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Opium Carcinogenicity: A Systematic Review of Experimental Studies

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ABSTRACT

Several epidemiological studies have reported that regular use of opium can be associated with an increased risk of developing cancers, including oesophageal, laryngeal, bladder, lung, and gastric cancer. In this systematic review, we aimed at investigating whether experimental studies support this finding and, if yes, how opium consumption can cause cancer. Most of the articles that have studied opium or its derivatives have found it as a carcinogen. However, due to the complex composition, different forms, and various ways of opium use, further comprehensive experimental studies are required. Using modern genomic and epigenomic methods seems to help determine the molecular mechanisms underlying opium carcinogenicity.

Keywords: Opium, Carcinogenicity, Guideline, Neoplasm

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INTRODUCTION:

An increasing number of epidemiological studies, especially in Iran, have suggested that opium use could cause cancer in humans. However, there is contradictory evidence about the carcinogenicity of other opioids (1-5). Opium is a highly addictive drug, which could lead to drug dependence and disorder. Opium is the most commonly consumed drug among Iranians, although the opiate trade has been banned since 1997 (6). The most recent national survey indicated that more than 2% of Iranians suffer from opium abuse disorder (7). Opium is a brown, bitter, and dried latex obtained from the unripe seed of *Papaver somniferum* (1). Over 50 various alkaloids such as noscapine, morphine, and thebaine are derived from the opium poppy. Some of these substances are classified as medicines. Morphine is the main alkaloid of opium. The mode of action of morphine and its derivatives relies on these alkaloids' action as mu and kappa opioid receptor agonists that is used as analgesia. Large amounts of morphine are prescribed for moderate to severe pain in cancer patients each year (8, 9). Noscapine is another important alkaloid derived from opium used in medicine and acting as a sigma receptor agonist (10). Unlike other opioids, noscapine does not cause addiction. Some studies indicate that this opium alkaloid can demonstrate anti-carcinogenic properties (11-16). There are a number of traditional narcotic derivatives of opium in the list of illegal narcotic drugs, including Teriak (air-dried and dark, sticky, or crumbly paste of raw opium), Shireh (refined opium made by boiling the raw opium or Teriak in hot water, and heating and passing it through filters for several times), Sukhteh (dry residue of the burned Teriak), and Tofaleh (residue of the filtered Teriak solution) (3, 8). Recent evidence suggests that the rate of opioid consumption is increasing in 25 OECD (Organisation for Economic Co-operation and Development) countries (17). Although many studies on humans have shown a higher risk of cancer incidence among opium users, opening the black box of the molecular pathways and mechanism of opium carcinogenicity is a challenge for health researchers. For instance, it is unclear whether opium is a genotoxic carcinogen or a non-genotoxic carcinogen (18-21). This study attempted to systematically review experimental studies, including in-vivo and in-vitro, to explore opium carcinogenicity.

METHODS

Search strategy and selection criteria:

We searched PubMed, Google Scholar, and Scopus to identify experimental studies on opium use and cancer. We searched PubMed with the terms "Opium", "Neoplasms" [MeSH term], "Carcinogenesis" [MeSH term], "Animal" OR "In-vitro", "Cell Line" OR "In-vivo", and "Experimental Study". Entry terms were used to search Google Scholar and Scopus databases. The PubMed search was limited to "Other Animals" (for species), and the Scopus search was filtered by "Article" (for document type), "Medicine" (for the subject area), and "Non-human Subjects" (for the keywords). All searches were updated in September 2019. No language limitation was applied. However, all found publications were in English.

Data extraction:

A total of 3067 articles were found through crude searches. After removing duplicates, 2016 unique records were screened. Of these, 1926 studies were excluded at the title and abstract evaluation phase. Finally, 90 articles were screened for full-text (**Figure 1**).

