A Review: Potential Pharmacological Uses of Natural Products from Laminaceae

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ABSTRACT
Natural products and their derivatives have been used as therapeutic agents from ancient times and in folklore for treatment of many diseases and illness. Many of the natural products from plants have been used as current drug candidates, either in their original or semi synthetic form and secondary metabolites of the plants also be serve as drug precursors, drug prototypes and pharmacological probes. Medicinal plants involve a multifaceted approach in current drug research as combining botanical, phytochemical, biological and molecular techniques. In drug discovery medicinal plants provides continually new and important lead constituents to against various pharmacological targets including cancer, HIV/AIDS, Alzheimer's, Malaria, Pain and Immune alteration and etc. Although, medicinal plants continue provide a new drug leads in drug discovery, and numerous challenges are encountered in procurement and selection of plant materials, screening method and the scale up of active compound, hence this brief review work presents a study of the importance of natural products, especially those derived from higher plants and aims to the highlight the pharmacological significant of Laminaceae family in terms of drug development. Most of the plants in laminaceae family are aromatic plants, they possesses Immunomodulatory activites. Salvia species is one of species in this family, hence aimed to studied the immunomodulatry activity of one of the salvia species.

Keywords: Drug discovery, laiminace, medicinal plants, natural products, pharmacological uses

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1. INTRODUCTION
Medicinal plants need more attention due to their important role in primary healthcare delivery system for improvement of people’s health [1]. For thousands of years, natural products have been the most successful sources of potential drug leads and played an important role in development of new drug leads against various pharmacological targets including cancer, HIV/AIDS, Alzheimer’s, malaria, and pain and the natural sources are using to treat and preventing the various human diseases throughout the world [2]. Natural products are the richest source of biologically active compounds, obtained from plants, animals, minerals etc., about 40% of all medicines were obtained from either natural products or their semi-synthetic derivatives and developed a lead compound originally obtained from a natural source [3, 4]. Indeed, over the last half century, most clinical applications of secondary metabolites of plants and their derivatives have been applied towards combating several human diseases like cancer and etc. The importance of natural products is clearly enormous and many higher plants contain novel metabolites with different biological properties, about 25% of the drugs from plants were prescribed worldwide and 121 active compounds being in current use [5]. Natural products research continues to explore a variety of lead structures, which may be used as templates for the development of new drugs by the pharmaceutical industry and will be, important sources of new pharmaceutical
compounds [6]. Several natural product drugs of plant origin have either recently been introduced to the United States market, including arteether, galantamine, nitisinone, and tiotropium, or are currently involved in late phase clinical trials.

In the 20th century, revolutionized thinking of pharmaceutical companies and drug development of organic chemistry, in the use of drugs as the receptor theory of drug action, it concluded by the scientists that the some mystical “power of life” are the factors required for the biological activity of the drug rather than individual chemical compounds in natural extracts. This lead to the beginning of a totally new era in pharmacology, as pure, isolated chemicals and structural modification to produced potentially more active and safe drug, instead of extracts. Indeed, many bioactive compounds and their chemical structures were elucidated and the economic power of the pharmaceutical companies was increasing [4]. Recently, natural product research has been renewed due to the failure of alternative drug discovery methods to deliver many lead compounds in key therapeutic areas such as immunosuppression, anti infectives, and metabolic diseases and there has been growing interest in alternative therapies and the therapeutic use of natural products, especially those derived from plants. This interest in drugs of plant origin is due to several reasons, namely, conventional medicine can be inefficient (e.g. side effects and ineffectve therapy), abusive and/or incorrect use of synthetic drugs results in side effects and other problems, a large percentage of the world’s population does not have access to conventional pharmacological treatment, and folk medicine and ecological awareness suggest that “natural” products are harmless [7].

Nowadays, secondary metabolites of plant such as alkaloids, flavonoids, tannins and other phenolic compounds etc., are the important sources of medicines, especially in developing countries still used plant based traditional medicine for their health care system and there is a tremendous increase in the consumption of herbs as an alternate source of medicine to maintain health and improve the quality of life [8, 9].

In industrialized countries, plant based traditional medicines (Phytotherapeutics are often called as complementary or alternative medicines), and their use has increased steadily over the last 10 years [10]. Based on the analysis, 88 single chemical entities isolated from 72 medicinal plants have been introduced into the modern therapy, many of which have similar therapeutic use and some of these plants derived compounds such as atropine (anticholinergic), codeine (cough suppressant), colchicine (antigout), ephedrine (bronchodilator), morphine (analgesic), pilocarpine (parasympathomimetic), and physostigmine (cholinesterase inhibitor) are still being used widely as single agent or combination formulations in prescription drugs. Most of the natural plant sources are obtained from different families one of this family Laminaceae is the most important source for lead compound to treat and preventing various diseases [8]. Hence the present work was concentrated on to reveal the pharmacological activities of the Laminaceae family and their involvement in new drug research in present scenario.

