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Marine Anti-HIV Drugs

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Abstract: *Strong therapeutic medicines have been developed with significant help from nature. In truth, terrestrially derived medications have generally dominated when examining the development of medicine in relation to the evolution of people. The marine environment, which makes up 95% of the biosphere, covers more than 70% of the earth's surface. Seas and oceans are home to a diverse range of marine plants, animals, and organisms, as well as secondary metabolites.*[1] *HIV-1 reverse transcriptase is a potential therapeutic target for the treatment of those living with HIV/AIDS or those who have previously displayed symptoms of the disease. It is critical to develop novel inhibitors for this enzyme since the amount of viral resistance to existing treatments is rising. Prior to 2004, no marine drug had received FDA approval; nevertheless, after that year, efforts to produce marine pharmaceuticals started.* [2]

Keywords: Reverse transcriptase, anti-retrovirals, marine biosphere, marine environment, and drug development

I. INTRODUCTION

As of 2020, there were 23,18,737 adults and 81,430 children living in the nation who are HIV positive.[/3] HIV assaults Immune cells related to lymphocytes, called CD4 Helper T cells, decrease the immune system's ability to combat illnesses like pneumonia, TB, and some forms of cancer. The most advanced stage of HIV infection, acquired immunodeficiency syndrome (AIDS), can take two to fifteen years to show symptoms, depending on the individual.
Acquired immune deficiency syndrome (AIDS), the final stage of a pathogenic disease caused by the human immunodeficiency virus (HIV), is one of the world's five worst diseases. AIDS is a disease that is still spreading and taking lives each year. The 5 million new HIV infections that happened in 2001 have resulted in 40 million people living with HIV/AIDS worldwide. Since the start of the pandemic just 20 years ago, there have been an estimated 24.8 million fatalities globally from AIDS and/or related opportunistic infections, and the death rate is not anticipated to decline anytime soon. AIDS claimed 3 million lives in 2001[4]

II. HISTORY OF MARINE DRUGS

The oldest known marine product is Tyrian purple, which the Phoenicians made from marine mollusks around 1600 BC. Fish and algae metabolites dominated the field of marine natural products for a very long period. Examples include vitamins A and D from fish liver oil, polyunsaturated fatty acids like docosahexaenoic acid and eicosapentaenoic acid, and marine biopolymers like agar and carrageenan.
The first true marine drugs were discovered in the 1950s when the Caribbean sponge Tethya crypta yielded spongothymidine and spongouridineq. The fungus Acremonium chrysogenum, which produced cephalosporin C, was discovered in water samples from the Mediterranean Sea near Sardinia in the 1940s and served as the impetus for the development of the cephalosporin antibiotic class. [5]

III. MARINE DRUGS USED FOR HIV

1. *Trichotannins*
2. *Red Sponge Styllissa Carteri*
3. *Sequins*
4. *Bioactive Peptides (Phospholipase A2) in Snake Venom*
5. *Polysaccharide Sulfate*
6. *Derivatives of chitin, chitosan, and chito-oligosaccharides*

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7. *Sponge Avarol*
8. *Mollusks or lamellarins*
9. *Sponge clathsterol*
10. *Sponge Neamphamide*
11. *Sponge dehydrofurodendin [7]*

Pholorotannins:

Fig No 1: Durvillaea Antarctica

Brown algae, including kelps and rockweeds/sargassacean species, as well as some red algae in smaller quantities, contain a type of tannin called phorotannins. These compounds are either condensed tannins (polyphloroglucinols), oligomers of phloroglucinol, or not hydrolyzable.As their name implies, tannins have the ability to precipitate proteins. It has been found that certain phlorotannins can oxidize and bond covalently with proteins.

