

Tutankhamun's Antimalarial Drug for Covid-19

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ABSTRACT

Drug repositioning is a strategy that identifies new uses of approved drugs to treat conditions different from their original purpose. Current efforts to treat Covid-19 are based on this strategy. The first drugs used in patients infected with SARS-CoV-2 were antimalarial drugs. It is their mechanism of action, i. e., rise in endosomal pH, which recommends them against the new coronavirus. Disregarding their side effects, the study of their antiviral activity provides valuable hints for the choice and design of drugs against SARS-CoV-2. One prominent drug candidate is thymoquinone, an antimalarial substance contained in *Nigella sativa* – most likely one of the first antimalarial drugs in human history. Since the outbreak of the pandemic, the number of articles relating thymoquinone to Covid-19 continuously increases. Here, we use it as an exemplary model drug, compare its antiviral mechanism with that of conventional antimalarial drugs and establish an irreducible parametric scheme for the identification of drugs with a potential in Covid-19. Translation into the laboratory is simple. Starting with the discovery of *Nigella sativa* seeds in the tomb of Pharaoh Tutankhamun, we establish a physicochemical model for the interaction of thymoquinone with both coronavirus and cells. Exploiting the predictive capability of the model, we provide a generalizable scheme for the systematic choice and design of drugs for Covid-19. An unexpected offshoot of our research is that Tutankhamun could not have died of malaria, a finding contrary to the mainstream theory.

Introduction

“How often have I said to you that when you have eliminated the impossible, whatever remains, however improbable, must be the truth?”

Sherlock Holmes in *The Sign of the Four*, Sir Arthur Conan Doyle.

In the pandemic of COVID-19, the exponential spread of the virus forces the science and medical community to focus on the quickest possible solution: drug repositioning. The handful of repositioned drugs that have been administered in Covid-19 presented considerable side effects. The ultimate motivation for the present study is derived from the analysis of the physicochemical properties of thymoquinone (TQ), a virtually side effect-free drug with

an extensive antiviral spectrum, complemented by antibacterial, anti-inflammatory and immunomodulatory properties, thereby recommending itself as an ideal prototype for the *de novo* design of drugs against SARS-CoV-2 [1–4]. The primary focus in current drug design strategies is the specific interaction of the drug with cell receptors. Instead, we follow a new path with focus on the interplay between drug and virus, and possibilities to control it via tunable physicochemical parameters of the drug, comprising hydrophobicity, size and redox potential (oxidation), complemented by cell-protective effects via change in endosomal pH. The model covering this dual impact justifies the use of the natural compound TQ in Covid-19. Its predictive capability sets the foundation for the systematic design of nanomedicines targeting SARS-CoV-2. Its central postulate is the concurrent extra- and intracellular protection

against SARS-CoV-2 via: I. binding of the drug to the hydrophobic domain of the viral spike, II. binding to the lipid viral envelope, III. oxidation of the virus and IV. variation in endosomal pH. None of the repositioned drugs, which are in use or have been used against the new coronavirus, presents a comparable antiviral potential. The antimalarial drugs chloroquine (CQ) and hydroxychloroquine (HCQ), as explored by Savarino et al., may serve here as a representative example [5]. Beyond the recommendation of TQ for immediate use in Covid-19, ideally in combination with nanocarriers to improve the bioavailability of the hydrophobic cargo [6], the generalizable model introduced in this article provides practical strategies that allow researchers to deviate from the usual trial and error path and systematically accelerate the development of nanomedicines ► **Fig. 1** against SARS-CoV-2 [7].

