Harnessing the Phytotherapeutic Treasure Troves of the Ancient Medicinal Plant *Azadirachta indica* (Neem) and Associated Endophytic Microorganisms

Authors

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Key words

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ABSTRACT

*Azadirachta indica*, commonly known as neem, is an evergreen tree of the tropics and sub-tropics native to the Indian sub-continent with demonstrated ethnomedicinal value and importance in agriculture as well as in the pharmaceutical industry. This ancient medicinal tree, often called the “wonder tree”, is regarded as a chemical factory of diverse and complex compounds with a plethora of structural scaffolds that is very difficult to mimic by chemical synthesis. Such multifaceted chemical diversity leads to a fantastic repertoire of functional traits, encompassing a wide variety of biological activity and unique modes of action against specific and generalist pathogens and pests. Until now, more than 400 compounds have been isolated from different parts of neem including important bioactive secondary metabolites such as azadirachtin, nimbidin, nimbin, nimbolide, gedunin, and many more. In addition to its insecticidal property, the plant is also known for antimicrobial, antimalarial, antiviral, anti-inflammatory, analgesic, antipyretic, hypoglycaemic, antiulcer, anti-inflammatory, antifertility, anti-carcinogenic, hepatoprotective, antioxidant, anxiolytic, molluscicidal, acaricidal, and antifilarial properties. Notwithstanding the chemical and biological virtuosity of neem, it has also been extensively explored for associated microorganisms, especially a class of mutualists called endophytic microorganisms (or endophytes). More than 30 compounds, including neem “mimetic” compounds, have been reported from endophytes harbored in the neem trees in different ecological niches. In this review, we provide an informative and in-depth overview of the topic that can serve as a point of reference for
an understanding of the functions and applications of a medicinal plant such as neem, including associated endophytes, within the overall theme of phytopathology. Our review further exemplifies the already-noted current surge of interest in plant and microbial natural products for implications both within the ecological and clinical settings, for a more secure and sustainable future.

Introduction

Neem (*Azadirachta indica* A. Juss.) is native to the Indian subcontinent and is often called a “wonder tree”. Considering the importance of neem in agriculture, medicine, industry, and environment, it is colloquially regarded as a tree for solving global problems [1]. India has a long history of using ethnomedicinal plants as traditional medicines (e.g., in Ayurveda, Unani, and Siddha). Neem is a preeminent natural resource containing a vast range of chemically diverse and structurally complex compounds possessing unique biological activities. It is interesting to note that over 400 secondary metabolites of different classes have already been reported from neem prospected from different ecological niches, which certainly justifies its historical use in the traditional medicinal sector ([1] and references therein).

Microbial associations are prevalent in plants; these multifaceted associations range from pathogenic, saprophytic, or opportunistic to more sustained mutualistic interactions such as mycorrhizal and endophytic (fungal, bacterial, and actinobacterial) [2]. Fungi are considered to be one of the most diverse life forms on earth. Although the magnitude of fungal diversity around the world is still open to debate, the estimate of hundreds to thousands of species to even millions has been put forth [2]. The most widely accepted estimate is that of Hawksworth [3] who estimated the size of 1.5 million species, out of which currently over 100,000 species have been discovered. Among the different niches that support the growth of microorganisms, particularly fungi, one unique and specialized habitat is inter- and intracellular spaces of higher plants. These microorganisms are called endophytes. The term “endophyte” was first used by De Bary [4], and the commonly accepted definition pertains to “fungi or bacteria which for all or part of their life cycle, invade the tissues of living plant and cause unapparent and asymptomatic infections entirely within plant tissues, without disease” [5]. Mostert and co-workers (2000) further postulated that “true endophytes are fungi whose colonization never results in visible disease symptoms” [6]. It is now well established that endophytes are capable of maintaining mutualistic associations with their host plants, which often lead to the co-evolution of certain functional traits such as the production of bioactive secondary metabolites. During their co-existence with host plants, endophytes encounter invasion by a plethora of specific and generalist pathogens. Therefore, in order to survive in their ecological niches, endophytes might evolve additional defense strategies such as production of chemical defense compounds, small-molecule chemical modulators for activating host plant defenses, and precursors to host plant secondary metabolites, among others. Thus far, endophytes have emerged as relevant sources of biologically active natural products, and they play an essential role in maintaining the ecological balance in plants. Endophytes harboring neem are, therefore, also an invaluable resource of both novel as well as well-known natural compounds having high and diverse biological functionality for significant medicinal, agricultural, and industrial exploitation [7]. In this review, we provide a detailed elaboration on the metabolites identified to date in the neem plant as well as their biological activities. Further, we discuss thoroughly endophytes reported from neem...
plants and the production of novel, biologically active metabolites.

Neem, the “Wonder Tree”

Neem (Azadirachta indica A. Juss.) is an indigenous medicinal plant of the Indian subcontinent [8]. The scientific name of this plant is derived from the Persian word “Azad dirakhat-I-Hind” meaning “noble or free tree of India” [9]. Neem had been described as early as 1830 by De Jussieu as an evergreen tree of the tropics and sub-tropics belonging to the family Meliaceae [10]. Medicinal properties of neem have been inscribed in the ancient testaments of Sanskrit literature as “Arishtha”, which translates to “reliever of sickness”. Dube (1996) described the ancient Indian names for the neem tree as prabhadrak (very useful), paribhadrak (spreading its utility over vast distances), sarvabhadrak (useful in every way), and rajbhadrak (best among all the useful trees), all pointing towards its colossal worth in the Indian way of life [11]. Neem is widely used as a folk medicine for various therapeutic purposes as well as a source of agrochemicals for many centuries in the Indian agricultural system. The essential components of neem and their uses are summarized in the Table 1.

Chemical Diversity of Compounds Reported from Neem

Around 406 compounds have been isolated from different tissues of neem, and several sporadic reviews have also been published on the chemistry and structural diversity of these compounds. The compounds have been divided into 2 major classes: isoprenoids and non-isoprenoids (Fig. 2). On the one hand, isoprenoids include diterpenoids and triterpenoids encompassing protomeliacins, limonoids, azadirone, and its derivatives; gedunin and its derivatives; vilasinin type of compounds; and C-seco-meliacins such as nimbin, salanin, and azadirachtin. On the other hand, non-isoprenoids are comprised of proteins (amino acids) and carbohydrates (polysaccharides), sulfur compounds, polyphenolics such as flavonoids and their glycosides, dihydrochalcone, coumarin, and tannins including aliphatic compounds, to name a few. The first isolated and characterized compound was nimbin, followed by nimbinin [12, 13]. A considerable assortment of compounds have been isolated from different tissues of neem including leaves, twigs, flowers, fruits, seeds, seeds oil, bark, and roots, which are summarized in the Table 1 along with their reported biological activities.

Selected Bioactive Principles of Neem and Their Specific Activity

Anti-inflammatory, analgesic, and antipyretic activities

Kaempferol, reported from neem as well as from a different, unrelated plant Rhamnus procumbens, was found to have anti-inflammatory and anti-ulcer activities [83, 207]. Anti-inflammatory and immunomodulatory activity was observed in 2 flavonoids, catechin and epi-catechin, reported from the bark of the neem tree [177]. Nimbidin, a major active component of the Azadirachta indica seed oil, was found to significantly inhibit some of the functions of macrophages and neutrophils relevant to the inflamma-
Immunostimulant activities

Neem oil is shown to selectively activate the cell-mediated immune mechanisms that elicit an enhanced response to subsequent mitogenic or antigenic challenges by acting as a non-specific immunostimulant [212]. Pre-treatment of rats with an odorous and volatile fraction of neem oil, coded NIM-76, was found to increase polymorphonuclear leukocytes, with a decrease in lymphocyte count displaying immunomodulatory efficacy [213].

Radiosensitizing effects

Neem oil was found to increase the radiosensitivity of the Balbc/3 T3 cells and severe combined immunodeficiency (SCID) cells during x-irradiation under aerobic conditions [214]. Application of neem oil reduced the G2 + M phase of the cell cycle, thereby inhibiting the repair of cells from lethal damage [214].

