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Natural Carbon Quantum Dots Derived from Medicinal Fruit Wastes for Early Fluorescence-Guided Detection and Suppression of Pancreatic Fibrosis: A Mechanistic Review and Research Roadmap

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ABSTRACT: Fibrosis of the pancreas resulting from the activation of PSCs to acquire a myofibroblast-like state characterized by secretion of collagen contributes both to chronic pancreatitis and the development of desmoplastic stroma associated with pancreatic cancer; however, this is hard to diagnose due to inaccessibility of the pancreas for biopsy procedures and inadequacy of currently available imaging methods that are unable to detect early stages of fibrotic lesions preceding symptoms. Fruit and medicinal plant wastes like citrus peel, grape pomace, mulberry, mango leaf, and others serve as a raw material to produce carbon quantum dots (CQDs), which have been independently found to exhibit tunable fluorescence and photostability required for bioimaging applications as well as antioxidant properties and ability to scavenge ROS due to their surface hydroxyl and carbonyl groups. The following two direct precedents set the context for this review: fruit waste-derived CQDs coupled with antibodies against a pancreatic

cancer biomarker CA 19-9 have already been employed for fluorescent immunoassay detection purposes, while in a completely different study carbon dots derived from mulberry were proven to inhibit kidney fibrosis in vivo by blocking PI3K pathway. As far as it can ascertain, no previous research has attempted to integrate these two lines of evidence in a single CQD-based approach. Specifically, no work has been done that would combine these two approaches into one carbon quantum dot-based technology, or would test the efficacy of such a technology in the treatment of the pancreatic tissue. The current review integrates the biological aspects of the process of pancreatic stellate cells activation, green chemistry of carbon quantum dots based on fruit waste, and the recent evidence of their potential in the anti-fibrotic activity in organs, suggesting an explicit, yet untested hypothesis that natural CQDs could be used to detect and prevent early stages of pancreatic fibrosis. A three-stage in vitro, animal and translational roadmap concludes this manuscript.

1. INTRODUCTION

Indeed, both chronic pancreatitis and ductal adenocarcinoma of the pancreas are characterized by the development of pancreatic fibrosis, and in both cases, the development of fibrosis is caused by the same key cellular process the transformation of quiescent pancreatic stellate cells (PSCs) storing vitamin A into actively reproducing cells characterized by α-SMA expression and the production of extracellular matrix i.e., transformation into the myofibroblast-like state [10]. In response to various triggers, such as alcohol, cigarette smoking, hyperglycemia, mechanical stress, and acinar cell damage, PSCs activate the release of a variety of inflammatory mediators, which include TGF-β, connective tissue growth factor, interleukins, and others, ultimately resulting in the secretion of type I and III collagens, thus forming a fibrotic tissue [9]. According to a recent study conducted in 2025, PSC activation in chronic pancreatitis is mediated by a non-canonical Hedgehog signaling pathway via the GLI2 transcription factor downstream of the TGF-β1/SMAD3 pathway and independent of the canonical SMO receptor, with conditional knockout of Gli2 gene in PSCs alleviating pancreatic fibrosis in the mouse model thus identifying GLI2 as a potential therapeutic target [11].

Early identification of the process still presents a major clinical challenge. The pancreas is retroperitoneal and difficult to biopsy routinely, and imaging techniques available today (CT, MRI) do not provide sufficient resolution to detect pre-symptomatic fibrotic changes at the level of individual stellate cell activation or early collagen formation, which already indicates that the disease process is well developed at that point [9] [12]. This detection problem coincides with a similar treatment problem: there are currently no FDA-approved anti-fibrotic treatments for the pancreas, and most research regarding possible mechanisms of action on PSC is pre-clinical.

In an independent materials science literature, which has developed over the last decade, carbon quantum dots have been demonstrated as highly versatile and low-toxicity agents for bioimaging, and has increasingly relied upon fruit and vegetable processing waste (citrus peels, grape pomace, mango leaves, banana peel, mulberry, and other agricultural waste products), which are renewable sources of abundant carbohydrates, phenolics, and proteins that are needed for CQD synthesis, as a source material for the synthesis of such particles [1] [4] [7]. Additionally, in an expanding subset of this literature, it has been shown that, if CQDs are produced using medicinal or antioxidant-containing plants, such CQDs will exhibit some residual ROS-scavenging or anti-inflammatory biological activity post-synthesis through surface functional groups that mimic the superoxide dismutase enzyme, or through nanozyme-like catalytic activity [13] [14] [17].

