Review

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Microbial endophytes: an untapped resource with antitumor and anti-microbial properties

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Abstract: Endophytes (mostly fungi and bacteria) are the microorganisms living in close symbiotic association with plants. Endophytes growing within medicinal plants in hostile environments are considered to produce novel as well as chemically and structurally diverse secondary metabolites. These metabolites are being used as clinical grade drug targets due to their less toxicity over other conventional drugs for diseases like cancer, microbial infections. Endophytes extracts are also exploited in food, agrichemical and biotechnology industries. Asparaginase of bacterial origin is widely used antitumor drug. The quint essential role of endophytes is their activity against microorganisms which can open gates in the field of biomedical research. This review mainly focuses on endophytes from medicinal plants as a source of antitumor and antimicrobial agents. Also highlights the need to focus on finding alternatives methods of endophytes isolation and production as well as characterization, purification and genetic transformations in order get maximum benefits.

Keywords: anti-microbial agents; antitumor agents; endophytes; medicinal plants; secondary metabolites

Introduction

Plants harbour different kinds of microorganisms known as epiphytes, endophytes (mostly fungi and bacteria) and pathogenic microorganisms. The term 'endophyte' was first introduced by de Bary (1866) [1]. The association of endophytes with plants is 400 million years old. It is believed, there are approximately 1 million species of endophytic fungi still to be discovered [2, 3]. The plants such as *Momordica charantia L.*, *Zingiber officinale* and *Cinnamomum zeylanicum* are used in Asian countries for traditional medicines since ages [4]. Recently, the microorganisms specifically endophytes harbouring medicinal plants also grabbed scientists interest for novel bioactive agents with therapeutic properties [5]. Endophytes were initially found in *Lolium temulentum* in the year 1904 [6]. These are considered to be better novel drug targets because of their structural diversity, low commercial production costs, and broad spectrum of these ingredients in treating various medical conditions.

Medicinal plants have a long history of producing beneficial compounds. The use of medicinal plants for treating fever, relieving joint pain and many seasonal flu is very common in developing countries [7]. Therefore, researchers focus on bioactive metabolites from medicinal plants and the plants which can survive unique hostile environmental conditions [8]. The Eastern coast of India has been explored for potential cytotoxic drug targets [9]. *Catharanthus roses*, a native medicinal plant belonging to subtropical regions in India is the producer of around 130 alkaloids and many bioactive metabolites with antitumor and antimicrobial properties [10, 11]. Extracts from Chinese medicinal plants for instance; *Cleome gynandra*, *Liriope spicata* and *Paris polyphylla* are serving as potential drug targets for many pharmaceutical companies as anti-cancer and anti-inflammatory agents [12-15]. South Africa is using around 3000 plants as medicines, and approximately 24,000 taxa with medicinal potential are still to be uncovered in the region [16, 17]. Therefore, exploring endophytes harbouring medicinal plants producing bioactive compounds are getting great attention.

Endophytes such as *Pestalotiopsis microspora* isolated from *Terminalia morobensis* produce antioxidants named as Pestacin and Isopectacin [18]. Endophytic fungi excrete the same set of detoxifying enzymes for colonizing the host plant [19]. An influence of host medicinal plants and environmental factors have been observed on the presence of the endophytic fungi within the plant as well as on the type of secondary metabolites secreted by them. For instance, in family *Rosaceae* the endophytes are isolated from leaf, flower and fruit, whereas in *Theaceae* family the endophytic fungi were found in the leaf [20, 21]. Bacterial endophytes can reside in any part of the plant due to their positive influence on the phenylpropanoid pathway, which is linked to the plant fitness [22, 23].

