Black Gold in Medicine: Rediscovering the Pharmacological Potential

Ulduz Hashimova * , Aliya Gaisina , Khatira Safikhanova

Posted Date: 11 November 2025

doi: 10.20944/preprints202511.0629.v1

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Article

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Ulduz Hashimova *, Aliya Gaisina and Khatira Safikhanova

Institute of Physiology named after academician Abdulla Garayev, Ministry of Science and Education, AZ1100 Baku, Azerbaijan

* Correspondence: ulduz.hashimova@science.az; +994502406393

Abstract

Beyond its conventional role as an industrial and energy resource, crude oil may also hold promise for drug discovery. This article seeks to provide a conceptual framework for reconsidering crude oil as a reservoir of pharmacologically relevant scaffolds and to outline methodological approaches for their systematic assessment**.** Its rigid sp^3-rich frameworks, together with sterane/hopane biomarkers, porphyrins, and functional aromatics, overlap structurally and pharmacologically with established therapeutic classes and are naturally present in crude oil in suitable abundance, offering opportunities to reduce synthetic effort and expand the chemical space accessible to drug discovery. Advances in petroleomics and in silico methodologies now enable petroleum-derived constituents to be characterized in terms of drug-likeness, bioactivity, and toxicity, providing a framework to reconsider crude oil as an unconventional but scientifically tractable resource for pharmaceutical innovation.

Keywords: petroleum-based medicine; Naftalan crude; petroleum biomarkers; sp^3 scaffolds; naphthenic acids; carbon nanostructures; drug discovery; multi-target therapeutics

1. Introduction

The pharmaceutical industry is undergoing a profound strategic transformation, as tightening regulatory requirements for evidence-based efficacy of new products, evolving healthcare business models, and the surge of personalized medicine compel a fundamental rethinking of the drug development paradigm — from molecular design to real-world application. Amid global demographic transition, including population aging, and the growing burden of chronic diseases, pharmaceutical companies are being forced to diversify both their R&D portfolios and feedstock strategies, accelerating the shift toward alternative platforms for therapeutic approaches to address long-term, complex healthcare demands [1–4].

For decades, conventional "drug-likeness" filters- such as Lipinski's Rule of Five, lead-like, and fragment-based criteria - have severely constrained the accessible chemical space, excluding many promising scaffolds due to solubility, permeability, or molecular weight cut-offs [5–7]. Meanwhile, the synthetic toolbox in drug discovery has changed little for decades: amide coupling, Suzuki–Miyaura cross-coupling, and SNAr still dominate keeping most small-molecule synthesis confined to flat sp^2 scaffolds often associated with limited bioavailability, low metabolic stability, and toxicity [8]. Together, these practices have contributed to a nearly 90% attrition rate between preclinical and clinical stages and have slowed innovation in small-molecule drug discovery [9]. Against this backdrop, concepts such as "escape from flatland" (greater sp^3/3D character), metabolite-likeness, and endogenite-orientation have entered the mainstream, accompanied by renewed interest in natural sources of bioactive compounds as drivers of novel therapeutic modalities that meet modern expectations for sustainability, safety, and efficacy [10–13].

 doi:10.20944/preprints202511.0629.v1

Within this rationale, petroleum— traditionally viewed only as an industrial and energy resource —emerges as a vast, underexplored reservoir of rigid, sp^3-rich scaffolds and biogenic derivatives for drug design, which is the central focus of this study.

