Althea Medical Journal
ISSN Online: 2337-4330
https://doi.org/10.15850/amj.v10n3.2905

Original Article

Garcinia Mangostana Pericarp Extract Protection on Reproductive Function of Obese-Diabetic Rats Model

Yora Nindita,[1] Vega Karlowee,[2] Irfan Kesumayadi,[3] Hermawan Istiadi,[2] Muflihatul Muniroh[4]

[1]Department of Pharmacology and Therapeutics, Faculty of Medicine Diponegoro University, Semarang, Indonesia, [2]Department of Anatomical Pathology, Faculty of Medicine Diponegoro University, Semarang Indonesia, [3]Faculty of Medicine Diponegoro University, Semarang Indonesia, [4]Department of Physiology, Faculty of Medicine Diponegoro University, Semarang Indonesia

Abstract

Background: Type 2 diabetes mellitus (T2DM) in obese has been considered a risk factor for male infertility. *Garcinia mangostana* pericarp extract (GMPE) is known to have anti-hyperglycemic, anti-diabetic, and anti-inflammatory effects. This study aimed to evaluate the effect of GMPE therapy on reproductive function in obese T2DM rats by examining testosterone level, testicular histopathological features, and hs-CRP level.

Methods: Thirty-six male Wistar rats, aged 2–3 months, were randomly divided into 6 groups and treated with a standard diet (NC), high-fat diet (HFD) with GMPE 200 mg/kgBW (obese GMPE control/OGC200), HFD with 45 mg/kgBW STZ-NA (obese-diabetic control/ODC), obese-diabetic rats with GMPE 100 (DG100); 200 (DG200); and 400 mg/kgBW (DG400). STZ-NA was administered after 8 weeks of HFD treatment and followed by GMPE for 8 weeks after T2DM was confirmed. The level of hs-CRP and testosterone were measured in the serum using an enzyme-linked immunosorbent assay. Testicular histopathological examination was measured after 8 weeks of treatment by using Modified Jonhson Score (MJS) with HE staining.

Results: ODC rats significantly showed increased hs-CRP level compared to NC (8.76±0.27 vs 0.30±0.07 ng/mL, p<0.001) and reduced testosterone level and MJS compared to NC (73.69±2.22 vs 170.14±1.34 ng/dL, 4.57±0.93 vs 9.87±0.16 MJS, respectively, P<0.001). Testosterone and hs-CRP levels showed a negative and significant correlation (r=-0.974 and p<0.001). On the treatment group, GMPE significantly reduced hs-CRP and increased testosterone levels in a dose-dependent manner.

Conclusion: GMPE effectively protects reproductive function in obese DM rats by increasing testosterone levels and advanced spermatogenesis, as well as decreasing hs-CRP level.

Keywords: hs-CRP, mangosteen pericarp extract, obese, testosterone, type 2 diabetes mellitus

Althea Medical Journal. 2023;10(3):136–143

Received: September 9, 2022
Accepted: June 17, 2023
Published: September 30, 2023

Correspondence:
dr. Yora Nindita, M.Sc., Ph.D, Department of Pharmacology and Therapeutics, Faculty of Medicine Diponegoro University, Semarang, Indonesia,
E-mail:
nindita.yora@fk.undip.ac.id

Introduction

Type 2 diabetes mellitus (T2DM) has become a major public health issue and is associated with a high incidence of infertility in men. Obese is considered a major risk of T2DM. In the obese subjects, there is a pathological proliferation (hyperplasia) and enlargement (hypertropia) of adipose tissue as a response to excessive nutrition that may reduce tissue oxygenation and cause cell hypoxia. It has an important role in the inflammation processes in adipose tissue by activating several pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor nuclear factor-α (TNF-α) that may induce insulin resistance and systemic inflammation response. Obese has been reported to be associated with the gonadal endocrine system's multiple alterations and low testosterone levels, which are essential factors for normal erectile function. Androgens are responsible for maintaining an adequate

level of nitric oxide (NO), a normal penile structure, and an endothelial function of the corpus cavernosum (CC) related to penile erectile response. Visceral obesity in men also increases the risk of arteriosclerosis and vessel endothelial dysfunction that are related to erectile dysfunction (ED). The prevalence of ED in diabetic patients increases two to four times more than that in normal subjects. This infertility problem is a sensitive health issue and is associated with depression in some patients, which causes it to be late diagnosed. Therefore, identifying some potent herbs is a good choice for study in the treatment of diabetic-suppressed reproductive function effects.[1,2]

