CHAPTER 2
REVIEW OF LITERATURE

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REVIEW OF LITERATURE

The history of Indian medicine can be traced back 4500 B.C. since very early days, the knowledge of ethnomedicine has been passed on from generation to generation among the tribals and it survived in certain restricted aboriginal habitations. Ethnobotany may be defined as an anthropocentric approach to botany, concerned with gathering of information on plants and their uses. Powers (1873-1874) [1] used the term Aboriginal botany - refers study of all the forms of vegetable world which the aborigines used for medicines, textile, fabrics, ornaments, etc., while the term Ethnobotany was first coined by Harshberger (1896) [2]. Cotton (1996) [3] reviewed various definitions given by earlier workers like Robbins et al., (1916) [4], Jones (1941) [5], Schultes (1960) [6], Bye (1992) [7] etc., and defined as the area which encompasses all the studies concerning with the mutual relationship between plants and traditional people.

The Oshadi Suktam of the Rigveda, the ancient repository of the India wisdom, perhaps the oldest scientific account on the classification of medicinal plants. A scientific and detailed account of medicinal plants was given in Charaka Samhita [8]. Sushruta Samhita (800-700 B.C.) described about Myriads of drugs like Opium, Rauwolfia, Nux-vomica, Aconite, Hasish, Datura, Mustard seeds, Lemon, Antimony, Sulphur, Gold, Human milk, Blood, etc [9]. Later Siddha system of medicine was evolved by sages in South India while Unani system was developed by Muslim physicians during the Mohammaden rule as a parallel system of medicine. The allopathic system of medicine originated in Europe and became dominant in India with the establishment of British Empire.
Coming back to the Mesopotamian civilization, the Sumerians (3000 – 1970 B.C.) and Babylonians and Assyrians (1970 – 539 B.C.) found the plants used as medicine and amulets. The first evidence, Neanderthals living 60,000 years ago in present day Iraq used plants such as holly hock [10, 11]. These plants are still widely used in ethnomedicine around the world. Hippocrates (460-372 B.C.) a great medicine man, was called by the Hakims (Mohammaden physician) as Abu-At-Tab (Father of medicine), mentioned 300 to 400 medicinal plants. This invention laid the foundation of medicine in Greece, which spread, over the world. Dioscorides, a Greek physician who lived in the first century A.D., wrote his “De Materia Medica” a medicinal plant catalog, describes 600 plants with their medicinal properties.

In 9th century A.D., Rhazes came forward as a noted physician among Arabs. Later Avicenna (980 – 1037 A.D.) was the greatest physician who wrote his famous Al-quanum fi al-Tibb (The cannon of medicine), which was utilized as a textbook till late 16th century in the European medical schools [12]. Arabs brought with them, their learning and practice of medical treatment during Moghul period to India. In the 8th or 9th century A.D. Charak’s work was translated and was popularised in Arabia. Rhazes (865-925 A.D) calls him Scarak, Avicenea (980-1037 A.D) quotes him as Scirak and Serapion mentions Charak by the name of Zarch. The fact that several standard Hindu works on medicine and Materia Medica were translated in to Arabic and that several Indian drugs like pepper, lac, nard, liquorice, asafoetida, Ocimum sanctum, Cinnamon, myrrh, red sander, Calamus and the Chebulic myrobalans indicates the extent of influence of Hindu medicine on Arab medicine [13].

The remarkable progress of the Hindu medicine declined with the invasion of the Greeks, Scythians, Huns, Moghuls and Europeans. However, with the establishment of British rule in India, there was further intermingling and also
introduction of some new medicinal plants constituting the present indigenous drugs. Organized study and research in ethnobotany with emphasis on tribal systems of medicine and culture are of recent origin. Ethnobotanical explorations with special reference to tribal medicine were carried out by a number of investigators all over the world. Thus the term *Materia Medica* (meaning medicinal materials) was synonymous with the substances and products derived from natural sources and were employed by the physicians of that era. Interestingly, however, most of the medicinally active substances identified in the 19th and 20th centuries were used in the form of crude extracts.

The potentiality of the Indian medicinal plants was, however, realized during the British period and since then many workers have attempted to find out the botanical source of many of the more important drug plants through the help of Vaidis, Hakims, Pansarles and local people [14]. Apart from the literature available in the form of Ethics, Books, Journals, a wide range of electronic information systems which cover different aspects of Ethnobotany like SEPSAL (Survey of Economic Plants for Arid and Semi Arid Lands) developed by Wickens *et al.*, 1985, [15], NAPRALERT (Natural Products Alert) given by Loub *et al.*, 1985 [16], PLANIMAL (Plant animal interactions) designed by Cotton and Hodgson, 1994 [17], while in India TGBRI (Tropical Botanical Garden and Research Institute, Trivandrum) created a data base i.e., INMEDPLAN and then FRLHT (Foundation for Revitalization of Local Health Traditions, Bangalore), MEDFLOR – INDIA data base was setup by IHS (Institute of Health systems, Hyderabad) sponsored by Girijan Cooperative Corporation (GCC) etc. All such databases comprises of anthropological, botanical and pharmacological references.
2.1 Medicobotanical studies

Foreign

The well-known ethnobotanist Richard Evan Schultes conducted ethnobotanical explorations in Oklahoma, Oaxaca, Mexico, Amazon and in other regions of America Schultes, 1963 [18]. Some of the important contributions to ethnobotanical studies in recent times include Siwakoti and Siwakoti, 2000 [19]; Gilani et al., 2001 [20]; Manandhar, 2002 [21]; Ramihantaniariyo et al., 2003 [22]; Manuel Pardo et al., 2004 [23]; Guarrera et al., 2005 [24]; Khan and Khatoon, 2008 [25]; Rahmatullah et al., 2009 [26]; Biswas et al., 2010 [27]; Ong et al., 2011 [28]; Prabhat Kumar and Lalramnghinglova, 2011 [29].

