Morphine and *Phoenix dactylifera* (dates) effects on the histological features of male rat reproductive organs

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**Background:** Previous studies have shown that morphine negatively effects male fertility while *Phoenix dactylifera* (dates) could cure male infertility by the exhibition of antagonist effects. This study was conducted to assess the possible ameliorating effects of dates on the histological features of morphine-induced male rat reproductive organs. **Materials and Methods:** Adult male Sprague Dawley rats age 7–9 weeks old, 200–250 g body weight (BW) were divided into six rats per each group: Group 1, force-fed with distilled water, 1 ml/kg BW for 35 days (control); Group 2, intramuscularly (IM) injected with morphine, 20 mg/kg BW for 7 days followed by force-fed with distilled water for 28 days; Group 3, force-fed with distilled water for 7 days followed by crude *P. dactylifera* extract, 200 mg/kg for 28 days; Group 4, injected (IM) with morphine, 20 mg/kg BW for 7 days followed by force-fed of crude *P. dactylifera* extract, 200 mg/kg for 28 days. Rats were sacrificed on day 36. The seminal vesicle (SV) and prostate gland (PG) were removed and fixed before histological processes. **Results:** In morphine-treated rats, the SV showed the absence of honeycomb-like appearance with flattened columnar cells while in the PG, eosinophilic secretion was noted to be absent from glandular lumina as compared to the control group. Administration of *P. dactylifera* extract in Group 4 showed improvement in histoarchitecture of the SV and PG with complex mucosal infoldings and glands luminal filled with secretion. **Conclusion:** *P. dactylifera* extract has a protective effect against the adverse effects of morphine on the male rat reproductive organs.

**Key words:** Dates, morphine, *Phoenix dactylifera*, prostate gland, rat, seminal vesicle

**INTRODUCTION**

In Malaysia, the number of drug abusers has increased from 15,101 (2010) to 21,777 (2014).[¹] Based on the National Anti‑Drugs Agency, 96.79% of the illicit drug users are men and most commonly, abused drugs are opioid, which refers to heroin and morphine.[¹] Morphine is an opioid pain medication that acts on the central nervous system (CNS) for strong analgesic action. Despite its beneficial use, it has some adverse side effects such as drowsiness, vomiting, constipation, and hormonal imbalance. Long term used of morphine causes oxidative damage to the liver, kidney, and brain.[²] In addition, excessive or repeated use of the drug may play a significant role in male infertility.[³,⁴] Several studies have shown that chronic morphine exposure adversely affected male fertility by reducing testosterone, luteinizing hormone (LH) and follicle‑stimulating hormone (FSH) levels as well as decreasing the partial weights of testes, seminal vesicles (SVs), and prostate glands (PGs).[⁵,⁶]

Columnar epithelial cells are the crucial part in the SV and PG as their functions are to secrete fructose and prostaglandins into their glandular lumina, which provides energy for sperm. Therefore, the decreased weight of the SV and PG could be due to the reduction...
in the height of columnar epithelial cells and secretion in the lumina of the glands.[7,8] Similarly, Londonkar et al.[9] found that morphine caused a reduction in the weight of epididymides and vas deferens. As a result of its gonadal activities inhibition, it also lowered the sperm count in the cauda epididymides. Through these studies, the authors suggested the main cause for the chronic morphine adverse effects was through hypothalamo-hypophyseal-gonadal axis that would lead to long-term endocrine disturbances during sexual maturation.[10] Due to these findings, therapeutic agents such as gonadal stimulating drugs to induce hormonal functions have been used as treatment for male infertility.

Traditional medicines are widely used and aggressively been studied by researchers as they are cheap and locally available. These medicines have minimum side effects as compared to modern medicines.[11,12] One of the fruits that have long been used as a therapeutic agent is dates (Phoenix dactylifera) which have potential in treating chronic toxicity of opioids such as morphine.[13] El-Kott et al.[14] reported that P. dactylifera extract possesses anti-oxidant and anti-inflammatory effects on male rats as it comes with various sources of vitamins and energy. Previous studies also confirmed that P. dactylifera contains cholesterol, carotenoid, and gonad-stimulating components that could stimulate gonadotropin activity.[15,16] The stimulation of gonadotropin-releasing hormone (GnRH) would increase the production of LH, FSH, and testosterone, thus improve the function of the male reproductive system. P. dactylifera suspensions were also noted to increase the weight of testis and epididymis as well as enhance the sperm motility, count, morphology, and its DNA quality.[17]

Even though it has been well established that P. dactylifera has ameliorating effects on male reproduction, to the best of our knowledge, the effects of P. dactylifera on morphine-induced infertility has not yet been examined. Therefore, the present study was conducted to observe such effects of P. dactylifera on the reproductive organs, the SV and PG, of male rats after morphine administration.

