Translational Research in Urology

Home Page: www.transresurology.com

Review

The Impact of Opium on Men's Fertility and DNA Fragmentation: A Literature Review

Alireza Namazi Shabestari[1], Seyed Saeed Tamehri Zadeh[2], Alimohammad Fakhr Yasseri[3], Mehdi Ebrahimi[4], Bassim Issa[5], Ramin Rahimnia[6*]

[1]*Department of Geriatric Medicine, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran*

2Prevention of Metabolic Disorders Research Center, Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran

[3]*Shariati Hospital, Alborz University of Medical Sciences, Alborz, Iran*

[4]*Department of Internal Medicine, Faculty of Medicine, Sina Hospital, Tehran University of Medical Sciences, Tehran, Iran*

5Urology department, Royal Bolton Hospital, Greater Manchester, United Kingdom

6Department of Medical Nanotechnology, School of Advanced Technologies in Medicine, Tehran University of Medical Sciences, Tehran, Iran

HIGHLIGHTS

- Morphine can decrease sperm chromatin condensation and increases the rate of sperm apoptosis.
- In cases of unexplained infertility in men, opium consumption should be considered as a possible factor..
- Genistein administration could increase the quality of spermatozoal changes.

ARTICLE INFO

Receive Date: 18 March 2023

Accept Date: 20 May 2023

Avaliable online: 10 June 2023

DOI: 10.22034/TRU.2023.393707.1144

***Corresponding Author**:
Ramin Rahimnia
Email: raminrahimnia4@gmail.com
Address: Department of Medical Nanotechnology, School of Advanced Technologies in Medicine, Tehran University of Medical Sciences, Tehran, Iran.

ABSTRACT

Addiction to opium and illicit substances has become a significant issue that must be dealt with because limitless complications can arise from their misusage. It's impossible to deny the significance of those. The relationship between OS (Oxidative stress), which eventually leads to DNA fragmentation and illicit substance addiction has been suspected, and there have been many attempts to prove it. Infertility involves many couples globally, and several causes are attributed to it. However, the reasons for many of these cases remain unknown. We investigated the review studies on the relationship between illicit substances and infertility. Surprisingly, the odds of fertility decrease in individuals who administrate illegal substances. Many studies have illuminated that in addition to hormonal modulation levels and pathological changes, DNA fragmentation should be considered as a cause of infertility. However, most studies were animal studies, and there is a lack of evidence in clinical studies. Antioxidants can be used as the first-choice treatment in patients with unknown causes of infertility. The outcomes of antioxidants in animal studies were satisfactory; however, against all the odds, the results in clinical studies were not as good.

Keywords: Substance Use; DNA Fragmentation; Infertility; Opium

Introduction

Opium's capacity for addiction, physically and mentally, has been well-demonstrated. Drug abusers usually encounter a defective cycle that consists of positive and negative parts leading the individual to consume drugs repetitively. The incidence of opium consumption has been rising sustainably. This is considered a prevailing problem that imposes a tremendous financial and social burden on the healthcare system (1).

A significant number of studies have focused on the

neurological aspects of opium addiction, and the effects of opium on the central nervous system have been clearly illustrated. Recently, much interest belonged in its influence on other organ systems, especially reproductive and cardiovascular systems, which have a connection with opium by three primary receptors (2-4).

Oxidative stress (OS) occurs when abnormal situations generate oxidants that exceed antioxidants, this can cause DNA damage and fragmentations (DF) (5). DF can result in a cascade of events by inducing protease activity and apoptosis, which account for some human disorders such as male infertility. Reactive oxygen species (ROS) produced by the integration of xanthine and xanthine oxidase generally participate in the normal process of capacitation of human spermatozoa (6). However, a high level of production and clearance of ROS are potent to trigger OS through a signaling loop. The process of impairment in sperm function is the leading cause of male infertility. It has been shown that chronic codeine exposure causes sperm DNA fragmentation and poor sperm quality primarily via oxidative stress rather than activation of caspase 3-dependent apoptosis (7, 8). Although some cases have well-known factors that play a pivotal role in male infertility, some patients cannot attribute their condition to any specific reason, these are denominated as idiopathic cases. The role of ROS in infertility has been proved, and it is thought that ROS production is the second primary reason for infertility, irrespective of congenital diseases (9) (Figure 1).