Garcinia mangostana Linn, which is also called *mangosteen* and belongs to the *Guttiferae* family, is known as a queen of fruit because of its distinctive and delectable tropical taste.[3] It is a popular fruit in tropical countries, mostly in Southeast Asia, and has been used as a medicine for hundreds of years around the world. Mangosteen has a potential secondary metabolite with biological effects that exist on leaves, bark, whole fruit, and pericarp part of fruit. It is known as xanthones, a class of polyphenolic compounds, with α- and γ-mangostin as the most abundant ones.[4] Previous pharmacologic studies have reported numerous therapeutic effects of this fruit, such as anti-inflammation, anti-dyslipidemic, anti-oxidant, hypoglycemic activity, and anti-obese.[5–10] However, there is still a lack of information about the mangosteen's therapeutic effect in improving reproductive function in diabetic conditions.

The aim of this study was to evaluate the therapeutic effect of *Garcinia mangostana* pericarp extract (GMPE) for reproductive function in T2DM rats by examining testosterone hormone levels and testicular histopathology. This study also measured inflammatory biomarkers of hs-CRP expressions since T2DM induces oxidative stress and inflammation. The mechanism underlying the effect of GMP on T2DM-suppressed reproductive function has not been sufficiently investigated. Therefore, the effect of GMPE on reproductive function in obese-diabetic rats model was evaluated.

Methods

This research was a true experimental with a post-test only control group design. The study was conducted at the animal testing laboratory, Faculty of Medicine, Universitas Diponegoro. Mangosteen extract was prepared by mixing dried and ground fruit pericarp (0.5 kg) in 95% ethyl alcohol (3 L) at room temperature for 48 hours. The solvent was then removed, resulting in brownish residue. Water was then added, producing the yellow solid residue. Then, it was concentrated under a rotary vacuum evaporator, producing a crude extract (35 g).[11]

A total of 36 male *Rattus norvegicus Wistar* strains weighing 150–200 g at 2–3 months of age were acclimatized for seven days. The rats were randomly divided into normal and obese groups. The obese group was induced by a high-fat diet (HFD) with a composition of 20% pork oil and 0.5% cholic acid for 8 weeks. The HFD is mixed into standard Comfeed II. After 8 weeks, the rats were randomly divided into an obese group and obese-DM groups. The obese-DM group was then injected with 45 mg/kgBW streptozotocin (Nacalai Tesque, Inc) and 110 mg/kgBW nicotinamide (Nacalai Tesque, Inc) intraperitoneally. Rats were classified as T2DM when they had fasting serum glucose levels >200 mg/dL. These T2DM rats were randomly divided into obese-diabetic control and treatment groups with 3 different doses of GMPE for 8 weeks.

The following list was group classified in this experiment: (i) Normal control (NC), the rats only receiving a standard diet, (ii) Obese GMP control (OGC200), the rats only received HFD with GMP extract of 200 g/kgBW, (iii) Obese-diabetic control (ODC), the rats receiving HFD and STZ-NA. (iv) Diabetic rats with GMP extract 1 (DG100), the rats receiving HFD and STZ-NA with GMP extract of 100 mg/kgBW, (v) Diabetic rats with GMP extract 2 (DG200), the rats receiving HFD and STZ-NA with GMP extract of 200 mg/kgBW, (vi) Diabetic rats with GMP extract (DG400), the rats receiving HFD and STZ-NA with GMP extract of 400 mg/kgBW. Testosterone, hs-CRP level and testicular histopathology were examined after 8 weeks of treatment.

A total of 2 mL of blood from sinus periorbital was collected for biochemical analysis. Serum levels of biochemical markers were evaluated with the use of commercial ELISA kits according to the manufacturer's instructions, testosterone (cat. no. EU0400, FineTest Ltd., China), and hs-CRP (cat. no. ER1048, FineTest Ltd., China).