Initially, endophytes were assumed to be pathogens who have lesser virulence or have extended periods of latency [24]. But today endophytes are reported to be hubs of novel bioactive compounds which may have a great medicinal potential. Recently, the attention has diverged to marine endophytes which harbour the relevant novel therapeutic target [25]. For instance, *Simplicillium obelavatum* a marine fungal endophyte from India showed promising antitumor

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activity against human leukemia cell lines [9]. Endophytes are omnipresent in plants as they are found in roots, leaves, flowers, seeds and stems tissues without causing any diseases [26-29]. During the process of colonization into epidermal cell layer of plant tissues, they produce secondary metabolites in the form of various phytohormones, abiotic stress tolerance, and excrete various alkaloids which induce resistance in plants against human pathogens, and also provide protection against root invasion by various fungal and insect pathogens [30-33].

Endophytes are considered to be in mutualistic association with plants for certain parts of their life, irrespective of causing internal infections to them [34]. This mutualistic interactions among host and endophytes inclined to the production of a plethora of secondary metabolites like quinones, steroids, terpenoids, xanthones and many more novel bioactive agents with promising applications as agrichemicals, antioxidants, cytotoxic agents, antifungal and other pharmacologically active compounds [35, 36]. The *Bacillus* class of endophytes is known to produce secondary metabolites of agricultural importance whereas bioactive metabolites from the actinobacteria class of endophytes find applications in veterinary and pharmaceutical industries [37]. *Aegle marmelos*, a traditional medicinal plant considered sacred in India, is used for curing various illnesses for more than 3 decades. A variety of endophytes associated with *Aegle marmelos* belong to *Curvularia australiensis*, *Alternaria citri macularis*, *Alternaria alternata*, *Cladosporium cladosporioides*. *Aspergillus niger*, etc. exhibit anti-microbial activities against various clinical pathogens [38].

Bacterial endophytes are microorganisms isolated from internal plant tissues, which do not lead to any symptoms or morphological changes within host plant tissues [39, 40]. Foliar endophytic bacteria such as *Fusarium oxysporum*, *Rhizoctonia solani*, *Sclerotinia sclerotiorum* and *Streptomycete* endophyte have shown potential applications in agrichemical as well as pharmaceutical industries [41]. In a recent study the endophytic bacteria from *Pseudobrickellia brasiliensis* showed promising anti-microbial activity against *Pseudomonas aeruginosa* [42]. Gram-positive bacteria, *Streptomyces* species is considered as the major producer of many natural biocontrol agents [43]. The bacterial endophytes such as *Bacillus amyloliquefaciens*, *Streptomyces sp.* and *Streptomyces laceyi* from plants *Ophiopogon japonicus*, *Maytenus hookeri* and *Ricinus communis* respectively have been reported with promising cytotoxicity against various types of cancers [37]. Endophytes are isolated from plants growing in all types of environments ranging from tropical to temperate and xerophytic to aquatic regions [44-47]. The plant-endophyte interaction helps host plant to develop tolerance against heat, drought and salt [48-50]. Due to the ability of endophytic microorganisms to produce specific enzymes during the process of colonization into host plant tissue they serve as biocatalysts to chemically transform many natural products and drugs [51]. According to metabolomics the endophytic genes are linked to the production of eco-friendly and novel secondary metabolites needed by host plants during its growth as well as against the microbial and insect pathogens [37].

There are many bio-active agents secreted from microbial endophytes which are doing wonders in biotechnology industries. For instance, laccase enzyme derived from fungus is used in pulp and paper industry, dye degradation, bioremediation, medical and personal care units [52]. Endophytes help in the reduction of the acrylamide formation in the baking industry. DSW Company is commercially producing L-asparaginase with a brand name Preventase which is produced using *Aspergillus oryzae* by Novozyme [53]. Secondary metabolites from endophytes associated with medicinal plants, as shown in Figure 1, are potential source for bioprospecting. Furthermore, gram-