**MATERIALS AND METHODS**

**Preparation of extract**
The P. dactylifera fruits were purchased from a local market. The fruits flesh were boiled with distilled water and pulverized using an electric blender. It was then filtered and freeze-dried to remove the water content until it became powder and kept in-20°C freezer. On usage, the powder was diluted with distilled water and stored in a refrigerator at 4°C to avoid any contamination. This solution was given to the rats at a dose of 200 mg/kg of body weight (BW).[18]

**Drug**

Morphine solution was obtained from the pharmacy of the University Malaya Medical Centre (UMMC). It was used as a stock solution to treat the rats at a dose of 20 mg/kg of BW.[19]

**Animal housing**

Experimental procedures were conducted based on the Guideline for Animal of the Institutional of Animal Care and Use Committee, University of Malaya [PASUM/30/12/2015/AB (R)]. Twenty-four male Sprague–Dawley rats (7–9 weeks) 200–250 g were obtained from UMMC, University of Malaya. The rats were reared in the animal house at the Centre for Foundation Studies in Science, University of Malaya (Pusat Asasi Sains Universiti Malaya, PASUM). The animals were acclimatized for a week before experiment. Two rats were housed per cage with sawdust as bedding under standard laboratory condition, 27°C room temperature with good ventilation. Light and dark periods were approximately 12 h/day, respectively. Chow food and tap water were given to the rats’ ad libitum for 35 days throughout the experimental periods.

**Experimental design**

Animals were grouped into four equal groups (6 rats each): (i) Group 1 was force-fed with distilled water, 1 ml/kg BW for 35 days, (ii) Group 2 was intramuscularly (im) injected with morphine, 20 mg/kg BW for 7 days followed by force-fed with distilled water for 28 days, (iii) Group 3 was force-fed with distilled water for 7 days followed by crude P. dactylifera extract, 200 mg/kg for 28 days, and (iv) Group 4 was injected (im) with morphine, 20 mg/kg BW for 7 days followed by force-fed of crude P. dactylifera extract, 200 mg/kg for 28 days. Rats were sacrificed on day 36 by overdose of ketamine-xylazine injection (im).

**Preparation of histological study**

The SVs and PGs were extracted, fixed in Davidson’s solution for 2 days and then stored in formalin solution (Cat no: K46046503441, Merck) prior subjected to histological processes. The tissues were dehydrated with a series of graded alcohol solutions. The dehydrated tissues were then infiltrated and embedded in a small block of paraffin wax (Paraplast, USA) before sectioning at 5 micrometer (µm) thickness by using a microtome (Cat no: 08050282, Feather). The tissue sections were then mounted on the microscope slides. This was followed by the tissue clearance process in xylene (Cat no: 1330-20-7, Systerm) and staining with hematoxylin and eosin solution. A mounting medium, dibutyl phthalate polystyrene xylene (Cat no: 100579, Merck) was used to adhere to the tissue on the slide with coverslip. The slides were then observed under light microscope (Olympus, Japan) with ×20 and ×40.
Histological study

General histoarchitecture of the seminal vesicle and prostate gland

The SV and PG were analyzed under light microscope for the general histoarchitecture. The normal SV consists of convoluted folds of mucosal layers which form the honeycomb-like appearance. The mucosal layer is made up of lamina propria and pseudostratified columnar cells. It is surrounded by outer longitudinal and inner circular layers of smooth muscles. The lumina are filled with acidophilic secretion. On the other hand, the mucosa of normal PG consists of lamina propria and two layers of epithelial tissue that are the outer layer of the low cuboidal and inner layer of tall columnar epithelia. The papillary infoldings of these layers are distinguished with the presence of glandular lumina for its eosinophilic secretion.[20,21]

Measurement of the columnar epithelial cells of the seminal vesicle and prostate gland

The SV and PG were analyzed under light microscope using NIS-Elements Imaging System Software (Nikon Corporation, Minato-ku, Tokyo 108-6290, Japan). The height of the columnar epithelial cells (length along the apical-basal axis) was measured in µm under x40 for SV and x20 for PG.[7]

Statistical analysis

Data analysis was performed with Statistical Package for Social Science (SPSS) Version 23.0 (IBM Corporation, Armonk, New York, U.S.) and the results were expressed as mean ± standard error the variables were compared using one-way ANOVA test and Duncan multiple range test P < 0.05 was considered statistically significant.

