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MEDICINAL ASPECTS OF OPIUM AS DESCRIBED IN AVICENNA'S *CANON OF MEDICINE*

OPIJUM S MEDICINSKOG GLEDIŠTA KAKO JE PRIKAZAN U AVICENINU *KANONU MEDICINE*

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Summary

Throughout history, opium has been used as a base for the opioid class of drugs used to suppress the central nervous system. Opium is a substance extracted from the opium poppy (Papaver somniferum L.). Its consumption and medicinal application date back to antiquity. In the medieval period, Avicenna, a famous Persian scholar (980-1037 AD) described poppy under the entry Afion of his medical encyclopedia Canon of Medicine. Various effects of opium consumption, both wanted and unwanted are discussed in the encyclopedia. The text mentions the effects of opioids such as analgesic, hypnotic, antitussive, gastrointestinal, cognitive, respiratory depression, neuromuscular disturbance, and sexual dysfunction. It also refers to its potential as a poison. Avicenna describes several methods of delivery and recommendations for doses of the drug. Most of opioid effects described by Avicenna have subsequently been confirmed by modern research, and other references to opium use in medieval texts call for further investigation. This article highlights an important aspect of the medieval history of medicine.

Key words: *Opium, Avicenna, History of medicine, Persia, Canon of Medicine*

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Introduction

Opium has traditionally been used as a natural base for opioid drugs throughout history. Opioids are a class of drugs used to suppress the central nervous system (CNS) [1]. This class is mostly used for its analgesic properties and more specifically to control pain in patients in conditions of chronic pain such as cancer. The antitussive effect of some opioids such as codeine is also commonly utilized in medical practice [2,3]. Opium is a substance extracted from the opium poppy *(Papaver somniferum L.),* which has been consumed since antiquity. According to research findings, it was used in the Neolithic, Bronze, and Iron Ages [4]. Sumerians are considered the first civilization to cultivate opium poppies in Mesopotamia in 3400s BC [5]. Poppy juice was extracted and consumed by the Assyrians, Babylonians, and Egyptians in the Middle East, and by the Greeks in the west [6]. Historically, opium juice was prepared for consumption in a variety of ways. One was by cutting off the leaves and capsules, grinding them in a press, and then mashing together in a mortar to make tablets. Another way, according to Dioscorides (circa 40-90 AD), was to slit the fruit with a small knife

> *"...after the dew-drops have become well dried. The knife must be drawn round the crown without piercing the fruit within; then the capsules must be directly slit on the sides near the surface and opened lightly, the juice drop will come forth on to the finger sluggishly but will soon flow freely" [7].*

Medicinal uses of opium were well known in these ancient civilizations. Opium was mentioned in the most important *medical* texts of the ancient world such as that of *Ebers Papyrus* (1550 BCE) and in the writings of *Dioscorides* (cover page) and *Galen* (129 – ca. 200 AD) [8]. Jamshid, the mythical king of Persia, features in the first account of a person using a medicinal plant such as poppy [9]. Opium poppy had an important role in the economy of Anatolian and Middle Eastern civilizations, both in terms of its medicinal and religious use [10]. The most often cited uses of poppy in ancient medicine were as a sedative [11] and an analgesic [12].

In medieval times, Islamic medicine flourished under Persian scholars such as Rhazes (865–925 AD), Haly Abbas (949-982 AD), and Avicenna (980-1037 AD). This period is referred to as the Golden Age of Islamic medicine [13]. Avicenna was a prominent scholar who greatly influenced the development of medical science. He wrote almost 450 treatises on a wide range of subjects, including medicine. One of these manuscripts is a large encyclopedia known