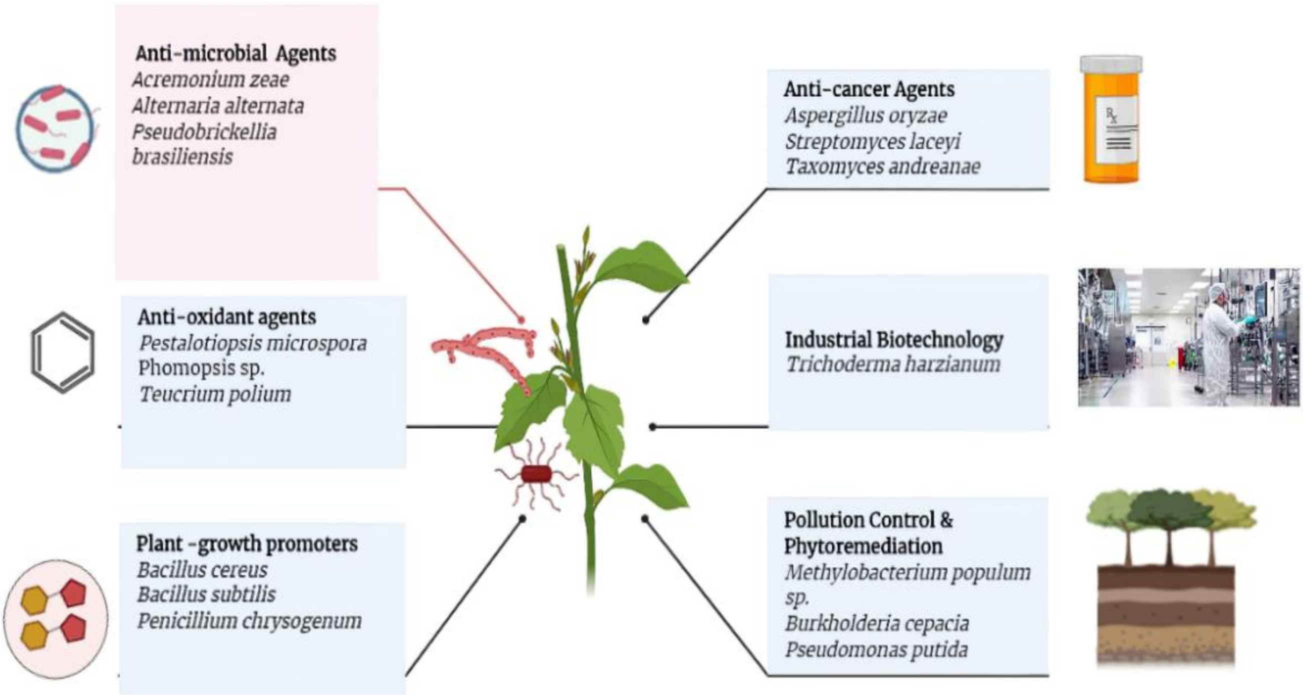

Figure 1: Bioprospecting abilities of endophytes from medicinal plants

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positive bacterial endophytes are an unlimited source of chemically diverse polysaccharides, polypeptides, plant hormones like auxins, gibberellins and enzymes used in food and medicine industries [37].

The rationale behind studying endophytes is that they can be used as potential sources of novel drugs. Moreover, bioactive compounds being produced because of interactions between endophytes and a eukaryotic host plant are assumed to be with reduced toxicity [27]. The existence of endophytes within host plants is specific [54]. This specificity leads to a chain of complex biochemical interlinkage between the endophytes and the host, opening doors for the selection of endophytes as novel drug targets [55]. Due to over-harvesting of the medical plants with bio-active molecules leading to their extinction, has also drawn the attention towards endophytes residing within medicinal plants as they are expected to have acquired the same type of secondary metabolites [8]. Moreover, the chemotherapeutic drugs like prednisolone, dexamethasone, vincristine, etoposide and cyclophosphamide are linked with certain side effects like immune-suppression, infertility, secondary neoplasm and vomiting [56]. Therefore, chemotherapeutic agents with no or minimum side effects are much needed.