RESULTS

Histology of the seminal vesicle

Control group

The histoarchitecture of SV in this group exhibited highly folded mucosal layers with tall pseudostratified columnar cells which form the honeycomb-like appearance. The lumina were filled with acidophilic secretion [Figure 1a].

Morphine group

The morphine group showed an absence of the honeycomb-like appearance. Columnar cells appeared to be flattened with the absence of acidophilic secretion in the glandular lumina as compared to the control group [Figure 1b].

Phoenix dactylifera extract group

Histological appearance of SV in this group was similar to that of in the control group with the presence of the honeycomb-like appearance. The gland was lined by pseudostratified columnar cells, and its acidophilic secretion was distinguished in the lumina [Figure 1c].

Morphine - Phoenix dactylifera extract group

Complex papillary infoldings of the tall columnar cells were observed in this group. The glandular lumina were filled
with eosinophilic secretion as compared to that of in the morphine group [Figure 2d].

Height of columnar epithelial cells in the seminal vesicle
The analysis of variance indicated that the treatments had significantly affected the height of columnar epithelial cells in all groups \( (P < 0.05) \) [Table 1]. The morphine group showed the significant lowest mean height of columnar epithelial cells \( (14.56 \pm 2.76 \mu m) \) among all groups \( (P < 0.05) \). The highest mean height of columnar epithelial cells was observed in the \( P. dactylifera \) group \( (23.00 \pm 4.54 \mu m) \) as compared with the other groups \( (P < 0.05) \) [Table 2].

Height of columnar epithelial cells in the prostate gland
The analysis of variance showed that the treatments had significantly affected the height of the columnar epithelial cells in all groups \( (P < 0.05) \) [Table 1]. The height of columnar epithelial cells in the morphine group was the lowest \( (20.09 \pm 3.59 \mu m) \) among all groups \( (P < 0.05) \) [Table 2].

DISCUSSION

Morphine has long been used as a medicinal treatment for its analgesic action. Many studies reported by researchers had shown that exposure to morphine increased the percentage of infertility among males.[22,23] In the present study, nonexistence of acidophilic secretion in the lumen with the absence of honeycomb-like appearance was observed in the SV of rats treated with morphine. Similarly, deficiency of eosinophilic secretion in the glandular lumina with less papillary infoldings of the columnar epithelial cells of the PGs was also noted in the same group of rats.

In addition, the height of the columnar epithelial cells of SV and PG of the rats was significantly reduced compared to other treatment groups. These findings were found to be concurrent with previous studies that showed similar adverse effects of morphine on the SV and PG.[4,24,25]

It was revealed that illicit drugs like morphine could cause damage to the structural integrity of the secondary sex organs by inhibition of the LH secretion, which subsequently leads to the reduction of testosterone levels.[25,26] Adams et al.[6] had shown that morphine reduced the LH and FSH as well as the testosterone by disrupting the GnRH in the pituitary glands which is essential for androgen synthesis. This was supported by another study which revealed that structural changes found in the secondary sex organs were caused by alteration in the gonadal and pituitary functions.[21,27] Therefore, this could be the reason for the disruption of SV and PG structures found in the present study since the development and function of the secondary sex organs are dependent on the production of the hormones.

Various medicinal plants, including dates fruits, were recommended for the treatment of various diseases as ingredients found in them possess anti-oxidant, anti-inflammatory, and antibacterial activities.[28] The therapeutic effect of \( P. dactylifera \) as a traditional medicine for male infertility had been shown by various studies conducted in the past few decades.[17,29,30] Similar findings were observed in the present study where \( P. dactylifera \) given to rats induced morphine have shown an improvement in the histoarchitecture of the SV and PG. Both glands have shown highly folded mucosal layers with a significant increase in the height of their epithelia. There was also the presence of acidophilic secretion in the lumina of the glands.

