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Review paper

A Review on Natural Products of Actinobacteria Reported from Different Habitats:

A Road-Way for Investigation of Bioactive Compounds for Bio-Medicinal Utility

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ABSTRACT

Actinobacteria are the valuable source of secondary products especially drugs that have been used from time immemorial in various cultures. This group of bacteria has been reported to have a variety of natural products that show evidence of diverse activities, such as antimicrobial, antioxidant, immunomodulatory, anti-inflammatory, anticancer, and antidiabetic activity. However, the activity bioactivity of the natural products could be varying depending on their genus/species, habitats and also isolation and extraction methods. In the present review, it has been highlighted the advantages of exploring novel habitats and also isolation of potential natural products from the promising and potential isolates that to have promising bioactive compounds. This review also suggested that partly analysis of the literature on habitats, promising habitats and biological activities highlights the isolation of potential actinobacteria from underexplored habitats, and also highlight the possibility of obtaining chemically diverse natural products. The present review revealed the various extracellular enzymes in actinobacteria and other bio-chemical agents, such as antidiabetic compounds.

1. Introduction

Exploring of natural products is an ancient and modern practice for obtaining a novel and potential bioactive compound for medicine and other sectors. Since, the starting of human race, exploring of natural products are the very known practices for novel and potential compounds for various applications, including diseases, agriculture, textiles, and others. It has been reported that natural products are the most successful source of potential drug leads (Rey-Ladino et al., 2011). Although it has been reported that their implementation in drug discovery and development efforts has demonstrated a decline in interest (Gayathri et al., 2011), nevertheless, to date, natural products continue to provide a unique and diverse chemical structure in comparison to combinatorial chemistry, which supports discovering novel and potential low-molecular-weight lead compounds. According to the World Health Organization (WHO), about 60% of the world's population depends on traditional medicine for their health care (El-Naggar et al., 2020). The use of traditional medicine came from natural products as well. So, it is possibly the use of natural products as medicinal agents in drug discovery and the development of lead drugs for the welfare of humans that are used in various specific natural resources such as plants and their parts and microbes to cure diseases. Considering under 10% of the world's biodiversity have been assessed for prospective biological activity significantly more beneficial natural lead compounds anticipated to be discovered with the question being how to access this natural chemical diversity (Kalyani et al., 2012). Studies have revealed the diversity of actinobacteria from various habitats, viz. marine sediments (Sirisha et al., 2013), wasteland alkaline and garden soil (Narendra et al., 2010), estuarine finfish *Mugil cephalus* Lin. (Murugan, 2007), near seashore sediment and seawater (Gulve and Deshmukh, 2012), sponges (Shamikh et al., 2020), laterite soil samples (Chinna Narasaiah et al., 2014), and mangrove sediments (Naligama et al., 2022). As per the reports, actinobacteria have been produced anti-diabetic agents (Gayathri et al., 2011; Saini et al., 2015), anti-bacterial (Gayathri et al., 2011), anti-fungal (Kavitha et al., 2010), anti-algal (Ravikumar et al., 2011), anti-malarial (Dahari et al., 2016), anti-inflammatory (Ravikumar et al., 2011), and anti-cancer (Olano et al., 2009). A broad classification of these activities is shown in Fig. 1.

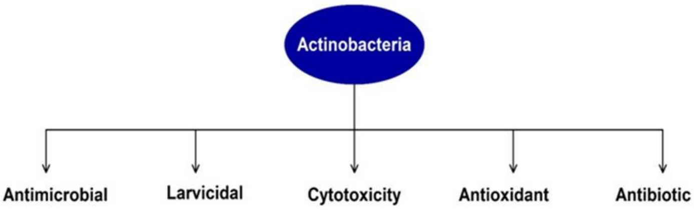

Fig. 1 Activities of actinobacteria

2. Various habitats

Actinobacteria have been demonstrated important biological contributions in terms of natural products in the fields of industry, research, and medicine (Chen et al., 2021). Actinobacteria are difficult to isolate using traditional isolation techniques, nevertheless. It has been noted that uncharted environments yield a greater number of isolates than other habitats. Fermented food could be one of the unknown habitats, particularly fermented soybeans from the northeastern state of India. Though it goes by a variety of regional names and reported for the generation of bioactive compounds from bacteria. "Hawaijar," a fermented formed of soybean, a native protein source in Manipur, north-eastern India. Actinobacteria are reported from Hawaijar along with other groups of bacteria. In this account, the authors try to hit on one of the natural resources, which are fermented soybeans and their associated microbes, especially actinobacteria. Actinobacteria are account for producing 70 -80% secondary metabolites. The diverse chemical structures produced by actinobacteria are unmatched by any other group. It has been assumed that obtaining of novel bioactive compounds from uninvestigated habitats granting the reasoning for the bioprospection of new habitats. These secondary metabolites are derived from actinobacteria contains bioactive compounds, antitumor compounds, antioxidant compounds and antifungal compounds (Fig. 2).