Endophytes as antimicrobial agents

Antimicrobial resistance (AMR) is one of the major concerns across the globe mainly because of resistance of *Mycobacterium tuberculosis* against multiple drugs and *Klebsiella pneumoniae*, *Salmonella* and *Staphylococcus aureus* emerging as major antibiotic resistant pathogens [57, 58]. Many clinical grade antibiotics are derived from endophytes associated with medicinal plants (Table 1) are used to treat various types of microbial infections. Therefore, scientists are looking for novel antimicrobial agents. Endophytes are thought to be a great source of novel chemical scaffolds because of their existence within plants surviving in extreme environmental challenges [59]. *Ziziphora capitata*, a medicinal plant secretes many types of flavonoids, steroids and a special essential oil known as pulegone which exhibits strong antibacterial and antifungal activity [60].

Bacterial endophytes

The existence of bacterial endophytes is described in all the plants studied [70]. Both culturable and unculturable bacteria from 200 genera from 16 phyla have been described in total, while major bacteria belong to *Acidobacteria, Actinobacteria, Aquificae, Bacteroidetes, Chlorobi, Chloroflexi, Cyanobacteria, Deinococcus Thermus, Firmicutes, fusobacteria, Proteobacteria, Spirochaetes* and *Verrucomicrobia* [71-74]. In one study, the antipathogenic and growth promoting properties of endophytic bacterium strain LDO2 against peanut plant could be potential biocontrol agents [75]. Gram-positive bacteria Actinobacteria alone is known to contribute about 45% of the antibacterial agents used across the globe [76]. Bacterial isolates from different actinobacteria species were tested using diffusion assay showed for inhibitory effects against bacterial pathogens including *Bacillus subtilis, B. cereus, Citrobacter freundii, Escherichia coli, Proteus mirabilis,* etc [77]. *Archis hypogaea (Pantoea), Withania somnifera (B. indicus, B. cereus, Pseudomonas sp., B. muralis), Tinospora cordifolia (Pseudomonas sp., B. cereus, B. pumilus), Solanum nigrum (Pseudomonas, Acientobacter), Panax Ginseng (B. megaterium, B. cereus, Micrococcus luteus, Lysinibacillus fusiformis), Solanum Tuberosum (Azospirillum, Burkholderia), Curcuma longa (P. putida, Clavibacter michiganensis), Mirabilis jalapa (Brevibacterium sp., Microbacterium sp.)* are important medicinal plants and their associated bacteria which lead to the production of many extracellular enzymes and chemical extracts like flavonoids, alkaloids, glycopeptides and sulfonamides which act as antibiotics [78-81].

Fungal endophytes

Endophytic fungi while residing in plants does not show symptoms in plants [76]. The plant and endophytic fungi interactions include commensalism, mutualism, balanced antagonism, latent type, virulence and pathogenicity [70]. Therefore, it leads to synthesis of certain secondary

Table 1: List of microbial endophytes and their host with potential antimicrobial properties

Microbial Endophyte	Host-Plant	Compound	Activity	Reference
Azotobacter chroococcum	*Curcuma longa*	Curcumin	Antifungal and Antibacterial activity	[61]
Trichoderma pseudokoningii	*Arabidopsis thaliana*	Trichokonin VI	Antifungal	[62]
Actinomycetes sp.	*Caulerpa Taxifolia*	DMS3	Antibacterial activity against Urinary tract infection bacteria	[63]
Trichoderma longibrachiatum	*Arabidopsis thaliana*	1,2-Benzenedicarboxylic Acid	Antifungal	[64]
Streptomyces sp. TP-A0556	*Aucuba japonica*	Coumarins TPU-0031-A and B	Antibiotic activity against Gram-positive and Gram-negative bacteria	[65]
Daldinia eschscholtzii A630	*Pogostemon cablin*	Eschscholzia	Antibacterial activities	[66]
Gliocladium sp.	*Eucryphia cordifolia*	Annulene	Volatile antimicrobial agent	[67]
Pestalotiopsis microspora	*Torreya taxifolia*	Torreyanic acid	Antibiotic	[68
Pseudomonas entomophila	*Aloe vera*	crude and ethyl acetate	Antibiotic	[69]
Colletotrichum gloeosporioides	*Vitex negundo*	Methanol	Antibiotic	[69]

