

Volume 2 • Issue 4

# Topics in Biomedical Research and Education

Official Journal

Research and Education Institute in Biomedical Sciences

ISSN: 2945 -0675

2024



# Topics in Biomedical Research and Education

## Quarterly Scientific Publication of REIBS

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Biomedical Sciences

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92-94 Kolokotroni str.

GR-185-35 Pireaus, Attika, Greece

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### Open Access Journal

ISSN: 2945-0675

October-December 2024 | Volume 2, Issue 4

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## Editorial

# The conceptual approach of the soul in ancient Greek philosophy and its relationship with humanism and ethics in the practice of medicine

Dimitrios Filippou

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The idea of the soul holds a vital role in ancient Greek philosophy, being a focus of inquiry for notable philosophers like Socrates, Plato, and Aristotle. The exploration of the soul encompassed not only human nature and existential questions but also ethical considerations and humanism, particularly in medical practices. In examining the soul's connection to ethics and humanism within the medical context, three primary phases emerge within ancient Greek thought: the Pythagorean and Pre-Socratic views, the philosophical insights of Socrates and Plato, and Aristotle's perspective.

### The soul in Pre-Socratic and Pythagorean thought

The first systematic approach to the soul arises from Pre-Socratic and Pythagorean thought, which attempted to explain the nature of life and the universe through abstract concepts and philosophical principles.

*The Pythagorean view of the soul:* Pythagoras (6th century BC), renowned chiefly for his mathematical insights, also made notable contributions to philosophical discussions regarding the soul. In Pythagorean philosophy, the soul is viewed not merely as an immaterial presence within the body but as having an eternal and divine essence. Pythagoras endorsed the concept of reincarnation, suggesting that the soul survives the physical body and moves into a new form after death. This perspective on the soul as immortal strengthened the belief that it is a core aspect of human identity, connecting individual existence to a broader cosmic law and moral framework. (Figure 1).

*The Presocratic approach to the soul:* Presocratic thinkers like Heraclitus and Anaximander advanced naturalistic and

cosmological perspectives regarding the soul.

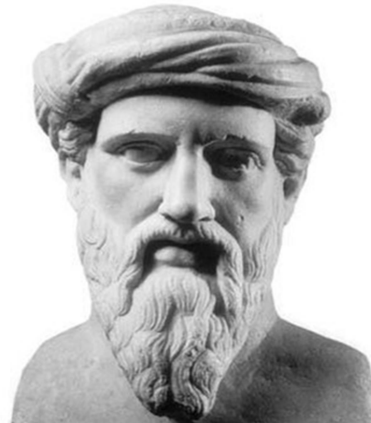


Figure 1. Pythagoras (Ancient Greek: Πυθαγόρας; c. 570 – c. 495 BC) was a philosopher and mathematician from ancient Greece, renowned primarily for his work in mathematics, particularly the Pythagorean Theorem, which connects the side lengths of a right triangle. He established the Pythagorean School and profoundly impacted philosophy, mathematics, and the understanding of numerical relationships found in nature.

Heraclitus posited that the soul represented cosmic order and constant transformation. He viewed the soul as intrinsically linked to fire, one of the essential elements of the universe, and as a participant in the harmony of the cosmos. This perspective indicated that the soul occupied an integral position in the universe rather than merely being an isolated fragment of human life. In a similar vein, Anaximander articulated a more abstract understanding of the soul as part of the "infinite" principle, or the indefinite essence that serves as the origin of all existence. This viewpoint implied a deeper connection between humanity and the cosmos, reinforcing the concept of the interrelationship between soul and body.

### The Socratic and Platonic view of the soul

The most important turning point in the

philosophical approach to the soul comes with Socrates and his student Plato, who connected the soul with ethics, knowledge and truth, creating an ethical framework that had a great impact on human behavior and the practice of medicine.

*Socrates and the soul as the center of ethics:* Socrates (469–399 BC) is regarded as one of the earliest philosophers to examine the soul as fundamental to human existence and ethics. His Socratic method, centered on dialectical dialogue, sought to promote self-understanding, viewing the soul as the foundation of virtue and morality. For Socrates, the soul enables individuals to navigate between right and wrong, making the care of the soul humanity's utmost responsibility. He famously stated, "Virtue is knowledge," asserting that true wisdom originates from the soul. In light of this, the practice of medicine takes on a profoundly humanitarian dimension, emphasizing that bodily treatment must go hand in hand with soul care. Socrates believed that a fulfilling life relies on the harmony between body and soul, suggesting that genuine health is unattainable without moral equilibrium. (Figure 2)

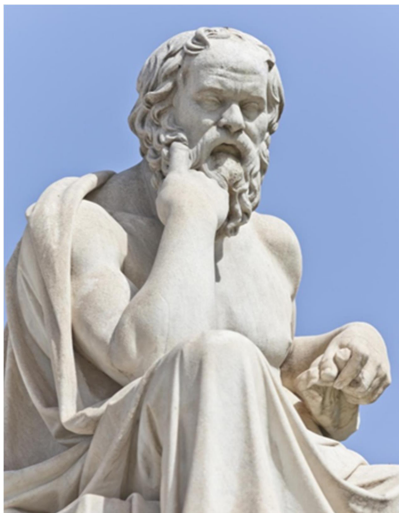


Figure 2. Socrates (born c. 470 bce, Athens [Greece]—died 399 bce, Athens) was an ancient Greek thinker regarded as a key figure in the development of Western political philosophy and ethical thought. His most notable contribution is the Socratic method, a form of inquiry that promotes critical thinking and self-examination. Socrates left no written records of his own teachings, and much of what we understand about him is derived from his disciples, such as Plato and Xenophon

*Plato and the immortality of the soul:* Plato

(427–347 BC), building on Socratic ideas, developed a comprehensive philosophical framework regarding the soul, connecting its immortality to ethics and the quest for truth. In the *Phaedo* dialogue, Plato depicts the soul as eternal and autonomous, separate from the body. He argues that the soul exists prior to physical form and persists after death. The Platonic conception of the soul is divided into three parts: the rational (which seeks truth), the thymic (associated with courage and emotions), and the volitional (relating to basic desires and necessities). This tripartite structure directly influences morality: a well-ordered soul is one that achieves harmony among these components. In Platonic thought, nurturing the soul and cultivating moral virtues extend beyond simple physical health. This holds significant consequences for healthcare, emphasizing that medical practice should extend beyond merely addressing physical ailments to also consider the individual's spiritual well-being. In the *Gorgias* dialogue, Plato posits that the most serious affliction is that of the soul, where the genuine remedy lies in ethical enhancement and aligning the soul with virtue. (Figure 3)

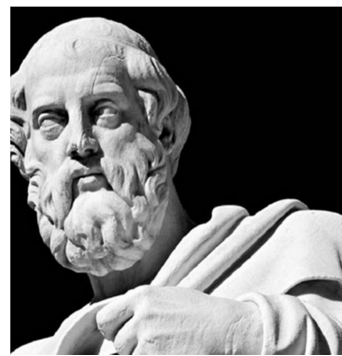


Figure 3. Plato born Aristocles (Ἀριστοκλῆς; c. 427 – 348 BC) was a classical Greek thinker, a disciple of Socrates and mentor to Aristotle. He established the Academy in Athens, which is recognized as one of the first centers for higher education in the Western civilization. His philosophical contributions, mainly composed as dialogues, delve into diverse areas like ethics, politics, and metaphysics, with significant texts such as "The Republic," "Phaedrus," and "The Symposium." His philosophy highlights the realm of forms or ideals and underscores the significance of rational inquiry.