Based on recent studies, we wanted to review DF due to opiate consumption and display how it can play a role in male infertility. In this paper, we review the impact of Opium on DNA fragmentation and later, on infertility. A limited literature search was conducted by an information specialist on resources including PubMed, the Cochrane Library, and a focused Internet search. The search strategy was based on controlled vocabularies, such as the National Library of Medicine's MeSH (Medical Subject Headings) and keywords. No filters were applied to limit the retrieval by study type. Where possible, recovery was limited to English, in documents published between January 1, 1985, and July 29, 2019. We aim to summarize the literature regarding the connection between Opium use and DNA fragmentation.

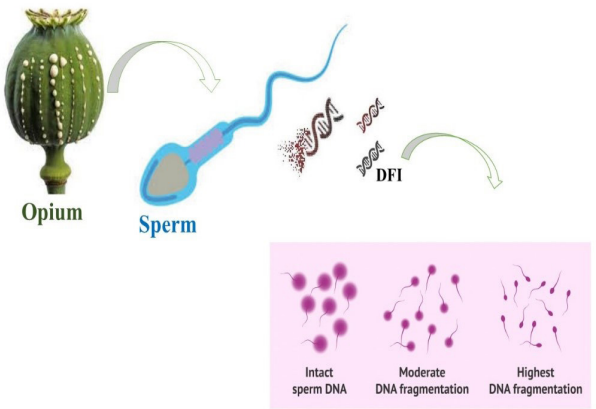

Figure 1. The sperm DNA fragmentation index (DFI) reflects the integrity of and the damage to the DNA, the genetic material of the sperm, thereby detecting potential sperm damage.

Opiate

Despite the debatable history of opium use for medical purposes for the first time, most authors agree that the spread of Opium began in the early eighth century in India (10). Opium poppy (morphine, thebaine, codeine, papaverine, noscapine, Etc.) was used for narcotics and sedation purposes. Nowadays, Opium-derived substances, including morphine, codeine, and hydrocodone, are used as solid painkillers. In contrast, heroin, derived from Opium, can be harmful to an individual's health and can cause a high grade of addiction (11).

DNA fragmentation

Apoptosis is characterized by a process that results in the breakdown of the cell's DNA into smaller fragments, almost similar to necrosis. DF occurrence depends on DNA fragmentation factors (DFF), containing 45-kDa and 40-kDa (12, 13).

During the apoptosis process, DFF45 is separated from DFF40 by caspase-3; then, DFF40 will be activated and will break DNA into smaller fragments that call DF (14). The disturbance of the apoptosis process can cause some disorders, including autoimmune diseases, cancer, etc.

Morphine

Morphine is one of the subdivided opioids that have been widely used as an analgesic in patients with severe and chronic pain (15). The half-life of morphine is between 1.5 to 7 hours, and various types of its products can be used depending on some factors. The analgesic pathway of morphine which is similar to codeine has been illustrated. When morphine binds to its receptor (Mu (μ) opioid receptor), the signal will be received by some enzymes that regulate its effect (16). On the one hand, quite a few investigations showed that morphine can interrupt the immune system. Morphine not only influences lymphocyte counts, thymic weight, and splenic weight but also decreases the lymphocyte mitogenic process. These effects are attributed to either the direct impact of morphine on its lymphocyte receptor or the indirect effect of morphine on the nervous system receptor (17, 18). Sabita et al. demonstrated that low and high doses of morphine increase apoptosis of lymph node lymphocytes through different pathways (19). A low dose is associated with an increase in caspase□3□ and caspase□8□mediated apoptosis. Whereas the high dose of morphine has its effect by changes in NO level. Some other studies indicated that morphine (20 mg/kg, SC, for four days) was accompanied by an increase in corticosterone level, which initiated the

