

Endophytic, Non-endophytic Fungal Alkaloids and its Applications

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Abstract

Alkaloids are a secondary metabolite, which are extracted from a wide – array of organisms include Bacteria, Fungi, Plants and Animals. Here in present review mainly focused on the alkaloids derived from endophytic fungi and non – endophytic fungi. Fungi have provided a great source of spirit for novel drug compounds as fungi derived alkaloids have done major boon to human health and well - being. In the present review listed 35 different group of alkaloids from endophytes. In which 12 different alkaloids are kept under derivatives of Indole group, 4 different alkaloids are kept under Quinoline group, 4 different alkaloids kept under amines and amide group, from non-endophytic alkaloid 27 different group of alkaloids are reported. In which 9 different type of alkaloid are mentioned under indole group of alkaloids, 4 alkaloids are reported under diketopiperazine alkaloids, 4 different alkaloids are mentioned under ergot group of alkaloids, 3 alkaloids under prenylated indole alkaloids, 3 alkaloids are mentioned under pyridine classes. The main applications of these alkaloids are antimicrobial, Antibacterial, Antifungal, Antiviral Activity Antihelmenthic, Anticancerous, Nutrient Pedaling, Photo stimulation, Endophytes in Tissue Culture Antidiabetic Activity, and Immunosuppressive Activity; hence all the alkaloids should be used as medicines in Ayurvedam. The alkaloids derived from different fungi were reviewed and their uses in medical fields were also report.

Key words: Indole Alkaloid, Endophytic alkaloid, nonendophytic alkaloid, Antiviral, Antidiabetic, Anticancerous.

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INTRODUCTION

Now a days, a disproportion of alkaloids has been found from marine as well as in mushroom, endophytic, non - endophytic fungi in plants, which shows grade biological properties like insecticidal, cytotoxic, anticancer therapies, antifungal, antiviral activities. Alkaloids are the salient secondary metabolites. Based on the biosynthetic precursor and heterocyclic ring system, the alkaloids have been categorized into different groups which include indole, Piperidine, tropane, purine, pyrrolizidine, imidazole, quinolizidine, isoquinoline, and pyrrolidine alkaloids. Many scientists have propositioned distinct classification for alkaloids. One of the famous classifications that fractionate entire alkaloid compounds into 3 categories.

1. TRUE ALKALOIDS: these are the compounds which are acquired from an amino acid and have a heterocyclic ring with nitrogen. Example: Nicotine etc.
2. PROTO ALKALOIDS: these are the compound, which are obtained from an amino acid and possess

nitrogen atom but it is not a segment of the heterocyclic ring. Example: Adrenaline etcetera.

3. PSEUDO ALKALOIDS: these are the compounds that do not derived from amino acids. Example: Caffeine etc.

Endophytic fungi are fungi that deaden indiscrete or proportion of their lifecycle colonizing interior intra cellularly inside tissues of the plants, generally do not cause any obvious symptoms of disease. These fungi can cause numerous secondary metabolites, some of these are alkaloids. The characterization of endophytic fungi is stressed as a significant position of causing for drug. Endophytic fungi generally attain nutrition or food and shelter from the host plant, reciprocated; they favor jeopardous amplified congruence to the host plants by generating some functional metabolites. Endophytic fungi inhere plant tissues without sabotaging or generating compounds that that attributable an infection to the host cell. Their coexistence means that the endophytes generate the similar or same substances to those arising from the plant. Endophytic fungi have been of immense

interest from the last 20 years as potential generator of biologically active resource. They are a wealthy notch of functional secondary metabolites that contain flavonoids, terpenoids, steroids, phenol, phenylpropanoid, quinines, indole derivatives, amines, alkaloids, amides, pyrrolizidines, aliphatic isocoumarin derivatives.

Endophytes were first noted by the German Botanist Johann Henrich Friedrich Link in 1809. They were conception to be plant parasitic fungi and they were conception to be plant parasitic fungi and they were subsequent named as 'Microzymas' by French scientist Antonie. Bechamp. Endophytes may be imparted either direct from parent to progeny or among individuals. Endophytes which transmitted from parent to offspring are ordinarily literalized clonal and impart through fungal hyphae penetrating the embryo within the host's seeds, while reproduction of the fungi via asexual conidia or through sexual spore initiatives to horizontal transmission, where endophytes may propagate between plants in a population or community. Endophytes and plants apparently involve in mutualism, with endophytes, firstly aiding in the health and abidance of the host plant with subjects like pathogens and disease, water and heat stresses, nutrient accessibility and sillabub soil quality etc. In consideration, the endophytes experience carbon for energy from the plant host. Plant microbe correlations are not rigorously mutualistic as endophytic fungi can efficiently bechance pathogens or saprotrophs generally when the plant is accentuating. Endophytes may bechance operative and reproduce beneath particular environmental situations or when their host plants are pressurized or start to aging, desperately localizing the quantity of carbon provided to the endophyte.

Endophytic Fungal Alkaloids

In this review, we tried to provide an overview of the alkaloids that are derived from the different endophytic and non- endophytic fungi and potential against different diseases. And here we have mentioned 35 different groups of alkaloids. 12 different alkaloids are mentioned under derivatives of Indole group, 4 different alkaloids from Quinoline group, 4 different alkaloids from amines and amide group, 3 type of alkaloids from pyridone group, 2 different alkaloid under pyridines alkaloid, 2 alkaloids from quinazolines, 2 different alkaloids from indolizidine alkaloid group, 2 different alkaloids from spiroheterocyclic alkaloid group, 2 different alkaloids from chromone alkaloid group, 2 different alkaloids from steroidal alkaloid group, 2 alkaloids are mentioned under indole diketopiperazine alkaloids, 2 alkaloids from

diketopiperazine alkaloid, 2 alkaloids from pyrrole group, 2 alkaloids from isoquinoline group, 2 alkaloid from indole – terpene alkaloid, 1 alkaloid from azaphilone alkaloid, 1 alkaloid from cinchona alkaloid group, 1 alkaloid from ergot group, 1 alkaloid from indole diterpene alkaloid, 1 alkaloid from loline group, 1 alkaloid from angularly prenylated indole alkaloid, 1 alkaloid from macfortine alkaloid, 1 alkaloid from benzophenanthridine alkaloid, 1 alkaloid from antileishmanial diketopiperazine alkaloid, 1 alkaloid from spiroquinazoline alkaloid, 1 alkaloid from flavipin derived alkaloid, 1 alkaloid from dioxopiperazine alkaloid, 1 alkaloid from dibenzo- α -pyrone alkaloid, 1 alkaloid from prenylated indole alkaloids, 1 alkaloid from polyketide isoquinoline alkaloid, 1 alkaloid from dimeric pyrrolidine alkaloid, 1 alkaloid from sesquiterpene alkaloid, 1 alkaloid from quinazolinone alkaloid, 1 alkaloid from epipolythiodioxopiperazine group and 1 alkaloid from oxepine containing diketopiperazine type alkaloid (Table 1).