### Aristotle and the soul as a form of the body

Aristotle (384–322 BC) provided a distinct yet

equally significant perspective on the soul, blending aspects of physiology with metaphysics. He regarded the soul as the body's form, the essence that imparts life and purpose to a living organism. In contrast to Plato, Aristotle viewed the soul as inseparable from the body, conceptualizing both as an interconnected entity that relies on one another for existence and functionality. (Figure 4)

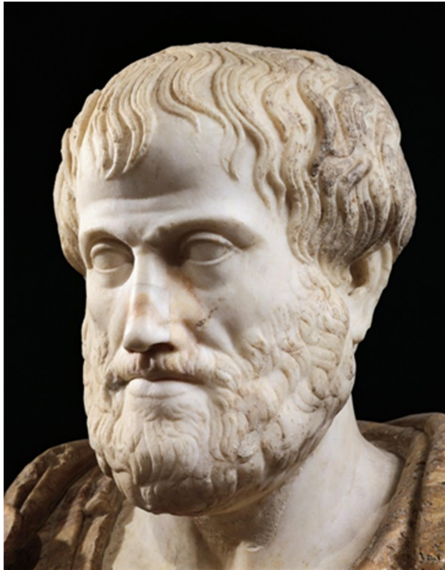


Figure 4. Aristotle was a philosopher and polymath from ancient Greece, living between 384 and 322 BC. He contributed greatly to numerous disciplines, such as logic, metaphysics, ethics, politics, aesthetics, and the natural sciences. He is considered one of the most pivotal figures in Western philosophy, influencing how various subjects are taught and perceived even in contemporary times.

*The functional approach of the soul:* In his treatise *On the Soul*, Aristotle explores the concept of the soul as the "enteleche" of the body, meaning it is the essence and guiding force that defines what the body is capable of becoming and achieving. The soul dictates the characteristics and activities of different living beings: for instance, the human soul encompasses the faculties of intellect and reasoning, whereas a plant's soul is limited to nourishment and growth. Aristotle's functional perspective on the soul has direct implications for medicine. He posits that health is achieved when the soul and body operate in harmony, fulfilling their inherent roles. Illness and dysfunction arise when this equilibrium is disturbed. Consequently,

medical practice is not merely about restoring physical capabilities but also about reinstating the balance between the soul and body.

*The ethics of medicine and the care of the soul:* In Aristotelian philosophy, ethics is fundamentally associated with the idea of 'happiness', a state of contentment and fulfillment achieved through virtuous actions. The soul, regarded as the wellspring of rational and moral virtues, requires appropriate nurturing and attention. Within this framework, medical practice transcends mere technical skill and transforms into a moral obligation focused on the holistic welfare of the patient. Aristotle's view of the soul presents a human-centered approach to medicine, where the doctor's role extends beyond physical healing to fostering the moral and psychological well-being of the patient. According to Aristotle, nurturing the soul is essential for attaining genuine health.

#### **The soul and ethics in medical practice**

The philosophical understanding of the soul in ancient Greek thought greatly influenced the ethics surrounding medical practices. In the ideas of Socrates, Plato, and Aristotle, health extends beyond merely avoiding illness; it encompasses the overall balance of both body and soul. Consequently, treatment is viewed as a comprehensive method that links the individual's physical and spiritual well-being.

*Medicine as a moral act:* From a philosophical perspective on the soul, medicine transcends being a purely technical endeavor. The relationship between doctor and patient embodies ethical significance at its highest level, as the physician's duty extends beyond just implementing medical expertise; it also encompasses nurturing the patient's soul. A doctor should assist the patient in regaining not only their physical well-being but also their mental equilibrium and moral integrity.

*The Hippocratic Oath:* The Hippocratic Oath serves as the cornerstone of medical ethics, embodying these philosophical ideals. In this oath, the physician commits to honoring the patient's



life and dignity, striving for what is good while shunning harm. Ancient Greek medical ethics is rooted in the philosophical idea of the soul as the source of human virtue and dignity. (Figure 5)



Figure 5. The Hippocratic Oath is a collection of ethical standards traditionally sworn by doctors to uphold key principles in medical practice, focusing on patient care and preserving professional integrity. It traces its roots to Hippocrates, a Greek doctor often considered the "Father of Medicine." The oath highlights the pledge to avoid harm (primum non nocere), safeguard patient confidentiality, and adhere to ethical medical practices.

The philosophical concept of the soul in ancient Greek thought played a crucial role in shaping humanism and medical ethics. Considered the essence of human life, the nurturing of the soul became a fundamental moral duty in philosophy and healthcare. Influenced by the teachings of Socrates, Plato, and Aristotle, the soul was intrinsically tied to moral excellence, with medical practice regarded as a noble endeavour focused on the holistic welfare of individuals.

*This article is dedicated to the sacred memory of my father Konstantinos D. Filippou, Prof. of Education and Philosophy.*

## Letter to the Editor

## The imperial Byzantine physician of the 10th century AD Theophanes Nonnus, the prolific writer in the court of the Emperor Constantine VII the Porphyrogenitus

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Theophanes Nonnus (or Nonnos, Greek: Θεοφάνης ο Νόννος), lived during the reign of Emperor Constantine VII the Porphyrogenitus. (Fig.1)



Figure 1. Miniature depiction of Constantine VII from the Byzantine Codex of the 15th century "Cronaca di Zonara e altri brevi testi di storia bizantina".

Because of his great education and skills became emperor's chief physician. Theophanes diligently collected what Orivasius, Aetius of Amida, Paulus of Aegina and Alexander Trallianus had written in their treatises, being a majestic compiler (Greek: επανιστής). This concept to compose an encyclopedia of medical knowledge after an order given by the emperor was a common practice during the Byzantine Empire [1-2]. Theophanes wrote a work of great interest on the History of medical terminology entitled "Synopsis in an Epitome of the Medical art" (Figure 2), containing two hundred and ninety-seven chapters. Other know works attributed to him are "Eye Diseases", "Dietary" and a pharmaceutical collection of seven

hundred and twenty-five chapters, named "Euporista" (Substances for best way to live), which may be found in the Paris National library [3-6]. Among others he gave instructions for the best eruption of new teeth, childhood epilepsy, prevention of infectious diseases and environmental contamination, tetanus, conjunctivitis, eye and uterine cancer, the treatment of heart shock and heart rhythm disorders, tonsillitis, bronchial asthma, linteria, drugs for gallstones, terror, migraine, coma, and the suicidal tendency of psychiatric patients. Theophanes was the first to apply an "abdominal puncture on ascites", a term he was the first to use [5, 7]. One of his mistakes in anatomy was that the "the larynx is the mouth (upper opening) of the tracheal artery". Meanwhile, he knew how to perform direct laryngoscopy [5, 8]. Theophanes second name "Nonnus" is under dispute, as many researchers based on a testimony of the Vienna Codex, attribute to him the name "Chrisovalantes", noting that this may have been derived from the Chrysovalantou Monastery or from the term "chrisovalanon" meaning "golden repository", a great epithet for a majestic physician. A family named "Chrysovalantitai" existed in the archives of the Byzantine Empire and there is a possibility that Theophanes was one of its members. Some researchers also believe that the order considered to have been given by Constantine the VII is rather a dubious belief, as Theophanes' work was much shorter than Oribasius' and there is the possibility that the emperor just adopted Theophanes work to promote his name, or just gave Theophanes name in a secondary value treatise, as Theophanes was his personal friend and desired to help his social

elevation. Whatever the case may be, Theophanes Nonnus' work stands as a significant echo of the 10th century Byzantine Medicine [9].