At the end of the experiment, the rats were terminated by carbon dioxide and cervical dislocation. The procedure was done by trained operator.

Histopathological assessment was carried

out in Hematoxylin and eosin stain (HE). Every sample was examined in 5 different fields of view with 400x magnification. Modified Johnson Scoring (MJS) was used for histopathological assessment. MJS was given a score 10 if there was complete spermatogenesis, a score 9 if there was any incomplete spermatogenesis with many late spermatids, a score 8 if there were less than 5 spermatozoa per tubules and a few late spermatids, a score 7 if there were many early spermatids but no spermatozoa or late spermatids, score 6 if there were few early spermatids but no spermatozoa or late spermatids, score 5 if there were many spermatocytes but no spermatozoa or spermatids, score 4 there were few spermatocytes but no spermatozoa or spermatids, score 3 if there were only spermatogonias, score 2 if the only presence of Sertoli cells and no germinal epithelial cells, and score 1 if there was no seminiferous epithelium.[12]

The data was normally distributed for hs-CRP and testosterone level and was presented as the mean±standard deviation, then analyzed using one-way ANOVA with posthoc LSD and Kruskal Wallis with posthoc Mann-Whitney test. A correlation of testosterone level and hs-CRP levels was analyzed using Spearman correlation. Data was considered significant if p-value<0.05. SPSS version 25 for Windows was used to analyze the data.

These research protocols have been approved by the Medical and Health Research Ethics Committee, Faculty of Medicine, Universitas Diponegoro, Semarang Indonesia No. 115/EC/H/KEPK/FK-UNDIP/VIII/2019.

Results

The highest hs-CRP level was found in the obese-diabetic control group, 8.76±0.27 ng/mL, and the lowest hs-CRP level was found in the normal control group, 0.30±0.07 ng/mL. Among treatment group, DG400 showed the lowest hs-CRP, 1.06±0.14 ng/mL (Figure 1). The GMPE could reduce hs-CRP levels in a dose-dependent manner. However, there was a significant difference between all treatment group and all control groups (p<0.05). The significance difference was also found between OGC200 and normal control (p<0.001).

The highest testosterone level was found in the normal control group, 170.14±1.34 ng/dL, and the lowest testosterone level was found in the obese-diabetic control group, 73.69±2.22 ng/dL. Among the treatment group, DG400 showed the highest testosterone level, 149.56±2.67 ng/dL (Figure 2). The GMPE could increase testosterone levels in a dose-dependent manner. However, there was a significant difference between all treatment

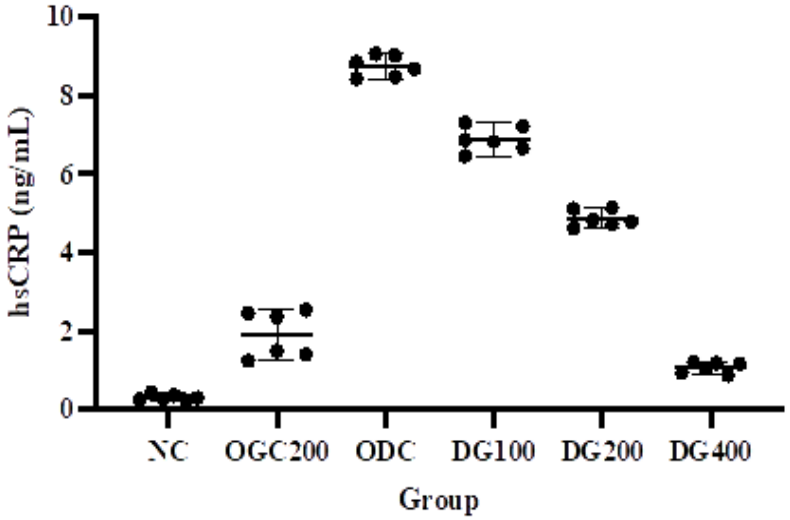

Figure 1 Scattered Plot Figure of hsCRP among Group

Note: NC= Normal control, OGC200; Obese GMP control with GMP extract of 200 g/kgBW, ODC; Obese-Diabetic control, DG100; Diabetic rats with GMP extract 100 mg/kgBW, DG200; Diabetic rats with GMP extract of 200 mg/kgBW, DG400; Diabetic rats with GMP extract 400 mg/kgBW