Table 1. A brief review of studies related to opium and fertility

First author	Year	DOI/PMID	Conclusion
Ghasemi-Esmailabad S (52)	2022	10.5935/1518-0557.20210110	Morphine can decrease sperm chromatin condensation and increases the rate of sperm apoptosis
Jalili C(53)	2016	PMID: 27200423	Genistein administration could increase the quality of spermatozoa and prevent morphine-induced adverse effects on sperm parameters.
Safarinejad MR(54)	2013	10.1016/j.reprotox.2012.11.010	In cases of unexplained infertility in men, opium consumption should be considered as a possible factor.
Subirán N (55)	2011	10.2119/molmed.2010.00268	The presence of the opioid system in sperm cells also represents a novel opportunity for reproductive management, for either enhancing the probability of fertilization or reducing it through the development of novel targeted contraceptives
Estomba H (56)	2016	10.1371/journal.pone.0152162	The role of the opioid receptors in spermatogenesis could help to develop new strategies to employ the opioid system as a biochemical tool for the diagnosis and treatment of male infertility
Takzare N (57)	2016	27326414	The population of spermatogenesis cycle cells at spermatogonia, spermatocyte, spermatid, and spermatozoa stages were significantly decreased in those rats that received opioids in comparison to the control group
Ajayi AF(58)	2020	0.1016/j.heliyon. 2020.e05589	Upregulation of estrogen signaling associated with enhanced testicular HER2 and Ki67 expression during the recovery period is seemingly beneficial in protecting against codeine-related testicular injury and infertility.

apoptosis thymocytes cycles and DF (20).

On the other hand, the bulk of indications showed that a low dose of morphine could hamper the destructive effects of oxidants on neural cells by inhibiting glycogen synthase kinase-3β and phosphatidylinositol 3-kinase, the latter being the target of rapamycin (21). Additionally, the antioxidant activity of morphine has been established based on different methods, including the thiocyanate method, which measures the total activity of morphine. According to Gulen's study, as the concentration of morphine increases (from 25 to 75 micrograms per ml), in vitro, incremental antioxidant activity increases in parallel. Finally, they highlighted the importance of morphine in decreasing antioxidant activity with attention to concentration (14). Amini et al., showed that in a low dose of morphine (maximum 1 Pm), anti-inflammatory, anti-apoptotic, and neuroprotective effects could be expected (22). Hence, it is reasonable to use a low dose of morphine in patients with inflammatory disorders and neurological disorders. In contrast, morphine will have detrimental effects on a patient's health if it is administrated at high intensity. They also revealed that in an individual with an addiction to methamphetamine, which has become a global concern, applying morphine to routine treatment may help the patient to deal with the terrible effects of methamphetamine more conveniently.

Codeine and Codeinone

Codeine's capacity as a painkiller is similar to that of morphine. It also has the same adverse effects such as constipation, nausea, vomiting, itching, dry mouth, and addiction. The pain relief potential of codeine is less in comparison to morphine due to the lower potency of the Mu (μ) receptor, which is the same receptor between morphine and codeine (23, 24). Codeine has three main compounds: morphine, codeine 6-glucuronide, and codeinone; which are different in structure and potency. Codeinone production is based on oxidizing codeine; it exhibits the extreme cytotoxicity of morphine compounds against human promyelocytic leukemia cells.

There are no extended studies regarding the influence of codeine compounds on DF yet. It was outlined that codeinone's potential to induce apoptosis or necrosis, which is greatest among morphine compounds, can be used as an antitumor factor besides usual cancer treatment (25). In addition to apoptosis, codeinone can increase antinociceptive activity that resembles the antitumor activity of codeinone (18, 26). Masami et al. investigated the strength of morphine alkaloids in cytotoxicity activity. They demonstrated that the role in the antitumor activity of codeinone had been well understood in patients with oral tumors. The feasibility of inducing apoptosis results from the unsaturated ketones in codeinone structure that can be reduced by applying N-acetylcysteine.

Cocaine

Cocaine addiction is widely shared among Western societies, and the medical use of cocaine is restricted to topical anesthesia (27). It involves a broad spectrum of ages, and its exposure may be responsible for some congenital malformations and stillbirths. Regarding prenatal cocaine exposure; some studies have shown lower brain volume in children exposed intrauterine to cocaine, which is the leading cause of inappropriate

behavior (28).

