

## New pathway to regulate nitrate absorption in plants

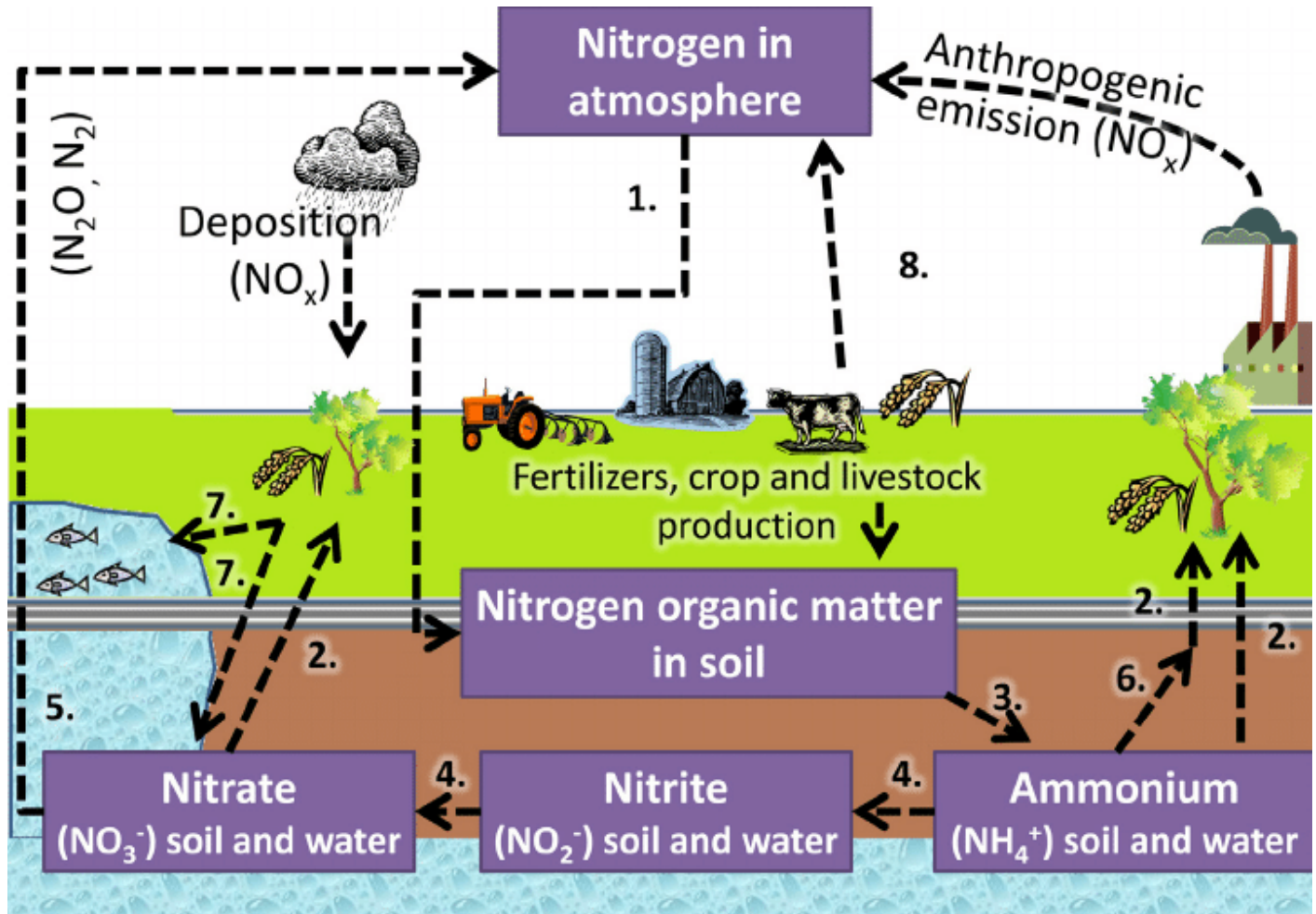
(GS Paper 3, Science and Tech)

### Why in news?

- Researchers led by those from the National Centre of Biological Sciences, Tata Institute of Fundamental Research, Bengaluru (NCBS-TIFR), have found a new pathway that regulates nitrate absorption in plants.

### Crux:

- The gene **MADS27**, which regulates **nitrate absorption, root development and stress tolerance**, is **activated by the micro-RNA, miR444**, therefore offers a way to control these properties of the plant.
- The researchers studied this mechanism in both rice (monocot) and tobacco (dicot) plants.