In the current pharmacological strategies to combat SARS-CoV-2, antimalarial drugs play a pivotal role [8]. In order to better understand and assess their mechanism of action, we start our investigation with a historical survey. The most prominent patient who is supposed to have died because of an infection with malaria was Pharaoh Tutankhamun. Tutankhamun died at an age of 19. The intrinsic cause of his death is still one of the major unsolved paleopathological problems. Since the discovery of his mummy in 1922 by Howard Carter, the scientific and medical community has not stopped the search for the root cause of his untimely death and to propose explanations for it. The results of the forensic examinations of the mummy and related archeological research are usually spectacular and published in the most prestigious journals. Since the discovery of the tomb, a plethora of treatises in both books and journals are dedicated to the mysterious circumstances of Tutankhamun's death. While the mainstream research supports the hypothesis that the boy pharaoh died because of an infection with

malaria [9, 10], some forensic experts express doubt on this theory and suggest instead, or as complement to it, the prevalence of various diseases, including but not limited to, sickle cell anemia and Gauche's disease [11], Köhler's disease [12], and infections following a knee fracture [13]. A chariot accident and murder are also discussed in the scientific literature.

From the cultivation of *Nigella sativa* in Egypt at the time of the 18th dynasty, the discovery of seeds of the plant in Tutankhamun's tomb and a note of Howard Carter made in preparation of the complete publication of Tutankhamun's tomb, indicating the medicinal utilization of the seeds [14], we can reduce the probability that the boy pharaoh died of an infection with malaria. Two independent motives support this expectation, a medical one and an archeological one: Several groups investigated the effect of the phytochemical TQ on the malarial parasite *Plasmodium falciparum* *in vitro* [15–18]. In all the cases, TQ showed a pronounced antimalarial activity, solitarily or combined with other compounds. One of the earliest studies on the antimalarial impact of *Nigella sativa* extracts demonstrated a suppressive effect on the parasite in rodents: "The antimalarial activities of *Nigella sativa* seed extracts observed in this study could have resulted from a single or combined action of these mechanisms. However, the active responsible principles are yet to be identified, which need further studies to elucidate the antimalarial mechanism of their action. In conclusion, the results of this study justify and confirm the usage of this plant in the Middle East folk medicine as parasitic remedy" [19]. While TQ is not explicitly mentioned in this work, subsequent research [15–18], supports the hypothesis that the antimalarial effect seen *in vivo* was due to its presence in *Nigella sativa*. The use of *Nigella sativa* is historically confirmed by the medieval physician Avicenna. Apparently, he exploited the antimalarial potential of *Nigella sativa* [20].



► **Fig. 1** Left: Black cumin, discovered in Tutankhamun's tomb, is a valued ingredient in the Egyptian cuisine. Middle: Illustration of one principle applied in nanomedicine: a drug (small spheres) is loaded into a biodegradable capsule, which is enclosed by a second capsule. The function of the outer capsule is comparable to that of a time bomb, it dissolves at a certain time point to safeguard that the cargo is not dispersed prior to reaching the target organs. The inner capsule is engineered such that it binds to the target organ cells via chemical affinity. Once it has reached the target organ it releases its cargo. Right: The drug binds to the fusion spikes of SARS-CoV-2, thereby inhibiting its attachment to cells. This scenario needs a large number of drug molecules, where spikes and molecules need to have comparable dimensions. In a best case scenario, the drug molecules break through the spike shield, enter the interspike space, bind to the lipid envelope, and oxidize the virus. The probability for this event is controlled by the polarity contrast between drug, spike and lipid envelope as well as by the surface density of the coffin nail shaped spikes. These ports of attack are different from the standard drug docking target envisaged in Covid-19, namely the membrane-associated-angiotensin-converting enzyme 2 (ACE2) receptor: the port of entry of SARS-CoV-2. [7]. Binding to the viral spike and/or lipid envelope and oxidizing the virus, instead of blocking cell receptors is equivalent with minimizing the adverse effects of a drug – a novel pharmacological approach, which could be fully exploited by the use of nanomedicines designed according to the principles summarized in ► **Fig. 2**. NB: ► **Fig. 1** is a visual transcript of the title of our article.