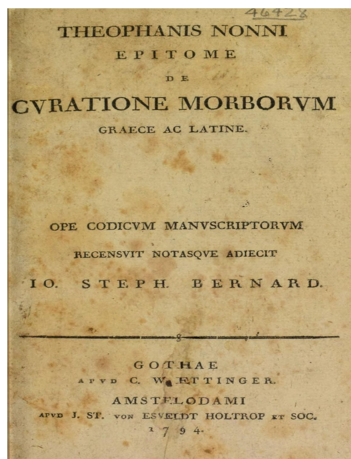


Figure 2. Theophanis Nonni Epitome de Curatione Morborum. Gothae, 1794.

The period of the Macedonian dynasty and the Emperor's Constantine VII the Porphyrogenitus was one of the most glorious and celebrated periods of the Byzantine Empire. Both science and art developed widely and their fruits resulted for the era to be characterized as the "Macedonian Renaissance". Theophanes was one of the most eminent physicians of the era in Constantinople, belonging to the inner circle of the Emperor. His writings included references in pathology, gynecology, neurology and pharmacology [10-11]. His practice was based in the ancient Greek and Greco-Roman medicine, introducing however his own medical views, emphasizing for example in antiseptics [12]. Although Theophanes grew up into one of the most significant medical figure of the Byzantine era, little is known for his life. This fact is testified in various Lexica, where only his name and profession is mentioned [13-14]. His figure was so important that had been included in Lexica of Ancient Greek Philology, probably due to the concept of the ancient Hellenic literature (Greek: αρχαία Ελληνική Γραμματεία), including all treatises in a unified base [15].

The mystic which surrounds Theophanes's life provokes researchers to connect fragments of his work and to unveil aspects from future findings.

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## REVIEW

**The role of medical cannabis in the cancer-related pain treatment**Sinou Natalia <sup>1,3</sup>, Sinou Nikoleta <sup>2,3</sup>, Filippou Dimitris <sup>3,4</sup><sup>1</sup> Medical Graduate, National and Kapodistrian University of Athens, Medical School<sup>2</sup> Medical student, National and Kapodistrian University of Athens, Medical School<sup>3</sup> Research and Education Institute of Biomedical Science<sup>4</sup> Surgery, National and Kapodistrian University of Athens, Medical School

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**Abstract**

**Introduction:** Pain is among others, one of the most common symptoms in patients facing malignancies. The pain may have a major negative impact on their quality of everyday life. Currently, the gold standard in the treatment of cancer-related pain suggested by WHO are the opioids. However, besides their multiple side effects, there is a small but significant number of patients that are not relief from pain using these drugs. Thus, there is a need of incorporating different drugs in the treatment of the cancer-related pain.

**Materials and Methods:** The aim of this review is to examine the potential of using medical cannabis in the treatment of pain caused by cancer, as long as it's side and adverse effects.

**Results:** Detailed research was conducted via the PubMed database using the keywords: "medical", "cannabis", "cancer" and "pain"

**Conclusion:** Current evidence for the use of cannabis and cannabinoids to relief cancer pain is weak, because of the existence of multiple adverse effects that cannot be overviewed. However, there is some evidence that indicate that medical cannabis could potentially be beneficially used as an adjunct to the already applying therapy. Further research needs to be done in this field of medicine in order to incorporate medical cannabis in guidelines for cancer pain management.

**Keywords:** Medical, Cannabis, Cancer, Pain

**Introduction**

It is common for patients who face cancer to experience multiple debilitating symptoms including nausea, anxiety, stress and mainly pain. In fact, pain in cancer patients is extremely common, particularly in advanced stages of the disease, with a prevalence exceeding 70%. There are multiple reasons for which patients who encounter cancer may experience pain. Pain may arise from the malignancy itself or it may be a result from the therapy against the disease. It can also be related to other comorbid illness or situation (1), (2). From now on, in this review the pain is defined as the pain related to the malignancy itself and does not correlate with the therapy or any other coexisting disease.

Although there is a lack of robust clinical data, the usage of cannabis products has been approved in multiple countries for certain medical indications

resistant to standard therapy, including nabilone for chemotherapy-induced vomiting and nausea. Therefore, an extend new field of exploration was the use of the medical cannabis in the treatment of cancer induced symptoms, such as chemotherapy related nausea, anxiety, depression, insomnia anorexia and most of all cancer related pain.

Cannabis is a plant-based substance made from multiple species within genus Cannabis. Cannabidiol (CBD) is a phyto-alkaloid derived from plants in the Cannabaceae family and genus Cannabis. According to the various targeted commercial purposes, cannabis plants have been under hybridization into hundreds of strains. There are various classification methods depending on their botanical morphology, subjective effects, chemotaxines and many other factors. Among all the cannabis components 9-delta-tetrahydrocannabinol (THC) and cannabidiol

(CBD) are the most abundant and as a result the most well studied cannabionoids. Apart from CBD and THC, cannabis constitutes of more than 500 organic compounds of which more than 100 belong to cannabinoid family. In addition to terpenes and flavonoids the interaction and the effect of the cannabionoids exert their affection on the endocannabinoid system (3). CBD may comprise even 90% of the plant extract, depending on the species and the extract procedure, along with many addable terpinenes and cannabinoids, including tetrahydrocannabinol (THC) (4). Currently cannabinoids drugs exist in synthetic THC form as nabilone and in an approximate 1:1 ratio THC:CBD plant extract as nabixomols (3). However, THC has psychoactive properties that provoke intoxication and impairment, limiting the use of this drug. On the contrary, CBD is no psychoactive and thus it does not lie under this restriction (4).

The aim of this review is to examine the use of the medical cannabis in the confrontation of the pain related to malignancy.

### Materials and Methods

Detailed research was conducted through the published bibliography via PubMed database. The keywords used for the search were “medical”, “cannabis”, “in”, “cancer” and “pain”. Data were extracted utilizing a common data elicitation form, using the aforementioned keywords. The study was made with respect to the PRISMA 2020 flow diagram for new systematic reviews which included searches of databases, registers and other sources guidelines. Specifically, as regards the PRISMA, the records that were initially identified through PubMed search were 124. These results derived after applying a filter of the last 5 years. There were 3 additional ones through review of references. Also, the full text articles assessed for eligibility were 14, and the records excluded articles, title and abstract non relevant were 110. There was 1 extra suitable article derived from the similar articles. All the reports assessed for eligibility were relevant, but 1 of them was written in german, so it was excluded. No duplicates were found. Finally, 17 references fulfilled the above-mentioned criteria and used in the present work.

