models. Considerably, in exploring the treatment for inflammatory-related diseases, adenosine receptors (AR) have emerged as promising therapeutic targets by modulating cyclic adenosine monophosphate (cAMP) expression. Therefore, this study aimed to evaluate the anti-inflammatory effects of *A. esculentus* extracts by its binding affinity to adenosine 2a (AR2a) and 3 receptors (AR3) and its effect on cAMP expression *in vitro*. The inflammatory-induced model was designed by administering 10 ng/mL of tumour necrosis factor-alpha (TNF- $\alpha$ ) into a synovial sarcoma cell line (SW982). The cells were treated with three different *A. esculentus* extracts that were extracted sequentially, with a range of concentrations of 100, 200 and 400  $\mu$ g/mL for 48 hours. Expression of AR2a, AR3 and cAMP was measured using commercialised kits. Findings showed that *A. esculentus* extracts upregulated the expressions of AR2a, AR3 and cAMP, proportionally with a concentration, significantly to the untreated induced cells and comparable to methotrexate, a positive control. The findings of this study were consistent with previous studies where AR2a interacts with members of the Gs family of G proteins, upregulating intracellular cAMP expression. However, current findings suggest that AR3 engages with the Gi/o family of G proteins and reduces the intracellular cAMP concentration. Despite AR3 reduces cAMP levels, it exhibits anti-inflammatory effects by modulating multiple physiological processes including inhibition of pro-inflammatory cytokines secretion, modulating immune cell migration, and attenuating nuclear factor kappa light chain enhancer of activated B cells (NF- $\kappa$ B) signalling pathway. Hence, *A. esculentus* offers promising anti-inflammatory effects through the binding of AR2a and AR3, proposed to be modulating the cAMP expression and another physiological signalling.

**Keywords:** *Abelmoschus esculentus*; anti-inflammatory; adenosine receptor; cAMP

# Natural products modulating nitric oxide signalling for the treatment of hypertension: A review

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**DOI** <https://doi.org/10.28916/lsm.7.1.2023.132>

## Abstract

The prevalence of hypertension is high worldwide, and the management of hypertension is still primarily dependent on synthetic drugs, which are costly and associated with various side-effects. These are hindering the availability and compliance to hypertensive treatment in some populations. The control of hypertension still remains a challenge. The search for an ideal antihypertensive drug, therefore, continues. In this regard, some plant products have been shown to have blood pressure lowering properties. Although the mode of action/s of many of these remains to be established, there are some that have been shown to modulate NO signalling and might be useful in the treatment of hypertension. This review summarizes several natural herbs that have been shown to possess antihypertensive properties involving modulation of nitric oxide (NO) signalling and have potential of being developed as alternative antihypertensive agents. It summarizes information on some of these herbs, their sources and mechanisms of action. It is of interest to note that several of these seem to have antihypertensive actions that involve multiple mechanisms including modulating the NO signalling pathway. A number of these seem to show great potential as either substitutes or as complements to the current antihypertensive agents.

**Keywords:** *Natural products; hypertension; antihypertensive; nitric oxide signalling*

# Does BMI influence oxygen saturation among the users of facemask and personal protective devices in six-minute walk test?

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DOI <https://doi.org/10.28916/lsm.7.1.2023.132>

## Abstract

Studies showed that obesity is associated with morbidity and mortality of many diseases by causing hypoxaemia. Apart from cardiopulmonary morbidities, obesity is known to inversely affect oxygen saturation (SpO<sub>2</sub>) levels and ventilation impairment with a ventilation-perfusion mismatch. A 6-Minute Walk Test (6-MWT) is a validated submaximal exercise method to measure physical exertion and has been widely used to study the changes in physiological parameters. This study aimed to measure the effect of Body Mass Index (BMI) on oxygen saturation SpO<sub>2</sub> when performing a 6-MWT among healthy adults wearing a facemask or Personal Protection Equipment (PPE). A study was conducted with 99 participants aged between 18 to 50 years in Ipoh, Malaysia. Participants were randomly separated into three groups of 33 each, one control group, a facemask group (used unvalved 3M9501+KN95(China) AS/NZS 1716P2 with white ear loop), and a full body PPE group (used head cap, shoe cover, body drape (Executive standard GB19082-2009 Hean Pharmaceutical) with face shield and latex-unsterilized hand glove). The SpO<sub>2</sub> was measured using fingertip pulse oximeter (C101A2; iMDK,China MDA approved) before and after 6-MWT which was performed according to the recommendations of American Thoracic Society. Analysis was done using ANOVA and Friedman test for comparison of pre- and post- tests. The mean BMI of all the participants was 22.79±4.71; 11% had BMI less than 18 kg/m<sup>2</sup>; 17% were overweight, and 9% were obese. The pre-test and post-test SpO<sub>2</sub> were 98.24±0.61Vs97.85±1.12, 98.30±0.84 vs 97.97±0.88, 98.36±0.65 vs 98.15±0.67 for control, facemask, and PPE groups respectively. The study found that SpO<sub>2</sub> changes in pre-test and post-test were significantly different (p<0.01) only in facemask group, but no significant differences found between other groups and had no association with BMI. This study resulted in findings that contrast the existing evidence that BMI influences oxygen saturation when using facemask or PPE.

**Keywords:** Oxygen saturation; 6-MWT; BMI, facemask; PPE

# Effect of rutin on body weight of streptozotocin-induced diabetic rats

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DOI <https://doi.org/10.28916/lsm.7.1.2023.132>

## Abstract

Published studies show that rutin has antidiabetic activity. To further understand the effect of rutin, this study was conducted to determine its effect on the body weight of streptozotocin-induced diabetic rats. The control and diabetic groups were given a vehicle. Diabetic rats were treated orally with rutin (100 mg/kg) and metformin (500 mg/kg) for 28 days. Body weight and fasting blood glucose were recorded; pancreas was dissected, processed, and stained for H&E. Data were analysed by ANOVA where  $p < 0.01$  was considered significant. Significant body weight loss and high blood glucose levels were observed in the diabetic group. Pancreatic islets destruction by streptozotocin may promote gluconeogenesis, resulting in body weight reduction. Similarly, body weight loss was observed in the metformin group but was not significant. Metformin treatment improved pancreatic islet recovery and reduced blood glucose levels in this group, possibly by improving body weight loss and suppression of gluconeogenesis respectively. Though metformin has a beneficial effect on obesity, its treatment could not help to improve the body weight of streptozotocin-induced diabetic rats. Despite showing a positive effect on the morphology of pancreatic islet repair, the rutin group showed significant reduction in body weight with high glucose levels. Rutin has been shown to prevent body weight loss in other diabetic studies; however, our study found no similarity with them. The duration of treatment in the study might be insufficient to demonstrate extensive morphological repair of the pancreatic islets cells. Extending the treatment duration with rutin could improve pancreatic repair and glucose regulation thus improving the body weight. It is unclear whether the excessive weight loss in rutin group was caused solely by high glucose levels or was exacerbated by rutin's anti-obesity activity. In conclusion, rutin did not improve body weight of the streptozotocin-induced diabetic rats with 28 days of treatment.