2. Petroleum in Medicine: Practical Insights

Petroleum is a multicomponent system, generated through microbial and thermocatalytic conversion of ancient organic matter (algae, bacteria, higher plants, plankton, microbial biomass, etc.). During the early stages of petroleum formation (diagenesis), under anoxic depositional conditions, anaerobic microorganisms predominantly mineralize protein and carbohydrate components, releasing O, N, and S as CO_2, NH_4^+, H_2S, and CH_4, while lipid and aromatic frameworks are preferentially preserved and transformed, leading to the formation of kerogen—a high-molecular-weight residue of organic matter. In the subsequent stage (catagenesis), as burial continues, within the so-called "oil window" (~60–120 °C, 2–5 km depth) and under increasing pressure, kerogen is transformed into a hydrocarbon-dominated mixture characterized by the prevalence of C–C/C–H skeletons. In practical petroleum chemistry, the vast diversity of components has been conveniently summarized by the SARA taxonomy—saturates (S), aromatics (A), resins (R), and asphaltenes (A). More fundamentally, the composition of petroleum **is determined by** the nature of organic precursor (marine algae, terrestrial plants, microbial biomass), depositional setting (marine vs. lacustrine, carbonate vs. siliciclastic), inorganic input from sediments and formation waters, and the degree of thermal maturity [14]. Under such harsh geological conditions, labile functional groups and reactive side chains are progressively eliminated, yielding relatively thermodynamically stable hydrocarbon structures. Yet, several fundamental molecular backbones—such as steroidal, hopanoid, and porphyrin structures—are selectively retained and serve as biomarkers, widely applied in crude oil fingerprinting [15].

In fact, the pharmaceutical and petroleum industries have a long history of operational synergy through established production chains. Although the pharmaceutical sector consumes only about 3% of global oil extraction, yet this amount covers almost 99% of its feedstock demand, including aromatics, C_2–C_3 olefins/methanol for API synthesis, and polymers (PEG, polypropylene, PVC) for excipients and packaging [16].

To date, the industrial-utilitarian narrative has overshadowed petroleum's centuries-old role in traditional medicine. Ancient medical sources — from Mesopotamia and Rome to the medieval Middle East and Europe — contain numerous references to how petroleum, long before it became a pillar of the energy sector, was esteemed as a natural remedy. The medicinal use of crude oil was geographically clustered around natural seeps and although mentioned only intermittently, was included in authoritative pharmacopoeias, while its industrial and energy value ultimately came to dominate on a global scale [17–19]. Through this lens, petroleum has been defined largely by environmental discourse, which has limited evidence-based evaluation of its potential for drug discovery.

Naftalan serves as a rare exception. This crude oil deposit near the Naftalan settlement, Azerbaijan, has been known from antiquity to the present day as a petroleum-based healing site. Initially integrated into official sanatorium/rehabilitation medicine in the former USSR and later adopted in Croatia, Naftalan's therapeutic properties also prompted the development of medical preparations and are now re-emerging as an empirical platform for early-stage drug discovery [20–23].

With a century-long history of therapeutic application across various modalities—whether through ointments, cosmetic products, therapeutic baths, or other topical procedures—a substantial body of clinical evidence has been accumulated to empirically validate the efficacy of Naftalan crude oil in the management of complex, chronic conditions such as inflammatory skin diseases (e.g., psoriasis, eczema), autoimmune and degenerative joint disorders (e.g., rheumatoid arthritis, osteoarthritis), neuropathic syndromes (e.g., polyneuropathies, post-injury pain), and vascular complications of metabolic disease [22–27].

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The ability of Naftalan crude to target multiple pathophysiological pathways—including nociceptive signaling, inflammatory cascades, neurodegenerative processes, and endothelial function—is inherently connected to crude oil's diverse organic makeup and is increasingly viewed as a legitimate asset for pharmaceutical R&D, akin to plant-derived alkaloids or marine biopolymers that have driven modern drug development [28,29]. (Adigozalova et al., 2019; Newman and Cragg, 2020).

While efforts to understand the mechanisms behind crude-oil–based therapies have been undertaken, they were largely constrained by the analytical tools available at the time. Numerous experimental studies were nevertheless conducted in the Soviet Union and later in post-Soviet countries, but most were published locally and remained largely inaccessible to the wider international community. Among the most conceptually ambitious was the so-called "precursor theory," proposed by Yusif Mamedaliyev in the early 1940s and still referenced today. This theory suggested that steranes present in crude oil could be metabolized into biologically active compounds within the human body [30]. Although intellectually compelling, the hypothesis lacked experimental validation, primarily because technologies capable of tracing such biochemical transformations at the molecular level did not yet exist. For the pharmaceutical sector, however, this remains a critical issue: elucidating the metabolic fate of crude-oil constituents is a prerequisite for assessing both their therapeutic potential and their safety.

