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Maestro, Marguerite, morphine: The last years in the life of Mikhail Bulgakov

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ABSTRACT

The manuscript pages of the final draft of *Master i Margarita*, the masterpiece by Mikhail Bulgakov, written in the last four years of his life (1936–1940), have been treated with a mixture of chromatographic beads, namely a strong cation exchanger and a C_8 resin. Potential substances captured by the beads, after harvesting them, were eluted with a mixture of isopropyl alcohol, dichloromethane and ammonium hydroxide and the eluate subjected to GC–MS analysis in order to detect the presence, if any, of drugs, due to the fact that the writer suffered intense pains caused by an inherited nephrotic syndrome. Indeed all the pages under investigation (a total of ten, taken at random among 127 foils) contained traces of morphine, from as little as 5 up to 100 ng/cm^2. In addition to the intact drug, we could detect one of its metabolites, namely 6-O-acetyl morphine. The significance of these findings in terms of a possible improvement of the novel and in terms of drug use (or abuse) in the modern world is discussed and evaluated.

Biological significance: The extraction of metabolites/proteins from the surface of the original manuscript pages of Bulgakov masterpiece *Master i Margarita* has permitted to monitor his health state and intake of medicaments over the last four years of his life. We have ascertained that: (1) he was assuming large doses of morphine as pain killers; (2) he was affected by a nephrotic syndrome, since we could identify three proteins known as biomarkers of this pathology. The double extraction procedure here reported could open up a novel field of investigation of (relatively) ancient manuscripts for metabolome/proteome analysis on the health status of the writer/artist.

1. Introduction

Master i Margarita is the most famous novel by Mikhail Bulgakov [1] and is listed among the top 100 books of the twentieth century. The novel alternates between two settings, the first one in 1930s Moscow and the second in the Jerusalem of Pontius Pilate. The Moscow stage is suddenly invaded by the magician Woland (Satan) with a retinue of devilish figures, Behemoth (a demonic black cat), Koroview (Fagotto, i.e. bassoon, perhaps a former member of an angelic choir), Azazello (a messenger/assassin, perhaps a fallen angel), Hella, a redheaded succubus (a vampiress) and Abadonna (an angel of death) who wreak havoc in the streets and palaces of the capital, targeting particularly the literary elite and its trade union MASSOLIT. Bulgakov started its writing in 1928 but burned the manuscript in 1930. He then began working on a second draft that was completed in 1936. Those were the darkest years of Stalin repression, with millions of Russians send to slave labor in working camps and in the Gulag archipelago [2]. The brutal and violent nature of the Kremlin Highlander had been understood by Lenin who, just prior to dying, tried to alert the Communist Party Committee not to elect him as the new leader, a move that Stalin emptied by totally isolating him in his death bed [3]. Upon consolidating his power, Stalin started a brutal repression by eliminating his opponents and spying on the entire population of the Soviet Union via the infamous secret police Cheka (NKVD). He had also started an agrarian reform that lead to famine all over the country and especially in Ukraine (the granary of Russia), where he almost entirely eliminated the land workers, labeled as kulaks, i.e. rich farmers believed to hide their products, thus starving the country. In 1928 the kulaks were 5,600,000 but their number in 1936 was reduced to a mere 149,000, more than five million farm workers having disappeared into nothingness. Famine was widespread and episodes of cannibalisms were reported. Yet these news did not filter through the tight control on all information media and Stalin managed to offer an idyllic vision of Soviet Union the world over (so much so that Walter Duranty, the New York Times correspondent in Moscow, winner of the Pulitzer Prize in 1932, wrote of a big Ukraine harvest and that talks of famine were ridiculous; workers paradise, was the motto). It was instead a reign of terror, and the atmosphere in the capital and all over the country was gloomy. It was against this dark setting that the novel took shape and Bulgakov expanded his narrative. If Moscow had become the reign of atheism and

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an evil city, it might just as well be colonized by Satan and his retinue. Yet there were deeper reasons for his attack to the Soviet society. Bulgakov was a brilliant mind and a writer of several theater pieces; envious critics though kept giving him bad reviews and forced government censors to prevent publication of any of his work and staging any of his plays. Thus, no small part of his novel is an outcry against a suffocating bureaucracy, a corrupt power and a humiliating censorship. The headquarter of this scum was Griboyedov's House, the residence of social climbers and their mistresses, bureaucrats, artists and writers who had sold their soul and wits to Stalin's power and were thus rewarded for their adulation to the regime with a care-free life in a luxury environment. Thus it is no wonder that one of the most exhilarating chapters is the destruction of the DramLit (House of dramatist and literates, a luxury, height-floor palace newly built for the MASSOLIT associates), operated by the Maestro's lover, Margarita who, transformed into a sorceress by Azazello, flies over it riding a broom and wreaks havoc in all apartments, starting from the one of the critic Latunskji, whom she believes had assassinated the Maestro, and destroying them systematically one by one, crashing the windows and flooding the floors (see chapter 21, The Flight). A literary revenge against the servants of the tyrant.

Although in 1936 the major plot lines of this version were in place, Bulgakov kept reshaping and elaborating the text anew in four following versions during the years 1936–1940 and he only stopped writing four weeks before his death in 1940. It is known that, in the last few years of his life, the author was suffering from a severe form of nephrosis (an inherited kidney disorder) that eventually took him to his grave. We were wondering if during these years he had been assuming drugs, at least as pain relievers. As we were allowed access, by Bulgakov's estate, to his final manuscript, we have explored the surface of several original pages in search of possible traces of drugs. The results of this investigation are given below.