Under comparable experimental conditions, procyanidins, profisetinidins, and gallotannins—three types of terrestrial tannins—did not seem to establish covalent connections with proteins. In addition to being crucial structural elements of brown algal cell walls, these phenolic chemicals seem to have a number of additional ecological functions, such as grazing defense and UV protection.In [9]

Phloroglucinol-based (13,5-trihydroxybenzene) polyphenolic compounds represent 5–12% of the dry mass of marine brown algae (Phacophyta). These compounds are known as phenols. Fourteen phlorotannins are produced by the polyketide (acetate-malonate) pathway of phloroglucinol oligomer polymerization. Many types of marine brown algae have been identified to contain phenols with biological activity that promotes health.

i. Fusiformis Hizikia ii. Excepción cava iii. Japanese laminaria iv. Kurome E. V. Okamurae Shige vi. Thurnbergii Sargassum vii. Bicyclis Eisenia viii. Pinnatifida undaria ix. Dodecylonifera

Though they have also been shown to be connected to the cell walls of marine microalgae, phorotannins are concentrated and conspicuous in the epidermal cortex of brown seaweeds. It is thought that phenol tannins help plants defend themselves by acting as a deterrent to herbivores and maybe as an appetite suppressant.(10)

Styllissa Carteri(Red Sponge)-

Marine sponges are an important source of naturally occurring substances with potent biological effects and unique structural characteristics. A number of compounds obtained from sponges have been effectively converted into medications with FDA approval for a range of medical applications. The bioactive potential of marine sponges in the Central Red Sea has not been fully explored because the Saudi Arabian coast is inaccessible. They have the potential to be antivirals based on their capacity to exhibit phenotypic similar vities.

Sponge-associated microbial symbionts perform essential ecological roles in addition to being essential components of marine benthic ecosystems. In the Red Sea, Stylissa carteri is a common species with modest microbiological

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abundance. Scientists are describing the roles and taxonomy of the most highly expressed bacterial genes in S. carteri. utilizing Illumina HiSeq for sequencing and the metagenomics Rapid Annotation utilizing Subsystem Technology (MG-RAST) method for annotation, bacterial mRNA was isolated from sponge total RNA. Members of Synechococcus have high expression levels of photosynthetic carbon fixation and archaeal ammonia oxidation. S. carteri symbionts exhibited the highest expression of several activities, including stress response and membrane transporters.

Fig No 2: Styllissa Carteri(Red Sponge)

Interestingly, a large number of methylotrophy-related genes were expressed by gammaproteobacterial symbionts.
In [14]
A kind of sponge known as Stylissa carteri, or Elephant Ear sponge, is found from the Red Sea to Australia. It often stands free-standing and has a muscular, yellowish-orange body with many spicules that grows up to 50 cm.In [15] Two novel compounds were isolated from the methanol extract of the Red Sea sponge Stylissa carteri: a ceramide called stylissamide A (1) and a cerebroside called stylissoside A (2). These were obtained using bioactivity-guided isolation supported by LC-HRESIMS metabolic profiling.In [16] Using mass spectrometry, it was possible to identify three previously identified compounds—debromohymenialdisine (DBH), hymenialdisine (HD), and oroidin—by determining the presence of likely HIV-1 inhibitory compounds in candidate HIV-1 inhibitory fractions.

Snake Venom (Phospholipase A2)-

The hydrolase enzymes, which are part of the phospholipases family and are extensively found in nature, are crucial for the metabolism of phospholipids as well as for the control of membrane lipid composition, signaling, digestion, and inflammation

A, B, C, and D are the four main families into which these proteins are classified according to the position of cleavage inside the phospholipid molecule. The most researched member of the phospholipases family is phospholipases A2 (PLA2s). These enzymes liberate free fatty acids and lysophospholipids by hydrolyzing the 2-acyl ester link in 2-sn phospholipids. Prostaglandins, thromboxanes, prostacyclins, and leukotrienes are examples of eicosanoids. They are metabolized from arachidonic acid, a free fatty acid, and are associated with a range of physiological and pathological effects, such as platelet activation and inflammation.

Toxins act directly on virus particles in the virucidal model, before infecting the cell monolayer; in the pre-infection model, toxins are administered prior to viral infection to uninfected monolayers; and in the post-infection model, the virus is adsorbed on cell monolayers, which is followed by toxin treatment. Based on this knowledge, we provide an overview of a possible mechanism of antiviral action mediated by sPLA2s from snake venom. By disrupting many phases of the viral replication cycle, such as entry, replication, and release, sPLA2s have demonstrated their efficacy as

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antiviral inhibitors (as illustrated in the above picture). According to recent research, sPLA2s can directly affect viral particles or interact with the virus or host cell components to have an antiviral effect on various stages of the viral cycle.