There are two pieces of information from this materials science literature, which it think are directly relevant to supporting the hypothesis proposed in this review, and have not yet been linked to the development of any form of pancreatic disease. Firstly, fruit waste CQDs conjugated with an antibody targeting carbohydrate antigen 19-9 (CA 19-9) – the clinical biomarker most commonly used to diagnose pancreatic cancer - have already been employed to develop a functional fluorescent immunosensor proving that the fluorescent detection of a pancreas-specific biomarker by using CQDs is feasible [18][19]. Secondly, even more impressively, carbon dots derived from mulberry fruits have been proven in a 2025 paper to reduce kidney fibrosis in vivo through their direct inhibition of PI3K

pathway - organ-specific anti-fibrotic activity of fruit-derived CQDs which, as far as it can say, is the closest available parallel to the suppression mechanism postulated in this review despite its testing in kidneys rather than the pancreas [8] [16]. In addition, a structurally similar plant-derived CQD has been independently proven to reduce liver fibrosis by means of its antioxidant activity [15].

What has not yet been studied in any of the scientific literature, however, is the interaction that the current review addresses: a fruit-waste-based single platform of CQDs engineered for both fluorescent-guided early detection of pancreatic fibrosis and stellate cell activation inhibition in the pancreas. The goals of this review include the following: (1) to highlight the cell biology of pancreatic stellate cell activation and fibrosis, including the exact mechanisms of stellate cell activation (TGF-β1/SMAD3/GLI2) that should be targeted; (2) to discuss the green chemistry, photophysics, and biological activities of fruit waste-based CQDs; (3) to examine the two most pertinent precedents – CQDs as pancreatic biomarker sensors and plant-derived CQD anti-fibrotic effects on organs – in great detail; and (4) to synthesize these threads into a five-step hypothetical mechanism of a dual-detection and -inhibition CQD platform for early pancreatic fibrosis. As with the research reviewed, this review presents no novel experimental results, and each step of the hypothetical mechanism outlined in Section 5 is described as such.

2. PANCREATIC STELLATE CELL ACTIVATION AND FIBROSIS

2.1 The quiescent-to-activated transition

The normal physiological state of PSCs is a quiescent and periacinar localization of cells with intracellular deposits of vitamin A-containing lipid droplets along with very low rates of proliferation and secretion. In conditions of trauma such as alcohol abuse, diabetes, frequent attacks of acute pancreatitis, physical damage, or the effects of secreted factors by tumour cells in the case of pancreatic ductal adenocarcinoma, vitamin A is depleted in PSCs and they acquire an activated myofibroblastic phenotype marked by expression of α-SMA, increased proliferation and migration ability, and active production of type I and III collagen, fibronectin, and laminin. This transformation process was proven in the earliest and highly important study where a rat model of chronic pancreatitis caused by an infusion of trinitrobenzene sulfonic acid was coupled with histological samples of human chronic pancreatitis and α-SMA and collagen (or procollagen mRNA) double-staining proved spatiotemporal correlation between the two processes [10].

2.2 Signalling drivers: TGF-β, Hedgehog, and beyond

TGF-β is perhaps the most consistently implicated PSC activator throughout the literature, both as a paracrine signal from damaged acinar cells and inflammatory infiltrate, and as a self-propelled autocrine loop after activation of PSCs [9]. A paper from 2025 went much further in elucidating this mechanism by identifying GLI2, the transcriptional effector of Hedgehog signalling, as one of the most upregulated targets in chronic pancreatitis patients' pancreas tissue, and demonstrating that GLI2 is activated via a non-canonical, receptor-independent SMO signalling pathway downstream of TGF-β1/SMAD3 signalling; knockout of Gli2 but not Smo was effective in reducing fibrosis severity in a mouse model of chronic pancreatitis, while pharmacological disruption of TGF-β1/SMAD3 signalling abolished GLI2 activation and PSC activation in vitro [11]. The importance of this pathway lies in its specificity, providing a clear target (TGF-β1/SMAD3→GLI2) instead of the broad "anti-inflammatory" approach of the existing PSC literature. In addition to the TGF-β1/SMAD3 pathway, there are other regulatory signals that activate PSCs CTCF, PDGF, activin A and Wnt/β-catenin signalling, and several counter-regulatory factors (bone morphogenetic proteins, follistatin and all-trans retinoic acid), which in preclinical models were able to inhibit the effects of TGF-β-mediated PSC activation [9][12]. Linked by the implementation of cutting-edge healthcare technologies and AI, for future translational and precision medicine approaches for disease diagnosis and management [20].

