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1 *History as a Source of Innovation in Antimicrobial Drug Discovery*

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3

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35

36 **Abstract**

37 The proliferation and prevalence of antibiotic-resistant bacteria despite modern medicine is
38 considered as one of the most alarming threats to global health. In the fear that the antibiotics
39 that work today may not work tomorrow, there is an urgent need to search and develop newer
40 drugs or therapeutic strategies to fight against micro-organisms immune to our current
41 approaches. From time immemorial, people have sought solutions to combat infections and
42 have proposed countless remedies, traces of which can be found in manuscripts preserved over
43 the past centuries. The re-examination and exploitation of these ancient remedies might be a
44 key to a vast pool of potential therapeutic strategies or drug candidates against antibiotic-
45 resistant pathogens. This, however, would first require the consideration of these ancient
46 solutions as scientifically pertinent leads for new therapies. The aim of this review is to give,
47 through a few examples, arguments in favor of rationality in the scientific approach of these
48 past physicians as well as of a medicinal interest in studying these ancient pharmacopoeias. To
49 narrow the scope of our research, we focused on the Arab Medieval Golden Medical Age, which
50 went on to inspire occidental medicine hundreds of years after its preeminence. We further
51 highlight the possibility of integrating these knowledge into innovative, modern therapeutic
52 options.

53

54 *Keywords: Arab Medieval Pharmacopeia, natural remedies, pathogens, antibiotic resistance*

55

56 **Introduction**

57 Pharmacy is born with humans, who found ways to relieve their physical suffering through
58 remedies prepared with natural ingredient. Thanks to the synergy of the gift of writing and
59 man's desire to alleviate his ailments, ancient and medieval pharmacopoeias contain
60 information on the use of medical material, that may be from plant, mineral, or animal origin.
61 It is thus still possible that these thousand-year-old pharmacopoeias hold secrets that could
62 contribute to nowadays medicines. Many leading drugs (anti-cancer, anti-malarial, painkillers,
63 etc.) are indeed derived from these ancestral traditional pharmacopoeias [1]. However, of the >
64 30,000 plants with therapeutic virtues described in traditional pharmacopoeias, less than 5,000
65 have been studied [2]. The question is whether and how to exploit this vast pool of potential
66 therapeutics [3,4].

67 In the last decade, medicinal plant research has turned to old medicinal-botanical texts, to study
68 the history and evolution of pharmacopoeias, and to identify lead compounds for new drug
69 discovery [5–8]. Despite this pivot in research focus, experiments that test the activities of entire
70 historical remedies are rare, difficult to conduct, and the subject of much misunderstanding.
71 This is due to several factors including:

72 - The folkloric image associated with ancient medicines. The frequent intrusion of the
73 magical and the sacred hinders the objective evaluation of remedies while their development
74 remained rationally designed at its base. It may therefore seem difficult to evaluate the
75 biological effect of each of the ingredients. However, very often this interference is not
76 constitutive, but superadded: the rational/irrational association can usually be clearly separated.
77 Further, the diagnosis of a malady can also be complex, often involving supernatural aetiologies
78 alongside natural causes. In contrast to modern medicine, which seeks a direct cause for a
79 pathology, ancient systems often seek to flush out deep-seated causes. This disorganizes and
80 devalues the care provided, which is nevertheless often rational.

81 - The difficulty of transposing ancient practices into our present culture. This requires
82 a huge interdisciplinary research effort alongside, a dialogue between disciplines, the
83 promotion of which is not yet obvious, a problem very well explained by Harrisson and
84 Connelly [9]. Furthermore, on the opposite of current medicines containing a single active
85 ingredient, medieval remedies are usually preparations made from several ingredients, acting
86 synergistically [10–12]. It is thus possible that each ingredient taken individually does not
87 carry a strong activity, but that the combination can bring a certain, desired effectiveness.
88 While this approach is not without interest, the effectiveness of the remedy, which is the sum
89 of its multiple actions, will be more difficult to evaluate and to determine, and is not
90 necessarily favored by current research.

91 - The juxtaposition of two medicines, traditional and modern. While modern medicine
92 has grown in power and prestige, traditional medicine fallen victim of trivialization and/
93 increasingly untrained body of people practicing this form of medicine over the course of many
94 years. This has resulted in some degradation of knowledge, and a more superficial scientific
95 approach. It is thus necessary to restore confidence and rationality in the study of traditional
96 medicines, and to find room for dialogue between both approaches, that are ultimately rather
97 complementary than opposed, *i.e.* [13–17].