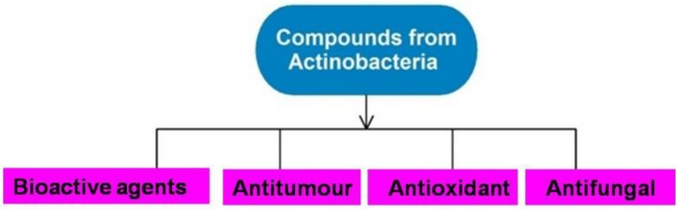

Fig. 2 Bioactive compounds from actinobacteria

When it comes to natural products and bioactive compounds, for screening enzymes in microorganisms –secondary metabolites in actinobacteria are started to show the results. In the last few years actinobacteria from India have been well recorded with the production of potential bioactive compounds from diverse habitats. Many habitats, such as marine soil and sediments, the vicinity of the coast, soil, the Krishna River, mangrove sediments, tropical forests, phoomdi soil, sponges, desert soil, wasteland and alkaline gardens, laterite soil, earthworm casting, sand dunes, estuaries, industrially polluted coasts, endophytes, and oil-polluted coastal regions, have all successfully isolated cases of actinobacteria (Table 1) and the numbers of actinobacteria, as in Fig. 3.

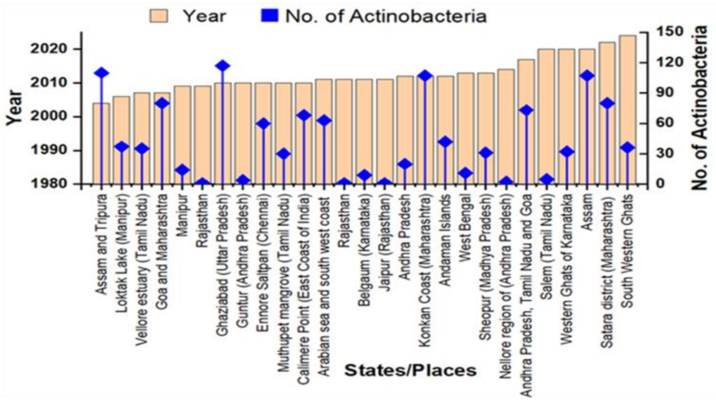

Fig. 3 Actinobacteria reported from different regions/habitats since 2004

Actinobacteria with potential for bioactivity have been reported from India in huge numbers. Furthermore, there are numerous findings on the anti-larvicidal and cytotoxic properties of actinobacteria from diverse ecosystems.

11% of actinobacteria from Andhra Pradesh, Gujarat, the Gulf of Mannar, Maharashtra, Karnataka,

