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Antimicrobial Metabolites Producing Soil Microorganisms: An update

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Abstract: Secondary metabolites are defined as small organic molecules produced by organisms which are not essential for their growth, development and reproduction. These compounds work as antimicrobial, antitumor and/or antiviral against pathogenic microorganisms. *Actinomycetes* are one of the most prominent species among various groups of microorganisms, which have the capacity of producing secondary metabolites. It has been reported that more than 70% of the antibiotics have been obtained from members of the *Actinomycetes* family till date. Hence it has been suggested that a large number of *Actinomycetes* may still be unknown with a potential to produce antibiotics. In present scenario, the emergence of multidrug resistant bacteria has forced the scientific community for the development of novel antibiotics for treatment of various human and animal diseases with such type of bacterial infections. This review has been carried out to update the scientific communities regarding the developments on antibiotics producing soil microorganisms.

Key words: Secondary metabolites, Actinomycetes, Pharmaceutical industries and Rhizosphere

Introduction

Secondary metabolites are produced by some microorganisms like bacteria, fungi, and *Actinomycetes. Actinomycetes* are one of the prominent species among various groups of microorganisms, which have the capacity of producing secondary metabolites [1]. *Actinomycetes* are Gram-positive bacteria but are distinguishable on basis of morphology, DNA rich in guanine plus cytosine (G+C) and nucleic acid sequencing and pairing studies from other bacteria. They are

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characterized by having a high G+C content (>55%) in their genomes [2, 3]. *Actinomycetes* are of universal occurrence in nature and are widely distributed in natural and man-made environments. They are usually found in large amounts in soils, fresh waters, lake, river bottoms, manures, composts and dust as well as on plant residues and also food products. However, the diversity and distribution of *Actinomycetes* that produce secondary metabolites can be determined by different physical, chemical and geographical factors [2]. *Actinomycetes* provide many important bioactive substances that have high commercial value. The basic ability to produce a variety of bioactive substances has been utilized in a comprehensive series of researches in number of institutional as well as industrial laboratories. This has resulted in the isolation of certain agents that were found as an application in combating a variety of human infections [4]. Since more than 70% of naturally occurring antibiotics have been isolated from different genus of *Actinomycetes.* Out of these different genus, *Streptomyces* is the largest genus involved in the production of many secondary metabolites [5], having different biological activities, such as antibacterial, antifungal, antiparasitic, antitumor, anticancer and immunosuppressive actions [2].

Rhizospheric soil: as a source of *Actinomycetes*

Rhizosphere is the plant-root interface, a word which has originated from the Greek word "rhiza", which means root. It is a narrow zone around and influenced by a plant root which is inhabited by a vast population of microbes affected by the chemicals which are released from the roots of plant. It is a unique biological niche with a diverse microflora comprising bacteria, fungi, protozoa and algae. The microbes inhabiting rhizosphere derives nutrition by input of organic materials from the plant roots**.** Roots have important roles for a plant which includes anchorage and up taking of essential nutrients and water for plant growth [6]. It is a dynamic region where various biological and chemical processes take place along with the variety of chemicals released by the roots and mediated by soil microorganisms [7]. The processes occurring here influence a variety of reactions which regulate carbon and other processes that sustain plant growth and have an essential role on the functioning of plant and microorganisms. The bacterial population in the rhizosphere is vast ranging from 10^8 to 10^9 per gram of rhizosphere soil. They cover an area of root about 4-10% especially on the root hair region. There is prevalence of essential nutrients required for growth releasing from soil minerals and also growth factors necessary for bacteria and are readily available in the root exudates of rhizospheric region. The aerobic bacteria are comparatively less in the rhizosphere as there is reduced oxygen level due to respiration by root.

The wide effect of rhizosphere is usually observed with bacteria than with the actinomycetes and fungi. The gram-negative, rod shaped and non-sporulating bacteria which respond to root exudates are dominant in the rhizosphere *(Pseudomonas, Agrobacterium* . Gram-positive rods, cocci and aerobic spore formers *(Bacillus, Clostridium)* are comparatively rare in the rhizosphere. The common genera of bacteria i.e. *Azotobacter, Micrococcus, Pseudomonas, Arthrobacter, Flavobacter, Mycobacterium, Agrobacterium, Alcaligenes, Cellulomonas* and others have been found to be either abundant or less populated in the rhizosphere [6]. The plenty of nitrogen fixing and phosphate solubilizing bacteria in the rhizosphere is considered important economically.