**Keywords:** *Diabetes mellitus; streptozotocin; body weight; rutin; metformin*



# Exosome encapsulated roselle extract modulates cardiac remodelling in hypercholesterolemia associated myocardial injury rats

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DOI <https://doi.org/10.28916/lsm.7.1.2023.132>

## Abstract

Roselle (*Hibiscus sabdariffa* Linn) is well-known for its cardioprotective potential contributed by its anthocyanin content, although the therapeutic application might be impeded by its low bioavailability shortcoming. Conversely, exosomes have attracted much attention as cardiac targeting therapy due to their excellent behaviour in encapsulating drugs, especially in natural-based products. However, there are still lacking study that investigates exosome-based approach in enhancing the roselle cardioprotective properties. Therefore, this novel study aimed to study the cardioprotective potential of exosome-encapsulated roselle extract (Aehs-Exo) on cardiac remodelling in hypercholesterolemia (HC) associated myocardial injury (MI) rats. A total of 18 Sprague-Dawley rats (250-300g) were randomly allotted into three groups (Control; HC-MI; Aehs-Exo). Rats were either fed with a self-made high cholesterol diet (HCD) (4% cholesterol) or standard chow for six weeks and followed up by another four weeks of Aehs-Exo (100mg/kg, p.o) or vehicle as treatment with diet maintained accordingly. At the end of the 10<sup>th</sup> week, rats were subjected to MI with isoprenaline hydrochloride (85mg/kg, s.c) for two consecutive days. As a result, marked elevation of body-mass index (BMI), total cholesterol (TC), HDL, LDL, TC/HDL ratio and cardiac troponin-T collectively suggest successful HC-MI induction. Histological observation of cardiac sections revealed marked deposition of fat cells, prominent perivascular fibrosis and myocardial necrosis accompanied by infiltrations of inflammatory cells. Interestingly, these histological changes were ablated by Aehs-Exo. Consistently, Aehs-Exo treatment can also modulate oxidative stress, as evident by significant downregulation of malondialdehyde level and marked upregulation of total-superoxide dismutase and reduced glutathione level seen in HC-MI rats. Despite that, Aehs-Exo supplementation could only significantly restore HDL and TC/HDL ratio. In conclusion, this study provides novel information on the cardioprotective potential of exosome-encapsulated roselle treatment which potentially helps treat HC-associated MI in clinical settings.

**Keywords:** Myocardial injury; exosome; roselle fibrosis; hypercholesterolemia

# The devastating effects of REM sleep deprivation on the endothelium in a rat model

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**DOI** <https://doi.org/10.28916/lsm.7.1.2023.132>

## Abstract

Rapid eye movement (REM) sleep deprivation is associated with oxidative stress, which leads to cardiovascular disease. This study aimed to investigate the effects of REM sleep deprivation on endothelial function and morphology in a rat model of REM sleep deprivation. Twenty-eight male Sprague-Dawley (SD) rats were randomly divided into four groups (n=7): free-moving control rats (FMC), 72-h REM sleep-deprived rats (REMs<sub>d</sub>), tank control rats (TC) and sleep recovery rats (SR). Rats were deprived of REM sleep using the inverted flowerpot technique. Blood pressure (SBP) was monitored, and the descending thoracic aorta was isolated to evaluate oxidative stress markers, *in vitro* functional study, and histomorphological examination. REMs<sub>d</sub> rats showed increased SBP, increased oxidative stress markers, induced endothelial dysfunction and endothelial cell damage. The levels of superoxide dismutase (SOD), total antioxidant capacity (TAC), catalase (CAT), and glutathione (GSH) were significantly decreased. At the same time, malondialdehyde (MDA) was significantly increased in the REMs<sub>d</sub> group compared to other groups. An altered vascular function indicated by impaired vasorelaxation and hypercontractility was demonstrated in REMs<sub>d</sub> rats. Furthermore, the endothelium histomorphology in REMs<sub>d</sub> group revealed features of endothelial damage. This study suggested that REM sleep deprivation is associated with oxidative stress responsible for developing endothelial dysfunction and damage. The adverse effects following REM sleep deprivation were reduced by sleep recovery.

**Keywords:** REM Sleep deprivation; endothelial dysfunction; oxidative stress; endothelial damage; rat model

# **Trans-resveratrol attenuation of TGF-B–CTGF signalling leading to reduced fibronectin deposition in dexamethasone-treated human trabecular meshwork cells**

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DOI <https://doi.org/10.28916/lsm.7.1.2023.132>

## **Abstract**

Increased deposition of extracellular matrix (ECM) proteins such as fibronectin (FN) in trabecular meshwork leads to elevated intraocular pressure (IOP) leading to glaucoma. TGF-B pathway via connective tissue growth factor (CTGF) is known to induce FN expression. Trans-resveratrol (TR) was previously shown to reduce the IOP in steroid-induced ocular hypertension. This study investigates whether the effect of TR is mediated via the reduction of FN deposition induced by dexamethasone treatment on human trabecular meshwork cells (HTMCs) if it is mediated via TGF-B-CTGF pathway. Primary HTMCs were incubated with 12.5  $\mu$ M of TR with or without 100 nM of dexamethasone. TGF-B1, TGF-B2, CTGF and FN gene and protein expressions were determined after 3-day using RTPCR and 7-day incubation using ELISA, respectively. The media of HTMCs treated with dexamethasone showed significantly higher TGF-B1, TGF-B2, CTGF and FN when compared to the control group ( $p < 0.05$ ). Co-treatment of HTMCs with dexamethasone and TR significantly reduced the genes and proteins expression of TGF-B1, TGF-B2, CTGF and FN when compared to dexamethasone-treated group ( $p < 0.05$ ). TGF-B including 1 and 2 is a profibrotic factor implicated in the pathogenesis of glaucoma that increases ECM deposition such as FN in the trabecular meshwork leading to increase aqueous humour outflow resistance that produce elevated IOP. The effects of TGF-B leading to increased FN is mediated by CTGF, a central modulator of tissue remodelling. Dexamethasone affects ECM homeostasis by interrupting the equilibrium between its synthesis and degradation. This effect by dexamethasone was associated with activation of upstream pathway the TGF-B and CTGF. TR has been reported to downregulate TGF-B expression, CTGF and various ECM components. Therefore, this study revealed that TR reduces the TGF-B-CTGF-FN pathway induced by dexamethasone could be the mechanism behind its IOP lowering effect. This study is supported by grant no. 600-RMC/GIP 5/3 (068/2022).

**Keywords:** CTGF; glaucoma; ocular hypertension; resveratrol; TGF-B

# Neuroprotective potential of *Polygonum minus* (daun kesum) extract against *in vitro* glutamate-induced toxicity

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DOI <https://doi.org/10.28916/lsm.7.1.2023.132>

## Abstract

Glutamate-induced neurotoxicity is caused by glutamate neurotransmitter dysregulation in the central nervous system and is associated with the pathogenesis of various neurodegenerative diseases. Oxidative stress presents as one of the pathological hallmarks of glutamate-induced toxicity that eventually triggers the cell death cascades that include mitochondrial dysfunction and apoptosis activation. *Polygonum minus* is a common herb and cooking ingredient found in Southeast Asia. It is reported to possess *in vitro* and *in vivo* antioxidant-associated neuroprotective properties. However, little is known about the neuroprotective potential of *P. minus* against glutamate-induced toxicity. This study aimed to evaluate the neuroprotective effect of *P. minus* essential oil (EO) in glutamate-treated HT22 mouse hippocampal cells. To assess its neuroprotective effect, co-treatment of *P. minus* EO (0.1 to 50 µg/mL) with glutamate (4 and 5 mM) for 24 hours was performed and cell viability was measured. Co-treatment of *P. minus* EO at 50 µg/mL with glutamate increased the viability of HT22 cells as compared to the control glutamate-treated cells. Mitochondrial function and apoptotic analyses were performed to understand the neuroprotective actions of *P. minus* extract using biochemical assays and Hoechst 33342 staining. Co-treatment of *P. minus* EO at 50 µg/mL with 4 mM glutamate reduced the intracellular reactive oxygen species (ROS) and mitochondrial membrane potential (MMP) levels in HT22 cells as compared to the control 4 mM glutamate-treated cells. *P. minus* EO at 50 µg/mL with glutamate (4 and 5 mM) reduced the activated caspases levels as compared to the control glutamate-treated cells. The percentage of apoptotic cells was also reduced as compared to the control 4 mM glutamate-treated cells. These results suggest that *P. minus* EO potentially exhibited antioxidative-associated neuroprotection against glutamate-induced apoptosis in HT22 cells. These findings warrant further studies to evaluate the precise mechanisms that confer the neuroprotective potential of *P. minus* extract.