Today, advanced analytical-chemistry techniques enable comprehensive compositional analysis, including heavy petroleum fractions, serving as a critical first step in identifying previously inaccessible molecular structures of significant pharmaceutical potential. When integrated into a comprehensive pipeline—from advanced computational modeling and virtual screening to in vitro and in vivo evaluation—these methods enable systematic exploration of bioactivity profiles, accelerating the identification of drug-like candidates within complex hydrocarbon matrices.

3. Pharma Matrix of Crude Oil: Structure Insights

Naftalan crude oil represents a distinctive class of biodegraded heavy crudes, with physicochemical properties setting it apart from conventional fuel-grade petroleum. It is characterized by high density (0.910–0.960 g/cm^3), extreme viscosity, and, most notably, a near-total absence of alkanes. In their place, it contains an unusually high proportion of naphthenic hydrocarbons—approximately 59.4–77.0% depending on stratigraphic horizon and processing method—and a remarkable enrichment in hydrogenated cyclic compounds, particularly decahydronaphthalenes (~59.7–60.1%). In addition, Naftalan oil shows elevated levels of trace elements (Ba, Fe, Ni, Ti, Zn) and even noble metals (Au, Pd, Pt, Rh, Te) [28,31].

Critically, such specific chemical profile grants access to a variety of non-flat, sp^3-rich rigid hydrocarbon frameworks—from simple mono- and bicyclic rings to more elaborate fused or bridged polycycles—that were long overlooked but are now emerging as a new trend in drug-discovery scaffold design. This paradigm shift, often described as the "escape from flatland", emphasizes the transition from flat aromatic systems to three-dimensional architectures [10,11]. Sp^3-rich frameworks provide structural and functional advantages: they improve shape complementarity with hydrophobic protein cavities, enhance metabolic stability, and can increase lipophilicity, facilitating membrane permeability. In contrast, planar aromatic systems are intrinsically rigid and conformationally restricted, often prone to rapid metabolic oxidation and associated with genotoxic risks due to their ability to intercalate with nucleic acids. Moreover, the sp^3-rich frameworks present in petroleum frequently retain stereogenic centers inherited from their biological precursors inherited from their biological precursors—steranes (from sterols), hopanes (from bacterial triterpenoids), chiral isoprenoids such as pristane and phytane, and a range of diterpenoid and triterpenoid derivatives—thereby introducing chirality that enhances selective interactions with biological targets. Together, these features provide advantages over planar plant-derived alkaloid frameworks and position them as ready-made bioisosteric replacements for classical functional groups [32,33].

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The most widely recognized and clinically validated petroleum-derived scaffolds are the adamantanes, also known as diamondoids: fully sp^3-hybridized hydrocarbon cages based on the adamantane framework (tricyclodecane, $C_{10}H$ that have a diamond-lattice-like carbon skeleton and exceptional stiffness and rigidity. First identified by Mobil Oil Corporation as problematic deposits clogging pipelines, diamondoids were later recognized as valuable molecular building blocks for pharmacologically active compounds [34,35]. Characterized by high symmetry (Td), complete saturation, and a compact three-dimensional cage architecture, these features account for their effectiveness in pharmacology and medicine—either as the so-called "lipophilic bullet," providing critical lipophilicity when appended to known pharmacophores, or through intrinsic activity linked to the modulation of ion channels, in particular NMDA receptors and viral proton channels. The rigid lipophilic cage further enhances membrane permeability and metabolic stability, and may preferentially partition into lipid rafts, thereby influencing membrane organization and associated signaling pathways. Adamantane itself has become the most extensively studied and clinically validated scaffold, forming the structural core of approved drugs such as rimantadine (antiviral), amantadine (anti-Parkinson's), and memantine (anti-Alzheimer's) [36]. More complex members of the family and their derivatives (amines, carboxylic acids, esters, anilines) have been investigated and show promising antiviral, anticancer, and neuroprotective activities, although none have yet reached clinical application [34,35]. Importantly, petroleum and natural gas condensates contain an even richer diversity of higher diamondoids, most of which remain unexplored as potential scaffolds for future drug discovery.