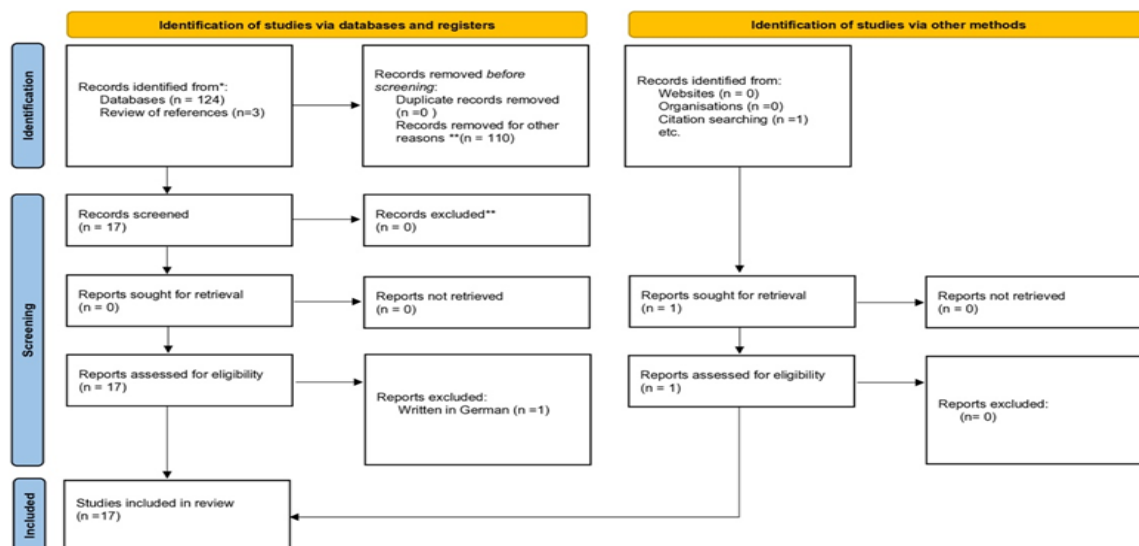


Figure 1: PRISMA 2020 flow diagram for new systematic reviews which included searches of databases, registers and other sources \*\*: title and abstract non relevant

## Results

There have been conducted several studies examining the use of medical cannabis in the treatment of cancer-related pain.

According to a systematic review and meta-analysis by Boland et al (5) (Boland EG, Bennett MI, Allgar V, Boland JW. Cannabinoids for adult cancer-related pain: systematic review and meta-analysis), there was not a positive effect by using neither nabiximols nor oromucoal spray (with 1:1 CBD:THC) on the NRS (Numeric Rating Scale) for pain intense score comparing to the placebo. However, as far as it concerns the adverse effects, the meta-analysis suggests significantly higher odds of somnolence and dizziness in cannabinoid group. A higher but not statistically significant odds of nausea and vomiting in the cannabinoid group is also reported. None of the studies included in the aforementioned metanalysis indicated beneficial use of cannabinoids, thus cannabinoids are not recommended for the cancer-related pain management. Similar are the results arising from another study (Safi K, Sobieraj J, Błaszkiwicz M, Żyła J, Salata B, Dzierżanowski T. Tetrahydrocannabinol and Cannabidiol for Pain Treatment-An Update on the Evidence.) (6)

However, there is a systematic review and meta-analysis by Wang L. (7) (Wang L, Hong PJ, May C, Rehman Y, Oparin Y, Hong CJ, Hong BY, AminiLari M, Gallo L, Kaushal A, Craigie S, Couban RJ, Kum E, Shanthanna H, Price I, Upadhye S, Ware MA, Campbell F, Buchbinder R, Agoritsas T, Busse JW. Medical cannabis or cannabinoids for chronic non-cancer and cancer related pain: a systematic review and meta-analysis of randomised clinical trials.) which indicates that not-inhaled medical cannabis and cannabinoids result in a tiny benefit in pain alleviation, physical function and sleep quality, along with various temporary side effects, compared to a placebo.

## Discussion

*Opioids in reducing cancer pain:* According to the World Health Organisation (WHO) the first step of the analgetic ladder for moderate to severe cancer pain management is the use of opioids. In clinical practice, the majority of cancer patients is going to

deal with the cancer pain by using the opioids. However, there is a small but significant number of patients that will not have adequate pain relief. Therefore, there is a crucial need for new pain-relieving methods and analgesics, supplementary to opioids to alleviate the pain of the patients with insufficient pain relief of cancer pain. However, opioids are associated with multiple unwanted side effect including tolerance and dependance, chronic constipation, loss of appetite, nausea, respiratory depression, sedation and drug induced hyperalgesia. As a result, their clinical use is limited (8).

*Pharmacokinetics:* The pharmacokinetics of cannabis and cannabinoids are different and depend on the dosage form. Cannabinoids are lipophilic and have a great width of distribution. THC is known to cross into placenta and breast milk. There are no data to indicate the presence of CBD or metabolites in human milk, although, animal studies highlight embryofetal developmental toxicity.

Cannabinoids are metabolized in the liver by the cytochrome P450 (CYP) isoenzymes using either hydroxylation or oxidation. After that, they are further metabolized by glucuronidation. The drug is finally excreted by both urine and feces, after the augment in solubility postmetabolism. THC is largely metabolized by isoenzymes CYP2C19, CYP2C9, and CYP3A4 and the CBD is predominantly metabolized by CYP2C19 and CPY3A4, but also CYP1A1, CYP1A2, CYP2C9, and CYP2D6. It is also suggested by in vitro data that CBD acts like an inhibitor to p-glycoprotein-mediated drug transport and substrates of uridine 5'-diphosphoglucuronosyltransferase 1A9 and T2B7 (9).

*Dosage:* The ideal dosage would be the one that would manage effective pain relief without any or at least any intolerable side effect (10). The complicity of the pharmacology, the variety of the capacities and the amounts of cannabinoids in the products, lead to the inability of the traditional pattern of dose guidance to be used in cannabis. The aforementioned factors in addition to the existence of other active compounds (flavonoids, terpenoids) and the lack of evidence based clinical trials and studies evaluating dosage forms, doses and finally

the interval between dosages depending on each indication, make it incapable for a safe and efficient dose to be recommended (9).

Furthermore, every patient does not respond to therapy same with other patients with the same disease. The response to the treatment depends on other medications, prior exposure and tolerance to the drug, coexisting diseases, food and the metabolism of the patient itself. Therefore, there is only a rough dosage guideline available and dose should be personalized for every patient. The gold standard is the titration, same as in every drug, beginning in a low dosage and titrating to the beloved response. This should also be applied because many of the undesired effects, such as fatigue, dizziness and psychotropic effects, start at an early low dose and tolerance develops overtime.

*Cannabis and cannabinoids in patients with cancer:* It is common for cannabis products to be used in the treatment of cancer patients. The symptoms that may be treated with the usage of cannabis and cannabinoids products are multiple such as chemotherapy related nausea and vomiting (21%) stress-anxiety (20%), depression-insomnia (9%), loss of appetite-weight gain (12%), well-being (17%), treatment of malignancy (4%) and pain (15%) (9).