Table 1: Mean square analysis of variance for the columnar epithelial cell height of seminal vesicle and prostate gland

| Source of variation | Df | Mean square | Seminal vesicle | Prostate gland |
|---------------------|----|-------------|----------------|---------------|
| Treatment           | 3  | 630.22*     | 436.61*        |               |
| Error               | 188| 14.44       | 13.69          |               |
| Total               | 192|             |                |               |

*Significant difference at \( P<0.05 \)

Table 2: Height of the columnar epithelial cells of seminal vesicle and prostate gland in rats treated with morphine and \( P. dactylifera \) extract \( (n=6) \)

| Group                  | Parameters (\( \mu m \)), mean±SE | Seminal vesicle | Prostate gland |
|------------------------|-----------------------------------|----------------|---------------|
| Control                | 20.98±3.90b                      | 26.36±3.64a    |               |
| Morphine               | 14.56±2.76a                      | 20.09±3.59a    |               |
| \( P. dactylifera \)   | 23.00±4.54b                      | 25.84±3.50b    |               |
| Morphine – \( P. dactylifera \) | 20.32±3.79ab                  | 26.13±4.04b    |               |

**Note:** Superscripts in the same column show significant difference at \( P<0.05 \).

\( P. dactylifera; \) SE=Standard error
Previous studies reported that the gonadotrophin like substances or steroidal compound presence in dates palm pollen would increase the gonadotropin activity in the pituitary glands of the rat.\textsuperscript{15,16,31} Stimulation of GnRH in the pituitary glands would increase the level of androgenic hormone such as testosterone levels in the male reproductive system.\textsuperscript{12,30} Since the SV and PG are hormone-dependent organs for its function and development, an increase in the androgen synthesis might be the reason for the improvement in the histoarchitecture of the SV and PG in \textit{P. dactylifera} group of the present study.

In comparison to other fruits, dates were found to contain extremely high levels of phenolics, which was hypothesized to have been formed as a result of exposure to extreme temperature and climate.\textsuperscript{34} Plant polyphenols have been found to possess a wide range of biological effects such as estrogenic and anti-estrogenic activity, anti-proliferative activity, induction of cell cycle arrest and apoptosis, prevention of oxidation, regulation of the host immune system, anti-inflammatory activity, up-regulation of genes producing anti-oxidant enzymes, and the ability to change cellular signaling.\textsuperscript{35} Dates with its anti-oxidant properties have the capacity to act as potent scavengers of reactive oxidative species. This would allow the body to sustain or recover its normal levels of endogenous enzymes such as catalases and peroxidases that protect the body at a cellular level from any toxicants exposure.

In addition, aqueous dates extract also possesses potent free radical scavenging activity. Aqueous \textit{P. dactylifera} extract of 0.8 mg/mL was shown to scavenge 50% of superoxide radicals formed by photoreduction of riboflavin and 100% of superoxide radicals at 1.5 mg/mL.\textsuperscript{34} This beneficial factor could also contribute to ameliorating the damage to the epithelial cells of the mucosal layers in the SV and PG of morphine-induced rats, as seen in the present study.

Based on the findings, the present study was the only study that focused on the potential healing effects of \textit{P. dactylifera} against the adverse effects of morphine on the SV and PG. However, there were a few limitations in this study. First, only a single dosage of morphine (20 mg/kg) was used, whereas drug users might be using higher dosages of morphine. Thus, higher multiple dosages of morphine could be used to strengthen this study. Second, the duration of morphine exposure in this study was limited to only 7 days, which might not reflect the longer duration used by drug users as a result of the drug’s addiction. As for the future study, we suggest investigating the hormonal levels, which are crucial for structural development and functioning of the male reproductive organs. Further study should also explore the underlying healing mechanism of \textit{P. dactylifera}.

**CONCLUSION**

It is apparent that \textit{P. dactylifera} exerts healing effects on the morphine-induced male rats’ reproductive organs. These beneficial effects of \textit{P. dactylifera} led to the improvement in the tissue histoarchitecture and function of columnar epithelial cells in the SV and PG. This study supports the use of an inexpensive dietary supplement such as the \textit{P. dactylifera} extract in improving male fertility among morphine addicts.

