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Critical Appraisal of North African Medicinal Plant Activity Against Carbapenem-Resistant *Klebsiella pneumoniae* and *Acinetobacter baumannii*

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ABSTRACT

Carbapenem-resistant *Klebsiella pneumoniae* and *Acinetobacter baumannii* cause hospital outbreaks across North Africa, where access to newer antibiotics is limited and plant-derived agents are widely proposed as alternatives. This critical narrative review appraises what the published evidence from Algeria, Egypt, Libya, Morocco and Tunisia can support. A scholarly index was searched on 9 October 2026, and complemented by a structured PubMed search; thirteen primary studies that tested plant-derived material against isolates documented as carbapenem-resistant or carbapenemase-positive were appraised, three of them in full text, across five domains: identity of the material, characterisation of the isolates, assay design, interpretation of potency and synergy, and translational depth. A minority of studies reported carbapenemase genes for the tested isolates, none of those read reported cytotoxicity, and stand-alone minimum inhibitory concentrations of oils and extracts generally exceeded conventional potency criteria. The strongest signal came from carvacrol- and thymol-rich oils of the mint family: in one Tunisian study carvacrol at 2–4 µg/mL lowered imipenem minimum inhibitory concentrations to the susceptible range in seven of twelve isolates, while five did not reach it. On a four-level evidence scale no candidate reached confirmatory readiness, one group reached the level of credible lead, and most other claims could not be falsified because the material or the isolates were undefined. The review proposes a minimum reporting standard and sets priorities: a shared set of genotyped isolates, authenticated and chemically defined material, reference-method testing adapted for volatile agents, selectivity and larval-model data, and tests against oxacillinase (OXA)-type carbapenemases.

التقييم النقدي لنشاط النباتات الطبية في شمال أفريقيا ضد بكتيريا *Klebsiella pneumoniae* و*Acinetobacter baumannii* المقاومة للكاربابينيمات

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الملخص

تُسبّب بكتيريا *Klebsiella pneumoniae* و*Acinetobacter baumannii* المقاومتان للكاربابينيمات فاشيات في المستشفيات عبر شمال أفريقيا، حيث يقلّ توافر المضادات الحيوية الحديثة وتُقترح المنتجات ذات الأصل النباتي على نطاق واسع بديلاً لها. تقيّم هذه المراجعة السردية النقدية ما يمكن أن تدعمه الأدلة المنشورة من الجزائر ومصر وليبيا والمغرب وتونس. أُجري البحث في فهرس علمي بتاريخ 9 أكتوبر 2026، وجرى تقييم عشر دراسات أولية اختبرت مواد نباتية المنشأ ضد عزلات متعددة المقاومة للأدوية أو مقاومة للكاربابينيمات، منها ثلاث دراسات قُرئت بنصّها الكامل، وذلك عبر خمسة محاور هي: هوية المادة النباتية، ووصف العزلات، وتصميم الاختبار، وتفسير الفاعلية والتآزر، والعمق الانتقالي نحو التطبيق. أبلغت دراسة واحدة فقط عن جينات الكاربابينيماز في العزلات المختبرة، ولم تُبلغ أي دراسة عن السمّية الخلوية، وتجاوزت التراكيز المثبطة الدنيا للزيوت والمستخلصات منفردةً في الغالب معايير الفاعلية المتعارف عليها. وجاءت أقوى إشارة من الزيوت الغنية بالكارفاكرول والثيمول من الفصيلة الشفوية، إذ خفّض الكارفاكرول بتركيز يتراوح من 2 إلى 4 ميكروغرام/مل التراكيز المثبطة الدنيا للإيميبينيم إلى المدى الحسّاس في سبع من اثنتي عشرة عزلة في دراسة تونسية واحدة، في حين لم تبلغه خمس عزلات. وعلى مقياس من أربعة مستويات للأدلة، لم يبلغ أي مرشح مرحلة الجاهزية التأكيدية، وبلغت مجموعة واحدة مستوى المرشح الواعد، وتعذّر دحض معظم الادعاءات الأخرى لأن المادة النباتية أو العزلات لم تكن محدَّدة. تقترح المراجعة حدًّا أدنى لمعايير الإبلاغ وتحدد الأولويات: مجموعة مشتركة من العزلات المحدَّدة وراثيًا، ومواد نباتية موثّقة ومعرَّفة كيميائيًا، واختبارات بالطريقة المرجعية مكيَّفة للمواد المتطايرة، وبيانات الانتقائية ونماذج اليرقات، واختبارات ضد الكاربابينيمازات من نوع الأوكساسيليناز (OXA).

الكلمات المفتاحية:
مقاومة البكتيريا للأدوية
المستخلصات النباتية
الزيوت الطيارة
التآزر الدوائي
اختبارات الحساسية الميكروبية
شمال أفريقيا

1. Introduction

Carbapenem-resistant *Acinetobacter baumannii* and carbapenem-resistant Enterobacterales, including *Klebsiella pneumoniae*, are classed by the World Health Organization (WHO) as critical-priority pathogens [1,2]. Their burden is highest where surveillance, infection control and access to new antibiotics are weakest. A global meta-analysis of 795 studies found carbapenem resistance in about three-quarters of *A. baumannii* isolates [3], and a meta-analysis of hospital-acquired *K. pneumoniae* infections found it in 28.7% [4]. In North Africa, hospital reports from Algeria, Egypt, Libya, Morocco and Tunisia describe *A. baumannii* producing the oxacillinase OXA-23 or New Delhi metallo-β-lactamase (NDM), *K. pneumoniae* producing OXA-48 or NDM, environmental and staff reservoirs, and, in one Tunisian hospital, extensively drug-resistant isolates for which the only active agents are not available in the country (Sections 3 and 8). That gap has turned attention to plants, which are embedded in the region's traditional medicine [5] and which laboratories there can collect, extract and test with modest resources. Researchers have approached the question from several directions. Global systematic reviews map antibacterial activity across hundreds of plant species, most often tested as crude methanol extracts against *Staphylococcus aureus* [6]. Reviews of herbal compounds against *A. baumannii* [7], of essential oils against WHO priority pathogens [8], and of African plants against multidrug-resistant bacteria [9] summarise promising constituents and synergies. A comparison of *A. baumannii* in the United Kingdom and Egypt notes that the contribution of Egyptian researchers to natural-product solutions is more notable than that of researchers in the United Kingdom [10], and a systematic review of plant-mediated silver nanoparticles against *Klebsiella* in Africa found 14 in vitro studies [11]. Primary studies from North African laboratories report essential oils and extracts active against multidrug-resistant and carbapenem-resistant isolates, with synergy against imipenem in several (Section 4).

What is missing is a critical appraisal of that evidence. Methodological critiques show that plant antimicrobial studies are hard to compare and reproduce: no internationally accepted standard exists for testing essential oils [12], published tests often omit composition, strain characterisation and quality controls [13], extract reporting is inconsistent [14], and crude materials and pure natural products can register activity in many assays for non-specific reasons [15,16]. We did not find a review applying these criteria to the North African evidence on carbapenem-resistant *K. pneumoniae* and *A. baumannii*; the closest syntheses we identified are pan-African, concern nanoparticles, or cover essential oils across all regions and pathogens. A catalogue of "plant X inhibits organism Y" would add little. The question that matters is which findings are strong enough to test further and which cannot be tested as published.

This review aims to organise the reported evidence on North African medicinal plants against carbapenem-resistant *K. pneumoniae* and *A. baumannii* by the identity of the material, the isolates and the assay, in order to separate findings that can be tested further from those that cannot.

2. Review methods and appraisal framework

2.1. Review type and question

This is a critical narrative review with a documented, structured search. It is a domain-based, framework-based review in the sense of Paul and Rialp Criado [17]: the evidence is sorted by an explicit framework, adapted here from the theory–context–characteristics–methodology logic of that work into material, isolates, assay and interpretation. The question is what the published evidence from North Africa can support about plant-derived agents against carbapenem-resistant *K. pneumoniae* and *A. baumannii*, and which

findings are strong enough to test further. A prior check for existing reviews, run on 9 October 2026, did not retrieve a review addressing this question; the closest we found were pan-African, nanoparticle-based or essential-oil reviews across all regions and pathogens (Section 1).