2. Role of Laminaceae in History of Drug Discovery

The Lamiaceae or labiatae plant family is one of the largest families among the dicotyledons; it is also termed as mint family, with 236 genera and more than 7,000 species of the order Lamiales. The largest genera of this families are saliva (900), scutellaria (360), stachys (300), plectranthus (300), Hyptis (280), Teucrum (250), vitex (250), Thymus (220) and Nepeta (200). [11]. Many plants of this family have been shown to impart an antioxidative effect in foods [12] and rich in terpenoids such as monoterpenes, diterpenes, triterpenes and also sesquiterpenoids, along with flavonoids and other phenolics [13] having a number of biological activities, including antimicrobial, anti-inflammatory, antioxidant, antiviral, cytotoxic, wound healing, neuroprotective, and anticholinesterase [14].

Plants in this family also have an important value in the sociocultural, spiritual and medicinal use in the rural and tribal lives of the developing countries [15]. Many active
essentials oils also obtained from this family and also famous for the presence of diterpenoids among its members. Lamiaceae family species are important for antimicrobial properties which are used in research of antimicrobial activities, for instance, *Salvia argentea L*, *Stachysannua L*, *Ballotanigra L*, *Melisa officinalis L* among others [16]. Aromatics plants and species have great importance for food, cosmetics and pharmaceutical industries [17]. Naturally growing Lamiaceae members have been used as tea, spice and for various medicinal purposes such as to treat fever, cough, headaches, wound healing heart diseases and stomach-aches [18]. Among this laminaceae family Salvia species are widespread plants in many countries. Salvia genera plants commonly as sage. Some of the specials are *S. sclarea*, [19] *S. pratensis* [20], *S. glutinosa*, *S. Officinalis*, Salvia lavandulaefolia and Salvia miltiorrhiza, these plants are cultivated mostly for its aromatic and widely used as essential oil. A study of the antibacterial activities of the essential oil of *S. officinalis* proved that sage essential oil in higher concentration exhibited a better efficiency than antibiotics [21]. Species belonging to the family Lamiaceae (Labiatae) are important sources of phenolic-type food preservatives and pharmaceuticals. This family also known as mint family due to many of the various herbaceous plants comprising under the genus *Mentha*, a taxon of about 25 species of aromatic, almost exclusively perennial plants in the mint family Lamiaceae. The main chemical constituents of this family are Eugenol, nerol, eugenol methyl ether, caryophyllene, terpinene-4-ol-decyladehyde, α-selinene, α and α-pinene, camphor and carvacrol, cineole, linalool, omega 3 and 6 fatty acids, dietary fibers, proteins, quercetin because of these constituents they play a vital role in preventing and treating various diseases such as hyperlipidimic, diuretic, anti-inflammatory activity, antimicrobial activity, antiviral, antifungal, immunomodulating activity etc.

3. Role of Laminaceae in Current Drug Research

Developing the therapeutic agents for the future, clearly involve the basic sciences disciplines that have always been at the core of drug discovery, namely, structural biology to provide information about the target biomacromolecules; chemistry to design and synthesize the drug candidates; and pharmacology to determine the effects of the interaction between drug and target. Taking drug discovery to the next level may require an entirely new approach, but more likely will instead result from the introduction of new disciplines and/or greatly improved technologies into the process seems likely that integrating sophisticated new computational, bioinformatics, pharmacogenomics, engineering, and/or nanotechnology methods into the process will lead to the next stage. Current research in drug discovery from medicinal plants involves a multifaceted approach combining botanical, phytochemical, biological and molecular techniques.

They have been searched for secondary metabolites that have various pharmacological activities such as antioxidant, anticholinesterase, antimicrobial, anti-inflammatory and cytotoxic activity [12]. Many researches were reported various pharmacological activities since 43 year (*Table 1*), reported the list of plants from laminaceae having different pharmacological activities till to date. In the present era increasing of numbers drug-resistant strains were observed due to excess utilization of antibiotic which create an urgent need to develop novel antimicrobial agents [22].