Fig No 3: Marine Venom Snake

Anti-HIV Activity Of Oscillatoria Agradhii-

HIV replication, the development of syncytiums between HIV-1-positive and -negative T cells, and the HIV-1 capture and transfer to CD4+ target T cells mediated by DC-SIGN are all inhibited by OAA and OPA. Consequently, a range of clinical isolates of HIV-1 and HIV-2 become non-contagious without the need for coreceptor usage. Investigations utilizing surface plplasmon resonance and flow cytometry revealed that both CBAs prevent the binding of the Man(1-2)Man-specific 2G12 monoclonal antibody (mAb). These CBAs suppressed the HIV-1 strains NL4.32G12res, NL4.3MVNres, and IIBGRFTres in addition to the wild-type strains. Except for OPA/GRFT, combination studies show that OAA and OPA cooperate with hippocampal hybrid agglutinin, 2G12 mAB, and griffithsin (GRFT).[24]

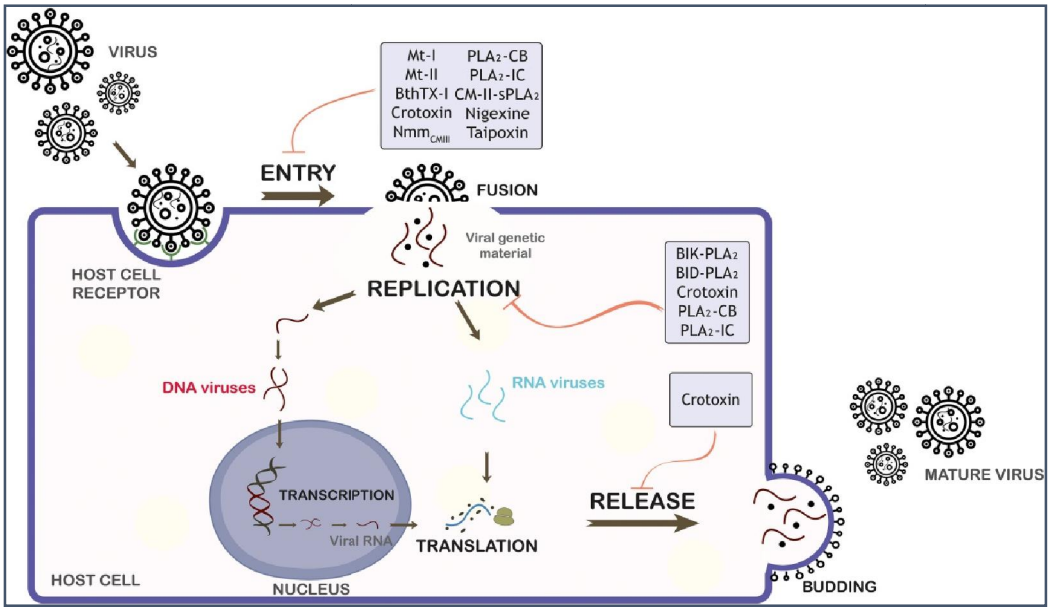

Fig No 4: Schematic Representation of Mechanism of Action of sPLAs from Snake Venom 0n viral replicative cycle

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Chitin,Chitosan,And Chitooligosaccharides Derivatives-

A long-chain polymer of N-acetylglucosamine, chitin is present in a wide variety of living things, such as fungi, insects, crabs, and invertebrates. One of the most prevalent polysaccharides, it is mostly derived from the shells of shrimp and crab. When chitin is partially deacetylated, it becomes chitosan, a partially deacetylated polymer of N-acetylglucosamine.

Through chemical modification, novel biofunctional materials with desired physicochemical properties and biological activity are created from chitin and chitosan. The biological activities of sulfated chitin and chitosan include hemagglutination inhibition, blood anticoagulation, anti-microbial, antioxidant, and anti-HIV-1 properties. Additionally, a few of these derivatives of sulfated chitin and chitosan have uses in medication delivery, metal ion adsorption, and the prevention of cancer metastases.