metabolites such as alkaloids, terpenoids, steroids, quinines, phenols, peptides, phenolic acids and flavonoids which are of great therapeutic and medicinal value against numerous diseases. It has been observed that most fungal endophytes belong to the *ascomycete* family [82]. The genetic diversity of fungal endophytes suggests the presence of a large number of antimicrobial scaffolds like ambuic acid (*Pestalotiopsis sp.*), pestalone (*Pestalotiopsis sp*.), dicerandrol C (*Phomopsis longicolla strain C81*), cryptosporidium (*Cryptosporiopsis sp.*), pyrrocidine A (*Acremonium zeae*), etc [83-87].

Various compounds with antimicrobial properties have been purified from endophytic fungi [88]. The present antibiotic resistance can be overcome by the use of bioactive secondary metabolites, for example antibacterial agents like fumitremorgin B and periconicins A and B are isolated from *Phomopsis sp*. and *Periconia sp*. respectively [89, 90]. The antimicrobial compound named 'Compound *Ophiopogon japonicus* Pill' has shown promising results against many bacteria and fungi [86, 87].

Mechanism of Action of endophyte derived antibiotics

Streptomyces a gram positive bacteria is the largest producer of many clinically important antifungals, antiparasitic, antibiotics and a wide range of immunosuppressants [91]. Daptomycin is the most important drug used for treating Methicillin-Resistant *Staphylococcus Aureus* (MRSA) [92]. Endophytic associated *Streptomyces sp*. encode the enzymes proteases, lyases, amylases, many proteins and secondary metabolites which develop symbiotic relationships between host plants [91]. *Streptomyces* derived antibiotics target the important cellular processes like protein synthesis, DNA replication, RNA synthesis and cell wall synthesis of the target microorganism [93, 94]. Streptomycin is a broad spectrum bactericidal antibiotic that elicit the inhibition in the protein synthesis of bacteria by binding to the 16S rRNA a component of 30S ribosome subunit blocking its binding to formyl-methionyl-tRNA and causing codon misleading [93-95].

Endophytes as antitumor agents

Across the world, one of the leading causes for death is cancer, due to immortality, limitless replicative potential, metastasis and invasive nature of cancerous cells [87]. The anticancer activities of the endophytes are due to the existence of cytotoxic compounds (Table 2) in endophytes [53]. Many studies revealed that endophyte extracts from different host plants exhibit a wide set of activities including antimicrobial, anticancer, cytotoxic, antioxidant, anti-inflammatory, etc. Endophytes secrete a large number of enzymes like amylases, chitinases, cellulases, laccases and xylanases find applications in various industries like pharma, paper and pulp, food and animal feed [96]. Medicinal plants like *Tinospora cordifolia, Curcuma longa*, *Cotus gneus*, *Withania Somnifera* and their associated fungi like *Aspergillus sp., Cladosporium cladosporioides, Curvularia brachyspora, Phyllosticta sp.* have active compounds like anaferine, withaferin, saponins, curcumin, tinosporaside etc. reported antitumor properties [80].

Bacterial endophytes

The conventional chemotherapy is known to have many side effects, hence directing the scientists towards the novel metabolites from endophytes associated with higher plants. Endophytic actinomycetes are associated with a diverse range of secondary metabolites exhibiting anticancer activities [37]. Endophytic *Streptomyces aureofaciens* produces 4-aryleoumarins which exhibit inhibitory effect against oncoproteins Bax and bcl-2 genes in human lung cancer cells [97]. Actinobacteria produce chemical scaffolds with antimicrobial and antitumor activities with range of applications in many industries [58]. Endophytes derived products have shown more efficacy and less side-effects as compared to other chemotherapeutic agents [27, 28]. The first clinically used L-Asparaginase was isolated from *Escherichia coli by* Mashburn and Wriston in 1964 and was found to be *E.coli* asparaginase II [98].