Camptothecine is a quinoline alkaloid, was produced by *Fusariumsolani*, *Formitopsis* sp. *Alternaria alternata* and *Phomopsis* sp., which has great activity in the clinical use against ovarian small lung and refractory ovarian cancers and also acts as a chemotherapeutic agent in the treatment of leukemia.

Penicillium sp., have the ability to produce alkaloids such as Shearinines A, D – K, Paspalitrem A, Paspaline, Penicidones A -C, Meleagrine, Chrysogine, Chrysogenamide A, Penioxamide A, Glandicoline B, Cerevisterol, Trihistanin, Peninsulfuranols A- F, Spirotryprostatin F, most of these alkaloids exhibited antimicrobial activity and anti-malignant activities on human cancer cell lines.

Chaetomium sp., produces alkaloids such as Chaetoglobosin B – D, F, G, Chaetominine, Swainsonine, Chaetofusin A – B, Chaetoseminudin F – G, which exhibited anticancer activity on breast cancer cell lines and antimicrobial activity.

Aspergillus fumigatus sp., produces alkaloids such as Pseurotin A, Asperfumoid, Pyripyropene A and E, Chaetominine, Tryptoquivaline J exhibited anti-inflammatory, immunosuppressive activities and Asperfumoid alkaloid showed Antifungal activity particularly against candida albicans.

Fusarium oxysporum produces Vinblastine and Vincristine which are used as an anticancer agent, and alkaloid Rohitukine used in chronic lymphocytic leukemia cancer treatment respectively.

Table-1: Alkaloids from Endophytic fungi

S. No	Class	Name of Alkaloid	fungal isolate	Host	Function	Reference
1	Amines and amides	Phomoenamides	<i>Phomopsis</i> sp. PUS-D15	Leaves of <i>Garcinia dulcis</i> Kuiz	Antibacterial	Zhang <i>et al.</i> , 2012
2	Amines and amides	p-aminoacetophenonic	<i>Streptomyces</i> sp.	Mangrove <i>Aegiceras corniculatum</i>	Pharmacological activities	Zhang <i>et al.</i> , 2012
3	Amines and amides	7-amino-4-methylcoumarin	<i>Xylaria</i> sp.	<i>Ginkgo biloba</i> L.	Antibacterial and Antifungal activities	Zhang <i>et al.</i> , 2012
4	Amines and amides	Ergot	<i>Clavicepspurpurea</i> <i>Claviceps</i> sp.	Rye, wheat and Millets grains	pharmaceutical uses	Zhang <i>et al.</i> , 2012
5	Azaphilone alkaloids	Chaetofusins A and B	<i>Chaetomium fusiforme</i>	Liverwort <i>Scapania verrucosa</i>	Antifungal activity	Kuklev <i>et al.</i> , 2016
6	Benzophenanthridine alkaloid	Sanguinarine	<i>Fusarium proliferatum</i> BLH51	<i>Macleaya cordata</i>	Antibacterial, Anthelmintic and Anti-inflammatory	Wang <i>et al.</i> , 2013
7	Chromone alkaloid	Rohitukine. flavopiridol	<i>Fusarium oxysporum</i> , <i>Fusarium solani</i> <i>Gibberella fujikuroi</i>	<i>Amoora rohituka</i> , <i>Dysoxylum binectariferum</i>	Chronic lymphocytic Leukemia cancer treatment, Anti – inflammatory, anticancer and immunotherapy.	Kumara P. M <i>et al.</i> , 2014
8	Cinchona alkaloids	Quinine, Quinidine, Cinchonidine, Cinchonine	<i>Diaporthe</i> sp.	<i>Cinchona ledgeriana</i>	Antimalarial	Maehara <i>et al.</i> , 2012
9	Dibenzo – α – pyrone alkaloid	Rhizovagine A	<i>Rhizopycnis vagum</i> Nitaf22	<i>Nicotiana tabacum</i>	Acetylcholinesterase inhibitory activity	Wang <i>et al.</i> , 2020
10	Diketopiperazine alkaloid	5S-hydroxynorvaline-S-IIe	<i>Penicillium</i> sp. GD6	Chinese Mangrove <i>Bruguiera gymnorrhiza</i>	Antibacterial	Jiang, C. S <i>et al.</i> , 2018
11	Diketopiperazine alkaloid	Tryhistatin	<i>Penicillium</i> sp. HS-3	stems of <i>Huperzia serrata</i>	Antimicrobial activity	Shan <i>et al.</i> , 2010
12	Diketopiperazine alkaloids	piperazine-2,5-dione -1 and 2	<i>Trichosporum</i> sp.	Seeds of <i>Trigonella foenum-graecum</i> (fabaceae)	Antileishmanial activities	Metwaly <i>et al.</i> , 2015
13	Dimeric pyrrolidine alkaloid	Collacyclumines A-D	<i>Colletotrichum salsolae</i> SCSIO41021	<i>Kandelia candel</i>	Antimicrobial activity	Lin <i>et al.</i> , 2020
14	Dioxopiperazine alkaloids	Dehydrovariecolorin L and dehydroechinulin	<i>Eurotium rubrum</i>	Stem of mangrove plant <i>Hibiscus tiliaceus</i>	Cytotoxic effect	Li <i>et al.</i> , 2008
15	Epipolythiodioxo piperazine (ETP)	Peninsulfuranols A - F	<i>Penicillium janthinellum</i> HDN13-309	Root of <i>Sonneratia caseolaris</i>	Cytotoxic activities	Zhu <i>et al.</i> , 2016
16	Ergot alkaloids	Fumigaclavine C and Pseurotin A	<i>Aspergillus</i> sp. EJC08	<i>Bauhinia guianensis</i> medicinal plant	Antibacterial	Pinheiro <i>et al.</i> , 2013
17	Flavipin – derived alkaloids	Azacoccones F-H	<i>Epicoccum nigrum</i> MK214079	Leaves of <i>Salix</i> sp.	Antibacterial activity	Harwoko <i>et al.</i> , 2020
18	Indole – diterpene alkaloids	Lolitrem B	<i>Epichole</i> sp	Rye grass	Toxicity in insects	Philippe, 2016
19	Indole alkaloid	Glandicoline B,	<i>Penicillium</i> sp	Roots of <i>Mauritia flexuosa</i>	Antimicrobial activity	Koolen <i>et al.</i> , 2012
20	Indole alkaloid	Piperine	<i>Periconia</i> sp.	<i>Piper longum</i>	Antituberculosis activity	Verma <i>et al.</i> , 2011
21	Indole alkaloids	Vincamine	<i>Geomyces</i> sp	<i>Nerium indicum</i>	Nootropic drugs - Cerebral insufficiencies treatment	Na <i>et al.</i> , 2016
22	Indole alkaloids	Vinblastine and vincristine	<i>Fusarium solani</i> , <i>Fusarium oxysporum</i>	<i>Catharanthus roseus</i>	Anticancer agents	Kumar <i>et al.</i> , 2013
23	Indole alkaloids	Fumitremorgin B and C	<i>Alternaria</i> sp. FL25	<i>Ficus carica</i>	Anticancerous activity	Feng <i>et al.</i> , 2010
24	Indole alkaloids	Cristatamins A-D	<i>Eurotium cristatum</i> EN-220	Marine alga <i>Sargassum thunbergii</i>	Antibacterial activity Cristatamins D showed average lethal activity	Du <i>et al.</i> , 2012