2.2. Scope

North Africa was defined as Algeria, Egypt, Libya, Morocco and Tunisia. A study was in scope if the plant material was native to, cultivated in or in traditional use in one of these countries, or if the work was done in a laboratory there. Plant-derived material included crude extracts, essential oils, fractions and pure constituents. Target organisms were *K. pneumoniae* and *A. baumannii* resistant to carbapenems (non-susceptible to imipenem, meropenem or ertapenem, or carbapenemase-producing). Studies of multidrug-resistant isolates without documented carbapenem resistance were recorded for context but were not included in the appraised corpus, which was restricted to studies testing isolates documented as carbapenem-resistant (non-susceptible to imipenem, meropenem or ertapenem) or carbapenemase-producing. Nanoparticles synthesised with plant extracts as reducing agents were excluded because activity may reflect the metal, as were phage, peptide and microbial products.

2.3. Search and screening

The search used a scholarly index of about 250 million records (OpenAlex and Semantic Scholar) on 9 October 2026, restricted to 2015–2026 for primary studies. About thirty queries were run in four families: plant evidence (plant, extract or essential oil with carbapenem-resistant *A. baumannii* or *K. pneumoniae*, by country and by plant genus), epidemiology (carbapenemases, outbreaks and prevalence in North Africa and Africa), assay methodology (potency criteria, essential-oil testing, synergy testing, authentication, assay interference and larval models) and novelty checks (existing reviews, publication curves, shared references). Each query returned 4 to 20 ranked records for title and abstract screening; index estimates of total matches ranged from about 50 to more than 1,000 per query. The search was extended by related-paper expansion from key studies and by reading the reference lists of full-text papers. Three primary studies were read in full text (Section 5), and the Libyan *Arbutus pavarii* study was read at abstract and journal-page level. Publication status and bibliographic details of every cited reference were checked against Crossref. To reduce dependence on a single index, the scholarly-index search was complemented by a structured PubMed query combining Medical Subject Headings and free-text terms for plant-derived material, the two pathogens, carbapenem resistance and the five countries, run on 23 October 2026; this retrieved additional eligible studies meeting the carbapenem-resistance criterion in Section 2.2. The identification, screening, exclusion and inclusion of records are summarised in Figure 1.

2.4. Data extraction and appraisal

For each primary study the following were extracted: country, plant material and its chemical characterisation, isolates and how resistance was established, assay and endpoint, controls, the minimum inhibitory concentration (MIC; converted to mass units where possible), synergy results, cytotoxicity and any in vivo work. Each study was appraised on five domains: D1 identity of the material, D2 identity and resistance profile of the isolates, D3 assay design, D4 interpretation of potency, selectivity and synergy, and D5 mechanism and translational depth (Section 5). Candidates were placed on a four-level scale from E1 (confirmatory-ready) to E4 (hypothesis only), defined in Section 6. Claim strength in this review was matched to the evidence type: an association or single-study finding is described as such, and a mechanism is called a hypothesis unless an orthogonal assay supports it.

2.5. Synthesis

Results are synthesised narratively in tables that place studies side by side on shared dimensions (Tables 1–7), with a comment under each. No meta-analysis was attempted because materials, isolates, units and methods were not comparable.

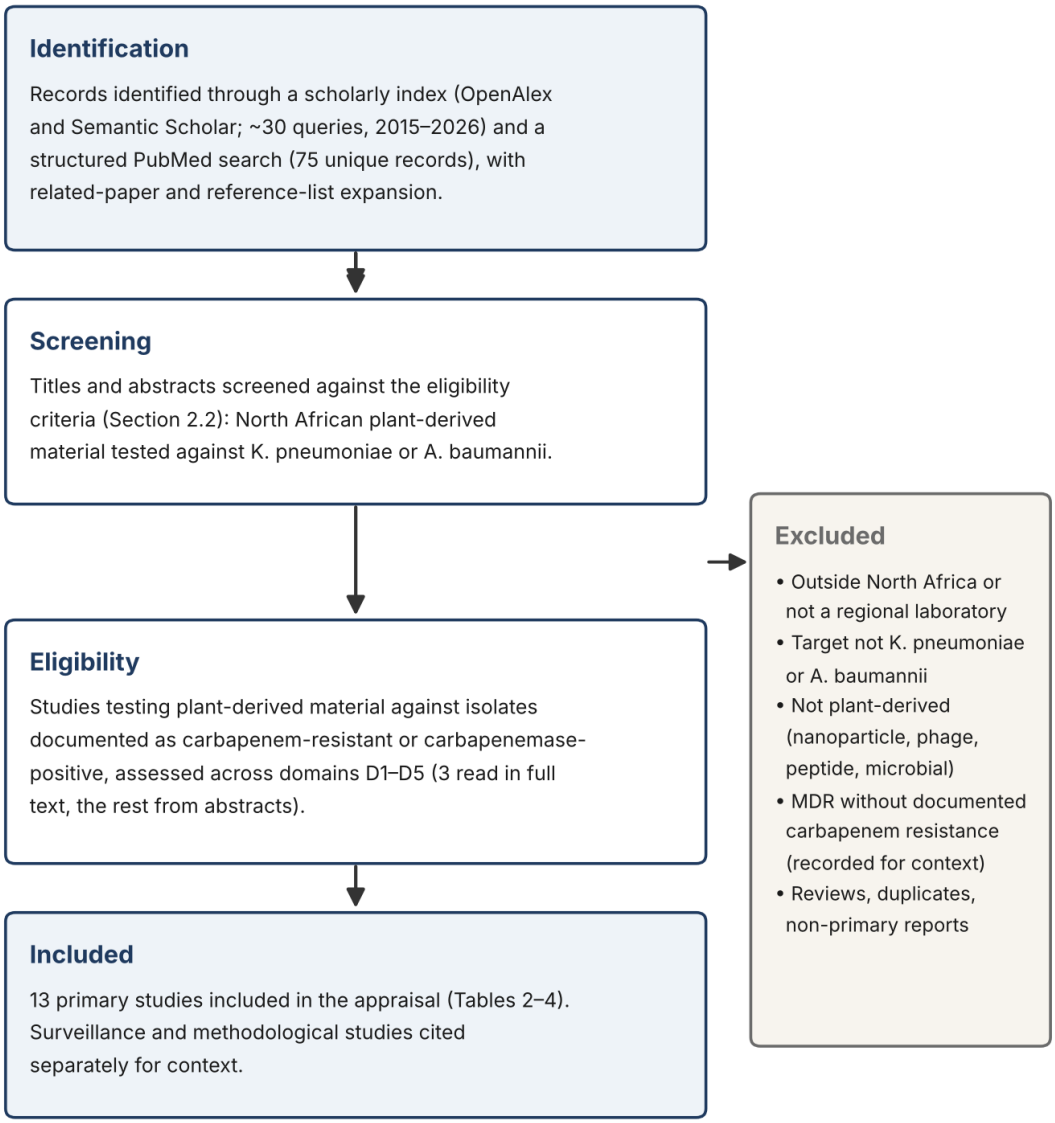

Figure 1. Flow of records through identification, screening and inclusion in the appraisal.

3. Carbapenem-resistant *K. pneumoniae* and *A. baumannii* in North African hospitals

Carbapenem resistance in North African hospitals is mostly enzyme-mediated and clonally structured, and that structure defines what any plant-derived agent would have to overcome. Globally, carbapenem resistance was reported in about three-quarters of *A. baumannii* isolates in a meta-analysis of 795 studies from 80 countries [3], and in 28.7% of hospital-acquired *K. pneumoniae* infections [4]. Surveillance in Africa is thin: carbapenem resistance in *Escherichia coli* and *Klebsiella* had been documented in 40 of 54 nations by 2019, with overlapping polymyxin resistance in 23 [18].