Hypoglycemic activities

Neem kernel powder, in combination with glibenclamide, yielded significant antidiabetic and antihyperlipemic effects in alloxan diabetic rats [215]. Antihyperglycemic effect of aqueous neem leaf extract was also observed in insulin-dependent diabetes mellitus and non-insulin-dependent diabetes mellitus animal models [216]. Mixed water extracts of Abroma augusta roots, when combined with the leaves of A. indica and given orally to alloxan diabetic rats, showed hypoglycemic action with decreased formation of lipid peroxides estimated as thiobarbituric acid reactive substance along with increased antioxidants in erythrocytes [217]. Extracts of A. indica combined with extracts of Vernonia amygdalina (Del.) was found to have enhanced anti-diabetic effect in albino Wistar rats [218]. Ethanolic extracts of A. indica in streptozotocin-induced hyperglycemia normalized the glucose level and reversed dyslipidemia [219]. Hypoglycemic action of ethanolic neem leaf extract was evaluated in diabetic rats, which demonstrated that after treatment for 24 h with a single dose of 250 mg/kg extract reduced glucose (18%), cholesterol (15%), triglycerides (32%), urea (13%), creatinine (23%), and lipids (15%) [220]. Further, in a multiple-dose study that lasted for 15 days, reduction of creatinine, urea, lipids, triglycerides, and glucose were

**Fig. 2** Chemical classification of Azadirachta indica (neem) derived compounds.

- **Neem-derived compounds**
  - Isoprenoids
    - Abietanoids
      - Abietanoids
    - Podocarpanoids
  - Triterpenoids
    - Protolimonoids (Protomeliacins)
      - Mononortriterpenoids
    - Dinortriterpenoids
  - Trinortriterpenoids
  - Tetrnor triterpenoids (Limonoids)
  - Pentanortriterpenoids
  - Hexanortriterpenoids
  - Octanortriterpenoids
  - Nonanortriterpenoids
  - Sulphur compounds
  - Carbohydrates
  - Proteins
  - Hydrocarbons
  - Phenols
  - Flavonoids
  - Coumarins

**Sulphur compounds**

**Carbohydrates**

**Proteins**

**Hydrocarbons**

**Phenols**

**Flavonoids**

**Coumarins**

**Neem-derived compounds**

- **Isoprenoids**
  - Diterpenoids
  - Triterpenoids
  - Sterols
  - Protolimonoids (Protomeliacins)
  - Mononortriterpenoids
  - Dinortriterpenoids
  - Trinortriterpenoids
  - Tetrnor triterpenoids (Limonoids)
  - Pentanortriterpenoids
  - Hexanortriterpenoids
  - Octanortriterpenoids
  - Nonanortriterpenoids
  - Sulphur compounds
  - Carbohydrates
  - Proteins
  - Hydrocarbons
  - Phenols
  - Flavonoids
  - Coumarins
Table 1 Biomolecules reported from different tissues of *Azadirachta indica*.

<table>
<thead>
<tr>
<th>Sl. No.</th>
<th>Plant tissue</th>
<th>Compounds</th>
<th>Compound class</th>
<th>Biological activity</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Leaves</td>
<td>Quercetin-3-α-β-d-glucopyranoside (isorquercitrin)</td>
<td>Flavonoids</td>
<td>n. a.</td>
<td>[14]</td>
</tr>
<tr>
<td>2</td>
<td>Leaves</td>
<td>3-hydroxystigmasta-5-en-7-one</td>
<td>Steroids</td>
<td>Antiplatelet aggregation</td>
<td>[15, 16]</td>
</tr>
<tr>
<td>3</td>
<td>Leaves</td>
<td>n-Hexacosanol</td>
<td>Miscellaneous compounds</td>
<td>Potent feeding stimulants for larvae of the silkworm</td>
<td>[17, 18]</td>
</tr>
<tr>
<td>4</td>
<td>Leaves</td>
<td>Tetratriacontane</td>
<td>Hydrocarbons</td>
<td>n. a.</td>
<td>[19]</td>
</tr>
<tr>
<td>5</td>
<td>Leaves</td>
<td>Hexacosene</td>
<td>Hydrocarbons</td>
<td>n. a.</td>
<td>[19, 20]</td>
</tr>
<tr>
<td>6</td>
<td>Leaves</td>
<td>β-carotene</td>
<td>Hydrocarbons</td>
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<td>[21]</td>
</tr>
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<td>7</td>
<td>Leaves</td>
<td>Nimbandiol</td>
<td>Pentanortriterpenoids</td>
<td>Antimalarial activity</td>
<td>[22]</td>
</tr>
<tr>
<td>8</td>
<td>Leaves</td>
<td>α-Linolenic acid</td>
<td>Fatty acids and their derivatives</td>
<td>Reduces cardiovascular disease</td>
<td>[23, 24]</td>
</tr>
<tr>
<td>9</td>
<td>Leaves</td>
<td>Xanthophylls</td>
<td>Miscellaneous compounds</td>
<td>Antioxidant activities</td>
<td>[20, 21, 25]</td>
</tr>
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<td>10</td>
<td>Leaves</td>
<td>Kaempferol-3-O-rutinoside (or nicotiflorin)</td>
<td>Flavonoids</td>
<td>n. a.</td>
<td>[26]</td>
</tr>
<tr>
<td>11</td>
<td>Leaves</td>
<td>Myricetin-3-O-rutinoside</td>
<td>Flavonoids</td>
<td>n. a.</td>
<td>[26]</td>
</tr>
<tr>
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<td>Leaves</td>
<td>Quercetin-3-O-α-L-rhamnoside</td>
<td>Flavonoids</td>
<td>n. a.</td>
<td>[26]</td>
</tr>
<tr>
<td>13</td>
<td>Leaves</td>
<td>Quercetin-3-O-rutinoside</td>
<td>Flavonoids</td>
<td>n. a.</td>
<td>[26]</td>
</tr>
<tr>
<td>14</td>
<td>Leaves</td>
<td>Quercetin</td>
<td>Flavonoids</td>
<td>Inhibitors of azoxymethanol-induced colonic neoplasia</td>
<td>[27–31]</td>
</tr>
<tr>
<td>15</td>
<td>Leaves</td>
<td>Rutin</td>
<td>Flavonoids</td>
<td>Inhibitors of azoxymethanol-induced colonic neoplasia</td>
<td>[27–29]</td>
</tr>
<tr>
<td>16</td>
<td>Leaves</td>
<td>Oxalic acid</td>
<td>Acids and their derivatives</td>
<td>n. a.</td>
<td>[32]</td>
</tr>
<tr>
<td>17</td>
<td>Leaves</td>
<td>Ascorbic acid</td>
<td>Acids and their derivatives</td>
<td>n. a.</td>
<td>[32]</td>
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<tr>
<td>18</td>
<td>Leaves</td>
<td>Melianol</td>
<td>Mononortriterpenoids</td>
<td>n. a.</td>
<td>[32]</td>
</tr>
<tr>
<td>19</td>
<td>Leaves</td>
<td>2′,3′-dehydrosalannol</td>
<td>Ring-C-seco-tetrano-triterpenoids</td>
<td>n. a.</td>
<td>[33]</td>
</tr>
<tr>
<td>20</td>
<td>Leaves</td>
<td>1,3-diacetyl-11,19-deoxo-19-oxomelia-carpin</td>
<td>Ring-C-seco-tetrano-triterpenoids</td>
<td>n. a.</td>
<td>[34]</td>
</tr>
<tr>
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<td>Leaves</td>
<td>Isoazadirolide</td>
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<td>n. a.</td>
<td>[35]</td>
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<td>22</td>
<td>Leaves</td>
<td>Desfurano-6-α-hydroxyazadiradione</td>
<td>Octanortriterpenoids</td>
<td>Insecticidal activity against fourth instar larvae of mosquito (<em>Anopheles stephensi</em>)</td>
<td>[36]</td>
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<td>23</td>
<td>Leaves</td>
<td>22, 23-dihyronimocinol</td>
<td>Tetranortriterpenoids</td>
<td>Insecticidal activity fourth instar larvae of the mosquito (<em>Anopheles stephensi</em>)</td>
<td>[36]</td>
</tr>
<tr>
<td>24</td>
<td>Leaves</td>
<td>Nimbocinolide</td>
<td>γ-Hydroxybutenolides</td>
<td>n. a.</td>
<td>[37]</td>
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<tr>
<td>25</td>
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<td>Isonimbocinolide</td>
<td>γ-Hydroxybutenolides</td>
<td>n. a.</td>
<td>[38]</td>
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<tr>
<td>26</td>
<td>Leaves</td>
<td>23-O-methylnimocinolide</td>
<td>γ-Hydroxybutenolides</td>
<td>Insect growth regulating effect on mosquitoes (<em>Aedes aegypti</em>)</td>
<td>[39]</td>
</tr>
<tr>
<td>27</td>
<td>Leaves</td>
<td>1, 7-O-deacetyl-23-O-methyl-7α-O-senecioylnimocinolide</td>
<td>γ-Hydroxybutenolides</td>
<td>Insect growth regulating effect on mosquitoes (<em>Aedes aegypti</em>)</td>
<td>[39]</td>
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<td>28</td>
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<td>Antimalarial activity</td>
<td>[40–42]</td>
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<td>[41–43]</td>
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<td>[41, 43]</td>
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<td>Steroids</td>
<td>Insecticidal activity</td>
<td>[20, 44]</td>
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<td>Leaves</td>
<td>Zafaral</td>
<td>Tetranortriterpenoids</td>
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<td>[45]</td>
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*continued*
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<td>34</td>
<td>Dried leaves</td>
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<td>n. a.</td>
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<td>Air dried leaves</td>
<td>Azadiractolide</td>
<td>Tetratiterpenoids</td>
<td>n. a.</td>
<td>[48]</td>
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<td>36</td>
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<td>Tetratiterpenoids</td>
<td>n. a.</td>
<td>[48]</td>
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<td>Glyceride</td>
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<td>[49]</td>
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<td>Fresh leaves</td>
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<td>Insect growth-regulating properties</td>
<td>[44]</td>
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<td>Fresh leaves</td>
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<td>[44]</td>
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<td>[45]</td>
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<td>[42, 52]</td>
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<td>Fresh green whole leaves</td>
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<td>[53]</td>
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<td>Odoratone</td>
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<td>Toxicity on fourth instar larvae of mosquitoes (Aedes aegypti)</td>
<td>[57]</td>
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<td>Meliacinol</td>
<td>Tetratiterpenoids</td>
<td>Protection against Tacaribe virus to mice brain</td>
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<td>Powdered neem leaves</td>
<td>3-deacetyl-3-cinnamoyl azadirachtin</td>
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<td>[58]</td>
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<td>Neeflone</td>
<td>Tetratiterpenoid</td>
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<td>Flowerone</td>
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<td>[61]</td>
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<td>Triterpenoid</td>
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<td>[60]</td>
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<td>Flower</td>
<td>Prenylated flavanones, 5,7,4′-trihydroxy-8-prenylflavanone</td>
<td>Flavanones</td>
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<td>59</td>
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<td>5,4′-dihydroxy-7-methoxy-8-prenylflavanone</td>
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<td>5,7,4′-trihydroxy-3′-8-diprenyllavananone</td>
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<td>61</td>
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<td>63</td>
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<td>Diterpenoids</td>
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<td>[185]</td>
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<td>Nimbilicin</td>
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<td>n. a.</td>
<td>[182]</td>
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<td>[182]</td>
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continued
observed [221]. In the year 2012, a new tetranortriterpenoid named meliacinolin was isolated from chloroform extract of dried neem leaves, which demonstrated in vivo inhibition of α-glucosidase and α-amylase enzyme activities in streptozotocin-nicotinamide-induced type 2 diabetes in mice [55]. Inhibition of both these enzymes offers an effective strategy of lowering the levels of postprandial hyperglycemia that prevents the digestion of carbohydrates, offering promising potential of meliacinolin as an antidiabetic agent [55].