					toward brine shrimp	
25	Indole alkaloids	Chetoseminudin F and G	Chaetomium sp.SYP-F7950	<i>Panax notoginseng</i>	Antibacterial activity	Peng <i>et al.</i> , 2019
26	Indole derivatives	Chaetoglobosin B-D, F-G	<i>Chaetomium elatum</i>	Isolated from soil	Anticancer agents	Zhang <i>et al.</i> , 2012
27	Indole derivatives	Shearinines A, D – K, Paspalitrem A And paspaline	<i>Penicillium</i> sp.	<i>Aegiceras corniculatum</i>	Showed blocking activity on large conductance calcium – activated potassium channels in vitro	Zhang <i>et al.</i> , 2012
28	Indole diketopiperazine alkaloids	Isovariecolorin 1	<i>Eurotium cristatum</i> EN-220	Marine alga <i>Sargassum thunbe</i>	Exhibited antioxidative activities and showed lethal activity against brine shrimp	Du <i>et al.</i> , 2017
29	Indole-diketopiperazine	Spirotryprostatin F	<i>Penicillium brefeldianum</i>	Solid cultures	Showed cytotoxic effects toward HepG2 and MDA – MB – 231 cells with inhibition concentration (IC50) values of 14.1 µmol/L and 35.5 µmol/L	Gao <i>et al.</i> , 2017
30	Indolizidine alkaloids	Swainsonine	<i>Chaetomium</i> sp.	<i>Swainsona canescens</i>	An α-mannosidase and mannosidase ii	Grum <i>et al.</i> , 2013
31	Indolizidine alkaloids	Swainsonine	<i>Alternaria oxytropis</i>	Astragalus and oxytropis genera	As a Selective inhibitor of both lysosomal acid and cytosolic α – mannosidase ii	Song <i>et al.</i> , 2019, Cook <i>et al.</i> , 2014,
32	Indolosesquiterp enoid alkaloids	Mycoleptodiscins A and B	<i>Mycoleptodiscus</i> sp.	<i>Desmotes incomparabilis</i> in Panama	Anticancer agent	Ortega <i>et al.</i> , 2013
33	Isoquinolone alkaloid	5-hydroxy-8-methoxy-4-phenylisoquinolin – 1 (2H)-one, 3-O-methylviridicatin and viridicatinol	<i>Penicillium</i> sp. R22	<i>Nerium indicum</i>	All three showed antifungal activities and viridicatinol showed antibacterial activity toward staphylococcus aureus with minimum inhibitory concentration (MIC) value of 15.6 µg/mL	Ma <i>et al.</i> , 2017
34	Loline alkaloids	Amino pyrrolizidines	<i>Neotyphodium uncinatum</i>	Meadow fescue grass	Defense mechanism toward insect herbivores	Blankenship <i>et al.</i> , 2001
35	Macfortine group of alkaloids	Chrysogenamide A	<i>Penicillium chrysogenum</i>	<i>Cistanche deserticola</i> Y.C. Ma	Showed a neurocyte protection effect toward oxidative stress – induced cell death in SH-SY5Y cells	Lin <i>et al.</i> , 2008
36	Meleagrine alkaloid	Meleagrine and chrysogine	<i>Penicillium</i> sp.	<i>Annona squamosa L.</i>	Meleagrine alkaloid exhibited inhibitory activities toward leukemia	Yunianto <i>et al.</i> , 2014
37	Mycoleptodiscin alkaloids	Mycoleptodiscin B	<i>Mycoleptodiscus</i> sp.	<i>Calamus thwaitesii Becc</i>	Antimicrobial activity	Dissanayake, <i>et al.</i> , 2016
38	Oxepine containing diketopiperazine type alkaloids	Varioloids A and B	<i>Paecilomyces variotii</i> EN – 291	Algal derived	Displayed potent activity toward the plant pathogenic fungus <i>Fusarium graminearum</i>	Zhang <i>et al.</i> , 2015
39	Polyketide isoquinoline alkaloid	Fusarimine	<i>Fusarium</i> sp. LN12	<i>Melia azedarach</i>	Antibacterial activity	Yang <i>et al.</i> , 2012
40	Prenylated indole alkaloid	Penioxamide A and 18-hydroxydecaurin B	<i>Penicillium oxalicum</i> EN – 201	From the Leaves of <i>Rhizophora stylosa</i>	Exhibited potent brine shrimp lethality with lethal dose (LD50) values of 5.6 and 2,3 µM respectively.	Zhang <i>et al.</i> , 2015
41	Prenylated indole alkaloids	Amoenamide C and Sclerotiamide B	<i>Fusarium sambucinum</i>	<i>Nicotiana tabacum</i>	Insecticidal activities	Zhang <i>et al.</i> , 2019
42	Protoberberine alkaloid	Palmatine 7 – N – oxide	Coelomycetes AFKR – 3	Young stems of yellow moon shed plant, <i>Archangelisia flava</i> (L.) Merr.	Antimicrobial activity toward pathogenic bacteria and fungi	Agusta <i>et al.</i> , 2014