### Role of Nitrogen:

- Nitrogen is one of the most important macronutrients needed for development of a plant. It is a part of chlorophyll, amino acids and nucleic acids, among others.
- It is mostly sourced from the soil where it is mainly absorbed in the form of nitrates and ammonium by the roots.
- Nitrates also play a role in controlling genome-wide gene expression that in turn regulates root system architecture, flowering time, leaf development, etc
- Thus, while a lot of action takes place in the roots to absorb and convert nitrogen into useful nitrates, the absorbed nitrates in turn regulate plant development apart from being useful as a macronutrient.

### Nitrate overuse:

- The overuse of nitrates in fertilizers, for instance, can lead to the **dumping of nitrates in the soil** which leads to accumulation of nitrates in water and soil. This accumulation adds to **soil and water pollution** and increased contribution to greenhouse gases.
- To avoid this, there should be optimal use of nitrates. Also, since the whole process of nitrate absorption takes place in the roots, a well-developed root system is needed for this to take place optimally.
- At one level, it is known that the hormone auxin is responsible for well-developed roots across all plants. A number of genes are known to help with auxin production, improved nitrate transport and assimilation in plants.

#### **Regulatory switches:**

- In addition to this route, several gene regulatory switches that regulate nitrate absorption and root development, such as the micro-RNA, miR444, are known in monocot plants, such as rice.
- The micro-RNA ‘miR444’ is specific to monocots. When this is not made, its target, MADS27, is produced in higher abundance, and it improves biosynthesis and transport of the hormone auxin, which is key for root development and its branching.
- This regulatory miR444 switch is known to turn off at least five genes called MADS box transcription factor genes.
- The speciality of the MADS box transcription factors is that they function like switch boxes of their own. They bind to their favourite specific DNA sequences and they switch the neighbouring genes “on.”

#### **Three-pronged effect:**

- The researchers have studied a target gene of miR444 called MADS27, a transcription factor which hasn’t been studied well before. They have found that this transcription factor has a three-pronged effect on the plant.
- First, it **regulates nitrate absorption by switching “on” proteins** involved in this process.
- Second, it **leads to better development of the roots by regulating auxin hormone** production and transport.
- Finally, and somewhat surprisingly to the researchers, it **helps in the abiotic stress tolerance** by keeping the main stress player proteins “on.”

#### **Way Forward:**

- Tinkering MADS27 expression by genome editing is the next step, so that the modified plants are acceptable to use directly.
- The larger goal of this study is to understand how epigenetics plays a role in regulating expression of such important genes.

## **India should support antibiotics development**

**(GS Paper 3, Science and Tech)**

#### **Context:**

- Antimicrobial resistance (AMR) is a looming public health crisis impacting every country globally with a disproportionate impact on lives and livelihood in low and middle-income countries.
- A recent report from the Global Research on AntiMicrobial resistance (GRAM) project found that in 2019, an estimated 4.95 million people suffered from at least one drug-resistant infection and AMR directly caused 1.27 million deaths.

#### **AMR burden in India:**

- AMR is one of **India’s major public health problems**, directly contributing to **about 30% of deaths due to neonatal sepsis across India**. These are due to multidrug-resistant (MDR) hospital-acquired infections in many cases.
- Over 30% of the COVID-19 deaths in India could be attributed to **failure to treat the secondary bacterial** infections caused by MDR pathogens with the appropriate antibiotics.
- **Irrational antibiotic use by the medical community**, the general public and the farmers generate drug-resistant superbugs. **Inadequate infection control measures** in the hospitals and the sanitation issues in the community result in the dissemination of these superbugs.

#### **What needs to be done by India?**

- To tackle the AMR crisis, there is need for **robust investment in research and development** of new antibiotics, rapid and affordable diagnostics, strengthening infection control and prevention practices, formulating and implementing antibiotic stewardship programmes across the country and ensuring equitable access to life-saving antibiotics.
- One such immediate intervention is a move by the **Government of India to pass legislation banning the use of streptomycin and tetracycline in agriculture** and the growth promotional use of colistin in poultry farming.



#### **Dry antibiotic pipeline:**

- During the last decade, the success rate from Phase 1 to FDA approval for new antibacterial drugs was found to be 16.3% in comparison to the overall industry average of 7.9%.
- Despite this higher success rate, antibiotic development suffers from a lack of investment and quick market uptake of newly approved products.
- The exit of big pharma from antibiotic development coupled with a lack of investment from venture capitalists and the paucity of enabling regulatory and policy solutions to support the commercial viability of antibacterial agents has pushed AMR into a global health crisis.