Fungal endophytes

Novel secondary metabolites are produced by fungal endophytes [49]. The absorptive mode of nutrition in fungi helps in the production of enzymes responsible for useful conversions. Chitin deacetylase, chitinase, chitosanase, alkaline protease, acidic protease, tannase, laccase, β-glucosidase are various enzymes that are synthesized by the endophytic fungi [27]. Ergoflavin is a secondary metabolite with anti-cytotoxic properties. Endophyte from Indian medicinal plant *Mimusops elengi* known to produce "Secalonic acid D " belonging to ergochrome class has shown promising cytotoxic activity on HL60 and K562 cells [99, 100]. The major endophytes producing antitumor activity are shown in Table 2. Fungi like *Aspergillus, Penicillium and Fusarium* sp. produces L-asparaginase [76]. Asparaginase derived from *Mucor* sp. and *Aspergillus terreus*, isolated from decomposing vegetable substrate was reported to be non-toxic and possessed myelo-suppressive and immunosuppressive activity [82].

M***echanism of action of microbial derived L-asparaginases***

L-Asparginase was first isolated in 1922 by Clementi from the serum of guinea pig and its antitumor potential was proved by Kidd in 1953 [101, 102]. L-asparaginases are found in all the natural sources like plants, animals and microorganisms, but only L-Asparaginases produced from microorganisms are proved to be clinically important [103]. The industrial preparations of asparaginase produced from *Escherichia coli* is called L-asparaginase, commercially available under the names Kidrolase, Elspar and Crasitin, Oncaspar marketed by Sigma-Tau Pharmaceuticals Inc. Gaitherburgis produced from *Erwinia chrysanthemi* and Pegylated *Escherichia coli* (pegaspargase) sold under the name of Erwinase is asparaginase isolated from *Escherichia coli* and chemically attached to polyethylene glycol [104-106]. L-asparaginase (L-asparaginase aminohydrolase) is an enzyme catalysing hydrolysis reaction involving the conversion of L-asparagine to L-aspartic acid and ammonia. This hydrolysis reaction is used in the treatment of acute lymphoblastic leukemia which is a crucial type of blood cancer [106]. Asparaginases are also effective against other forms of cancer like chronic leukemia, myelocytic leukemia, acute myelomonocytic leukemia, melanosarcoma treatment and lymphosarcoma [107].

Table 2: List of microbial endophytes of medicinal plants with potential anti-tumor activities.

Microbial Endophyte	Host- Plant	Compound	Activity	Reference
B. amyloliquefaciens sp.	*Ophiopogon japonicus*	Exopolysaccharides	Human gastric carcinoma cell lines (MC- 4 and SGC-7901	[108]
Streptomyces sp. Strain Is9131	*Maytenus hookeri*	Maytansine	Human gastric, Leukemia, Liver and Lung Tumor cell lines	[109, 110]
Streptomyces laceyi	*Ricinus communis*	Salaceyins	Human Breast Cancer	[111]
Streptomyces aureofaciens	*Z. officinale*	4-arylcoumarins	Murine Lung carcinoma	[111]
Streptomyces sp.	*Boesenbergia-rotunda*	biphenyls	Human Liver and Hela cervical tumor cell lines	[112]
Aspergillus versicolor	*Eichhorniacrassipes*	Flaquinolone	Cytotoxic activity	[113]
Talaromyces sp.	*Tillandsia catimbauensis*	L-asparaginase	Acute Lymphoblastic Leukemia, non-Hodgkin's lymphoma	[114]
Taxomyces andreanae	*Taxus brevifolia*	Taxol	Anticancer	[115]
Talaromyces pinophilus	*Withania somnifera*	Withaferin A and Withanolide A	Renal Cancer, Skin Cancer, Prostate Cancer,etc.	[61, 116]
Cladosporium oxysporum	*Moringa oleifera*	Taxol	Cytotoxic activity	[117]
Eurotium sp.	*Curcuma longa*	Curcumin	Blood cancer	[61]

L-asparaginase is a non-essential amino acid in normal human cells produced by the conversion of aspartate to asparagine by aspartate synthetase located on chromosome no. 7q 21.3 [118]. In cancerous cells L-asparagine is an essential amino acid, therefore serum asparagine is their only source [106]. L-asparaginases degrade serum levels of L-asparagine into aspartate and lead to arrest of lymphoblasts in the G1 phase ultimately causing their apoptosis (Figure 2) [113, 116, 119]. L-asparaginases are also known to interfere with the signalling pathway needed for the production of many important transcription factors and proteins [120]. Mechanism of L-asparaginase on normal cells and lymphoblasts is represented in Figure 2.