The second reason in favor of the hypothesis that Tutankhamun did not die of malaria is derived from the state of medicine in ancient Egypt. According to the papyri describing medical practice, as well as according to reports from Herodotus, medical knowledge in ancient Egypt had an excellent reputation. The same holds for pharmacological practice. "Egyptian medicine was regarded as high science, and the profession certainly must have attracted the best minds in the country. What military drill was to Sumer and mathematical astronomy was to Babylonia, medicine was to Egypt" [21]. Thus, the prospect that the characteristic manifestations of malaria were known to physicians of the 18th dynasty and that the anti-malarial effect of *Nigella sativa* was also known and accordingly therapeutically exploited, is realistic, in particular in view of the limited arsenal of medicinal plants available in ancient Egypt. The following summary, although not complete, provides a coherent impression for the advanced state of medicine in ancient Egypt: "For example, the Ebers papyrus, the largest (110 pages and 20 meters long) and one of the oldest preserved medical documents dating from 1552 BC, describes many diseases concerning the heart and vessels. It also contains chapters on contraception, diagnosis of pregnancy and other gynecological matters, intestinal disease and parasites, eye and skin problems, dentistry and the surgical treatment of abscesses and tumors, bone-setting and burns. Mental disorders such as depression and dementia are also covered" [22].

Following the same line of reasoning, we could also reduce the probability that Tutankhamun died of sickle-cell anemia, another candidate made responsible for his death [11]. This is indicated by the effect of an oil extracted from *Nigella sativa* seeds on venous blood samples from patients with sickle-cell anemia. Motivated by the anti-sickling effect observed *in vitro*, the authors recommended a clinical trial to investigate the anti-sickling effect of the *Nigella sativa* *in vivo* [23]. Clearly, our analysis does not exclude that Tutankhamun suffered of malaria and/or sickle cell anemia. However, his treatment with *Nigella sativa* would most likely have been instrumental to keep at least these two pathological conditions at bay. This speculative picture receives support from the presence of *Nigella sativa* seeds in his tomb. If they were not placed into the tomb for decorative purposes then the only motive could have been to protect him in the afterlife, justified by their medicinal use during his lifetime, thus in agreement with the note of Carter [14]. This preliminary probabilistic expectation is derived from results of contemporary research documenting the antiviral, antibacterial, anti-inflammatory and immunomodulatory effects of *Nigella sativa* in conjunction with historical evidence on the advanced pharmacological and medical practice in ancient Egypt. Hence, it is virtually impossible that the Egyptian doctors, who were known to record the effect of the prescriptions used, could have overlooked the therapeutic effects of the plant. With this plausibility scheme that makes both the existence and use of a natural antimalarial drug 3350 years ago credible – ignored by archeologists and allowing us to span a bridge to medicine in general, and nanomedicine in particular –, we turn our attention to the modern antimalarial drugs CQ and HCQ. The initial attempts to treat Covid-19 with CQ and HCQ were complemented by several research articles dedicated to the elucidation of the mechanism of action by which these antimalarial drugs interact with cells infected with SARS-CoV-2. One of

the simplest antiviral mechanisms emerged from a predictive model put forward in 2003 by Savarino et al. [5], who also hypothesized about the suitability of HCQ against SARS. Remarkably, the same mechanism is applicable to the interaction of TQ with SARS-CoV-2. The big picture portrayed here puts us not only into the position to approximate the root cause of Tutankhamun's death but, most importantly, to also motivate the use of TQ as a viable drug against Covid-19.

Materials and Methods

Nigella Sativa

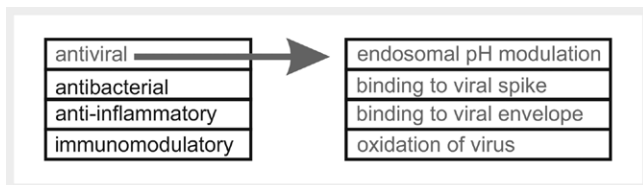
Nigella sativa (black seed) also known as black cumin, is an annual flowering plant in the family Ranunculaceae native to China, the Indian Subcontinent, West Asia, Eastern Mediterranean and Northern Africa. It is a widely used medicinal plant in various traditional medicines, in particular in the aforementioned regions, but it is almost entirely unknown to Western medicine. The Persian physician Avicenna, regarded as the father of early modern medicine, described *Nigella sativa* in his *Canon of Medicine* as a treatment for dyspnea [24], a condition frequently accompanying asthma and pneumonia. The prevalence of dyspnea in infections with SARS-CoV-2 is already a strong indication for the use of *Nigella sativa* in Covid-19.