India

The Pioneer of Indian ethnobotany is Janaki Ammal, 1956 [30] and there after Jain, 1965 [31] documented diversified knowledge on crude drugs in association with Ministry of Environment and Forests, Government of India. A good number of scientists worked on ethnobotany of different tribes inhabited in various forests and hills and reported several interesting drug yielding plants used for different ailments, some of the important contributions are as follows-

Andhra Pradesh

Andhra Pradesh State received little attention in ethnobotanical studies particularly on folklore survey. Roxburgh, 1795-1820 [53] initiated the ethnobotanical investigations in the state and reported on therapeutic uses of certain plants used by the local tribes.


Raja Reddy and Sudarsanam, 1987 [90] enumerated 57 plants used by the tribal’s and non-tribal’s and for different diseases of their domestic animals in Chittoor district. Pratap et al., 2001 [91] reported ethno medical studies in talakona forest range of Chittoor, Andhra Pradesh. Jyothi et al., 2010 [92] reported the ethnobotanical survey of medicinal plants used in the treatment of dermatogenic diseases in Chittoor district, Andhra Pradesh. Pratap et al., 2010 [93] published a critical note on herbal remedies for snakebites in ethnic practices of Chittoor district.

2.2 Trichome studies

Trichomes are specialized epidermal cells found on the aerial surfaces of plants especially in tropical and subtropical regions and exhibit different shapes and forms. Trichomes serve a variety of functions, depending on their location. As leaf hairs, they reflect radiation, lower temperature, and reduce water loss [94] and also provide defense against insects. Trichomes may be unicellular or multicellular, branched or unbranched. According to secretory activities, trichomes can be classified into glandular, consisting of a stalk terminating with a glandular head, or nonglandular, consisting of elongated tapering structures.
The family Lamiaceae is enriched with aromatic species used as folk medicines, fragrances, etc., because of the essential oils produced in glandular hairs spread over the aerial vegetative and reproductive organs. In Lamiaceous members, there are two types of trichomes: peltate and capitate [95]. Detailed microscopic studies on capitate trichomes, with a uni or a bicellular head, was analysed in *Mentha piperita* [96], *Monard afistulosa* [97] and *Nepetae racemosa* [98]. Glandular trichomes were observed in *Thymus lykae* [99] Non-glandular and glandular trichomes were observed in *Thymus lykae* [100]. Capitate and peltate glandular trichomes were observed in *Lavandula pinna* [101]. Eight types of trichomes were identified in *Teucrium polium* [102]. Leaf capitate trichomes were observed in *Leonotis leonurus* [103]. No reports were seen on trichomes of *L. nepetiifolia*, hence, conducted with a maximum attention.

### 2.3 Phytochemistry

The plant kingdom represents an enormous reservoir of pharmacologically valuable molecules to be discovered [104]. Among the estimated 3,50,000 plant species on the earth, only a small percentage has been pharmacological screening is even smaller. About 65-80% of the world’s population, which lives in developing countries, depends essentially on plants for primary health care. According to the World Health Organization (WHO), a medicinal plant was defined as any plant, which contains precursors of chemotherapeutic semi synthetic substances (WHO, 1979) and plays a central role in the health care systems of large proportions of the world’s population [105].

Natural pharmaceuticals (Naturaceuticals), neutraceuticals and cosmeceuticals are of great importance as a reservoir of chemical diversity aimed at new drug discovery and are explored for antimicrobial, cardiovascular, immunosuppressive and
anticancer drugs. In addition many neutraceuticals are being consumed in unregulated markets for perceived benefits in health care and improvement of quality of life. Around 80% of all such products are of plant origin. Currently, the major pharmaceutical companies have demonstrated renewed interest in investigating higher plants as sources for new lead structures for the development of synthetic molecules and also for the development of standardized phytotherapeutic agents with proved efficacy, safety and quality [106]. Numerous drugs have entered the international pharmacopoeia through the study of ethnopharmacology and traditional medicine. Traditional folk-driven drug development will be used in reverse pharmacology path and reduce time and cost of development.

In general, the search for the medicinal plants can follow three main routes: random, ethno (including ethnobotanical, ethnomedical and ethnopharmacological) and ecological search [107]. However, while using the ancient texts, one must consider the fact that the plants may have evolved over a period of time resulting in changes in their phytochemical composition and hence their medicinal properties and therefore validation is required. Nevertheless, the success rates of the ethno-based approaches are substantially higher than those of random screening since the continued use of crude preparations are infact comparable to small-scale clinical trials.