### Anti-ulcer effects

The aqueous leaf extract of neem showed anti-ulcer properties in stressed rats by preventing mast cell deregulation and increasing the amount of adherent gastric mucus [221]. Neem leaf extract exhibited anti-ulcer activity on gastric lesions in rats by blocking acid secretion through inhibition of H⁺-K⁺-ATPase and by preventing oxidative damage and apoptosis [222].

<table>
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<td>n. a.</td>
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n. a.: not available
Antifertility effects
Prolonged antifertility effects were observed by a single intrauterine administration of neem oil in female Wistar rats [223]. In another study, a single dose of 50 µl of neem oil on each side of the lumen of the vas deferens of male Wistar rats acted as a long-term male contraception [224]. The neem oil fraction NIM-76 was shown to have spermicidal activity in vivo not only in rats but also in rabbits and rhesus monkeys; NIM-76 was further found to affect the motility of sperm leading to the observed infertility [225, 226]. Aqueous extract of old and tender neem leaf was found to immobilize and kill 100% human spermatozoa within 20 s [227].

Antimalarial activities
Gedunin, a tetratornortriterpenoid isolated from neem, was reported to be active against Plasmodium falciparum, the causative organism of malaria [228]. The antimalarial activity of the limonoids (meldenin, isomeldenin, nimocinol, and nimbandiol) isolated from the ethanolic extract of fresh neem tree was reported to be active against chloroquine-resistant P. falciparum strain K1 [229]. Schwikkard and van Heerden (2002) discussed the antimalarial activity of neem compounds such as the limonoid gedunin, meldenin, and azadirachtin [230]. NeemAzal, a commercial neem seed extract containing the limonoid azadirachtin as the main component, was found to block the activity of rodent malarial parasite, Plasmodium berghei, in its vector Anopheles stephensi [231].

Antiretroviral activities
An acetone-water extract of neem leaves was found to prevent the invasion of human lymphocytes by human immunodeficiency virus (HIV), thereby protecting the target cells without any adverse effects [232]. The acetone-water extract significantly increased CD4 cell count in HIV I or HIV II patients that also led to a substantial increase in mean body weight, hemoglobin concentration, lymphocyte differential count with no adverse effects, and abnormalities in kidney and liver function parameters [233].

Antifungal activities
Khan and Shah (1992) tested leaf extracts of A. indica on wheat seed mycflora and noted considerable reduction in seed mycflora vis-à-vis better seed germination [234]. Suresh et al. (1997) studied the antifungal activity of polar extract and the impure HPLC fractions of green leaves of A. indica against groundnut rust disease (causal agent Puccinia arachidis Speg.) [235]. Govindachari et al. (1998) also showed the synergetic effect of various neem terpenoids on different fungal pathogens [236]. Minimum inhibitory concentration (MIC) of neem seed extract was found to be 31 µg/ml against clinical isolates of dermatophytes (Trichophyton rubrum, Trichophyton mentagrophytes, and Microsporum canis) [237]. Wang et al. (2010) reported a significant reduction in the growth of the pathogens Monilinia fructicola, Penicillium expansum, Trichothecium roseum, and Alternaria alternata by neem seed kernel extracts [238].