The most active chitosan derivative was that which was sulfated at the O2 and/or O3 sites in the glucosamine residues. This derivative effectively inhibited HIV-1 replication in MT-4 cells. The positively charged V3-loop in the gp120 protein and the anionic polymer interacted electrostatically to prevent the virus from fusing with the cell membrane... The effectiveness and specificity of the inhibitors were found to be dependent on the position of the sulphate groups in the glucosamine residue, even though anionic chitosan derivatives were found to be similarly able to inhibit retroviral infection to sulfated polysaccharides like heparin and dextran sulphate.

Sulfated chito-oligosaccharide works by preventing HIV-1gp120 from binding with the CD4+ cell surface receptor, hence inhibiting viral entrance and virus-cell fusion. Therefore, CH and its sulfated derivatives might prove beneficial in the future as antiviral medications. In order to understand more about the antiviral properties of sulfated chitosans, Gao et al. (2018) investigated the anti-HPV activities of 3,6-osulfated CH (36S). 3,6-O-sulfated CH may have anti-HPV properties by specifically targeting the viral capsid protein and modulating the host PI3K/AKT/mTOR pathways, the researchers found.(26]

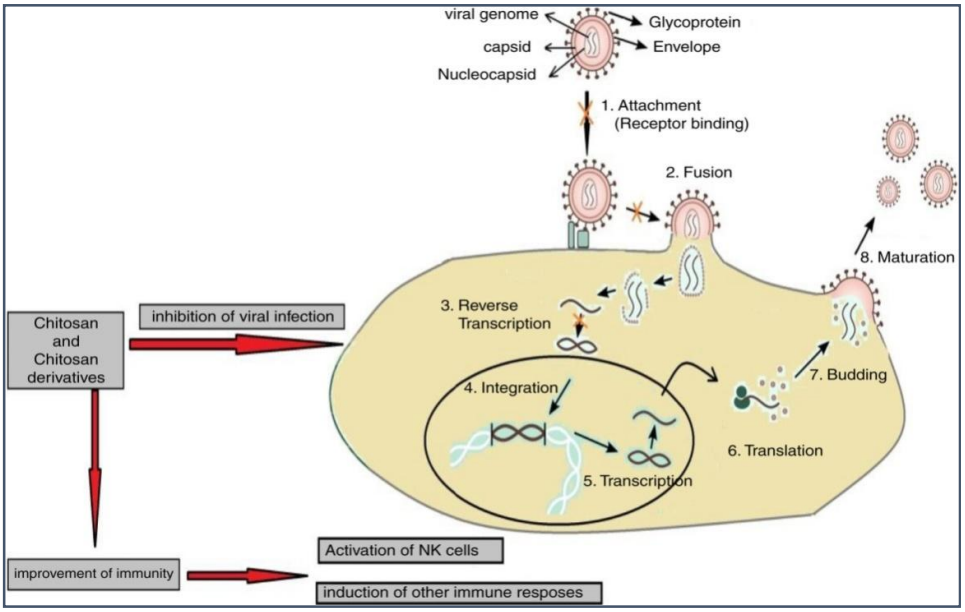

Fig No 5: ***Mechanism of Action of Chitin as an Anti-viral agent***

IV. CLINICAL TRIALS AND DEVELOPMENT

Clinical trials and the development of marine-derived anti-HIV compounds represent a crucial phase in translating promising laboratory findings into tangible treatment options. This section delves into the progress made, challenges encountered, and the potential future impact of these compounds in the fight against HIV/AIDS.

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A. Overview of Clinical Trials Involving Marine-Derived Anti-HIV Compounds

Clinical trials serve as the bridge between preclinical research and actual therapeutic applications. Understanding the landscape of clinical trials involving marine-derived anti-HIV compounds provides insights into the current status of their development. Various compounds derived from marine sources have undergone rigorous testing to evaluate their safety, efficacy, and potential side effects in human subjects.

In recent years, clinical trials have explored the efficacy of marine-derived compounds in different stages of HIV infection. Substances extracted from marine organisms, such as sponges and algae, have demonstrated inhibitory effects on viral replication in early-phase trials. The diversity of these trials reflects the expansive range of marine organisms being investigated and the varied mechanisms through which they may combat HIV.