In *A. baumannii*, OXA-23 is the dominant acquired carbapenemase in the North African reports, usually in the international clone sequence type 2 (ST2), with NDM-1 or NDM as a second determinant in Algeria, Morocco and Tunisia (Table 1) and in Libyan hospitals [19]. In *K. pneumoniae*, OXA-48 has been the regional workhorse in Tunisia and Algeria [20,21], while Libyan hospitals report NDM-1 and, more recently, NDM-5 [22,23]. Libyan hospital data are consistent with this picture: in a Tripoli bloodstream-infection series only 34% of *Klebsiella* and 7% of *Acinetobacter* isolates were susceptible to imipenem [64], and an Al-Bayda intensive care survey recovered an *A. baumannii* resistant to all tested agents except colistin, including imipenem, from ward surfaces [65]. The environment matters as much as the patient. In a Tunisian intensive care study, 27 of 206 sampled items (14%) and the hands of 8 of 54 staff (15%) carried carbapenem-resistant *A. baumannii*, and patient isolates shared extensive genomic similarity with the environmental strains [24]; NDM-1/OXA-23 producers have also been recovered from hospital surfaces in Algeria [25].

Table 1. Carbapenemase determinants reported in North African hospital studies of *K. pneumoniae* and *A. baumannii*.

Country	Isolates and setting	Determinants reported	Reference
Tunisia	263 *K. pneumoniae*, teaching hospital, 2023; 12 extremely drug-resistant isolates sequenced	OXA-48 and NDM-5 in 12/12; ST101, ST147, ST383; 101/263 carbapenem-resistant	[26]
Tunisia	Carbapenem-resistant *A. baumannii* from ICU patients, surfaces and staff, Sousse	OXA-23 or NDM-1; ST2 and ST85; *armA*	[24]
Algeria	68 Gram-negative isolates, 2015	OXA-48 in 5 Enterobacteriaceae (*K. pneumoniae* ST101, ST147, ST163, ST2017); OXA-23 in all *A. baumannii* (ST2)	[21]
Algeria	*A. baumannii* from inanimate hospital surfaces	NDM-1 and OXA-23	[25]
Morocco	111 *A. baumannii* (81 clinical, 30 environmental); 23 carbapenem-resistant	OXA-23 in 16/23; NDM in 5/23; GES in 15/23	[27]
Egypt	74 carbapenem-unsusceptible *A. baumannii*	OXA-23 and ISAba1 in all isolates; OXA-58 in one	[28]
Libya	72 Gram-negative isolates from patients and environment, Sirte	NDM-1 most frequent (n = 13); VIM; OXA-23 in 6 *A. baumannii*; OXA-48 in 3 *K. pneumoniae*	[22]
Libya	56 *K. pneumoniae* (46 clinical, 10 environmental), Benghazi ICUs	NDM-5 in 45/46 clinical isolates; OXA-48 in 26/46; colistin resistance without *mcr*	[23]

ICU, intensive care unit; ST, sequence type; OXA, oxacillinase; NDM, New Delhi metallo-β-lactamase; VIM, Verona integron-encoded metallo-β-lactamase; GES, Guiana extended-spectrum β-lactamase; ISAba1, insertion sequence Aba1; *armA*, 16S rRNA methyltransferase gene; *mcr*, mobile colistin resistance gene.

The table has two consequences that the plant literature largely ignores. First, isolates are frequently multiply resistant at the mechanism level. Co-production of OXA-48 and NDM-5, together with colistin resistance, left only eravacycline and aztreonam–avibactam active in vitro against the Tunisian extremely drug-resistant isolates, and nine of ten patients treated with broad-spectrum regimens died [26]. A plant extract that inhibits an isolate described only as "multidrug-resistant" has therefore not been shown to act on a carbapenemase producer, and the distinction is not academic. The clones are also few, which makes a small strain panel defensible only if it is typed by sequence type and carbapenemase gene.

Second, local surveillance and plant testing are rarely done on the same isolates. Few reports pair a hospital resistance survey with extract testing on the same collection; one Libyan example is the survey of 244 Gram-negative isolates from Misurata, Libya, in which carbapenem resistance exceeded 60% in *A. baumannii*, *K. pneumoniae* and *Pseudomonas aeruginosa* and metallo-β-lactamase activity was found in 54.5% of resistant *K. pneumoniae* [29]. Carbapenemase detection by polymerase chain reaction (PCR) has been reported from every country in Table 1, so the absence of isolate characterisation in most plant studies from the same countries (Table 2) is better explained by study design than by a technical barrier.

4. The evidence base: what has been tested, where and against what

The North African literature on plant activity against carbapenem-resistant *K. pneumoniae* and *A. baumannii* is small, spread across five countries, and skewed towards essential oils and towards *A. baumannii*. The general literature on antibacterial plant extracts is large and still growing: an index query on 9 October 2026 for plant extracts or essential oils with antibacterial activity returned about 1,500 original studies from 2016 to 2026, with annual counts rising from 85 in 2016 to 192 in 2023. Within that mass, the studies that tested plant-derived material in North African laboratories against multidrug-resistant or carbapenem-resistant *A. baumannii* or *K. pneumoniae* number thirteen (Table 2).

Table 2. Primary studies from North African laboratories testing plant-derived material against multidrug-resistant or carbapenem-resistant *A. baumannii* or *K. pneumoniae*.

Study (country)	Plant material	Isolates and how resistance was established	Assay	Reported activity
Alwashaish et al. [29] (Libya)	*Arbutus pavarii* leaf, stem, fruit; aqueous and ethanolic extracts; catechin and quercetin by HPLC	Carbapenem-resistant, MBL-positive *A. baumannii*, *K. pneumoniae* and *P. aeruginosa* from a 244-isolate survey; disc diffusion and phenotypic MBL tests; no genotyping	Disc diffusion	Mean zone 9.3–9.5 mm (SD 7.3–7.6 mm) at the highest concentration
Jilani et al. [30] (Tunisia)	*Thymus vulgaris* essential oil (carvacrol 78.8%) and carvacrol	12 clinical *A. baumannii*; imipenem MIC 4–2048 µg/mL by broth microdilution; carbapenemases not typed	Broth microdilution; checkerboard with imipenem	Oil MIC 312–1250 µg/mL; carvacrol 64–128 µg/mL; FICI below 0.5 reported for all isolates
Laktib et al. [31] (Morocco)	*Lavandula mairei* essential oil (carvacrol 77.3%)	Carbapenem-resistant *A. baumannii* from two ICU environments; OXA-23 and NDM-1 by PCR and sequencing	Disc diffusion; broth microdilution	Zones 28.7–40 mm; MIC and MBC 0.39–3.125 µL/mL
Saleh et al. [32] (Egypt)	Commercial cinnamon, thyme, clove and caraway oils	37 imipenem-resistant *A. baumannii* (MIC 8–1024 µg/mL) from Cairo hospitals; species by *bla*OXA-51-like PCR; carbapenemases not typed	Resazurin broth microdilution; checkerboard; time–kill in two strains	Cinnamon oil MIC 0.25–2% v/v; imipenem MIC lowered at least 2-fold in all 37 strains

