Comparative Analysis of Medieval and Modern Scientific Research on Ageing Reveals Many Conceptual Similarities

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Abstract
Ageing is the main risk factors for many degenerative diseases and the search for anti-ageing cures has been a quest for humanity since ancient times. It is well-known that medieval elites were deeply interested in understanding the mechanisms of ageing and in developing anti-ageing interventions to extend healthy lifespan. However, it is little appreciated that many parallels exist between medieval science and current biomedical research on ageing; remarkably, similar aspects of human ageing were deemed interesting and worthy of investigation by both medieval and modern researchers. In this article, I examine the experiences of medieval Europe that have contributed to the formation and historical persistence of long-lasting attitudes about the ageing process. In particular, I highlight similarities between hypotheses formulated by medieval scholars and current research themes and interventions that have been experimentally proven to combat ageing. Specifically, I report how prominent medieval scholars such as Roger Bacon understood that ageing is a process influenced by both intrinsic (hereditary) and extrinsic (environmental) factors, and that hormesis, exercise, blood-derived factors, and dietary restriction can delay ageing. Thus, the experimental evidence recently gathered on the molecular mechanisms of ageing provides answers for long-lasting questions that were already formulated by medieval scholars.

Keywords: Medieval science; Anti-ageing research; Theriaca; Hormesis; Dietary restriction; Exercise; Parabiosis; Roger bacon

Introduction
The late-medieval Wolseley map (1448) depicts an island in the Atlantic Ocean where supposedly no ageing and death were experienced. Myths of mortality and extreme longevity, such as the "fountain of youth" (Figure 1), were common throughout ancient and medieval times and were usually associated with distant geographic locations, far to reach for most European inhabitants. These legends are a clear demonstration of the medieval credence that lifespan could be extended and that age-related diseases could be avoided. These beliefs sparked investigations on the mechanisms of ageing and the search for interventions that could prevent frailty or even restore a youthful state [1-13]. Several medieval treatises of the 13th and 14th century demonstrate the profound interest in understanding and combating ageing, with the ultimate goal of the prolongatio vitae, i.e. extending lifespan. These include the De retardation accidentium senectutis (The slowing of accidents of old age), written by the lord of the castle of Goet [1]; De conservation ejventut is et retardation sesenectut is (Preservation of youth and old age retardation) by Arnoldus de Villanova [14]; Deregiminesenum (The state of the elderly) by Al-Razi [3]; Essays on health by Maimonides [15]; Parvanaturalia (Short treatises on nature) and Deaetate (On age) by Albertus Magnus [16]; Gerontocemia scilicet desenurncuraataquevictum (Gerontocemia namely the care and diet for the elderly) by Gabriele Zerbi [17,18]; The cure of age and preservation of youth by Roger Bacon [19]; and De vita longa (On long life) by Marsilio Ficino [20]. These and other medieval treatises [21,22] in turn provided the basis for prominent renaissance works by Luigi Cornaro (1475-1566) and others [5,23]. Although medieval medical treatises on ageing were not experimentally grounded, there are several conceptual similarities between hypotheses that were formulated by medieval scholars to explain the causes of ageing and our current understanding of this process. It is now known that both genetic pathways and environmental interventions influence ageing in humans and other organisms [24]. These recent findings are well in line with the hypothesis posited by the franciscan friar Roger Bacon (1214-1294), who proposed that ageing is influenced by inherent hereditary factors.

Figure 1: The search for interventions to extend lifespan in the Middle Ages. (A) The fountain of youth as painted by the Master of the Castel of Manta, near Saluzzo, Italy (1411-1416), represents the deep interest of medieval men in understanding the causes of ageing. The legend of the fountain of youth was a popular one in the Middle Ages and inspired many widespread tales and works of arts. (B) The golden head, symbol of the Alla testa d’oro pharmacy in Venice, renowned in all Europe for the production of theriaca, the first medical preparation thought to act as a hormetic drug. (C) Theriaca box seal (17th century), with the emblems of Venice and Alla testa d’oro pharmacy. Theriaca was produced in several Italian cities since the Middle Ages till last century and sold throughout Europe.