Medicinal plant materials should be collected in the proper season so as to ensure the best possible quality of both the starting material as well as the finished product. Information such as the correct plant parts is seasonal or replenishable should be obtained. Seasonal variation can affect the chemical composition of the plants and thus its biological activity. The time of harvest should also depend on the plant part to be used since it depends on the plant species the level of biologically active
constituents can vary in different parts at different stages of the plant growth and development. Kursar et al., 1999 [108], found that younger leaves of tropical rainforests plants contained secondary metabolites that were either present in very little quantities or totally absent in matured leaves. The extracts from these younger leaves showed better biological activity when tested for anticancer activity or activity against *Bacillus subtilis* and *Artemia saline* (Brine shrimp). The water and temperature stress related increase in the content of active constituents such as the total phenolic compounds was shown in *Hypericum brasiliense* [109].

Natural products are being widely used in the form of medicinal plants as pathfinder molecules for the discovery and validation of drug targets, herbal products and finished products or phyto-pharmaceuticals. Plants are capable of synthesizing an overwhelming variety of low-molecular-weight organic compounds called secondary metabolites, usually with unique and complex structures. The production of secondary metabolites in plants is an ecological and evolutionary perspective. Secondary metabolites (SM) are present in higher plants with high structural diversification. Altogether, the pattern of secondary metabolites in a given plant is complex. It changes in a tissue and organ specific regularly; differences can be seen between different developmental stages of individuals and populations. SM can be present in the plant in an active state or as a “prodrug” that becomes activated upon wounding, infection or in the body of an herbivore. The biosynthesis of some SM is induced upon wounding or infection and SM are made de novo ‘phytoalexins’. Presently, ~100,000 such compounds have been isolated from higher plants [110].

In contrast to primary metabolites, secondary metabolites do not have nutrient characteristics for human beings, however, they can protect human beings against diseases. The drugs contained in medicinal plants are known as active principles and
act as novel drug prototypes [111-112]. The drugs have complementary and overlapping mechanisms of action in human body, including antioxidant properties, modulation of detoxification enzymes, stimulation of the immune system, and modulation of hormone metabolism including antibacterial and antiviral effect.

The most commonly encountered secondary metabolites of plants (phytochemicals) are saponins, tannins, flavanoids, alkaloids, anthraquinones, cardiac glycosides and cyanogenic glycosides. The pharmacological properties of antinutritional factors in plants were reviewed [113]. The presence of these secondary metabolites in plants probably explains the various uses of plants for traditional medicine. Traditionally, the discovery of active components from natural products chiefly relies on various chemical experiments and biological assays, which were routinely achieved by a sequential process [106]. In this process the products from microbial fermentation or plant extracts were firstly separated into many fractions. Then, bioassays were performed for each fraction to select the most active samples for further separation. Following the separation and bioassay loop, some active substances (“leads”) were purified through chemical methods [114]. The obvious disadvantage in this method is its high cost and labour consumption, as well as the low efficiency in drug discovery. Therefore, new methods are needed to accelerate the pace of identifying active substances from natural products and to reduce the costs for drug discovery. Recently, drug discovery and development is one of the most rapidly developing areas that increasingly depend on information.

The period 1817-1837 may be regarded as the most significant in the discovery of alkaloids. The work on glucosides started in 1837 by Liebig and Wohler. The systematic work on essential oils and the preparation of their individual components was done by Wallach [115]. In India screening of drugs started in 19th
century which is followed by screening and analysis of secondary metabolites like alkaloids, saponins, flavonoids, terpenoids etc [116, 117 and 118]. The Tanzanian medicinal plants were screened for different secondary metabolites by Chhabra et al., 1984 [119]. Harborne, 1984 [120] expressed the significance of phytochemical analysis and its importance for the establishment of alternative medicine.

**Review of literature on phytochemistry with special reference to Lamiaceae:**

The chemistry of Lamiaceae is among the most diverse and interesting of flowering plant families. Thousands of compounds belonging to different chemical classes were reported from members of the family, among them most predominant are diterpenoids.

The major phytochemical surveys in Lamiaceae include those made on the basis of chemical components [121, 122], essential oils, flavonoids [123, 124, 125], alkaloids [126], fatty acids [127, 128], terpenoids [129, 130] and Iridoids [131, 132]. In this family, tannins, iridoids, and saponins are common, and alkaloids are also present in a few genera [132]. Flavones and flavone glycosides are important compounds of *Mentha* species [133]. *Ballota* species contains diterpenes particularly furanolabdane diterpene [134]. *Leonotis* species possesses many organic compounds related into tannins, quinones, saponins, alkaloids, resins and terpenoids [135, 136].

The compound clerodin was the first compound of the clerodane diterpenoid series isolated from *Clerodendrum infortunatum* [137]. Antioxidative flavonoids such as luteolin and apigenin isolated from *Ajuga* species [138]. Rahman et al., 2009 [139] isolated D-glycoside from the petroleum ether extract of *Ocimum* species, while Scarpati et al., 1999 [140] isolated two iridoid glucoside lamiol, lamioside from *Lamium amplexicaule*. Suksamran et al., 1999 [141] isolated insect growth hormone pterosterone in *Vitex glabrata*. Phytochemical investigation on the methanolic extract
of *Thymus serpyllum* resulted to the isolation of two new compounds 3-ketotriacontanoic acid and 27-ketotriacontanol [142].