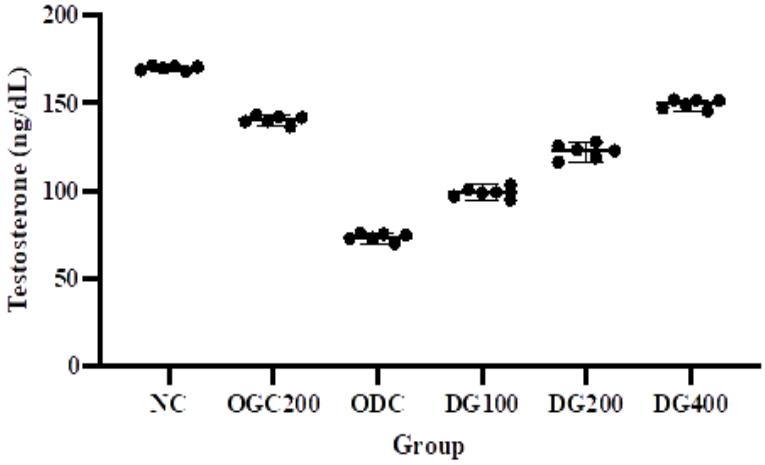

Figure 2 Scattered Plot Figure of Testosterone among Group

Note: NC= Normal control, OGC200; Obese GMP control with GMP extract of 200 g/kgBW, ODC; Obese-Diabetic control, DG100; Diabetic rats with GMP extract 100 mg/kgBW, DG200; Diabetic rats with GMP extract of 200 mg/kgBW, DG400; Diabetic rats with GMP extract 400 mg/kgBW

groups and all control groups (p<0.001) (Table 4). The significant difference was also found between OGC200 and normal control (p<0.001).

Testosterone and hs-CRP levels showed a negative and significant correlation (r=-0.974 and p<0.001) (Figure 3). This indicated that a higher level of hs-CRP was correlated with a lower testosterone levels. The simple linear regression equation for these variables is Y=-10.06X +165.8.

The highest testicular histopathology score was found in a normal control group, 9.87±0.16, and the lowest testicular histopathology was found in the obese-diabetic control group, 4.57±0.93 (Figure 4). Among the treatment group, DG400 showed the highest testicular histopathology, 9.47±0.33, and no significance difference was found compared to normal control and OGC 200 (p=0.086 and p=0.175, respectively). A significance difference was found between DG100 with a normal control group and OGC200 (p=0.005 and p=0.014, respectively). DG200 also showed a significance difference with a normal control (p=0.025). No significant difference was found between OGC200 and normal control (p=0.719).

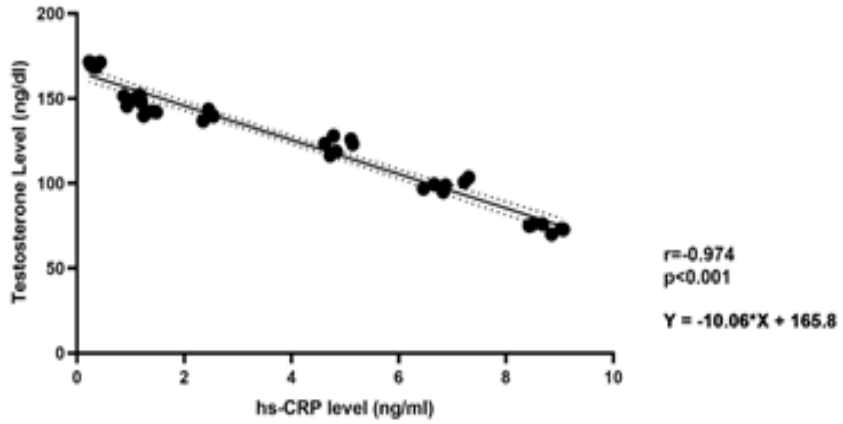

Figure 3 Scatter Dote of hs-CRP Level (X-axis) and Testosterone Level (*y*-axis)