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properties and extrinsic (environmental) factors [1]. Many medieval scholars, including Roger Bacon, postulated that delaying ageing can prevent the onset and/or limit the progression of age-associated diseases and that in turn the occurrence of diseases can accelerate or worsen ageing. For example, it was a common medieval belief that infections contribute to ageing; hence many physicians highlighted the importance of hygiene to decrease the risk of infections and to delay ageing. The strong connection between ageing and disease lead Zerbi to compile a list of the clinical aspects of 300 diseases commonly seen in old age [17] and to postulate that these diseases start to develop between 30 and 60 years of age and manifest themselves after 60 years of age. This clinical definition is well in line with the current understanding of the development of many age-related diseases such as frailty and sarcopenia (the progressive age-related loss of muscle mass and strength), which starts at around 30 years of age and leads to phenotypic defects that are typically prominent after 60 years of age [25]. In addition to Zerbi, other medieval scholars sub divided ageing into distinct progressive phases, with the lifespan being divided typically into 3, 4, 6 or 7 distinct periods each associated with progressive physical decay, as also represented in many medieval art works (Figure 2) [26,27]. The association between ageing and pathologies also sparked the first anatomical investigations of ageing via the dissection of the bodies of old people and centenarians by Leonardo da Vinci and others [28-30]. In addition to a link with disease, medieval scholars also noticed a connection between ageing and physiological processes. For example, Marsilio Ficino postulated a causal connection between reproduction and ageing [31], and recent scientific researches have indeed highlighted that exceptional longevity can be associated with decreased reproduction [32]. In addition to examining the ageing process in humans, medieval scholars have tried to understand the basic mechanisms governing ageing through the analysis of long-lived organisms. In the Parvanaturalia, Albertus Magnus discussed the observation that life span greatly varies among different animal species such as shellfish, crocodiles, and whales [16,22]. In the De regimen synonym, the medieval mesopotamia doctor Al-Razi hypothesized that anti-ageing ‘substances’ are born underground and can be found in the viscera of long-lived animals [33]. The intuition that the extreme longevity of long-lived animal species may provide clues on the general mechanisms of ageing is underlying many current studies on the diversity of lifespan across species. These studies are helping identifying the genetic pathways and molecules (‘substances’) regulating ageing. For example, current researches have provided evidence that sea clams are among the longest-lived animals [34], and that tissue homogenates from these animals are extremely resistant to various types of proteostatic stress [35]. Although the molecular mechanisms responsible for this protection have not been defined, it will be interesting to see whether they are unique to these species or rather extremely efficient or enhanced versions of protein homeostatic systems found also in shorter-lived organisms. Furthermore, many plants and trees are known to have extremely long lifespans and are among the longest-living organisms [36]. Perhaps this explains why medieval physicians proposed fruit and botanical extracts as staples for anti-ageing treatments [37], a hypothesis that has been confirmed by the isolation of many anti-ageing compounds, such as resveratrol, from plants [38].

In addition to understanding the causes of ageing, medieval scholars proposed several interventions to reduce functional senescence and extend life span. A prominent medieval and ancient medical practice was based on the idea that exposure to low levels of poisons or stressors mounts an adaptive stress response that protects from subsequent exposures to harmful levels of poisons, and protects from ageing and diseases, a concept now known as "hormesis". For example, low levels of poisonous arsenic salts were used to treat many diseases, such as cancer and malaria [39]. However, the most notable example of medieval "hormetic" anti-ageing intervention is the theriaca (also known as theriac or "treacle") whose name derive from the Greek therion, a word that indicates all poisonous animals. In medieval times, this was a complex mixture of many animal and vegetal ingredients. This expensive medicine was believed to be a cure for all diseases and ageing and an antidote against poisons [40]. The original recipe of theriaca dates back to 120 BC and MithridatesVI king of Pontus, who self-administered non-lethal doses of many poisons throughout his life with the goal of developing resistance to any future attempts to assassinate him with poisons. Subsequently, Andromacus the Old, physician to the roman emperor Nero, re-elaborated the recipe by including the use of viper's meat. As such, the theriaca magna (also known as Andromacus' theriaca) was considered a panacea by the roman doctor Claudius Galen, and was produced during public ceremonies in many Italian cities throughout the Middle Ages and sold throughout Europe (Figure 1). Although Avicenna and others believed that the medical properties of theriaca arise from the combination of its ingredients, the viper's meat used for its preparation was by itself considered an elixir of long life by Roger Bacon [1,19]. Snake meat and skin were indeed used as medical preparations as such [40], in line with Hildegard von Bingen's idea that "something bad often dispels a bad thing".

Current biomedical research is now defining the genetic and molecular pathways responsible for sensing different types of environmental and cellular stressors and for mounting adaptive