Kaplan, 1968 [143] isolated two labdane diterpenoids marrubiin and premarrubiin from *Leonotis leonurus*. Haptemarium, 1994 [144] isolated five different labdane type diterpene lactones from *Leonotis ocymifolia*. Gareth et al., 1964 [145] isolated a crystalline solid compound dubin (C_{21}H_{30}O_{6}) from *Leonotis dubia*. Phytochemical studies of *L. nepetifolia* revealed presence of iridoid glycosides, phenyl ethanoid glycosides, labdanoid diterpenoids and coumarins etc [146]. Purushotaman et al., 1974 isolated leonotin from *Leonotis nepetifolia* (L.) R.Br. [147].

### 2.4 Antimicrobial activity

The medicinal value of plants lies in some chemical substrates that produce a definite physiological action on the human body. The use of plant extracts and phytochemicals, with established antimicrobial properties, could be of great significance in preventive and/or therapeutic approaches. The most important antimicrobial compounds of plant origin are alkaloids, flavonoids, tannins and phenolic compounds. The increasing prevalence of multi-drug resistant strains of bacteria and the recent appearance of strains with reduced susceptibility to antibiotics raised the spectrum of ‘untreatable’ bacterial infections and adds urgency to the search for new infection-fighting strategies. Contrary to synthetic drugs, antimicrobials of plant origin usually are not associated with many side effects and have an enormous anti-infective potential in numerous infectious diseases. WHO reports revealed more than 80 per cent of the world population relies on traditional folk medicine for primary health care needs.
A continued search for medicinal plants during last several years yielded good number of plants, which are of great use in the treatment of diseases and promotion of health. Such investigations are likely to lead not only to discover new drugs but also reveal new types of chemical substances containing biological activity [148].

In India herbal medicines have been the basis of treatment and cure for various diseases in traditional methods practiced such as Ayurveda, Unani and Siddha. Although reports of antibacterial activity of indigenous plants have been published from many regions [149, 150] they have not been systematically conducted, except in few cases, they’re by leading to confusion in drawing meaningful conclusions [151, 152]. In recent years, antifungal properties of medicinal plants have been reported from different parts of the world; however, such reports are available only on few Indian medicinal plants [153, 154, 155, 156].

Several phytochemists and pharmacologists isolated novel antimicrobial natural products from several plant species that are used in different traditional systems of medicine. Those products are alkaloids [157], flavonoids [158], coumarins [159], amides [160], essential oils [161] and saponins [162].

Due to increasing incidence of multiple resistance in human pathogenic microorganisms in recent years, largely due to the indiscriminate use of commercial antimicrobial drugs have been employed to cure pathogenic infections. The number of resistant strains of microbial pathogens is growing since penicillin resistance and multi resistance pneumococci caused a major problem in South Africa [163].

The increase in the resistance of microorganisms is mainly due to indiscriminate use of commercial antimicrobial drugs that prompted the scientists to search for new antimicrobial substances from various sources including medicinal plants [164]. Medicinal plants have been used for centuries as remedies for human
diseases because they contain components of therapeutic value. Today 88 per cent of the global population turn to use plant derived medicines as their first line of defense for maintaining health and combating diseases. One hundred and nineteen secondary plant metabolites derived from plants are used globally as drugs, 15% of all angiosperms have been investigated chemically and of that 74% of pharmacologically active plant derived components were discovered [165].

Recently, the acceptance of traditional medicine as an alternative form of health care especially in all developing countries. The discovery of penicillin from the fungus *Penicillium notatum* by Flemming, (1928), prompted the discovery of such bioactive metabolites in the pharmaceutical industry today in large scale [166]. It is reported that on an average two or three antibiotics derived from microorganisms are launched each year. After a down turn in that pace in recent decades the pace is again quickening as scientists realized that the effective life span of any antibiotic is limited. Although, a number of antibiotics are widely used in medicine, the search for such potential substances from plants will continue as better and safer drugs to bacterial and fungal infections are still needed, because of their biodegradable nature and being relatively safer for human beings and non target organisms in the environment. A number of reports concerning the antibacterial screening of plant extracts of medicinal plants have appeared in the literature [167, 168, 169].

This rich diversity of phytochemicals has partly arisen because of evolutionary selection for improved defence mechanisms against a broad array of microorganisms, insects, nematodes and even other plants [170]. Plant “immune systems” effectively prevent infections caused by the majority of phytopathogen [171]. The defence chemicals produced by plants are commonly classified either as *phytoanticipins*, the molecules that are present constitutively in an inactive form (e.g. glucosides) or as
**phytoalexins**, whose levels increase strongly in response to microbial invasion and generated by *de novo* synthesis in response to a specific infection [172].

Phytoanticipins are low molecular weight products, which are present in plants before the challenge by microorganisms, are produced from preexisting constituents after microbial attack [173]. These phytochemicals, such as glucosinolates, cyanogenic glucosides, and saponin glycosides are normally stored as less toxic glycosides in the vacuoles or cellwalls of plant cells. If the integrity of the cell is broken when penetrated by a microorganism or due to other damage, the glycoside comes into contact with hydrolyzing enzymes present in other compartments of the cell, releasing a toxic aglycone [174].