**Keywords:** Glutamate, neurotoxicity, neurodegenerative diseases, *Polygonum minus*, neuroprotection

# Detecting the genetic link between BPA and obesity using Bioinformatics analysis

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**DOI** <https://doi.org/10.28916/lsm.7.1.2023.132>

## Abstract

Bisphenol A (BPA) is an endocrine-disrupting agent used in the production of polycarbonate plastics and epoxy resins. There is a strong correlation between BPA exposure and several chronic metabolic disorders, including obesity. However, the genetic link between BPA and obesity remains unclear. The current study aimed to use a toxicology network approach to investigate the possible effect of BPA in inducing obesity and reveal the underlying mechanism of action. BPA-targets genes were predicted using the Swiss Target and SuperPred databases while, obesity-associated genes were retrieved from the databases Online Mendelian Inheritance in Man (OMIM), Disease Gene Interaction (DisGeNet), and Gene Cards database. The common genes between BPA and obesity were sorted using interactiVENN. STRING database and Cytoscape software were used to construct protein-protein interaction (PPI) and compound-target pathway networks, respectively. The DAVID bioinformatics tool was utilized to conduct gene ontology (GO) and KEGG-pathway analysis. A total of 37 genes were found to be linked between BPA and obesity with PPI. The results of GO analysis revealed that biological processes associated between obesity and BPA include response to a xenobiotic stimulus. The KEGG-pathway enrichment analysis result showed that the serotonergic synapse pathway is closely involved in the development of obesity. As a conclusion, our research provides a valid theoretical foundation for the potential mechanism of BPA-inducing obesity. However, to validate these computational findings, additional *in vitro* and *in vivo* experimental validation is required.

**Keywords:** BPA; obesity; bioinformatics; KEGG pathway

# The effects of 1-methylpropyl 2-imidazolyl disulfide (PX-12) on the cytotoxicity and 2D migration of hypoxia-induced MDA-MB-231 breast cancer cells

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DOI <https://doi.org/10.28916/lsm.7.1.2023.132>

## Abstract

Breast cancer has become one of the most common diagnosed cancer and the fifth leading cause of cancer mortality. Studies have shown that exposure of breast cancer cells to hypoxia, or a low oxygen environment, enhances the aggressiveness of their metastasis and invasion phenotypes. 1-methylpropyl 2-imidazolyl disulfide, also known as PX-12 is a thioredoxin-1 (Trx-1) inhibitor that has been demonstrated to show potential effects in antitumor properties targeting the thioredoxin system which lead to the suppression of the growth of cancer cells. The anticancer activity of PX-12 against osteosarcoma, colorectal, hepatocellular carcinoma and lung cancer in-vitro have been reported. However, the understanding and effects of PX-12 to reduce the breast cancer migration and metastasis, particularly in hypoxia-induced environments remains poor. This study aims to observe the cytotoxic effect of PX-12 and migration of hypoxia-induced MDA-MB-231 breast cancer cells. PX-12 is hypothesized to reduce the cytotoxicity and migration of hypoxia-induced MDA-MB-231 cells. MDA-MB-231 breast cancer cell lines were seeded on 96-well plate prior to 3-(4,5-dimethylthiazol-2-yl)-2, 5-diphenyl-2H-tetrazolium bromide (MTT) to observe the cytotoxicity effects of PX-12. Scratch migration assay was performed to determine the migratory capacity of MDA-MB-231 cells. Dimethylallyl glycine (DMOG), a hypoxia-mimetic, was used to induce hypoxia conditions. Based on the MTT assays, the IC<sub>20</sub> and IC<sub>50</sub> values for MDA-MB-231 cells treated with PX-12 at 24 hours in normoxia condition were ranging from 16 µM and 88 µM while the IC<sub>20</sub> and IC<sub>50</sub> values in hypoxia condition were ranging from 13 µM and 81µM, respectively. Scratch migration assay showed a trend of reduction in the percentage of cell migration upon treatment with PX-12 starting from the concentration of 8µM to 128 µM. PX-12 has shown to have the cytotoxic effect in MDA-MB-231 cells and reduced the migration of hypoxia-induced breast cancer cells.

**Keywords:** *breast cancer; metastasis; hypoxia; 1-methylpropyl 2-imidazolyl disulfide; PX-12; DMOG*

# ***Elateriospermum tapos* yoghurt: Breaking the cycle of obesity and cognitive deficit across generations**

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DOI <https://doi.org/10.28916/lsm.7.1.2023.132>

## **Abstract**

Maternal obesity has been linked to the inheritance of obesity and neurodevelopmental delays in offspring. However, recent discoveries have shown that certain flavonoids have the ability to modulate lipid metabolism, reduce fat absorption, and reverse memory decline. *Elateriospermum tapos* (*E. tapos*) a natural tropical fruit known for its high levels of flavonoid compounds, was the focus of this research, aimed at preventing the transgenerational inheritance of obesity and neurodevelopmental delays in the offspring of maternal obese dams through the supplementation of *E. tapos* yoghurt. In this experimental study, a total of 48 female Sprague Dawley (SD) rats were divided into 6 groups, each consisting of eight rats. Obesity was induced over a period of 16 weeks using a high-fat diet pellet. On the 17<sup>th</sup> week, the rats were allowed to mate, and pregnancy was confirmed through vaginal smear. The obese-induced group was further divided into negative and positive control groups, followed by three different concentrations (5, 50, and 500 mg/kg) of the treatment group. Changes in body weight and calorie intake were recorded weekly, and the place and object recognition test were conducted on postnatal day 21 on both the mothers and offspring. The results revealed a significant reduction ( $P < 0.05$ ) in weight, calorie intake, and adipose tissue mass in both the obese dams and their offspring in all treatment groups compared to the control group. Behavioral data demonstrated a significant increase ( $P < 0.05$ ) in exploration rate among offspring in the 500 mg/kg treated group compared to the control groups. In conclusion, *E. tapos* yoghurt, as a prebiotic supplement, exhibited lipid-lowering activity, modulated digestion, and ultimately improved declarative memory in the offspring through the action of its flavonoids.