Table 1 Actinobacteria and their activity reported from various habitats

States/Places	Habitats	No. of actinobacteria	Antidiabetic activity	Antimicrobial activity		Enzymes secretion	Other biological activities		Ref.
				No. of isolates showed antibacterial activity	No. of isolates showed Antifungal activity		Melanin production	Larvicidal activity	
Salem (TN)	Mine soil	5	NR	1	NR	NR	NR	NR	El-Naggar et al. 2020
Andhra Pradesh	Soil sediments & marine	20	NR	3	NR	NR	NR	NR	Kalyani et al. 2012
Ghaziabad (UP)	Wasteland alkaline and garden soil	117	NR	15	NR	NR	NR	NR	Narendra et al. 2010
Vellore estuary (TN)	Estuarine finfish *Mugil cephalus* Lin.	35	NR	NR	NR	Cellulase	NR	NR	Murugan et al. 2007
Konkan Coast (Maharashtra)	Seashore sediment	107	NR	8	8	NR	NR	NR	Gulve and Deshmukh, 2012
Guntur (AP)	Terrestrial	4	NR	NR	1	NR	NR	NR	Kavitha et al. 2010
Arabian sea and south west coast	Marine and soil sediments	63	NR	5	5	NR	NR	NR	Ravikumar et al. 2011
Manipur	Soil and sediment	14	NR	NR	NR	Protease	NR	NR	Ningthoujam et al. 2009
Rajasthan	Desert soil	1	NR	NR	NR	NR	1	NR	Diraviyam et al. 2011
Ennore Saltpan (Chennai)	Nearby korttalaiyar river, Ennore creek and the Bay of Bengal	60	NR	1	1	Chitinase	NR	NR	Lakshmipathy and Krishnan, 2010
Muthupet mangrove (TN)	Marine sediment	30	NR	NR	NR	NR	NR	Larvicidal activity	Murugesan et al. 2010
South Western Ghats	Tropical montane forest	36	NR	NR	NR	Urease Tyrosinase	NR	NR	Rinoy et al. 2012
Satara district (Maharashtra)	Krishna River	80	NR	NR	NR	Chitinase	NR	NR	Rammali et al. 2022
Calimere Point (East Coast of India)	Seashore	68	NR	25	16	NR	NR	NR	Vijaykumar et al. 2010
Goa and Maharashtra	Marine sediments	80	NR	18	7	NR	NR	NR	Thakur et al. 2007
Assam and Tripura	Protected forest	110	NR	65	47	NR	NR	NR	Kokare et al. 2004
Loktak Lake (Manipur)	Soil sample collected from Phoomdi of Loktak Lake	37	NR	12	12	NR	NR	NR	Shantikumar et al. 2006
Rajasthan	Desert soil	1	NR	100	NR	NR	NR	NR	Selvameenal et al. 2009

NS	*Streptomyces hygroscopicus-limoneus* *S. calvus* *S. dimorphogenes*	NS	Voglibose Acarbose Valienamine Adiposin-1 Trestatin-B	NR	NR	NR	NR	NR	Kameda et al. 1984; Mahmud 2003; Truscheit et al. 1981; Okose et al. 1983; Yokose et al. 1984; Mazumdar et al. 2023
Belgaum (Karnataka)	Soil	9	NR	6	1	NR	NR	NR	Khwaja et al. 2011
Andaman Islands	Mangrove sediments	42	NR	22	NR	NR	NR	NR	Mangamuri et al. 2012
West Bengal	Dump soil (Hospital waste dump soil)	11	NR	1	NR	NR	NR	NR	Saha et al. 2013
Sheopur (MP)	Soil	31	NR	6	NR	NR	NR	NR	Chaudhary et al. 2013
Nellore region of AP	Mangrove soil	2	NR	2	2	NR	NR	NR	Janardhan et al. 2014
AP, TN and Goa	Maine soil	73	NR	8	8	NR	NR	NR	Kavitha and Savithri 2017
Rajasthan	*Thar* Desert	*Saccharothrix* sp. TD-093	NR	Showed activity	No activity	NR	NS	NA	Ibeyaima et al. 2017
Jaipur (Rajasthan)	Sandy soil	1	NFAT-133	NR	NR	NR	NR	NR	Kulkarni-Almeida et al. 2011
Western Ghats of Karnataka	Forest soil	32	NR	7	4	NR	NR	NR	Siddharth et al. 2020
Assam	Pobitora Wildlife Sanctuary Kaziranga National Park	107	NR	51	59	Amylase Cellulase Protease Lipase Esterase	NR	NR	Sharma and Thakur 2020
India	Fermented foods	Reported actinobacteria, but not specified	NR	NR	NR	Bioactive peptides Biogenic amines Antioxidant Antihypertensive Antibacterial	NR	NR	Shah et al. 2023

Orissa, Tamil Nadu, and West Bengal, as per the report of Kathiresan et al. (2005). The sludge soil harbored the maximum number of actinobacteria that were active against test organisms as per the reports (Kathiresan et al., 2005). It is also reported that after sludge soil habitat, river bank is next, followed by forest, ravine, and saline, which are unexplored habitats for actinobacteria. So, actinobacteria isolateon from unexplored habitats is an important research area for potential and promising bioactive compounds and their derivatives, and there are possibilities of obtaining novel products from unusual environments. The variety of terrestrial actinobacteria is of remarkable significance in several fields of science and medicine, especially in antibiotic production.

Actinobacteria are very rarely reported in fermented foods, but as per the reports, actinobacteria are isolated from Baijiu, distilled liquors (Chen et al., 2022). Also, Chen et al. (2022) reported actinobacteria in Kraut, a fermented product. In context of the India, especially the north eastern states, the authors came across about fermented foods and its associated microbes especially actinobacteria (Tamang et al., 2016), but the reports are very less in number.