#### **Why is the market for antibiotics broken and the drug pipeline ultra thin?**

- Unlike most new drugs, post-approval, **new antibiotics are used sparingly** (antibiotic stewardship practices) and reserved mainly for cases in which older antibiotics are ineffective.
- In addition, the **reimbursement mechanisms in several countries discourage hospitals** from using an expensive novel broad-spectrum antibacterial agent when a cheaper generic option is available.
- These unique challenges in the current treatment guidelines and archaic reimbursement models contribute to commercial failure and restricted or lack of access for patients in dire need of these life-saving agents.
- Most major pharma companies have exited the AMR space because of the **low return on investment (ROI)**. Surprisingly, around 80% of the antibiotics currently in the clinical pipeline are developed by small biotech companies.

#### **The push-pull model:**

- Small companies are getting early-stage funding from public-private partnerships like CARB-X (the Combating Antibiotic Resistance Bacteria Biopharmaceutical Accelerator), which has provided more than \$360 million in funding for 92 antibacterial projects over the past five years.
- This funding is an example of the push model that has catalysed the creation of a robust pipeline of projects in early discovery.
- The **pull vector may come from the “Pioneering Antimicrobial Subscriptions to End Upsurging Resistance” (PASTEUR) Act**, if and when the U.S. government passes it. Companies that develop critically needed antibiotics for drug-resistant infections would receive a federal government contract ranging from \$750 million to \$3 billion spread over ten years.
- To incentivise the creation of new treatments, the U.S. Congress enacted the **Generating Antibiotic Incentives Now Act (GAIN Act)** of 2012, which provides benefits to manufacturers of Qualified Infectious Disease Products (QIDPs) including five years of additional non-patent exclusivity.
- In addition, the recent creation of the AMR Action Fund with a mandate to invest more than \$1 billion to address the current funding gaps in the development of new antibiotics will give a boost to late-stage molecules in clinical development.

### **India’s patent law safeguards under fire** (GS Paper 2, Governance)

#### **Why in news?**

- Recently, the Economic Advisory Council (EAC) to the Prime Minister recommended the period within which patent applications are open to challenge by the public be restricted to a mere six months from the date of its publication.

#### **Why it matters?**

- The price-lowering effect of competition and domestic manufacturing of medicines can transform how diseases get treated in resource-poor settings.
- Decisions made by Indian patent offices can negatively impact generic competition and supply worldwide, relying on the availability of affordable medicines made in India.



## Background:

- In 2005, lawmakers from all political parties amended Indian patent law to ensure that the Indian patent office did not grant monopolies on old science or for compounds already in the public domain.
- The new law now prevents drug corporations from indulging in “evergreening”, a common abusive patenting practice aimed at obtaining separate patent monopolies relating to the same medicine.
- And to bring this to the notice of the patent examiners, the amended patent law allowed any person to file a pre-grant opposition ‘anytime’ before the patent office decides to grant or reject a patent application.

## Concerns:

- Since the Indian Patent Offices receive an average of 50,000 patent applications a year, examiners often miss critical information about the patent application under consideration.
- A recent study on pharmaceutical patent grants in India revealed that **7 out of 10 patents are granted in error by the Indian Patent Office**. A robust pre-grant opposition system provides an additional administrative layer of scrutiny that prevents the grant of frivolous patents through third parties’ participation in the review process.
- Evergreening monopolies on medical products is a lucrative game for pharmaceutical corporations allowing them to charge high prices.
- The commerce ministry, responsible for administering the patents act, is now under pressure to restrict pre-grant patent oppositions.

## Pre-grant oppositions:

- In 2005, the first challenge to a pending patent claim on a medicine was filed by Cancer Patient Aid Association (CPAA) before the Indian patent office.
- CPAA highlighted that the Swiss corporation Novartis’ patent application on Imatinib Mesylate (Gleevec), a life-saving anti-cancer drug, claims a salt form of old medicine, a common practice within the pharmaceutical industry, and should not be considered patentable.
- The patent office subsequently rejected the patent, which was later **upheld by the High Court and the Supreme Court**.
- The pre-grant opposition by CPAA on the cancer drug protected the price reduction from over Rs. 14 lakh per patient per year from Novartis to less than Rs. 40,000 per patient per year from generic manufacturers.
- Several such challenges before the patent office have successfully ensured the availability of affordable HIV medicines to millions living across the developing world.
- The 99% reduction in the prices of antiretrovirals following the generic competition, from \$10,000 per person per year down to less than \$100, has been a critical factor in the expansion of antiretroviral treatment to millions in low and middle-income countries.