43	Pyridine alkaloid	Pyripyropene A and E, 1,11-dideacetyl-pyripyropene A, Chaetominine, Tryptoquivaline J, Fumitremorgin C, 1-acetyl- β -carboline and nicotinic acid	<i>Aspergillus fumigatus</i> HQD24	Chinese mangrove plant <i>Rhizophora mucronate</i>	They exhibited immunosuppressive and cytotoxic activities	Zou <i>et al.</i> , 2021
44	Pyridines	Penicidones A -C	<i>Penicillium</i> sp.	Stem of <i>Quercus variabilis</i>	Anticancer agent Showed moderate cytotoxicity on human cancer cell lines	Zhang <i>et al.</i> , 2012
45	Pyridone alkaloid	Campyridones A-D	<i>Campylocarpon</i> sp. HDN13-307	From the Roots of mangrove plant, <i>Sonneratia caseolaris</i>	Exhibited cytotoxic activity toward P388 cells	Zhu <i>et al.</i> , 2016
46	Pyridone alkaloids	Fusapyridons A and B	<i>Fusarium</i> sp. YG - 45	<i>Maackia chinensis</i>	Displayed antimicrobial activity toward <i>Pseudomonas aeruginosa</i> and <i>staphylococcus aureus</i>	Tsuchinari <i>et al.</i> , 2007
47	Pyridone alkaloids	Tolypyridone A	<i>Tolypocladium cylindrosporium</i> (endolichen fungus)	<i>Lethariella zahlbruckneri</i>	Cytotoxic effects on human tumor cells	Li <i>et al.</i> , 2015
48	Pyrrole alkaloid	N-[4-(2-formyl-5-hydroxymethyl-pyrrol-1-yl)-butyl]-acetamide	<i>Fusarium incarnatum</i> (HK100504)	<i>Aegiceras corniculatum</i>	Cytotoxic activities	Li <i>et al.</i> , 2008
49	Pyrrolidones alkaloids	Phomapyrrolidones A-C	<i>Phoma</i> sp.	<i>Saurauia scaberrinae</i>	Showed poor antitubercular activity at subcytotoxic concentrations	Wijeratne <i>et al.</i> , 2013
50	Quinazoline alkaloid	(1R,4R)-1,4-(2,3)-indolmethane-1-methyl-2,4-dihydro-1H-pyrazino-[2,1-b]-quinazoline-3,6-dione	<i>Penicillium vinaceum</i>	<i>Crocus sativus</i>	Antifungal agent	Zheng <i>et al.</i> , 2011
51	Quinazolines	Chaetominine	<i>Chaetomium</i> sp.	<i>Adenophora axilliflora</i> leaves	Anticancer agent Exhibited high cytotoxicity toward human leukemia K562	Zhang <i>et al.</i> , 2012
52	Quinazolinone alkaloids	Aniquinazolines A-D	<i>Aspergillus nidulans</i>	<i>Rhizophora stylosa</i>	Showed antibacterial and cytotoxic activity	An, <i>et al.</i> , 2013
53	Quinoline	Camptothecine (CPT)	<i>Fusarium solani</i> , <i>Fomitopsis</i> sp., <i>Alternaria alternata</i> and <i>Phomopsis</i> sp.	<i>Nethapodytes fortida</i> (grass), and <i>Miquelia dentata</i> Bedd	As a chemotherapeutic agent in the treatment of leukemia and clinical use toward ovarian, small lung and refractory ovarian cancers	Zhang <i>et al.</i> , 2012, Pund, Joshi 2017 and Shweta <i>et al.</i> , 2013
54	Quinoline	Aspernigerin	<i>Aspergillus niger</i>	<i>Cynodon dactylon</i> (plant)	Cytotoxic potential to the cancer cell lines nasopharyngeal epidermoid KB with inhibition concentration value (IC50) 22 μ g	Zhang <i>et al.</i> , 2012
55	Quinoline	Penicinoline	endophytic fungus <i>Penicillium</i> sp.	Mangrove	Showed cytotoxicity against 95 – D and HepG2 cell lines with IC values 0.57 μ g/mL and 6.5 μ g/mL	Zhang <i>et al.</i> , 2012
56	Quinoline and iso quinoline	Asperfumoid	<i>Aspergillus fumigatus</i> CY018	<i>Cynodon dactylon</i> (plant)	Antifungal, has specific activity toward <i>Candida albicans</i>	Zhang <i>et al.</i> , 2012
57	Sesquiterpene alkaloids	Huperzine A	<i>Paecilomyces tenuis</i> YS-13	<i>Huperzia serrata</i>	Acts as a cholinesterase inhibitor and improves neurotransmitters in the brain	Su <i>et al.</i> , 2014
58	Spiro – heterocyclic alkaloid	3'S- pestaloamide A	<i>Pestalotiopsis</i> sp.	<i>Isodon xerophilus</i>	Exhibited the latent cancer immunotherapy activities	Daley <i>et al.</i> , 2021

59	Spiro-heterocyclic γ - lactam alkaloid	Pseurotin A	<i>Aspergillus fumigatus</i>	stem of <i>Erythrophleum fordii olive</i>	Which performed indirect anti – inflammatory activity with inhibition concentration (IC50) value of 5.20 μ M	Hawary <i>et al.</i> , 2020
60	Spiroquinazoline alkaloids	Alantryptinone, alantryptinone, alantryptinone and alantryptinone	<i>Eupenicillium</i> sp.	<i>Murraya paniculate</i>	Medicinal use	Barros <i>et al.</i> , 2005
61	Steroidal alkaloid	Peimisine and imperialine-3 β -D-glucoside	<i>Fusarium redolens</i> 6WBY3	<i>Fritillaria unibracteata</i> var. <i>wabuensis</i>	Immunosuppressive and hepatoprotective agents	pan <i>et al.</i> , 2015
62	Steroidal alkaloids	Peimisine and Peiminine alkaloids	<i>Fusarium</i> sp.	<i>Fritillaria Unibracteata</i> var. <i>wabuensis</i>	Has a various toxicological and pharmacological effects on humans	pan <i>et al.</i> , 2014
63	Terpenoid indole alkaloids	Vincristine and Vinblastine	<i>Talaromyces radicus</i>	<i>Catharanthus roseus</i>	Which induce Apoptotic cell death	Palem <i>et al.</i> , 2015