Antibacterial activities
Mahmoodin, a novel limonoid, isolated from neem oil, showed significant antibacterial activity against various Gram-positive and Gram-negative bacteria [71]. Aquaneem, an emulsified product prepared from the neem kernel, exhibited antibacterial activity against Aeromonas hydrophila and Pseudomonas fluorescens as well as Myxobacteria sp., which are pathogenic to fish [239]. Moreover, SaïRam and co-workers (2000) studied the antimicrobial activity of the extract NIM-76 against certain bacteria, fungi, and Poliovirus and compared the same with neem oil [240]. The results revealed that NIM-76 inhibited the growth of various bacterial pathogens tested including Escherichia coli and Klebsiella pneumoniae. The extract also showed antifungal activity against Candida albicans and antiviral activity against Poliovirus replication in Vero cell lines. Overall, NIM-76 showed stronger anti-microbial activity as compared to the neem oil. Neem seed kernel extract was found to be active against Bacillus mycoides, B. thuringiensis, B. subtilis, Nocardia sp., and Corynebacterium fascians in in vitro assays [241]. In another study, neem mouthwash was found to show antibacterial activity against salivary levels of Streptococcus mutans and Lactobacillus [242]. Neem leaf extract gel also showed antiplaque activity [243]. Polyester/cotton blend fabric treated with neem extract was reported to have antibacterial activity against both Gram-positive (Bacillus subtilis) and Gram-negative bacteria (Proteus vulgaris) [244]. Neem oil was also found to be active against Staphylococcus aureus, Salmonella typhi, Pseudomonas aeruginosa, and Escherichia coli [245, 246]. The tetratornortriterpenoid, nimolicinol, isolated from neem, was reported to be moderately antibacterial against several human pathogenic bacteria [93, 95]. The antibacterial activity of neem leaf extract and various phytoconstituents of neem such as alkaloids, steroids, tannins, glycosides, flavonoids, and saponins were evaluated and confirmed to have antibacterial efficacies, with crude flavonoids revealing maximum antibacterial activities [247]. 9-Octadecanoic acid-hexadecanoic acid-tetrahydrofuran-3,4-diyl ester obtained from neem oil was found active against Staphylococcus aureus, Escherichia coli, and Salmonella sp. in vitro assays [113]. M-Octadecanoic acid-3,4-tetrahydrofuran diester, isolated from the petroleum ether extract of neem oil, also showed potent antibacterial activity [248]. Alcoholic extracts of neem leaves were found to be active against the human bacterial pathogens Bacillus pumilus, Pseudomonas aeruginosa, and Staphylococcus aureus [249].

Antiviral activities
Foliar application of neem seed oil, when compared with neem seed oil-free extract, inhibited transmission of potato virus Y to sweet pepper by the green peach aphid, Myzus persicae (Sulzer) suggesting that the oil interferes with virus transmission [250]. A methanolic extract fraction of leaves of neem showed antiviral activity against the Coxackie B group of viruses [251]. Crude aqueous extract of neem leaves was reported both in vitro and in vivo to display antiviral activity against the replication of Dengue virus type-2 [252]. Aqueous neem bark extract, at concentrations ranging from 50 to 100 µg/ml, when pre-incubated with herpes simplex virus type 1 (HSV-1), considerably blocked its entry into cells; additionally, virions treated with the extract failed to bind to the cells, suggesting role of the extract either as an attachment-blocker or having direct anti-HSV-1 property. Furthermore, cells treated with extract also inhibited herpes simplex virus type 1 glycoprotein-mediated cell-cell fusion and polykaryocyte formation,
signifying an additional role of the bark extract at the viral fusion step [253]. The crude acidic extract of leaves and seeds and alkaline extract of seeds were found to show high antiviral activity against HSV-1 when compared with the well-known antiviral drug acyclovir [254].

**Anticarcinogenic activities**

Azadirone, a limonoidal constituent isolated from methanolic extract of neem leaves, was found to be a potent cytotoxic agent with good in vitro and in vivo activities [255]. The studies also revealed that the α,β-unsaturated enone moiety, or its equivalent conjugated system of A-ring, C-7 acetyloxy/chloroacetyloxy or keto group of B-ring and the furan moiety, are the structural requirements for the potent activity of azadirone and its analogs [255]. Four prenylated flavanones, 5,7,4′-trihydroxy-8-prenylflavanone, 5,4′-dihydroxy-7-methoxy-8-prenylflavanone, 5,7,4′-trihydroxy-3,8-diprenylflavanone, and 5,7,4′-trihydroxy-3,5′-diprenylflavanone, were isolated by activity-guided fractionation from the methanolic extract of the flowers of neem, which acted as potent antimutagens against Trp-P-1 (3-amino-1,4-dimethyl-5H-pyrido[4,3-b]indole) in the Salmonella typhimurium TA98 assay [61]. Aqueous extract of neem was found to show chemopreventive potential when given to Syrian male hamsters having 7,12-dimethylbenz[a]anthracene (DMBA) induced b uccal pouch carcinogenesis by modulation of lipid peroxidation, antioxidants, and detoxification systems [256]. Pre-treatment with ethanolic neem leaf extract significantly lowered the concentration of lipid peroxides and increased antioxidant levels on induced oxidative stress by the potent gastric carcinogen N-methyl-N-nitro-N-nitrosoguanidine (MNGN) in male Wistar rats suggesting its chemoprotective effects [257]. Significant anticarcinogenic potential was also found in leaf extracts of A. indica in a tumor model system (p < 0.005 to p < 0.001) [258]. Subapriya et al. (2005) suggested that the chemopreventive effects of ethanolic neem leaf extract might be mediated by the induction of apoptosis [259]. Treatment of rats by aqueous neem extracts significantly decreased the proliferating cell nuclear antigen labeling indices of colon epithelium and aberrant crypt foci, suggesting a chemopreventive role in the short-term colon carcinogenesis bioassay [260]. Nimboide, a triterpenoid isolated from the flowers of the neem, was found to have antiproliferative activity and apoptosis-inducing property against U937, HL-60, THP1, and B16 cancer cell lines [261]. The acidic extract of leaves and neutral extract of seeds possessed anticancer activity, inhibiting Ehrlich ascites carcinoma cell line growth and IC₅₀ values were 669.43 and 724.63 µg/ml, respectively [254]. 7-Deacetyl-7-benzoyloxyproazidarine, 7-deacetyl-7-benzoylguadin, and 28-deoxonimboide exhibited potent cytotoxic activity against HL60 leukemia cells while 4 other compounds (7-benzoylnimbocin, epoxazidarine, gedunin, and ochnchin acetate) exhibited cytotoxic activity against 1 or more cell lines [114]. Cytotoxic activities of nimboide isolated from branches and leaves against HL-60 have also been reported [121]. Sulfonouquinovosydacglyceride, a water-soluble constituent of dried neem leaves, showed anti-cancerous activity in human leukemic cell lines U937 and K562 with IC₅₀ of 9 µg/ml [49]. Nimboide was shown to exert apoptotic activity in estrogen-dependent (MCF-7) and estrogen-independent (MDA-MB-231) human breast cancer cell lines activating caspase-8, caspase-9, caspase-3, and cleavage of PARP [122]. Induction of apoptosis in human breast cancer cells by nimboide ratifies its future in cancer treatment as a chemotherapeutic agent [122]. NIM-76, a volatile fraction of neem oil, was reported to have no mutagenic effects and regarded as safe concerning genotoxic potential in humans [262]. In vitro inhibition of growth of mouse sarcoma was found on treatment with neem leaf glycoprotein (25 µg/mice/wk subcutaneously for 4 wks) [263]. This anti-tumor immunity inhibiting the growth of mouse sarcoma was reported to be associated with increased expression of CD69, CD44, and Ki67 on CD8+ T cells [263]. Neem leaf glycoprotein showed no toxicity to various physiological functions of Swiss mice and Sprague-Dawley rats even though type 1 cytokines increased in serum with a decrease in type 2 cytokines and total IgG content in leaf glycoprotein-treated mice [264]. Change in type 1 cytokines were associated with increased anti-tumor immunity [264]. Neem oil limonoids were found to induce caspase-dependent and apoptosis-inducing factor-mediated apoptosis, as well as autophagy in cancer cells [265].

**Hepatoprotective activities**

Aqueous leaf extracts of neem significantly prevented changes in the serum levels of bilirubin, protein, alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase, and prevented the histological changes, thus having an antihepatotoxic activity against the damage induced by antitubercular drugs in rats [266]. Chattopadhyay and Bandyopadhyay (2005) discussed the possible mechanism of hepatoprotective activity of neem leaf extracts against paracetamol-induced hepatic damage in rats and concluded that hepatoprotective activity was possibly due to its potent antioxidant activity [267]. Mercury-induced oxidative damage in hepatic tissues was improved with neem leaf extract through its antioxidant effects [268].

**Antioxidant activities**

Sithisarn et al. (2006) compared free radical scavenging activity of Siamese neem tree leaf extracts against the 2,2-diphenyl-1-picryl-hydrazyl (DPPH) radical and reported that most active extract was obtained with the leaf decoction method showing antioxidant activity with half-maximal effective concentration (EC₅₀) of 31.4 µg/ml [269]. In another study, significant antioxidant properties were observed in leaf and bark extracts/fractious of neem, while bark was found to possess higher phenolic content than the leaves [270].