Drimanes are a family of bicyclic sesquiterpenes ($C_{15}H_{28}$) based on a trans-decalin core, with homo-drimanes representing extended variants of this skeleton. First isolated as drimenol from *Drimys winterii*, these frameworks are widespread in plants, fungi, and marine organisms, and were also detected in petroleum as early as the 1970s [37]. They are thought to originate from the degradation of higher plant triterpenes or bacteriohopanoids during diagenesis, giving rise to characteristic 8β(H)-drimane and homodrimane isomers. Pharmacologically, drimane-type sesquiterpenoids have demonstrated a broad spectrum of experimental activities, including anticancer, anti-inflammatory, antiviral, antifungal, neurotrophic, and enzyme-inhibitory effects [38]. Although diverse drimane and homo-drimane derivatives have been identified in crude oils, their evaluation as scaffolds for drug discovery remains limited.

Decalins (decahydronaphthalenes, $C_{10}H_{18}$) are simple saturated bicyclic hydrocarbons composed of two fused cyclohexane rings in cis- or trans-configuration. They represent one of the most fundamental rigid sp^3 scaffolds, occurring both as synthetic models and as structural motifs in a wide range of bioactive terpenoids and steroids [39]. In petroleum, decalins are characteristic constituents of naphthenic crudes, such as Naftalan oil (Azerbaijan), where decahydronaphthalenes account for up to ~60% of the hydrocarbon fraction, making them a structural hallmark of this crude and a plausible contributor to its reported therapeutic effects. While petroleum-derived decalins themselves have not yet been systematically investigated in clinical medicine, decalin motifs are widely represented in natural products and synthetic scaffolds of pharmacological relevance. Notable examples include decalin–tetramic acid hybrids such as equisetin and zopfiellamides with broad-spectrum antibacterial and antifungal activity, macrolides such as nodusmicin effective against drug-resistant pathogens, and synthetic decalin-based scaffolds for FKBP51 inhibitors currently under investigation as potential treatments for depression, obesity, and cancer [40].

Steranes and hopanes are polycyclic hydrocarbons derived from steroids and pentacyclic triterpenes during diagenesis and catagenesis. Steranes contain the tetracyclic steroid nucleus (gonane, cyclopentanoperhydrophenanthrene), directly homologous to the core of cholesterol and human steroid hormones (e.g., androstane-, estrane-, and cholestane-type derivatives), and are intrinsically chiral, with multiple stereogenic centers controlling biological specificity. In contrast, hopanes possess the pentacyclic skeleton derived from bacterial hopanoids, reflecting prokaryotic membrane architecture. Both classes are essential to membrane organization, contributing to the formation and stabilization of lipid rafts—nanodomains that modulate receptor clustering, signal

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transduction, and viral entry—so petroleum-derived sterane and hopane frameworks may provide a basis for biomedical applications targeting membrane-associated signaling [41–44]. Traditionally considered solely as geochemical biomarkers, these compounds have only recently been evaluated for their pharmacological potential, with Naftalan oil representing one of the first systematic case studies. Calculated reactivity descriptors and PASS-based screening predicted anti-inflammatory, antimicrobial, antiviral, hepatoprotective, immunomodulatory, and antitumor activities, while QSAR models suggested low to moderate toxicity (LD_{50} ≈ 750–1400 mg/kg). This integrated virtual pipeline provides a rationale for prioritizing petroleum-derived biomarkers as candidate scaffolds ([45].