Non-Endophytes

Saprophytes are also known as Saprotoph or saprobe, organism that feeds on nonliving organic substance called as detritus at an infinitesimal stage. The etymology of the term saprotroph comes from the Greek word ‘Sapros’ means rotten and term ‘trophe’ means nourishment. Saprophytic organisms are contemplated endangerment to decomposition and nutrient cycling and inhere fungi, some bacteria and also fungus like organisms called as water molds. Saprophytic fungi are the broadest swarm of fungi, which are accountable for digesting and reprocessing dead plant and animal substances. These are the fruit bodies we can see on dead trees, leaf pieces, even on excrement. Saprotophs feed by a method called as absorptive nutrition. In which nutritional substance such as dead organism or other non - living organic substance. Saprophytes directly breakdown by a different type of enzymes that are produced by the saprotroph. The enzymes coder the detritus into candid forms, which are then absorbed by the cells to nourish the organism. Enzymes play major role in decreasing the assemblage of dead organic substances and in reprocessing needful nutrients, specifically Carbon and Nitrogen Fungi that disincorporate leaves and twigs in organic trash, which are present on the forest floor, inhere, *Marasmius* and many other species. Some fungi; for example, *Pilobolus*, feed mainly on the herbivores dung. Wood carrion fungi, including turkey Tails, *Pleurotus* and *Ganoderma* sp. saprophytic fungi can also show negative commercial impacts to the wood industry, dis-incorporate both cut timber and dead rind of living trees. Damnum to houses from ‘dry rot’ is affected by the wood – spoil species *Serpula lacrymans*.

Parasitic and pathogenic fungi conform symbiotic association with other living organisms, likewise to mycorrhizal fungi; still they welfare to the damnum of their host. Several lacerate acts on trees and other plants, and also attacks mushroom and occasionally portrayal the host species unidentifiable. Though animal kingdom members are incurring to parasitic fungal infection. Parasitic fungi can be an

unbelievably ruinous force, occasionally afflict commercial logging action and forest administration attempts. At Mount rainer, white pine blister, a fungal disease caused by *Cronartium ribicola* frightens more – Heave white bark pine. White pine blister rust was initiated to North America in the early 20th century. It affects branch swelling, branch death, and blights from which orange vesicle appear. Anyways affected trees generally die, occasionally within a few years of infection. Significantly, this fungus depends on two unlike varieties of hosts to full fill its life cycle. Spores sorted by affected white bark pine trees do not go on to affect other trees. In lieu, they infect smaller plants for examples, Gooseberry, Currant and also Indian paintbrush. Parasitic fungi are coming in close connection with their host plants, with the help of motile zoospores; this can break down the cytoplasm from where they will colonize the entire plant.

Nonendophytic Fungal Alkaloids

Not only endophytic fungi have future and feature in the synthesis of secondary metabolites particularly alkaloids, but we can also extract alkaloids from non – endophytic fungi. These alkaloids have proven themselves their requirements in pharmacological activities, not only in medicinal field but also in the agricultural field. Under non-endophytic alkaloid we have reported 27 different group of alkaloids. 9 different type of alkaloid are mentioned under indole group of alkaloids, 4 alkaloids are reported under diketopiperazine alkaloids, 4 different alkaloids are mentioned under ergot group of alkaloids, 3 alkaloids under prenylated indole alkaloids, 3 alkaloids are mentioned under pyridone, 2 alkaloids under benzodiazepine alkaloids, 2 alkaloids under quinazoline, 2 alkaloids under sesquiterpene alkaloid, 2 alkaloids under indole diketopiperazine alkaloids, 2 alkaloids are reported under clavine, 1 alkaloid under pyridone, 1 alkaloid under isoquinolone, 1 alkaloid under imidazolone, 1 alkaloid under peptide ergot, 1 alkaloid under pyrrole based dimeric alkaloid, 1 alkaloid under pyrrole – imidazole, 2 alkaloid under

spiroindolinone alkaloids, 1 alkaloid under azaphilone, 1 alkaloid under indole based cytochalasin alkaloid, 1 alkaloid under tyrosine, 1 alkaloid under isoechinuline type, 1 alkaloid under diastereomeric quinolinone alkaloids, 1 alkaloid under piperazine, 1 alkaloid is mentioned under dioxopiperazine alkaloids, 1 alkaloid under pentacyclic alkaloid, 1 alkaloid under mixture of quaternary alkaloids, 1 alkaloids under pyrrolidine and 1 alkaloid under epipolythiodioxopiperazine (Table 2).

Claviceps species produces alkaloids such as Clavine, Elymoclavine – O – β – D – fructoside, γ – ergokryptinine, these alkaloids showed their activities in the production of antimigraine drugs, uterotonics,

and also as prolactin inhibitor, antiparkinson agent and pain releivers.

Chaetomium globosum produces alkaloids such as Chaetoglobinol A, Chaetocochin J exhibited antibacterial activity particularly against *Bacillus subtilis*, and Armochaeglobines A and B alkaloid showed anticancer activities on human cancer cell lines.

Aspergillus ochraceus produces alkaloids such as Circumdatin A – C, Spermides A, used for gastrointestinal and central nervous system disorders and displayed average inhibition activity against *Pseudomonas aeruginosa* with a minimum inhibition concentration (MIC) value of 0.8 μ M respectively.