Previously it has been studied that approximately four hundred bacterial isolates were isolated from rhizosphere of some plants collected from Egypt and screened for production of chitinases enzyme. It has been studied that, microbial population were higher in the rhizospheric soil than in the non rhizospheric soil. The bacterial population was highest followed by fungus and actinomycetes. In the medicinal plants, the maximum rhizosphere effect was observed in *Annona squamosa* and the minimum effect was seen in *Eclipta alba* and *Cassia auriculata*. The dominant species of bacteria observed was *Bacillus* followed by *Pseudomonas, Micrococcus, Enterobacter, Corynebacterium* and *Serratia*. Streptomyces species were found to be dominant followed by Deuteromycetes and Frankia among the actinomycetes [9]. From previous studies it has been reported that twenty *Pseudomonas fluorescence* strains were isolated from different soil samples that were collected from rhizosphere region of rice in different states like Andhra Pradesh and Tamilnadu and were further characterized. On the basis of dual culture test, one of the *P. fluorescence* was isolated and identified. It was then fermented for secondary metabolite production at small scale and extracted from ethyl acetate. The structure of the compound was elucidated by high-resolution NMR spectroscopy. In previous studies it has been reported that about 360 bacteria isolated from the rhizospheres of a system of rice intensification (SRI) fields that were characterized for the production of siderophore, fluorescence, indole acetic acid (IAA), hydrocyanic acid (HCN) and solubilisation of phosphorus. Out of these seven most promising isolates were screened for their antagonistic potential against *Macrophomina phaseolina* which was responsible for causing charcoal rot in sorghum by dual culture assay, blotter paper assay and in greenhouse [10].

The actinomycetes are less stimulated in the rhizosphere than bacteria. The bacteria are suppressed by the increase in antagonistic *actinomycetes*, among these the phosphate solublizers (e.g. *Nocardia, Streptomyces)* have a dominant role to play [11].

Secondary metabolites: As an antibiotic

Secondary metabolites are classically organic compounds produced from microorganisms during the modification of primary metabolite synthases. Secondary metabolites don't have a role in the growth and development of microbes and are usually formed in the stationary phase. Many among secondary metabolites have ecological functions; which include defence mechanisms, also function as antibiotics and by producing pigments. Many secondary metabolites show antibacterial or other inhibitory activities [12]. The inhibition of other competitive cells would leave more nutrients for the survival of species producing these metabolites. The secondary metabolites have importance in industrial microbiology, for instance Atropine derived from various plants, is a competitive antagonist for acetylcholine receptors, which can be used in the treatment of bradycardia. Antibiotics are one of the most important and widely employed secondary metabolites produced by the bacteria. The soil microbes are the major source of antibiotics. Various bacterial strains are selected for antibiotic production as its isolation, culturing, maintenance and strain improvement is easy. Filamentous soil bacteria of the genus *Streptomyces* are widely recognized as industrially important microorganisms because of their ability to produce many kinds of secondary metabolites such as antibiotics [13]. Antibiotics such as erythromycin, which have been derived from the *Saccharopolyspora erythraea*, are commonly used antibiotic with a wide antimicrobial spectrum. Bacitracin, derived from organisms classified under *Bacillus subtilis*, is an antibiotic usually used as a contemporary drug. Bacitracin is naturally synthesized as a non-ribosomal peptide synthetase that can synthesize peptides and used as an antibiotic.