*Adverse effects and side effects:* The two main cannabinoids of cannabis are  $\Delta$ 9-tetrahydrocannabinol ( $\Delta$ 9-THC) and cannabidiol (CBD). There is a hesitancy in prescribing cannabis for medicinal use. This is due to the undesirable psychotropic effects of the constituent ( $\Delta$ 9-THC) as well as due to other side effects of this substance such as tachycardia, altered cognitive perception, anxiety and other behavioral issues. Moreover,  $\Delta$ 9-THC may provoke an alteration in the immune system function, augmenting the susceptibility of a patient to microbial infections. Further, despite the established anti-cancer capacities of  $\Delta$ 9-THC, this cannabinoid has been accused to provoke tumor growth, metastasis and invasion in some cancer cell types. In breast tumor for instance,  $\Delta$ 9-THC mediated tumor increase and metastasis was related to the inhibition of the anti-tumor specific immune responses in vivo. Finally, studies

demonstrate that cannabis is linked with the evident reduced efficiency of immune checkpoint inhibitors.  $\Delta$ 9-THC has a maximum tolerated daily dose of 15-90 mg in adult patients approximately, and this small dose requires an ongoing individualized adjustment to make sure that the adverse effects are tolerated to each patient.

Concerning CBD in some cases it is believed that it may cause somnolence and fatigue. However, not permanent or serious adverse effects (such as life-threatening, hospitalization or surgery requiring interventions, temporary or permanent disability and death) were mentioned (11). Moreover, CBD crosses the placenta and reaches the breast milk, so it is of grave significance to abstain while pregnant or postpartum/ breast-feeding. Further, due to accumulation, it is highly possible for CBD to cause hepatotoxicity (12). Finally, it is believed that in the majority of cases there is not a great difference by using the cannabinoids for cancer pain relief (13).

*Advantages of medical cannabis:* In the contrary to  $\Delta$ 9-THC, CBD (the second most abundant compound in cannabis) is well tolerated in patients even in relatively high doses. CBD is also believed to have anti-psychotic, anti-convulsive, anti-inflammatory, anxiolytic and relaxing properties (12). Further, it was observed that the use of an oromucosal spray of cannabinoids ( $\Delta$ 9 -THC: CBD) for a long period, contributed to the reduction of cancer-related pain without increasing the dose in patients. In fact, the particular spray was found to be efficient to patients resistant to opioids analgesics. Moreover, it was demonstrated that nabilone not only contributed to the nausea, anxiety and pain problem in high staged cancer people, but also it diminished the use of other drugs including non-steroid anti-inflammatory, anti-emetics, anti-depressing and opioids drugs, comparing to the untreated with the specific drug patients (14). In addition, during the last decades it has been demonstrated multiple studies, that cannabinoids have antitumor properties in various cancer cell types including breast tumor, melanoma, pancreatic cancer, brain tumors and lymphomas among others (15).

## Conclusion

The outcomes of the conducted studies indicate that nabixomole which constitutes of both THC and CBD, might be an efficient adjunct to cancer pain management in those patients who are not optimized on opioid treatment. Therefore, medical cannabis might be more beneficial as an adjunct to the standard therapy rather than as a replacement (9).

There is insufficient evidence to conclude that a single low dose morphine equivalent or a single synthetic THC counterpart is more effective in relieving moderate to severe cancer pain. Moreover, there is low certainty evidence that CBD improves on specialized palliative care alone in terms of reducing pain in patients with advanced cancer (16).

Current studies indicate that there is a potential benefit of the use of the medical cannabis in the cancer-related pain treatment. However, the scale and the amount of the studies conducted are limited. Further research should be done in this field to establish the use and the efficacy of this promising product in the management of an extremely common symptom that multiple patient encounter (10). Thus, the guidelines recommend that health care providers should use and educate patients with the already available and established information. It is highly possible that for some patients, cannabis and cannabinoids might be an arrow in the quiver of their health providers, but until more data support their use in the cancer treatment, they cannot be widely suggested (9).

More studies need to be conducted in order that medical cannabis can be safely and effectively incorporated into medical treatment plans against cancer in general and cancer-related pain especially (17).

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## Review

### GLP-1 Receptor Agonists and Cholelithiasis: A Comprehensive Review

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#### Abstract

GLP-1 receptor agonists (GLP-1 RAs) have emerged as a novel class of antidiabetic medications, displaying potential in optimizing glycemic control and offering cardiovascular advantages for individuals with type 2 diabetes. Moreover, GLP-1 receptor agonists are utilized in the treatment of childhood and adolescent obesity. Currently, there are seven GLP-1 receptor agonists available, including exenatide twice-daily, exenatide extended-release (ER) once-weekly, lixisenatide once-daily, liraglutide once-daily, dulaglutide once-weekly, semaglutide once-weekly, and oral semaglutide once-daily.

Aim of this systematic review is to provide an all-inclusive analysis of the existing literature exploring the association between GLP-1 receptor agonists and cholelithiasis, assess the risk of cholelithiasis induced by GLP-1 RAs, and establish its significance. A thorough examination was conducted using the PubMed database with the keywords: "glp-1 receptor agonists" AND "glp-1" AND "cholelithiasis." No further filters were applied. The last research was conducted on 26 November 2023.

Based on the research findings, it has been determined that the utilization of Glp-1 RAs in the management of type 2 diabetes and obesity may be connected to a heightened susceptibility to cholelithiasis. However, further extensive investigations are necessitated to conclusively ascertain the statistical significance of this increased risk in relation to the use of GLP-1 RAs for obesity treatment.

*Keywords:* glp-1, glp-1 receptor agonists, cholelithiasis, obesity, type 2 diabetes

#### Introduction

GLP-1 receptor agonists exhibit insulinotropic and glucagon static properties, exhibiting considerable efficacy correlated with glucose levels. Consequently, they effectively reduce elevated plasma glucose concentrations.(2) Since 2005, GLP-1 RAs have been approved for the treatment of type 2 diabetes and are currently recommended in the initial stages of the treatment protocol. This recommendation is based on the proven benefits of GLP-1 RAs, which include weight reduction, glycemic efficacy, and favorable cardiovascular and renal health outcomes, as indicated in the latest guidelines.(5) Additionally, GLP-1 receptor agonists have a central mechanism of action that effectively decreases appetite and food consumption, making them a valuable therapeutic option for addressing obesity.(9)

However, there have been reports of gallbladder-related adverse events (such as cholelithiasis and cholecystitis) in clinical trials that study the metabolic effects of GLP-1Ras.

#### Materials and Methods

Detailed research was conducted through the published bibliography via PubMed database. The keywords used for the search were "medical", "cannabis", "in", "cancer" and "pain". Data were extracted utilizing a common data elicitation form, using the aforementioned keywords. The study was made with respect to the PRISMA 2020 flow diagram for new systematic reviews which included searches of databases, registers and other sources guidelines. Specifically, as regards the PRISMA, the records that were initially identified through PubMed search were 124. These results derived

after applying a filter of the last 5 years. There were 3 additional ones through review of references. Also, the full text articles assessed for eligibility were 14, and the records excluded articles, title and abstract non relevant were 110. There was 1 extra suitable article derived from the

similar articles. All the reports assessed for eligibility were relevant, but 1 of them was written in german, so it was excluded. No duplicates were found. Finally, 17 references fulfilled the above-mentioned criteria and used in the present work.