98 Although discredited in recent years, traditional medicines have nevertheless been marked
99 throughout their history by a rationality, a scientific approach enabling the emergence of
100 remedies that we could quite rightly consider as innovative by modern standards despite being
101 designed millennia ago. It is important to remember that traditional practices were characterized
102 by the seal of research, carried out by prominent scientists who led to major discoveries and
103 developments. Ancient pharmacopoeias could again be considered as a relevant starting point
104 for the search for new remedies. This will be illustrated through a few examples from the
105 literature. We focused on the medieval Arab period perceived as the golden age of ancient

106 medicine, and through the lens of the fight against microbial infections, one of the major
107 medical concerns of the medieval period.

108

109 **1. Antibiotic resistance**

110 Infections have marked human history. Even if nowadays, except for the COVID-19 pandemic,
111 infections are considered less anxiety-provoking compared to other pathologies such as cancer,
112 this has not always been the case: at medieval times, drinking water, cutting, or injuring oneself
113 could lead to dangerous or even fatal infections. As these infections were a daily preoccupation,
114 physicians also developed many leading remedies to counter them [4].

115 The advent of antibiotics, with Fleming's discovery of penicillin in 1928, a compound produced
116 by the fungus *Penicillium notatum*, revolutionized the treatment of infections [18,19], leading
117 to the belief that microbial infections were 'over'. The use of traditional medicines was thus no
118 longer relevant and lost much of its prestige. This was nevertheless regardless of the ability of
119 bacteria to resist antibiotics. If microbes can produce antibiotics (most of the antibiotics used
120 are of microbial origin), it is indeed logical that other microbes have found ways to resist these
121 same antibiotics. These resistances have then spread widely with the unreasonable use of
122 antibiotics, *i.e.* [20–22].

123 Indeed, quite quickly after their introduction to the market, bacteria strains resistant to
124 antibiotics were detected. This was the case for penicillin, with resistant *Staphylococcus aureus*
125 found in the 1940s [23,24]. *Streptococcus pyogenes* resistant to sulfonamide was also readily
126 detected in military hospitals during the second World War [25–27]. *Mycobacterium*
127 *tuberculosis* with streptomycin resistance was revealed as well in 1948 [28]. Resistance to
128 multiple drugs was first observed in the late 1950s to 1960s among enteric bacteria, like
129 *Escherichia coli*, or other from the *Shigella* and *Salmonella* genus [29]. These resistances cause

130 also a gradual re-emergence of pathologies like tuberculosis, since the 1980s, mainly due to
131 multi-drug resistant strains, enhanced by emergence of the human immunodeficiency virus
132 [30].

133 As a consequence of the pervasiveness of the above strains of bacteria, the emergence of
134 antibiotic resistance has been rising rapidly all over the world. Ultimately, a new resistance
135 appeared with every new antibiotic synthesized (Figure 1). Subsequently, we are now presented
136 with an ever-increasing global health threat. In 2019, a study showed the involvement of
137 antibiotic-resistant bacteria in the deaths of greater than 1.2 million people [31]. This may be
138 attributed to different factors, such as the abusive use of antibiotics, as well as a shortage of
139 new drug development by the pharmaceutical industry [32].

140 In the fear that antibiotics that are effective today might no longer be functional tomorrow, and
141 with the rapid spread of antibiotic resistance, there is an important need to develop new
142 strategies to limit the use antibiotics and to find new therapeutic solutions. Ancient societies
143 have used and/or combined countless natural substances to treat diseases, trying, testing, and
144 improving these strategies over the course of many centuries. Keeping these facts in mind, it
145 seems only logical that they could very well serve as the basis for the discovery of new
146 therapeutic strategies. However, the establishment of interdisciplinary consortia dedicated to
147 the study of these remedies must be implemented, as well as the demonstration of the interest,
148 feasibility, and future prospects of such approaches.

149

150 **2. Rationality in the design of remedies**

151 If different pinpoint studies already highlighted some interest in studying past remedies or
152 highlighted antibiotic use from past records, *i.e.* [33–40], the consideration of these past
153 remedies as a reservoir of pertinent strategies to combat infection would require a more

154 complex and coordinated strategies, involving intense collaboration between art, social and
155 experimental sciences.