Soil microbial interactions

An ecological niche is composed of many microhabitats; each microhabitat is composed of a microscopic diversity which includes bacteria, protozoa, fungi, and a macroscopic diversity that includes plants and insects. Soil is a complex medium in which one can encounter many kinds of microbial communities. Application of nucleic acid-based techniques to analyse soil microbial communities has revealed high prokaryote diversity. The microbial diversity or communities present in soil principally depend on the composition of the soil and many physical chemical properties that the medium possesses [14]. Also, the flora and decomposing organic matter on the surface of the soil will influence vastly with the microbial diversity present. For example, the fallen trees, barks and flowers provide nutrients both to the microbes and plants present, through microbial degradation of carbohydrates, lipids and proteins to sugars, fatty acids, glycerol and amino acids and respectively to mineralization. Besides providing these nutrients, plant secondary metabolites that are generally toxic to micro- organisms will need to be degraded or detoxified by certain microbes. These degraders (microbes) are selectively pressured and ultimately evolve to produce novel secondary metabolites possibly to counteract the toxic plant secondary metabolites. Microbes present in medium possess advantages that will permit or facilitate their survival in that medium. For example, Skujins research has demonstrated that in desert crusts or in soil that has low water availability, gram-positive and spore forming microbes are most abundant. The gram-positive bacteria possess a thicker layer of murein in their cell wall which makes the cell less vulnerable to the limiting conditions present in these habitats. Also, spore forming bacteria can resist long periods of desiccation and limiting nutrient conditions since they compact and protect their genomic material in the bacterial spore, until conditions are favourable for sporulation to occur.

Antimicrobial Metabolite Producing Soil Microbes

Many groups of microorganisms like gram-positive, gram-negative bacteria and fungi have the ability of synthesizing antimicrobial agents. The top cultivable antimicrobial agent producers present in soils are the *Actinomycete*s. The *Actinomycetes* are a group of gram-positive bacteria that exhibit characteristics of both bacteria and fungi. Antimicrobial agents produced by the soil-borne microorganisms like *Actinomycetale*s, *Pseudomonas aeruginosa*, *Staphylococcus spp. etc* [15, 16] in the industrial areas and agricultural soil have been reported to modify with diverse amounts of municipal solid waste compost (MSWC) or farmyard manure (FM). It was proved, by16S rDNA PCR, RFLP and sequencing methods for *Actinomycetales* isolates. It was investigated that antibiotics are the most important commercially exploited secondary metabolites produced by the bacteria and is widely employed. Fungal strains and Streptomyces species are extensively used in industrial production of antibiotics. *Bacillus* species being the predominant soil bacteria and their resistant endospore formation with the production of vital antibiotics like bacitracin etc. [17].

These microbes produce filamentous structures which agglomerate forming pseudo-mycelia. *Actinomycete*s are also spore forming microbes, characteristic shared with fungi. Some of the characteristics that they share with bacteria are the formation and composition of the cell wall, the flagella and the ribosome. About 10% - 33% of the total bacterial community present in soil is comprised by these bacteria, being the genera *Streptomyces* and *Nocardia* is the most abundant *Actinomycetes* found in soil [18]. The genus *Streptomyces* is the responsible of the synthesis of the majority of antimicrobial agents with clinical importance amphotericin, erythromycin, streptomycin, tetracycline, and rifamycin. Protein synthesis is the mode of action of all the above except for amphotericin which attacks the cell membrane. Also the majority of these antibiotics are of broad spectrum. These microbes exhibit a vast metabolic versatility. They can complete many physiological cycles that produce intermediate molecules such as enzymes or secondary metabolites with antibacterial, antifungal and antiviral capabilities. Another group of gram-positive bacteria present in soil and responsible for the production of anti- microbial agents with clinical and agricultural importance is the genus *Bacillus*. This genus is characterized by being spore forming gram-positive bacilli. It has been demonstrated that these microbes produce antimicrobial agents in various stages of their growth curve. For example, *B. subtilis* can produce non-ribosomal oligopeptides with antifungal and antimicrobial properties such as surfactins, inturinics and bacilysin. Ribosomal antibiotics are also synthesized by this strain which include subalancin and subtilosin. Cyanobacteria are known to be colonized by various heterotrophic bacteria. With a view to understand the associated organisms from cyanobacterial products especially 6 different Spirulina products such as two forms of Spirulina powder, one crunchy form and three different tablets were selected. The screening for new antibiotic-producing microorganism isolates showed antagonistic activity and isolated from waste soil samples from various regions in the industrial areas in Dheradun, Uttarakhand, India. The methods of modified agar-streak and agar-plug methods were used for primary screening [19].