Parts of the mechanism of action which recommends TQ for the treatment of infections with SARS-CoV-2 have been derived from the methodical analysis of its therapeutic action spectrum and antiviral potential. The first comprises the antiviral, antibacterial, anti-inflammatory and immunomodulatory effects of TQ, the second comprises the physicochemical effects by which it protects cells from being infected by SARS-CoV-2 both in the extra- and intracellular space [4].

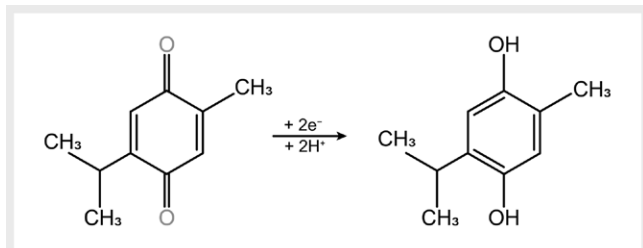
Results and Discussion

Thymoquinone: Shield and sword against SARS-CoV-2

The most studied active constituent of *Nigella sativa* is TQ. Its clinical importance is dictated by its antiviral, antibacterial, anti-inflammatory and immunomodulatory effects, documented in our earlier article [4]; a relevant overview is provided in ref. [25]. For the prevention of an infection with SARS-CoV-2 the antiviral effect of TQ is sufficient. However, treatment of Covid-19 demands the successive action of all four individual effects. Alternative formulas, including natural extracts such as artemisinin [26] and cannabidiol [27], or synthetic drugs initially developed for the treatment of infections with malaria, Ebola virus and HIV, do not present a comparable therapeutic spectrum. Concerning the antiviral potential of TQ, our physicochemical model revealed the simultaneous action of four different modes of defense: I. binding of TQ (hydrophobic) to the viral envelope, II. oxidation of the virus and III. cellular protection via modulation of endosomal pH [4]. Mode IV, so far not addressed in the literature, is mediated by the binding of TQ to the hydrophobic domain of the spikes of the coronavirus (► **Fig. 1**), [28]. The modes I to IV are effective both prior to the invasion of the cell



► **Fig. 2** Self-explanatory visual synopsis of the fourfold action spectrum of TQ (left) and its fourfold antiviral potency (right). The model presented in this article is based on an irreducible set of parameters, including pH, nonspecific binding (hydrophobicity), size and redox potential.



► **Fig. 3** Structural formula of thymoquinone. Left: the molecule in its quinone form. Right: the molecule in the corresponding hydroquinone form [4].

by the virus and *a posteriori*. As we will show later, understanding the probabilities of the events I to IV is the precondition for the systematic selection of drugs that are suitable for a combinatorial therapy using TQ – or the choice of new drugs – in Covid-19.

If we further consider that the interaction of a drug with a quasi-life form such as SARS-CoV-2, as opposed to a living cell, can be described in terms of physical and physicochemical parameters only, then it becomes clear that for the neutralization and/or destruction of the virus, observation of the minimalistic set of parameters (► **Fig. 2**) is sufficient. In physics, the predictive capability of minimalistic models is usually enormous. If indeed superficial contacts between drug and virus are sufficient to neutralize the latter then it is safe to assume that nanomedicines allowing to precisely implement the abovelisted set of physical and physicochemical parameters will be superior to conventional drugs whose function is restricted to the protection of the cells. This expectation is in agreement with the fact that the drug-virus system under consideration is more of physical than of biological nature. These assumptions are fairly plausible and have a great simplifying effect on the subject, and until there is more definite evidence of their inadequacy it does not seem worthwhile to try more complicated schemes.