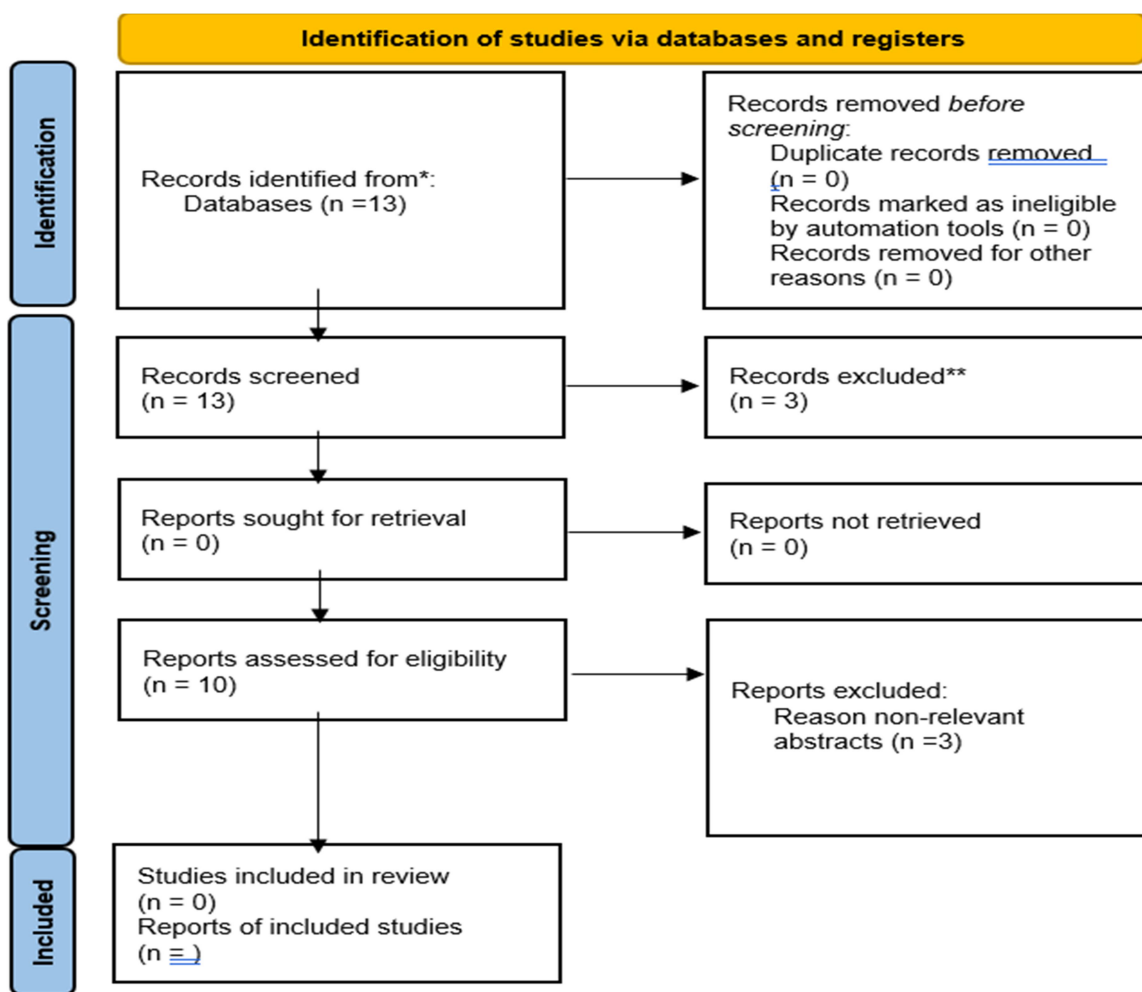


Figure 1: PRISMA 2020 flow diagram for new systematic reviews which included searches of databases, registers and other sources. \*\*: title and abstract non relevant

### Results

Research has shown that GLP-1 receptor agonists have been associated with an increased risk of cholelithiasis among patients. While some studies have found this risk to be significant, others have been unable to provide definitive evidence. As a result, a clear conclusion cannot be drawn at this time. However, when considering the favorable

effects of these drugs on glucose metabolism, blood pressure, body weight, and cardiovascular and renal health, the overall risk/benefit profile of these agents for treating type 2 diabetes and obesity patients is beneficial. It is recommended to assess the presence of gallstones and risk factors for cholelithiasis in all patients before initiating incretin-based therapy.

Studies	Regimen	Patient sample size	Control sample size	Cholelithiasis cases
1	Semaglutide	201	67	5 ( 4% )
2	Semaglutide	*	*	*
3	GLP-1 Ra	17,232	14,8772	141 for GLP-1 Ra group 99 for control group
4	Liraglutide	12411	9093	276 for GLP-1 Ra group 119 for control group
	Semaglutide	8598 9855	5062 7528	
	Dulaglutide	9536 6878	9501 7149	190-92 153-102
	Exenatide			190-154
	Albiglutide	5355	3291	36-30
	Oral semaglutide	4983	4032	
	Lixisenatide			28-21 39-26
5	Tirzepatide	4621	2215	1394-235
6	Subcutaneous semaglutide	3150	1657	29-8
	Oral semaglutide	4116	2236	30-18
7	Subcutaneous semaglutide	1642	1644	36-27
	Oral semaglutide	1591	1592	4-2
8	GLP-1 Ra	Not mentioned	Not mentioned	Not mentioned
9	Liraglutide	Not mentioned	Not mentioned	37

Table: Data derived from the summary of product characteristics, as the manuscripts did not describe these data.

### Discussion

Semaglutide, a Glp-1 RA that has undergone investigation, is being used as a subcutaneous treatment once a week at a dose of 2.4 mg in adults with obesity, in combination with lifestyle intervention. This treatment has demonstrated clinically proven benefits in improving

cardiometabolic risk factors and promoting weight loss. Out of a group of 201 participants, only five individuals (4%) in the semaglutide group experienced acute cholelithiasis, whereas none of the 67 participants in the placebo group had a similar occurrence. However, the researchers did not consider this percentage to be statistically significant.(1) Additionally, a separate study revealed that cholelithiasis was observed with greater frequency in the group receiving semaglutide compared to the group receiving a placebo (0.6% versus 0.1% with placebo).(2) In the same study, findings indicated an elevated risk of cholelithiasis (2.5% versus 1.0%) among patients receiving liraglutide, a Glp-1 RA employed in the treatment of obesity.(2) There is documented evidence of a 28% increased risk for cholelithiasis with GLP-1RA treatment. However, it remains uncertain whether this risk is consistent across all agents.(2) Recently released data confirmed that therapy with GLP-1 receptor agonists is associated with a significantly increased risk of cholelithiasis (MH-OR [95% CI] 1.30 [1.01-1.68], P = .041).(3) Further research has verified that the administration of GLP-1 RAs is correlated with heightened risks of cholelithiasis (RR, 1.27; 95% CI, 1.10-1.47; I2 = 0%). A detailed breakdown of these risks for each individual agent is also provided.(4) In comparison to the control group, randomization to liraglutide and dulaglutide treatments showed an elevated risk for gallbladder or biliary diseases (RR, 1.79; 95% CI, 1.45-2.25 and RR, 1.35; 95% CI, 1.06-1.73 respectively). Randomization to subcutaneous semaglutide and exenatide also demonstrated an increased risk, although it was not statistically significant (RR, 1.28; 95% CI, 0.99-1.65 and RR, 1.23; 95% CI, 1.00-1.52 respectively). On the other hand, oral semaglutide, lixisenatide, and albiglutide did not exhibit an increased risk. Notably, higher doses of subcutaneous semaglutide (≥1.0 mg) were associated with an increased incidence of gallbladder or biliary diseases (RR, 1.58; 95% CI, 1.13-2.22).(4) Moreover, the utilization of GLP-1 RAs exhibited a substantial correlation with elevated risks of