Phytoalexins are low molecular weight products that are produced in response to elicitors such as microbial, herbivorous or environmental stimuli [175]. Once plant detects a pathogen signal, a complex mixture of secondary metabolites is produced to control the invader. The molecules that are synthesized de novo may lead to activation of respective genes and enzymes required for their synthesis. Phytoalexins are chemically diverse and may include many chemical classes such as simple phenyl propanoid derivatives, alkaloids, glycosterosids, flavonoids, isoflavonoids, various sulphur products and terpenes. There is no boundary between phytoalexins and phytoanticipins and in one plant species a certain chemical can function as a phytoalexin, whereas it has the function as a phytoanticipin in another species [176]. It is important to point out that the distinction between phytoanticipins and phytoalexins is not based on their chemical structure but rather on how they are produced. Thus the same chemical may serve as both phytoalexin and phytoanticipin, even in the same plant [177]. Naturally occurring alkaloids and their synthetic derivatives have analgesic, antisplasmodic and bactericidal principles [178]. Each of
this group of compounds has been reported to possess antimicrobial activity [179, 180] and reportedly exert their effects by affecting the cell membrane integrity of bacteria [181].

Intrinsic resistance to antimicrobials is a natural property of bacteria that is frequently associated with cellular impermeability imparted by the outer layers limiting the uptake of antimicrobial products [182]. It is widely recognized that Gram-negative bacteria are generally less susceptible to antimicrobial products than Gram positive; their cell walls present a more significant barrier to entry [183]. Mycobacteria and bacterial spores are among the least susceptible cell types, due to the innate presence of waxy cell envelope and a spore coat, respectively.

It is estimated that over 12000 different species of fungi exist; about one hundred of them are pathogenic to humans. Fungi cause numerous diseases of serious concern in plants, humans and animals. Allergies produced by fungal spores also causing a big problem.

Fungi are ubiquitous and able to use a wide range of substances as their carbon, nitrogen and energy metabolism [184]. Most food are prone to biodeterioration by moulds and other fungi during post-harvest processing, transport and storage, rendering them unfit for human consumption by retarding their nutritive value and often by producing mycotoxins. A significant portion of the cereals produced in the world are reported to be contaminated with mycotoxins and other fungal metabolites which are reported to be toxic to man and animals [185]. Pesticides have made great contribution for quick and effective management of plant diseases and microbial contaminations in several agricultural commodities [186]. Excessive usage of pesticides in agriculture to overcome pre-harvest and post harvest problem has resulted in many toxic epidemics. It is now realized that chemical fungicides cause
serious environmental problems and are toxic to non-target organisms. Reports are available on many phytopathogenic microorganisms having acquired resistance to synthetic fungicides [187]. This seriously hinders the management of diseases of crops and agriculture products [188]. Thus there is an urgent need to search for an alternative method for prevention of biodeterioration of grains during storage without any toxicity to the consumer, which is eco-friendly and effective.

The search for antifungal compounds has become growing importance mainly as a result of an increasing occurrence of systemic mycoses, associated primarily with immunodeficiency diseases (such as AIDS) and an increased use of immune-suppressors. The fungal infections observed in immune suppressed or HIV infected patients are mainly candidiasis, cryptococcosis and aspergillosis [189]. Currently these structural classes of compounds find wide therapeutic application for the treatment of disseminated mycoses, namely polyene antibiotics (amphotericin B), flucytosine, systemic azoles. Amphotericin B was the first clinically used systemic antifungal antibiotic and after more than 20 years it is still the most effective therapeutic agent for disseminated mycoses [190]. Although the search for antifungal natural compounds has been focused on microorganisms over the last several decades, higher plants appear to be a good basis for antifungal constituents. Agents with antifungal activity are widely distributed among higher plants, but very few have been evaluated for their activity against human pathogenic fungi and scarcely one has been evaluated in animal models of disseminated mycoses [191].

Among many plants used as antimicrobials, the Lamiaceae species are important because these are considered to have better antibacterial activity against pathogens, which are locally available. The potent antimicrobial activity of Coleus
aromaticus may be attributed to various phytochemical constituents present in the crude extract [192].

The following species of Lamiaceae family have been reported with antimicrobial activity:

Screening of ethanol extracts for antimicrobial activity of some Lamiaceae species of Indian folklore were evaluated by Sarac et al., 2006 [193]. Essential oil of Hyptis suaveolens inhibits the growth of both Gram-positive and Gram-negative bacteria [194], while acetone extract of the whole plant inhibit the growth of Staphylococcus aureus, S. albus, S. epidermidis and Bacillus subtilis [195]. The ethanol extract and volatile oil of Ocimum basilicum inhibit the growth of Escherichia coli and Staphylococcus aureus [196]. The essential oil of Thymus pannonicus showed potent antimicrobial activity [197]. Antibacterial evaluation and minimum inhibitory concentration (MIC) of Ocimum sanctum against human pathogens [198]. Mentha arvensis showed significant antimicrobial activity [199].

2.5 Antioxidant activity

Free radicals play a significant role in various pathological conditions such as tissue injury, inflammation process and neurodegenerative diseases. Antioxidants have an important role to protect the human body against damage by the free radicals. Oxidative stress has been recognized to have a pathological role in many types of chronic diseases such as diabetes, heart diseases and cancer. Oxidative stress occurs when the formation of free radicals increases [200]. In oxidative stress, the balance between the formation of reactive oxygen species and amount of antioxidants is destroyed. Oxidative stress causes damage to cell components, such as proteins, lipids and nucleic acids [201, 202].
Recently there has been an upsurge of interest in the therapeutic potential of medicinal plants as antioxidants in reducing free radical induced tissue injury [203]. It has been mentioned by many authors that antioxidant activity of plants is due to their phenolic compounds [204, 205]. These free radical scavenger help in preventing stress induced diseases such as melanoma, cardiac disorders, diabetes mellitus, inflammatory and neurogenerative diseases, cancer [206, 207]. Human body contains anti-free radical defence systems, which include antioxidant enzymes like catalase, peroxidase and superoxide dismutase and antioxidants like ascorbic acid and tocopherol [208] (Table 2).