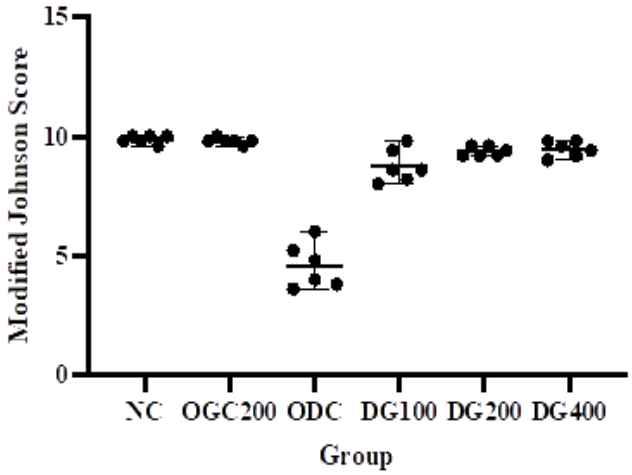

Figure 4 Scattered Plot Figure of Modified Johnson Score among Group

Note: NC= Normal control, OGC200; Obese GMP control with GMP extract of 200 g/kgBW, ODC; Obese-Diabetic control, DG100; Diabetic rats with GMP extract 100 mg/kgBW, DG200; Diabetic rats with GMP extract of 200 mg/kgBW, DG400; Diabetic rats with GMP extract 400 mg/kgBW

Discussion

The GMPE is well known as an herbal medicine in tropical countries. The raw pericarp of mangosteen is not consumable due to its strange taste, so it often becomes waste. Nowadays, it is very popular to develop mangosteens pericarp into herbal medicine due to its various beneficial effects, especially GMPE capsules that have been widely commercialized. The GMPE could prevent most non-communicable diseases, such as DM, cardiovascular disease, cancer, mental illness, and chronic obstructive pulmonary disease.[13–15]

The previous study reported higher hs-CRP levels in diabetic rats induced with STZ 60 mg/kgBW, 12.3±0.9 ng/mL.[16] The hs-CRP level in our study was lower than the previous study, 8.76±0.27 ng/mL. This is presumably due to the lower STZ dose, 45 mg/kgBW, used in our study resulting in lower hs-CRP level. Meanwhile, the HFD diet in the previous study led to a mild increase of hs-CRP level, 1.053±0.0067 ng/mL.[17] In our study, the OGC200 showed a higher hs-CRP level compared to the previous study. This mechanism remains unclear whether the moderate increase of hs-CRP in

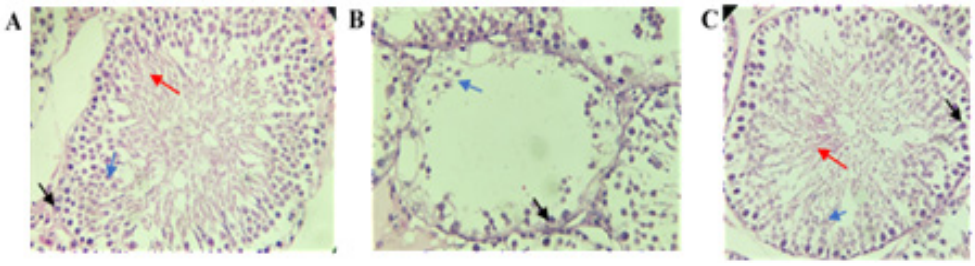

Figure 5 Testicular Histopathology Examination with HE Staining 400x Magnification

Note: (a) A full spermatogenesis with MJS 10 was mostly found in normal rats, (b) The diabetic rats showed late spermatogenesis with MJS 4, no spermatids were found, and (c) the OGC200 and DG mostly showed many late spermatids with MJS 9. Black arrow indicates spermatogonia, blue arrow indicates spermatocytes, and red arrow indicates spermatids. HE; Hematoxylin and eosin stain, MJS; Modified Johnson Scoring OGC200; Obese GMP control with GMP extract of 200 g/kgBW, DG; Diabetic rats with GMP extract

OGC200 is due to the consumption of GMPE itself, or presumably more severe obesity, or any external factors such as different measurement methods, rats genetic, and environmental factor.