Use follows mechanism – mechanism dictates use

The transport of endocytosed viruses has been instructively depicted by Savarino et al. [5]. In a recent study focusing on Covid-19, Liu et al. [29] adapted the model of Savarino et al. to SARS-Cov-2: “Since acidification is crucial for endosome maturation and function, we surmise that endosome maturation might be blocked at intermediate stages of endocytosis, resulting in failure of further transport of virions to the ultimate releasing site”.

Acidification is equivalent with a decrease in pH. Furthermore, closer examination of the chemical interplay of TQ with the virus showed that by its reduction to the corresponding hydroquinone form, TQ is acting as an oxidizing agent [25, 30], functionally similar to reactive oxygen species (ROS) with the capability to kill the new coronavirus. The process is illustrated in ► **Fig. 3**.

Based on our hypothesis [4], it is reasonable to assume the following scheme: In a first step TQ oxidizes some material inside the endosome, analog to the characteristic action of ROS. In this process protons are removed from the proximal environment of TQ, actually leading in a second step to an increase in pH. Besides this indirect mechanism of action, there exists a second modality by which TQ could neutralize a virus: The ROS-like character of the TQ molecule could be a direct route to oxidize a virus via surface contact, where the contact is facilitated by the hydrophobic character of the compound [30]. It is likely that both mechanisms occur in nature.

The Sign of the Four

The natural compound TQ recommends itself for both the prevention and treatment of Covid-19. Two reasons justify this expectation: The fourfold action spectrum (antiviral, antibacterial, anti-inflammatory and immunomodulatory effect), on the one hand, and the envisaged synergy of the fourfold antiviral potency of TQ, on the other hand (► **Fig. 2**). Its antiviral effect is expected to be so powerful that one would be surprised if its antiviral effect is not superior to that of CQ and HCQ, whose capacity is virtually restricted to the modulation of pH in endosomes, and according to the FDA Safety Announcement [04–24–2020] have not been shown to be safe and effective for treating or preventing COVID-19. It is worth noting that CQ and HCQ are cationic amphiphilic drugs [31, 32]. This implies that during their transit through the body the antimalarial drugs could be immobilized on surfaces in the predominantly hydrophilic environment, prior to reaching the target organs. The few antimalarial molecules which eventually reached their destination could enter into the cells invaded by the virus, in agreement with their amphiphilic character. In contrast, the hydrophobic nature of TQ prevents it from immobilization during its journey to the target organs. However, as a hydrophobic molecule, it can and will be probably partly removed from the blood stream, oxidized in the liver and eventually excreted. Its hydrophobic nature and smaller size relative to CQ and HCQ, safeguards that TQ could more easily cross the plasma membrane of cells. *En route* to infected cells TQ has the capability to inactivate SARS-CoV-2 prior to invading the cells, simply by binding to the lipophilic envelope of the virus and to kill it by oxidation and/or to bind to the hydrophobic domain of its spikes, thereby inhibiting its attachment to cells, in harmony with the nonpolar nature of the compound. For the hydrophobic TQ, drug delivery systems targeting the lungs could be prepared in a one stage process. Immobilization of the polar CQ in hydrophobic nanoparticles is less trivial. The double fourfold potential of TQ can only be fully exploited by the use of nanomedicines (► **Fig. 1**). In summary, the principal result of our study is a predictive model optimized towards a minimum number of parameters. Their consideration will enable the design of nanomedicines based on TQ as well as of delivery systems using powerful combinations of drugs, thus exploiting the potential offered by nature

and avoid anti-synergistic effects. To illustrate one combinational approach it suffices to remember that according to our model, TQ protects the cell from viral infections by endosomal inactivation, analog to the rise in pH described in the pioneer work of Savarino et al. [5] and Liu et al. [29]. Obviously, a drug mixed with TQ whose effect is a decrease in pH would be contraproductive when it comes to the design of nanomedicines using a combination of drugs.