**Keywords:** Obesity; transgenerational inheritance; *E. tapos* yoghurt; weight reduction; learning ability

# The link between obesity and COVID-19 and the role of leptin: A systematic review

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## Abstract

Obesity leads to elevated levels of leptin in the bloodstream. Obesity is recognized as a significant risk factor for ICU admission and invasive mechanical ventilation (IMV) among individuals infected with COVID-19. Nevertheless, it remains unclear whether the increased leptin levels establish a connection between obesity and the severity of COVID-19 in comparison to patients with normal weight. Therefore, this systematic review was undertaken to investigate the relationship between leptin, obesity, and the severity of COVID-19. A thorough search of five databases was performed to identify published studies focusing on individuals with obesity who were infected with COVID-19, and its relationship with leptin. Three authors screened and reviewed the articles based on predefined inclusion criteria. The review incorporated a total of 92 studies, revealing that COVID-19 patients with a comparable BMI to control subjects exhibited elevated serum leptin levels. Most studies indicated that obesity increases the risk of COVID-19 infections, hospitalizations, ICU admissions, and the need for IMVs. These risks were particularly prominent among younger patients below the age of 60 or those with diabetes, a phenomenon known as "diabesity". However, the correlation between obesity and mortality rates remained unclear based on the available evidence. Obesity is associated with persistent effects of COVID-19 over an extended period, commonly referred to as "long COVID." Multiple studies have reported an obesity paradox and observed J-shaped or U-shaped associations between obesity and the severity of COVID-19 outcomes. Considering that obese individuals typically have elevated levels of leptin in their plasma and obesity itself is an independent risk factor for COVID-19, we proposed that leptin may have a substantial involvement in the development of severe COVID-19 infection among patients with obesity. Further studies are necessary to further elucidate the mechanism of leptin and explore its impact on the immune response in COVID-19 patients with obesity.

**Keywords:** *Leptin; obesity; COVID-19; BMI*



# Evidence of nitric oxide-cyclic GMP-Potassium channels involvement in antinociceptive activity of 3-(2,5-dimethoxy phenyl)-1-(5-methyl furan-2-yl) prop-2-en-1 (DMPF-1) compound using behaviour-induced nociception

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DOI <https://doi.org/10.28916/lsm.7.1.2023.132>

## Abstract

Chalcones are interesting and versatile compounds due to their various pharmacological properties. Important biological activities of chalcone have been reported for decades using different experimented models. The 3-(2,5-dimethoxy phenyl)-1-(5-methyl furan-2-yl) prop-2-en-1 (DMPF-1) is one of the chalcone analogues that showed to have analgesic properties. The present study examines the possible nociceptive modulatory activity exerted by the DMPF-1 compound in behavioural-induced nociception in animal model using ICR mice. Administration of the DMPF-1 compound at a dose of 1 mg/kg intraperitoneally exerted a pronounced antinociceptive effect against the acetic acid-induced nociception. The antinociceptive effect of the DMPF-1 compound was reversed by the pre-treatment of the animals with the nitric oxide precursor; L-arginine (100 mg/kg; i.p.), and the soluble guanylyl cyclase inhibitor; oxadiazole (4,3-a) quinoxaline-1-one (ODQ) (2.0 mg/kg; i.p.). A similar inhibitory pattern was observed upon the challenge of DMPF-1 against various potassium channel inhibitors, including glibenclamide (10 mg/kg; i.p.) and tetraethylammonium (4 mg/kg; i.p.). Overall, these findings suggest the possible contribution of nitric oxide-cyclic GMP-potassium signalling pathway in the antinociceptive profile exerted by the DMPF-1 compound. This chalcone analogue and its molecular structure might be further investigated as a model that could be used to obtain a more potent analgesic.

**Keywords:** 3-(2,5-dimethoxy phenyl)-1-(5-methyl furan-2-yl) prop-2-en-1, DMPF-1; nitric oxide; L-arginine; potassium channel

# Effects of Kelulut honey on androgen receptor expression and distribution in letrozole-induced polycystic ovary syndrome rats

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**DOI** <https://doi.org/10.28916/lsm.7.1.2023.132>

## Abstract

Polycystic ovary syndrome (PCOS) is a combination of endocrine, metabolic and reproductive disorders. The abnormalities in PCOS have been shown to be associated with dysregulation of sex steroid receptors. Kelulut honey (KH) is reported to be effective in both female and male reproductive disorders due to its excellent anti-inflammatory, anti-diabetic and antioxidant properties. However, no study has yet been conducted to investigate the effect of KH on sex steroid receptors in PCOS. Therefore, this study investigated the isolated and combined effects of KH, metformin or clomiphene on androgen receptor (AR) mRNA expression and protein distribution in letrozole-induced PCOS rats. PCOS was induced in female Sprague-Dawley (SD) rats with 1 mg/kg/day letrozole for 21 days. The PCOS rats were then divided into six treatment groups: untreated, metformin (500 mg/kg/day), clomiphene (2 mg/kg/day), KH (1 g/kg/day), combined KH (1 g/kg/day) and metformin (500 mg/kg/day), and combined KH (1 g/kg/day) and clomiphene (2 mg/kg/day). All treatments were administered orally for 35 days. AR mRNA expression and protein distribution were determined by quantitative polymerase chain reaction (qPCR) and immunohistochemistry, respectively. In this study, we demonstrated the aberrant expression of AR in PCOS-induced rats compared to normal control rats. It was also found that treatment with KH normalised the expression and distribution of AR and was comparable to that of clomiphene and metformin. Thus, this study confirms the aberrant expression of AR in PCOS and shows that treatment with KH can normalise the AR profile. The results of this study may provide a basis for future clinical trials on the use of KH as a regulator of AR expression in patients with PCOS.

**Keywords:** Honey; PCOS; androgen receptor; sex-steroid receptor

# Evaluating the potential antiviral activity of novel N-substituted 5-(phenylamino)uracil derivatives against type 2 dengue virus (DENV2) *in vitro*

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DOI <https://doi.org/10.28916/lsm.7.1.2023.132>

## Abstract

Dengue viruses (DENV) which cause dengue viral hemorrhagic fever and dengue shock syndrome have become a serious public health threat to Malaysia and Southeast Asian countries for the past decades. Despite being associated with high morbidity and mortality rates, no vaccine or antivirals are available for DENV infection treatment or prophylaxis. Novel 5-(phenylamino)uracil derivatives are non-nucleoside analogues which previously showed activity against hepatitis C and chikungunya virus, however, their activity against DENV2 remains unknown. This study aimed to screen the antiviral activity of 11 novel N-substituted 5-(phenylamino)uracil derivatives against DENV2 on Vero 76 cells using cell viability assay. Vero 76 cells were seeded into 96 well plates containing DMEM supplemented with 1% FBS and 1% penicillin and streptomycin and incubated overnight. Next, DENV2 with MOI of 0.5 was added into each allocated well and followed by 100  $\mu$ L of tested compounds dissolved in 1% DMSO with concentration ranged from 1.5 to 100  $\mu$ M in triplicate. The plates were incubated at 37 °C with 5% CO<sub>2</sub> for 96 hours. After 96 hours, MTS assay was performed, and the absorbance was read at 490 nm. Non-treated DENV2 infected and non-infected Vero 76 cell were used as the controls. The same experiments were repeated with MOI of 1 and 2 of DENV2. Statistical analysis was performed. The cells infected with DENV2 showed significant reduction of cell viability compared to that in non-infected Vero 76 cells. However, there was no significant difference in cell viability between the DENV2-infected cells treated with tested compounds and viral control after 96 hours of incubation with all tested concentrations for all three MOI. In conclusion, the primary screening of 11 novel N-substituted 5-(phenylamino)uracil derivatives against DENV2 revealed no antiviral activity against DENV2 *in vitro*.