RESULTS:

Among 90 full-text screened articles, 36 were about opium or its alkaloids, which were carefully studied, and the data table was prepared. Data were extracted based on the bibliography (first author, year, the type of

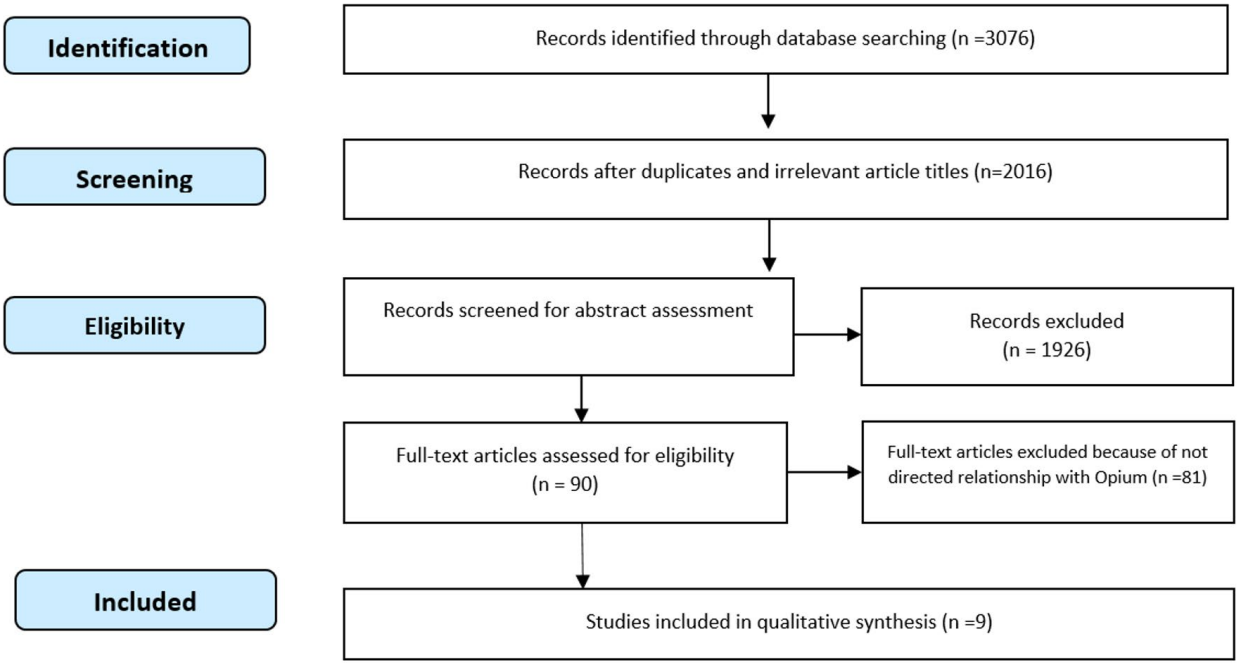

Figure 1. Flowchart for selection of studies

opium sample, and the type of study) and results of the selected articles. The summary of the results obtained from these 36 articles, including 52 tests, is presented in **Table 1.** The complete table of opium derivatives and opium alkaloids (noscapine, morphine, and heroin) are provided in **Table 2** and **Supplementary Table 1.**

Noscapine

Thirty-five studies (23 articles) were on noscapine alkaloids. Among these, 22 were in-vitro studies. Twenty-one experimental studies reported that noscapine could inhibit cancer growth in experimental studies (15, 16, 22-39), while one article did not report any effects (40). There were 13 in-vivo studies among noscapine articles. Interestingly, all of them indicated the cancer-protective effect of noscapine.

Morphine and Heroin

Four articles investigated the effects of morphine and heroin on cancer. Among these, two studies indicated the tumor-suppressive effect of morphine, while one reported its carcinogenicity (4, 41, 42). One article also reported that heroin decelerated tumor growth in mice (43).

Opium

Nine articles examined the carcinogenicity of opium or its common derivatives like Teriak, Shireh, Sukhteh, and Tofaleh. Some of them included both laboratory tests and animal models, whereby the results of the in-vivo and in-vitro studies were separately reported in **Table 2**. Most of these articles indicated the carcinogenicity of opium or its derivatives. We re-evaluated

their data and matched the similarity among materials and methods with standard carcinogenicity criteria, including OECD and ARRIVE (Animal Research: Reporting of In-Vivo Experiments) guidelines, standard test conditions, dose-response association, etc. (51-54). It was finally found that only nine studies had applied carcinogenicity tests on opium. Among these studies, 13 tests were performed on cancer cells or laboratory animals. Data on these nine articles are presented in **Table 2**.