156 A pioneering interdisciplinary consortium (Ancientbiotic, <https://ancientbiotics.co.uk/>) has
157 been set up to study a 10th Century medical text known as ‘Bald’s Leechbook’ containing a
158 plentitude of remedies. From this book, a collyrae (Table 1) has been chosen to highlight the
159 potential of these medicines to combat infections. The goal was equally to study the medical
160 approaches of past physicians as much as to demonstrate the efficacy of an ancient remedy. By
161 faithfully reproducing this remedy, the authors were able to show that it drastically limited the
162 growth of bacterial pathogens like *Staphylococcus aureus*, *Pseudomonas aeruginosa* or
163 *Neisseria gonorrhoeae in vitro*, and/or on a mouse model of eye infection, with a reasonable
164 safety profile [41–44].

165 The same studies also showed that the mixture of ingredients in Bald's eye drops is more
166 effective than the addition of each individual components, implying that the combination of
167 specific ingredients, none of which may have significant antibacterial activity, the mixture
168 overall may still present promise. Consequently, it seems possible that some of the
169 combinations developed by these physicians were designed through rational methods.
170 Furthermore, this permits the plausibility that one could construct a remedy of therapeutic
171 potential with individually uninteresting ingredients. So, the idea would be to consider these
172 ingredients in the context of all or part of the remedies, rather than investigating each ingredient
173 individually.

174 As a follow-up of this study, the consortium also developed a software to analyze the entire
175 manuscript on order to highlight the most promising remedies. Groups of ingredients were
176 revealed. Some of them were often used together, such as aloe vera and sarcocolla [45]. Another
177 recent computer analysis equally highlighted the recurring appearances of combinations of
178 ingredients, like saffron and opium or fennel and celery seeds, when analyzing remedies for

179 urinary tract diseases identified in different Arabic pharmacopoeias spanning over the course
180 of > 3 centuries [46]. These re-occurring combinations point to a rational approach to the
181 development of treatments, where a base of certain ingredients would have been maintained
182 and used as a framework for the design of new candidates. The same ingredients could produce
183 synergistic activity if combined, and should deserve special attention. Thanks to these studies,
184 it becomes more and more evident that the science of medicine in medieval times was the result
185 of a very rational and scientific approach, far from the folkloric image it usually has. Further
186 study of remedies from other manuscripts and ancient practices will be required to confirm
187 these initial hypotheses and/or to possibly allow the identification of innovative active
188 principles from complex combinations or even unexpected materials [35,47], for example
189 through the development of other consortia.

190 While traditional remedies were developed from such common ingredients, many remedies also
191 contain toxic molecules, among which the most emblematic being heavy metals, such as lead,
192 mercury, and arsenic. Reconsidering these remedies for future development also requires to
193 prove that ancient physicians perfectly mastered the use of these ingredients, took into account
194 their toxicities, and did not take ill-considered risks concerning the health of their patients. One
195 example is lead, widely used since antiquity to prepare make-up products (including kohl) or
196 remedies. Two recent studies have analyzed such uses, based on makeup found in Egyptian
197 tombs [48], and the reconstitution of a cutaneous remedy reported by Al Kindi (Table 1), from
198 the medieval Arab period [49]. These two studies demonstrated that ancient alchemists
199 mastered the transformation of metals and were able to confer them different therapeutic
200 potentials, depending on the transformation processes used. In the “khols” used for make-up,
201 litharge was transformed into laurionite and phosgenite, with pro-inflammatory properties,
202 which prevented infections [48]. Reconstruction and analysis of the ancient remedy showed
203 that alchemists were also able to obtain soluble lead with anti-inflammatory properties, to

204 promote healing [49]. Moreover, the toxicity of lead was reported as early as antiquity [50]. As
205 an anti-infective, it was mostly used cutaneously. Such use limited the diffusion of this metal
206 in the body, restricting its action on the local site of infection. These precautions may therefore
207 have changed the benefit-risk balance of lead. Overall, the evidence suggests that ancient
208 physicians knew about the inherent toxicity of toxic ingredients like metals, and handled
209 carefully their use.

210 These few examples show us that the study of the history of medicine combined with more
211 modern investigation to characterize these remedies could prove the rationality of the
212 approaches followed by these physicians. One of the periods where this scientific approach was
213 at its peak, both in terms of the variety of actors and of the scientific approach, is the medieval
214 Arab period (Table 1). The methodology applied by these scientists could still be relevant today
215 and will be explained in the following section.

216

217 **3. The Arab medieval Golden age of medicine**

218 Among the scientific fields studied in the medieval Arab world, medicine was certainly the
219 most studied and the most developed. It is customary to say that this was the golden age of Arab
220 medicine with considerable scientific contributions between the 9th and 13th centuries, *i.e.* [51–
221 55]. Many of the achievements of Arab-Muslim physicians were based on the legacy of Greek
222 and Roman physicians [51,56]. This effervescence of knowledge and intelligence then spread
223 throughout the world and profoundly influenced medical theory, surgical practice and other
224 disciplines.