Table-2: Alkaloids from Non endophytic fungi

S. No	Class	Name of Alkaloid	Fungal isolate	Host	Function	Reference
1	Azaphilone alkaloid	N-glutarylchaetoviridins A – C	<i>Chaetomium globosum</i>	Deep sea sediment sample collected in south china sea	Exhibited a broad spectrum of cytotoxicity toward MGC – 803 and HO8910 with the inhibition concentration (IC50) values of 6.6 and 9.7 μ M	Sun <i>et al.</i> , 2019
2	Benzodiazepine alkaloids	Circumdatin A-C	<i>Aspergillus ochraceus</i>		Utilized for Gastrointestinal and central nervous system disorders	Rahbaek <i>et al.</i> , 1999
3	Benzodiazepine and indole alkaloids	Circumdatins K and L and 5 – chlorosclerotiamide	<i>Aspergillus westerdijikiae</i>	Deep sea	Exhibited cytotoxicity toward human carcinoma cell lines	Peng <i>et al.</i> , 2013
4	Clavine alkaloids	Fumigaclavine A and B	<i>Aspergillus fumigatus Fres</i>	osprey		Spilsbury <i>et al.</i> , 1961
5	Clavinet type alkaloid	Triseclavine and isosetoclavine	Elymus type ergot fungus, Agropyrum type fungus	<i>Pennisetum typhoideum</i> Rich	Pharmacological functions	Abe <i>et al.</i> , 2014
6	Diastereomeric quinolinonealkaloids	Peniprequinolone	<i>Penicillium janczewskii</i>	Marine sample	Exhibited average cytotoxicity on cancer cell lines	He <i>et al.</i> , 2005
7	Diketopiperazine alkaloid	Penicillivinacine	<i>Penicillium vinaceum</i>	Marine derived	Exhibited antimigratory functions toward the highly metastatic triple negative human breast cancer cells	Asiri <i>et al.</i> , 2015
8	Diketopiperazine alkaloid	Chrysopiperazines A and B	<i>Penicillium chrysogenum</i>	Gorgonian derived	Antimicrobial activity	Xu <i>et al.</i> , 2019
9	Diketopiperazine alkaloids	Effusin A	<i>Aspergillus effuses</i> H1-1	Mangrove rhizosphere soil	Showed cytotoxic activities on P388 cells	Gao <i>et al.</i> , 2012
10	Diketopiperazine alkaloids	Golmaenone, neoechinulin A	<i>Aspergillus</i> species	Marine derived	Displayed a significant radical scavenging activity toward 1,1-diphenyl -2-picrylhydrazyl with inhibition concentration (IC50) values of 20 and 24 μ M, and also Using as sunscreen	Li <i>et al.</i> , 2004
11	Dioxopiperazine alkaloid	Dehydroxybisdethiois(methylthio)gliotoxin	<i>Pseudallescheria</i>	Marine derived fungus culture	Showed potent antibacterial activity toward the methicillin – resistant and multidrug – resistant staphylococcus aureus	Li <i>et al.</i> , 2006
12	Epipolythiodioxopiperazine	Verticillin A, H, gliocladicillin A, C	Bionectriaceae		Exhibited cytotoxicity toward a panel of human malignant cell lines	Figuerola <i>et al.</i> , 2012
13	Ergot alkaloid	Clavine alkaloid, D-lysergic acid and its derivatives and ergopeptines	Claviceps	cereals	Used in pharmatech industry, where they utilized for synthesis of anti – migraine drugs, uterotonics, prolactin inhibitors and antiparkinsonian agents	Hulvova <i>et al.</i> , 2013
14	Ergot alkaloid	Elymoclavine – O – β – D – fructoside	Claviceps strain SD 58		Pharmacological activities (Pain releivers)	Flieger <i>et al.</i> , 1989

15	Ergot alkaloids	Clavines, ergonovine alkaloids	<i>Claviceps purpurea</i>	Rice		Tsai <i>et al.</i> , 1995
16	Ergot and clavine alkaloids	Chanoclavine, agroclavine, penniclavine, elymoclavine, ergonovine, ergonovinine	<i>Balansia epichole</i>	Smut grass		Bacon <i>et al.</i> , 1979
17	Imidazolone alkaloids	Tricladins A and B	<i>Tricladium</i> species		Exhibited marginal cytotoxicity toward MDA – mb-231 human breast cancer cells	Zou <i>et al.</i> , 2011
18	Indole 2,5 – diketopiperazine alkaloids	Eurotiumins A – E	Marine derived fungus Eurotium sp. SCSIO F452	South china sea sediment sample	Exhibited important radical scavenging functions toward DPPH	Zhong <i>et al.</i> , 2018
19	Indole alkaloid	Communesins G and H	<i>Penicillium rivulum Frisvad</i>		Inactive in antimicrobial, antiviral and anticancer assays	Dalgaard <i>et al.</i> , 2005
20	Indole alkaloid	7-chlorofischerindoline	<i>Neosartorya hiratsukae</i>		Exhibited antibacterial and cytotoxic activity	Paluka <i>et al.</i> , 2020
21	Indole alkaloids	Hirsutellones A – E alkaloids	<i>Hirsutella nivea</i> BCC2594 (insect pathogenic fungus)		Exhibited important growth inhibitory activity toward Mycobacterium tuberculosis H37Ra	Isaka <i>et al.</i> , 2005
22	Indole alkaloids	Notoamides A-D	<i>Aspergillus</i> species		Notoamides A-C, Exhibited average cytotoxicity toward cancer cell lines	Kato, <i>et al.</i> 2007
23	Indole alkaloids	Shearinines D, E and F	<i>Penicillium Janthinellum Biourge</i>		Induce apoptosis in human Leukemia HL-60 cells	Smetanina <i>et al.</i> , 2007
24	Indole alkaloids	17-epi-notoamides Q and M	<i>Aspergillus</i> species		Exhibited antibacterial activity toward Staphylococcus epidermidis	Chen <i>et al.</i> , 2013
25	Indole alkaloids	Fumigatosides E and F	<i>Aspergillus fumigatus</i>	Deep sea	Showed antifungal activity	Limbadi, <i>et al.</i> , 2018
26	Indole alkaloids	Glyantrypine	Cladosporium species. PJX-41	Mangrove derived fungus	Showed important effects toward influenza virus A (H1N1)	Peng <i>et al.</i> , 2013
27	Indole alkaloids	Chaetoglobinol A, Chaetocochin J	<i>Chaetomium globosum</i>	Rice culture	Showed antibacterial activities toward Bacillus subtilis	Xu <i>et al.</i> , 2015
28	Indole alkaloids	4-(3-indolyl) butane-1,2,3-triol; 3-(3,3-diindolyl) propane-1,2-diol; and 3-(3-indolyl) propane -1,2,3-triol	Balansia epichole (Weese)	Laboratory culture	Parasitizes pasture grasses	Porter <i>et al.</i> , 1977
29	Indole based cytochalasanalkaloids	Armochaeglobines A and B	<i>Chaetomium globosum</i>	Arthropod derived, <i>Armadillidium vulgare</i>	Anticancer activity on human cell lines	Chen <i>et al.</i> , 2015
30	Indole diketopiperazine alkaloids	Spirotryprostatins C-E, 13-oxoverruculogen	<i>Aspergillus fumigatus</i>	Holothurian	Exhibited cytotoxic activities	Wang <i>et al.</i> , 2008
31	Isoechinulin type alkaloids	Neoechinulin A, Preechinulin, Isoechinulin A	Nigrospora genus	Soft coral Dendronepht hya sp.	Showed antifouling activities toward the larval settlement of barnacle Balanus Amphitrite	Sun <i>et al.</i> , 2014
32	Isoquinoline alkaloid	Ampullosine	<i>Sepadonium ampullosporum</i>		Exhibited antifungal activity toward the phytopathogenic fungus Cladosporium cucumerinum	Quang <i>et al.</i> , 2010
33	Mixture of quaternary alkaloid	Tannic, caffeic and ferulic acids	<i>Argemone Mexicana</i>		Exhibited antifungal activity	Singh <i>et al.</i> , 2010
34	Pentacyclic spiroindolinone alkaloid	Citrinadin A	Marine derived fungus, <i>Penicillium citrinum</i>	Marine red alga	Showed antimicrobial activity	Tsuda <i>et al.</i> , 2004
35	Peptide ergot alkaloid	γ -ergokryptinine	<i>Claviceps purpurea</i> CCM 8059		Used in agriculture and medical fields	Cvak <i>et al.</i> , 2005

