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Anti-Virulence Potential of Nanoformulated Cinnamomum bark Against Multidrug-Resistant Uropathogenic Escherichia coli

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Abstract

Urinary tract infections (UTIs) are a significant health issue in the global community, with *Uropathogenic Escherichia coli* (UPEC) as its primary cause. The increasing issue of antimicrobial resistance, particularly in multidrug-resistant (MDR) UPEC strains, has necessitated a search to find alternative methods of treating infections other than normal medicines. The promising approach has been taken to anti-virulence therapy which focuses on the mechanisms by which bacteria cause disease but not on the bacteria directly, imposing no direct selective pressure on them. Simultaneously nanotechnology offers new methods of making natural products more functional by increasing their bio availability and delivering it to the appropriate location. This comprehensive review unites all our current understanding of the pathogenesis of UPEC and emphasizes the molecular pathways of type 1 fimbriae (FimH) and curli (CsgD-regulated) in adhesion and biofilm formation. We comprehensively study the phytochemical structure and the antibacterial properties of *Cinnamomum* bark with a special focus on its anti-virulence activity against UPEC. We also examine how we can green manufacture the iron oxide nanoparticle using plant extracts and the reason as to why we want to make *Cinnamomum* nanoformulated. Phytochemicals from cassia. Anti-virulence practices, bioactive plants, and nanotechnology should be combined to provide a new approach towards managing MDR UPEC infections. This discussion outlines knowledge gaps, and provides potential future research directions in the development of effective, resistance-preventive treatment regimens.

Keywords: Antibiotic resistance, *Cinnamomum*, CsgD, FimH, *Uropathogenic Escherichia coli* (UPEC), Iron oxide nanoparticles

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Introduction

Urinary tract infections (UTIs) are among the most prevalent bacterial illnesses in clinical practice, impacting almost 150 million individuals globally each year [1,2]. The clinical spectrum extends from asymptomatic bacteriuria to severe, life-threatening urosepsis, resulting in considerable morbidity and economic burden [3]. *Uropathogenic Escherichia coli* (UPEC) is responsible for 75-95% of community-acquired urinary tract infections (UTIs) and 40-50% of healthcare-associated cases, making it the main cause of these infections [4]. The advent and global spread of antimicrobial resistance (AMR) has made it harder to treat UTIs. Multidrug-resistant (MDR) UPEC bacteria, especially those that make extended-spectrum β-lactamases (ESBLs) and carbapenemases, have few treatment choices and are linked to higher rates of treatment failure, longer hospital stays, and higher death rates [5,6]. The World Health Organization has recognized ESBL-producing *Enterobacteriaceae* and carbapenem-resistant E. *E. coli* is one of the most important pathogens that needs immediate study and development of novel antibiotics [7]. The AMR threat has sparked interest in alternative therapeutic approaches that bypass the constraints of traditional antibiotics. Anti-virulence therapy focuses on the mechanisms that make bacteria pathogenic instead of the processes that are necessary for development. This has the potential benefit of disabling pathogens without creating the selection pressure that leads to the evolution of resistance [8]. UPEC pathogenicity depends on a complex set of virulence factors, such as adhesins (type 1 fimbriae, P fimbriae, curli), toxins (hemolysin, cytotoxic necrotizing factor), methods for getting iron, and the ability to build biofilms [9,10]. Medicinal plants have long been source of vital treatment compounds, as nearly 80 percent of the world's population relies on traditional medicine based on plants as their primary healthcare source [11]. *Cinnamomum cassia* (L.) J. Presl or Chinese cinnamon is an aromatic evergreen tree, the bark of which has been used in ancient medicine over thousands of years [12]. A range of bioactive secondary metabolites, including cinnamaldehyde (the major constituent), phenolic acids, proanthocyanidins, and coumarins, have been identified through phytochemical analyses and have shown various biological activities, including antimicrobial, anti-inflammatory, and antioxidant activity [13,14]. Nanotechnology has turned out to be a ground breaking technology in enhancing the medicinal values of natural compounds. Nanoparticles, defined as materials of at least 1-100 nanometers in size, possess physicochemical properties unique to them such as a high surface to volume ratio, quantum effects and high reactivity [15]. Green nanoparticles production through plant extracts offers environmental sustainability, low cost, and biocompatibility and plant phytochemicals are as reducing and capping agents [16]. Iron oxide nanoparticles (Fe_2O_3 and Fe_3O_4) have received considerable interest in the biomedical field due to their superparamagnetic properties, biocompatibility and magnetic responsiveness [17]. This in-depth review ties all that we have known regarding the disease-causing nature of UPEC and how *C. Cassia* can prevent its propagation. *C. Cassia* phytochemicals and how green-synthesized nanoparticles are used to enhance the efficacy of treatments. We critically examine the molecular pathways of crucial virulence factors (FimH, CsgD) and the phytochemical composition of *C. Cassia* and the rationale of nanoformulation. This review aims to enable the development of novel anti-virulence interventions against MDR UPEC infections by identifying gaps in the body of knowledge and recommending research directions into the future.