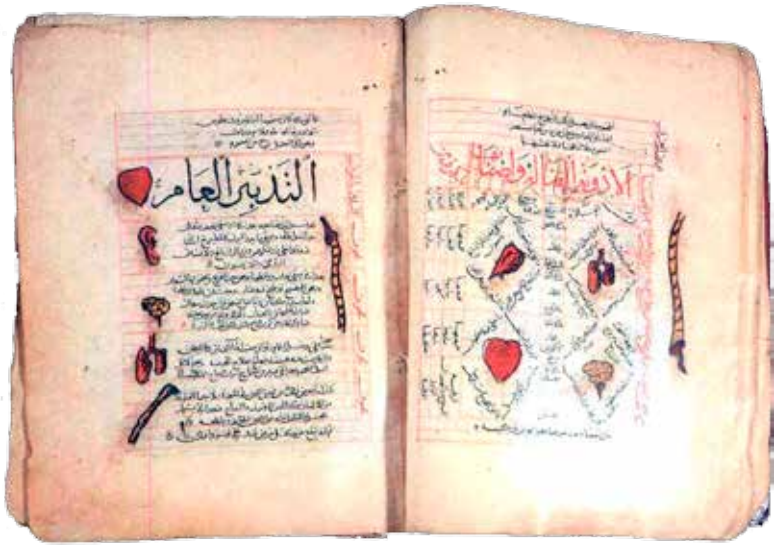
Statue of Avicenna, in front of entrance door of central building of Shiraz University of Medical Sciences, Shiraz, Iran

Avicenina statua ispred ulaza u središnju zgradu Sveučilišta medicinskih znanosti u Shirazu, Iran

as the *Canon of Medicine*. It was one of the most important medical references in the west until the 16th century [14].

The *Canon of Medicine* frequently refers to opioids. The book has five volumes, the first of which is on the basics of medicine. In this volume, Avicenna discusses the pathophysiology of pain and analgesia. The second volume on pharmacology (pharmacopeia or *Qarabadin*), arranged in alphabet order, contains descriptions of drugs; simple medicines as well as compound ones, and includes details such as characteristics, methods of preparation, toxicology and shelf life in a chapter entitled *Afion* Avicenna discusses opium. The third volume is on disease diagnosis and treatment classified by organ systems. Opium is often referred to in this volume for the treatment of various diseases. In the fifth volume, under the chapter on toxicology, Avicenna discusses opium toxicity [15, 16].

Avicenna's pioneering work in medicine is pertinent to scholars of the Islamic period, as it presents the views on medicinal uses of opium of the period. An understanding of the Islamic age as a bridge between ancient civilizations and the Renaissance can shed more light on the development of knowledge regarding medicinal uses of opium [17]. This review of Avicenna's work heads in that direction.



Canon Medicinae of Avicenna, Damascus, National Museum.
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(http://islamic-arts.org/2012/science-in-islam-the-forgotten-brilliance/)

Analgesic effect

The most important medicinal effect of opium is its analgesic effect. Opioids have long been used for pain relief [18]. Opium has been used to treat moderate to severe, acute and chronic pain. Avicenna mentioned the analgesic effect of opium as a single therapeutic agent or as a constituent of other mixed herbal applications to treat various conditions such as headache, arthralgia, otalgia, toothache, labor, kidney and bladder pain. Avicenna has advised:

> *You can use opium topically for painful joints affected by gout*

Interestingly, he points out the contraindications of opium use; while it may act as an effective analgesic in some conditions such as acute abdominal pain. it can also lead to painful bowel obstruction. These are his words:

> *Opioid administration is so dangerous in bowl obstruction because it prevents bowl movements that resolve the obstruction.*

He also recommends that opium is avoided as analgesic in other painful conditions. He prefers treating the cause of pain rather than relieving pain with opium:

Pain can be alleviated in three ways:

By eliminating the cause of pain
By the use of sedatives such as alcohol
By the use of analgesics such as opium

But the true way for pain relief is the first one.

Avicenna also discussed the mechanism of opium's analgesic action according to the four humors theory, as follows:

Opioids are drugs which prevent nerves to conduct painful sensory impulses due to its cooling effect.

Hypnotic effect

Due to the development of new synthetic drugs to treat insomnia, the hypnotic effect of opioids is nowadays generally considered as a side effect of this class of drugs. However, opium and alcohol are the oldest known hypnotic agents used by humans [19]. Avicenna too mentions opium for the treatment of insomnia, as follows:

Opioids can be used orally or rectally in patients with insomnia

Avicenna recommended the use of opium in small doses and in combination with other agents to treat insomnia because he believed that long-term use of opium would cause sleep disturbance. Avicenna also mentions opioids in the differential diagnosis of a coma and distinguished the analgesic and hypnotic effects of opioids, as follows:

Some of the hypnotic opioids can also show analgesic effects.