**Table 2: Major antioxidants and their role**

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<th>Antioxidants</th>
<th>Role</th>
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<tr>
<td>Superoxide dismutase</td>
<td>Dismutates superoxide radical to H₂O₂</td>
</tr>
<tr>
<td>Catalase</td>
<td>Dismutates H₂O₂ to H₂O.</td>
</tr>
<tr>
<td>Glutathione peroxidase</td>
<td>Removes H₂O₂ and lipid peroxides.</td>
</tr>
<tr>
<td>α-Tocopherol</td>
<td>Breaks lipid peroxidation, superoxide and hydroxyl radical scavenger.</td>
</tr>
<tr>
<td>Beta carotene</td>
<td>Superoxide and OH⁻ scavenger, prevents oxidation of vitamin A</td>
</tr>
<tr>
<td>Ascorbic acid</td>
<td>Superoxide and OH⁻ scavenger and neutralizes oxidants from stimulated neutrophils and regeneration of vitamin E</td>
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Plant organisms being devoid of motility and immune systems, have elaborated alternative defence strategies, involving the huge variety of secondary metabolites as tools to overcome stress constraints by adapting to the changed environment for better survival. The large diversity of chemical types and interactions displayed by the secondary metabolites can underlie the impressive multiplicity of
protective functions ranging from toxicity and light / UV shielding to signal transduction [209, 210, 211 and 212]. Recently, an increasing amount of evidences substantiates the functioning of secondary metabolites as antioxidants and antiradicals, assisting the plants with oxidative stress arising in hostile environments [213, 214].

Many synthetic antioxidant components (BHT and BHA) used in foodstuffs were shown to be toxic or have mutagenic effects. In both cases wide preference for antioxidants from natural rather than from synthetic sources. Antioxidants are abundant in fruits and vegetables, as well as in other foods including nuts and grains [215].

The list is ever growing, involving hydroxy and thiol group containing compounds, such as ascorbic acid and lipoic acid, O-dihydroxygroup containing flavonoids, such as quercetin, aliphatic and arylamines, unsaturated fatty acids, carotenoids [216, 217]. Chelation of transition metals (Fe) by flavonoids such as quercetin inferences with the generation of reactive oxygen species (ROS) thus contributing to a powerful antiradical performance [218]. Carotenoids are the hydrophobic molecules are the best candidates to protect lipophilic surfaces such as membranes [219]. Ortho-dihydroxy substitution in the B-ring of anthocyanins potentiating the antioxidant capacity was proposed as a protective mechanism in a physiological disorder of cotton (leaf reddening), due to oxidative stress provoked by Na⁺ / K⁺ imbalance. Flavonoids (quercetin glycosides) and cinnamic acid derivatives endowed with high ROS scavenging capacity were suggested as a rationale of drought tolerance in cotton [219].

A great number of in vitro methods have been developed to measure the efficiency of natural antioxidants either as pure compounds or as plant extracts. In
vitro methods can be divided into two major groups: 1) Hydrogen atom transfer reactions like Oxygen Radical Absorbance Capacity (ORAC), Total radical trapping antioxidant potential (TRAP) and β-carotene bleaching; 2) Electron transfer reactions like triox equivalent antioxidant capacity (TEAC), Ferric reducing antioxidant power (FRAP), α,α-diphenyl 1-1-picryl-hydrazyl radical scavenging assay (DPPH), superoxide scavenging assay, hydroxyl radical scavenging assay, nitric oxide scavenging assay and total phenol assay. These methods are popular due to their high speed and sensitivity. Due to complex native of secondary molecules more than one method is required to evaluate the antioxidant capacity.

Antioxidant effects of various medicinal plants used in traditional therapeutics are associated with their antioxidant properties [220]. Phenolic acids, flavonoids and tannins are the most commonly found polyphenolic compounds in plant extracts [221]. Flavonoids are 15-carbon compounds generally distributed through-out the plant kingdom [222]. Flavonoids and many other phenolic compounds of plant origin have been reported as scavengers of reactive oxygen species (ROS), and are viewed as promising therapeutic drugs for free radical pathologies [223, 224]. Tannins are naturally occurring, high molecular weight polyphenols, which can be divided into hydrolysable tannins and condensed tannins. Tannins are the most abundant antioxidants in the human diet and they exhibit many biologically important functions, which include protection against oxidative stress and degenerative diseases [225]. The oxidation inhibiting activities of tannins have been known for a long time [226].

The following plants of Lamiaceae have been reported with antioxidant activity-
A number of phenolic compounds with strong antioxidant and antimicrobial activities have been identified in plants, especially in those belonging to the Lamiaceae. The major phenolic compounds found in plants are secondary metabolites possessing high antioxidant activity and it is wide spread in the species of Lamiaceae [227]. Many plants, especially those belonging to the Lamiaceae show strong antioxidant activity [228, 229 and 230]. The essential oils of Lamiaceae were rich in oxygenated terpenes and showed considerable radical scavenging and antioxidant activities revealing their potential for therapeutic uses [231].