Tables 3 and **Table 4** summarize the results of the re-evaluation of articles in terms of testing raw opium and matching them with standard guidelines (51-54). The quality (high, moderate, and low quality) of strains, animals, and cells were determined by matching them with previous guidelines based on using suitable materials; checking strains for contamination, sensitivity, and mutation; proper concentration and condition during the procedure; and considering pre-incubation in the studies.

As an illegally marketed drug, opium contains various types of plant alkaloids as well as impurities. **Supplementary Tables 2** and **3** provide an example of these materials. These data were obtained from the analysis of a sample of opium and its four well-known derivatives, Teriak, Shireh, Tofaleh, and Sukhteh (the Iranian names of these products), at the Cancer Biology Research Center (CBRC) of Tehran University of Medical

Table 1. Summary of the results of the studies

Substances	Type of Study	Species/Cell line	Conclusion	Comment
Opium (9 articles including: 13 tests)	In vitro (8)	(Bacteria reverse mutation) (Mammalian cell assays)	Carcinogen (6)	Carcinogenicity test
		(Mammalian cell assays)	Protective (2)	
	In vivo (5)	Mice, rat and Hamster	Carcinogen (3)	Carcinogenicity test
		Rat	Protective (1)	
		Mice	No effect (1)	
Noscapine (23 articles including: 35 tests)	In vitro (22)	Cancerous cell lines	Carcinogen (0) Protective (21) No effect (1)	Anticancer effect evaluation
	In vivo (13)	Mice	Protective (13	Anticancer effect evaluation
Other Opioids (Morphine & Heroine (4 articles)	In vitro (1)	Cancerous cell lines	Protective (1)	Anticancer effect evaluation
	In vivo (3)	Rat	Carcinogen (1)	Carcinogenicity test
		Mice and Rat	Protective (2)	Carcinogenicity test, Anticancer effect evaluation

Table 2. The summary of included studies

Opium

In vitro (bacterial reverse mutation test) studies

	Author (Year)	Type of opium or extraction	Cell line type/ Animal Species	Concentration	Technique	Clinical Index	Result	Conclusion	Risk of Bias Assessment
1	Mottaghi, M.[44] (2018)	Opium	*Salmonella typhimurium* TA100	0,001- 0.01- 0.02- 0.04- 0.08- 0.16 g/ml	• Ames test	• Mutation	• Not mutagenesis in 0.001 but mutagenesis in other dosages	carcinogen	4
2	(Friesen, M.[5] (1985)	Opium pyrolysates	*Salmonella typhimurium* TA98		• Ames test • HPLC	• mutagenesis	• very mutagen	carcinogen	4
3	Malaveille, C.[45] (1982)	Opium pyrolysates and sukhteh	*Salmonella typhimurium* TA98 and TA100 strains	30-550 mg	• Ames test • HPLC • Preparation of liver post-mitochondrial fraction • Treatment with nitrous acid test	• Plate incorporation assays	• Induce mutation	carcinogen	4
4	Hewer, T.[46] (1978)	Opium pyrolysates	*Salmonella typhimurium* TA98 and TA100	4.16 mg	• Ames test • Preparation of liver post-mitochondrial fraction	• mutagenicity	• Induce mutation	carcinogen	4