## What needs to be done?

- Prescribing a timeline and cutting short the window period for pre-grant opposition makes it difficult to challenge frivolous patent applications on drugs and vaccines. The information in patent applications does not permit the public to rapidly identify the claimed medical product.
- The identification and further analysis are time-consuming as several applications are pending on the same medicine, vaccine or technology.
- Reducing the opportunities for filing challenges to pending patent claims will not increase efficiency or reduce pendency. On the contrary, pre-grant oppositions provide information to the examiners that can help speed up the examination process and deny invalid patents.

## The real challenge:

- The humanitarian medical organisation, Médecins Sans Frontières (MSF), has supported hundreds of pre-grant oppositions in India, working closely with patient groups to safeguard generic competition to increase access to affordable medicines from India.
- Tackling the overwhelming number of evergreening patent claims on known drugs and technologies is the real challenge for the Indian patent office. The attempt to dilute the timeline on pre-grant opposition diverts from the real problem.

## How will G-7's infrastructure plan impact India?

(GS Paper 2, International Relation)

### Why in news?

- Recently, the G-7 grouping launched a **U.S.-led \$600 billion Partnership for Global Infrastructure and Investment (PGII)** at their summit in Germany's Schloss Elmau, where India was among five special invitees.
- The initiative was billed as a “**values-driven, high-impact, and transparent infrastructure partnership** to meet the enormous infrastructure needs of low- and middle-income countries and support the U.S. and its allies' economic and national security interests.”
- The PGII would offer a counter to China's Belt and Road Initiative (BRI) for projects worldwide that was formally launched five years ago.



### What was India's response?

- India was not privy to PGII consultations, nor was the infrastructure plan part of the documents that were signed by **India, Indonesia, South Africa, Senegal and Argentina**, who were part of the “**G-7 outreach**” invitees to the summit. The EU has participated in the G-7 since 1981 as a “nonenumerated” member.
- At the Quad Summit in Tokyo, Indian Prime Minister had attended the launch of the U.S. led “Indo-Pacific Economic Initiative” (IPEF) with similarly sudden plans, and India had joined as an “initial” or founding partner country.
- It also came as a surprise that India hadn't endorsed the PGII plan given that the U.S. billed it as a rival to China's BRI, with much more sensitivity to sustainable debt burdens and environmental concerns.
- India has actively opposed the BRI because it had ignored these reasons and for its “violation of territorial integrity”.

### Is there any specific role for India?

- The PGII will have **four key priorities on infrastructure**: climate and energy security, digital connectivity, health and health security, and gender equality and equity, all of which are priority areas for India as well.
- The PGII “factsheet” released by the White House also includes a specific plan for **investment in an Agritech and Climate sustainability fund** that would “invest in companies that increase food security and promote both

climate resilience and climate adaptation in India, as well as improve the profitability and agricultural productivity of smallholder farms.”

- The **India fund would target \$65 million by September 2022**, and a target capitalisation of \$130 million in 2023.
- The U.S. government’s International Development Finance Corporation (DFC) would mobilise \$30 million in private capital for the fund.

#### **What could be some of the reasons for India’s reticence on PGII?**

- The Ministry of External Affairs has not yet expanded on its initial response to the PGII, and it is quite possible, that once it has studied and verified its strategy, it will endorse it.
- One of the reasons for some scepticism in India is that the PGII is one of a number of U.S.-led economic initiatives announced globally and in the Indo-Pacific, **without much clarity on whether they would overlap, or run concurrently with each other.**
- At the Quad Summit, U.S. committed to a \$50 billion infrastructure fund over five years. The PGII announcement for \$600 billion over five years also comes a year after the U.S. led a G-7 initiative to counter China’s “strategic competition” and to narrow the roughly \$40 trillion “infrastructure gap” in the developing world.
- In 2021, the Biden administration also revived a Trump administration project for the **“Blue Dot Network Initiative”** to certify infrastructure projects, but had stopped short of funding them.

#### **Consistency in decision making:**

- Another reason for the Indian reaction, could be to show consistency, given India’s earlier reaction to the BRI, when it was first announced by Xi Jinping in 2013, years before the formal launch in 2017.
- When China first unveiled the BRI, India’s initial response was also that this was a plan with geopolitical consequences that India had not been consulted on.
- India said it would have to study before responding. It is possible that the Indian government’s cautiousness on PGII is about striking a similar balance.