There is enough evidence of death in CNS tissue due to maternal exposure to cocaine. This was due to cell apoptosis through particular pathways (29, 30). However, the mechanisms have not been identified clearly. Genes encode apoptosis in brain cells and play a substantial role in the devastating cell death mechanism, according to Lidow et al.,'s study. They clarified the interactions between cocaine and apoptosis genes that make fetal CNS cells vulnerable to apoptosis signals (31). One of the significant causes of death in cocaine abusers is cardiac abnormalities, ranging from arrhythmias to sudden cardiac death. Many efforts have been made to understand the reasons for death in individuals who use cocaine. Cocaine use leads to a rise in the blood level of catecholamine, which has been linked with a risk of cardiovascular events by a plethora of Reactive Oxygen Species (32). The other mechanism for cardiac cell death is calcium overload, which initiates the cascade of interactions based on Fleckenstein et al.'s study. In summary, both catecholamine release and rise in calcium blood level are the mainstays of severe cardiac events resulting from apoptosis and necrosis in addiction to cocaine (33, 34) (Table 1).

Infertility

Infertility has become one of the significant concerns of society, with the prevalence of 60-80 million couples which is steadily rising (35). The definition of infertility has been described as not gaining achievement in pregnancy after at least one year of consecutive unprotected intercourse, which is related to both male and female factors. Infertility can be categorized into primary and secondary infertility based on the history of successful conception. It can be divided into three groups considering causes: male factors, female factors, and a combination of them (36).

Causes of male infertility

Concerning male infertility, viable spermatogenesis necessitates appropriate communication between endocrine, paracrine, and autocrine systems that can be disturbed by various factors that lead to infertility (37). A few acquired and congenital situations, such as testicular torsion, orchitis, well-known cytotoxic drugs, and Klinefelter syndrome, may interrupt spermatogenesis, mainly causing azoospermia. At the same time, most infertility factors that are recognized as idiopathic factors have not been elucidated clearly. Although many factors have been identified underpinning infertility, a widespread study discussing infertility factors does not exist. Oddly enough, male fertility has decreased recently, and clear reasons for male infertility remain uncertain (38). It is believed that environmental factors may be the prominent cause of the increasing incidence of male infertility.

Causes of female infertility

Female infertility encompasses a variety of causes, from anatomical problems, which are the most important causes of infertility, to unknown causes (39). The age of women at the time of attempting pregnancy has risen during the last 20 years, and this is one of the reasons for the growing incidence of infertility among women. As age increases, the ovary becomes less effective, the chance of chromosomal abnormalities increases, and the number of intercourses decreases remarkably. In women with ovarian failure, further the anatomical and pathological causes, numerous endocrine disorders possibly impair the physiological function of the ovary (40). The role of pelvic adhesions in female infertility due to free radicals should not be neglected (41). It is hypothesized that ROS production is dependent on the air of the operative room following surgery, and ROS worsens the situation by progressing pelvic adhesions.

Infertility and DNA fragmentation

Damaging the DNA of sperm can emerge with six mechanisms, which can interfere with either the process of sperm maturing or during sperm transport. DF happens throughout spermatogenesis and moves toward seminiferous tubules and epididymis. Besides, DF is induced by endogenous endonucleases, radiotherapy, chemotherapy, and environmental factors (42). First, Aitken et al. in 1987 stated the role of OS in male infertility by ROS with interrupting sperm plasma membrane integrity (43, 44). After that, Iwasaki et al. showed that with an increase in ROS, an inevitable decrease in the motility and intensity of sperm would happen (44, 45). There are reports that ROS is the critical factor in 25-40% of males with idiopathic infertility regardless of varicocele existence. ROS can be originated from white blood cells, primarily polymorpho nuclear leukocytes. Consequently, the high level of white blood cells is accompanied by a high level of ROS through simple pathways. Therefore, it can be expected that situations causing leukocytopenia, can reduce fertility odds by enhancing the level of ROS (46).

Infertility and illicit drugs

Despite the role of illicit substances in emerging oxidative stress (OS), the susceptibility of human spermatozoa to OS is inconsistent with the idea that supports the responsibility of opium in the morphology and motility of sperm abnormalities (47). From the many clinical and experimental studies on illicit substances' effect on male production, only some of them describe that base on DNA damage. In contrast, the rest of the studies described that on account of hormonal changes, vasoconstriction of testicular blood, decrease in the diameter of seminiferous tubules, and amount of total germ cells (48, 49).