Cognitive effects

Opioid abuse can lead to acute or chronic cognitive disturbance [20]. It seems that Avicenna was familiar with these effects:

Opium can cause memory and reasoning dysfunction

Antitussive effect

Narcotics (such as codeine) have widely been used as antitussives. It is believed that their antitussive effects are primarily related to the μ-opioid and κ-opioid receptors in the CNS [21]. Avicenna recommended the use of opium to treat cough as follows:

> *If all other treatments fail, opioids can be used to treat severe cough.*

Respiratory depression

Avicenna mentions opium as a cause of abnormal breathing.

> *Opium may lead to difficulty breathing, which can lead to death.*

Respiratory suppression was considered a side effect of topical opioid application on the chest in patients suffering from fever associated with tuberculosis.

> *Avoid topical use of these drugs on the chest, they can interfere with respiratory organs and suppress them.*
>
> *Avicenna has also commented on the mechanism of opioid-related respiratory depression, blaming the respiratory muscle spasm for respiratory failure. Current understanding of opiates fails to fully explain the mechanisms behind opioid-induced respiratory depression, but it seems that Mu- and κ-opioid receptor agonists reduce the final motor output, mainly by inhibiting the medullary inspiratory neuron network [22].*

Gastrointestinal effects

Avicenna believed that opium caused constipation and recommended opium to treat severe diarrhea. The constipating effect of opiates has been confirmed by recent research [23]. Although opium is not normally the first choice in the treatment of diarrhea because of its side effects, it is still used [24]

> *If diarrhea leads to fainting and other treatments fail, you can use opioids to stop diarrhea.*

Dyspepsia, as a proven side effect of opiates [25] is another sequela of oral opium use referred to in the *Canon of Medicine*:

> *Opium ingestion can cause dyspepsia.*

Neuromuscular disturbances

Different mechanisms have been suggested to clarify the occurrence of neuromuscular disturbances from chronic consumption of opiates. Accumulation of neuroexcitatory opioid metabolites may have a relevant role in producing this unwanted effect [26].

Avicenna mentions this effect as follows:

> *Muscle spasm may be an adverse effect of opioid therapy.*

Sexual dysfunction

Opiates can disturb sexual function [27]. This effect is considered part of the wide opiate-induced neuroendocrine dysfunction that causes an imbalance in the levels of sexual hormones [28].

Avicenna refers to this effect as follows:

> *Patients with sexual dysfunction should avoid opiate use; it can aggravate their problem.*

He also recommends opioids as an appropriate treatment for "excessive sex drive":

> *Patients with disturbingly high libido can use opioids topically.*

Nowadays, opiate antagonists are used to treat idiopathic erectile dysfunction in men [29].

Toxicity of opioids used in therapy

Avicenna was familiar with potential risks of opioid toxicity:

> *I saw a patient who died due to rectally administered opium.*

Avicenna generally discourages the use of opioids as much as possible. They are only to be used as the last line of treatment:

> *Physicians should be able to predict the duration and severity of pain and patient's tolerance and then weigh the risks and benefits of opium administration.*
> *Between opioids select the less potent and combine it with its antidote.*

He also suggests "pulse monitoring" as a way to prevent overdosing:

> *If you have no other option but to use opioids, closely monitor patient's pulse to avoid overdosing.*

Opium poisoning

The fifth volume of the *Canon of Medicine* has a chapter with a detailed description of poisoning. Avicenna has divided poisons according to their origin into mineral, herbal, and animal. He discusses the mechanisms of opium poisoning , clinical manifestations, and treatment against herbal poisons. The following quotation is from the section on clinical manifestations of poisoning:

> *A patient with opium poisoning shows the following symptoms:*
>
> *Cold extremities*
> *Pruritus*
> *Opium smell*
> *Vertigo*
> *Hiccup*
> *Disturbed vision*
> *Impatience*
> *Difficulty breathing*
> *Yellowish or dark skin color on extremities*
> *Pale face and lips*
> *Drowsiness and inability to talk*
> *Depressed eye*
>
> *After having gone through these symptoms, the patient develops a respiratory problem, cold breath?? and cold sweating, which lead to death.*