2.3 Oxidative stress as an upstream driver

In almost all of the PSC activation factors (alcohol metabolism, hyperglycemia, repetitive inflammation), the production of reactive oxygen species is a common upstream process that not only leads to injury but also serves to amplify the very inflammatory pathway via TGF-β and NF-κB that keeps the PSCs activated. It is the exact mechanistic way in which the hypothesis proposed in section 5 works: the compound which is going to scavenge the ROS in early PSC activation stage will be working in the upstream part of the TGF-β1/SMAD3/GLI2 pathway.

3. FRUIT-WASTE-DERIVED CARBON QUANTUM DOTS: PHOTOPHYSICS AND BIOACTIVITY

3.1 Green synthesis from agricultural and medicinal plant waste

CQDs have been successfully produced from fruit and plant waste through a one-pot hydrothermal or microwave-assisted synthesis technique wherein the carbohydrate-, phenolic-, and protein-containing waste is subjected to carbonisation and surface passivation to obtain sub-10 nm water soluble, fluorescent carbon nanoparticles [2][22]. This methodology has recently been extended to several types of fruit and vegetable wastes: orange, lemon, and kiwi peels, resulting in blue fluorescent CQDs, whose emission depends on the excitation wavelength; in 2026, orange peel-derived blue-emitting CQDs were developed which showed improved quantum yield and lifetime of the radiative state; grape seed and pomace waste, constituting about 13.5-14.5 % of grape production, resulting in nitrogen/sulfur co-doped CQDs; butternut squash peel, resulting in CQDs with quantum yield of 13.5 % and demonstrating antibacterial and antioxidant effects; mango leaves and mulberry material, each producing highly fluorescent and biocompatible CQDs intended for use in "theragnostics" (combination of therapy and diagnostics) biology-related applications. In a parallel stream of research on CQDs obtained from byproducts of the biorefinery process, it was shown that CQDs from waste autohydrolyzate contain high sp2/sp3 carbon content, exhibit blue-green fluorescence with a quantum yield of about 13 %, and are highly photostable and thermally stable [23].

3.2 Intrinsic antioxidant and anti-fibrotic bioactivity

Another discrete subset of literature has developed around direct testing of the biological activity of the CQDs, finding consistent evidence that the CQDs synthesized from antioxidant-rich or traditional medicinal plant materials maintain a functional ability to scavenge reactive oxygen species. Superoxide dismutase-mimic carbon dots synthesized from Glycyrrhiza (licorice) maintained an activity exceeding 13,340 U/mg, which was effective enough to lower hepatic inflammation and oxidative damage in a murine model of sepsis-induced liver injury through activation of Keap1/Nrf2-mediated antioxidants and blockade of NF-$\varkappa$B-driven inflammation; another CQD nanozyme system has proven efficient at broad-spectrum hydroxyl radical, superoxide, and ABTS radical scavenging with subsequent lowering of pro-inflammatory cytokines release during the cellular anti-inflammatory testing [13] [14]. Naturally derived carbon dots have proven to be effective in protecting against acute kidney injury by reducing ROS production and inhibition of NF-$\varkappa$B-mediated inflammatory response [17].

The most directly pertinent evidence to this review's hypothesis are two recent studies that have progressed from the general antioxidant effects to a proven anti-fibrotic effect at the organ level. Specifically, carbon dots prepared from Vaccaria Semen carbonisata enhanced antioxidant activity (SOD, GSH) and inhibited peroxidation products (MDA) in an experimentally induced fibrosis of the liver caused by carbon-tetrachloride, significantly reducing the extent of fibrosis [15]. Even more directly pertinently, M-CDs (carbon dots synthesized from mulberry fruit) in an experiment done in 2025 were found to be capable of inhibiting kidney fibrosis via the specific mechanism of inhibition of PI3K pathway a specific molecular pathway, rather than just a general antioxidant effect, and the only example of such a mechanism found for now for any organ [16].