36	Piperazine alkaloid	Herquiline alkaloid	<i>Penicillium herquei</i> Fg-372	Soil sample collected at Saitama Prefecture, Japan	Inhibits blood platelet aggregation induced by adenosine diphosphate	Omura <i>et al.</i> , 1979
37	Prenylated indole alkaloids	Asperversiamides	<i>Aspergillus versicolor</i>	Marine derived	Showed anti – inflammatory activities	Li <i>et al.</i> , 2018
38	Prenylated indole alkaloids	17 – O – ethylnotoamide M	<i>Aspergillus sulphureus</i> and <i>Isaria felina</i>	Marine derived fungi	Inhibit the formation of colony of the human prostate malignant cells 22Rv1 at non – cytotoxic of 10µM	Afiyatullof <i>et al.</i> , 2018
39	Prenylated indole alkaloids	Speramides A	<i>Aspergillus ochraceus</i> KM007	Fresh water derived	Displayed moderate activity toward <i>Pseudomonas aeruginosa</i> with a minimum inhibition concentration (MIC) value of 0.8µM	Chang <i>et al.</i> , 2016
40	Pyridinone alkaloid	1,4-dihydroxy-5-phenyl-2-pyridinone alkaloid	<i>Septoria pistaciarum</i>		Showed average in vitro antimalarial activities toward chloroquine – sensitive (D6) and resistant (W2) strains of <i>plasmodium falciparum</i> and also active toward both methicillin – sensitive and methicillin – resistant <i>staphylococcus aureus</i>	Kumarihamy <i>et al.</i> , 2010
41	Pyridone alkaloid	Arthpyrones D – K	<i>Arthrinium</i> sp. UJNMF0008	Deep sea derived	Exhibited Average to significant antibacterial activity toward <i>Mycobacterium smegmatis</i> and <i>Staphylococcus aureus</i> and also exhibited cytotoxicity toward two human Osteosarcoma cell lines	Bao <i>et al.</i> , 2018
42	Pyridone alkaloid	Militarinones D	<i>Paecilomyces militaris</i>		Displayed cytotoxic activities and negligible neuritogenic activity in PC – 12cells	Schmidt <i>et al.</i> , 2003
43	Pyridone alkaloids	Arthpyrones A- C	<i>Arthrinium arundinis</i> ZSDS1 – F3	Sponge derived	Antimicrobial activity	Wang <i>et al.</i> , 2015
44	Pyrrole – imidazole alkaloids	Fungerin	<i>Fusarium</i> species		Antifungal agent	Kato <i>et al.</i> , 1996
45	Pyrrole based dimeric alkaloid	Hirsutellone A	<i>Trichoderma gelatinosum</i> BCC7579		Anti - tubercular agent	Supothina <i>et al.</i> , 2007
46	Pyrrolidine alkaloids	Aegyptolidines A and B	<i>Aspergillus aegyptiacus</i>	Cotton textile yield	Exhibited average cytotoxic effect on murine lymphoma tumor cell line	Ibrahim <i>et al.</i> , 2015
47	Pyrrolidinone alkaloid	Ascosalipyrrolidinone A	<i>Ascochyta salicorniae</i> (obligate marine fungus)	Green alga Ulva species	Showed anti-plasmodial effects against <i>Plasmodium falciparum</i> strains K1 and NF 54, and also exhibited antimicrobial activity and hindering tyrosine Kinase P56 ^{lck}	Osterhage <i>et al.</i> , 2000
48	Quinazoline alkaloid	Aurantiomides A-C	<i>Penicillium aurantiogriseum</i> SP0-19	Sponge	Exhibited average cytotoxicity toward HL-60, P388 and BEL-7402 cell lines	Xin <i>et al.</i> , 2007
49	Quinazolinone alkaloids	Penipanoids A, B and C	<i>Penicillium paneum</i> SD – 44	Marine Sediment – derived	Exhibited antimicrobial activity	Li <i>et al.</i> , 2011
50	Sesquiterpenoid alkaloid	Eurochevalierinealkaloid	<i>Eurotium chevalieri</i>		Showed antimalarial functions toward <i>Mycobacterium tuberculosis</i> , and also exhibited cytotoxicity toward cancer cell lines	kanokmedh akul <i>et al.</i> , 2011
51	Spiroindolinone alkaloids	Cycloexpansamines A and B	<i>Penicillium</i> sp. (SF-5292)		Moderately inhibited the protein's activity Tyrosine phosphatase 1B	Lee <i>et al.</i> , 2015
52	Tyrosine alkaloids	Gymnastatin Z, Phomacin B and Triticone D	<i>Westerdykella dispersa</i>	Marine sediment	Exhibited antibacterial and cytotoxic activities on human malignant cancer cell line	Xu <i>et al.</i> , 2017
53	Zwitterionic sesquiterpene alkaloid	Conсорamides A – C	<i>Irpex consors</i>	Culture broth	Exhibited antibacterial and antioxidant properties	Kim <i>et al.</i> , 2021

APPLICATIONS

1. BIOLOGICAL ROLES OF ENDOPHYTIC FUNGI

The potentiality of endophytic fungi is to synthesize new and notable bioactive secondary metabolites. These are more significant in the field of Pharmaceutical, industrial and agriculture. The several natural resources synthesized by endophytic fungi contain identical structures and bioactivities toward different diseases. Instead of a vast bund, this dedicates huge capabilities for oppression of secondary yields for medicinal, agricultural and industrial utilization.