225

226

227

229 Several factors have led to this Golden Age among them being religious support. As this period
230 was deeply religious, such positions could easily favor, delay, or condemn medical progresses.
231 The guidelines of the Prophet clearly for example encouraged such studies. The extension of
232 the Muslim Empire during this time brought out an exchange of ideas from various part of the
233 world from India to Iran, or Spain, (Figure 2). Communication routes also became safer,
234 facilitating travel and trade. Alongside these developments, Arabic language was unified as an
235 international one, which facilitated the exchange of scholarly ideas [54]. The ancient
236 manuscripts of greek, latin or even sanskrit [57] were translated in Arabic by the most
237 competent scholars. Another significantly contribution to the Golden Age was the
238 establishment of a paper mills in Baghdad (for a long time the nerve center of the Arab-Muslim
239 world [58]) to replace parchment (skin of animals) or papyrus (plant origin) by paper using
240 linen. This enabled many people to gain access to books and develop their education [54]. The
241 most precious texts were stored in the House of Wisdom, founded in Baghdad in 1005 by the
242 Caliph Al Mamun [56].

243 Important advances were also made in chemistry, where Arab alchemists became familiarized
244 with plants and developed different techniques such as distillation, crystallization, calcination,
245 *etc* [54]. An entire outgrowth of alchemy consisted in isolating and studying a broad variety of
246 natural sources, minerals, and compounds, to discover a magic ‘elixir’ or a medical potion that
247 would preserve people from all fatal diseases.

248 Likewise, in microbiology, plague and leprosy were considered as infective and contagious
249 diseases. For example, Islamic practitioners introduced the concept of quarantining (XIth
250 century) as a form of disease control. Hygienic methods were also implemented at the same
251 time, in the form of proper sterilization, putting in place practices such as the use of alcohol
252 prior to surgery and skin wounds treatment [54].

253 Developments also occurred in pharmacology. Practitioners became acquainted with herbs,
254 introduced new drugs such as camphor, musk, sandalwood, developed excipients, created
255 flavoring extracts, and experimented with poisons and antidote [59,60]. The first pharmacy was
256 established in Baghdad in 754. Four centuries later, the pharmacology science was separated
257 from both medicine and alchemy, these disciplines becoming independent (illustrated Figure
258 3).

259 *Medical education and institution*

260 Physicians during this era had to follow long training courses, often being six to seven years in
261 duration. This education comprised of an initial theoretical training in sciences, subsequently
262 followed by clinical training in hospitals. Medical practice was even governed by a code of
263 ethics towards patients, colleagues, and community [61,62].

264 Secular hospitals developed throughout the Arab world, the first being established in Damascus
265 in 706. These hospitals were well equipped. Patients monitoring, drug development and clinical
266 trials were reported and provided key record for the development of the scientific method [63].

267 *Famous figures of the Arab medicine age*

268 Among the era's many prominent figures was Zakarya Al-Razi, known in Latin as Rhazes
269 (Figure 2, Table 1), a pharmacologist and physician from Persian origin who headed the hospital
270 founded in Baghdad [64]. Zakarya Al-Razi chose to devote his life to medical research and
271 became the founder of chemotherapy by using the mineral drugs for external and internal use
272 in cancers [64]. Since his youth, he was interested in alchemy, and years later he was the first
273 to introduce metal-chemical preparations such as arsenic, copper sulfate, iron sulfate, and
274 different forms of mercury to develop new drugs [65]. He went on to write his famous book *Al-*
275 *Hawi*, an encyclopedia of 30 volumes that provides a general description of disorders, fevers,
276 plagues, and skin diseases, that was accompanied by a complete pharmacopeia, tables of

277 terminology, weights, and measures [65]. It is noteworthy that he was the first to use opium as
278 an anesthetic and that he tested it on animals before administrating it to humans [64].

279 One of the most famous muslim scientist is Abdu Ali Ibn Husayn ibn Abdullah Ibn Sina, also
280 known as Avicenna (Figure 2, Table 1). Of persian origin, from Rayy, he was known as the
281 prince of medicine and he developed a methodological approach that would be taught in
282 European universities until the 19th century [64]. His book *Al-Qanun fi al-Tibb -Canon of*
283 *Medicine-* became a famous medical works, considered to represent the first pharmacopeia,
284 including more than 600 medicinal chemical, and physical properties [66]. In addition to these
285 accomplishments, Avicenna was the first to describe many different microbiological diseases
286 such as anthrax and tuberculosis, and emphasized the crucial role of hygiene and dietetics [54].
287 He stressed the need to study new drugs before releasing them to the patients by setting rules
288 to test their effectiveness [64].