Study (country)	Plant material	Isolates and how resistance was established	Assay	Reported activity
Mahmoud et al. [33] (Egypt)	*Syzygium aromaticum* bought at a local market; water, ethanol and ethyl acetate extracts	Ten *A. baumannii* from 110 samples, seven imipenem-resistant by automated MIC; six tested; carbapenemase genes not sought	INT-reduction broth assay; MBC	Ethanol extract MBC 0.04–0.125 mg/mL; imipenem at 0.02 mg/mL killed all six isolates
Mohamed et al. [34] (Egypt)	Cinnamaldehyde (cinnamon constituent)	Carbapenem-resistant strains among 23 clinical *A. baumannii*	MIC; biofilm inhibition; electron microscopy	Strong anti-planktonic activity; biofilm inhibition 49.5–71.2% at ½ MIC
Benhadid et al. [36] (Algeria)	*Myrtus communis* essential oil (α-pinene 24.8%)	Panel including carbapenemase-positive and -negative *K. pneumoniae* and *A. baumannii*	Disc diffusion; MIC	Good activity except against *Pseudomonas*; per-isolate values not given in the abstract
Bekka-Hadji et al. [37] (Algeria)	*Mentha pulegium* (pulegone 74.8%) and *Artemisia herba-alba* essential oils	Imipenem-resistant *A. baumannii* S3310 producing OXA-23 (single strain); ATCC controls	Disc diffusion; broth microdilution; antibiotic-combination disc	Oil MIC 1.2 µL/mL; disc-level synergy with amikacin, ceftazidime and imipenem; no FICI
Edziri et al. [38] (Tunisia)	*Cinnamomum verum* bark methanolic extract (trans-cinnamaldehyde dominant); voucher CV12	Imipenem-resistant *A. baumannii* and MRSA; reference and clinical MDR strains; no genotyping	Broth microdilution; crystal-violet biofilm; antibiotic-interaction disc screen	MIC 0.625–5 mg/mL, MBC 2.5–20 mg/mL; imipenem-resistant *A. baumannii* most susceptible; biofilm reduced
Jilani et al. [42] (Tunisia)	*Cinnamomum verum* essential oil (cinnamaldehyde 70.15%) and cinnamaldehyde	XDR *A. baumannii* and *K. pneumoniae*; imipenem MIC ≥4 µg/mL; carbapenemase by mCIM	Broth microdilution; checkerboard with imipenem	Oil MIC 0.312–5 mg/mL; cinnamaldehyde 128 µg/mL; FICI <0.5 for all; imipenem MIC lowered to susceptible range
Abdel-Halim et al. [51] (Egypt)	Celastrol and thymol (plant constituents)	85 clinical *K. pneumoniae*; 43 meropenem-resistant, 39 carbapenemase-producing; *bla*KPC/VIM by PCR	Disk diffusion; checkerboard; carbapenemase-inhibition; docking	Meropenem MIC reduced 4–64-fold with celastrol plus thymol; carbapenemase hydrolysis inhibited
Abdel-Halim et al. [52] (Egypt)	Coumarin (plant constituent)	Carbapenem-resistant *K. pneumoniae*; NDM-1, VIM-2, OXA-9 by PCR	Combined-disk; checkerboard; enzyme-inhibition; qRT-PCR; docking	Coumarin–meropenem FICI ≤0.5; carbapenemase activity and gene expression reduced
Mourabiti et al. [63] (Morocco)	Quercetin, kaempferol, caffeic acid, 3,4-dihydroxybenzoic acid (polyphenols)	Carbapenemase-producing clinical *K. pneumoniae*, *E. coli* and *P. aeruginosa*	AlamarBlue MIC; checkerboard with cefotaxime; nitrocefin β-lactamase assay; docking/MD	MIC 12.5–25 mg/L; quercetin or kaempferol with cefotaxime synergy; quercetin fully inhibited β-lactamase

FICI, fractional inhibitory concentration index; HPLC, high-performance liquid chromatography; ICU, intensive care unit; INT, iodonitrotetrazolium; KPC, Klebsiella pneumoniae carbapenemase; mCIM, modified carbapenem inactivation method; MBC, minimum bactericidal concentration; MBL, metallo-β-lactamase; MD, molecular dynamics; MIC, minimum inhibitory concentration; MRSA, methicillin-resistant *Staphylococcus aureus*; NDM, New Delhi metallo-β-lactamase; OXA, oxacillinase; PCR, polymerase chain reaction; qRT-PCR, quantitative reverse transcription PCR; SD, standard deviation; XDR, extensively drug-resistant. Values are given as reported by the original authors; volume-based oil concentrations are not converted.

Three patterns stand out. First, the plant list is varied but the chemistry is not: the most active oils in Table 2 are carvacrol- or thymol-rich Lamiaceae oils (*Thymus*, *Origanum*, *Lavandula*), so the field is largely re-testing one family of phenolic monoterpenes under different species names. Second, "North African" often describes the laboratory rather than the plant. The Egyptian studies relied mainly on cinnamon and clove, spices of tropical origin sold across the region, so their findings say little about the regional flora. Third, evidence for *K. pneumoniae* remains, despite recent carbapenemase-inhibition studies [51,52], thinner than for *A. baumannii*. The retrieved *K. pneumoniae* work was mostly done on multidrug-resistant rather than carbapenem-resistant isolates, for example 25 multidrug-resistant isolates treated with tea tree and thyme oils plus amikacin [39]; carbapenemase-typed *K. pneumoniae* were tested only in compound studies [51,52] and one Moroccan polyphenol study [63], and no North African essential-oil study used carbapenemase-typed *K. pneumoniae* from Morocco, Tunisia or Algeria.

Study design is also uneven. Three of the thirteen studies report carbapenemase genes for the tested isolates [31,51,52], and three more used phenotypic carbapenemase or metallo-β-lactamase tests [29,36,42]. None of the thirteen reports a cytotoxicity or selectivity index in the sources examined, and the appraised corpus contains no in vivo experiment against a carbapenem-resistant target organism.

Broader syntheses exist but do not answer the regional question. A scoping review of essential oils against WHO priority pathogens covers the past decade across all regions [8], a review of African medicinal plants against multidrug-resistant bacteria is weighted towards southern African species [9], and a systematic review of plant-mediated silver nanoparticles against *Klebsiella* in Africa found 14 studies, four from Egypt and one from Tunisia [11]. The silver, not the plant, may drive activity in those nanoparticle studies, which places them outside the present scope. Null results are rare: a Libyan study of ivy (*Hedera helix*) leaf extracts found no activity,

with MICs above the highest concentration tested [40], and a Libyan study of *Artemisia campestris* reported only modest zones against uropathogens [41]. Both are useful calibration points in a literature otherwise dominated by positive reports.

5. Appraising the evidence: five domains that decide what an MIC can mean

Whether a reported MIC against a "carbapenem-resistant" isolate means anything depends on five design features, and the North African studies meet them unevenly. The appraisal below applies five domains (D1–D5) to the studies read in full (Table 3) and draws on abstracts for the rest.

5.1. D1: Identity of the plant material and the extract

The tested material must be traceable to an authenticated plant and described chemically as tested. One Tunisian study sets the standard: the *Thymus vulgaris* material was deposited as a voucher in a university herbarium, and the oil was characterised by gas chromatography–mass spectrometry (GC-MS) as a carvacrol chemotype (78.8%) [30]. At the other end, clove was bought at a market and photographed "for documentation" without a voucher [33], and commercial oils were used without authentication [32]. The latter matters because the composition reported for the cinnamon oil (longifolene 45.1%, coumarin 33.9%, cinnamaldehyde 6.7%, with listed constituents summing to roughly 149%) cannot be taken at face value, and differs sharply from a *Cinnamomum verum* oil reported with 70.2% cinnamaldehyde in a separate report [42]. Chemotype variation is the rule, not the exception: the thyme oil in one study is a carvacrol oil, whereas other reports describe thymol, *p*-cymene or camphene as dominant [30]. Because carvacrol and thymol carry much of the activity, an MIC for "thyme oil" is not comparable across studies without composition. Reporting guidance exists (the Consensus statement on the Phytochemical Characterisation of Medicinal Plant extracts, ConPhyMP) [14], DNA barcoding can supplement morphological identification when combined with chemical fingerprints [43,44], and a review of published broth-dilution tests of two essential oils against one Gram-positive species listed, among other pitfalls, variable composition that authors rarely underlined and clinical strains used without an antibiogram [13].

5.2. D2: Identity and resistance profile of the isolates

Carbapenem resistance is not a single phenotype. The meaningful descriptors are species-level confirmation, a reference-method carbapenem MIC, the carbapenemase gene, and the sequence type, and Table 1 shows why: regional isolates are dominated by a few clones with co-produced enzymes. Species were confirmed by *bla*OXA-51-like PCR in one Egyptian study [32] but by biochemical tests alone in the Tunisian study, which also used *E. coli* American Type Culture Collection (ATCC) 25922 rather than an *A. baumannii* reference as its susceptible control [30]. Neither typed carbapenemases. The Moroccan study that did, finding OXA-23 and NDM-1 in ICU environmental isolates, is the regional exception [31]. The Egyptian clove study shows the risk of relying on the label: seven of ten isolates were imipenem-resistant by automated MIC, six were chosen for testing by phenotype, and imipenem at 0.02 mg/mL killed all of them, so the tested set cannot be taken as evidence against carbapenem-resistant organisms [33]. None of the studies in Table 2 reports the sequence type of the tested isolates in the sources examined.