Future challenges and scope of endophytes research

Endophytes associated with medicinal plants are being mined for diverse range of novel therapeutic as well as industrially important secondary metabolites [106]. It is believed that a large number of endophytes are still to be screened for their potential active chemical scaffolds. Further, the complexity in structure of secondary metabolites limit their application in combinatorial chemical synthesis approach [121]. Better techniques for isolation of endophytes from their host plant are needed. No doubt, solid state fermentations (SSF) and submerged fermentation techniques have brought revolution in the liquid cultivation, higher production volumes and also reduced the catabolite repression and downstream procedures [122].

The biochemical interactions between endophyte and host plant during their symbiotic association are poorly understood. Plant tissue culture techniques using fungal endophytes are hard to achieve due to their genetic instability. Also, the classification of endophytes using bioinformatics methods might involve errors; for instance, *Colletotrichum*, its sequences are wrongly labelled in GenBank [85, 121]. The genetic modification in the endophytes can lead to the production of more sustainable clinically grade drug targets as well as biofuel to meet the demanding and sustainable fuel needs of the globe. Different bioprospecting studies involving ecosystem sampling of the host plant, examining endophytes from medicinal plants used traditionally in treating diseases and studying phylogenetic analysis of the same medicinal plant species can lead to the discovery of the potential endophytes [123].

Another major obstacle is that a large number of valuable plants harbouring endophytes are being destroyed for commercial benefits by humans. A new culturing technique needs to be framed for the cultivation of unculturable endophytes by designing sophisticated incubators or simulation models imitating the natural endophyte environments. The role of endophytes in cleaning the environment by reducing waste, phytoremediation and nutrient cycling has been highlighted recently [124]. More insights into endophyte research can lead to the discovery of potential drug leads against deadly diseases like Cancer, AIDS, Antibiotic resistances, COVID-19 etc.

Conclusion

The current review describes that endophyte derived extracts are rich in novel secondary metabolites with antitumor and antimicrobial properties. The endophytes surviving within medicinal plants living in hostile environments produce chemical scaffolds of clinical importance. The anticancer agents such as L-asparaginases produced from fungal endophytes are less immunogenic