In vitro (mammalian cell assays) studies

	Author (Year)	Type of opium or extraction	Cell line type/ Animal Species	Concentration	Technique	Clinical Index	Result	Conclusion	Risk of Bias Assessment
5	Khaleghi, M.[47] (2016)	Opium	AA8 cell line A.G.S. cell line Hela cell line HepG2 cell line MCF7 cell line N2a cell line PC12 cell line WEHI cell line	2.86 x 10^{-4} g/ml	• M.T.T. assay used to study cell viability. • Annexin V staining for apoptosis	• Cell Proliferation • Apoptosis	• Induce apoptosis	protective	4
6	Arababadi, M.K.[48] 2015)	Opium	Jurkat cells	2.86×10^{-5} g/ml	• Annexin v staining • R.N.A. extraction, reverse transcription and quantitative real-time PCR	• Apoptosis	• Change in apoptosis rate of the cell line	protective	4
7	Friesen, M.[5] (1985)	Opium pyrolysates	Syrian hamster embryo cells, C3H, IOT1/2 cells	0.5 mg/ml	• M.T.T. assay • Preparation of mitochondrial fraction	• Apoptosis	• Induce apoptosis	carcinogen	
8	Perry, P.E[49] (1983)	Opium pyrolysates and sukhteh	Chinese hamster ovary (C.H.O.) cells and Human peripheral blood lymphocyte and *Salmonella typhimurium* TA98	30 µg/ml	• Sister chromatid exchange (S.C.E.) • Making s9 mixture • Preparation of liver post-mitochondrial fraction	• Mutation induction • Plate incorporation assays	• Induce mutation	carcinogen	4

Table 2. Continue...

Opium

In vivo studies

	Author (Year)	Type of opium or extraction	Cell line type/ Animal Species	Number of animal in each group	Dosage/route of exposure/ time of exposure	Technique	Clinical Index	Result	Conclusion	Risk of Bias Assessment
9	Alzaidi, M. A.[21] 2018)	Opium	Male Wistar rats 140-180 g	54 rats divided into 3 groups treated with: 1. purified water 2. DEN 3. opium (experimental group)	300 mg/kg Oral 16 weeks (5 times in a week)	• Hematoxylin and eosin stain • RT-PCR	• Histopathology changes • Gene expression	• No carcinogenic changes were observed in the opium-treated animals at the end of week 20 • The treatment of animals with opium significantly inhibited the increased level of CDK2 • Opium did not induce significant alteration in the expression ofP53, p21, cdk2, e-Cdh, and n-Cdh genes involved in the gastrointestinal tumors.	Protective	5
10	Tsuda, H.[50] (1993)	Opium	Male F344 rats	260 rats divided into 3 groups (2 groups in experiment 1 followed in 3 groups in experiment 2) Experiment 1-2: 1. DEN/IQ/Captaful/HCE/DES-OP/ DDT/HCB 2.saline/corn oil-DMSO/com oil 3. DEN/IQ/Captaful/HCE/DES-OP/ DDT/HCB (different dose)	60 mg/kg Intraperitoneal 2 weeks	• Glutamine S-transferase P form positive liver cell foci	• Number of Glutamine s transferase p form positive	• Not a promoter but have a carcinogen effect	Carcinogen	5
11	Friesen, M.[5] (1985)	opium pyrolysates	Female Syrian golden hamsters, 8 weeks old	3 groups of 10 Female Syrian golden hamsters: 2 experimental groups 1 control group	1.659 mg/ animal intratracheal instillations 114 weeks (once in a week)	• Transformation assays	• Body-weightm • Survival rate	• Hyperplasia • No change in body weight	Carcinogen	5
12	Friesen, M.[5] (1985)	opium pyrolysates	C57BL/6 mice and Female C.B.A. mice20-24 weeks old	3 groups of 27 Female and 30 Male C57BL/6 mice: 2 experimental groups 1 control group 27-35 Female C.B.A. mice	40 mg. per mouse Oral/ Subcutaneous injection 114 weeks (once in a week)	• Mass spectrometry • HPLC • UV spectroscopy • tH-Fourier transform nuclear magnetic resonance (I H.FTNMR) spectroscopy • Preparation of liver post-mitochondrial fraction	• Morphological change	• Tumorogenesis result	Carcinogen	5
13	Friesen, M.[5] (1985)	opium pyrolysates	Female Swiss mice (SPF) 52-day-old	30 Female Swiss mice	28.8 mg Mouse skin test 114 weeks (once in a week)	• Tests on mouse skin	• Tumor size	• No increase	No effect	5

Table 3. Result of matching articles with standard guidelines (OECD guidelines and standard protocols)