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**Conflicts of interest**

There are no conflicts of interest.

**REFERENCES**

1. National Anti-Drugs Agency. Drug Information 2014. Malaysia: National Anti-Doping Agency; p. 1-87. Available from https://www.adk.gov.my/en/public/drugs-information-books/. [Last accessed on 2015 Dec 18].

2. Sani IH, Umar MI, Mohamad N, Rao US, Khalili RM, Bakar NH. Reviews on calcium mediated secondary messengers in chronic opioid exposure/addiction. J Appl Pharm Sci 2015;5:114-9.

3. Hsiao PN, Chang MC, Cheng WF, Chen CA, Lin HW, Hsieh CY, \textit{et al}. Morphine induces apoptosis of human endothelial cells through nitric oxide and reactive oxygen species pathways. Toxicology 2009;256:83-91.

4. Ghouisi M, Yousofvand N. Impact of morphine dependency and detoxification by methadone on male’s rat reproductive system. Iran J Reprod Med 2015;13:275-82.

5. James RW, Heywood R, Crook D. Effects of morphine sulphate on pituitary-testicular morphology of rats. Toxicol Lett 1980;7:61-70.

6. Adams ML, Sewing B, Forman JB, Meyer ER, Cicero TJ. Opioid-induced suppression of rat testicular function. J Pharmacol Exp Ther 1993;266:323-8.

7. Welsh M, Moffat L, Jack L, McNally A, Brownstein D, Saunders PT, \textit{et al}. Deletion of androgen receptor in the smooth muscle of the seminal vesicles impairs secretory function and alters its responsiveness to exogenous testosterone and estradiol. Endocrinology 2010;151:3374-85.

8. Tlachi-López JL, López A, Hoffman K, Velázquez-Moctezuma J, García-lorenzana M, Lucio RA. Rat dorsal prostate is necessary for vaginal adhesion of the seminal plug and sperm motility in the uterine horns. Biol Res 2011;44:259-67.
9. Londonkar RL, Sharangouda S, Patil SB. Morphine induced inhibition of the activities of accessory reproductive ducts in male rats orient. Pharm Exp Med 2008;8:67-72.

10. Yilmaz B, Konar V, Kutlu S, Sandal S, Canpolat S, Gezen MR, et al. Influence of chronic morphine exposure on serum LH, FSH, testosterone levels, and body and testicular weights in the developing male rat. Arch Androl 1999;43:189-96.

11. Wangchuk P. Health impacts of traditional medicines and bio-prospecting: A world scenario accentuating Bhutan’s perspective. J Bhuian Stud 2008;18:116-34. Available from: http://www.bhutanstudies.org.bt. Last accessed on 2016 May 10.

12. Prasad S, Tyagi AK. Traditional medicine: The goldmine for modern drugs. Adv Tech Biol Med 2015;3:e108.

13. Sani IH, Bakar NH, Rohin MA, Suleiman I, Umri MI, Mohamad N. Phoenix dactylifera Linn as a potential novel anti-oxidant in treating major opioid toxicity. J Appl Pharm Sci 2015;5:167-72.

14. El-Kott AF, Sayed AA, El-Sayad SM, Abdoulrahman MH. The pharmaceutical effect of dates palm fruit extract (Phoenix dactylifera L) against amitraz-induced infertility in male rats. Adv Life Sci Technol 2014;22:14-26.

15. Mehraban F, Jafari M, Akhtarbar Toori M, Sadeghi H, Joodi B, Mostafazade M, et al. Effects of date palm pollen (Phoenix dactylifera L.) and Astragalus ovina on sperm parameters and sex hormones in adult male rats. Iran J Reprod Med 2014;12:705-12.

16. Al-Chalabi S. Effect of aqueous extract of Date Palm Pollen (DPP) on the sperm characteristic and serum testosterone FSH and LH values in albino male rats treated with sodium fluoride. Iraqi J Vet Med 2014;38:41-7.

17. Bahnmanpour S, Talaei T, Vojdani Z, Panjehshahin MR, Poostpasand A, Zareei S, et al. Effect of Phoenix dactylifera pollen on sperm parameters and reproductive system of adult male rats. Iran. J Med Sci. 2006;31:208-12.