5.3. D3: Assay design

Broth microdilution is the reference format [45], but it was designed for soluble drugs. Essential oils are volatile and hydrophobic, and no internationally accepted standard exists for them [12]. Emulsification method alone changes measured antimicrobial activity, with Gram-negative bacteria least susceptible [46]. The studies in Table 2 handle this differently: dimethyl sulfoxide (DMSO) to a final concentration of 0.05% or less [30], a 5% Tween 60 stock [32], or no stated final solvent concentration [33]. Units are the next obstacle: µL/mL [31], % v/v [32], mg/mL and µg/mL [30]. Converting a volume-based oil MIC to mass units requires a density that is seldom reported, so cross-study comparison needs an assumption. Diffusion assays, used alone in the Libyan studies, measure diffusibility as much as potency. In the *Arbutus pavarii* study the mean zone of about 9 mm carried a standard deviation of about 7 mm, which suggests that many isolates produced no zone at all [29].

5.4. D4: Interpreting potency, selectivity and synergy

Two conventional criteria frame potency. For crude extracts, MIC or half-maximal inhibitory concentration (IC_{50}) values above about 100 µg/mL, and for pure compounds values above about 25 µM, are not considered a convincing in vitro proof of concept, and cytotoxicity should be measured in parallel [47,48]. Tables 2 and 3 show how few North African findings clear that bar on their own. The thyme oil MICs (312–1250 µg/mL) are 3 to 12 times the extract criterion, and carvacrol at 64–128 µg/mL equals 0.43–0.85 mM, 17 to 34 times the compound criterion (molecular mass 150.2 g/mol). The Moroccan lavender oil MICs of 0.39–3.125 µL/mL correspond to roughly 0.35–3 mg/mL, assuming a density near 0.9–1.0 g/mL, and the Egyptian cinnamon oil MICs of 0.25–2% v/v to roughly 2.5–20 mg/mL on the same assumption. Only the ethanolic clove extract (MBC 0.04–0.125 mg/mL) approaches the criterion, and in that study the comparator imipenem was active at a lower concentration still.

The case for activity therefore rests on synergy at low concentrations, and here interpretation needs care. A fractional inhibitory concentration index (FICI) of 0.5 or below is the conventional synergy cut-off, with values above 0.5 up to 4 read as indifference

[49]. A synergy label is not the same as restored susceptibility. In the Tunisian study, thyme oil lowered the imipenem MIC for the twelve isolates to 0.5–128 µg/mL; seven fell to 2 µg/mL or below, the susceptible range of the European Committee on Antimicrobial Susceptibility Testing (EUCAST) for *A. baumannii*, while five stayed above 4 µg/mL, including two at 64 and 128 µg/mL [30]. The corresponding carvacrol combinations reached 2 µg/mL or below in seven isolates and left one at 8 µg/mL. Those carvacrol concentrations in the combinations (2–4 µg/mL) are the most interesting number in the corpus, because they approach the compound-level criterion. FICI values also flatter combinations when the antibiotic MIC is very high (a drop from 2048 to 64 µg/mL yields a low index while leaving the isolate resistant). Selectivity data are absent from the studies in Table 2. By comparison, a bioassay-guided study of pentagalloyl glucose from *Schinus terebinthifolia* against carbapenem-resistant *A. baumannii* reported MICs of 64–256 µg/mL against a keratinocyte IC_{50} of 256 µg/mL, a selectivity window of roughly 1 to 4, and concluded that topical use was the realistic ceiling [50].

5.5. D5: Mechanism and translational depth

Docking and molecular dynamics were used to nominate targets in two of the three studies read in full: guanosine against penicillin-binding proteins 1 and 3 [33] and carvacrol against D-alanine–D-alanine ligase [30]. A calculated binding energy is a hypothesis about a purified enzyme, not evidence that the compound engages that target inside a Gram-negative cell behind an outer membrane and efflux systems. Membrane-active phenolics such as carvacrol, thymol and cinnamaldehyde are also the kind of promiscuous natural products that register activity in many assays for non-specific reasons [15,16], which argues for counter-screens rather than mechanism claims drawn from a single assay type.

Table 3. Appraisal of the three North African studies read in full, by domain.

Domain	Jilani et al. [30] (Tunisia)	Saleh et al. [32] (Egypt)	Mahmoud et al. [33] (Egypt)
D1 Material identity	Met: herbarium voucher; chemotype by GC-MS of the tested oil	Not met: commercial oils; no authentication; composition implausible	Partly: extraction described; market-bought, no voucher; GC-MS of extracts
D2 Isolates	Partly: 12 clinical isolates; carbapenem MIC by broth microdilution; biochemical identification; carbapenemases not typed; *E. coli* control	Partly: 37 imipenem-resistant isolates by broth microdilution; *bla*OXA-51-like PCR; *A. baumannii* 17978 control; carbapenemases not typed	Not met for carbapenem resistance: 7 of 10 imipenem-resistant; six tested selected by phenotype; imipenem killed all at 0.02 mg/mL
D3 Assay	Mostly met: cation-adjusted broth, 10^5 CFU/mL, DMSO ≤0.05%, triplicate; volatility not addressed	Partly: resazurin broth microdilution; 5% Tween 60 stock; MIC in % v/v	Partly: INT colorimetric assay; decimal dilution series; final solvent concentration not stated
D4 Interpretation	Partly: FICI reported; MICs above potency criteria; imipenem restored to susceptible range in 7 of 12; no cytotoxicity	Partly: FICI reported; synergy at mg/mL oil concentrations; no selectivity data	Not met: extract MBC compared with imipenem; docking compared with imipenem
D5 Translation	Docking and 100-ns dynamics; no in vivo or toxicity data	RT-qPCR and time–kill in two strains; no in vivo data	Docking only

CFU, colony-forming units; DMSO, dimethyl sulfoxide; FICI, fractional inhibitory concentration index; GC-MS, gas chromatography–mass spectrometry; INT, iodonitrotetrazolium; MBC, minimum bactericidal concentration; MIC, minimum inhibitory concentration; PCR, polymerase chain reaction; RT-qPCR, reverse transcription quantitative PCR. Domains D1–D5 are defined in Section 2.4 and described in Sections 5.1–5.5.

Table 4. Cross-study summary of how far each appraised study meets domains D1–D5.

Study	D1 Material	D2 Isolates	D3 Assay	D4 Interpretation	D5 Translation
Alwashaish [29]	Partly (HPLC; extract)	Partly (MBL phenotype; not typed)	Not met (disc only)	Not met (zones; no cytotoxicity)	Not met
Jilani [30]	Met (voucher; GC-MS)	Partly (not typed)	Mostly met (CLSI broth)	Partly (FICI; no cytotoxicity)	Partly (docking; no in vivo)
Laktib [31]	Partly (GC-MS)	Met (OXA-23/NDM typed)	Partly (µL/mL units)	Partly (no selectivity)	Not met
Saleh [32]	Not met (commercial; implausible)	Partly (not typed)	Partly (% v/v units)	Partly (mg/mL; no selectivity)	Partly (RT-qPCR; time–kill)
Mahmoud [33]	Partly (no voucher; GC-MS)	Not met (imipenem-susceptible set)	Partly (solvent not stated)	Not met (compared with imipenem)	Not met (docking only)
Mohamed [34]	Partly (pure compound)	Partly (not typed)	Partly (MIC; biofilm)	Partly (no selectivity)	Partly (EM; no in vivo)
Benhadid [36]	Partly (GC-MS)	Partly (per-isolate absent)	Partly (disc; MIC)	Not met (values not given)	Not met
Bekka-Hadji [37]	Met (voucher; GC-MS)	Partly (single OXA-23 strain)	Partly (µL/mL; disc combo)	Not met (disc synergy; no FICI)	Not met
Edziri [38]	Met (voucher; HPLC-MS)	Partly (not typed)	Partly (disc interaction)	Not met (no FICI/selectivity)	Partly (docking)
Jilani [42]	Partly (market; GC-MS)	Partly (mCIM; not genotyped)	Met (CLSI; checkerboard)	Partly (FICI<0.5; no cytotoxicity)	Partly (docking + MD)
Abdel-Halim [51]	Partly (pure compounds)	Met (carbapenemase genotyped)	Partly (enzyme assay)	Partly (no selectivity)	Partly (enzyme; docking)
Abdel-Halim [52]	Partly (pure compound)	Met (NDM/VIM/OXA typed)	Partly (enzyme; qRT-PCR)	Partly (gene expression)	Partly (enzyme; qRT-PCR)