cholelithiasis at higher dosages (RR, 1.56; 95% CI, 1.36-1.78), nonetheless, no notable association was observed at lower dosages (RR, 0.99; 95% CI, 0.74-1.33;  $P = .006$  for interaction).(4) A lengthier period of treatment with GLP-1 RAs (greater than 26 weeks) was found to have a higher probability of increasing the risk for gallbladder or biliary disease (relative risk (RR), 1.40; 95% confidence interval (CI), 1.26-1.56). However, a shorter duration of treatment (equal to or less than 26 weeks) did not exhibit the same association (RR, 0.79; 95% CI, 0.48-1.31;  $p=0.03$  for interaction).(4) Tirzepatide, a dual glucose-dependent insulinotropic peptide (GIP) and glucagon-like peptide-1 receptor agonist (GLP-1 RA), has obtained approval from the US Food and Drug Administration in May 2022.(5) In various studies, incidents of cholelithiasis were observed, but the combined proportion was found to be statistically insignificant at 0.95% (95% CI, 0.51%-1.52%) with the 5-mg dose.(5) Additionally, it should be noted that the incidence of cholelithiasis showed a further decrease with the administration of both 10- and 15-mg doses, however, no statistically significant differences were found between these two doses.(5) Reports of cholelithiasis were higher with both formulations of semaglutide (oral-subcutaneous) versus comparators, consistent with a meta-analysis that reported a significant increase in cholelithiasis with GLP-1RAs versus comparators.(6) In the context of Asian patients with type 2 diabetes, a notable correlation between GLP-1RAs and heightened risk of cholelithiasis was observed, particularly among patients over the age of 60, female patients, and those undergoing treatment for more than 120 days following initiation.(7) Liraglutide, but not dulaglutide, was associated with an elevated risk.(7) Moreover, calculating Mantel-Haenszel odds ratio (MH-OR, 95%CI), GLP-1-RA significantly increased the risk of cholelithiasis (MH-OR 1.28 [1.11, 1.48]).(8) Cholelithiasis was detected in 2.5% of patients who received liraglutide, compared to 1.0% of patients who received a placebo.(9) A possible mechanism of biliary sludge and bile stone formation could be

decreased gallbladder motility. Exenatide and albiglutide, based on acute intervention studies, demonstrated a reduction in gallbladder emptying induced by cholecystokinin. Changes in bile salts, specifically altered deoxycholic acid levels in plasma following liraglutide treatment, may lead to supersaturated bile. Nevertheless, the clinical implications of these alterations remain uncertain.(2,10)

### Conclusion

The usage of GLP-1 RAs has been approved for the treatment of type 2 diabetes since 2005. In recent years, these agents have also been included in the treatment protocol for weight loss and obesity. Due to this reason, not many studies have been done regarding to treatment of obesity with GLP-1 RAs. So, we cannot extract with assurance that the increased risk of cholelithiasis, due to these agents, is statistically significant. It is imperative to evaluate the overall beneficial risk/benefit profile of treatment for each patient, considering their individual risk factors. This approach ensures that treatment is tailored to each patient's needs and that the benefits outweigh any potential risks.

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Historical Vignette

**Evangelismos: A glimpse in the history of one of the oldest clinics in Heraklion**

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**Abstract**

Healthcare evolved gradually in Crete and was characterized by the development of numerous clinics in Heraklion before the establishment of a general hospital in the late 20th century. A notable milestone in this evolution is the General Clinic of Evangelismos, which was originally functioning as the French School of Nuns, which was founded in 1906 and operated for 35 years, before being repurposed as a German Military Hospital during World War II. After the war, physicians Konstantinos Markatatis, Evangelos Chatzakis, and Konstantinos Karyotakis acquired the building, which later became the General Clinic “Evangelismos”. It operated until 1985 and in 2002 was occupied by anarchists. The building remains a symbol of Heraklion’s evolving healthcare landscape up until this day.

*Keywords:* State of Crete (Romanized: Kritiki Politeia), Municipality of Heraklion, French School of Nuns.

**Introduction**

The history of healthcare in Crete is interesting, since it did not evolve rapidly, but gradually in the span of numerous years. During this period of time, a great number of clinics operated in Heraklion, since there wasn’t a general hospital to be of medical assistance for the people of the city until the late decades of the 20th century. Even though at the end of the Ottoman period some laws concerning public health were passed, but there was still significant work that needed to be done. The main

concern of the autonomous government was the management of epidemics and sexually transmitted infections, as well as the safety of food and beverage, while at the same time trying to transition towards a modern health system [1]. A significant milestone in the history of medical care in Heraklion is undoubtedly the operation of the General Clinic of Evangelismos, which first operated as a French School of Nuns. Evangelismos clinic existed in an era when a series of private clinics have tried to ameliorate health care in the island of Crete [Table 1] [2]. This historical vignette presents its history.

A/A	Clinic and Specialty	Leading physicians and specialty	Address in Heraklion
1	Pananeio Municipal Hospital: Pathology and Surgery Department, as well as 2 branches for syphilitic women and infectious diseases	The Hospital’s Brotherhood in the time of its inauguration included notable figures of the time, specifically: a) Rifaat Afentakis, the Ottoman Mayor of the city of Heraklion, b) Aristidis Zafeiridis, a physician, c) Ioannis Hatzidakis, a physician and Curator of antiquities, d) Aristidis Stergianidis, a lawyer, and e) Fazil Bey Hatzifazilazade, the Ottoman official of the city	
2	Saint Minas Clinic, Pathology and Surgery Department	Litinas (owner), Tzevas (coroner), John Athitakis	Milatou street
3	Saint Marina Clinic	Papageorgiou Konstantinos (pathologist)	Merambellou street

		and Manolopoulos (urologist)	
4	Saint Panteleimon Surgical Clinic	Baltzakis (surgeon) and Stelios Androulakis (pathologist)	Trifitsou Street
5	Saint John Neurology Clinic		Saint John region
6	Saint Eleftherios Maternity Clinic	Paterakis (obstetrician)	Arkadiou Square
7	Apostolos Pavlos Clinic	Vangelis Stamatakis (pathologist), Sifis Michelakis (surgeon) and Michalis Nikoloudis (cardiologist)	Karterou street
8	Saint Titus Clinic	Fakiolakis and Dagantas	Minotaur street
9	Saint Paraskevi Clinic	Kouvidis	Kourmoulidon street
10	Saint George Clinic	Procheraris and Kritsotakis (surgeons), Foundoulakis (pathologist), Marangakis (otolaryngologist) and Stavros Makrydakias (urologist)	Chatzidakis Street
11	Obstetrics-Gynecology clinic of Ieronimakias		Delimarkou street
12	Blue Cross		Taxiarchou Markopoulou street
13	Neurology clinic of Konios		
14	Obstetrics clinic of Lignos		Kantonoleon street
15	Obstetrics clinic of Makaronas-Tzani		Monis Kardiotissis street
16	Surgical clinic Megalochari	Manolis Manouras and Zouridakis (surgeons), Manousos Panagiotakis (urologist) and Tamiolakis (pathologist)	Stratigou Pezanou street
17	"Megalochari" maternity clinic of Aslanidis		Next to IKA
18	Clinic of obstetrician Baltzakis		Marogiorgi street
19	Ophthalmology Clinic	First of Papamatthaiakis, later taken over by ophthalmologist Georgios Markakis	Monis Kardiotissis street
20	Neurology clinic	Christoforos Papaioannou	Pateles region
21	Otolaryngology clinic	Yiannis Syngelakis	Sfakion street
22	Timios Stavros clinic	Pigakis and Poulinakis	Thalita and Lachana streets
23	Gynecology clinic	Fanourakis	Miliaras street
24	Otolaryngology clinic	Flourakis	Smyrnis street
25	Clinic	Chavakis	Alikarnassos region
26	Polyclinic	Stelios Yamalakis (surgeon) and Polioudakis and Souriadakis (pathologists)	Dentidakidon street
27	Clinic	Mavroforos	1821 street
28	Clinic	Kostas Voyiatzakis	Psaromiligon street
29	Ippokratio clinic	Xekardakis (pathologist) and Poulanakis, Varouchakis, and Malliarakis	
30	Evangelismos clinic	Chatzakis, Kargiotakis, Ioannis Datseris, and Kostas Markatatos	Theotokopoulou street