**Effects on CNS**

Anxiolytic activity of leaf extracts of A. indica was studied in rats [271]. Neem extracts could attenuate anxiogenic and appetite-suppressing effects of stress by decreasing the brain’s 5-hydroxytryptamine and 5-hydroxyindolacetic acid concentration in albino Wistar rats [272]. The pharmacotherapeutic value of neem leaves was also seen in anxiety disorders of albino Wistar rats [273].

**Molluscicidal activities**

Singh and co-workers (1996) showed the effect of leaf, bark, cake, neem oil, and the neem-based pesticides, achook and nimbecide of neem, against the snails *Lymnaea acuminata* and *Indopla*...
norbis exustus and found that pure azadirachtin was more toxic compared to synthetic molluscicides [274]. In another study, crude extracts of bark, roots, and leaves of neem at 500 mg/kg and 700 mg/kg were found lethal to edible tropical land snails Archachatina marginata and Limoc bliria aurora (Jay) after exposure for 72 h and 48 h, respectively [275].

**Insecticidal activities**

The neem tree is well known for its insecticidal properties, which has been documented in a large assortment of studies. Insect growth-regulating properties were found in 23-O-methylnimocinolide and 1, 7-O-deacetyl-23-O-methyl-7α-O-senecioylnimocinolide [39] belonging to γ-hydroxybutenolides group of compounds. Siddiqui et al. (2002) reported desfurano-6α-hydroxy-azadiradione and 22, 23-dihydronimocinol as having insecticidal activity against the fourth instar larvae of mosquito (Anopheles stephensi) [36]. Two nitrogen-containing limonoids, salanolactam-21 and salanolactam-23, have been reported from neem seed kernels, which possess antifeedant activities [151]. Various tetratetrontriperenoids–meliatetraolenone, zafaral, 6a-O-acetyl-7-deacetylnimocinol, meliacinol, 17β-hydroxyazadiradione, azadironic acid, limocin-A, limocin-B, epoxazadiradione, mahmoodin, gedunin, 7-deacetylgedinun, 1, 3-di-O-acetylvilasinin, 1-O-tigloyl-3-O-acetylvilasinin, nimbin, azadiradione, and 7-deacetylnaziadore–isolated from different tissues of neem have been reported to either have insecticidal activities or insect anti-feeding activities (see Table 1). Additionally, azadirachtin and related compounds, such as 6-deacetylnimbin, nimbinol B, salannin, 3-deactylsalannin, salanol, and salanol acetate, have been isolated from various tissues of neem and also have insecticidal or insect anti-feeding properties. Insect growth-regulating activity was observed in desfuranoazadiradione, an ocotnatrterpenoid isolated from fresh fruit coets [77, 82]. Melacin, a dinorpteronpezisol isolated from fruit coets, was found to be toxic against mosquito (Anopheles stephensi) [77, 78]. β-sitosterol, a steroid, has also shown insecticidal potential [276, 277]. Olorodine (protilimonoisolated from methylan extract of fresh leves, has demonstated a lethal effect on the fourth instar larvae of mosquitoes (A. stephensi) [56]. Larvicidal properties of neem oil were also reported against A. stephensi, Culex quinquefasciatus, and Aedes aegypti [278].

Neem-based shampoos, amended with neem seed extract, are effective against all stages of head lice [279]. Extracts of neem oil [280], petroleum ether extracts of neem oil, and its 4 fractions separated by column chromatography [281] were reported to be lethal in in vitro assays against rabbit mite Sarcoptes scabiei var. cuniculi larvae. Further, octadecanoic acid-tetrahydrofuran-3,4-diy ester isolated from an active fraction of the chloroform extract of neem oil was reported to have acaricidal in vitro activity against S. scabiei larvae [282]. Neem oil microemulsion was very effective against Sarcoptes scabiei var. cuniculi larvae in vitro [283].

**Antifilarial activities**

Alcohol and aqueous extracts of flowers of A. indica showed inhibition of cattle filarial parasite Setaria cervi [284].

**Synthesis and biological sources of azadirachtin**

In addition to its remarkable insecticidal activity, azadirachtin also exhibits a range of other biological properties. The first complete structure of azadirachtin was elucidated by Nakanishi and co-workers in 1975 [285] using extensive NMR spectroscopy, which was further revised by Kraus in 1985 [87], who proposed a C13–C14 epoxide. However, it took 22 y for azadirachtin to be produced by total synthesis [286, 287]. Initially, Veitch and co-workers discussed the probable route leading to the successful synthesis of azadirachtin [288]. This was followed by Jauch (2008) [286] and Ley et al. (2008) [287] who reported the full mechanism of complete chemical synthesis of azadirachtin. Meanwhile, another group focused on the biotechnological approaches for the production of azadirachtin; its production was reported using A. indica cell suspension cultures [289]. Further, azadirachtin biosynthesis could be induced in hairy root cultures of A. Indica [290], which was enhanced in hairy root cultures of A. indica by Satdive et al. in 2007 [291]. Production of azadirachtin in neem callus and suspension cultures has also been reported [292]. Another method of androgenic culture of A. indica showed increased azadirachtin production [293]. In 2012, Kusari and coworkers reported the biosynthesis of azadirachtin by an endophytic fungus, Eupenicillium parvum, isolated from neem [294].

**Endophytic microorganisms (endophytes)**

Endophytes are one of the predominant classes of microorganisms, which reside inside healthy tissues of host plants; endophytes include bacteria, fungi, nematodes, and viruses. Fungal endophytes (or endophytic fungi) are a dynamic and multiform group of microorganisms that are ubiquitous in plants thriving in every ecological niche (Fig. 3). Fungal endophytes have been found associated with algae [295], lichens [296], mosses [297], ferns [298], conifers [299], large trees [300], small trees [301], palms [302, 303], mangroves [304], halophytes [305], grasses [306], marine sponges [307], and seagrasses [308] to name a few. Endophytic fungi were isolated from every plant tissue including bark, flower, leaves, petals, root, seed, and twigs [7, 309–311]. Further, endophytic fungi are well-established producers of a plethora of bioactive compounds and extracellular enzymes such as amylase, cellulase, chitinase, chitosonase, laccase, lipase, pectinase, and protease [312–315]. Being colonizers of host tissues, the endobiome plays a crucial role in creating an extra layer of protection to their host during several adverse conditions [316, 317, 373]. They also modulate host metabolism for enhanced production of high-value secondary metabolites in medicinal plants like Withania, Coleus, Papaver; this positive modulation is a result of significant-high expression of genes and transcription factors of biosynthetic pathways [318–320]. Occasionally, few endophytic species mimic host metabolic pathways and produce host signature metabolites independently [294]. Therefore, unmatched beneficial traits of the endophytes were well recognized by research communities, and several of these endophytes have been utilized for several industrial and agricultural purposes.