Uropathogenic *Escherichia coli* (UPEC): Pathogenesis and Determinants of Virulence.

UPEC Pathogenic Cycle.

The pathophysiology of UPEC works in a premeditated, multi-step cycle (Figure 1) that enables it to colonize, remain in the urinary system, and spread [9,18]. The colonization begins in the vaginal introitus and

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periurethral region and the bacteria migrate to the bladder along the urethra. In the bladder, UPEC meets the glycosaminoglycan (GAG) layer that covers the uroepithelium and starts to stick to the surface umbrella cells using type 1 fimbriae [19].

After adhering, UPEC penetrate bladder epithelial cells via a zipper-like mechanism that entails FimH-mediated alteration of the host cell cytoskeleton [20]. After being taken in, bacteria break out into the cytoplasm and quickly multiply, creating intracellular bacterial communities (IBCs)—biofilm-like structures made up of thousands of bacteria surrounded by a polysaccharide matrix [21]. When bacteria near the edge spread out by fluxing after IBC maturation, they assume filamentous shapes, which render them difficult to ingest by neutrophils [22].

Some bacteria that infiltrate cells become inactive inside superficial epithelial cells, creating quiescent intracellular reservoirs (QIRs) that stay inside membrane-bound compartments and are not killed by antibiotics or immune cells [23]. When epithelial cells die or the immune system is weakened, bacteria in QIRs can become active again, leading to recurrent infections, typically with the same strain that caused the first one [24]. In individuals with weakened host defenses, UPEC can ascend to the kidneys, resulting in pyelonephritis and potentially distributing hematogenously to induce urosepsis [25].

Type 1 Fimbriae and FimH Adhesin

Type 1 fimbriae are hair-like surface appendages that are 1–2 μm long and 7 nm wide. They are made up of repeated protein subunits that are expressed by the fim operon (fimB-E-A-I-C-D-F-G-H) [26]. The FimH adhesin, located at the tip of the fimbriae, binds to uroplakin receptors to make it easier for mannose-sensitive cells to stick to uroepithelial cells [27]. FimH is a protein made up of 279 amino acids and two domains: an N-terminal lectin domain that contains the mannose-binding pocket and a C-terminal pilin domain that holds the adhesin to the fimbrial shaft [28].

One of the most interesting things about FimH is that its adherence depends on shear, which means that UPEC can stick tightly even when urine is flowing, but it can also detach to spread [29]. When shear stress is low, FimH takes on a low-affinity shape and quickly breaks apart. When shear stress is strong, mechanical force causes domain separation and a change in shape to a high-affinity shape, which greatly slows down the pace of dissociation [30].

In addition to adhesion, FimH facilitates various pathogenic functions, including invasion (activating host cell signaling through FAK and PI3-kinase), biofilm formation (crucial for initial biofilm development), intracellular survival (regulating host cell apoptosis), and immune modulation (interacting with TLR4) [31,32]. The fimH gene is very similar in most UPEC isolates, and some variations are linked to higher virulence and biofilm production, which makes FimH a good target for treatment [33].