Significant antioxidant activity of Ocimum sanctum was reported [232]; methanol extract of Oreganum vulgare showed effective antioxidant activity [233] and that of Salvia reuterana exhibit highest antioxidant and total phenols [234]. The aqueous leaf extract of Leonotis leonuras exhibited strong antioxidant activity both in vitro and in vivo, which may be due to the high content of phenolics, flavonoids and proanthocyanidins as antioxidant compounds. No attempts were made on L. nepetifolia; hence, present work gains importance.

2.6 Anthelmintic activity

The anthelmintic assay was conducted according to Ajaiyeoba et al., 2001 [235] with minor modifications, which was done on adult Indian earthworms Pheretima posthuma, since, its anatomical and physiological resemblance with the intestinal roundworm parasite of human beings [236]. Because of easy availability, earthworms have been used widely for the evaluation of anthelmintic compounds in vitro.

Some Indian anthelmintic plants that are used traditionally to cure helminthic diseases reveal that there are number of medicinal plants, which possess significant efficacy against a range of helminth parasite species [237, 238, 239, 240]. Essential
oil of *Ocimum sanctum* possesses significant anthelmintic activity against *Coenorhabditis elegans* [241]. Whole plant extracts of *Hyptis suaveolens* showed potent anthelmintic activity [242]. Chloroform extracts of *Mentha piperita* showed significant anthelmintic activity [243]. Methanol extracts of *Nepeta cataria* evaluated anthelmintic activity against gastrointestinal nematodes of sheep [244]. Leaf extract of *Leucas cephalotes* showed significant anthelmintic activity against intestinal worms [245]. *Clerodendrum colebrookianum* possess significant anthelmintic activity against intestinal tapeworms [246], while root extracts of *Coelus aromaticus* showed significant anthelmintic activity against Indian adult earthworms [247].

Aqueous extracts of *Leonotis leonurus* possess significant anthelmintic activity against *Haemonchus contortus* [248]. Methanol extracts of *Leonotis ocymifolia* possess significant anthelmintic activity against egg hatching and larval development of *Haemonchus contortus* [249].

### 2.7 Antitumor activity

Cancer, one of the most life threatening diseases and serious public health problems in both developed and developing countries, characterized by the irregular proliferation of abnormal cells that invade and disrupt surrounding tissues [250]. Due to the toxic and adverse side effects of synthetic drugs, herbal medicine received maximum attention to improve the fulfillment of future health care demands [251].

Crown gall is a neoplastic disease of plants caused by *Agrobacterium tumifaciens* [252, 253], which occurs in more than 60 families of dicotyledons and many gymnosperms [254]. The Ti-plasmid causes the plant’s cells to multiply rapidly without going through apoptosis, resulting in tumor formation similar in nucleic acid content and histology to human and animal cancers [255, 256]. The potato disc assay demonstrates the inhibition of tumor formation on potato discs; materials (e.g. plant
extracts) that inhibit these plant tumors have a high predictability of showing activity against the P388 (3PS) leukemia in mice [257]. Development of a simple antitumor prescreen using a convenient and inexpensive plant tumor assay systems can offer numerous advantages as alternatives to extensive animal testing in the search for new anticancer drugs.

Therefore, investigations for finding new anticancer compounds are imperative and interesting. After taking into consideration the immense side effects of synthetic anticancer drugs, many researchers are making concerted efforts to find new and natural anticancer compounds. The screening of plant extracts has been of great interest to scientists in the search for new drugs for effective treatment of several diseases [258]. Antibiotics from *Streptomyces* species, including bleomycin, dactinomycin, mitomycin, anthracyclines daunomycin and doxorubicin are important anticancer agents. Drug discovery from medicinal plants has played an important role in the treatment of cancer and indeed, over the last half century most of the plant secondary metabolites and their derivatives have been used towards combating cancer [259]. Several plant-derived compounds have been approved as anti-cancer drugs i.e. vinblastine, vincristine, etoposide, teniposide, taxol, topotecan and irinotecan.

Anticancer activity of many plant-derived saponins, ginsenosides, soyasaponins and saikosaponin-d [260] has already been reported. The pharmacological potential of many plants has been reported to be associated with steroidal or triterpenoid groups [261].

The following plants of *Lamiaceae* family have been reported with antitumor activity-

*Clinopodium vulgare* extracts were evaluated using *in vitro* screening of antitumor activity [262]. Chloroform fraction of *Scutellaria barbata* and its active
constituents showed significant antitumor activity [263]. Leaves of *Plectranthus amboinicus* possess significant antitumor activity [264]. Aqueous extract of *Carica papaya* leaves exhibit potent antitumor activity [265].