**Fungal endophytic diversity of A. indica**

Following-up the cues on ethnoherbal history of neem, Rajagopal and Suryanarayanan (2000) investigated and isolated...
endophytic fungi from green and senescent leaves of A. indica from Chennai, India, continuously for 2 y on a monthly basis. They reported 5 selected endophytes, 4 of which were sterile forms and the fifth was identified as Fusarium avenaceum [321]. They proposed that the restricted number of endophytic fungal genera and the absence of common endophytic fungi in the neem leaves could be due to the antifungal metabolites present in the leaves. The frequency of colonization of green leaves by endophytes was maximal during the rainy season although no new endophyte species could be discovered. It was found that the occurrence of foliar endophytes was influenced by seasonal changes [311, 322]. Since this was also found to be the case with the foliar endophytes of neem, it was suggested that the occurrence of foliar endophytes in tropical trees was influenced by the environment, soil type, and chemistry of the host tissue [321]. Mahesh and co-workers (2005) studied endophytic mycoflora harboring the inner bark of A. indica and reported 77 endophytic fungal isolates belonging to 15 genera [323]. Among them, 71.4% were hyphomycetes, followed by 18.2% coelomycetes, 6.5% ascomycetes, and 3.9% sterile mycelia. The colonization frequency was found to be 38.5%. Although Rajagopal and Suryanarayanan (2000) recovered only Fusarium avenaceum and 4 sterile forms of endophytes [321], Mahesh and co-workers (2005) were able to recover endophytic genera such as Curvularia, Cochlonema, Gliomastix, and Verticillium sp. [323]. Later, the same group identified endophyte diversity in bark segments of A. indica, which exposed high species richness with an average of 20 species, and prevalent colonization of Trichoderma and Chaetomium globosum was observed [324]. Verma and co-workers (2007) studied the fungal endophytes of A. indica in several of its natural habitats in India and recovered a total of 233 isolates of endophytic fungi, representing 18 fungal taxa from segments of bark, stem, and leaves [310]. Interestingly, in the whole study, the authors observed that hyphomycetes were the most prevalent group (62.2%), followed by the coelomycetes (27.4%) and a minor percentage by mycelia-sterilia (7.7%). The leaf samples from all locations were nearly constant in their endophytic composition, whereas the bark samples showed maximum diversity at different locations. This study also revealed, for the first time, that endophytes of genera Periconia, Stenella, and Drechslera were associated with A. indica. Not only was the endophytic fungal colonization frequency higher in leaves (45.5%) than bark (31.5%), but the maximum species richness and frequency of colonization also were as well [310]. Shao and coworkers (2008) have studied the distribution of endophytic fungi in A. indica from Yuanjiang county of Yunnan Province, PR China [325]. They isolated a total of 372 endophytic fungal strains from the stem, leaves, and fruits. Colletotrichum was found to be the most dominant genera, followed by Alternaria and Xylaria. Another group characterized 85 endophytic fungi belonging to 10 genera, which were isolated from 200 segments of fresh A. indica leaves collected from the Panchmarhi biosphere reserve [326]. Here, the most dominant endophytes observed were Trichoderma, Pestalotiopsis, and Penicillium sp.

Rajagopal and Suryanarayanan (2000) found that even though the endophytic genera Phomopsis, Phyllosticta, and Xylaria are ubiquitous and commonly isolated from many hosts, these were absent from the leaves of the neem plants under their study [321]. However, these genera were found to be endophytic in neem leaves by other studies [310,323,325]. Dominant endophytes fungi isolated from the inner bark of A. indica from South India were Trichoderma, Penicillium, and Pestalotiopsis spp. [323], while those from North India were typically Phomopsis oblonga, Cladosporium cladosporioides, Pestalotiopsis sp., Trichoderma sp., and Aspergillus sp. [310]. Further, isolated species had exhibited inhibitory properties against Trichophyton, Microsporum [327]. In China, Colletotrichum was reported as the most dominant genera,
followed by Alternaria and Xylaria [325]. This clearly indicates that endophyte diversity and species richness are not only dependent on specific hosts but also are location and niche specific. This further illustrates the importance of sampling different tissues of a given plant at several locations to obtain an enormous species diversity of endophytes. Taken together, endophytic fungal diversity in neem has been found to be highest in stems (42%), followed by bark (20%), while leaves and fruits harbor a similar percentage of endophytic fungi (19%) (Fig. 4). With the isolation of endophytic fungi from roots and fruits of neem, in addition to previous isolation and characterization from leaves, stems and bark, Verma and colleagues completed sampling of all organs of selected neem trees for their endophytic microflora [7, 300, 303]. Overall, a unique diversity pattern emerges from these studies: endophytic fungi isolated from A. indica belong mostly to the phomycetes, followed by coelomycetes and finally, ascomycetes [310, 313, 321, 323, 325].

**Endophytic actinomycetes of A. indica**

In addition to endophytic fungi, neem plants have been studied for the presence of associated endophytic actinomycetes. Kharwar and coworkers characterized 55 endophytic actinomycetes from 20 different samples, 60% of which showed in vitro inhibitory activity against 1 or more pathogenic fungi or bacteria [313]. Actinomycetes were most commonly recovered from roots (54.5% of all isolates), followed by stems (23.6%), and finally, leaves (21.8%). The dominant genus was Streptomyces (49.09% of all isolates), while Streptosporangium (14.5%), Microbispora (10.9%), Streptoverticillium (5.5%), Saccharomonospora sp. (5.5%), and Nocardia (3.6%) were also isolated. In another study, Gohain and coworkers identified the actinomycetes diversity of 6 medicinal plants collected from Gibbon wildlife sanctuary, Assam, and revealed that A. indica possesses the high Shannon index diversity (1.49) with predominance of Streptomyces species and Streptomycetes significantly expressed Polyketide synthase-II (PKS) gene [328]. Endophytic actinomycetes species isolated from A. indica improved plant growth of tomato through the production of siderophores and Indole acetic acid, and inhibited the growth of the pathogen Alternaria alternata that causes blight disease in tomato [324]. Further, an actinomycete Micromonospora costi has been isolated from A. indica from Thailand. The unique characteristics of this species include the presence of meso-diaminopimelic acid in peptidoglycan and the presence of phospholipids like diphasphatidylglycerol, phosphatidylethanolamine, and phosphatidylinositol in the plasma membrane [329].

**Metabolomics of Endophytes**

In 1993, the landmark discovery of biosynthesis of the anticancer compound paclitaxel (Taxol) by endophytic Taxomyces andreanae [330] captured the attention of the scientific community towards endophytes as a treasure trove of novel, unique, bioactive natural products. A considerable number of discoveries followed the remarkable work, which cemented the virtually inexhaustible biosynthetic capabilities of endophytic fungi. Some important compounds produced by endophytic fungi are antifungal compounds such as cryptocandin A [331], cryptocin [332], ambuic acid [333], 334], pestaloside [335] and jesterone [336]; antibacterial compounds such as cytosporone A [337, 338] and javanicin [314]; anticancer compounds such as torreyanic acid [339], vincristine [340], chaetoglobosin A [341], penicillicins A1 and B1 [342], and camptothecin [343]; antioxidants like pestacin [344] and isopestacin [345]; and immunosuppressant subglutinols A and B [346] and HIV-1 integrase inhibitors [347]. Several reviews exemplify the vast chemical diversity of compounds produced by endophytes isolated from various plants prospected from different parts of the world [313, 348, 349]. Recently, Chutulo et al. (2018) briefly reported the metabolites produced by endophytes isolated from neem plant and their activities [350]. The bioactive compounds produced by endophytes not only have an ecological significance but also provide a scientific handle to study the biochemical and molecular blueprints associated with their production [351]. Herein, we present detailed elaboration on the recent developments in compounds identified from the endophytic fungi of neem plant.

**Bioactive natural compounds of endophytic fungi isolated from A. indica**

Over 30 compounds have already been reported to be produced by neem-associated fungal endophytes. For instance, chlorinated oxazinane derivatives, 10-membered lactones, solanapyrone analogues, naphthaquinones, anthraquinones, naphthodianthrone derivatives, and ring-C-seco-tetranortriterpenoids are some of the essential compound classes reported to be biosynthesized by endophytes associated with neem (Fig. 5 and Table 2).

Two new chlorinated, epimeric 1,3-oxazinane derivatives possessing nematicidal activity were characterized from Geotrichum sp. residing endophytically in leaves of neem [352], namely 1-ethanone (1) and 1-[(2R*,4S*,5R*)-2-chloro-4-methyl-1,3-oxazinan-5-yl]ethanone (2), an epimer of the first. Another nematicide active against the nematodes Bursaphelenchus xylophilus and Panagrellus redivivus, identified as [2,3-dihydro-2-[(1-methylethenyl)-1-benzofuran-5-yl]methanol (3), was also reported from Geotrichum sp. in addition to 1-(2,4-dihydroxyphenyl)-ethanone (4) [352]. Ten-membered lactones viz. 8a-acetoxy-5α-hydroxy-7-oxodecan-9-olide (5), 7α,8α-dihydroxy-3,5-decadien-10-olide (6), 7α-acetoxymultipolide A (7), 8α-acetoxymultipolide A (8), and multipolide A (9) have been reported from Phomopsis sp. isolated from neem tree bark [7, 300, 303].
Fig. 5 Bioactive natural compounds isolated from endophytic fungi of A. indica.
### Table 2 Major bioactive compounds derived from endophytic fungi of *Azadirachta indica*.