Study	D1 Material	D2 Isolates	D3 Assay	D4 Interpretation	D5 Translation
Mourabiti [63]	Partly (commercial)	Met (carbapenemase producers)	Partly (nitrocefin assay)	Partly (ADMET in silico)	Partly (docking/MD)

Met, criterion largely satisfied; Partly, partially satisfied or partly reported; Not met, not satisfied or not reported in the sources examined. Domains D1 (material), D2 (isolates), D3 (assay), D4 (interpretation) and D5 (translation) are defined in Section 2.4 and Sections 5.1–5.5; study references are as in Table 2.

6. Plants and compounds by evidence level: promising versus untestable

Only one class of candidate, carvacrol- and thymol-rich oils used as adjuvants to carbapenems, currently has a design that others could test and extend; most other claims cannot yet be falsified because the material or the isolates are undefined. To make that distinction explicit, each candidate in the corpus is placed on a four-level scale proposed here (Table 5), adapted from an evidence-calibration ladder and applied to the domains in Section 5. E1 (confirmatory-ready) requires authenticated, chemically defined material, genotyped carbapenem-resistant isolates from more than one clone, reference-method MICs, and selectivity data. E2 (credible lead) requires that material identity and assay design are sound and the activity or synergy is interesting, but isolate typing or toxicity is incomplete. E3 (screening-level) covers positive results whose interpretation is limited by undefined material or isolates, or by diffusion-only data. E4 (hypothesis only) covers computational predictions, multidrug-resistant isolates only, or conflicting data. No candidate reaches E1.

Table 5. Candidates by evidence level, with what would upgrade each.

Candidate	Best available evidence	Level	What would upgrade it
Carvacrol- and thymol-rich Lamiaceae oils (*Thymus vulgaris*, *T. capitatus*, *T. algeriensis*, *Lavandula mairei*, *Origanum glandulosum*) and their constituents	Twelve Tunisian carbapenem-resistant *A. baumannii* isolates: oil MIC 312–1250 µg/mL, carvacrol 64–128 µg/mL, carvacrol 2–4 µg/mL lowering imipenem MICs to the susceptible range in 7 of 12 isolates [30]; Moroccan *L. mairei* oil active against OXA-23/NDM-1 environmental carbapenem-resistant *A. baumannii* [31]	E2	Carbapenemase-typed clinical *K. pneumoniae* and *A. baumannii* of several clones; vapour-loss controls; cytotoxicity and tolerability; a decision on the intended use (adjuvant, topical or environmental)
Carbapenemase-targeting compounds (thymol with celastrol; coumarin)	Meropenem MIC reduced 4–64-fold in carbapenemase-producing *K. pneumoniae* with NDM-1, VIM and OXA genes; enzyme-level inhibition shown [51,52]; polyphenols (quercetin, kaempferol) inhibited KPC-2, NDM-1 and OXA-48 in vitro and in silico [63]	E2	Regional plant sources for the compounds; confirmation with purified enzyme kinetics; toxicity and pharmacokinetics
Cinnamon oil and cinnamaldehyde	Imipenem MIC lowered at least 2-fold in 37 Egyptian carbapenem-resistant *A. baumannii* isolates at oil concentrations of mg/mL [32]; anti-biofilm activity [34]; a Tunisian bark extract was most active against imipenem-resistant isolates [38]; FICI below 0.5 with imipenem in extensively drug-resistant isolates [42]	E3	Authenticated oil with defined cinnamaldehyde content; compound-level testing; concentrations compatible with topical or systemic exposure
Myrtus communis oil and extracts	Reported activity against multidrug-resistant isolates including carbapenemase-positive *K. pneumoniae* in Algeria [36]; a Moroccan oil gave MICs of 2.64 mg/mL for *A. baumannii* and 6.6 mg/mL for *K. pneumoniae* [53]	E3	Per-isolate MICs on characterised carbapenem-resistant isolates; chemotype control
Arbutus pavarii (Libyan endemic)	Mean inhibition zones of about 9 mm with large variance on MBL-positive isolates; catechin and quercetin by HPLC [29]	E3	Broth-microdilution MICs; fractionation; conservation-compatible sourcing
Syzygium aromaticum clove extracts (Egypt); pulegone-rich *Mentha pulegium* and *Artemisia herba-alba* oils (Algeria)	Ethanol-extract MBC 0.04–0.125 mg/mL against isolates not shown to be carbapenem-resistant [33]; disc-diffusion synergy of pulegone-rich oil with imipenem and amikacin against an OXA-23 *A. baumannii* strain [37]	E3–E4	Isolates defined as carbapenem-resistant; authenticated material
Docking-derived claims (guanosine, carvacrol against single enzymes)	Binding energies and molecular dynamics [30,33]	E4	Target-engagement data in whole cells; resistant-mutant mapping

E1–E4, evidence levels defined in Section 6; FICI, fractional inhibitory concentration index; MIC, minimum inhibitory concentration; NDM, New Delhi metallo-β-lactamase; OXA, oxacillinase; VIM, Verona integron-encoded metallo-β-lactamase.

Three observations follow. First, the one E2 group is also the best-explained chemically. Carvacrol and thymol are membrane-active phenols whose behaviour is well characterised, which makes them useful as adjuvants in a microplate but also means their activity is expected across many organisms; the question for carbapenem-resistant *A. baumannii* and *K. pneumoniae* is not whether they inhibit growth but whether a safe, deliverable concentration does something a carbapenem cannot do alone. The Tunisian combination data are interesting because the carvacrol concentrations (2–4 µg/mL) are low, and unconvincing as a therapeutic claim because 5 of 12 oil combinations left imipenem MICs above the resistant breakpoint.

Second, the plants that dominate North African ethnobotany are almost absent from the carbapenem-resistance literature. Pomegranate, mastic (*Pistacia lentiscus*), *Nigella sativa*, henna and wormwood are widely used, yet the search retrieved no carbapenem-specific MIC data for them; the one comparative report used well diffusion on unspecified Gram-negative clinical isolates and recorded zones of 11–17 mm for *N. sativa* extract and 16–32 mm for henna [54]. Traditional use is a reason to look, not evidence of anti-carbapenem activity. In a Moroccan ethnobotanical survey the most cited species were *Origanum compactum*, rosemary and *Mentha pulegium*, and digestive disorders accounted for 40% of treated

conditions, not nosocomial infection [5].

Third, claims become "untestable" for three recurring reasons: the material cannot be re-made (no voucher, unknown supplier batch, implausible composition), the isolates cannot be re-identified (described only as multidrug-resistant, or carbapenem-resistant by diffusion alone), or the evidence is a calculation rather than an observation. A claim of any of these kinds may be correct, but a laboratory elsewhere cannot confirm or refute it, and that is the practical meaning of the E3 and E4 levels.

7. Synergy, efflux and anti-virulence claims

Synergy, efflux inhibition and anti-virulence claims are the most clinically ambitious in the corpus and the least secure, because they are measured at sub-inhibitory concentrations of incompletely defined material in a handful of isolates. They fall into five groups, summarised in Table 6 with the assay that would confirm each.

Table 6. Mechanistic claims in the North African literature and the evidence needed to confirm them.