Li et al., exposed male rats to cocaine daily for almost three months, and they saw the highest rate of apoptosis

of seminiferous tubules on day 30 which persisted until day 90 (50). They showed the insults of cocaine by inducing apoptosis. According to Yamamoto's study, the apoptosis effect of methamphetamine started from a 5mg/kg dosage in rats and tubules. Apoptosis was dependent on dosage and a higher dosage showed a higher rate of apoptosis (51). Barneys et al. performed a study on rats treated with three different dosages of 3, 4. Methylenedioxymethamphetamine or ecstasy (0.5mg/kg, 5mg/kg, 10mg/kg). They showed that sperm concentration and motility were notably decreased at 5mg/kg and 10mg/kg, mainly due to the increasing rate of DNA damage. The study's other finding was interstitial adenoma in the case group, which can occur regardless of sperm concentration and motility. The effect of opium on infertility based on DF is limited. Although opium affects fertility through intrinsic and extrinsic pathways by inducing apoptosis, an increase in apoptotic molecules may be in normal cell death (Table 1). Tramadol administration is associated with decreases in sexual hormonal levels and disruption of the pathology of seminiferous tubules similar to apoptotic cells in rats. Most studies have addressed the link between opium addiction and male infertility, and there is scarce evidence concerning opium addiction and female infertility. Asadikaram et al. studied the effect of opium addiction on both rats with diabetes and rats with no diabetes. The study found that the rate of apoptosis in the ovary of female rats increases in rats who are addicted to opium and if they have diabetes (52).

Treatment

Some antioxidants have shown promising results to prevent the destructive effect of ROS on cell DNA. Lipid peroxidation, the leading cause of DNA damage, could be suppressed by glutathione peroxidase. Hence the motility of sperm can be saved, according to Juan et al.,'s study, which agrees with Lewis et al.,'s analysis. It showed the efficiency of antioxidants in reducing the DF of sperm. However, no differences were observed in sperm parameters in the treatment group (53-56). Following Eskenazi et al.,'s study, vitamins C and E as antioxidants have a beneficial effect on sperm count and motility in healthy, non-smoking males (57). DF and inflammatory processes that happen in individuals with oral consumption of codeine can modulate the level of testicular enzymes and, apart from that, cause changes in the morphology of testis cells. Given an overview by Lombardo et al., the outcomes of using antioxidants in men with infertility often were unmet, they need more relevant studies to support this idea. In addition, they indicated that antioxidants are perhaps concomitant with some complications and suggested pros and cons before administering antioxidants to patients. Collectively, antioxidants should be considered one of the treatment choices in men with idiopathic infertility.

Conclusions

The rate of fertility decreases in individuals who administrate illicit substances and many studies illuminated that in addition to the hormonal modulation levels and pathological changes, DNA fragmentation should be considered as a response mechanism. Thus, antioxidants can be used in patients with infertility for unknown reasons. The outcomes of antioxidants in animal studies were satisfactory; however, against all the odds, the results in human clinical studies were not as good as in experimental studies. We suggest perfuming more clinical studies regarding the relationship between illicit substances and infertility, and more extensive studies are warranted to establish the reverse relationship between them. Soon, the medication of opioids will be limited to some occasions regarding the infertility problem of patients. The limitation was the limited geographic diversity of published articles.

Authors' contributions

All authors contributed equally.

Acknowledgments

Special thanks to the Urology Research Center (URC), Tehran University of Medical Sciences, Tehran, Iran.

Conflict of interest

The author declares that there are no conflicts of interest.

Funding

No Funding.

Ethical statements

Not applicable.

Data availability

Data will be provided on request.