In this study, DM significantly reduced testosterone levels. By using the same ELISA kit measurement, the previous study found that rats induced T2DM with STZ 35 mg/kgBW had testosterone levels of approximately 178 ±42.8 ng/dL.[18] Our obese-diabetic control has a lower testosterone level, 73.69±2.22 ng/dL. In addition to the higher STZ applied in our study, based on our knowledge, HFD might also contribute to infertility by decreasing testosterone levels. However, this HFD effect could not be examined in our study because OGC200 showed no significant difference compared to the normal control group. This is presumably since the GMPE could maintain the testosterone levels in obese rats. Moreover, our normal control group also showed lower testosterone level compared to normal control group in the previous study. Different rat strains, maturity, and sexual interactions may also contribute to different testosterone levels.[19]

DM and obesity can progress to reproductive complications. In men with DM, several complications that often occur are testicular dysfunction, impotence, decreased fertility potential, and retrograde ejaculation. The alteration of testosterone levels in men with DM is due to the impairment of Leydig cell. Moreover, oxidative stress due to DM complications may lead to mitochondrial and DNA damage during spermatogenesis. Obesity can cause an increase in visceral adipose tissue, resulting in increased conversion of testosterone to estradiol. In addition, leptin release from adipocytes disrupts the hypothalamic-pituitary axis by suppressing the action of gonadotrophins on Leydig cells.[20]

In our study, GMPE could significantly reduce hs-CRP and increase testosterone levels in obese diabetic rats, dose-dependently. This finding is consistent with previous research. The hs-CRP level is a specific marker for inflammation, and a previous study found that 2,520 mg/day of GMPE might be given to diabetic patients for 90 days, resulting in a reduction in hs-CRP level.[21] Testosterone levels are a marker of reproduction due to its function in stimulating spermatogenesis. The previous study also proved that 25 mg/kgBW isolates of α-mangosteen from GMPE could improve testosterone levels equivalent to 1 mg/kgBW of gliclazide.[22]

Our study also found a negative correlation between hs-CRP and testosterone levels ($r=-0.974$ and $p<0.001$). This indicates that higher levels of hs-CRP correlate with lower testosterone levels. Previous study also documented that CRP was negatively correlated with total testosterone ($r=-0.471$, $p=0.001$) but not calculated free testosterone ($r=-0.238$, $p=0.11$).[23,24] Higher levels of inflammatory markers such as IL-6, IL-1β, TNF-α, and CRP are associated in men with hypogonadism or low testosterone levels.[25] Testosterone therapy also documented leading to reduction of IL-6, IL-1β, and TNF-α. The mechanism underlying testosterone has a protective effect against inflammation because androgens inhibit adipose tissue deposition, resulting in a reduction in fat mass, which is a source of many inflammatory cytokines.[26] Thus, the strong negative correlation between hs-CRP and testosterone levels in our study is presumably due to the direct pathway of obese-DM induced by hs-CRP level as well as the indirect pathway of obese-DM induced by low testosterone levels, resulting in higher hs-CRP levels.

On histopathological examination, DG200 and DG400 showed better improvement in spermatogenesis compared to the obese-diabetic control group. This is presumably due to higher testosterone levels compared to the obese-diabetic control group. However, only DG400 showed no significant difference compared to the normal control group.

The underlying mechanism of reproductive protection in obese-DM rats is due to GMPE containing oxygenated and prenylated xanthone derivatives. There were 14 xanthone derivatives identified in the previous study.[27] The GMPE, with optimization extraction protocols, has α-mangostin concentration 121.01 mg/g.[28] On T2DM, the xanthone compound is important for sensitizing the insulin receptor.[29] This compound also contributes to reducing the progression of metabolic syndrome through activation of mitogen-activated protein kinase (MAPK), suppression of NF-kB, and inhibition of adipocyte differentiation and improvement of lipid profile via SirT1-AMPK and peroxisome proliferator-activated receptors (PPAR) pathways.[30] Besides xanthone, GMPE also has a potential antioxidant capacity that contains various bioactive compounds, for example, flavonoids and phenolic acids. These bioactive compounds also contribute to reducing the progression of T2DM via inhibition peroxidation chain reactions. Thus, the GMPE

is a potential herbal medicine for protecting reproductive function in obese-diabetes rats.