2. Materials and methods

2.1. Chemicals and reagents

C_8 sorbent, strong cation (SCX) exchanger, morphine standard, isopropyl alcohol, dichloromethane, and all other chemicals were from Sigma-Aldrich, St. Louis. MO, USA.

2.2. Sample sources and permissions

The various manuscript pages analyzed (a total of 10, taken at random among the 127 sheets as written by Bulgakov) were obtained from the "Pashkov Home" at the Government's Russian Library (Moscow) and from private collections before sales at the "Nikitsky Auction" that took place on 27 March 2014.

2.3. Solid-state extraction of drugs

For solid-state extraction of morphine and its derivatives (if any) from the original manuscript pages wet ground C_8 beads and strong cation exchanger (both 10 μm size; in a 1:1 mixture) were laid on the page surfaces and the contact allowed for 1 h (see Fig. 1A for the lay-out). The reason for this special arrangement is that the ground C_8 beads would fill up the interstices among the large SCX beads, thus ensuring a double mechanism of capture: via ionic interaction (SCX resin) and via hydrophobic interactions as well (C_8 granules). After harvesting, a mixture of isopropyl alcohol, dichloromethane and ammonium hydroxide (20:10:1 v/v) was adopted for eluting any captured material from the beads. The solvents were then evaporated to dry conditions (50 °C) before chromatographic examination. The extract, after purification, was added with 10 μL BSTFA (N,O-Bis(trimethylsilyl)trifluoroacetamide) agent (70 °C) for a 10 min treatment. The solution was finally concentrated under a stream of nitrogen, after which 5 μL aliquots were injected into a gas chromatographer coupled with a mass spectrometer (GC–MS).

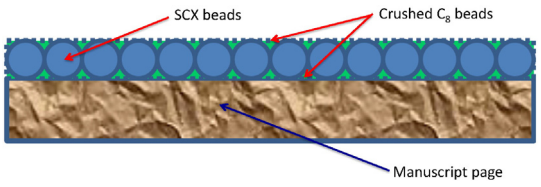

Fig. 1. Set-up for harvesting potential drugs from the manuscript pages of Bulgakov's novel. Intact SCX beads and C_8 fragments are seen aligned along the surface.

2.4. Gas–liquid chromatography mass spectrometry (GC–MS)

GC–MS was run in a HP 6890 series GC, Split-less injector; 6890 series MS selective detector (EI mode 70 eV HP) [4]. Column length 40 m; 5% phenyl methyl siloxane capillary column HP-5MS (id 0.25 mm). Morphine-d_3 was used as internal standard. GC–MS was run with a linear temperature program from 30 °C to 68 °C. A fused-silica capillary column and He as the carrier and makeup gas were used. The period of peak separation was ~20 min. The morphine amount levels from each manuscript page were of the order of 2–7 ng/cm^2; in some page areas these levels were as high as 100 ng/cm^2 morphine.

3. Results

Fig. 1A shows the method adopted for extraction of possible traces of morphine or other drugs from the surface of 10 different pages, taken at random from a total of 127 sheets hand-written by Bulgakov in the last four years of his life. Fig. 2 shows the GC elution profiles of the material eluted from the beads, as graphically illustrated in Fig. 1A. Peak M (morphine) has been identified by mass spectrometry (see below) and also because it co-eluted with a standard of morphine, whose retention profile is shown in the upper-right insert. Fig. 3A gives the MS spectrum of a pure morphine standard whose formula is reproduced in the insert. Fig. 3B gives the corresponding MS spectrum of the LC peak eluted at 7.6 min, also identified as morphine. In both cases, the peak annotated with m/z = 286 represents the mass of the intact molecule. There is more to it, though: as shown in the retention profile of Fig. 2, among the additional peaks eluting at 10 to 13 min, one has been identified as 6-O-acetyl morphine (6-O-AcM), whose spectrum and formula are shown in Fig. 4. In this last case, the peak at m/z = 327 represents the mass of the intact molecule, whereas the other peaks annotated with lower m/z values represent the fragmentation pattern (MS/MS spectrum).

In general, the morphine levels in the various pages ranged from as little as 2 up to 100 ng/cm^2. The possible sources of the morphine presence on the various pages could be: (a) saliva and fingerprints (due to oral drug delivery) and (b) fingerprints alone (sweat components). It should be understood that the samples might have been cross-contaminated because of non-ideal storage conditions. It is quite surprising that morphine should still be present undegraded after such a long period of 75 years. One of the main reasons could be due to the fact that there were no bleaching agents in the paper.

Fig. 5 gives two separate fragments of the initial page of "Patriarch Ponds" (p. 3) and of the dialog between Jesus and Pilatus (early variant of the novel's part "Pontius Pilate", which was not included into the final published version of the novel, p. 35). This is an example of two pages containing low traces of morphine (about 5 ng/cm^2).

Fig. 6 is an example of Bulgakov's novel plan page. One can appreciate the extensive revisions in part of the text. The upper third line is a planning of the events that would occur in the narration during the days from Wednesday till Saturday. In between the two last days the Witches Sabbath would take place. The two blue and red moon-like crescents represent the finish and start of events that would occur

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