Study type	Follow the carcino-genicity guidelines	Number or Code of guideline/ series	Authors/ year	Standard test condition								Carcinogenicity	Dose-response relationship
				Standard protocol/ vehicle/ solvent	Strain/cells/animal characteristics quality*	Strain/ cells/ animal type	Using activation system (in vitro tests)	Treatment procedures Quality	Standard duration time (in vivo tests)	Controls			
										negative	Positive		
In vitro	Yes	Similar to OECD (T.G. No.471)	Mottaghi, M. [44] (2018)	Standard	High	Suitable	Used	High		Standard	Standard	Carcinogen	Considered
			Friesen, M. [5] (1985)..	Standard	Moderate	Suitable	Used	Moderate		Lack of enough information	Standard	Carcinogen	Considered
			Malaveille, C. [45] (1982)	Standard	High	Suitable	Used	Moderate		Standard	Standard	Carcinogen	Considered
			Hewer, T. [46] (1978)	Standard	Low	Suitable	Used	Low		Lack of enough information	Standard	Carcinogen	Considered
	Yes	Similar to OECD Series No.214	Friesen, M.[5] (1985)	Standard	Moderate	Suitable	Used	High				Carcinogen	No information
	Yes	Similar to OECD (T.G. No.479)...	Perry, P.E [49] (1983)	Standard	High	Suitable	Used	High		Standard	Standard	Carcinogen	Considered
	No †	Propidium Iodide Cell Cycle Staining Protocol	Arababadi, MK. [48] (2015)	Standard	Standard		Standard condition (followed by commercial kits)					Protective	
		M.T.T. test protocol and P.I. staining	Khaleghi, M. [47] (2016)	Standard	Standard		Standard condition (followed by commercial kits)					Protective	
In vivo	Yes	Similar to T.G. No.451	Friesen, M. [5] (1985)††	Standard	Low (less than standard number)	Suitable		Low (no information about dose selection)	Not standard †††	Standard		Carcinogen	Not considered
			Alzaidi, M.A. [21] (2018)	Standard	Moderate (less than standard number)	Suitable		Low (no information about dose selection)	Not standard duration (too short)	Standard		Protective	
			Tsuda, H. [50] (1993)	Standard	High	Suitable		High	Not standard duration (too short)	Standard		Carcinogen	Considered

* The quality of strain, animal and cell are determined by level of matching with guideline based on the using suitable material, checking strains about contamination, sensitivity and mutation, suitable concentration and condition during the procedure and considering pre-incubation in the studies (High quality, Moderate quality, and low quality)
** The mentioned article include 3 types of studies
*** Guideline NO.479 was deleted on 2nd April 2014
† There is no approved OECD guidelines for this two protocols
††Friesen 1985 article includes 3 animal carcinogenicity studies on opium pyrolysates with different administration route
†††Duration time is around 12 month (carcinogenicity rodent studies normally should be 24 months but 12 month is acceptable too). In this case the number of administration in a week is not acceptable

Table 4. Result of matching articles with ARRIVE guideline

Article	Ethical statement	Study design		Experimental procedures*	Experimental animals	Housing and husbandry			Sample size	Experimental outcomes	Statistical methods	Allocating animals
		randomization procedure	experimental unit			Housing	Husbandry conditions	Welfare-related assessments				
Alzaidi,M.A. [21] (2018)^	approved by the institutional Animal care and use Committee	Considered	Group animals in cage	Not standard procedure	Standard strain	Animal housed in stainless steel cages with	25±1 °C temperature and 60% humidity under controlled light (12-h light/12-h dark) free access to food and water	Acclimatization to the environment for 2 weeks	Less than standard number	Clearly defined	Lack of enough information	Animals randomly divided to three equal groups
Friesen,M. [5] (1985)	No information	Lack of enough information	Group animals	Not standard procedure	Standard strain	Lack of enough information	Lack of enough information	Lack of enough information	Less than standard number	Clearly defined	Provided	Lack of enough information
Tsuda,H.[50] (1993)	No information	Lack of enough information	Group animals in cage	Not standard procedure	Standard strain	Housed five per plastic cage on wood chips for bedding	22±2 °C temperature and 60% humidity under controlled light (12-h light/12-h dark) on oriental M.F. basal diet and tap water ad libitum	acclimatization to the environment for 1 weeks	Standard	Clearly defined	Provided	Lack of enough information

*Important features which are considered as indexes for experimental procedure include: concentration, route of administration, time of day, and duration (explained in details in Table 3)

Sciences.