There are several limitations in this study. First, the chemical compounds of GMPE were not characterized in this study. It is very important to know the concentration of xanthone, especially α-mangostin, using our maceration method. Second, several factors might affect the testosterone level measurement in rats, especially sexual interaction and sexual behavior of rats that were not identified in this study. Third, the obese control rats in our study were also given GMPE 200 mg/kgBW. Thus, this might alter the variables observed in our study, and the interpretation of the HFD effect is biased by GMPE. However, this group could represent GMPE in obese rats.

In conclusion, GMPE effectively protects reproductive function in obese-DM rats by increasing testosterone levels and advanced spermatogenesis. GMPE also significantly decreased hs-CRP levels. Further study on sperm morphology and motility is recommended. Administering GMPE to humans as a complementary herbal medicine requires further study to establish its therapeutic effect in humans.

References

1. García-Cruz E, Leibar-Tamayo A, Romero J, Piqueras M, Luque P, Cardeñosa O, et al. Metabolic syndrome in men with low testosterone levels: relationship with cardiovascular risk factors and comorbidities. J Sex Med. 2013;10(10):2529–38.
2. Shamloul R, Ghanem H. Erectile dysfunction. Lancet. 2013;381(9861):153–65.
3. Ibrahim MY, Hashim NM, Mariod AA, Mohan S, Abdulla MA, Abdelwahab SI, et al. α-Mangostin from Garcinia mangostana Linn: an updated review of its pharmacological properties. Arabian J Chem. 2016;9(3):317–29.
4. Wang MH, Zhang KJ, Gu QL, Bi XL, Wang JX. Pharmacology of mangostins and their derivatives: a comprehensive review. Chin J Nat Med. 2017;15(2):81–93.
5. Cho BO, Ryu HW, So Y, Lee CW, Jin CH, Yook HS, et al. Anti-inflammatory effect of mangostenone F in by suppressing NF- κ B and MAPK activation. Biomol Ther (Seoul). 2014;22(4):288–94.
6. Syam S, Bustamam A, Abdullah R, Sukari MA, Hashim NM, Mohan S, et al. β mangostin suppress LPS-induced inflammatory response in RAW 264.7 macrophages in vitro and carrageenan-induced peritonitis in vivo. J Ethnopharmacology. 2014;153(2):435–45.
7. Liu Q, Li D, Wang A, Dong Z, Yin S, Zhang Q, et al. Phytochemistry nitric oxide inhibitory xanthones from the pericarps of Garcinia mangostana. Phytochemistry. 2016;131:115–23.
8. Liu Y, Park J, Chang KH, Chin YW, Lee MY. α- and γ-mangostin cause shape changes, inhibit aggregation and induce cytolysis of rat platelets. Chem Biol Interact. 2015;240:240–8.
9. Taher M, Zakaria T, Susanti D, Zakaria Z. Hypoglycaemic activity of ethanolic extract of Garcinia mangostana Linn. in normoglycaemic and streptozotocin-induced diabetic rats. BMC Complement Altern Med. 2016;16:135.
10. Muniroh M, Nindita Y, Karlowee V, Purwoko Y, Rahmah ND, Widyowati R, et al. Effect of Garcinia mangostana pericarp extract on glial NF - κ B levels and expression of serum inflammation markers in an obese - type 2 diabetes mellitus animal model. Biomed Rep. 2021;15(1):63.
11. Jariyapongskul A, Areebambud C, Suksamrarn S, Mekseepralard C. Alpha-mangostin attenuation of hyperglycemia-induced ocularhypoperfusion and blood retinal barrier leakage in the early stage of type 2 diabetes rats. Biomed Res Int. 2015;2015:785826.
12. Mushtaq H, Alam S, Khan MA. Histopathological patterns of testicular biopsies in male infertility. J Islamabad Med Dent Coll. 2013;2(4):81–6.
13. Ashton MM, Dean OM, Walker AJ, Bortolasci CC, Ng CH, Hopwood M, et al. The therapeutic potential of mangosteen pericarp as an adjunctive therapy for bipolar disorder and schizophrenia. Front Psychiatry. 2019;10:115.
14. Baroroh K, Suradi S, Rima A. Pengaruh ekstrak kulit manggis terhadap perbaikan klinis, kadar interleukin-6 dan malondialdehyde plasma pasien PPOK eksaserbasi akut. J Respir Indones. 2018;38(3):164–72.
15. Boonprom P, Boonla O, Chayaburakul K, Welbat JU, Pannangpetch P, Kukongviriyapan U, et al. Garcinia mangostana pericarp extract protects against oxidative stress and cardiovascular remodeling via suppression of p47phox and iNOS in nitric oxide deficient rats. Ann Anat. 2017;212:27–36.