3.3 CQD-based detection of pancreatic biomarkers

In terms of sensing, two independent proof-of-concept studies have proven that CQD-based platforms are already technically able to detect pancreas-related biomarkers directly, although neither one of them had a specific focus on fibrosis. Specifically, a fluorescence immunoassay using CQD-gold nanocomposite was used to detect CA 19-9, which is the main serological marker for pancreatic cancer, via a sandwich-type immunoassay by exploiting glucose-based CQDs as reducing and stabilizing agents, where the fluorescence signal intensity was directly proportional to the level of antigens [21]. Secondly, nitrogen-doped graphene quantum dots were exploited for microRNA sensing associated with pancreatic cancer, thus establishing another independent CQD-family based platform, capable of molecular sensing of pancreas-related biological markers [21]. Neither one of these platforms has the capacity to sense fibrotic collagen or PSC activation markers, and indeed this is a major gap addressed specifically by the roadmap proposed in Section 6, although they show that the underlying chemical mechanism (CQD-antibody or CQD-oligonucleotide bioconjugation) works.

Collagen fluorescence without any modification of engineered target biomarker detection is feasible on its own: collagen fluorescence and second-harmonic generation (SHG) have already been applied for fibrosis staging in kidney, lung, liver, and bone marrow tissues label-free, with dual channel two-photon and SHG system successfully demonstrating the ability to detect minimal fibrosis in tiny tissue samples at earlier stages [22]. Thus, there is another way to achieve the goal of the detection component of this review's hypothesis: CQDs fluorescence does not need to work alone; they could be combined with or separated from the collagen fluorescence signal that is known from literature and that, to the best of the knowledge, has not been tried yet for any organ, including the pancreas.

Table 1 summarises the major sources of fruit-waste CQDs considered in this review, along with their properties and application potential for pancreatic fibrosis.

Table 1. Selected fruit/plant-waste-derived carbon quantum dot sources and their documented or plausible relevance to pancreatic fibrosis detection and suppression

Fruit/plant waste source	Reported CQD properties	Relevance to a pancreatic fibrosis application
Citrus peel (orange, kiwi, lemon)	Blue-fluorescent, excitation-wavelength-tunable emission; enhanced quantum yield with stable radiative lifetimes	Established, reproducible synthesis platform; citrus flavonoid-derived surface groups plausibly contribute intrinsic antioxidant activity
Grape seed/pomace	Nitrogen/sulfur co-doped CQDs; good biocompatibility; fluorescence probe activity for ascorbic acid and Cu(II)	Grape by-products are a defined agricultural waste stream (13.5-14.5% of total production) with documented polyphenol-rich surface chemistry [5]
Mulberry	Fluorescent CDs with high water dispersibility, high quantum yield, broad pH/ionic stability	Direct precedent: mulberry-derived CDs already shown to attenuate organ fibrosis (kidney) via PI3K inhibition in vivo [16]
Butternut squash / banana / mango (peel, leaf waste)	Blue fluorescence, quantum yields in the 10-15% range, antibacterial and antioxidant activity confirmed	Demonstrates that fruit-waste CQDs commonly carry intrinsic antioxidant bioactivity in addition to fluorescence, relevant to the suppression arm of this review's hypothesis [3] [6]

4. A PROPOSED MECHANISTIC MODEL: CQDS FOR FLUORESCENCE-GUIDED DETECTION AND SUPPRESSION OF PANCREATIC FIBROSIS

There have been no published studies that have synthesized a CQD sensing platform using fruit waste, tested it for fluorescence guided diagnosis of pancreatic fibrosis, and its ability to inhibit pancreatic stellate cell activation. The following hypothesis has been developed through the explicit synthesis of the three literatures described above (Section 2, Section 3.1 & 3.2, and Section 3.3) in the form of a five step hypothesis based upon the two nearest precedents to this topic (CA 19-9 CQD immunosensing and mulberry-CD kidney anti-fibrotic activity).