289 Another interesting figure in the history of medieval science is Abu Yusuf Yaaqub Ibn Ishaq
290 Al Kindi (Figure 2, Table 1), considered as the Father of Arab philosophy. He was interested
291 in a variety of subjects ranging from metaphysics, philosophy and logic to optics and
292 pharmacology [67]. Among his many medical writings, the most reputable and well-known
293 might well be the medical formulary “*Aqrabadhin*”. This term is derived from the Greek word
294 for 'list'. The book details the pharmaceutical preparations derived from botanical sources,
295 animals, and minerals, in the form of lists of medications [67,68]. He also wrote a treatise *Risala*
296 *fi ma' rifat quwwat al-adwiya al-murakkaba*, translated as *De gradibus*, and devoted to quantify
297 the strength of drugs by exploiting mathematical rules [69].

298 Diya al-Din Abu Muhammad Abdallah Ibn Ahmad Ibn al Baytar (Figure 2, Table 1) is another
299 famous Arab scientist, a famous Muslim botanist and pharmacologist during the Medieval
300 times. He belonged to a scientific family. His father Ahmad Ibn Abd-al Malik taught him his
301 knowledge and passion for natural sciences [70]. He studied the Galenic pharmacopeia, which

302 was based on the identification of the active principles of medicinal plant extracts. His capital
303 work, entitled, *Kitab al-Gami' li-mufradat al-adwiya wa-l-agdiya* translate to 'Collection of
304 simple remedies and food' [69] is considered as his seminal work, based on Dioscorides, Galien,
305 Al-Razi and Ibn Sina, on which he applied his own observations and corrections and mentioned
306 the simple nutrients and about 1400 drugs based on plants, animals, and mineral reigns [70].

307 *Drug development during the Arab Medieval ages*

308 During the Medieval ages, Arabs contributed riveting interesting advances to health and
309 medicine. During this time, the use of drugs still relied upon scientific hypotheses introduced
310 by the Greeks, related to 'the theory of bodily humors'. Essentially, this theory states that
311 humans fell ill due to imbalances of these humors in the body [71]. Hippocrates (Figure 2,
312 Table 1) stated that the human body is made up of four substances: yellow bile, black bile,
313 water, and blood, to which he connected an element in the universe with atmospheric conditions
314 for each substance. Arab physicians agreed with this theory [72] and affirmed that physical and
315 spiritual wellbeing is essential, and that a disease should be viewed as an opportunity to purify
316 and balance the emotional and physical feelings via rest, a regime of healthy food, breathing
317 fresh air, and practicing good hygiene [73]. Even if this theory has proven incorrect, the
318 development of drugs still responded to scientific standards, and were further framed by ethic
319 rules [74].

320 It is import to note that the origin of drug development has been based on the sum of
321 accumulated knowledge from pre-Islamic periods, such as that of the Egyptian or Chinese
322 medical systems, the Greek and Roman legacies still remaining the basis of the developed
323 knowledge throughout the Arab Medieval ages. Arab physicians then improved these
324 knowledge, enhancing also the concept of trials which is the basis of nowadays scientific
325 approaches. Once a remedy was identified, either based on plants, animals, metals and/or
326 minerals, its efficiency and toxicity was tested. Then, the administrated remedy could be either

327 a simple diet or a simple drug based on plants, minerals and metals, or to a mixture of one or
328 more of the aforementioned (Figure 4) [74,75].

329 Ibn Sina largely studied the nature and qualities of simple drugs in vol. 2 of the *Canon*, he then
330 proceeded to set rules to be respected in the drug development process. These remained the
331 basis of testing drugs [74]:

- 332 - The drug must be cleaned from any foreign agents.
- 333 - Drugs must be tested on two different diseases to be sure of the effects.
- 334 - The mechanism of action must be monitored.
- 335 - The drug must be tested on animals then on human, because if it is carried on animals
336 only, the effect on humans cannot be proven.

337 Altogether, it appears that Arab physicians developed a scientific method based on
338 experimentation, evidence-based knowledge, clinical trials, animal and/or human trials,
339 concepts that are also found in the contemporary scientific method.