The regulation of Curli Fimbriae and CsgD

Curli is thin, clumping fibers that look like amyloid and are made by *E. coli* and related *Enterobacteriaceae*, which make up the main protein part of the extracellular matrix in biofilms [34,35]. Two operons that are transcribed in different directions control curli biogenesis: csgDEFG (which controls and assembles components) and csgBAC (which makes structural components) [36]. The csgD gene codes for a transcriptional regulator with 216 amino acids (FixJ/LuxR family) that controls biofilm development [37]. CsgD takes in a lot of different environmental signals, such as temperature (ideal ≤30°C), osmolarity (produced by

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low osmolarity), oxygen (induced under microaerophilic conditions), nutrients, and stress signals [38]. When activated, CsgD attaches to the csgBAC promoter, which starts the transcription of the main curli subunit (CsgA) and the nucleator protein (CsgB) [39]. The assembly of curli happens by a nucleation-precipitation process. Unfolded CsgA and CsgB are secreted through the CsgG outer membrane channel, with CsgE functioning as a periplasmic chaperone and CsgF helping CsgB integrate and work [40]. CsgB on the surface starts the process of CsgA polymerization into β-sheet-rich amyloid fibers, which make up the curli structure [41]. Curli regulated by CsgD help form biofilms (which are important for mature biofilm architecture), stick to abiotic surfaces, extracellular matrix proteins, and host cells, activate the immune system (recognized by TLR2), resist antimicrobial peptides and complement, and form persisters [42,43]

UPEC Biofilm Formation

Biofilms are organized groups of microbes that are held together by a matrix of extracellular polymeric substances (EPS) that the microbes make themselves. This helps bacteria survive environmental stress, host immune defenses, and antimicrobial treatments [44]. Biofilms are responsible for over 80% of chronic bacterial infections, including catheter-associated UTIs (CAUTI), which are the most prevalent type of infection that happens in healthcare settings [45]. Biofilm development occurs in five sequential stages: (i) reversible attachment mediated by physicochemical forces and surface structures (flagella, type 1 fimbriae); (ii) irreversible attachment characterized by upregulation of adhesins and loss of motility; (iii) microcolony formation and initial EPS production; (iv) biofilm maturation, which involves the establishment of three-dimensional architecture with water channels and metabolic heterogeneity; and (v) detachment and dispersal via active (enzymatic degradation) or passive (shear stress) mechanisms [46,47].

The EPS matrix is made up of 85–90% of biofilm biomass and is a complex mix of polysaccharides (cellulose, poly-β-1,6-N-acetylglucosamine [PGA]), proteins (curli, type 1 fimbriae, flagella), extracellular DNA (eDNA), lipids, and ions [48]. Biofilm production is controlled by complex networks that include quorum sensing systems (AI-2 and AI-3), two-component systems (EnvZ/OmpR, CpxA/CpxR, and QseBC), global regulators (CsgD, H-NS, and Crp), and cyclic-di-GMP, which is the second messenger [49,50].

UPEC's Resistance to Antimicrobials

Worldwide Impact and Epidemiology

Antimicrobial resistance (AMR) is one of the most serious public health problems of the 21st century. In 2019, it was responsible for an estimated 1.27 million fatalities and 4.95 million deaths [51]. According to forecasts, drug-resistant diseases might kill 10 million people a year by 2050, and the total economic cost could exceed $100 trillion USD [52]. *Escherichia coli* is the primary pathogen responsible for AMR-related fatalities, indicative of its widespread occurrence and rising resistance rates [51].UPEC isolates are becoming more resistant to antibiotics that are widely used. In community-acquired UTIs, the resistance rates to trimethoprim-sulfamethoxazole are between 20% and 40%, fluoroquinolone resistance is between 10% and 30%, and third-generation cephalosporin resistance (ESBL-associated) is between 5% and 15% [53,54]. Multidrug resistance (MDR), which means resistance to three or more types of antibiotics, affects 40–60% of healthcare-associated UTIs. ESBL development impacts 20–40% of cases, while carbapenem resistance affects 5–15% [55].