Claim	Evidence in the corpus	Limits	Confirmatory evidence
Potentiation of a carbapenem	Checkerboard FICI at or below 0.5 for thyme oil and carvacrol with imipenem [30]; cinnamon oil with imipenem [32,42]	Index flatters combinations when the antibiotic MIC is very high; volatile agents may be lost from plates; restoration of susceptibility is incomplete in many isolates	Time–kill curves on typed isolates; agent concentration under which the isolate reaches a susceptible category; resistant-mutant selection
Efflux inhibition	Imipenem resistance reversed by CCCP in 26 of 37 isolates; cinnamon oil lowered *adeB*, *adeC*, *adeJ* and *adeK* transcripts in two strains [32]	CCCP is a non-specific proton-gradient uncoupler; transcript changes at near-inhibitory oil concentrations may reflect general stress; two strains only	Dye-accumulation assays; pump-deletion or overexpression strains; transcript data on sub-inhibitory exposure
Carbapenemase inhibition	Reduced hydrolytic activity in crude periplasmic extract (coumarin; celastrol) and lower carbapenemase transcripts (coumarin) in NDM-1/VIM/OXA-producing *K. pneumoniae* [51,52]	Crude extracts rather than purified enzymes; metallo-β-lactamase focus although OXA-type enzymes dominate regionally (Table 1); docking energies are predictions	Purified-enzyme kinetics with OXA-23, OXA-48, NDM and VIM; comparison with a reference inhibitor
Down-regulated capsule or virulence genes	Tea tree and thyme oils with amikacin lowered *wcaG*, *rmpA*, *magA*, *uge* and *wabG* transcripts in multidrug-resistant *K. pneumoniae* [39]	Transcript level only; isolates multidrug- rather than carbapenem-resistant	Capsule quantification; serum-resistance and animal virulence assays
Anti-biofilm activity	Cinnamaldehyde inhibited biofilm formation by 49.5–71.2% at ½ MIC in Egyptian *A. baumannii* [34]; *Origanum glandulosum* nanoemulsion active at sub-MIC [35]	Biomass stains cannot separate lower growth from lower matrix; preformed biofilm eradication seldom tested	Preformed-biofilm eradication on relevant surfaces; viability counts

CCCP, carbonyl cyanide *m*-chlorophenyl hydrazone; FICI, fractional inhibitory concentration index; MIC, minimum inhibitory concentration; NDM, New Delhi metallo-β-lactamase; OXA, oxacillinase; VIM, Verona integron-encoded metallo-β-lactamase.

Two points deserve emphasis. First, the most direct mechanism tests in the corpus measured carbapenemase hydrolysis rather than inferring it from docking [51,52], and these studies used genotyped carbapenemase producers. They are methodologically ahead of the essential-oil studies, but they used compounds that are not specific to North African plants, and the enzymes inhibited were mostly metallo-β-lactamases, with only computational and nitrocefin data so far extending to OXA-48 [63], whereas OXA-23 and OXA-48 dominate the regional isolates in Table 1. Whether any plant constituent inhibits OXA-type carbapenemases in whole cells is therefore the open question with the most direct clinical bearing.

Second, a synergy result is a statement about concentrations, and the clinically relevant question is whether the required concentration of the plant agent is achievable and tolerable. The Tunisian authors point to the approval of carvacrol as a food additive [30], but food-additive status concerns ingestion at flavouring levels, not systemic exposure, and it says nothing about intravenous, inhaled or wound-bed delivery. The Egyptian cinnamon-oil combinations were active at roughly 3 mg/mL of oil (0.31% v/v in the time–kill assays) [32], which would be a topical, not a systemic, concentration. A durable test of any potentiator is whether resistance emerges against it: serial-passage experiments with pentagalloyl glucose produced no resistant mutants over 21 days [50], and no North African study reports the equivalent for an oil or extract.

8. From the bench to the outbreak: translational gaps

The outbreak setting favours non-systemic uses of plant agents, such as surface and environmental decontamination, skin and wound care, and topical delivery, and these are the uses with the weakest evidence in the corpus. The epidemiological data in Section 3 show why. In a Tunisian intensive care study 14% of sampled items and 15% of staff hands carried carbapenem-resistant *A. baumannii* and patient isolates shared extensive genomic similarity with the environmental strains [24], and NDM-1/OXA-23 producers have been recovered from inanimate hospital surfaces in Algeria [25]. Device biofilms are part of the same problem: in a Misurata study, *K. pneumoniae* and *A. baumannii* recovered from urinary catheters were predominantly strong biofilm producers [66], the setting in which the sub-inhibitory anti-biofilm effects noted in Section 7 would have to act. The Moroccan lavender-oil study used environmental isolates from two ICUs [31], which fits that logic. Yet no study in the corpus compares a plant agent with an established disinfectant on contaminated

surfaces or skin, so the leading plausible use has no comparator data. Systemic use faces a larger gap. The carbapenem-potentiation concept assumes that the plant agent can be delivered at a concentration close to its in vitro effective level, which for most oils in Table 2 is in the mg/mL range. The in vivo evidence from North African laboratories against carbapenem-resistant organisms is limited to a cyanobacterial extract in a murine pneumonia model with carbapenem-resistant *K. pneumoniae* (MIC 500–1000 µg/mL) [55] and a biosynthesised zinc oxide nanoparticle in a rat burn-wound model with carbapenem-resistant *A. baumannii* (MIC 250–1000 µg/mL) [56]. Neither is a plant. A low-cost step between microplate and mammal is the *Galleria mellonella* larval model, which has been used to test antimicrobial combinations against carbapenem-resistant *K. pneumoniae* [57], has an established protocol for antimicrobial screening [58], and suits laboratories without large animal facilities [59,60].

Tolerability is the least developed part of the literature. Essential oils and their phenolic constituents irritate tissue at the concentrations at which they inhibit Gram-negative bacteria, and tolerability can be profiled with simple assays. A recent study of oregano oil, carvacrol and thymol, for instance, used corneal opacity, chorioallantoic membrane and haemolysis assays and found no corneal irritation above the MIC but mild to moderate irritation in the membrane assays [61]. None of the North African studies in Table 2 reports comparable data. Formulation is a further variable: the Algerian *Origanum glandulosum* oil was more active than its nanocapsules and nanoemulsion against planktonic cells, although the nanoemulsion was more potent against biofilm at sub-inhibitory concentrations [35].

A final consideration is access. In the Tunisian hospital collection described above, in vitro activity remained only for eravacycline and aztreonam–avibactam, neither of which is available for clinical use in the country [26], while current treatment guidance for carbapenem-resistant *A. baumannii* relies on newer agents such as sulbactam–durlobactam and cefiderocol [62]. That gap explains the interest in alternatives. It is also a reason to hold plant-derived candidates to the same standard of evidence as any other, not to a lower one, and to keep them from displacing infection prevention, given the patient, staff and environmental reservoirs documented above.

9. Limitations

This is a structured narrative review, not a systematic review, and its limits follow from that design. The search combined a scholarly index (OpenAlex and Semantic Scholar records, accessed through a literature-search tool) on 9 October 2026 with a structured PubMed search on 23 October 2026, but did not cover PubMed, Scopus, Web of Science or regional repositories such as African Journals Online. Studies in regional journals, theses, and French- or Arabic-language reports are therefore likely under-represented, which matters for Algeria, Morocco and Tunisia in particular. No protocol was registered, and screening, extraction and appraisal were done by one reviewer without duplicate checking or a formal risk-of-bias instrument.

The appraisal framework (domains D1–D5 and evidence levels E1–E4) is proposed here and has not been validated. The levels are structured judgements, and a different reviewer could place a borderline study differently. Three studies were read in full (Table 3); others were appraised from abstracts and, for some, accessible text, so details such as voucher specimens or carbapenemase genotyping reported only in a methods section may have been missed. Table 2 entries for those studies should be read as minimum statements of design quality. Conversions from volume-based to mass-based concentrations assume a density of 0.9–1.0 g/mL, which the original studies did not report.