Heavy crude oils may host **nanostructures** of pharmaceutical relevance. In 2020, researchers at the Max Planck Institute for Coal Research (MPI für Kohlenforschung, Mülheim) reported the presence of a broad spectrum of fullerenes in the asphaltene fraction of heavy oil, including classical buckminsterfullerenes and buckybowls—hemispherical aromatic structures with unique reactivity and potential applications in biomedicine, catalysis, and drug development [46].

Naphthenic acids—mixtures of cycloaliphatic carboxylic acids abundant in naphthenic crudes such as Naftalan—combine lipophilicity and polarity through sp^3-rich cyclic cores and a carboxyl group. Their structural analogy to prostaglandins suggests possible roles as bioisosteres in inflammatory and age-related processes, though biomedical data remain limited and at times contradictory [47].

Aromatic hydrocarbons—planar conjugated π-systems ranging from simple benzenes to polycyclic aromatic hydrocarbons (PAHs)—are ubiquitous in petroleum, where low-molecular-weight compounds (phenol, cresols, chlorocresols) constitute an important feedstock for medicinal chemistry. By contrast, polycyclic fractions within asphaltenes are generally regarded as waste and a source of environmental concern. Pharmacologically, aromatic scaffolds engage targets via π–π stacking with aromatic residues and hydrophobic interactions in receptor binding sites; heteroaromatics add hydrogen-bonding capacity and electronic modulation. Notably, extended PAHs can intercalate into DNA, a mechanism underlying the activity of anthracyclines and related agents, but also their genotoxic liabilities. In addition, PAHs partition into lipid bilayers, where they may influence membrane fluidity, lipid raft stability, and receptor clustering. From a druggability perspective, however, increasing aromatic ring count correlates negatively with oral bioavailability and aqueous solubility and raises safety risks through high plasma-protein binding and CYP/hERG liabilities [48]. Even so, heteroaromatic and fused aromatic systems remain foundational in drug discovery—forming the backbone of many antibiotics, antivirals, antipsychotics, and anticancer agents—provided planarity and polarity are carefully optimized [4,49–52].

Petroporphyrins—naturally occurring metalloporphyrins in crude oil—are structurally related to biological tetrapyrroles such as heme and chlorophyll. These macrocyclic compounds, primarily nickel- and vanadium-complexes, were first identified in petroleum in the 1930s. Like their biological counterparts, petroporphyrins are essentially planar, a conformation that supports π-conjugation, metal coordination, and characteristic optical properties. Their porphyrin scaffold includes chemically accessible meso- and β-positions, making them promising substrates for structural modification. Recent structural studies (UV–vis, FT-ICR MS, AFM) have shown that petroporphyrins preserve their geometric substitution patterns even in more complex forms, highlighting their stability and potential as modifiable scaffolds [53]. While porphyrin derivatives are already approved in photodynamic therapy (e.g., temoporfin, verteporfin) and are being explored as antioxidants, radioprotectors, and antimicrobial agents, petroleum-derived porphyrins remain an underexplored resource in pharmaceutical chemistry, despite their ready availability and inherent structural diversity [54–56].

Organosulfur compounds are abundant in petroleum and generally seen as toxic, but Ichthyol (ammonium bituminosulfonates), derived from sulfur-rich shale oil, represents a notable exception. Used in dermatology for over a century, it demonstrates antiseptic, anti-inflammatory, and

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immunomodulatory effects, now supported by modern studies confirming activity even against resistant strains of *Staphylococcus aureus* [57,58].

4. Translational Perspectives of Crude Oil – Derived Drug Discovery

The data reviewed in this article emphasize that crude oil is more than a petrochemical feedstock: it can be regarded as a structurally intricate mixture comprising molecular motifs that range from flat aromatic units to rigid, three-dimensional architectures. Many of these structures display drug-like features and may serve as direct templates for medicinal chemistry and rational drug design, thus opening new translational opportunities. Identified biological activities of petroleum-derived scaffolds align with pressing unmet medical needs, including oncology (over 30% of global R&D efforts), cardiometabolic disorders, antimicrobial and immunomodulatory therapies, and the fast-growing neuroscience field addressing neurodegeneration and psychiatric conditions [4]. Advances in chemical biology and in silico technologies now enable these components to be positioned not merely as generic leads but as sources of first-in-class molecules with novel mechanisms of action, a paradigm highly relevant given the stagnation of conventional drug discovery [59]. Importantly, biomarkers from Naftalan oil show predicted low toxicity and multi-target potential, a strategy increasingly adopted by the pharmaceutical industry to address multifactorial diseases and reduce polypharmacy [60,61].