**Keywords:** DENV2; Vero-76 cells; cell viability; antiviral drugs; N-(phenylamino)uracil derivatives

# Diabetic wound healing study treated with gel formulation of *Lawsonia inermis* (Henna) extracts (ethanolic and aqueous)

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**DOI** <https://doi.org/10.28916/lsm.7.1.2023.132>

## Abstract

Prevalence of diabetes increases over the years and one of the disease major concerns is its complications on delayal of wound healing process. Previous studies found that *Lawsonia inermis* (Henna) has therapeutical properties that help to enhance wound healing process. However, information regarding the uses of *L.inermis* to remedy diabetic wound is inadequate. Hence, this study aimed to evaluate the effectiveness of *L.inermis* extract gel formulation in diabetic wound model in rats. *L.inermis* gel is subjected to stability test through physical and chemical assessment. Total of 42 Sprague Dawley rats (except normal group) were induced with single dose (55mg/kg) of streptozotocin (STZ) and divided into six groups (n=6) that treated with: (i) Solcoseryl; (ii) Untreated; and gel of *L.inermis* (iii) 2.5% aqueous (iv) 5.0% aqueous, (v) 0.5% ethanol, (vi) 1.0% ethanol accordingly. Excisional wound was created on rat's dorsal (Day 0) and daily treatment started on Day 1 until Day 18. Wound contraction rates were calculated as a percentage rate and images taken to assess contraction progress. On day 18<sup>th</sup>, harvested skin was stained using Haematoxylin and Eosin and Masson's Trichrome. Stability of gel formulation was maintained with reliable pH value and viscosity. Wound size reduce faster in treatment group, while the wound contraction rates (%) was accelerated after treated using *L.inermis* extract gel compare to solcoseryl as control positive (85.14±0.05). Observation shows, treatment using *L.inermis* showed faster re-epithelization, increase epidermal thickness and collagen production by day 18. *L.inermis* extract gel formulations have potential to become an alternative treatment in diabetic wound due to its ability to reduce the duration of healing process.

**Keywords:** *Lawsonia inermis* (Henna); gel formulation; diabetic wound healing

# Effect of olanzapine on high fat diet induced metabolic abnormalities in zebrafish model (*Danio rerio*)

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DOI <https://doi.org/10.28916/lsm.7.1.2023.132>

## Abstract

Olanzapine, a second-generation antipsychotic drug, often used as 1<sup>st</sup> line drug for most of the psychiatric illness treatment such as depression, schizophrenia as less causes of extrapyramidal symptoms. Long-term Olanzapine treatment causes adverse effect like gain weight are found in most of the consumer especially female. It is suspected that weight gain is due to olanzapine effect on neurotransmitter receptors (5-HT, DA, muscarinic and histamine) which the effect on these receptors increase the appetite and food intake of individual leading weight gain. Understanding olanzapine's weight gain mechanism is essential, as it can lead to health issues such as CVS and abnormal lipid metabolism. Evaluating its interaction with high-fat diets is crucial for comprehensive assessment. In this study, *Danio rerio* as a model in wet lab, be fed high fat diet along with olanzapine to study their relationship in weight gain and assess olanzapine's effect on lipid metabolism, body weight, and food intake. Treatment for 28days, there is significantly increase of weight gain, hyperphagia are shown most obviously in 0.5uM olanzapine treatment zebrafish, while 5uM olanzapine treatment zebrafish have increased the most weight compare to others group, this can be due to alternation of leptin and adiponectin adipocytokines in body lead to abnormal lipid metabolism and increase appetite. One-way Anova result was F ratio is 8.573 with P value 0.0005, proved significantly increase of weight gain happen in zebrafish. LC 50 test 4 concentration tested within 7 days by using zebrafish embryos, 60uM have the lowest survival rate (68%) while 15uM having highest survival rate (99%). In summary, olanzapine does induce weight gain together with high fat diet in zebrafish by increasing the appetite of zebrafish provide evidence supporting the validity of this model for olanzapine-induced obesity.

**Keywords:** *Danio rerio* (zebrafish), olanzapine induce weight gain, LC50 on zebrafish, high fat diet

# The effects of Zerumbone on 3D migration and invasion of hypoxia-induced colon cancer cells

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**DOI** <https://doi.org/10.28916/lsm.7.1.2023.132>

## Abstract

Colon cancer is a leading cause of cancer-related deaths worldwide due to its metastatic potential. The low survival rate for colorectal cancer is attributed to the invasive behavior of cancer cells, which migrate and establish new tumors. However, current treatments, including radiotherapy, encounter obstacles in dealing with hypoxia, a condition where cancer cells adapt and become more aggressive and invasive. Zerumbone (ZER), a phytochemical derived from *Zingiber zerumbet*, was previously shown to exhibit chemopreventive and anti-cancer properties. However, the effects in inhibiting cancer cell migration and invasion in a hypoxic microenvironment is yet to be explored. Hence, this study aims to explore the effects of ZER on the migration and invasion of hypoxia-induced colon cancer cells in 3D culture setting. 3D transwell migration and invasion assays were performed to determine the effects of different concentration of ZER in the background of normoxic and hypoxic condition on the invasiveness of the HCT116. Migrated and invaded cells were stained and counted under microscope after they migrated through the 8µm pores from the upper chamber of the transwell. Transwell 3D migration and invasion assay results indicated that IC<sub>50</sub> of ZER significantly ( $p < 0.05$ ) inhibit the migration and invasion of HCT116 colon cancer cells by effectively reduced the number of migrated and invaded cells in both normoxic and hypoxic conditions. Previous studies demonstrated that ZER treatment exhibits anti-metastatic properties by inhibiting the Fak/PI3K/NF-κB-uPA pathway in HCT116 cells and reducing CXCR4 and HIF-1α expression in breast and pancreatic tumors. ZER may exhibit anti-migratory properties and reduced cancer cell invasiveness in hypoxic cancer cells, and inhibitory effects on hypoxia-induced human colorectal carcinoma cell invasion. Thus ZER may be a potential candidate for anti-cancer agent to reduce tumor invasion and metastasis in the future. IC<sub>50</sub> of ZER reduced the number of invasive cells and the concentration.

**Keywords:** Colon cancer; Zerumbone; migration; invasion; metastasis; hypoxia

# Optimisation of immobilized pH gradient range for serum proteomic analysis of post Covid-19 syndrome patients using two-dimensional electrophoresis

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DOI <https://doi.org/10.28916/lsm.7.1.2023.132>

## Abstract

Discovery of diagnostic protein marker for Post COVID-19 Syndrome (PCS) is vital as currently PCS is a diagnosis of exclusion needing various investigations and time consuming. Two-dimensional electrophoresis (2-DE) is used for proteomic profiling analysis to identify candidate protein markers which is simpler to run, easy to reproduce and cost effective. This study aimed to compare serum proteins profiles between broad and narrow range of immobilized pH gradient (IPG) to optimize 2-DE methods in proteomic analysis of serum PCS patients. Pooled serum of five PCS patients, matched for age, gender and race was cleaned up. Two µg of these extracted proteins were uploaded onto 7 cm of IPG strips pH range of 3-10 and 4-7 respectively. The proteins were separated via the first dimension by isoelectric focusing (IEF) system. The strips then transferred to precast gels and processed for second dimension of protein separation using Sodium dodecyl-sulfate polyacrylamide gel electrophoresis (SDS-PAGE). The gels then stained using Bio safe Coomassie Stain and destained using miliQ water. The gel images were analysed using PD Quest software. A total of 122 protein spots were detected in 3-10 gel, with most proteins concentrated at the centre region. Using the similar sensitivity parameter, higher protein spots were detected with a total of 261 for pH 4-7 gel with better protein spots intensity and resolution. The intensity of proteins expression was greater in plasma reference gel than the serum 3-10 gel, but the appearance was improved in serum 4-7 gel. In conclusion, for 2-DE proteomic analysis, using an IPG strip of pH 4-7 is recommended for further serum PCS patient proteomic analysis as it yielded more protein spots with better resolution and intensity compared to pH 3-10 as a narrow IPG pH range allows more migration distance between proteins in a more focused pH range.