Genus *Salvia* (Sage) is one of the most well-known Lamiaceae family, which has wide distribution, with nearly 1000 species in three regions of the world: Central and South America (500 spp.), Central Asia/Mediterranean (250 spp.), and Eastern Asia (90 spp) [23]. *Salvia* (sage) species have been used as folk medicine for cognitive brain function, along with various biological activities, since ancient times. Sage extracts possess antioxidant, estrogenic, and anti-inflammatory properties, anticholinesterase effects and also be used against memory loss. Some researchers have been investigated the anti cholinesterases and anti-alzheimer’s effect from salvia species and most of the studies...
reported the phytoconstituents of salvia species consist with the severap pharmacological uses such as cholinesterase inhibition, antioxidant [24] and anti-inflammatory, larvicidal activity with respectively monoterpenoids and diterpene (Scareol), oil and diterpenoids, sesquiterpene such as Germacrene D.

Table 1: List of Laminaceae Plants Involved in Different Potential Pharmacological Uses

<table>
<thead>
<tr>
<th>S.No.</th>
<th>BIOSYNTHETIC NAME</th>
<th>COMMON NAME</th>
<th>CHEMICAL CONSTITUENTS</th>
<th>PHARMACOLOGICAL USES</th>
<th>REFERENCES</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.</td>
<td>Thymus vulgaris L.</td>
<td>Thyme</td>
<td>Volatile oil of Thymol, Carvacol</td>
<td>Antiseptic, antimicrobial, anthelmintic, Antibacterial and anti fungal, hepatotoxic, Appetite stimulant,</td>
<td>[31,32]</td>
</tr>
<tr>
<td>4.</td>
<td>Lavandula angustifolia</td>
<td>Lavender English, Ostokodus</td>
<td>Linanol, Perillyl Alcohol, Linalyl Acetate, Camphor, Limonene, Tannins, Triterpenes, Coumarinscineole and Flavonoids.</td>
<td>Inflammation, Coughing, Digestive Problems and act as a Sedative.</td>
<td>[33,34]</td>
</tr>
<tr>
<td>7.</td>
<td>Ocimum sanctum</td>
<td>Sacred basil, kals tulsi, veranda.</td>
<td>Volatile Oil (0.8%), Nerol, Caryophyllene, Terpinene-4-ol, deyladethylene, A-Selene, A-Pine</td>
<td>Smooth muscle relaxants, Cardiac depressants, Antiferlity, Adaptogenic, Immunomodulator y properties</td>
<td>[43,44]</td>
</tr>
<tr>
<td>9.</td>
<td>Origanum dictamnus</td>
<td>Dittany of crete</td>
<td>Flavonoids, Glycosides, Essential Oil have Carvacrol, A-Terpinene, P -Cyrene, Caryophylylene, Borneol, Terpinen-4-ol and Carvacrol, Methyl Ether.</td>
<td>Antioxidant, Antibacterial, Antifungal, Diaphoretic, Carminative, Antispasmodic and Analgesic activities.</td>
<td>[16,47-49]</td>
</tr>
<tr>
<td>10.</td>
<td>Origanum majorana</td>
<td>Sweet marjoram Knotted marjoram Sampisitsha</td>
<td>Polyphenols, Monoterpenes, Antioxidants, Arbutin, 5,6,3'- Trihydroxy- 7,8,4'-Trihydroxylavone, Hesper etin, Hydroquinone, Rosemarinic</td>
<td>Antioxidant, Antifungal, Antimicrobial activities, Antimetastatic and antitumor growth effects on Human Breast Cancer Cells, Anti-proliferative</td>
<td>[50-55]</td>
</tr>
<tr>
<td></td>
<td>Plant Name</td>
<td>Common Name</td>
<td>Active Compounds</td>
<td>Medicinal Properties</td>
<td>Ref.</td>
</tr>
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<tr>
<td>11</td>
<td><em>Origanum vulgare</em></td>
<td>Oregano</td>
<td>Sabinene (Monoterpene), (Z)-B Ocine (Monoterpenes), Terpinen-4-ol (Oxygenated Monoterpenes), Spathulenol (Oxygenated Sesquiterpene), Carvacrol and Thymol.</td>