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How Resistance Works

UPEC utilize many molecular methods to circumvent antibiotic action [56,57]: enzymatic inactivation is the most common mechanism, especially the synthesis of β-lactamase. Extended-spectrum β-lactamases (ESBLs), mostly from the CTX-M, TEM, and SHV families, break down penicillins, cephalosporins, and monobactams but can still be stopped by β-lactamase inhibitors [58]. Carbapenemases (class A KPC, class B NDM/IMP/VIM, class D OXA-48) hydrolyze carbapenems, which means that there aren't many ways to treat them [59]. The worldwide spread of NDM-1 (New Delhi metallo-β-lactamase-1) on promiscuous plasmids has led to the emergence of really pan-drug-resistant strains when it interacts with plasmid-mediated colistin resistance (mcr genes) [60]. Target modification transpires via mutations in genes that encode antibiotic targets, such as DNA gyrase (gyrA, gyrB) and topoisomerase IV (parC, parE), which transfer fluoroquinolone resistance, as well as ribosomal alterations that impart aminoglycoside and tetracycline resistance [61]. Loss of porins (OmpF, OmpC) makes it harder for antibiotics to get into cells, which lowers their absorption [62]. Efflux pumps, especially the RND family AcrAB-TolC, move different types of antibiotics out of cells, which leads to MDR phenotypes [63].

Clinical Consequences

The confluence of several resistance pathways in UPEC isolates presents considerable treatment problems. Infections caused by ESBL-producing UPEC are linked to delayed proper treatment, longer hospital stays, and greater death rates than infections caused by strains that are not resistant [64]. Carbapenem-resistant E. Infections caused by *E. coli* have few treatment choices, and typically require combination therapy with last-resort drugs (colistin, tigecycline, fosfomycin) that are quite toxic [65]. The rise of plasmid-mediated colistin resistance (mcr genes) puts the last line of defense against organisms that are resistant to carbapenems at risk [66].

Medicinal Plants and *Cinnamomum cassia*

Phytochemical Diversity and Antimicrobial Mechanisms

Medicinal plants generate several secondary metabolites that fulfill ecological roles (defense, attraction, signaling) and possess medicinal qualities [67]. Major classes of phytochemicals are phenolics (phenolic acids, flavonoids, tannins, and coumarins) made through the shikimate and phenylpropanoid pathways; terpenoids (monoterpenes, sesquiterpenes, diterpenes, triterpenes, and saponins) made through the mevalonate and MEP pathways; and alkaloids made from amino acids [68]. Plant-derived compounds exhibit antimicrobial activity through various mechanisms, including membrane disruption (lipophilic compounds insert into lipid bilayers), cell wall interference (phenolics inhibit peptidoglycan synthesis), protein/enzyme inhibition (tannins precipitate proteins), nucleic acid interactions (alkaloids intercalate into DNA), quorum sensing inhibition, efflux pump inhibition, and anti-virulence mechanisms (inhibition of adhesion, biofilm formation, and toxin production) [69,70].

Cinnamomum cassia: A Look at Its Plants and Chemistry

Cinnamomum cassia (L.) J. Presl (also known as *Cinnamomum aromaticum Nees*) is an evergreen tree that grows naturally in southern China and is grown in many parts of Southeast Asia [71]. The bark, which is the main medicinal element, has 1–4% volatile oils, with trans-cinnamaldehyde (75–90%) being the main one. Other minor components include cinnamyl acetate, coumarin, eugenol, and others [72]. Cinnamomum contains phenolic

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chemicals. Cinnamic acid, p-coumaric acid, caffeic acid, ferulic acid, gallic acid, vanillic acid, and protocatechuic acid are all found in cassia bark [73]. Proanthocyanidins (condensed tannins) exist in oligomeric to polymeric forms and help fight bacteria and free radicals [74]. Diterpenes (cinncassiols, cinnzeylanine), triterpenes, polysaccharides (arabinoxylans, glucans), and minerals are some of the other parts [75].