### 2.8 Antidiabetic activity

Diabetes is a metabolic disease that has become a serious problem of modern society due to the severe long-term health complications associated with it. In particular, type 2 diabetes mellitus (T2DM) is the most encountered form of diabetes, accounting for more than 80 per cent of the total cases of diabetes [266]. Glucose metabolism disturbances are major factors leading to diabetes. The insulin released by the pancreatic β-cells is the hormone responsible for glucose homeostasis [267]. Insulin stimulates hepatocytes, myocytes, and adipocytes to uptake glucose from the circulatory system. Depending on need, glucose can either be used as an energetic source by glycolysis, or alternatively, stored as glycogen inside muscle or liver cells. The ruthless utilization of insulin leads to develop insulin resistance, which is characterised by the inability of cells to respond to normal required levels of circulating insulin [266], thus leading to the occurrence of the disease. Natural compounds may be feasible alternatives for the treatment of diabetes or reinforcements to currently used treatments. They may even reduce the risk of the disease. Large amounts can be consumed in everyday diet, which is a positive aspect. There are a large number of plants and natural biomolecules that have been discussed in literature for their antidiabetic effects. For example, plants have been used since ancient times to prevent conditions associated with diabetes [268]. The mechanism is most often not completely understood, but more and more studies are being conducted to elucidate the mechanisms of action of different plants and natural compounds. This mini review aims to discuss some key aspects related to the potential use of plants and
natural biomolecules for the prophylaxis and treatment of type 2 diabetes as well as the potential mechanisms of action.

Plant extracts with antidiabetic action, there are more than 1000 plant species being used for the treatment of T2DM worldwide. In parts of the world where the population has restricted access to the healthcare system, the use of medicinal plants for the treatment of T2DM is widespread. In many cases, very little is known about the mechanism of action of traditionally used antidiabetic plants, thus preventing them from being used in standard diabetes care. Recently, more research is being focused on elucidating the action of these plants and their active constituents. A number of Lamiaceous medicinal plants that are currently used for their antidiabetic properties, together with their active biomolecules, based on recent studies are enumerated (Table 3).
Table 3: Lamiaceous plants reported to be used traditionally to treat diabetes

<table>
<thead>
<tr>
<th>Species</th>
<th>Parts</th>
<th>Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Ajuga bracteosa</em></td>
<td>All</td>
<td>Used to treat diabetes (Marles and Farnsworth, 1995) [269]</td>
</tr>
<tr>
<td><em>Ajuga iva</em></td>
<td>Aerial parts</td>
<td>Decreases blood glucose in STZ-treated rats (Hilaly and Lyoussi, 2002) [270]</td>
</tr>
<tr>
<td><em>Ajuga remota</em></td>
<td>Leaf</td>
<td>Used to treat diabetes (Abdulkadir, 1985) [271]</td>
</tr>
<tr>
<td><em>Calamintha ammonostema</em></td>
<td>Root, Stem</td>
<td>Used to treat diabetes (Marles and Farnsworth, 1995) [269]</td>
</tr>
<tr>
<td><em>Calamintha umbrosa</em></td>
<td>All</td>
<td>Hypoglycemic activity in rats (Dhar et al., 1968) [272]</td>
</tr>
<tr>
<td><em>Clerodendranthus phlomoides</em></td>
<td>All</td>
<td>Hypoglycemic activity (Marles and Farnsworth, 1995) [269]</td>
</tr>
<tr>
<td><em>Hyptis suaveolens</em></td>
<td>Aerial parts</td>
<td>Used to treat diabetes (Marles and Farnsworth, 1995) [269]</td>
</tr>
<tr>
<td><em>Lavandula multifida</em></td>
<td>Flower</td>
<td>Hypoglycemic activity (Gamez et al., 1987) [275]</td>
</tr>
<tr>
<td><em>Lavandula stoechas</em></td>
<td>Leaf, Flower</td>
<td>Hypoglycemic activity (Gamez et al., 1987) [275]</td>
</tr>
<tr>
<td><em>Leonotis leonurus</em></td>
<td>Leaf, Flower</td>
<td>Used to treat diabetes (Marles and Farnsworth, 1995) [269]</td>
</tr>
<tr>
<td><em>Lycopus virginicus</em></td>
<td>Leaf, Flower</td>
<td>Used to treat diabetes (Marles and Farnsworth, 1995) [269]</td>
</tr>
<tr>
<td><em>Mentha longifolia</em></td>
<td>All</td>
<td>Used to treat diabetes (Aswal et al., 1984) [274]</td>
</tr>
<tr>
<td><em>Nepta ciliaris</em></td>
<td>All</td>
<td>Hypoglycemic activity in rats (Abraham et al., 1986) [273]</td>
</tr>
<tr>
<td><em>Ocimum americanum</em></td>
<td>Seed</td>
<td>Reduces blood glucose (Ivorra et al., 1989) [276]</td>
</tr>
<tr>
<td><em>Ocimum gratissimum</em></td>
<td>Leaf</td>
<td>Extracts lower blood glucose in alloxan treated rats (Ivorra et al., 1989) [276]</td>
</tr>
<tr>
<td><em>Salvia lavendulifolia</em></td>
<td>Flower</td>
<td>Reduces blood glucose in alloxan treated rats (Ivorra et al., 1989) [276]</td>
</tr>
<tr>
<td><em>Salvia canariensis</em></td>
<td>Aerial parts</td>
<td>Used to treat diabetes (Marles and Farnsworth, 1995) [269]</td>
</tr>
<tr>
<td><em>Teucrium deverianum</em></td>
<td>Aerial parts</td>
<td>Reduced blood glucose in alloxan treated rats (Ivorra et al., 1989) [276]</td>
</tr>
<tr>
<td><em>Teucrium royleanum</em></td>
<td>All</td>
<td>Used to treat diabetes (Marles and Farnsworth, 1995) [269]</td>
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</table>