Actinomycetes: Major source for Antibiotic production

Actinomycetes are the most widely distributed group of microorganisms in nature which primarily inhabit the soil. They have provided many important bioactive compounds of high commercial value and continue to be routinely screened for new bioactive compounds. These searches have been remarkably successful and approximately two thirds of naturally occurring antibiotics, including many of medical importance, have been isolated from *Actinomycetes*. Almost 80% of the world's antibiotics are known to come from *Actinomycetes*, mostly from the genera *Streptomyces* and *Micromonospora* [1, 20]**.** According to the World Health Organization, over-prescription and the improper use of antibiotics has led to the generation of antibiotic resistance in many bacterial pathogens. Nowadays, the drug resistant strains of pathogen emerge more quickly than the rate of discovery of new drugs and antibiotics. Because of this, many scientists and pharmaceutical industry have actively involved in isolation and screening of *Actinomycetes* from different untouched habitats, for their production of antibiotics. Serious infections caused by bacteria have become resistant to commonly used antibiotics and become a major global healthcare problem in the 21st century. *Staphylococcus aureus*, for instance, a virulent pathogen that is responsible for a wide range of infections, has developed resistance to most classes of antibiotics. It has been reported that the twenty-five strains of actinomycetes were isolated from samples of water, soil and tree barks collected at two sites located in the north–east of Algeria. Antimicrobial activity was tested using the agar cylinder method against three Gram-positive bacteria, three Gram-negative bacteria [21]. 445 *Actinomycetes* were isolated from 16 medicinal plant rhizospheres soil. According to morphological study and chemotaxonomic studies, 89% were observed from genus *Streptomyces*, 11% non-Streptomycetes and 3 isolates were unclassified. 23 (5.2%) *Streptomyces* isolates showed activity against phyto-pathogenic fungi. It was reported that the strain *Streptomyces* had the ability of inhibiting the growth of a wide range of Gram-negative and Gram-positive bacteria [22]. The culture broth from cultured strain was extracted with ethyl acetate and the contents of the residue were subjected to Liquid Chromatography Mass Spectrum (LCMS) profiling. The chromatographic purity of the peak exhibited the antimicrobial activity at a Retention time (RT) of 16.2 min was 48%, and the compound was purified had revealed that A-4 and A-4 actinomycetes mutant strains (out of the six strains selected from the nine actinomycetes that were screened) were evaluated for maximum antibiotic production using various carbon and nitrogen sources, in a medium formulation study [5].The antibacterial activity of isolated actinomycetes colonies from soil samples collected from different regions in Rajshahi, Bangladesh. Thirty actinomycetes colonies were isolated as pure culture from five soil samples using Starch casein- nitrate-agar medium. The isolates were grouped in five colour series based on their aerial mycelia colour and screened for their antibacterial activity against a variety of test bacteria. 53.3% of the isolates were found to have moderate to high activity against four gram-positive and four gram-negative bacteria. In many isolates, inhibitory activity against indicator bacteria was observed, which proved that Bangladeshi soil has a potential to be explored for antibacterial secondary metabolites**.** Majority of the *Actinomycetes* in soil that are potential drug sources remain uncultivable and therefore inaccessible for novel antibiotic discovery on isolation of *Actinomycetes* and suggested that only 10% of the *Actinomycetes* are isolated and cultivable from nature [23]. Most of the antibiotics in use today are derivatives of natural products of *Actinomycetes* and fungi**.** *Actinomycetes* can be isolated from soil and marine sediments. It has been reported that soils have been screened by the pharmaceutical industry for about 50 years, only a small fraction of the surface of the globe has been sampled and also only a small fraction of *Actinomycetes* taxa has been studied. This study was undertaken to isolate *Actinomycetes* from the soil samples of wasteland and garden of Ghaziabad, India and also lead to assess their anti-bacterial properties [24]. The resistance problem demands that to discover new antibacterial agents effective against pathogenic bacteria resistant to current antibiotics [5]. So we need to screen more and more *Actinomycetes* from different habitats for anti- microbial activity in hope of getting some *Actinomycetes* strains that produce antibiotics that have not been discovered yet and active against drug resistant pathogens. In a previous study reported that a total of 117 *Actinomycetes* strains were isolated from the wasteland alkaline and garden soil samples of the Ghaziabad and screened for their antibacterial activity, they were evaluated for their inhibitory activities. The cultural characteristics of isolates were also studied in different culture media. The results indicated that six isolates were highly active against *Staphylococcus aureus* strains. Seven isolates were highly active with an inhibition zone more than 20 mm in diameter. Most of the isolates inhibited growth of the Gram negative bacteria tested. All the antibiotic producing *Actinomycetes* were isolated at different temperatures from non-agricultural wasteland alkaline soil and compost rich garden soil. Fifteen isolates showed activity against bacteria in which most of them from wasteland alkaline soil where the less interference by human for agriculture or other purpose. These micro- organisms may have capability to produce some of the most important antibiotics ever developed prior to isolation and purification of antibiotics.