<td>Antioxidant, Anti bacterial, Anti fungal, Diaphoretic, Carminative, Antispasmodic and Analgesic activities.</td>
<td>[16, 49, 56, 57]</td>
</tr>
<tr>
<td>12</td>
<td><em>Marrubium vulgare</em></td>
<td>Hore hound or hoarhound</td>
<td>Marrubiin, Marrubenol and Phenylpropanoid Esters, Carvacrol, B –Phellandrene.</td>
<td>Antihypertensive, Antispasmodic, Immunomodulating, Antioedematogenic</td>
<td>[58-59]</td>
</tr>
<tr>
<td>14</td>
<td><em>Hyssopus officinalis</em></td>
<td>Hyssop</td>
<td>Quercetin, 7-O-B-Dapiofuranosyl-(1→2)-B-Dxylopyranoside, Quercetin 7-O-B-D-Apiofuranosyl-(1→2)-B-D-Xylopyranoside 30-Ob-D-Glucopyranoside, Apigenin, Luteolin, Diosmin, Phenolic Compounds</td>
<td>Antifungal and insecticidal, Antiviral properties, Myorelaxant, Antiplatelet, α-Glucosidase inhibitory activity.</td>
<td>[61-67]</td>
</tr>
<tr>
<td>15</td>
<td><em>Agastache Mexicana</em></td>
<td>Mexican giant hyssop Toronjil morado, toronjil rojo,</td>
<td>Flavonoids -Hesperitin Quercetin, Phenolic Compounds</td>
<td>Anxiogenic or anxiolytic like behaviors, Vasorelaxant, Antioxidant, Antinociceptive and Anti-inflammatory effects, Insomnia and CV disorders</td>
<td>[69-70]</td>
</tr>
<tr>
<td>16</td>
<td><em>Agastache rugosa</em></td>
<td>Korean mint, blue liquorice</td>
<td>Methyleugenol, Estragole, Eugenol, Thymol, Pulegone, Limonene, Caryophyllene, Phenylpropanoids.</td>
<td>Nematicidal Activity, Treatment of Anorexia, Vomiting and Antimicrobial, Anti-Fungal and Antiviral Activity.</td>
<td>[71-74]</td>
</tr>
<tr>
<td>17</td>
<td><em>Minthostachys molls</em></td>
<td>Muna</td>
<td>Neomenthol, Menthol, Menthone and Piperitone, Carvacryl Acetate and Pulegone</td>
<td>Insecticide Activity, Antimicrobial Activity, Antimicrobial Activity, Aphrodisiac, Anti-Diarrheic, Anti-Rheumatism.</td>
<td>[75-78]</td>
</tr>
<tr>
<td>18</td>
<td><em>Minthostacys verticillata</em></td>
<td>Peperina</td>
<td>Pulegone, Menthone, Limonene</td>
<td>Diarrhea and vomiting, Digestive, Sedative, Antispasmodic bronchodilating agent. Insecticidal, fungicidal, and antiparasitic properties, Antimicrobial activity</td>
<td>[79-82]</td>
</tr>
<tr>
<td>19</td>
<td><em>Melissa officinalis</em></td>
<td>Melissa, lemon balm, Barangbo Badranj buyeh</td>
<td>Carvacrol, Citral, Sabinene</td>
<td>Blood depreurative, Sedative, Diuretic, wound healing, Gout, Dyspepsia, Emmenogogue, Joints pain Diaphoretic Spasm, Ulcer healing properties, Human CNS choknergic receptor binding, Antiinflammatory, Cytotoxic (MTT), Antiviral, Anti-HSV- 1.</td>
<td>[83-85]</td>
</tr>
<tr>
<td>20</td>
<td><em>Perilla frutescens</em></td>
<td>Perilla</td>
<td>Perilloside E 7-(2-O-B-D-Glucuronyl-B-D-Glucuronolxylo)-5,3′,4′-Trihydroxylavone, Shionin, Sutellarin, Coumaroyl Tartaric Acid, Luteolin, Linolenic Acid, Oleic Acid.</td>
<td>Antioxidant, Analgesic and Anti-abortive agent, Asthma, Chronic bronchitis and Vomiting.</td>
<td>[86-90]</td>
</tr>
</tbody>
</table>
Sclareol also have significant cytostatic and cytotoxic effect. Many studies on the essential oil of S. fruticosa reported 1,8-cineole to be the main component, followed by camphor, α-thujone, β-thujone, (Figure 1) and β-caryophyllene. The species is known to contain biologically active sesquiterpenes (Figure 2) and diterpenes, besides the high content of oxygenated monoterpenes [114].