Most of these toxic effects have been confirmed by current research [30]. Avicenna says that these symptoms can have a two-day delay after opium ingestion. He also proposes seven grams as the lethal dose for opium. He also discusses the effect of alcohol on opium poisoning:

> *Patients may have concurrent alcohol poisoning. It can have a synergistic effect with opium poisoning and decrease its lethal dose. On the other hand, alcohol may serve as an opium antidote. This effect depends on the amount of ingested alcohol.*

Drug administration and dosing

It seems that opiate delivery methods were more varied ten centuries ago than today. According to Avicenna's *Canon of Medicine* opiates were applied as oral, topical, rectal, and intranasal treatments. Here are the quotes Avicenna repeats throughout the text:

Smelling of Egyptian opium is hypnotic.
In this type of headache, rub opioid-based drugs on the temporal area.

Other forms of opiates were also popular such as syrups, tablets, smoke, enema, and ear drops.

Equivalent doses of opiates

"Equivalent dose" is a concept comparing the potency of different drugs from the same class. Avicenna used this concept to compare opiates:

Instead of opium, a physician can administer Bhang seed (Cannabis sativa L.) in triple weight or "Mohrgiyah" in double weight.

Conclusion

The history of opioid consumption dates back to antiquity. But it seems that the knowledge about the drug improved during the Islamic Golden Age, as did other aspects of medicine. Avicenna's *Canon of Medicine* was one of the main reference books in both east and west until the 16th century. His views on opioids provide an insight into its use in the past and into the 11th century knowledge about opioids. After Avicenna, knowledge about opioids continued to develop in Islamic civilizations. In the 16th century, a Persian physician, Emadodin Mahmoud-Ibn Masoud Shirazi wrote a comprehensive textbook about opioids entitled *Resaleh Afiounieh,* which translates to "a treatise on opioids" [31]. Back then, it was the largest and most comprehensive reference book covering all aspects of opioids, including details on botany, cultivation, therapeutic use, side effects, addiction, and treatment of addiction [32]. It shows the growth of medicinal knowledge on opium and opioids in the medieval Persia.

Avicenna provides a detailed description of opium in the context of humoral physiology. Although he did not have the modern insight into the molecular activity of opioids, he was familiar with their therapeutic effects such as analgesic, hypnotic, and antitussive. These effects have later been confirmed by modern pharmacology. The toxic effects of opioids are also discussed in detail by Avicenna. He used different methods of administration which are now being rediscovered, such as the topical use of opioids. Many of his observations have been confirmed by current medical research. This shows the depth of knowledge and the validity of these historical concepts. Moreover, some of Avicenna's suggestions are yet to be validated by current

medical practice. For instance, Avicenna has suggested multiple mixed drug formulations that can be evaluated in clinical trials.

Reviews of medical histories such as texts by Avicenna give us a clear insight into the ideas of the past and may be helpful for future research. On the other hand, they also shed light on the dark passages of medical science history, that is, on the other side of this shining coin.

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Sažetak

Opijum se kroz povijest rabio kao temelj za opioide koji suprimiraju na središnji živčani sustav. To je tvar koja se ekstrakcijom dobiva iz makovih glavica (Papaver somniferum L.). *Uporaba opijuma i njegova medicinska primjena bili su poznati još u antičko doba. U srednjem je vijeku poznati perzijski učenjak Avicena (980. –1037.) spominjao mak u svojoj medicinskoj enciklopediji Medicinski kanon pod natuknicom afion. U enciklopediji se raspravlja o različitom djelovanju opijuma, povoljnom i štetnom. Spominje se da opioidi ublažavaju bol, djeluju poput hipnoze, protiv kašlja, na probavu, na um, na oslabljene funkcije disanja, poremećaj živčano-mišićnog sustava tespolne funkcije, a govori se i o trovanju opioidima. Avicena je opisao nekoliko načina primjene i dao preporuke vezane uz doze lijeka. Većina učinaka na koje se Avicena osvrće, kasnija su istraživanja potvrdila, a drugi srednjovjekovni izvori koji govore o uporabi opijuma zanimljivi su za buduća istraživanja. U ovome se članku ističe jedan važan aspekt povijesti medicine srednjega vijeka.*

Ključne riječi: *opijum, Avicena, povijest medicine, Perzija, Kanon medicine*