Moving from concept to practical application will require considerable multidisciplinary effort, integrating expertise from chemistry, pharmacology, toxicology, and computational sciences. Unlike botanical or microbial natural product databases, there is no integrated pharmacological resource covering oil-derived molecules. Petroleomics — ultrahigh-resolution mass spectrometry of crude oils — has revealed thousands of individual components (≥3000 identified, potentially tens of thousands with isomers) across C_{10}–$C_{>50}$ hydrocarbons and heteroatom-containing derivatives, with dedicated workflows for classification [62,63].

Yet, while such approaches have established powerful databases for geochemistry and ecotoxicology, they remain largely disconnected from pharmacological contexts. A translational framework would require systematic annotation of descriptors—including sp^3 fraction, lipophilicity, polar surface area, chirality, and quantum-chemical reactivity indices—to transform petroleomic fingerprints into pharmacologically meaningful data streams [64,65]. Once such datasets are established, they could be feed into the classical drug-discovery pipeline: starting with in silico approaches (virtual screening, molecular docking, QSAR modeling, structure-based optimization), extending to in vitro functional assays (receptor binding, enzymatic and cell-based systems), and culminating in vivo validation studies to assess pharmacokinetics, efficacy, and safety.

Although this strategy offers a pathway for incorporating petroleum into pharmaceutical R&D, significant challenges remain—and many are not entirely unique to petroleum. Natural products from plants and microbes likewise present issues of chemical complexity, inherent toxicity, and the need for scalable purification [66,67]. Crude oil, however, is an extraordinarily complex mixture, with many constituents occurring as unresolved isomeric ensembles, complicating isolation and structural elucidation. Certain fractions, such as PAHs and naphthenic acids, are well known for their toxicity and ecotoxicological impact, underscoring the need for early toxicity prediction and rigorous filtering before pharmacological exploration. Technical barriers also persist and reproducible separation methods, scalable purification strategies, and integration of advanced analytics with machine learning will be essential to navigate this chemical complexity.

5. Conclusion

The medicinal use of petroleum is not a new or regionally confined concept: crude oil derivatives have occasionally entered medical practice, often through the repurposing of by-products. The evidence reviewed here demonstrates that crude oil harbors a broad spectrum of biologically relevant scaffolds, ranging from rigid sp^3-rich frameworks such as adamantanes, steranes, and hopanes, to

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planar π-systems including porphyrins and functional aromatics, several of which overlap structurally and pharmacologically with established therapeutic classes. Importantly, these motifs occur in petroleum at industrial scale, offering an opportunity to reduce synthetic effort while simultaneously expanding the chemical space accessible to drug discovery. Yet, petroleum-derived pharmacology is not a clearly defined field: while petroleomics has revealed extraordinary molecular diversity for geochemical purposes, its integration into drug discovery remains limited. Bridging this gap—through safety assessment, biological profiling, and cheminformatics-driven scaffold design—could lay the groundwork for a distinct field of petroleum-based pharmacology.

Author Contributions: U. Hashimova has conceptualized research and have made substantive contributions to the final review and editing of the manuscript A. Gaisina collected the data and drafted the initial version of the article A. Gaisina and Kh. Safikhanova performed the formal analysis and data curation and contributed to writing the manuscript. All authors have read and approved the final version of the manuscript.

Data Availability Statement: All data used in this article are available within the main text. Further inquiries should be directed to the corresponding author.

Acknowledgments: The author(s) declare that no Generative AI was used in the creation of this manuscript.

Conflicts of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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