340

341 **Conclusions - Perspectives**

342 Health care systems have always been deeply embedded in economic, religious, and societal
343 beliefs, and therefore are reflections of their perspective eras. Where aforementioned periods
344 are religious, an inter-relationship between medicine and belief is widely found, in different
345 forms depending on the period, disturbing the perception and relevance of the medical and
346 pharmacological advances of these periods. However, these inter-relations have never
347 prevented the rational development of medicine, and all the great civilizations have developed
348 a wisdom, an art of health and healing that is, empirically solid with proofs of effectiveness.
349 This rationality reaffirmed in past scientific developments encourages to re-investigate ancient

350 practices and pharmacopoeias. The latest technological advances also allow to surmount the
351 barriers of the study of these ancient remedies [76–78].

352 The greatest benefit of history is the ability to collect knowledge from the past and integrate it
353 with that of today to improve future knowledge. Since ancient times, plants, insects, animals,
354 minerals, turned out to be an exceptional large source of bioactive molecules: they have already
355 provided mankind with new first-class remedies [79]. The study of these pharmacopoeias is
356 now turning to more complex remedies that provide a synergy of action compared to isolated
357 ingredients. This synergy allows therapeutic strategies to be multiplied from ingredients which,
358 taken individually, would have be of little medicinal interest. These studies are nevertheless
359 complex and require the establishment of important interdisciplinary networks, ranging from
360 history to biology, to chemistry and to pharmacology. Recognition of these networks and the
361 valorization of their added value remain a challenge.

362 The Arabic Golden Age were an important period in the evolution of ancient medicines and
363 laid the foundations for a modern scientific approach. Their knowledge largely inspired
364 Western medicine from the Middle Ages to the Renaissance. The numerous manuscripts found
365 allowed to collect a large amount of information on medical practices and pharmacopoeias, and
366 to follow these practices in time and space. By focusing mainly on remedies preserved over a
367 wide geographical or temporal scale, the highest potential of being of interest may be selected.

368 The search for antibacterial solutions is particularly well suited to this approach, as infections
369 were a daily concern in the Middle Ages, and the solutions proposed are numerous: we thus
370 have access to a vast repertoire of potential solutions. This research is even more relevant in
371 view of the context of increasing bacterial resistance to antibiotics. The unreasonable use of
372 antibiotics, both in human and animal health, as a preventive measure, for pathologies that do
373 not require antibiotics has led to a situation where the search for alternatives becomes crucial.
374 These ancient pharmacopoeias contain a vast array of information on both innovative molecules

375 and synergistic strategies making it more difficult for resistance to appear, while potentially
376 reducing the impact on the surrounding microbiota (bactericidal molecules taken individually
377 being less deleterious). Thus, it appears that history holds a vast repertoire of remedies that
378 might lead to medical innovation. Another option for these remedies, some of which have been
379 preserved throughout history, still used today in the traditional Arab pharmacopoeia, and whose
380 efficacy has been validated historically and through today's scientific prism, is that they could
381 find a place in an integrated healthcare offer.

382 Medical systems are constantly evolving. The introduction of a new medical system occurs
383 when the old one is challenged. This evolution often results in an interweaving of innovations
384 and old practices, even if the integration of ancient practices is done with parsimony or defiance
385 [80]. This has always been the case, and is still true today, a time when we are witnessing a
386 crisis in health care related to inadequate delivery and adaptation to changing patient
387 expectations. This crisis of confidence amplifies the growing demand for complementary and
388 alternative medicines, which have their origins in ancient and/or traditional practices. This is
389 reflected in the growing number of patients (over 70% according to the WHO) who are already
390 turning to these practices. And, even if there is a complementarity between these two forms of
391 wisdom, modern medicine being on one hand and traditional medicines on the other, it is their
392 connection that seems to be problematic today. This complementarity, which stems from
393 differences in the way health and pathology are defined, studied and perceived, could also be
394 at the source of the difficulties in uniting them. As such, it is imperative to study the cultures
395 and societies that have laid the foundations of past medicine [81]. Characterizing the scientific
396 approach by which these medicine and pharmacopoeias have been developed, understanding
397 how the different health systems have intertwined with each other over time would help to
398 rationalize the debate, and ultimately, why not, lay the foundations for a modern conception of
399 a common medicine?

400

401 **Authors contribution**

402 All authors contributed similarly, and PF acted as project supervisor

403

404 **Conflict of interest**

405 The authors declared no conflict of interest

406

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610 **Figure Legends**

611

612 **Figure 1. A timeline of the evolution of antibiotic resistance.**

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614 **Figure 2. Map of the Arab Empire in Medieval times.** The name of famous scientists cited
615 in the text, their time and place of birth are given.