Both terrestrial and marine habitats are well explored habitats. Actinobacteria from marine sediments, terrestrial, saltpan, soil, mangrove, wasteland, mine soil, desert, lake, and forest from India (Andhra Pradesh, Assam, the cold desert of the Himalaya, Gujarat, Kerala, Karnataka, Madhya Pradesh, Maharashtra, Manipur, Tamil Nadu, Tripura, Uttar Pradesh, and West Bengal) have been reported, identified, and screened for their natural products. Most actinobacteria are reported from soil, marine, and wasteland, potential compounds are only isolated from unexplored habitat. Extreme habitats have also been documented for the production of melanin by actinobacteria. *Streptomyces rochei, S. actousus* (Strain CL-30), *S. pseudogriseolus, Streptomyces* sp. VITDDK2, *Streptosporangium* sp., *Saccharopolyspora* sp., *Micromonospora brevicatiana, Glycomyces, Nocardiopsis, Nocardiodes, Actinopolyspora, Kibdelosporangium, Actinosynnema, Actinomadura, Thermoactinobacteria, Kineosporia, Pseudonocardia* sp. VUK-10, *Saccharopolyspora* sp., and *Nocardia* are reported that producing various natural products. The various activity, such as antimicrobial activity, enzyme secretion property, and cyto-toxicity property of *Nocardiopsisprasina* HA-4 (Ningthoujam et al., 2009), *Nocardiopsis*s p. VITSVK5 (Vimal et al., 2010), *Streptomyces* sp. D5 (Diraviyam et al., 2011), and *Rhodococcus canchipurensis* sp. nov. (Li et al., 2014).

3. Natural products

Actinobacteria are known to produce chemically diverse compounds with a broad series of natural tricks. Industrially significant bioactive compounds are also known to be produced by this group of bacteria. There are countless questions in the fields of medicine, industries, and research which could be answered by exploiting the actinobacteria from various unexplored regions. India also contributes to the field of research by investigating and analyzing the actinobacteria from various habitats. According to this report, the possibilities for obtaining actinobacteria are greater in unexplored habitats.

In 2010 and 2011, Deepika and Kannabiran (2010) reported heavy metal resistance and biosurfactant activity of actinobacteria in marine soil and saltpan soil. Lakshmipathy and Krishnan (2010) reported a potential actinobacteria from marine soil. Murugesan et al. (2010) reported the actinobacteria from Tamilnadu (Muthupet mangrove), which exhibited anti-larvicidal activity. Murugesa et al. (2010) reported that 76.66% of actinobacteria that to have active against larvae, indicated the possibility of obtaining active compounds that could active against the various larvae.

4. Enzymes secretion

In 2001, Sharma and Pant reported *Rhodococcus* species that degraded crude oil (Sharma and Pant, 2001). An amylase (Narendra et al., 2010; Selvam et al., 2011), cellulase (Murugan et al., 2007), gelatinase (Maiti and Mandal, 2019), lipase (Selvam et al., 2011; Sharma and Thakur, 2020), and xylanase (Bhatt and Das, 2024), chitinase (Sarkar and Suthindhiran, 2022), asparaginase (Basha et al., 2009), glutaminase (Basha et al., 2009), esculinase (Sivakumar et al., 2006), keratinase (Subash et al., 2024), protease (Jayasree et al., 2010), tyrosinase and urease (Rinoy et al., 2012) are the industrially important enzymes produced by species of *Streptomyces* under actinomycetales, as in Fig. 4. This group of bacteria is well known for the production of enzymes, which could be scaled up at the industrial level. A amylase, chitinase, asparaginase, esculinase, gelatinase, lipase, keratinase, protease, tyrosinase, urease, and xylanase are the enzymes which are documented from actinobacteria, as in Table 1.