Time is running

Sometime after the outbreak of Covid-19 it became evident that the long-term complications of infections with the new coronavirus are much more serious than the initial expectation focusing on the mortality rate only. In view of the complications observed in patients who survived an infection, it is becoming increasingly clear that the ideal drug against Covid-19 has to simultaneously satisfy three requirements: I. to eradicate the virus circulating in the body as fast as possible, II. to protect the cells from the virus, and III. to do no harm to the body. Under these circumstances, TQ appears as a model drug, which can be used in Covid-19, or whose special properties can inspire the design of powerful new drug solution, specifically solutions based on nanomedicine. A recent brain study suggested that the common herpes virus HSV-1 can trigger Alzheimer's [33]. Recently, Ezzat et al. identified the viral protein corona as a critical factor for viral–host interactions and showed that respiratory syncytial virus (RSV) and HSV-1 accumulate a protein corona in biological fluids, and that HSV-1 triggers amyloid- β aggregation [34]. Until now the literature is discussing cases where patients with Alzheimer's disease got infected with SARS-CoV-2. There is already an alarming overlap of symptoms between Alzheimer's and Covid-19, including but not limited to, disorientation, fatigue and loss of smell. Considering the possibility that SARS-CoV-2 could trigger Alzheimer's as well, it would be prudent to start *in vitro* experiments, similar to the protocols performed in refs. [33] and [34].

Conclusion

We have started this study with an exploration of the implication of the discovery of *Nigella sativa* in Tutankhamun's tomb. There are two reasons for this approach, the first has a medical and the second an archeological background. At the beginning of the outbreak of Covid-19 in Europe, one of the authors contracted a severe infection presenting all the lead symptoms of Covid-19. The treatment included the ingestion of an oil extracted from *Nigella sativa* [4]. The motive for the use was a literature search documenting the antiviral, antibacterial, anti-inflammatory and immunomodulatory effects of TQ. The search was preceded by the study of archeological reports about the discovery of *Nigella sativa* seeds in the burial chamber of Tutankhamun and the note of Carter on its medicinal use, which sparked the interest in the plant. Surprisingly, the note of Carter remained practically unnoticed by the medical, pharmaceutical and archeological community. Thus, consideration of archeological findings can not only fertilize modern medical and pharmacological knowledge but also provide an inspirational ground in innovative drug design: Comparison of the action spectra of TQ and HCQ with emphasis on the currently discussed antiviral mechanism of HCQ led us to develop a predictive model

allowing for the design of nanomedicines targeting SARS-CoV-2. The model has the power to reverse the popular curse of Tutankhamun into a blessing. However, its predictive capability is by no means restricted to natural compounds; its validity is universal and can be directly implemented into combinatorial drug design in order to systematically accelerate the development of nanomedicines which can *specifically* target SARS-CoV-2. The current clinical attempts to treat Covid-19 focus primarily on a limited arsenal of existing drugs initially designed against infections with malaria, Ebola virus, HIV, etc. With exception of HCQ, whose suitability against SARS was predicted by Savarino et al. [5], drug recommendations for Covid-19 evolve at the moment from trial and error processes on a clinical level with many undesired surprises. The desperate race against time is further complicated by the emergences of new mutants of SARS-CoV-2 [35] – one more reason for favoring predictive modelling in pharmacology and medicine. The advantage of our approach consists in its capability to rapidly select potentially effective drugs from a large pool of compounds. Notably, the prediction of our model was recently confirmed by *in silico* calculations [36, 37]. Considering the safety profile of TQ and other phytochemicals [38] the fastest way for identifying effective drugs against SARS-CoV-2 consists in reducing the pool of potential candidates to phytochemicals. This trend was recently endorsed by the WHO: On September 19, 2020 the Regional Expert Committee on Traditional Medicine for COVID-19 formed by the WHO, has highlighted the need for accelerated research and development programmes, including on traditional medicines [39].

Conflict of Interest

The authors declare that they have no conflict of interest.

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