B. Challenges and Successes in the Development Process

The development of marine-derived anti-HIVdrugs is not without its challenges. One primary obstacle is the complexity of the compounds themselves. The intricate structures of these marine molecules can pose synthesis challenges, making large-scale production for clinical use economically and logistically demanding. Additionally, issues related to bioavailability and pharmacokinetics must be addressed to ensure the effective delivery of the drug to its target within the body.

However, despite these challenges, there have been notable successes. Some marine-derived compounds have shown impressive antiretroviral activity in clinical trials, rivaling or surpassing conventional treatments. The success stories underscore the potential of marine organisms as sources of novel therapeutic agents. Learning from these successes can guide future research and development efforts, inspiring the exploration of additional marine environments for untapped resources

C. Future Prospects for Marine-Derived Drugs in HIV Treatment

Looking ahead, the future of marine-derived anti-HIV drugs appears promising but requires strategic planning and continued research efforts. As more compounds move through the various phases of clinical trials, it becomes crucial to assess their long-term safety, potential drug interactions, and overall efficacy. Researchers and pharmaceutical companies must collaborate to streamline the drug development process, addressing challenges related to production, scalability, and affordability.

Furthermore, the integration of marine-derived compounds into existing combination therapies could enhance the overall effectiveness of HIV treatment regimens. Synergies between marine compounds and conventional antiretroviral drugs may lead to more potent, diverse, and resilient treatment options, potentially reducing the development of drug resistance.

In conclusion, the clinical trials and development of marine-derived anti-HIV compounds mark an exciting frontier in the battle against HIV/AIDS. While challenges persist, the successes achieved to date and the ongoing research efforts signal a shift toward a more diversified and sustainable approach to HIV treatment. As we advance, the cumulative knowledge gained from clinical trials will not only contribute to expanding our antiretroviral arsenal but may also pave the way for innovative treatments derived from the richness of the marine environment. This underscores the importance of continued investment and collaboration in the exploration of marine biodiversity for therapeutic solutions to global health challenges.

V. SAFETY AND SIDE EFFECTS

The safety profile of marine-derived anti-HIV compounds is a critical aspect of their development and potential clinical use. Understanding the safety and potential side effects is essential for evaluating the feasibility and ethical implications of these compounds as therapeutic options. This section explores the safety considerations associated with marine-derived anti-HIV drugs, examining their profiles in comparison to conventional treatments.

A. Examination of Safety Profiles of Marine-Derived Compounds

Before any drug can be considered for widespread clinical use, a comprehensive understanding of its safety profile is paramount. Marine-derived compounds, with their diverse chemical structures and unique origins, undergo thorough

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safety assessments in preclinical and clinical settings. These assessments include studies on acute and chronic toxicity, potential carcinogenicity, and adverse effects on vital organs.

Research on the safety profiles of marine-derived compounds often involves both in vitro and in vivo studies. These investigations aim to identify potential red flags and ensure that the therapeutic benefits of these compounds outweigh any associated risks. It's crucial to establish a balance where the anti-HIV properties of these compounds are maximized, and any potential harm is minimized.

B. Comparison with Conventional Anti-HIV Drugs

To evaluate the safety of marine-derived anti-HIV compounds comprehensively, a comparative analysis with conventional antiretroviral drugs is essential. This involves assessing not only the direct safety of the compounds but also understanding how they interact with the human body, potential drug-drug interactions, and the risk of developing resistance.

Conventional antiretroviral drugs, while effective, are known to have side effects ranging from metabolic issues to gastrointestinal problems. Comparing the safety profiles of marine-derived compounds with these established drugs provides valuable insights into their relative merits and drawbacks. If marine-derived compounds exhibit comparable or superior safety profiles, it strengthens their potential as alternative or complementary treatments.

C. Potential Side Effects and Mitigations

Despite rigorous safety assessments, no drug is entirely without side effects. Understanding the potential side effects of marine-derived anti-HIV compounds is crucial for managing patient expectations and ensuring the overall well-being of individuals undergoing treatment.