Secondary metabolites are produced by some organisms such as bacteria, fungi, plants, Actinomycetes and so forth. Among the various groups of organisms that have the capacity to produce such metabolites, the actinomycetes occupy a prominent place. Actinomycetes are of universal occurrence in nature and are widely distributed in natural and man-made environments. They are found in large numbers in soils, fresh waters, lake, river bottoms, manures, composts and dust as well as on plant residues and food products. However, the diversity and distribution of actinomycetes that produce secondary metabolites can be determined by different physical, chemical and geographical factors. Actinomycetes provide many important bioactive substances that have high commercial value. Their ability to produce a variety of bioactive substances has been utilized in a comprehensive series of researches in numerous institutional and industrial laboratories. This has resulted in the isolation of certain agents, which have found application in combating a variety of human infections. That is why more than 70% of naturally occurring antibiotics have been isolated from different genus of Actinomycetes. Out of these different genuses, *Streptomyces* is the largest genus known for the production of many secondary metabolites, which have different biological activities, such as antibacterial, antifungal, anti-parasitic, antitumor, anticancer and immunosuppressive actions. A previous study reported the enumeration of total heterotrophic bacteria including *Actinomyces* and fungus from the rhizosphere and non rhizosphere soils of easily available medicinal plants in and around Thanjavur, Tamil Nadu. In this the maximum rhizospheric effect (507 CFU/ml) of gram negative bacteria was reported in *Solanum nigrum* and the minimum (95 CFU/ml) of gram negative bacteria effect was seen in *Leucas aspera*. The bacterial isolates were also able to produce phytohormone i.e., indole 3- acetic acid (IAA).The bacterial colonies were characterized and dominance of gram positive was observed [25]. Previously it has been reported that tetracyclines (TCs) were polyketide natural products that includes a number of clinically important antibacterials like oxytetracycline (5-hydroxy-TC, OTC) and chlortetracycline (7-chlor-TC, CTC). TCs were supposed as the first major class of therapeutics in order to earn the distinction of broad-spectrum antibiotics [26, 27].

Soil an inexhaustible source of microbial secondary metabolites

Soil micro-organisms have been utilized as a rich source for obtaining therapeutically important molecules. Soil is enriched with different types of pathogenic and non-pathogenic bacteria, fungi, *Actinomycetes* and other types of microbes [28]. A single gram of soil can contain 100 million bacteria, 1 million *Actinomycetes* & 100,000 fungi. The exact proportion of each of these organisms will depend on soil conditions such as available moisture, aeration, organic matter levels and the type of plants present. Chemical conditions such as acidity & alkalinity will greatly affect organism population. Fungi favour acidic soils whereas *Actinomycetes* prefer alkaline conditions. Until recently, microbiologists were greatly limited in their study of natural microbial ecosystems due to the inability to cultivate most naturally occurring microorganisms. DNA analysis methods proved that the number of microbes in the soil is much higher than formerly thought. It was estimated that about 1% of the aquatic and 10% of the terrestrial microorganisms (perhaps only 0.1% of soil microbes), are readily cultured or “culturable” by conventional methods. So far we only know approx. 5% of the total species of fungi and 0.15% of the bacteria. Among them only a small fraction has been examined for metabolic profile. The rest of (99.9%) of the population may represent novel genetic diversity. These microorganisms represent a diverse and still undiscovered reservoir of novel strains that may produce novel natural compounds [21].

It is estimated that approximately 1.5 million fungal species are present on Earth. Fungi and particularly endophytes were found as a large hit rate of novel biological active compounds where endophytic fungi screened for biological activities. The pharmaceutical potential of endophytic fungi was truly verified with the finding of the taxol producing endophytic fungus *Taxomyces andreanae* [26].