**Keywords:** *Optimisation; proteomic; post Covid-19 Syndrome; 2-dimensional electrophoresis; immobilized pH gradient*

# Antifungal activity of *Baeckea frutescens* leaves extracts towards *Malassezia furfur*

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## Abstract

Dandruff is a common condition characterized by flaking of the scalp and itching, often caused by the presence of fungi from the genus *Malassezia*. This study focuses on *Malassezia furfur* (*M. furfur*), a lipid-dependent fungus associated with dandruff and seborrheic dermatitis. Plant-derived compounds have gained attention for their therapeutic potential, including antifungal properties. *Baeckea frutescens* (*B. frutescens*) is a flowering plant that has been widely used in traditional medicine in its native countries. This study aims to evaluate the antifungal properties of *B. frutescens* against *M. furfur* by measuring the inhibition zone. Leaves of *B. frutescens* were extracted with different types of solvents (95% ethanol, 50% ethanol and water) and agar well diffusion methods was conducted to investigate the antifungal effect of the extracts. The bacteria were grown in the laboratory by using Sabouraud Dextrose Agar (SDA) plates and incubated at 37°C for 7 days. The antifungal effect was evaluated through the zone of inhibition. Three extracts of *B. frutescens* showed antifungal activities towards *M. furfur*. Ethanol 50% v/v extract have the highest mean of inhibition zone (30.5 mm) followed by ethanol 95% v/v extract (30 mm) and water extract (24 mm). *B. frutescens* ethanol extracts have the highest antifungal activity and may be used to treat dandruff caused by *M. furfur*

**Keywords:** Antifungal; *Malassezia furfur*; *Baeckea frutescens*



# Optimization of a two-dimensional electrophoresis protocol for plasma proteomic profiling of obese schizophrenia patients

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DOI <https://doi.org/10.28916/lsm.7.1.2023.132>

## Abstract

The proteomic approach is particularly effective for studying the association between obesity and schizophrenia. It allows for a comprehensive analysis of the complete proteome, leading to substantial breakthroughs in biomarker discovery and drug development. Isoelectric focusing (IEF) and SDS-PAGE procedures are combined in the proteomic approach known as two-dimensional electrophoresis (2-DE), which separates proteins according to their isoelectric point and mass. This study aimed to investigate optimized conditions for the 2-DE technique by focusing on the selection of an immobilized pH gradient (IPG) strip. Protein extraction was performed on pooled plasma samples from 10 obese schizophrenia patients. The extracted protein samples were loaded onto two different pH (7 cm) IPG strips. The pH ranges between (i) 3 – 10 and (ii) 4 – 7. IEF was conducted following the PROTEAN IEF Cell System protocol, followed by SDS-PAGE. The resulting gels were stained with BioSafe Coomassie stain and washed with milliQ water. The stained gels were scanned, and the images were analyzed using PD Quest software. High-abundance proteins with a molecular weight range of 60 – 80 kDa were detected on both IPG strips. The results showed that using a pH 3 – 10 IPG strip, 245 protein spots were detected and distributed throughout the gel, with a notable concentration in the middle. Whereas using a pH 4 – 7 IPG strip resulted in the detection of 321 protein spots, indicating a higher quantity of protein spots with increased intensity. This is attributed to the improved fractionation of proteins resulting from the narrower and more focused pH range. Thus, it can be inferred that utilizing this pH range will yield optimal outcomes in protein separation and analysis. This study suggests selecting a pH 4 – 7 IPG strip is the recommended choice to achieve enhanced resolution and precise detection of protein spots in plasma samples from obese schizophrenia patients when employing the 2-DE method.

**Keywords:** *Proteomics; 2-Dimensional electrophoresis; IPG strip; protein separation*

# Evaluation of antidiabetic and antioxidant potentials of *Paederia foetida* twigs in high-fat diet-low dose streptozotocin Sprague Dawley rats

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**DOI** <https://doi.org/10.28916/lsm.7.1.2023.132>

## Abstract

*Paederia foetida* (PF) is an edible plant that has antioxidant and antidiabetic activities in an in vitro evaluation. Combining the high-fat diet and streptozotocin rat model mimics the natural history and metabolic characteristics of Type 2 Diabetes Mellitus (T2DM). This rodent model was the first time implemented in this plant. This study was conducted to determine the antidiabetic and antioxidant effect of PF twigs in high-fat diet fed-low dose STZ - induced Sprague Dawley rats to provide essential information required for safe use in human. Fourty two male Sprague Dawley rats were divided into six groups 8 umbers each groups, i.e., normal control, obese control, diabetic control, and three diabetic treated groups (50 mg/kg, 100 mg/kg PF and 300 mg/kg metformin). The PF wigs extract and metformin were orally administrated to the rats for 28 days in the sub-chronic study. The rats were sacrificed after four weeks of the treatment. The blood samples were collected by cardiac puncture, and serum was separated and analyzed for lipid profile, renal function, liver function test, and hematological parameters. The liver and heart were surgically removed and homogenized with cold phosphate buffer saline using a homogenizer. The samples were centrifuged for 10 min at 4000 rpm, and the supernatants were collected. Two antioxidant enzymes (GPH and CAT activities) and two oxidative stress markers (PCO and rat RAGE levels) were measured. Repeated single oral administration of 50mg/kg PF twigs extract on diabetic rats for 28 days revealed this dosage as the most effective by lowering the blood glucose (27.2%), comparable to metformin (23.1%). The results also showed a good hematology, lipid, renal, and liver functions and close to the normal range of control rats, indicative of non-toxic effects. Treatment with 50 mg/kg PF twigs extract also displayed significant antioxidant properties that reduce oxidative stress in protein carbonyl content and exhibited better clinical signs of hyperglycemia and oxidative stress marker. PF supplementation or metformin reversed the clinical manifestation of Type 2 diabetes mellitus, but PF alleviated biochemical alteration of T2DM better than metformin.

**Keywords:** *Paederia foetida*; antidiabetic; antioxidant; type 2 diabetes mellitus

# Potential pharmacotherapy of tocotrienol rich fraction against age-related macular degeneration: A mechanism of action

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DOI <https://doi.org/10.28916/lsm.7.1.2023.132>

## Abstract

One of the main causes of visual loss in the elderly is age-related macular degeneration (AMD). The need for AMD prevention is growing as the geriatric population increases worldwide. Retinal damage induced by oxidative stress is a major causative factor of AMD. A wide variety of nutrients, such as minerals and vitamins, have been associated with reducing the risk of AMD. Initial results from the Age-Related Eye Disease Study (AREDS) indicated that supplementation with antioxidants was associated with a reduced risk of AMD progression. In this paper, we reviewed the potential of tocotrienol-rich fraction (TRF) to be used in slowing the progression of AMD through reducing oxidative stress, inflammation, dysregulated lipid metabolism, and angiogenesis. This was done by reviewing the interventional studies that used tocotrienol or TRF on the above-mentioned mechanisms. PubMed and Medline search engines were used to collect publications published between 1996 and 2022. This was accomplished by using a single or combination of keywords, such as AMD, TRF, oxidative stress, inflammation, angiogenesis, lipid metabolism. Only full paper publications published in English were selected for this review. TRF was reported to have potent antioxidant, anti-inflammatory, and anti-angiogenic properties. Other than that, TRF also was reported to improve the lipid metabolism. Therefore, TRF has good potential as a novel therapeutic to ameliorate the underlying mechanisms of AMD pathogenesis.