Abbreviations

DFF DNA fragmentation factors
OS Oxidative stress
ROS Reactive oxygen species

References

1. Vander Borght M, Wyns C. Fertility and infertility: Definition and epidemiology. Clinical biochemistry. 2018;62:2-10.
2. Winters BR, Walsh TJ. The epidemiology of male infertility. Urologic Clinics. 2014;41(1):195-204.
3. Bidary MZ, Sahranavard M, Rezayat AA, Omranzadeh A, Hoseiny SH, Kabirian A, et al. Opium as a carcinogen: A systematic review and meta-analysis. EClinicalMedicine. 2021;33:100768.
4. Peart JN, Gross ER, Gross GJ. Opioid-induced preconditioning: recent advances and future perspectives. Vascular pharmacology. 2005;42(5-6):211-8.
5. Ziaee M, Hajizadeh R, Khorrami A, Sepehrvand N, Momtaz S, Ghaffari S. Cardiovascular complications of chronic opium consumption: A narrative review article. Iranian Journal of Public Health. 2019;48(12):2154.
6. Safarinejad MR, Asgari SA, Farshi A, Ghaedi G, Kolahi AA, Iravani S, et al. The effects of opiate consumption on serum reproductive hormone levels, sperm parameters, seminal plasma antioxidant capacity and sperm DNA integrity. Reproductive Toxicology. 2013;36:18-23.
7. Homa ST, Vassiliou AM, Stone J, Killeen AP, Dawkins A, Xie J, et al. A comparison between two assays for measuring seminal oxidative stress and their relationship with sperm DNA fragmentation and semen parameters. Genes. 2019;10(3):236.
8. de Lamirande E, Lamothe G. Reactive oxygen-induced reactive oxygen formation during human sperm capacitation. Free Radical Biology and Medicine. 2009;46(4):502-10.
9. Ajayi AF, Akhigbe RE. Codeine-induced sperm DNA damage is mediated predominantly by oxidative stress rather than apoptosis. Redox Report. 2020;25(1):33-40.
10. Molavi N, Ghaderi A, Banafshe HR. Examining metabolic profiles in opioid-dependent patient. International Journal of Medical Toxicology and Forensic Medicine. 2020;10(3):28681.
11. Sheweita SA, Tilmisany AM, Al-Sawaf H. Mechanisms of male infertility: role of antioxidants. Current drug metabolism. 2005;6(5):495-501.
12. Clarence-Smith WG. Opium, Empire and the Global Political Economy; a Study of the Asian Opium Trade, 1750–1950. By Carl A. Trocki. pp. xiv, 208, 4 maps. London, Routledge, 1999. Journal of the Royal Asiatic Society. 2001;11(1):128-30.
13. Meyer RE. The heroin stimulus: Implications for a theory of addiction: Springer Science & Business Media; 2012.
14. Zanos P, Georgiou P, Wright SR, Hourani SM, Kitchen I, Winsky-Sommerer R, et al. The oxytocin analogue carbetocin prevents emotional impairment and stress-induced reinstatement of opioid-seeking in morphine-abstinent mice. Neuropsychopharmacology. 2014;39(4):855-65.
15. Zhu G, Zhang Y, Dong J, Liu Y, Zhao F, Li T, et al. Association between body mass index and male sperm apoptosis and apoptosis-related factors. Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy. 2021:1043-51.
16. Mirzaei A, Zendehdel K, Rashidian H, Aghaii M, Ghahestani SM, Roudgari H. The Impact of OPIUM and Its Derivatives on Cell Apoptosis and Angiogenesis. Translational Research In Urology. 2020;2(4):110-7.
17. Dinda A, Gitman M, Singhal PC. Immunomodulatory effect of morphine: therapeutic implications. Expert Opinion on Drug Safety. 2005;4(4):669-75.
18. Madariaga-Mazón A, Marmolejo-Valencia AF, Li Y, Toll L, Houghten RA, Martinez-Mayorga K. Mu-Opioid receptor biased ligands: A safer and painless discovery of analgesics? Drug discovery today. 2017;22(11):1719-29.
19. Roy S, Wang J, Kelschenbach J, Koodie L, Martin J. Modulation of immune function by morphine: implications for susceptibility to infection. Journal of Neuroimmune Pharmacology. 2006;1:77-89.
20. Roy S, Loh HH. Effects of opioids on the immune system. Neurochemical research. 1996;21:1375-86.
21. Roy S, Barke RA, Loh HH. MU-opioid receptor-knockout mice: role of μ-opioid receptor in morphine mediated immune functions. Molecular brain research. 1998;61(1-2):190-4.
22. Gross ER, Hsu AK, Gross GJ. Opioid-induced cardioprotection occurs via glycogen synthase kinase β inhibition during reperfusion in intact rat hearts. Circulation research. 2004;94(7):960-6.
23. Gülçın I, Beydemır Ş, Alici HA, Elmastaş M, Büyükokuroğlu ME. In vitro antioxidant properties of morphine. Pharmacological Research. 2004;49(1):59-66.
24. Amini K, Zhaleh H, Tahvilian R. Effects of low-dose morphine suppress methamphetamine-induced cell death by inhibiting the ROS generation and caspase-3 activity. Bratislavske Lekarske Listy. 2019;120(5):336-43.
25. Chen ZR, Irvine RJ, Somogyi AA, Bochner F. Mu receptor binding of some commonly used opioids and their metabolites. Life sciences. 1991;48(22):2165-71.
26. Pasternak GW, Pan Y-X. Mu opioids and their receptors: evolution of a concept. Pharmacological reviews. 2013;65(4):1257-317.
27. Hatsukari I, Hitosugi N, Ohno R, Hashimoto K, Nakamura S, Satoh K, et al. Induction of apoptosis by morphine in human tumor cell lines in vitro. Anticancer research. 2007;27(2):857-64.
28. Takeuchi R, Hoshijima H, Onuki N, Nagasaka H, Chowdhury SA, Kawase M, et al. Effect of anticancer agents on codeinone-induced apoptosis in human cancer cell lines. Anticancer research. 2005;25(6B):4037-41.
29. Sert S. Anestezi teknikerlerinin lokal anestezik toksisitesi ve tedavisi hakkındaki bilgi düzeyleri: Anket çalışması. 2021.
30. Cone-Wesson B. Prenatal alcohol and cocaine exposure: influences on cognition, speech, language, and hearing. Journal of communication disorders. 2005;38(4):279-302.
31. Xiao D, Zhang L. Upregulation of Bax and Bcl-2 following prenatal cocaine exposure induces apoptosis in fetal rat brain. International Journal of Medical Sciences. 2008;5(6):295-302.
32. Ajayi A, Akhigbe R. In vivo exposure to codeine induces reproductive toxicity: role of HER2 and p53/Bcl-2 signaling pathway. Heliyon. 2020;6(11):e05589.
33. Faa G, Manchia M, Pintus R, Gerosa C, Marcialis MA, Fanos V. Fetal programming of neuropsychiatric disorders. Birth Defects Research Part C: Embryo Today: Reviews. 2016;108(3):207-23.
34. de Oliveira MR, Jardim FR. Cocaine and mitochondria-related signaling in the brain: a mechanistic view and future directions. Neurochemistry international. 2016;92:58-66.
35. Cerretani D, Fineschi V, Bello S, Riezzo I, Turillazzi E, Neri M. Role of oxidative stress in cocaine-induced cardiotoxicity and cocaine-related death. Current medicinal chemistry. 2012;19(33):5619-23.
36. Stankowski RV, Kloner RA, Rezkalla SH. Cardiovascular consequences of cocaine use. Trends in cardiovascular medicine. 2015;25(6):517-26.
37. Olayemi F. Review on some causes of male infertility. African Journal of Biotechnology. 2010;9(20).
38. Toshinobu M, Akira T, Yasushi M, Eitetsu K, Mikio N, Kazuo S. Male infertility and its causes in human. Advances in Urology. 2012;2012:1-7.
39. Sudha G, Reddy K. Causes of female infertility: a crosssectional study. International journal of latest research in science and technology. 2013;2(6):119-23.
40. Unuane D, Tournaye H, Velkeniers B, Poppe K. Endocrine disorders & female infertility. Best Practice & Research Clinical Endocrinology & Metabolism. 2011;25(6):861-73.
41. Alpay Z, Saed GM, Diamond MP. Female infertility and free radicals: potential role in adhesions and endometriosis. Journal of the Society for Gynecologic Investigation. 2006;13(6):390-8.
42. Henkel R, Leisegang K. Origins of sperm DNA damage. Male infertility: contemporary clinical approaches, andrology, ART and antioxidants. 2020:361-75.
43. Muratori M, Marchiani S, Tamburrino L, Baldi E. Sperm DNA fragmentation: mechanisms of origin. Genetic Damage in Human Spermatozoa. 2019:75-85.
44. Aitken RJ, Baker MA. Causes and consequences of apoptosis in spermatozoa; contributions to infertility and impacts on development. International Journal of Developmental Biology. 2013;57(2-3-4):265-72.
45. Gholami K. Experimental Approaches for Fertility Preservation in Prepubertal Boys Undergoing Oncological Therapy. Translational Research in Urology. 2020;2(4):123-6.