Antimicrobial and Anti-virulence Functions

C. Cassia extracts and isolated chemicals demonstrate extensive antibacterial efficacy against both Gram-positive and Gram-negative bacteria, fungi, and viruses [76]. Minimum inhibitory concentrations (MICs) against *E. coli* range from 250-2000 µg/mL depending on extract type, strain susceptibility, and assay conditions [77]. The range of 250–2000 µg/mL for *E. coli* depends on the type of extract, the strain's susceptibility, and the circumstances of the assay [77]. Cinnamaldehyde, the main bioactive component, has antimicrobial effects through a number of different ways: it breaks down membranes (increasing permeability and ion leakage), stops cell division (by interfering with FtsZ), stops energy metabolism (by inhibiting glycolytic enzymes), stops quorum sensing (by reducing AI-2 production), stops biofilm formation (by downregulating csgD and fimH), and stops efflux pumps [78,79] .

In addition to direct antibacterial actions, C. Cassia chemicals show that they can fight UPEC's pathogenicity. Cinnamaldehyde diminishes type 1 fimbriae production by downregulating fimH, hence reducing adhesion to bladder epithelial cell [80]. Sub-MIC doses prevent biofilm development by lowering the expression of csgD and csgA, which stops the generation of curli and cellulose and breaks up established biofilms [81]. Cinnamaldehyde also stops the synthesis of hemolysin, which protects red blood cells from being broken down by toxins [82].

Nanotechnology and Eco-Friendly Synthesis

Basic Ideas

Nanotechnology is the study and manipulation of matter at scales ranging from 1 to 100 nanometers, where distinctive size-dependent phenomena facilitate innovative applications [83]. Nanoparticles have different properties than bulk materials. As an example, their surface area-volume ratio (over 30% of the atoms are on the surface) is high, their optical properties vary with their size (surface plasmon resonance), they can be superparamagnetic (in small enough magnetic particles), they are more reactive, and they exhibit quantum effects [84].

Green Synthesis using Plant Extracts

Plant extract-based green syntheses are more eco-friendly, less harmful to human health, and less expensive than conventional physical and chemical methods [85]. Plant phytochemicals such as phenolics, flavonoids, terpenoids, and alkaloids are both reducing agents (change metal ions into nanoparticles) and capping agents (stabilize nanoparticles and prevent their aggregation) [86]. Plant-mediated synthesis involves three stages, namely (i) the activation phase, which involves reduction of metal ions and nucleation, (ii) the growth phase, which involves coalescence of nuclei into larger particles by the action of phytochemicals that control the final size and shape of the particle, and (iii) the termination phase [87].

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Nanoparticles of Iron Oxide.

Magnetite (Fe_3O_4) and maghemite [88] are iron oxide nanoparticles that have been of biomedical interest due to their magnetic properties and biocompatibility. These nanoparticles exhibit superparamagnetism when small enough (less than 20 nm), i.e. they do not retain any remanent magnetism due to the removal of the magnetic field. This prevents their sticking together and makes them applicable in medicine [89].

Plant extracts have been shown to successfully produce nanoparticles of regulated size, shape, and surface chemistry by green manufacture of iron oxide nanoparticles [90]. Phytochemicals diminish Fe^{3+}/Fe^{2+} ions and stabilize the resultant nanoparticles via surface contacts [91]. Characterization of iron oxide nanoparticles utilizes various techniques: UV-Visible spectroscopy (for synthesis confirmation and stability), FTIR (for surface functional groups and capping agents), XRD (for crystal structure, phase composition, and crystallite size), TEM/SEM (for size, morphology, and distribution), AFM (for surface topography), DLS (for hydrodynamic size and zeta potential), and VSM (for magnetic properties) [92].

Nanoformulated Plant Extracts: Reasons and Benefits

Combining plant extracts with nanoparticles has many benefits [93,94]:

1. Better bioavailability (protection from breaking down, better solubility)
2. Controlled release (delivering bioactive chemicals over time)
3. Less harmful (lower doses needed, more targeted)
4. Synergistic effects (the combined actions of nanoparticles and phytochemicals)
5. Better stability (protection against oxidation and photodegradation)
6. Targeted delivery (making the surface work for active targeting)

Nanoformulated plant extracts have shown stronger antimicrobial and anti-virulence effects than free extracts. They have lower MICs, better biofilm inhibition, and better effectiveness against MDR strains [95,96] .

Combining and Looking Ahead

Why Nanoformulated C. Cassia against UPEC

The coming together of anti-virulence methods, *C. Cassia* phytochemicals and nanotechnology provide a strong justification for the development of innovative therapies against MDR UPEC.