It has been reported in a literature survey done from 1988-1992 revealed that more than one thousand new secondary metabolites detected in *Actinomycetes*. Most of the secondary metabolites identified were produced by *Streptomyces* sp. The order actinomycetales produce compounds usually medium to large size molecules with an average molecular weight of 400-800bp. In the 800-1200 bp molecular weight, the total numbers of active products were twice as of *Streptomyces* products that were indicating the higher representation of the more complicated structures. Among the antibiotics produced exclusively from *Actinomycetes* are: glycopeptides antibiotics, macrolides, polyene antibiotics, amino-glycosides, anthracylines, polyether antibiotics; the novobiocin related glycosidic antibiotics, streptothricins, actinomycins and echinomycin; elfamycins, glutarimides, orthosomycins. The predominant part of the large, 18 to 60 member macrocyclic lactones derivatives (including over 1000 compounds), thiostreptonline thiazolyl peptides (140), cyclopolylactones (~40) are derived also from various actinomycetales species .

Soil is the most common habitat of *Streptomyces.* It has 1 - 20% of the total viable count and 64-97 % of the cultivable *Actinomycetes*. Soil based *actinomycetes* produce over 70% of naturally occurring antibiotics. It is commonly believed that the number of *Actinomycetes* increases relative to other microorganisms with increasing depth of soil sampling. The B horizon of soil with a pH of 6-7, low humus and low moisture content (5-11 inches deep in the soil) is a preferable habitat for the sporulation of *Streptomyces* spp. The more arid the soil and cooler the climate is, the higher is the percentage of the *Streptomyces* in the total count of *Actinomycetes*. Optimum temperature is about 28-37^{0}C, bacteria and fungi were more numerous at a temperature range of 5-15^{0}C. Neutral to alkaline media favours the growth of *Actinomycetes*. It has been observed that the *Streptomyces* in soil grow attached to surfaces, such as plant residues or fungal hyphae and they may have an important ecological role in the degradation of litter in soil. *Streptomyces* may play a role in promoting plant growth, through control of root pathogens or in some indirect way, since some species are able to produce antifungal compounds. Many *Streptomyces* spp. are commercially used as biocontrol agents [21]**.** Previously the process of isolation of antibiotic producing *Actinomycetes* diversity from Javadi hills of Tamil Nadu has been reported from soil samples using nalidixic acid and nystatin supplemented starch casein agar along with *actinomycetes* isolation agar medium. These colonies were characterized based on their mycelium structure, colour and arrangement of spores on mycelium [26]. The presence of *actinomycetes* isolates with different morphology in soil samples collected from rhizospheric regions of different plants from a farm in Sungai Ramal Luar, Malaysia. Among 300 *actinomycetes* obtained, 50 fast-growing isolates were present and four potential antibiotic producing isolates were obtained by employing primary and secondary screening [22].

Optimization of Culture condition for maximum antibiotic production

For an economic production of antibiotics, the production and growth parameters e.g. temperature, agitation, aeration and concentration of nutrients can be optimized to give maximum yields out of minimum investment of time, energy and money. Many techniques are available in the fermentation medium designer's toolbox (borrowing, component swapping, biological mimicry, one-at-a-time, statistical and mathematical techniques, experimental design and optimization, artificial neural networks, fuzzy logic, genetic algorithms, continuous fermentation, pulsed batch and stoichiometric analysis). Each technique has advantages and disadvantages, and specific situations where they are best applied. No one 'magic bullet' technique exists for all situations. However, considerable advantage can be gained by logical application of the techniques, combined with good experimental design [26].

The two ways by which the problem of medium component limitation has been addressed by researchers worldwide, are classical and statistical. In classical medium optimization we change one factor (medium component) at a time while keeping all other components fixed. This process requires a lot of labour and time. Statistically based experimental design is a more efficient approach to deal with a large number of variables compared with the traditional optimization method. Moreover, if there are statistical interactions between factors, useful information will not be obtained by classical approach. Application of statistical methods requires information about the factors that are suitable for maximum antibiotic production. This idea can be achieved by classical method or with the help of PBD design, which is also a statistical design but it does not give any idea about the interaction effects among the medium components. It gives an idea about positive or negative effect of fermentation parameters [29].

Conflict of interest: None

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