16. Sibiya N, Ngubane P, Mabandla M. Cardioprotective effects of pectin–insulin patch in streptozotocin-induced diabetic rats. J Diabetes. 2017;9(12):1073–81.
17. Tandiari D, Yustisia I, Santoso A, Cangara H, Hamid F, Daud NA. Effect of high-fat high fructose diet and carbon tetrachloride on high sensitivity C reactive protein (hsCRP) levels male Wistar rat. Indones J Biomed Sci. 2021;15(1):71–4.
18. Sudirman S, Su C, Tsou D, Lee M, Kong Z. Hippocampus kuda protein hydrolysate improves male reproductive dysfunction in diabetic rats. Biomed Pharmacother. 2021;140:111760.
19. Shulman LM, Spritzer MD. Changes in the sexual behavior and testosterone levels of male rats in response to daily interactions with estrus females. Physiol Behav. 2014;133:8–13.
20. Beatrice AM, Dutta D, Kumar M, Siddegowda SK, Sinha A, Ray S, et al. Testosterone levels and type 2 diabetes in men: current knowledge and clinical implications. Diabetes Metab Syndr Obes. 2014;7:481–6.
21. Handayani O, Sargowo D, Rohman MS, Satrijo B, Tjahjono CT, Hendrawan D. The effect of add-on garcinia mangostana L. extract on endothelial dysfunction in type 2 diabetes mellitus subjects with high risk framingham score: a cohort study. Heart Sci J. 2020;1(1):21–5.
22. Nelli GB, K AS, Kilari EK. Antidiabetic effect of α -mangostin and its protective role in sexual dysfunction of streptozotocin induced diabetic male rats antidiabetic effect of α -mangostin and its protective role in sexual dysfunction of streptozotocin induced diabetic male rats. Syst Biol Reprod Med. 2013;59(6):319–28.
23. Tremellen K, McPhee N, Pearce K. Metabolic endotoxaemia related inflammation is associated with hypogonadism in overweight men. Basic Clin Androl. 2017;27:5.
24. Tremellen K, McPhee N, Pearce K, Benson S, Schedlowski M, Engler H. Endotoxin initiated inflammation reduces testosterone production in men of reproductive age. Am J Physiol Endocrinol Metab. 2018;314(3):E206–13.
25. Traish A, Bolanos J, Nair S, Saad F, Morgentaler A. Do androgens modulate the pathophysiological pathways of inflammation? appraising the contemporary evidence. J Clin Med. 2018;7(12):549.
26. Bianchi VE. The anti-inflammatory effects of testosterone. J Endocr Soc. 2019;3(1):91–107.
27. Yang R, Li P, Li N, Zhang Q, Bai X, Wang L, et al. Xanthones from the Pericarp of Garcinia mangostana. Molecules. 2017;22(5):683.
28. Ghasemzadeh A, Jaafar HZE, Baghdadi A, Tayebi-meigooni A. Alpha-mangostin-rich extracts from mangosteen pericarp : optimization of green extraction protocol and evaluation of biological activity. Molecules. 2018;23(8):1852.
29. Watanabe M, Gangitano E, Francomano D, Addessi E, Toscano R, Costantini D, et al. Mangosteen extract shows a potent insulin sensitizing effect in obese female patients : a prospective randomized controlled pilot study. Nutrients. 2018;10(5):586.
30. Tousian-Shandiz H, Razavi BM, Hosseinzadeh H. Review of garcinia mangostana and its xanthones in metabolic syndrome and related complications. Phyther Res. 2017;31(8):1173–82.