Table 2. Proposed mechanistic model linking fruit-waste-derived carbon quantum dots to fluorescence-guided detection and suppression of early pancreatic fibrosis. Every linkage is a hypothesis synthesised from indirect, adjacent-context (largely non-pancreatic) evidence; none has been tested directly in this combination

Step	Proposed mechanistic link	Supporting (indirect) evidence
1	Fruit-waste CQDs, functionalized or conjugated to a fibrosis/tumor-associated ligand (e.g., anti-CA 19-9), preferentially	CQD/gold nanocomposite immunosensing already demonstrated for the pancreatic biomarker CA 19-9;

	accumulate at sites of early pancreatic stellate cell activation and collagen deposition	collagen itself is intrinsically fluorescence-detectable via two-photon/SHG imaging in other fibrotic organs
2	CQD fluorescence provides a exogenous, tunable contrast signal that complements intrinsic collagen autofluorescence, enabling earlier and more sensitive detection of nascent fibrotic foci than histochemical staining alone	Tunable, excitation-wavelength-dependent CQD photoluminescence with high photostability; established use of two-photon/SHG collagen imaging for early-stage fibrosis staging in kidney and lung
3	Surface hydroxyl/carbonyl groups on fruit-waste CQDs scavenge ROS (superoxide, hydroxyl radicals) generated during pancreatic stellate cell activation, reducing oxidative activation signal	SOD-mimetic and nanozyme ROS-scavenging activity directly demonstrated for plant-derived carbon dots in liver and kidney injury models
4	Reduced oxidative and inflammatory signalling attenuates TGF-β1/SMAD3 and non-canonical Hedgehog (GLI2) pathway activation in pancreatic stellate cells, limiting their transition to the α-SMA+, collagen-secreting myofibroblast-like phenotype	TGF-β1/SMAD3-GLI2 axis established as a direct driver of PSC activation and fibrosis in chronic pancreatitis; PI3K-dependent fibrotic signalling directly inhibited by mulberry-derived CDs in kidney fibrosis
5	The same CQD platform therefore functions bimodally — as a fluorescent detection probe for early fibrotic change and as a low-toxicity antioxidant/anti-fibrotic agent — reducing collagen deposition and stellate cell activation markers over sustained exposure	Plant-derived CDs have independently demonstrated anti-fibrotic efficacy (liver, kidney) and fluorescence-based biomarker detection (pancreatic CA 19-9) in separate studies, but never combined in one theranostic platform or tested in the pancreas

The bifunctional (theranostic) nature of steps 1-2 compared to 3-5 was intentional and, in the view, represents the distinguishing characteristic of the hypothesis in relation to either a strictly diagnostic or strictly therapeutic application of CQDs in Table 2. A single CQD system that is both a fluorescent agent (allowing for detection) and an antioxidant/anti-fibrotic agent (allowing for suppression) wouldn't need two different agents or two different times of administration – but it would mean that there are two distinct ways in which the model could fail: the detection process in steps 1-2 and the suppression process in steps 3-5 could be effective or ineffective independently of each other.

5. TRANSLATIONAL ROADMAP: FROM HYPOTHESIS TO EVIDENCE

The testing of the hypothesis in Section 4 involves a multi-phase research program where detection and suppression are considered as separate issues; none of the above has been carried out, but this is a suggested methodology for consideration.

5.1 Phase 1 — CQD synthesis, characterisation, and in vitro dual-function screening

Step 1 entails the development of candidate CQDs from the selected waste source (based on the highest precedent of success, which currently lies in using mulberry as a starting point because of the proven effect on kidney antifibrotic effects and with comparable CQDs made from citrus or grape waste as comparators since of the good knowledge of their photophysics) and their physicochemical characterisation (particle size, quantum yield, functional groups on the surface, and zeta potential). In detection step screening, the CQDs will be added to the culture of either primary or immortalised PSCs (in an activated state induced through treatment with TGF-β1 - the standard way to induce

fibrogenesis in cells, according to this literature), and the fluorescence will be correlated with the expression of α-SMA and collagen. In the suppression step screening, the same cells in the same activated state will be assessed for reactive oxygen species, activation of TGF-β1/SMAD3/GLI2 pathway (using western blotting or qPCR), the expression of α-SMA, and collagen secretion.