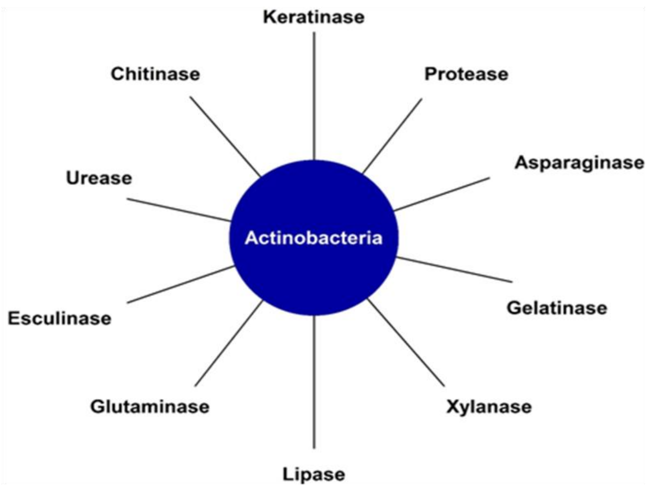

Fig. 4 Enzymes found in actinobactera

5. Anti-inflammatory and Anti-oxidant properties

Anti-inflammatory activity has been reported from the extracts obtained from actinobacteria (Baskaran et al., 2022). Anti-inflammatory activity has also been reported from soil based actinobacteria from different extremely cold sites (Rammali et al., 2022). *Streptomyces* species from bamboo rhizosphere soil has been reported that has anti-oxidant activity (Govindaraj et al., 2023), also have antibacterial activity. **A**ntioxidant activity in addition to scavenging activity for ABTS, DPPH, and superoxide radicals of *S. levis* strain HFM-2 isolated from human gut has also been reported (Verma et al., 2023). *S. lavendulae* stain CSA5 is reported for antimicrobial, cytotoxic and antioxidant properties (Kumar et al., 2014). There is other strain also that has anti-oxidant properties, such as *S. variabilis* (Dholakiya et al., 2017). *S. variabilis* has been reported from the under explored sea sediment of Alang, Gulf of Khambhat (Gujarat), India (Dholakiya et al., 2017).

5.1 Secretion of pigment

Indian actinobacteria are also screened for the production of melanin (Diraviyam et al., 2011). Diraviyam et al. (2011) also reported the secretion of melanin pigment by Streptomyces griseorubiginosus D5 (Diraviyam et al., 2011). Recently, Sunil et al. (2012) reported the production of melanin by actinobacteria; melanin production is one of the most significant properties in screening of actinobacteria morphologically (Attimarad et al., 2012).

5.2 Anti-tumor activity

Streptomyces species is reported for its cytotoxic activity (Narendra et al., 2010). Balagurunathan et al. (2011) reported *S. griseorubiginosus* (D5) from desert soil (Diraviyam et al., 2011). Compounds against tumor cell lines have been reported (Rajesh et al., 2013). *Streptomyces* sp. CMAA 1527 and *Streptomyces* sp. CMAA 1653 are documented that produce a natural product that control proliferation of breast (MCF-7), glioblastoma (U251), lung/non-small (NCI-H460) and kidney (786-0) human cancer cell lines (Silva et al., 2020). Actinobacteria are also reported for producing anti-colorectal cancer (CRC) drugs (Bahrami et al., 2022). A report suggested that the chemical structure of 232 Natural Products (NPs) presenting anti-CRC activity. Majority of the NPs are originated from marine actinobacteria followed by other habitats like terrestrial and plants. The NPs are primarily made by *Actinomadura, Micromonospors, Saliniospors* and *Streptomyces*. Among them, *Streptomyces* has been predominantly contributing in generating compounds (over 76%) exclusively (Bahrami et al., 2022).

5.3 Production of antibiotics

Actinobacteria are very well known for producing bioactive substances, especially antibiotics active against bacteria and fungi. On the contrary, actinobacteria are well known for producing extracellular enzymes. Rajendra et al. (2003) documentted *Pseudonocardia* sp. B6273 from marine that produced phenazostatin D (1a) a new phenazine derivative. The configuration of this compound has been reported to be the *meso*-form of phenazostatin B (1b). Phenazostatin D has been reported inactive against the tested microorganisms (Maskey et al., 2003). The known phenazine antibiotic methyl saphenate is also produced by *Pseudonocardia* sp. B6273. In 2011**,** Gulve and Deshmukh (2012) reported an unexplored habitat, *i.e.,* the coastal sediments of the Konkan Coast of Maharashtra, and isolated various enzymes. India is rich in flora and fauna (Vijaykumar et al., 2010). There are various regions and habitats yet to be investigate for actinobacteria. *Rhodococcus* sp. NCIM 5126 reported from a chronically oil-polluted coastal area near Mumbai Harbour and degraded a liphatic and aromatic nature but not the asphaltene fractions (Sharma and Pant, 2001). A total of one hundred ninety-two actinomycetes have been reported from near shore (marine environment) of Point Calimere, East Coast, India (Thakur et al., 2007). These isolates have been reported for antimicrobial activity against the test bacteria.