46. Dohle GR. Male infertility in cancer patients: review of the literature. International journal of urology. 2010;17(4):327-31.
47. Simpson DS, Oliver PL. ROS generation in microglia: understanding oxidative stress and inflammation in neurodegenerative disease. Antioxidants. 2020;9(8):743.
48. Jacobsen FM, Rudlang TM, Fode M, Østergren PB, Sønksen J, Ohl DA, et al. The impact of testicular torsion on testicular function. The world journal of men's health. 2020;38(3):298.
49. Aghamir SMK, Salavati A, Yousefie R, Tootian Z, Ghazaleh N, Jamali M, et al. Does bone marrow–derived mesenchymal stem cell transfusion prevent antisperm antibody production after traumatic testis rupture? Urology. 2014;84(1):82-6.
50. Li C, Frantz KJ. Attenuated incubation of cocaine seeking in male rats trained to self-administer cocaine during periadolescence. Psychopharmacology. 2009;204:725-33.
51. Gholipour F, Shams J, Zahiroddin A. Protective effect of coenzyme Q10 on methamphetamine-induced apoptosis in adult male rats. Novelty in Biomedicine. 2017;5(3):127-32.
52. Asadikaram G, Asiabanha M, Sayadi A, Jafarzadeh A, Hassanshahi G. Impact of opium on the serum levels of TGF-β in diabetic, addicted and addicted-diabetic rats. Iranian journal of immunology. 2010;7(3):186-92.
53. Colasante A, Minasi MG, Scarselli F, Casciani V, Zazzaro V, Ruberti A, et al. The aging male: relationship between male age, sperm quality and sperm DNA damage in an unselected population of 3124 men attending the fertility centre for the first time. Archivio Italiano di Urologia e Andrologia. 2018;90(4):254-9.
54. Mirzaei A, Khatami F, Ebrahimi M, Mousavibahar SH, Narouie B. The Effect of herbal extracts on the treatment and prevention of prostate cancer: a literature review. Translational Research in Urology. 2019;1(2):67-73.
55. Atqiaee K, Mohammadi Tofigh A, Salehpour S, Mirshemirani A. Leydig Cell Tumor in Children: a Case Report and Literature Review. Translational Research In Urology. 2020;2(2):32-6.
56. Aghamir MK, Hosseini R, Alizadeh F. A vacuum device for penile elongation: fact or fiction? BJU international. 2006;97(4):777-8.
57. Eskenazi B, Kidd S, Marks A, Sloter E, Block G, Wyrobek A. Antioxidant intake is associated with semen quality in healthy men. Human reproduction. 2005;20(4):1006-12.