5.2 Phase 2 — In vivo proof-of-concept

A validated animal model of pancreatic fibrosis such as either chronic pancreatitis induced by caerulein or the trinitrobenzene sulfonic acid ductal injection technique used to investigate PSC activation [10] would be appropriate here because of the literature precedent for this model, allowing either systemic or, in the case of the inaccessibility of the pancreas, endoscopic ultrasound guided local delivery of the CQDs and in vivo imaging for biodistribution and uptake by the pancreas over time. Measures for success would include correlation between in vivo CQD fluorescence signal intensity and ex vivo fibrosis score (Sirius Red, α-SMA immunohistochemistry, collagen content), as well as the same PSC activation and TGF-β1/SMAD3/GLI2 pathway markers from Phase 1 now measured on the tissue level, along with conventional toxicology/biodistribution criteria (serum chemistry, off target organ CQD uptake) since the pancreas-targeting nanomaterial faces a very different safety profile.

5.3 Phase 3 — Early translational and clinical feasibility work

Considering the preliminary nature of the present hypothesis based on precedents from other organs rather than pancreatic evidence, it would be inappropriate to consider further administration in humans without first independently reproducing the Phase 2 anti-fibrotic effects and conducting a complete assessment of nanotoxicology in this particular organ system. It would be more reasonable to start with the application of the leading CQD formulation in an ex vivo setting for human chronic pancreatitis or pancreatic cancer surgical samples (margins or biopsies when available), which could serve as the first step to validate the main claim behind the detection arm, namely correlation between CQD fluorescence and histological fibrosis, using the existing standard methods of staining and second harmonic generation mentioned in Section 3.3.

6. CHALLENGES AND LIMITATIONS

There are several factors that need to be taken into account regarding this hypothesis. Perhaps the most significant limitation is the organ specificity: the strongest anti-fibrotic properties of CQDs derived from plants have been shown for the kidney and liver, but not the pancreas, which have their unique characteristics of fibrotic environment, blood supply, and enzymatic environment (digestive enzymes being particularly abundant in the latter). Similarly, the fact of detection is based on indirect evidence, as CQD-based CA 19-9 immunosensing has been done in vitro using immunoassay, without demonstrating the CQDs as an imaging modality in vivo or intraoperatively, while the exact detection of fibrotic collagen deposits (and not a cancer biomarker) has never been attempted with any CQD technology in any organ. Pancreatic access, however, is a real limiting factor regardless of biological issues: the location in retroperitoneum and closeness to major vessels and the duodenum make delivery and visualization of CQDs much more difficult compared to other organs, which is duly acknowledged in the Phase 2/3 pathway outlined in this review (via EUS guidance and ex vivo analysis of the samples). The toxicity and long-term clearance of CQDs in particular from pancreatic and peripancreatic tissue are completely unknown at this point; what toxicological information there is on CQDs is mostly in regard to liver, kidney, and biodistribution of CQDs in other systems. Moreover, the potential for inflammation from a foreign body in the highly susceptible tissue of the pancreas (CQDs, which might induce even mild local inflammation, could potentially exacerbate rather than alleviate the activation of PSCs) makes the testing of the safety of these particles in the pancreas of exceptional importance. Finally, reproducibility of batch-to-batch synthesis of green CQDs from agricultural waste is currently an issue in this materials science field.

7. CONCLUSION

Two precedents, published independently of each other but directly relevant to the question namely, the use of CQDs to detect the presence of a biomarker for pancreatic cancer via fluorescence and the use of mulberry CQDs to reverse fibrosis in the kidneys due to a specific molecular mechanism demonstrate that the individual elements which compose the hypothesis in question are not speculation, taken individually. It has yet to be seen what will happen when they are brought together namely, the creation and evaluation of a single platform of fruit-waste-derived CQDs which are

used for the fluorescent detection and antioxidant inhibition of pancreatic fibrosis. The process will be undertaken using the described in vitro, animal and ex vivo programme of tests using human tissues described in Section 5. This will involve starting from the more easily tractable task of investigating whether the mulberry or citrus CQD is capable of maintaining its fluorescent and antioxidative characteristics when used on an activated pancreatic stellate cell model. Given the real and ongoing clinical necessity of diagnosing pancreatic fibrosis at an earlier stage and in a less invasive manner and the sustainability benefits of reusing fruit production waste as the basis for the material, it consider this an interesting avenue to pursue.

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