616

617 **Figure 3. Illustration of a medicine preparation.** Folio from a dispersed manuscript of an
618 Arabic translation of the *Materia Medica* of Dioscorides [56,82]

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620 **Figure 4. Drug development process during the Arab medieval age,** adapted from [74,83]

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623 **Table 1.** Glossary of terms and names used in the review

Family term	Name	Description
Infection		
	Present definition	Development in a living being of micro-organisms that can cause injury by multiplying and possibly secreting toxins or spreading through the bloodstream
	Past definition	Infections are described by the symptoms they cause. Their description should inform us on the nature of the infection with today standard's. This usually demands a broad-ranging, interdisciplinary approach, to study the manuscript, understand the description of the disease, symptoms, the curative ingredients and infer from these descriptions a plausible causing agents, that is not without difficulties [84–86].
Professionals		
	Physician	A person able to practise medicine, from the diagnostic to the treatment (except surgery)
	Alchemist	A person who practises alchemy, the medieval forerunner of chemistry, concerned with the transformation or transmutation of matter, through distillation, crystallisation...

	Pharmacist	A person who can prepare and sell certain medicines by prescription only. They were aware of the importance of raw materials, botanic and the importance of the preparation protocol precision
	scholar	A person who is highly educated or has an aptitude for study.
Time period		
	Antiquity	30 th century BC -5 th century
	Medieval time	5-15 th century
	Arab medical golden age	9-13 th century
Famous figures		
	Hippocrates	Born around 460 BC in Cos and died in 377 BC in Larissa, was a Greek physician of the Periclean century, but also a philosopher, traditionally considered as the father of medicine
	Dioscorides	Born between 20-40 in Anazarbe and died around 90. He was a Greek physician, pharmacologist and botanist whose work was a major source of knowledge about remedies of a plant, animal or mineral nature during the 1,500 years. He is the author of the treatise ' <i>De materia medica</i> '.
	Zakarya Al-Razi	Born in 865 in the town of Clay, died around 925 in Tehran was a Persian multidisciplinary scholar who

		made important contributions to medicine, alchemy and philosophy
	Abu Yusuf Yaaqub Ibn Ishaq Al Kindi	Born in 801 in the town of Koufan, died in 873 in Bagdad. As an encyclopaedic mind, he sought to synthesise, organise and evaluate all the knowledge of his time (philosophy, mathematics, astronomy, physics, chemistry, technology...)
	Abdu Ali Ibn Husayn Ibn Abdullah Ibn Sina	born in 980 in Ravi, died in 1037 in Hamadan, philosopher and physician, author of reference works in medicine and philosophy
	Diya al-Din Abu Muhammad Abdallah Ibn Ahmad Ibn al Baytar	born around 1197 in the province of Malaga and died in 1248 in Damascus, an Arab-Andalusian physician, who published several works in which he brought together the pharmaceutical knowledge of his time
Remedies		
	collyrae from the Bald's Leechbook	Make an eyesalve against a wen: take equal amounts of an Allium species and garlic, take equal amounts of wine and oxgall, mix with the alliums, put in a brass vessel, let stand for nine nights, clarify well, put in a horn and at night apply to the eye with a feather [44]