2. NUTRIENT PEDALLING

It is an important procedure that appears enduringly to balance nutrients and wreak them accessible for each element of the environment.

The decadence of the dead biomass evolved into one crucial step to carryback used nutrients to the ecosystem, which in return else becomes available to the living beings. The primary significant characterizations in biodegradation to the trashery of its host plants. They have capacity to disintegrate involute substances into candid form.

Another significant characterization is bioremediation, which explains as a custom of uncapping of pollutants and eyes from the atmosphere by the utilize of microorganisms. It depends on the utilize of microorganisms. It depends on the life procedure of microbes to disintegrate these wastes substances and it has become contingent due to innumerable microbial variety.

3. PHOTOSTIMULATION

Endophytes also takepart in the uptake of necessary nutrients essential for plant growth. They educe uptake of Nitrogen and in giant fescue adjustment to Phosphorous blemish. A novel strain of fungus *Cladosporium sphaerospermum* extracted from the glycine max (L) Merr roots. Exhibited the aura of higher aggregates of bioactive GA3, GA4 and GA7, which persuade inordinate plant growth in both rice and soyabean types. The endophytes roles are thoroughly recorded forharborage of plant in soil, absorption of nutrient storage, water and ion and vegetative growth of plants, the root system is in close relationship with a broad range of soil microbial populations.

4. ENDOPHYTES IN TISSUE CULTURE

Endophytes are principally precious to the host plants and for plant tissue culture. The ideal host plants and for plant tissue culture. The ideal goal of tissue culture is to grow uncontaminated plants. Even after stature fumigation of the explants, autoclaving and ultraviolet treatment of nutrient medium for tissue culture, endophytic fungi/ bacteria/ actinomycetes start

developing from tissue cultured explant. These endophytes are commonly contemplated as pollutants impacting in complete waste of time, media and explants and also imperiled species of microbes, can be protected by this technique. Also, endophytic species constitution and plant genotype in conjunction under tissue culture circumstances are the basic ingredient for accomplishment of plant tissue cultures with promoted resumption potentiality. Interconnection between the endophytes and particular secondary compounds filtered from plant may be an utmost surface for darkening or browning and cell death, some endophytes were extracted in broth / cultures from roots and plant photosynthetic tissues.

5. ANTIVIRAL ACTIVITY

The alluring utilize of antibiotic products from endophytic fungi are the obstruction of viral growth. Two novel human cytomegalovirus protease hinders, cytonic acids A and B were illuminated by using mass spectrometry and nuclear magnetic resonance techniques and obtained to be effective toward virus growth. Some metabolites from endophytic fungi of xerophytic plants serve as a feasible source for recognizing paladin inhibitors of Human Immunodeficiency virus 1 replication.

6. ANTICANCER ACTIVITY

Paclitaxel and some of its derivatives indicate the top crucial category of antitumor agents generated by endophytes. The method of work of paclitaxel is to intercept tubulin molecules from depolymerizing throughout the cell division procedure. It is the first billion dollars anticancer drug in the world and which is utilized to trat a numerous tissues of human proliferating disease. Taxomyces andreae lay out an another for synthesis of taxol through torreyanic acid is another significant antitumor agent synthesized from *P. microspore* extracted from *T. taxifolia*.

Hypocera Lixii, a novel endophytic fungus synthesized Cajanol, an anticancer agent, which is extracted from *Cajanus cajan*. First time, the endophytic fungus *M. fragilis* is capable to synthesize these bioactive metabolites, scilicet, Podophyllotoxin and Kaempferol. Also, Guanacastane diterpenoids described from the plant endophytic fungus *Cercospora* species.

7. ANTIDIABETIC ACTIVITY

A non-peptidal fungal metabolite was extracted from an endophytic fungus *Pseudomassaria* species gathered from an African rainforest. The nature has given enormous natural resources, which can be expurgated for their medicinal utilizations. The antidiabetic and hypolipidemic activity of endophytic fungi extracted from *Salvadora oleoides* in glucose aristocrat, fasting and alloxan fomentation diabetic Wistar albino rats and inquest new antidiabetic drugs

from fungal endophytes name as *Aspergillus* species, *Phoma* species, and some unknown species; those noticeably decrease blood glucose level by glucose endurance test. α – amylase obstructive – generating endophytic actinomycetes from the leaves and stem of *Leucas ciliate* and *Rauwolfia densiflora*, two of the popular medicinal plants utilized in the diabetic treatment.

8. IMMUNOSUPPRESSIVE ACTIVITY

An endophytic fungus *Fusarium subglutinans* extracted from *T. wilfordii* generates subglutinol A and B, which function as the immunosuppressive agent. Now days, these drugs are used to deter allograft dismissal in transplant patients and in coming days they could be utilized to treat autoimmune disease like rheumatoid arthritis and insulin dependent diabetes. Pestalosite, pestalpyrone and hydroxyl pestalopyrone extracted from *P. microspore* contains plant toxic features. Pseudomycins are antifungal substances, these are antifungal substances, and these substances exhibited strong effectiveness toward human pathogen *Candida albicans*, which are peptide antibiotics possessing remarkable amino acids such as L – hydroxy aspartic acid, L -chlorothreonine and the two D and L – diaminobutyric acid. Ambuic acid which is a cyclohexanone juncture to the Pseudomycins family extracted from *Pestalotiopsis microspore* and effective toward human pathogens. Munumbicins, which is a bioactive substance, extracted from *Streptomyces* species. Which are more effective towards gram negative and as well as gram positive bacteria. Munumbicins E – 4 and E – 5 exhibited antimalarial functions, this was more effective as compared with that of chloroquine.

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