18. Bahnmanpour S, Kavooosi F, Talaei T, Panjehshahim MR. Effects of dates palm (Phoenix dactylifera) gemmule extract on morphometric parameters of reproductive tissues, hormones and sperm quality in rat. Anat Sci 2013;10:144-50.

19. Tokunaga Y, Muraki T, Hosoya E. Effect of repeated morphine administration on copulation and on the hypothalamic-pituitary-gonadal axis of male rats. Japan J Pharmacol 1977;27:65-70.

20. Stevens A, Lowe J. Human Histology. 3rd ed. Philadelphia: Elsevier/ Mosby; 2005.

21. Lina S, Hashida NH, Eliza H. Role of Habbatus sauda towards the histological features of nicotine treated male rats seminal vesicle and prostate gland. Biomed Res 2014;25:11-8.

22. Cicero TJ, Nock B, O’Connor L, Meyer ER. Role of steroids in sex differences in morphine-induced analgesia: Activational and organization effects. J Pharm Exp Ther 2002;300:695-701.

23. Takzare N, Samizadeh E, Shoar S, Majidi Zolbin M, Naderan M, Lashkari A, et al. Impacts of morphine addiction on spermatogenesis in rats. Int J Reprod Biomed (Yazd) 2016;14:303-8.

24. Cicero TJ, Meyer ER, Wiest WG, Olney JW, Bell RD. Effects of chronic morphine administration on the reproductive system of the male rat. J Pharmacol Exp Ther 1975;192:542-8.

25. Cicero TJ, Bell RD, Meyer ER, Schweitzer J. Narcotics and the hypothalamic-pituitary-gonadal axis: Acute effects on luteinizing hormone, testosterone and androgen-dependent systems. J Pharmacol Exp Ther 1977;201:76-83.

26. Purohit V, Singh HH, Ahluwalia BS. Evidence that the effects of methadone and marijuana on male reproductive organs are mediated at different sites in rats. Biol Reprod 1979;20:1039-44.

27. Cicero TJ, Schainker BA, Meyer ER. Endogenous opioids participate in the regulation of the hypothalamus-pituitary-luteinizing hormone axis and testosterone’s negative feedback control of luteinizing hormone. Endocrinology 1979;104:1286-91.

28. Rahmani AH, Aly SM, Ali H, Babiker AY, Srikar S, Khan AA. Therapeutic effects of date fruits (Phoenix dactylifera) in the prevention of diseases via modulation of anti-inflammatory, anti-oxidant and anti-tumour activity. Int J Clin Exp Med 2014;7:483-91.

29. Abedi A, Parviz M, Karimian SM, Sadeghipour Rodsari HR. The effect of aqueous extract of Phoenix dactylifera pollen grain on sexual behavior of male rats. J Phys Pharm Adv 2012;2:235-42.

30. Orabi SH, Shawky SM. Effect of dates palm (Phoenix dactylifera) seeds extracts on hematological, biochemical parameters and some fertility indices in male rats int. J Sci Basic Appl Res 2014;17:137-47.

31. Hassan WA, El-Kashlan AM, Ebssan NA. Egyptian date palm pollen ameliorates testicular dysfunction induced by cadmium chloride in adult male rats. J Am Sci 2012;8:659-69.

32. Ahmed MB, Hasona NA, Selemain AH. Protective effects of extract from dates (Phoenix dactylifera L) and ascorbic acid on thioacetamide-induced hepatotoxicity in rats. Iran J Pharm Res 2008;7:193-201.

33. Rasekh A, Jashni HK, Rahamanian K, Jahromi AS. Effect of palm pollen on sperm parameters of infertile man. Pak J Biol Sci 2015;18:196-9.

34. Vinson JA, Zubik L, Bose P, Samman N, Proch J. Dried fruits: Excellent in vitro and in vivo antioxidants. J Am Coll Nutr 2005;24:44-50.

35. Rodrigo R, Libuy M, Feliu F, Hasson D. Polyphenols in disease: From diet to supplements. Curr Pharm Biotechnol 2014;15:304-17.

36. Vayalil PK. Antioxidant and antimutagenic properties of aqueous extract of date fruit (Phoenix dactylifera L. Arecaceae). J Agric Food Chem 2002;50:610-7.