<table>
<thead>
<tr>
<th>Sl. No.</th>
<th>Compound</th>
<th>Derivative</th>
<th>Activity</th>
<th>Endophytic fungi</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1-[(2R*,4S*,5S*)-2-chloro-4-methyl-1,3-oxazinan-5-yl]ethanone (1)</td>
<td>Chlorinated oxazinane derivate</td>
<td>Nematicidal</td>
<td><em>Geotrichum</em> sp.</td>
<td>[352]</td>
</tr>
<tr>
<td>2</td>
<td>1-[(2R*,4S*,5R*)-2-chloro-4-methyl-1,3-oxazinan-5-yl]ethanone (2)</td>
<td>Chlorinated oxazinane derivate</td>
<td>Nematicidal</td>
<td><em>Geotrichum</em> sp.</td>
<td>[352]</td>
</tr>
<tr>
<td>3</td>
<td>[2,3-dihydro-2-(1-methylthienyl)-1-benzofuran-5-yl]methanol (3)</td>
<td>Benzofuran derivative</td>
<td>n. a.</td>
<td><em>Geotrichum</em> sp.</td>
<td>[352]</td>
</tr>
<tr>
<td>4</td>
<td>1-(2,4-dihydroxyphenyl)-ethanone (4)</td>
<td>Polyphenol</td>
<td>Nematicidal</td>
<td><em>Geotrichum</em> sp.</td>
<td>[352]</td>
</tr>
<tr>
<td>5</td>
<td>8α-Acetoxy-5α-hydroxy-7-octadecan-9-olide (5)</td>
<td>10-membered lactone ring</td>
<td>Antifungal</td>
<td><em>Phomopsis</em> sp.</td>
<td>[353]</td>
</tr>
<tr>
<td>6</td>
<td>7α,α-Dihydroxy-3,5-decadien-10-olide (6)</td>
<td>10-membered lactone ring</td>
<td>Antifungal</td>
<td><em>Phomopsis</em> sp.</td>
<td>[353]</td>
</tr>
<tr>
<td>7</td>
<td>7α-Acetoxymultipolide A (7)</td>
<td>10-membered lactone ring</td>
<td>Antifungal</td>
<td><em>Phomopsis</em> sp.</td>
<td>[353]</td>
</tr>
<tr>
<td>8</td>
<td>8α-Acetoxymultipolide A (8)</td>
<td>10-membered lactone ring</td>
<td>Antifungal</td>
<td><em>Phomopsis</em> sp.</td>
<td>[353]</td>
</tr>
<tr>
<td>9</td>
<td>Multipolide A (9)</td>
<td>10-membered lactone ring</td>
<td>Antifungal</td>
<td><em>Phomopsis</em> sp.</td>
<td>[353]</td>
</tr>
<tr>
<td>10</td>
<td>Solanapyrone N (Methyl 4-Amino-6-[[1R,2S,4aR,8aR]-1,2,4a,5,6,7,8,8a-octahydro-2-methylnaphthalen-1-yl]-2-oxo-2H-pyran-3-carboxylate) (10)</td>
<td>Solanapyrone analogues</td>
<td>Antifungal</td>
<td><em>Nigrospora</em> sp.</td>
<td>[354]</td>
</tr>
<tr>
<td>11</td>
<td>Solanapyrone O (11)</td>
<td>Solanapyrone analogues</td>
<td>Antifungal</td>
<td><em>Nigrospora</em> sp.</td>
<td>[354]</td>
</tr>
<tr>
<td>12</td>
<td>Solanapyrone C (12)</td>
<td>Solanapyrone analogues</td>
<td>Antifungal</td>
<td><em>Nigrospora</em> sp.</td>
<td>[354]</td>
</tr>
<tr>
<td>13</td>
<td>Nigrosporalactone (13)</td>
<td>Lactones</td>
<td>Antifungal</td>
<td><em>Nigrospora</em> sp.</td>
<td>[354]</td>
</tr>
<tr>
<td>14</td>
<td>Phomalactone (14)</td>
<td>Lactones</td>
<td>Antifungal</td>
<td><em>Nigrospora</em> sp.</td>
<td>[354]</td>
</tr>
<tr>
<td>15</td>
<td>Javanicin (15)</td>
<td>Naphthaquinone</td>
<td>Antibacterial</td>
<td><em>Chloridium</em> sp.</td>
<td>[314]</td>
</tr>
<tr>
<td>16</td>
<td>Chrysophanol (16)</td>
<td>Anthraquinone</td>
<td>Antibacterial</td>
<td><em>Aspergillus aculeatus</em></td>
<td>[355, 356]</td>
</tr>
<tr>
<td>17</td>
<td>Emodin (17)</td>
<td>Naphthodianthrone derivative</td>
<td>Antibacterial, anticancerous</td>
<td><em>Aspergillus aculeatus</em></td>
<td>[355, 357, 358]</td>
</tr>
<tr>
<td>18</td>
<td>Succinic acid (18)</td>
<td>Dicarboxylic acid</td>
<td>Weak insecticidal activity against <em>Plutello xylostella</em></td>
<td><em>Aspergillus aculeatus</em> and <em>Xylaria</em> sp.</td>
<td>[355, 359]</td>
</tr>
<tr>
<td>19</td>
<td>1,5-Dimethyl citrate (19)</td>
<td>Oxobutanoate</td>
<td>n. a.</td>
<td><em>Aspergillus aculeatus</em></td>
<td>[352]</td>
</tr>
<tr>
<td>20</td>
<td>5-Hydroxymellein (20)</td>
<td>Isocoumarin</td>
<td>Weak insecticidal activity against <em>Plutello xylostella</em></td>
<td><em>Xylaria</em> sp.</td>
<td>[359]</td>
</tr>
<tr>
<td>21</td>
<td>5-methylmellein (21)</td>
<td>Isocoumarin</td>
<td>Weak insecticidal activity against <em>Plutello xylostella</em></td>
<td><em>Xylaria</em> sp.</td>
<td>[359]</td>
</tr>
<tr>
<td>22</td>
<td>5-carboxymellein (22)</td>
<td>Isocoumarin</td>
<td>Weak insecticidal activity against <em>Plutello xylostella</em></td>
<td><em>Xylaria</em> sp.</td>
<td>[359]</td>
</tr>
<tr>
<td>23</td>
<td>Hymatoxin C (23)</td>
<td>Diterpene</td>
<td>Weak insecticidal activity against <em>Plutello xylostella</em></td>
<td><em>Xylaria</em> sp.</td>
<td>[359]</td>
</tr>
<tr>
<td>24</td>
<td>Hymatoxin D (24)</td>
<td>Diterpene</td>
<td>Weak insecticidal activity against <em>Plutello xylostella</em></td>
<td><em>Xylaria</em> sp.</td>
<td>[359]</td>
</tr>
<tr>
<td>25</td>
<td>Halorosellinic acid (25)</td>
<td>Ophiobolane sesterterpene</td>
<td>Weak insecticidal activity against <em>Plutello xylostella</em></td>
<td><em>Xylaria</em> sp.</td>
<td>[359]</td>
</tr>
<tr>
<td>26</td>
<td>Cerebroside C (26)</td>
<td>Sphingolipids</td>
<td>Weak insecticidal activity against <em>Plutello xylostella</em></td>
<td><em>Xylaria</em> sp.</td>
<td>[359]</td>
</tr>
<tr>
<td>27</td>
<td>(2S,3S,4R,2′R)-2-[(2′-Hydroxytetraconta-2,4-dien-1,3,4-triol)]</td>
<td>Ceramides (Lipids)</td>
<td>Weak insecticidal activity against <em>Plutello xylostella</em></td>
<td><em>Xylaria</em> sp.</td>
<td>[359]</td>
</tr>
<tr>
<td>28</td>
<td>Cerevisterol (28)</td>
<td>Steroids</td>
<td>Weak insecticidal activity against <em>Plutello xylostella</em></td>
<td><em>Xylaria</em> sp.</td>
<td>[359]</td>
</tr>
<tr>
<td>29</td>
<td>Adenosine (29)</td>
<td>Purine nucleoside</td>
<td>Weak insecticidal activity against <em>Plutello xylostella</em></td>
<td><em>Xylaria</em> sp.</td>
<td>[359]</td>
</tr>
</tbody>
</table>