1. Focusing on virulence instead of viability potentially diminishes selective pressure for resistance evolution [97].

2. FimH and CsgD are proven molecular targets for anti-virulence intervention, and they are known to play a role in adhesion, invasion, and biofilm formation [98].

3. C. Cassia phytochemicals, especially cinnamaldehyde, show a number of anti-virulence effects, such as lowering the levels of fimH and csgD [99].

4. Nanoformulation enhances absorption and can be released slowly and can be used to deliver drugs to the specific sites of infection [100].

5. Iron oxide nanoparticles provide magnetic targeting features and the potential for theranostic applications (integrated therapy and imaging) [101].

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Research Priorities and Knowledge Gaps.

Although there may be good foundations, there are still huge gaps in knowledge:

2. Mechanistic understanding: Detailed molecular pathways of C-downregulation of fimH and csgD. We must find out the name of cassia chemicals.

2. Effects that depend on concentration: We need to do systematic research on how sub-MIC affects the expression of virulence genes.

3. Optimizing nanoformulation: To improve nanoparticle size, stability, loading efficiency, and release kinetics, all of the factors that affect them need to be optimized in a systematic way.

4. Synergistic mechanisms: C. interactions. We should determine what cassia phytochemicals and iron oxide nanoparticles are.

5. In vivo efficacy: Studies using animal models are necessary to confirm in vitro results and evaluate pharmacokinetics, biodistribution, and toxicity.

6. Resistance potential: Longitudinal studies to determine the effectiveness of anti-virulence therapy in the enhancement of resistant mutants are necessary.

What Comes Next

Future studies should focus on:

1. High-throughput screening of C. Cassia phytochemical libraries targeting FimH and CsgD.

2. Studies of the structure-activity link to improve anti-virulence activity.

3. Creating tailored nanoformulations with surface functionalization for UPEC-specific delivery.

4. Combinatorial methods that combine nanoformulated C. Cassia used with standard antibiotics for synergistic effects.

5. Theranostic uses utilizing magnetic characteristics for imaging-guided therapy.

6. Clinical translation via stringent preclinical assessment and initial-phase clinical studies.

Final Thoughts

Uropathogenic *Escherichia coli* continues to be the primary etiological agent of urinary tract infections globally, with increasing antibiotic resistance jeopardizing effective management. Anti-virulence medication that targets important pathogenic pathways is a promising alternative to traditional antibiotics. It may also lower the pressure for resistance to evolve. *Cinnamomum cassia* bark, abundant in bioactive phytochemicals, notably cinnamaldehyde, demonstrates diverse anti-virulence properties, including the downregulation of essential virulence genes (fimH, csgD) and the prevention of biofilm formation. Nanoformulation of *C. Cassia* extracts combined with green-synthesized iron oxide nanoparticles improve bioavailability, allow for regulated release, and may help with targeted delivery. The combination of anti-virulence methods, bioactives from medicinal plants, and nanotechnology is a new way to fight MDR UPEC infections. Systematic examination of identified information gaps will facilitate the advancement of effective, resistance-preventive treatment approaches for this progressively complex clinical issue.

Conclusions

The findings of this study support that urinary tract infections (UTIs) due to UPEC and associated with multi-drug resistant (MDR) strains can be treated successfully using innovative nano-biotechnology. The use of iron oxide nanoparticles synthesized through a green chemical process, conjugated with cinnamon extracts, allows for disruption of important virulence factors of UPEC without creating microbial resistance. This new means of treating UTIs describes a new paradigm shift as a targeted, eco-friendly and very effective type of therapy.

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Author's Declaration

- We hereby confirm that all the Figures and Tables in the manuscript are original and have been created by us.
- We have obtained ethical clearance for our study from the local ethical committee at [Al-Nahrain University/College of Biotechnology]. This approval underscores our commitment to ethical research practices and the well-being of our participants.
- Ethical Clearance: The project was approved by the local ethical committee at [Al-Nahrain University/College of Biotechnology], ensuring adherence to ethical standards and the protection of participants' rights and welfare.

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