DISCUSSION and CONCLUSION:

Epidemiological studies have reported that regular use of opium can be associated with an increased risk of several types of cancer. In this systematic review, we explored whether the experimental studies could support the carcinogenicity of opium, although the studies on this issue are limited. Among the available studies, nine articles that had performed 13 different cell or animal tests on opium and its derivatives were selected to be assessed. Most of these assays confirmed the carcinogenicity of opium.

Although many articles have worked on opioid alkaloids (mainly noscapine and morphine), they have not considered these materials' carcinogenicity in their investigations. These compounds have been studied more likely due to their potential anti-cancer effects, and most of the related studies have been conducted on cancer cell lines or animal models (22-40).

Noscapine and morphine have many clinical applications and therapeutic effects. Morphine is used as a potent analgesic drug in treating cancer patients (55). Therefore, it is not expected that such well-known and widely used products, which have undergone numerous efficacy and safety tests, show carcinogenic effects. Surprisingly, nearly all the articles studied here indicated noscapine's protective effect against cancer (15, 16, 22-39).

Available opium and its derivatives in the black market contain many impurities (**See Supplementary Tables 2 and 3**), including phytochemical composition, lead, or toxic heavy metals, and various substances (some of which are toxic) (56, 57). This means that such substances can play a role in opioid-related harms. There have been numerous reports of lead poisoning among people who regularly use opium (58, 59). Therefore, studies on opium alkaloids may not be helpful to show the toxicity of these impurities or the carcinogenicity of crude opium, and further studies are required to address this issue specifically.

On the other hand, among the studies aimed at observing or rejecting the carcinogenic effects of opium and its derivatives, most have confirmed these compounds' carcinogenicity (5, 44-46, 49, 50). Nearly all these studies have been conducted based on known tests or well-known protocols for carcinogenicity (51-54). All studies reported the Ames test result on opium have shown that it is mutagenic (5, 48-50). This result from the Ames test indicates the probability of its carcinogenicity. Four studies have been done on mammalian cells, two of which have reported the carcinogenicity effect of opium (5, 49), while two have reported the protective roles of opium against cancer (47, 48). Of the five animal studies, three showed carcinogenicity of opium (50), one study found no effect (5), and one study showed its protection against tumor progression (20).

We could not find any comprehensive experimental research articles studying the carcinogenicity of opium. Several reasons explaining the lack of such studies are as follows:

Carcinogenicity tests usually require several related and sequential steps to be taken to lead to the necessary results. Completing all the steps is usually complicated and time-consuming. Most of the current guidelines for carcinogenicity tests involve long-term bioassays (several weeks or months) in the animal laboratory. Due to the long period, cost, and need for special facilities and equipment, such studies are beyond many researchers and research centers' reach. In addition, opium is used by various routes, such as ingestion, smoking, or inhalation. However, there has been no comparison among different routes of use in experimental investigations. Besides, opium smoke contains large amounts of potentially combustible carcinogenic compounds such as Poly Aromatic Hydrocarbons that do not exist in the crude opium itself. Furthermore, the opium in the black markets contains numerous impuri-

ties that can affect the analyses and make experimental study design complicated. Classic carcinogenicity tests are a set of complementary laboratory and animal tests, while none of the conducted studies have performed or completed all series of tests. Thereafter, the exact pathway of the carcinogenicity of opium is still unclear, and future experimental investigations are required in this regard. Moreover, the use of new genomic and epigenetic screening techniques is not observed in most of the included studies.

In conclusion, crude opium has a complex composition and has many impurities that vary in the consumer market. This makes experimental research on this material challenging. There is not much experimental research on this substance. Thus, we could not find any comprehensive experimental research articles studying the carcinogenicity of opium. However, most of the studies found in this search indicate that this substance can be carcinogenic. Through empirical research, further studies are needed to provide an accurate answer to whether opium is carcinogenic and what molecular mechanisms are involved.

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