Salvinorin - A (Figure 3) is the main active psychotropic molecule in Salvia divinorum. Salvinorin A, a neoclerodane diterpene, is the most potent naturally occurring hallucinogen known and rivals the synthetic hallucinogen lysergic acid diethylamide in potency. Recently, the molecular target of salvinorin - A was identified as the kappa opioid receptor (KOR). Salvinorin A represents the only known non-nitrogenous KOR selective agonist. Based on the selectivity of salvinorin A for the KOR, this receptor represents a potential molecular target for the development of drugs to treat disorders characterized by alterations in perception, including schizophrenia, Alzheimer's disease and bipolar disorder [115].
Figure 1: Structures of some monoterpenoids found in Salvia species

Figure 2: Structures of some sesquiterpenoids found in Salvia species

Figure 3: Salvinorin A

Figure 4: Some of the chemical Constituents and structures of *Rosmarinus officinalis* L.
Table 2: Chemical Constituents and their Pharmacological Activity of Some Laminaceae Plants [118,120]

<table>
<thead>
<tr>
<th>S. NO.</th>
<th>BIOLOGICAL NAME</th>
<th>CHEMICAL CONSTITUENTS AND STRUCTURE OF THE CONSTITUENTS</th>
<th>PHARMACOLOGICAL ACTIVITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td><em>Leonurus</em> <em>heterophyllus</em> L</td>
<td><img src="image1.png" alt="Chemical Structure" /></td>
<td>AChE enzyme inhibitory activity</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>LEOHETERONIN A</strong> <strong>LEOPERSIN G</strong></td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td><em>Micromeria cilicica</em> (<em>Clinopodium cilicicum</em>)</td>
<td><img src="image2.png" alt="Chemical Structure" /></td>
<td>BChE enzyme inhibitory activity</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>SUDACHITIN</strong> <strong>ISOMUCRONULATOL</strong></td>
<td></td>
</tr>
<tr>
<td>3.</td>
<td><em>Origanum</em> species</td>
<td><img src="image3.png" alt="Chemical Structure" /></td>
<td>Memory enhancing, Antioxidant, Antibacterial, Anti-inflammatory and antispasmodic effects</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>SORGEROLONE</strong></td>
<td></td>
</tr>
<tr>
<td>4.</td>
<td><em>Rosmarinus officinalis</em> L.</td>
<td><img src="image4.png" alt="Chemical Structure" /></td>
<td>Antioxidant and cytotoxic activity, Neuroprotective, antimicrobial, anti-inflammatory activity</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>ROSMARINIC ACID</strong> <strong>CARNOSOL</strong> <strong>CARNOSIC ACID</strong> <strong>LUTEOLIN</strong> <strong>THYMOL</strong> <strong>CARVACROL</strong> <strong>EUGENOL</strong></td>
<td>Modulate the neuroprotective defense system against cellular stress.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Carnosol have the potential to protect cortical neuronal cells by activation of the keap1/nrf2 pathway.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Monoterpenes, triterpenoids and Apigenin act against alzheimer’s disorder by cox-2 inhibition.</td>
</tr>
</tbody>
</table>
One of the most active phytochemical products from the Lamiaceae family plants is rosmarinic acid, particularly rosemary (Rosmarinus), sage (Salvia), lemon balm (Melissa officinalis), catmint (Nepeta), and lavender (Lavandula), and other phenolics that have strong antioxidant, anti-inflammatory, and neuroprotective effects in the treatment of neurological disorders, particularly AD [116]. As terpenoids, triterpenoids, especially oleane, ursane, and lupane triterpenoids, Ursolic/oleanolic acid (Figure 4) or betulinic acid and their derivatives are important potential agents in the treatment of AD. Diterpenes, especially phenolic ring-containing diterpenes, such as abietanes, were tested for anticholinesterase activity. Ferruginol and taxodione are fairly common abietanes isolated from a number of Salvia species that exhibited high BChE inhibition activity and weak-moderate AChE inhibition activity. Several abietane diterpenoids, including Carnosol and Carnosic acid and quinoid abietanes, such as Tanshinones, should also be considered potential anti-Alzheimer agents [117].

Essential oils of some of the salvia (Satureja, Thymus, Origanum, and Thymbra) species are known to be rich in the monoterpene thymol and carvacrol as well as β-pinene. Volatile constituents of the essential oils are likely to readily cross the blood-brain barrier due to their small molecular size and lipophilicity. Their volatile nature may also enable their administration as an inhaled vapor [118]. Therefore, consumption of Lamiaceae plants rich in thymol and carvacrol is useful in the treatment of AD [119].

CONCLUSION

Aromatic plants have possessed several pharmacological activities with presence of serveral phytoconstituents. However, most of the aromatic plants are not yet exploited for their bioactivities. In reference to the above discussion we focused on investigator of immunomodulatory effect on one of the salvia species with different extraction procedure by employing in-vitro and in-vivo screening methods.

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