Though substantial work has been carried out successfully in various fields, the diversity of the extreme environments remains unexplored, including protected areas in north-eastern hills regions, the Thar Desert, the Bay of Bengal, the Indian Ocean, and its nearby areas. This report revealed the diverse actinobacteria in the Bay of Bengal and their potential as a source of unique bioactive compounds. Actinobacteria are enlisted (Table 1) from various habitats and their bioactive compounds and enzymes. Nearly 13% of actinobacteria are reported from Indian habitats, and there is a high possibility of isolating actinobacteria from new habitats for obtaining a diverse and potential actinobacteria and their natural products, which could help in discovery of novel compound and for tackling human-related diseases.

One hundred ten actinomycetes are reported from protected forests in Assam and Tripura; 47% of actinomycete is active against bacteria and 65% active against fungi, respectively (Kokare et al., 2004). Kokare et al. (2004) reported eighty actinobacteria from marine habitats (sediments), in Goa and Maharashtra, showing 18% activity against antibacterial and 7% against antifungal, respectively (Shantikumar et al., 2006). Similarly, seashore sediments in Maharashtra reported one hundred and seven actinobacteria (Gulve and Deshmukh, 2012).

8% of actinobacteria are active against bacteria and fungi. A soil sample collected from Phoomdi (Loktak Lake), Manipur, exhibits activity against bacteria and fungi. Thirty-seven actinobacteria are isolated from Loktak Lake, and 12% of actinobacteria are active against bacteria and fungi, respectively (Selvameenal et al., 2009). *S. hygroscopicus* subsp. *ossamyceticus* strain D10 exhibits maximum activity against bacteria (Kameda et al., 1984).

5.4 Anti-diabetic compounds

Compounds such as, voglibose, acarbose, valienamine, adiposin-1, and trestatin-B are reported from *S. hygroscopicus-limoneus*, *S. calvus*, and *S. dimorphogenes* respectively (Mahmud, 2003; Truscheit et al., 1981; Okose et al., 1983; Yokose et al., 1984; Mazumdar et al., 2023; Khwaja, 2011), and these compounds are used in the administration of type-2 diabetes. Recently, *Streptomyces* sp. strain PBR11 has been from forest derived soil reported that produced anti-diabetic compounds (Mangamuri et al., 2012).

6. Conclusion

Various habitats are reported from India with the isolation of actinobacteria that produced the potential natural products, but there are some gaps in the investigation pipeline of actinobacteria, such as fermented habitats. Although there is a report on the actinobacteria reported from fermented foods, but very less is known from fermented soybeans from India for antidiabetic compound and other properties. Most of the actinobacteria were characterized and investigated for their antimicrobial and enzymatic activity level only. So, there is a high chance of obtaining potential bacteria including actinobacteria that produce potential antidiabetic compounds with other bioactivity from fermented habitat by implementing various methods, approaches, and techniques, or a fusion of various approaches, for exploring the new compounds from unexplored habitats. Exploration of actinobacteria and the habitats in India is in its infant stage, this is why the there is a diversion towards the development of methods, techniques, and approaches for successful isolation, identification, characterization, and molecular analysis of actinobacteria including exploration of new habitats. It is hence proved, the most protected, conserved, and unexploited area (Table 1) is the most favorable habitat for the hunting of novel actinobacteria with the secretion of novel compounds for the welfare human and their society.

So, this review suggested there are high chances of obtaining diverse actinobacteria and extracting high percentage of natural products, such as, anti-diabetic agents, antimicrobial compounds, anti-cancer compounds, and enzymes from unexplored habitats. The isolation, characterization, and studies of bioactive from actinobacteria from various habitats in India could be a pathway for the breakthrough of potential bioactive compounds, and also to open a gateway to discover unexplored habitats, including fermented foods.

The production levels of bioactive compounds are restricted to a few habitats that need to be deal with and could expand by exploring the unexplored habitats. There are few reports on the diversity of actinobacteria, novel compounds, and natural products from various environments, but substantial bioprospecting of actinobacteria for bioactive molecules has not been explored in many habitats of north-eastern India. There is little information on the antitumor compounds, antioxidant activity, anti-diabetic activity, cytotoxicity, and larvicidal activity of actinobacteria, which again opens a gateway to the researchers to exploring new habitat(s) and isolation of actinobacteria for investigating the bioactive compounds. These gaps could be fulfilled by exploring new habitats.

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Declaration of Interest Statement

There are no conflicts of interest, and also no where this MS is submitted for publication.

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