Table 1. Private clinics in Heraklion city in the early 20th century. Dimitris Savvas, Clinics in old Heraklion, 16/5/2023. Retrieved from: <https://maleviziotis.gr/2023/05/16/οι-κλινικές-στο-παλιό-ηράκλειο/>

**The French Schools of Nuns of Heraklion.** It was back in 1906 when the French School of Nuns was built in Heraklion, based on designs of Konstantinos Tsantirakis [Figures 1-2] [3]. This school was a model educational institution, which

operated under the direction of Mother Superior Gabrielle Rio of the Monastery of St. Joseph of the Apparition, and included a kindergarten, an elementary school and a high school [4].

ΣΤΟΙΧΕΙΑ	ΕΓΓΡΑΦΩ	ΠΑΡΑΡΤΗΤΕΣ	ΣΥΜΠΛΗΡΩΜΑΤΟΣ
ΚΠ1-111	11-10-1905	...	...
ΚΠ1-112	04-11-1905	...	...
ΚΠ1-113	10-11-1905	...	...
ΚΠ1-114	09-03-1905	...	...
ΚΠ1-115	17-12-1905	...	...
ΚΠ1-116	11-07-1906	...	...
ΚΠ1-117	06-02-1906	...	...
ΚΠ1-118	09-03-1906	...	...
ΚΠ1-119	20-02-1906	...	...
ΚΠ1-120	20-02-1906	...	...
ΚΠ1-121	05-08-1906	...	...
ΚΠ1-122	12-03-1906	...	...
ΚΠ1-123	13-08-1906	...	...
ΚΠ1-124	13-08-1906	...	...
ΚΠ1-125	01-06-1906	...	...
ΚΠ1-126	16-06-1906	...	...
ΚΠ1-127	20-06-1906	...	...
ΚΠ1-128	06-03-1906	...	...
ΚΠ1-129	12-03-1906	...	...

Figure 1. Architectural Designs 1900-1910. Evangelismos can be found at ΚΠ1-124 (red arrow). Document type: Permit Application, Date: 28/4/1906, Owner: St. Markatatos, Location: Soultan Ibrahim, Consulting Engineer: E. Basias, Inspecting Engineer: Kyriakos?, Date of Preparation: 05/05/1903, Remarks: E2, S1. The document was found at: Archive Department, Vikelaia Municipal Library of Heraklion.

Before the start of World War II in 1941, the young ladies of Heraklion received a high-level classical education, and thousands of them attended the French School of Nuns, where they were also taught foreign languages, music, home economics, handicrafts and dance.

and turn into a German Military Hospital [5]. Sisters from the same monastery established the first French school in Chania in 1985, which engaged in significant philanthropic activities, especially in the first years of its' operation, and functioned until 1983, for 131 years, as well as a French language school in Rethymno [Figure 3 & Figure 4] [6].

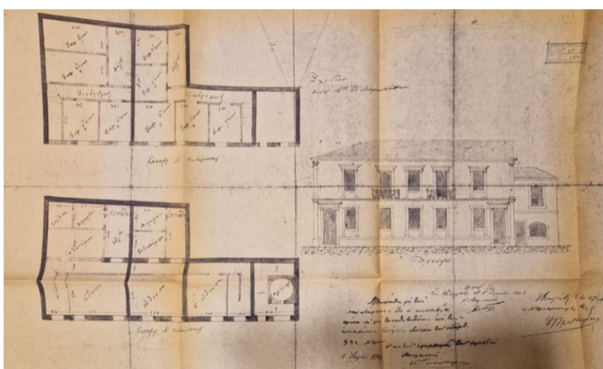


Figure 2. Constructional diagram found at: Archive Department, Vikelaia Municipal Library of Heraklion.

The building of the school, which had a rather impressive architecture for its time, would house the French Schools of Nuns for 35 years, until June of 1941, when it was forced to cease its operations

**General Clinic Evangelismos and its' neglect.** Following the liberation in 1945, the property was initially rented and then bought in 1949 by physicians Konstantinos Markatatis, Evangelos Chatzakis, and Konstantinos Karyotakis. They converted it into a medical facility named General Clinic "Evangelismos" [Figure 5], which operated until June of 1985, when physician Iordanis Datsaris announced the suspension of its operations [7].



Figure 3. Sister Placide with students of the French Convent School "Saint Joseph de l'Apparition", 1930, Archive of Konstantinos E. Mamalakis, Heraklion, Museum of History of Crete



Figure 4. Nuns and students outside the building of The French Schools of Nuns, Evangelismos building, Newspaper Patris, June the 9th, 1985.

A few years before the closure of the clinic, the one-third share of Konstantinos Markatatis was bequeathed to the planned Medical School of the University of Crete, "...From the Evangelismos Clinic, I own one-third, which I donate to the University of Crete, which is expected to be established soon, as an initial contribution for future benefactors". After the closure of the clinic, the heirs of the remaining two-thirds offered to sell their shares to the Municipality of Heraklion, but their offer was rejected at the time by the municipal authorities. It was a decade later that the University of Crete acquired the remaining shares, taking full ownership of the building, which remained for approximately 18 years unused. In May 2002 Evangelismos became occupied by anarchists and in 2015 some maintenance and restoration efforts were made, funded by the occupants and supported by sympathizers of the occupation [Figure 6] [4].



Figure 5. Private Clinic Evangelismos, Newspaper Patris, June the 9th, 1985.

### Epilogue

The changes and challenges faced by Heraklion's healthcare system can be reflected at the transformation of the building housing the French School of Nuns into the General Clinic "Evangelismos" and its subsequent period of neglect and occupation by anarchists. From a center of education, to a medical facility and finally an occupied space, Evangelismos depicts the complexities of historical preservation and adaptation, since it didn't manage to become a place that would house the advancing medical education and research. Evangelismos serves as a key point for the community of Heraklion, as well as a testament of the many hardships that Heraklion's healthcare infrastructure went through, while trying to adapt to the rapidly changing times.



Figure 6. Evangelismos Clinic nowadays, retrieved from: [https://www.kritipoliskaixoria.gr/2023/09/blog-post\\_233.html](https://www.kritipoliskaixoria.gr/2023/09/blog-post_233.html).

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