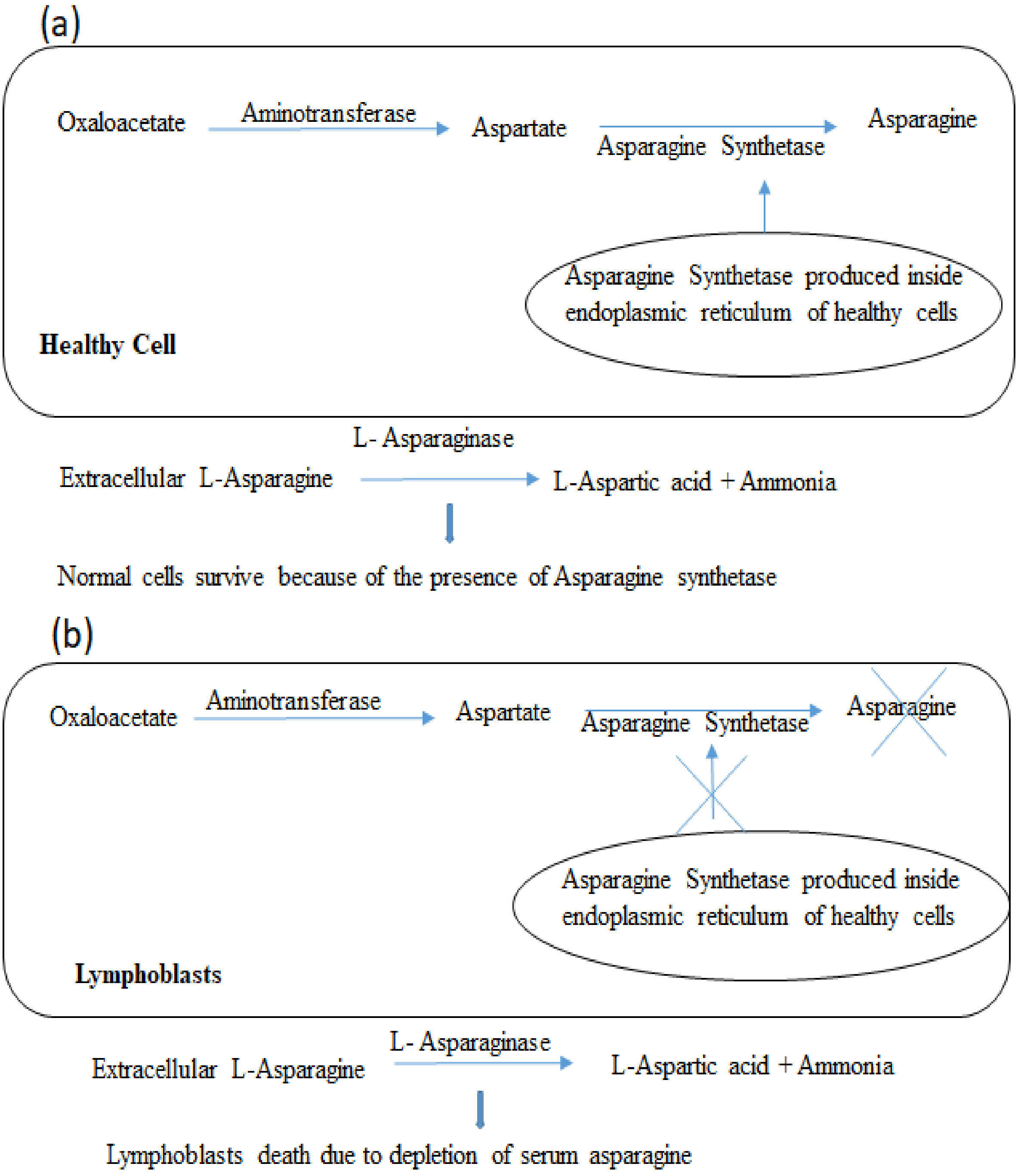

Figure 2: Illustrating the action of L-asparaginase on a) Normal cells and b) Tumor cells

when compared to the asparaginases produced by native bacteria. Endophyte species of Aspergillus, *Talaromyces*, *Eurotium*, *Streptomyces* and *Trichoderma*, from medicinal plants such as *Tinospora cordifolia*, *Curcuma longa*, *Withania Somnifera*, *Aegle marmelos* produce a battery of enzymes, alkaloids and flavonoids which produce clinically important drugs and chemical extracts used in industrial biotechnological processes. Incorporating the isolation, characterization and biochemical examinations of endophytes in the undergraduate teachings can generate astonishing results in endophytic studies and help in exploring the unexplored secondary metabolites [123]. A large number of plants and their associated symbionts are still to be unravelled. Hence, more intensive biochemical, genomic and metabolomic studies are needed to undiscover the complex host-endophyte relationships, to understand the complexity and diversity of the secondary metabolites produced by them. The isolation of endophytes from host plants and profound study of endophyte extract purification and testing is desired to compare their efficiency with existing commercial bioactive compounds.

Declarations

Author Contribution

PK suggested the review topic and conducted the literature search. PK and GK both made substantial contributions to the structure of the manuscript. PK wrote the first draft and both authors contributed critically to the draft. Both authors approved the article for publication.

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