**Keywords:** Age-related macular degeneration; tocotrienol-rich fraction; oxidative stress; inflammation; angiogenesis; lipid metabolism

# Optimization of nanostructured lipid carrier for astaxanthin loaded

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## Abstract

Astaxanthin is a carotenoid belongs to the class of xanthophyll that can be found in *H. pluvialis* microalgae. This compound possesses various therapeutic properties that include potent antioxidant and anti-diabetic. Despite its excellent pharmacological activity, this highly lipid soluble carotenoid has poor oral bioavailability which hindered its clinical applications. For this reason, nanostructured lipid carrier (NLC) was design and developed to enhance the oral bioavailability of astaxanthin through hot homogenization method. In this study, response surface methodology (RSM) was employed to optimize the composition of lipid phase (palm oil and cocoa butter) and surfactant, Tween 80 to ensure small particle size with uniform shape and optimum surface charge is produced. The optimum composition of lipids and surfactant suggested by RSM was prepared accordingly and validated by using a student t-test between the theoretical prediction and the actual experimental values. The analyses showed that the optimum composition was found essential to produce NLC with size, zeta potential and polydispersity of 250 nm, -30 mV and 0.35 respectively. Data showed no significant difference between the predicted and experimental values for all three responses, indicating there were good agreement and response surface models were verified. Thus, this study exhibited the feasibility of NLCs as a good candidate for oral delivery of astaxanthin and therefore represents a new promising pharmacotherapeutic concept of astaxanthin.

**Keywords:** Astaxanthin; optimization; nanostructured lipid carrier (NLC); Response surface methodology (RSM)

# Oral Supplementation of Astaxanthin Promotes Bone Fracture Healing in an *in vivo* model

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DOI <https://doi.org/10.28916/lsm.7.1.2023.132>

## Abstract

Bone fracture is defined as full or partial break in the continuity of bone tissue. In Malaysia, the hip fractures are expected to increase from an estimated 5,880 hip fractures in 2018 to 20,893 in 2050. This has caused significant burden to healthcare and economic sector. Fractured bone healing is a coordinated process involving growth factors, cytokines and bone cells but could be adversely affected due to the deteriorated biological process that is excessive production of reactive oxygen species (ROS) at the fracture site, accompanied by disruption of blood flow to bone ends. The current management of fracture include anti-resorptive and anabolic agents. However, their long-term administration may lead to undesirable side effects. Administration of antioxidants such as astaxanthin (AST) is therefore a rational approach to suppress the destructive effects of free oxygen radicals and have a positive effect on the fractured bone healing process. Hence, in this study, we aimed to evaluate the effect of AST on fracture healing process in a rodent model. Fracture was performed on the right tibiae of male Sprague-Dawley rats using pulsed ultrasound and stabilized using plate fixation method. Rats was randomly assigned into control and AST group which were supplemented with palm oil and 10mg/kg AST, respectively for 8 weeks following fracture procedure. Whole-body and regional bone mineral density (BMD) was measured at the start of treatment, one and two months, using dual-energy x-ray absorptiometry (DEXA). At the end of eight-week treatment, animals were sacrificed and the right tibia samples were harvested. Supplementation of AST group is expected to accelerate fracture healing compared to control group.

**Keywords:** Astaxanthin; antioxidant; bone fracture; osteoblast; osteoclast

# Antioxidant effects of tocotrienol-rich fraction supplementation on obesity-induced oxidative stress in female mice : A systematic review

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DOI <https://doi.org/10.28916/lsm.7.1.2023.132>

## Abstract

Adverse reproductive outcomes are associated with obesity. Obesity induces oxidative stress damage in female reproductive system which eventually leads to infertility. Tocotrienol-rich fraction (TRF), a potent antioxidant has been proven to exert a protective effect in female reproductive system in animals that have been challenged by various oxidative stress conditions. The purpose of this systematic review is to provide evidence-based literature on the antioxidant properties of TRF on the oxidative stress damage in female reproductive system of obese mice. A scientific search was conducted using Science Direct, Google Scholar, PubMed, Ovid, Medline and SCOPUS for the related studies published between the years 2019 and 2023. The articles that met the criteria were used in this study. The early search resulted in five suitable articles, but only three articles that met the criteria were chosen in the study. These three studies demonstrated a positive relationship between TRF supplementation and oxidative stress in female reproductive system. We deduced that the antioxidant properties of TRF can be used as an alternative to prevent obesity-induced oxidative stress in female reproductive system. Thus, it is proposed that more studies can be conducted to determine the mechanism of action of TRF which will provide a wider perspective in improving the impaired reproductive outcome in maternal obesity.

**Keywords:** *Antioxidant; tocotrienol-rich-fraction (TRF); obesity; oxidative stress; female reproductive system*

# Innovation of nanohydrogel-thermosensitive curcumin as a drug delivery method for cancer treatment

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**DOI** <https://doi.org/10.28916/lsm.7.1.2023.132>

## Abstract

The main side effects of cancer chemotherapy encourage the development of new drugs derived from plants. Curcumin (*Curcuma longa* Linn) has pharmacological activity as an anti-cancer which can be developed into nanothermogel drugs. Thermosensitive hydrogels have been widely developed as drug delivery systems because they retain bioactive agents that are sensitive to temperature changes. This study aims to determine the optimum formula and profile of the physical properties of the preparation including the value of viscosity, pH, and gel time. This design of this study is a laboratory experimental research. This research used 3 variations : formula 1 (P407 43%, HPMC 9,87%, curcumin 2%), formula 2 (P407 36%, HPMC 8%, curcumin 1%) and formula 3 (P407 50%, HPMC 8% ,curcumin 3%). The evaluation test of the physical properties of curcumin thermosensitive hydrogel are viscosity, pH, and gel time test. The results of the analysis obtained 3 formulas with a viscosity response are 594,56; 315,94; 10679,10 cp.s.; pH response at 7,1; 6,69; 6,82 and the response time to the gel is 281; 100; and 226 seconds. Then it was analyzed using One Way Anova test, the value of Viskosity test, pH test, and gel time test sig value < 0,05. The effect of combination Polox, HPMC, curcumin is able to leverage therapeutic benefits by improving bioavailability and pharmacokinetics which in turn improves binding, and targeting of tumor. Based on the response of the physical properties of the formula, the optimum composition ratios were formula 3. The addition of poloxamer 407, HPMC, and curcumin concentrations has an effect on the results of the physical properties test of the curcumin thermosensitive hydrogel formula, namely viscosity, pH, and gel time.

**Keywords:** *Hydrogel thermosensitive; breast cancer; curcumin; drug delivery*

# Diversification of porang's starch (*Amorphophallus oncophyllus*) as a non-carcinogenic sunscreen

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DOI <https://doi.org/10.28916/lsm.7.1.2023.132>

## Abstract

These recent years carcinogenic substances have been found in some sunscreen products. For example, FDA has banned the use of benzene derivate from the sunscreen formulation. The starch of porang (*Amorphophallus oncophyllus*) can reflect the sunlight and prevent UV radiation to penetrates the skin and can be used in a sunscreen formulation. Moreover, the utilization of *Amorphophallus oncophyllus* has not been as great as its abundance. The objective of this study is to determine the best sunscreen formulation from the variation of starch concentrations. The design of this study is experimental research conducted in the laboratory. This study used starch with concentrations of 5%, 10%, and 15% as the sunscreen formulations. The evaluation of sunscreen carried out are physical examination, SPF values, and the irritation test. Data analysis is carried out descriptively based on the parameters of each test and statistical test result. The result shows that the variation of porang's starch concentrations affected the physical properties, SPF values, and irritation test results. Based on literature, the porang's starch as sunscreen can also be considered carcinogenic substances free.