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**Figure 2:** The representation of lifespan in the medieval period. The three ages of life, represented by the three kings in Gentile da Fabriano’s Adoration of the magi (1423; Uffizi Gallery, Florence). From left to right: Melchior, Balthazar, and Gaspar respectively represent old age, middle age, and youth. The subdivision of lifespan into three ages echoes the current clinical understanding on the progression of many age-related diseases such as frailty and sarcopenia.
normal GDF11 levels in the blood delays the ageing of many tissues and toxins, oxidative stress, mitochondrial dysfunction, and others [39,41-43]. For example, heat shock early in the life span induces the cytoplasmic unfolded protein response (UPR), which protects from subsequent challenges to protein folding later in life [41]. In addition to hormesis, several medieval physicians interested in anti-ageing interventions pointed to the importance of dietary restriction. Maimonides, Arnoldus de Villanova, Roger Bacon and other medieval scholars emphasize that dietary modulation is key to combat ageing [5], recalling the quotation Est modus in rebus (there is a mean in all things) of the ancient Roman poet Horace, who valued moderation (mediocritas) in all things. Importantly, the concept of moderation and dietary restriction elaborated in ancient and medieval times will be echoed in Luigi Cornaro’s Trattato de la vita sobria [23], which has inspired modern studies on dietary restriction. Recent investigations have indeed provided experimental evidence for a role of dietary restriction in delaying ageing and extending healthy lifespan in many organisms, including the nematode Caenorhabditis elegans, the fruit fly Drosophila melanogaster, and higher organisms, such as mice, monkeys and even humans [44-46]. These studies therefore have proven valid a long-standing hypothesis that traces back to the work of medieval scholars. In addition to anti-ageing remedies based on diet and hormesis, medieval scholars also thought of exercise as a means to delay ageing. Roger Bacon suggested in his seminal work on ageing. The cure of age and preservation of youth that exercise could be an effective intervention to delay ageing and age-related diseases [1,19]. Arnoldus de Villanova proposed that idleness should be avoided and indicated several exercise regimens suited for old age, including frequent walking, rhythmic bending and climbing towards higher places [37]. Other historical sources, including medieval Persian manuscripts, also highlight the importance of exercise in preventing ageing [47]. In line with this hypothesis, there is growing evidence that skeletal muscle contractile functions and exercise can preserve metabolic homeostasis, delay the progression of many age-related diseases, and perhaps even extend lifespan [25,48,49]. The mechanisms involved are presumably based on increased nutrient utilization by muscle (which should mimic a condition of limited nutrient availability, i.e. dietary Restriction, for other tissues) and secretion of muscle-derived signalling factors (myokines) into the blood, from where they can act systemically to regulate age-related processes in other tissues [50,51]. Another medical intervention that was proposed to delay ageing was based on the rejuvenating action of blood-derived factors. The medieval scholar Marsilio Ficino (1433-1499) thought of his De vita longa [17] that blood is the manifestation of the spiritus vitalis, i.e. a fountain of life that regulates ageing and life span [20]. On this basis, he postulated that transfusion or transmission of blood can prolong lifespan, and that bloodletting should be limited or avoided. He also advocated the drinking of blood from young donors as a therapy to cure or delay ageing in old people, believing that the blood can enter the circulation from the stomach (the place where the blood was believed to be formed anew from the digested food [52] due to its affinity to the patient’s blood [31]. Therefore, Marsilio Ficino considered the blood a vivifying substance that can be transferred from a donator to a patient and be used as anti-ageing therapy. Ficino’s proposal recalls current research that has established important roles for circulating endocrine factors in the inter tissue regulation of systemic ageing and lifespan in many organisms [53,54]. For example, blood levels of GDF11 (growth differentiation factor 11) decline during ageing in mice and restoring normal GDF11 levels in the blood delays the ageing of many tissues such as the brain, heart, and skeletal muscle [55-58]. Many ageing studies on the role of blood-derived signalling factors have employed a technique called parabiosis, whereby the blood circulation of one mouse is connected with the blood circulation of another mouse of the same or different age. By using this technique, scientists have observed rejuvenation of old mice when connected to the circulation of young mice, an effect that was absent when the circulation of an old mouse was connected to the circulation of another old mouse.

Current researches are defining the circulating signalling factors responsible for these effects, with GDF11 being one of the most important ones identified to date. In this article, I have highlighted key examples of remarkable conceptual continuity anti-ageing research from medieval times to nowadays. Importantly, similar aspects of human ageing were deemed interesting and worthy of investigation by medieval scholars and modern researchers. Moreover, hormesis, dietary restriction, and the role of exercise and blood-derived factors were the theoretical principles underlying many medieval anti-ageing interventions. For the first time in history, it is now possible to use simple model organisms, genetics, and molecular cell biology to unravel key mechanisms and pathways regulating ageing. The experimental evidence recently gathered indeed provides evidence for the validity of anti-ageing regimens based on hormesis, dietary restriction, exercise, and blood-derived factors. The remarkable parallels between medieval science and current anti-ageing research suggest a previously unanticipated persistence of ideas about the causes of ageing and potential therapies. On this basis, it is possible to hypothesize and theories on ageing that are deeply rooted in history have contributed to the formation of contemporary attitudes about the ageing process which in turn have influenced the trajectory of biomedical research in this field.

References