continued
from stems of *A. indica*. These compounds exhibited antifungal activities against *Aspergillus niger*, *Botrytis cinerea*, *Fusarium avenaceum*, *Fusarium moniliforme*, *Helminthosporium maydis*, *Penicillium islandicum*, and *Ophiostoma minus* [353]. Multiplolid A (9), previously isolated from the fungus *Xylaria multiplex* [360], was also isolated from endophytic *Phomopsis* sp. associated with neem [353]. The main difference between multiplolid A (9) and 7a,8a-dihydroxy-3,5-decadien-10-olide (6) is that the epoxide moiety at C-3 and C-4 in the former is substituted by a double bond in the latter [360]. Solanapyrones have been previously reported as phytotoxins from *Ascocytba robie* [361–363] and *Alternaria solani* [364,365]. Interestingly, 2 analogs solanapyrone N (10) and solanapyrone O (11) were isolated from *Nigraspera* sp. recovered from stems of *A. indica*, with both being structurally different in the substitution pattern of the a-pyrene unit compared to other solanapyrones [354]. Solanapyrone N (10), solanapyrone O (11), solanapyrone C (12), nigrosoractolactone (13), and phomolactone (14) were shown to possess antifungal activities [354]. Structurally-related analogs of solanapyrones have also been isolated from an unidentified marine fungus associated with the surface of the green alga *Halimeda monile*, which demonstrated anti-algal activity [366]. Wu et al. [367] isolated guanine sesquiterpenes and isopimarane diterpenes from *Xylaria* sp. isolated from *A. indica*, and these compounds have shown inhibitory activities against *Candida albicans*, *Hormodendrum compactum*, and *Pyricularia oryzae* with MIC values ranging between 16 µg to 256 µg/ml. Similarly, 5 new guanine sesquiterpenes were further isolated from *Xylaria* sp. which also possesses antipathogenic activities [368]. Recently, Chatterjee et al. [369] identified the metabolites produced by *Alternaria alternata* isolated from *A. indica* showing inhibitory activities against Gram-negative and Gram-positive bacteria.

The highly functionalized antibacterial naphthaquinone, javanin (15), has been reported from an endophytic fungus *Chloridium* sp. isolated from roots of *A. indica* [314], which displayed strong inhibition of *Pseudomonas aeruginosa* and *P. fluorescens*. Chrysophanol (16), emodin (17), succinic acid (18), and 1,5-dimethyl citrate (19) have been obtained from the broth extract of an endophytic fungus *Aspergillus aculeatus*, a resident of *A. indica* [355]. Chrysophanol (1,8-dihydroxy-3-methylanthracenedione) (16), an anthaquinone responsible for antimicrobial efficacy against *Bacillus subtilis* and *Staphylococcus aureus*, was detected in the extract of *Colobrini gregii* [356]. Emodin (17) and related compounds were previously described as having significant inhibitory activities against P-388 leukemia in mice [357]. Emodin (17), postulated as the primary precursor in the endophytic biochemical pathway to the naphthodianthrone derivative hypericin, also showed antimicrobial activity against the Gram-positive bacterium *Staphylococcus aureus*, Gram-negative bacteria *Klebsiella pneumoniae* f. sp. * comma, Pseudomonas aeruginosa*, *Salmonella enterica* f. sp. * enterica*, and fungal organisms *Aspergillus niger* and *Candida albicans* [358]. Eleven compounds, namely 5-hydroxymellein (20), 5-methylmellein (21), 5-carboxymellein (22), hymatoxin C (23), hymatoxin D (24), halorosellinic acid (25), cerebrosides C (26), (25,35,4R,2′R)-2-(2′-hydroxytetrahydroxycosanoylaminio)-octadecane-1,3,4-triol (27), cerevisterol (28), adenosine (29), and succinic acid (18) have been reported to be produced by endophytic *Xylaria* sp. YC-10 isolated from the stems of *A. indica* collected in Yuanjiang County, Yunnan Province, P.R. China [359]. Although all the compounds exhibited weak insecticidal activity against *Plutella xylostella*, 9 of these compounds were reported from *Xylaria* for the first time [359]. Further, Verma et al. [370] attempted to synthesize silver nanoparticles from the extracts of endophytic fungus *Aspergillus clavatus* and tested against human pathogens such as *Candida albicans*, *Pseudomonas fluorescens*, and *Escherichia coli*, and they were effective against pathogens at 9.7 µg/ml (minimum fungicidal concentration) and 5.83 µg/ml (minimum inhibitory concentration). Kusari et al. [312] identified and quantified azadirachtin A (30) and B (31) as biosynthetic products of a novel neem-associated endophytic fungus, *Eupenicillium parum* [294]. This study highlighted an interesting plant-endophyte association where plant “mimetic” compounds are produced by endophytes to render similar functional traits in their ecological habitats.

**Outlook**

*A. indica* (neem) and its endophytic microflora represent an extensive repertoire of diverse natural products having different biological activities. On the one hand, neem (host plant) is a rich source of compounds such as the azadirachtins and related tetrannortriterpenoids. On the other hand, endophytes associated with neem have a massive potential in synthesizing bioactive and chemically novel compounds. It is noteworthy that a large number of diverse endophytic fungi and actinomycetes have been isolated from *A. indica* in a relatively small period. Concomitantly, a large number of compounds have been isolated from neem and its endophytes, even though their biochemical and overall ecological connotations are not clearly understood. Except for a few studies, endophytic microorganisms of neem remain poorly investigated. Recently, an epigenetic study was conducted to induce the anti-

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**Table 2 Continued**

<table>
<thead>
<tr>
<th>Sl. No.</th>
<th>Compound</th>
<th>Derivative</th>
<th>Activity</th>
<th>Endophytic fungi</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td>Azadirachtin A (30)</td>
<td>Ring-C-seco-tetrano-triterpenoids</td>
<td>Insecticidal activity</td>
<td><em>Eupenicillium parum</em></td>
<td>[294]</td>
</tr>
<tr>
<td>31</td>
<td>Azadirachtin B (31)</td>
<td>Ring-C-seco-tetrano-triterpenoids</td>
<td>Insecticidal activity</td>
<td><em>Eupenicillium parum</em></td>
<td>[294]</td>
</tr>
</tbody>
</table>

n. a.: not available
microbial activity and production of cryptic metabolites from *Streptomyces coelicolor* (AZRA 37) of neem plant, and the increased antimicrobial activity coupled with induced protein production were registered [371]. Extensive research is required to assess the hidden endophytic populations of neem. In particular, endophytic actinomycetes associated with neem can serve as a precious and reliable resource of novel compounds, given that they are well-known prolific producers of bioactive metabolites [372]. It has already been firmly established that endophytes have unique functions in hosts such as plant protection, nutrient supply, phosphate solubilization, and mineral transport. Besides, endophytic fungi can also confer a profound impact on the host system by not only enhancing growth and fitness but also strengthening their tolerances to abiotic and biotic stresses. It has been proposed that during evolution, some co-existing endophytes and their host plants have established a unique relationship with one another and significantly influenced the formation of secondary metabolites in plants such as neem. These findings open new platforms for enhancing growth as well as for improved production of valuable metabolites using endophytes in the host plant. However, mechanisms underlying plant-endophyte interactions are still open to future research. It is known that during endophyte infection, selected plant-specific metabolites play a significant role in colonization and the establishment of endophytic interactions. These substances not only play a crucial role in defense and competition but also might be needed for specific interaction and communication with the endophyte(s). As highlighted in this review, endophytic associations have been studied, using a bird’s-eye view from the host plant’s side, which resulted in detailed and comprehensive knowledge related to various microbes associated with different species or cultivars. However, how the host plant (*A. indica*) responds varies depending on the endophyte strain and plant environment. The mechanisms behind such selective priming remains obscure. Extricating the changes in transcriptome and, subsequently, metabolome – both of neem as well as associated endophytes – under the influence of abiotic and biotic environmental factors will throw light into the genetic and biochemical mechanisms underlying neem-endophyte interactions.

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**Conflict of Interest**

The authors declare that they have no conflict of interest.

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