**Keywords:** *Porang; Amorphophallus oncophyllus; non-carcinogenic; sunscreen*



# Zinc oxide nanoparticles and drug metabolism: Exploring the influence of nanoparticles size on cytochrome P450 enzyme inhibition

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**DOI** <https://doi.org/10.28916/lsm.7.1.2023.132>

## Abstract

The increasing demand for zinc oxide nanoparticles (ZnO NPs) in biomedical applications has raised concerns regarding their unintended exposure to humans and the environment. Although previous studies have demonstrated the hepatotoxicity of ZnO NPs, their impact on major cytochrome P450 (CYP) isoforms responsible for drug metabolism remains unexplored. This study aims to investigate the influence of ZnO NP size on the inhibition of major human drug metabolizing CYP isoforms, namely CYP3A4, 2D6, 2C9, and 2C19. In this study, ZnO NPs with different sizes (<50nm, <100nm, and bulk) were characterized using Field Emission - Scanning Electron Microscopy (FE-SEM), Ultraviolet-Visible (UV-Vis) spectroscopy, and Energy Dispersive X-ray (EDX) spectroscopy. Fluorescence-based enzyme assays were employed to assess the inhibitory effects of ZnO NPs on CYP isoforms, while molecular docking provided additional insights into the ZnO NP-CYP interactions. Herein, our results showed significant inhibition of all tested CYP isoforms in the presence of ZnO NPs, with inhibitory potency dependent on NP size. However, no inhibition was observed in CYP2C19 in the presence of <100nm ZnO NPs. Notably, the inhibitory potency of ZnO NPs was shown to be more pronounced in CYP2C9 isoenzymes with the lowest IC<sub>50</sub> value (12.76 µg/ml in <50nm ZnO nanoparticles and 16 µg/ml in <100nm ZnO nanoparticles), followed by CYP3A4, CYP2D6 and, CYP2C19. Therefore, caution should be exercised when co-administering ZnO NPs with drugs metabolized by these CYP isoforms. These findings underscore the importance of considering physicochemical properties, such as size and shape, in assessing the toxicity of ZnO NPs. Understanding the physicochemical properties of ZnO NPs is essential for evaluating potential risks and designing safer nanoparticles for biomedical applications.

**Keywords:** *Zinc oxide nanoparticle; size; shape; Cytochrome P450 (CYP); enzyme inhibition.*

# Mechano-stimulation alleviates pain of intraoral injection of local anaesthesia – a systematic review

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DOI <https://doi.org/10.28916/lsm.7.1.2023.132>

## Abstract

Injections of intraoral local anaesthesia is often perceived as painful and are associated with avoidance of dental treatment among patients. Numerous pain-relieving strategies, including the application of mechanical stimulation, specifically vibration, to alleviate intraoral injection pain, are therefore being investigated. This study aimed to systematically review published articles on the effectiveness of vibration in reducing injection pain of intraoral local anaesthesia used for dental procedures. A literature search was conducted using PubMed, Web of Science, Cochrane, and Scopus until September 2022 and the P-values of pain intensity and anxiety parameters were compared. Risk of bias assessment among the shortlisted randomized control trial (RCT) studies was performed using the Cochrane Risk of Bias 2 (ROB2) tool. In this systematic review, a total of 20 RCT studies that applied vibration alone, vibration with pre-emptive analgesia, or vibration in combination with cold were included. The shortlisted studies were mainly presented with low, or some concern risk of bias, based on the ROB2 tool. Pain intensity in most (90%) of dental patients receiving mechano-stimulation during the intraoral local anaesthesia injection were generally reduced, with half of them also reported on improved in anxiety, particularly in paediatric patients. The application of mechanical stimuli appeared effective in reducing the pain of intraoral local anaesthesia injection in dental patients, suggesting a potential application of the gate control theory in dentistry.

**Keywords:** *Intraoral injection; local anaesthesia; vibration; pain modulation; mechano-stimulation*

# The neuroprotective effect of combination of spirulina (*Spirulina platensis*) and golden sea cucumber (*Stichopus variegatus*) on dementia model rats induced by trimethyltin

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DOI <https://doi.org/10.28916/lsm.7.1.2023.132>

## Abstract

Dementia is a decline in cognitive function that affects memory, language, and behavioral deficits that can be caused by oxidative stress. Spirulina (*Spirulina platensis*) and golden sea cucumber (*Stichopus variegatus*) have antioxidant activity that has the potential to prevent neurodegenerative diseases. The purpose of this study was to examine the effect of the combination of spirulina and golden sea cucumber on spatial memory, antioxidant activity (SOD and MDA), and caspase 3 and Bcl2 gene expression in a dementia model rat. Rats were divided into 6 groups, namely the normal control group (CMC-Na and NaCl 0.9%), the negative control (CMC-Na and TMT), the positive control (citicoline 200 mg/Kg BW and TMT), and the test control injected with TMT and given a combination of spirulina and golden sea cucumber (ST) dose 200 mg/Kg BW with three ratios, namely ST-3: 1, ST-1: 1, and ST-1: 3. Extract and citicoline were given from day 1 to day 28, while TMT injection was given in a single dose of 8 mg/Kg BB on day 8. On days 29–35, spatial memory tests were carried out using the Morris Water Maze (MWM) test. Thereafter, the animals were sacrificed, and the brains were taken for biochemical observations (SOD activity and MDA levels) and the hippocampus for histological observations (caspase 3 and Bcl2 gene expression). The test results were statistically analyzed using ANOVA or Kruskal-Wallis with a significance level of 5%. Test results showed that ST-1:3 can improve the spatial memory of dementia model rats in the MWM test, showing antioxidant activity with increased SOD activity and decreased MDA levels, as well as a decrease in caspase 3 expression and an increase in Bcl2 expression in both CA1 and CA2-CA3 regions. The ST-1:3 group showed almost the same test results as rats given citicoline. In conclusion, the study suggests that the combination of spirulina and golden sea cucumber can potentially prevent dementia.

**Keywords:** Dementia; golden sea cucumber; oxidative stress; spirulina; TMT

# Trends on omics approaches in drug discovery – A bibliometric analysis

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## Abstract

Genomics, transcriptomics, proteomics and metabolomics are studying the interactions, function, structures, activities of the genetic sequence, the complete set of RNA, of proteins and of metabolites respectively. Omics approaches are increasingly being used in drug discovery. This study aimed to identify the most productive author, country, institutions, most impactful paper and emerging research trends in this field. A total of 37,304 articles were obtained from the Scopus database on 21<sup>st</sup> July 2023 for the period of the year 2000 – 2023, and analysed by Harzing Publish or Perish and Vosviewer. The most productive author in this area is Matthias Mann, and the United States being the most productive country in publishing this topic followed by China. The most productive institution is Ministry of Education China contributing 2.91% of the total publications. This study provides a comprehensive overview of omics approaches in drug discovery using bibliometric analysis and offers insights to guide future researchers embarking on this research area.

**Keywords:** *Genomics; transcriptomics; proteomics; metabolomics; bibliometric*

**Citation:**

Balan, S. S., Basir, R., Yong, Y. K., Mohammed Izham, N. A., Chia, J. S. M., Othman, F., Lim, J. C. W., Md Tohid, S. F., Bahari, H., & Tham, C. L. (2023). 36th Malaysian Society of Pharmacology and Physiology Annual Scientific Meeting 2023. *Life Sciences, Medicine and Biomedicine*, 7(1).  
<https://doi.org/10.28916/l SMB.7.1.2023.132>



**Life Sciences, Medicine and Biomedicine**  
**ISSN: 2600-7207**

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