Author (s) biosketches
Namazi Shabestari A, Assistant Professor, Department of Geriatric Medicine, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran.
Email: namazialireza109@yahoo.com
Tamehri Zadeh SS, MD, Prevention of Metabolic Disorders Research Center, Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran.
Email: tamehrysaeed@gmail.com
Fakhr Yasseri A, Assistant Professor, Shariati Hospital, Alborz University of Medical Sciences, Alborz, Iran.
Email: yasseri_2006@yahoo.com
Ebrahimi M, Assistant Professor, Department of Internal Medicine, Faculty of Medicine, Sina Hospital, Tehran University of Medical Sciences, Tehran, Iran.
Email: m¬_ebrahimi49@yahoo.com
Issa B, MD, Urology department, Royal Bolton Hospital, Greater Manchester, United Kingdom.
Email: Issa.bassim@gmail.com
Rahimnia R, Assistant Professor, Department of Medical Nanotechnology, School of Advanced Technologies in Medicine, Tehran University of Medical Sciences, Tehran, Iran.
Email: rrahimnia@tums.ac.ir

How to cite this article
Namazi Shabestari A, Tamehri Zadeh SS, Fakhr Yasseri A, Ebrahimi M, Issa B, Rahimnia R. The Impact of Opium on Men's Fertility and DNA Fragmentation: A Literature Review. Transl. res. urol. , 2023 June;5(2):66-73.
DOI: 10.22034/TRU.2023.393707.1144
URL: https://www.transresurology.com/article_171463.html