The corpus itself carries bias. Positive reports dominate, null results are rare, and the studies appear in journals with different editorial standards, which this review did not assess. The plant-extract literature is also moving quickly, and studies published in the weeks before the search date may not yet be indexed.

10. Future directions and a minimum reporting standard

The most useful next step is not another screen of extracts but a shared, typed set of isolates tested against authenticated, chemically defined material by a common protocol. The field has most of the components already. North African laboratories routinely characterise carbapenemase genes and clones (Table 1), several groups have herbarium and GC-MS capacity [30,31], and the assay formats are cheap. What is missing is coordination. The priorities below are grouped by what they would change.

10.1. Theory: what is the plant agent supposed to do?

Each study should state the intended role before testing: an adjuvant that restores a carbapenem, a topical or environmental antimicrobial, or an anti-virulence agent. The role dictates the assay, the acceptable concentration and the comparator. For adjuvants, the endpoint is not an FICI but the antibiotic MIC category reached at a tolerable adjuvant concentration. For topical or environmental use, the comparator is an established antiseptic or disinfectant, and the endpoint is log-reduction on a relevant surface. Whether carvacrol- and thymol-rich oils act on carbapenemases, on the outer membrane or on both is unresolved, and a comparison of whole oils with their pure phenols in the same assay (a carvacrol oil, a thymol oil, and each pure compound at matching concentration) would show how much of the activity is explained by the major constituent.

10.2. Methods: the design changes that matter most

Four changes would raise most studies by one evidence level. First, authenticate and chemotype the material (voucher, plant part, origin, distillation or extraction method, GC-MS of the tested batch). Second, characterise isolates by species, carbapenem MIC and carbapenemase gene, and report the sequence type for a subset, using at least ten non-duplicate isolates from at least two clones. Third, use reference-method broth microdilution adapted for volatile and hydrophobic agents (sealed plates, a documented solvent or emulsifier at a non-inhibitory final concentration, MICs in mass units with the density stated), with at least three independent experiments. Fourth, add selectivity and time–kill data to any synergy claim, and test whether resistance emerges on serial passage. The larval *Galleria mellonella* model is the realistic first in vivo step in resource-limited laboratories [58,59].

10.3. Constructs: regional plants and the OXA problem

The regional plants most used in traditional medicine, among them pomegranate, mastic, *Nigella sativa*, henna, wormwood and *Arbutus pavarii*, lack carbapenem-specific MIC data. Bioassay-guided fractionation with a selectivity measure, as in the pentagalloyl glucose work [50], is the model to follow. Mechanistic work should address OXA-23 and OXA-48, which dominate the regional isolates, because most enzyme-level inhibition data so far concern metallo-β-lactamases, with OXA-48 addressed only by computational and nitrocefin evidence [51,52,63]. Efflux claims need accumulation assays and pump-deficient strains, not transcript data alone.

10.4. Context: obstacles and how to address them

Three obstacles recur. Sequence typing and GC-MS are unevenly available, which argues for shared reference facilities and exchange of typed isolate panels with deposited sequence data. Wild harvest of endemic species such as *Arbutus pavarii* raises conservation questions that cultivation or sustainable-sourcing agreements should address before scale-up. Finally, negative results rarely reach print. The Libyan study showing no activity for ivy extracts [40] illustrates the value of reporting them, and a regional register of tested materials and outcomes would reduce duplication. Once at least five studies meet the E2 standard on comparable isolates, a registered systematic review with meta-analysis of MICs becomes feasible; at present heterogeneity in material, isolates, units and methods prevents pooling.

10.5. A proposed minimum reporting standard

Table 7 condenses the appraisal domains into a checklist that authors, reviewers and editors can apply. It builds on the ConPhyMP guidelines for extract characterisation [14] and on reference methods for MIC determination and synergy testing [45,49], and adds the isolate and interpretation items specific to carbapenem-resistant organisms.

Table 7. Proposed minimum reporting standard for studies of plant-derived agents against carbapenem-resistant Gram-negative bacteria.

Domain	Items to report
D1 Material	Accepted species name; voucher number and herbarium; plant part, collection site and date; extraction or distillation method and solvent; GC-MS or LC-MS profile of the tested batch, with identification method; for commercial products, supplier, lot number and batch profile; ConPhyMP extract type
D2 Isolates	Species identification method; source, ward and date; meropenem and imipenem MIC by broth microdilution; carbapenemase genes (OXA-23-like, OXA-24/40-like, OXA-48-like, NDM, VIM, IMP, KPC); sequence type for a subset; at least ten non-duplicate isolates from at least two clones; reference strains of the same species; per-isolate MICs in a supplementary table
D3 Assay	Reference method and version (CLSI M07, EUCAST/ISO 20776-1); medium and inoculum; solvent or emulsifier and final concentration, with a solvent-only control; handling of volatile agents (sealed plates); MIC and MBC in µg/mL (and µM for pure compounds), with density stated for oils; positive-control antibiotic with quality-control ranges; at least three independent experiments
D4 Interpretation	MIC compared with potency criteria (about 100 µg/mL for extracts, about 25 µM for compounds); cytotoxicity and selectivity index; for synergy, FICI with the threshold used, the resulting antibiotic MIC category and the adjuvant concentration, confirmed by time–kill
D5 Translation	Mechanistic claims labelled as hypotheses unless supported by an orthogonal assay; serial-passage resistance data; in vivo model with exposure data; negative and null results reported

CLSI, Clinical and Laboratory Standards Institute; EUCAST, European Committee on Antimicrobial Susceptibility Testing; FICI, fractional inhibitory concentration index; GC-MS, gas chromatography–mass spectrometry; IMP, imipenemase; ISO, International Organization for Standardization; KPC, *Klebsiella pneumoniae* carbapenemase; LC-MS, liquid chromatography–mass spectrometry; MBC, minimum bactericidal concentration; MIC, minimum inhibitory concentration; NDM, New Delhi metallo-β-lactamase; OXA, oxacillinase; VIM, Verona integron-encoded metallo-β-lactamase; ConPhyMP, Consensus statement on the Phytochemical Characterisation of Medicinal Plant extracts.

11. Conclusions

The evidence that North African medicinal plants act on carbapenem-resistant *K. pneumoniae* and *A. baumannii* is, at present, a set of promising screens rather than a body of confirmed findings. Resistance in the region is enzyme-mediated, clonal and carried by environmental and staff reservoirs (Table 1). Against that background, carvacrol- and thymol-rich oils from *Thymus*, *Lavandula* and *Origanum* inhibit *A. baumannii* in vitro, and in one Tunisian study carvacrol at 2–4 µg/mL lowered imipenem MICs to the susceptible range in seven of twelve isolates while five did not reach it. Their stand-alone MICs exceed conventional potency criteria by several-fold to two orders of magnitude, no study reported cytotoxicity, and few reported carbapenemase genes for the tested isolates.

The literature disagrees less about results than about what a result means, because materials, isolates, units and methods differ too much to compare. The contribution of this review is a five-domain

appraisal, a four-level evidence scale on which no candidate reaches confirmatory readiness, and a minimum reporting standard (Table 7). On that scale one group of candidates, carvacrol- and thymol-rich oils as carbapenem adjuvants, is a credible lead that others can test; most other claims cannot be falsified as published because the plant material or the isolates are undefined.

The path forward is concrete: a shared set of genotyped isolates, authenticated and chemically defined material, reference-method testing adapted for volatile agents, selectivity and larval-model data, tests against OXA-type carbapenemases, and head-to-head comparison with established disinfectants for the environmental and topical uses that the outbreak setting makes most plausible.

Declarations

Author contributions: S.M. Al-Aswad: Conceptualization, Methodology, Investigation (literature search, screening and data extraction), Formal analysis, Data curation, Visualization, Writing – original draft, Writing – review & editing, Project administration. A.M. Abobaker: Resources (provision of literature sources), Writing – review & editing (revision, formatting and proofreading). All authors read and approved the final manuscript.

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Data availability: No new data were generated. The sources analysed are listed in the References, and the study-level extractions are given in Tables 1–7.

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