	Lead-based cutaneous remedy from Al Kindi.	1 part of quicklime (CaO) and 1 part of litharge (PbO) are passed through a clay. They are covered with wine vinegar. Olive oil is added and also sheep fat. It is boiled together and stirred with a rod until it is mixed and almost black. The heating is renewed until the viscosity is like thick honey [49]
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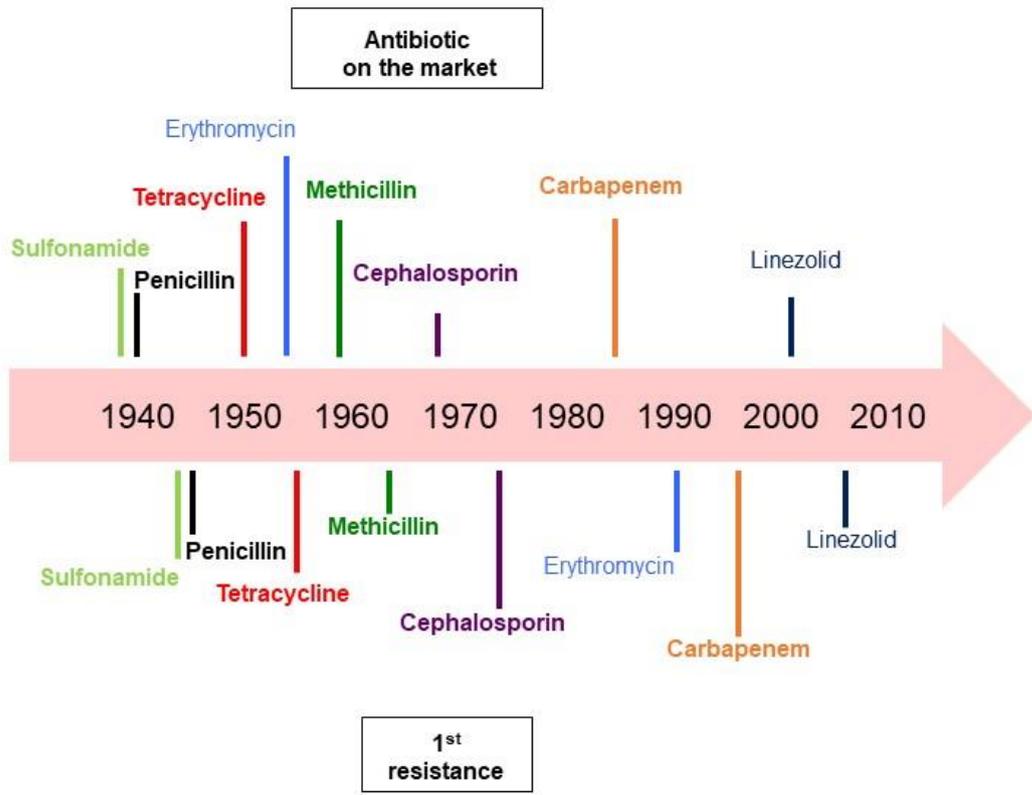


Figure 1

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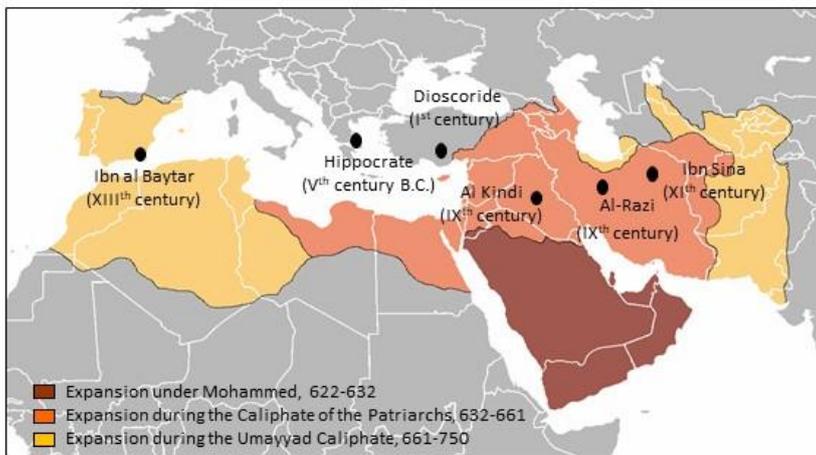
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677 **Figure 2**



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700 **Figure 3**



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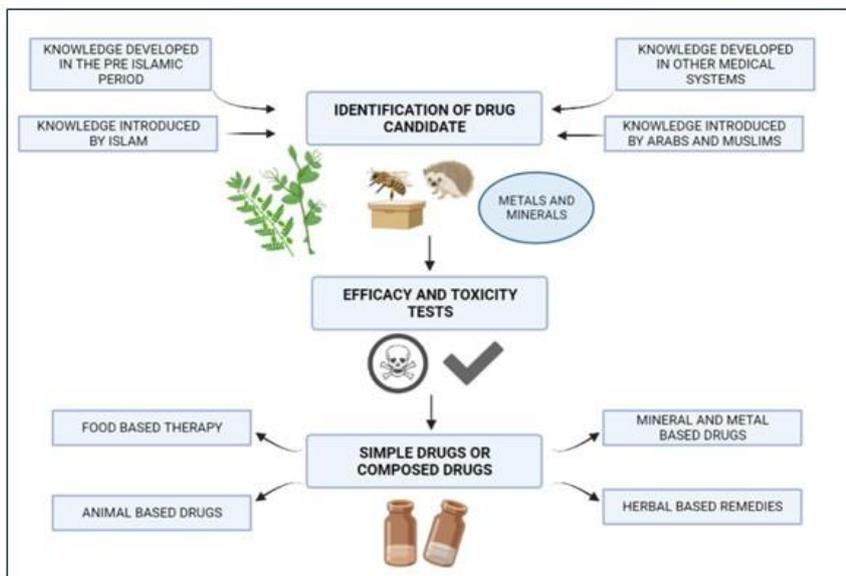


Figure 4