Common side effects associated with antiretroviral drugs include nausea, fatigue, and immune system dysregulation. For marine-derived compounds, side effects may vary based on their specific mechanisms of action. Some compounds may interact with other medications, leading to unforeseen complications.

Mitigation strategies play a pivotal role in addressing side effects. This involves developing protocols for monitoring patients during treatment, adjusting dosage regimens, and identifying populations that may be more susceptible to certain side effects. Additionally, ongoing research may lead to the development of formulations that minimize adverse reactions while maximizing therapeutic efficacy.

In conclusion, the safety and side effect profile of marine-derived anti-HIV compounds is a dynamic field of study. As these compounds progress through clinical development, ongoing research is essential to refine our understanding of their safety parameters. A comprehensive analysis, including comparisons with existing antiretroviral drugs and strategies for mitigating potential side effects, contributes to the responsible and ethical advancement of marine-derived compounds as viable options in the fight against HIV/AIDS.

VI. RESISTANCE AND CHALLENGES

The potential emergence of resistance and various challenges associated with marine-derived anti-HIV drugs pose significant considerations in their development and clinical application. This section explores the dynamics of resistance, strategies to overcome it, and the broader challenges influencing the utilization of these compounds in the context of HIV treatment.

A. Exploration of Potential Resistance Mechanisms

Antiretroviral resistance is a persistent challenge in the field of HIV/AIDS treatment, and understanding the potential resistance mechanisms to marine-derived compounds is essential. HIV has a remarkable ability to mutate, and prolonged exposure to any antiretroviral agent can lead to the selection of drug-resistant variants. Investigating the specific mechanisms through which HIV may develop resistance to marine-derived compounds is critical for devising effective strategies to prevent or manage resistance.

Resistance can occur at various stages of the viral life cycle targeted by these compounds. It may involve alterations in the viral proteins targeted by the drugs or changes in the cellular factors that interact with the compounds. Research in

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this area provides valuable insights into the resilience of HIV and informs the design of combination therapies that minimize the risk of resistance.

B. Strategies to Overcome Resistance

Developing strategies to overcome resistance is imperative for ensuring the long-term efficacy of any antiretroviral therapy. In the context of marine-derived compounds, several approaches can be considered to address and mitigate resistance.

Combination Therapies:

Utilizing marine-derived compounds in combination with conventional antiretroviral drugs can create a multi-faceted attack on the virus, reducing the likelihood of resistance development. This approach leverages the strengths of different compounds and targets multiple stages of the viral life cycle simultaneously.

Rotational Therapy:

Implementing rotational therapy involves periodically changing the antiretroviral regimen to prevent the virus from adapting to a single drug. This strategy, applied to marine-derived compounds, could be a proactive measure to minimize the emergence of resistance.

Drug Modification:

Continual research and modification of marine-derived compounds can lead to the development of analogs or derivatives with increased potency and a reduced likelihood of resistance. Understanding the structural aspects contributing to resistance allows for the design of compounds that are less susceptible to viral mutations.

VII. CONCLUSION

The exploration of marine-derived anti-HIV drugs represents a promising frontier in the pursuit of innovative and effective treatments for HIV/AIDS. The comprehensive review has highlighted the diverse mechanisms of action exhibited by these compounds, their progression through clinical trials, and the crucial considerations of safety, potential side effects, resistance mechanisms, and developmental challenges. While successes in clinical trials underscore the potential of marine-derived compounds, challenges such as production scalability, bioavailability optimization, and regulatory complexities must be diligently addressed. Strategies to overcome resistance, including combination therapies and drug modifications, offer avenues for enhancing the long-term efficacy of these compounds. The ethical considerations of sustainable sourcing and the environmental impact of drug development underscore the need for a balanced and responsible approach. As research continues to unfold, the cumulative knowledge derived from the exploration of marine biodiversity not only expands our antiretroviral arsenal but also exemplifies the importance of interdisciplinary collaboration and ongoing commitment to combating global health challenges. The integration of marine-derived anti-HIV drugs into mainstream treatment protocols holds the potential to significantly contribute to the comprehensive management and eventual eradication of HIV/AIDS.

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